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The Efficacy and Safety of Convalescent Plasma for COVID-19 Patients: A Meta-Analysis Based on Double-Blinded Parallel-Arm Randomized Placebo-Controlled Trials

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Keywords:

Coronavirus disease 2019 (COVID-19); Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Convalescent plasma (CP); Outcome; Efficacy; Safety; Adverse events (AEs); Serious AEs; Meta-analysis

1. Abstract

1.1. Background: Convalescent plasma (CP) was demonstrated promising benefit for clinical practice involved in efficacy and safety in previous coronavirus pandemics, however, the efficacy of CP from COVID-19 sufferers are still controversial and unascertainable based on current randomized controlled trials (RCTs). The urgent needs for affirmative replies on the efficacy and safety of CP for COVID-19 patients must be developed as soon as possible.

1.2. Objective: To corroborate the efficacy and safety of CP based on high-quality double-blinded, parallel-arm placebo-control randomized clinical trials and provide evidence-based support for clinical application of CPagainst COVID-19.

1.3. Methods: Such medical electronic databases as Embase, PubMed, and Web of Science were retrieved from inception to March 12, 2022. This meta-analysis synthesizes such dichotomous outcomes as the incidences of28-day mortality, hospitalization rate, invasive mechanical ventilation, adverse events (AEs) and serious AEs using intention-to-treat (ITT) analysis. Statistical analysis, using Review Manager (RevMan) 5.4.1 software, Mantel-Haenszel (M-H) statistical method and random effects (RE) analysis model, risk ratios (RRs) plus their 95% confidence intervals (CIs) as effect measures, were performed. Two reviewers independently searched, screened, included the eligible clinical trials, extracted data of concern from them and assessed the risks of bias (ROB) of the included articles with the Cochrane ROB tool 1.0 and RevMan 5.4.1 software. The effect measures of RRs plus their 95% CIs in this meta-analysis will be computed as dichotomous outcomes of interest. Statistical heterogeneities, subgroup analysis and sensitivity analysis will be fulfilled to explore the heterogeneities and their causes. We evaluate the quality of evidence and put forward strength of recommendations for clinical practice based on the GRADE approach. This prospective meta-analysis protocol has been registered on PROSPERO.

1.4. Results: 697 references were preliminarily identified from the databases of concern and manual retrieves, and 9 eligible double-blinded, parallel-arm, placebo-control randomized clinical trials with 1898 subjects in the intervention group and 1696 participants in the control group were ultimately included in the meta-analysis. 7, 4, 3, 3 and 3 eligible trials are adjudged as low

ROB for mortality, the rate of hospitalization, the incidence of invasive mechanical ventilation, AEs and serious AEs, respectively; all the rest of included trials are defined as high risk corresponding to the respective outcome. The meta-analysis on the hospitalization rate was abandoned because of high heterogeneity (I2=92%) among the inclusion trials. The RRs, 95%CIs and P-values were 0.78 [0.62, 0.97], P = 0.03 on mortality; 0.84 [0.50, 1.42], P = 0.51 on invasive mechanical ventilation; 1.01 [0.78, 1.32],P = 0.92 on AEs; 0.96 [0.73, 1.28], P = 0.80 on serious AEs, respectively, with low or medium levels of heterogeneity; which indicate that CP infusion in COVID-19 patients can efficaciously reduce mortality by 22%, and exhibit excellent safety and not decrease the incidence of invasive mechanical ventilation. Sensitivity analysis on mortality with the combining effect measure (RR 0.83 [0.66, 1.06], I2 0%, Z-value 1.46, P = 0.14) after deleting the study by O'Donnell showed that there is not different between the intervention group and control group, hinting that the deleted study may be more efficacious for reducing mortality. Subgroup analysis on mortality based on age showed that CP therapy in COVID-19 patients aged ≤ 60 years old may more efficaciously reduce mortality by 36%. Sensitivity analyses and subgroup analyses on the other outcomes present robust pooling outcomes. The registration code on PROSPERO is CRD42022324324.

1.5. Conclusions: Administration of CP to COVID-19 patients, especially to COVID-19 patients aged ≤ 60 years old, may efficaciously reduce mortality with excellent safety, but does not reduce the incidence of invasive mechanical ventilation.

2. Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is one of seven known human-infected coronaviruses, was identified in Hubei province, China in December of 2019andcaused a pleomorphic spectrum of clinical presentations from asymptomatic infection to critical illness, life-threatening status and death1. COVID-19induced by multiple variants currently has dispersed to most parts of the world, triggered a human crisis and globally endangered public health and socioeconomic status. The typical clinical characteristics of COVID-19include such three domains as fever, dry cough, dyspnea, fatigue, myalgia, anosmia, and ageusia in symptoms and signs 2,ground-glassopacityin posterior and peripheral areas of the bilateral lungs in computed tomography and lymphopenia, elevated inflammatory biomarkers and D-dimers in laboratory parameter [3].

Although the action mechanisms of CP directed against COVID-19 are not comprehended yet, the potential therapeutic mechanisms may be simultaneously or/and separately touch upon the following profiles, intensified neutralizing antibodies from CP targeted against the membrane spike protein of SARS-Cov-2 should retard the attachment of the SARS-CoV-2 to angiotensin converting enzyme 2 receptors resided in host cell surface and block viral entry into the host cell [4], such the immunomodulatory mechanisms as disturbing complement activation, antibody-dependent cytotoxicity and phagocytosis associated with CP infusion may facilitate restricting the more deleterious inflammatory cascade than the virus itself [5], the IgG of anti-A isoagglutin in lying in subjects with O-type blood would prevent the coupling of SARS-CoV-2 with its receptor and block the virus entry into the targeted cells [6].

CP infusion in previous coronavirus pandemics [7-10], in early observational studies [11, 12], RCTs [13-15] and Meta-Analysis [16, 17] demonstrated promising benefit for clinical outcomes in patients with COVID-19; but the recent RCTs [3, 18] exhibited no favorable and satisfactory clinical efficacies. Up to now, there are still no favorable specific therapy options for COVID-19, some promising and encouraging therapeutic at tempts to treat this disease are still on the road [3].The CP from sufferers infected by SARS-CoV10 and influenza virus [9] has long been successfully used and shown conclusive efficacious evidence for a few decades. However, the efficacy of CP from COVID-19 sufferers is still controversial and unascertainable based on current clinical trials with different efficacy in term of mortality either favorable efficacy from several studies11-15or unfavorable efficacy from the otherstudies [3, 18].

A hypothesis is that the intravenous infusion of CP with high titers of neutralizing antibodies would benefit improvement in clinical outcomes in COVID- 19 patients. The main goals of this meta-analysis are to evaluate the specific efficacy and safety of CP for COVID-19 patients based on randomized, double-blinded, placebo-controlled, parallel-arm clinical trials and provide evidence-based support for clinical practice.

3. Methods

This investigator-initiated systematic review and meta-analysis are implemented with a prospective protocol registration on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/#myprospero) and as per the present methods as recommended in AMSTAR 2 [19], the PRISMA statement [20], and Cochrane Collaboration recommendations [21].

4. Inclusion Criteria

The qualified papers will satisfy all the following requirements:①the published original randomized, double-blinded, placebo-controlled, parallel-arm clinical trials involved in the efficacy or safety of the CP therapy;②all included participants must meet the following requirements: aged 18 years or older, laboratory-confirmed COVID-19, with or without underlying diseases;③CP plus local standard care in the intervention group, placebo (normal saline (NS) or non-convalescent plasma) plus local standard care or merely local standard care in the control group; ④eligible studies at least included one of such outcomes of concern as the incidences of 28-day mortality, hospitalization, invasive mechanical ventilation, AEs and serious AEs.

5. Exclusion Criteria

The papers with one of the following requirements, such as articles on non-RCT, crossover RCT, hyperimmune RCT, trial protocol, single-arm trial, observation trial, case report or cohort trial, review or meta-analysis, position paper, letter, editorial, comment, fingerpost or recommendation, erratum and correction, conference abstract, animal trial, and article unavailable full text, will be discarded.

6. Retrieval, Screening, Data extraction

We comprehensively searched such medical databases as PubMed, Embase and Web of Science using the following search strategy formulations: ((convalescent plasma) AND (((Covid-19) OR (Covid 19)) OR (SARS-CoV-2))) AND ((((trial) OR (trials)) AND ((control) OR (controlled))) AND ((randomised) OR (randomized)))to retrieve as accurate and complete studies of concern as possible up to March 12, 2022, abided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart20. We included all published original double-blinded, parallel-arm, placebo-controlled randomized, clinical trials on the efficacy and safety of CP infusion for COVID-19 patients limited to English. The two authors (LP and LX) must independently complete retrieval based on the above-mentioned search strategy, screening based-on inclusion and exclusion criteria, extracting data of interest, respectively; any divergences in results of retrieval, screening and data extraction must be settled by mutual negotiation.

7. Risk of Bias Assessment

The Cochrane ROB1.0 tool22, which includes such 7 domains of bias as (I) selection bias(random sequence generation), (II)selection bias (allocationconcealment), (III) performance bias (blinding for participants and personnel), (IV) detection bias (blinding for outcome assessment), (V) attrition bias (incompleteoutcome data), (VI) reporting bias (selective reporting), and (VII) other bias, will be used to evaluate the ROBs of included articles. Two authors (LP and TY) will independently assess the ROBs of all included eligible articlesbased on ROB 1.0 tool and draw ROB summary with RevMan 5.4.1 software, respectively. Any divergence will be disposed of by discussion with each other when necessary.

8. Sensitivity Analysis and Subgroup Analysis

Sensitivity analysisis performed to both demonstrate robustness of conclusions and seek out the reasons for heterogeneityby successivelyeliminating one included study.If significant heterogeneity is definite(I2>75%),possible sources of heterogeneity must be investigated via subgroup analysis or sensitivity analysis based on specific status.

9. Statistical Analysis

Statistical analysis is performed using RevMan Version 5.4.1 software, M-H statistical method and RE analysis modelto synthetize the eligible inclusion data and arrive at a total effect measure of RR and 95% CI on every outcomeof concern.The heterogeneity test is quantitatively assessed using I2 statistic (significantat $P<0.10$). Thelevels of heterogeneity are defined as high, medium and low levels when I2values were 75–100%, 50–75% and 0–50%, respectively.RE analysis model will be applied if I2 is <75%. Otherwise, the narrative review must betaken into account. The cumulative effects of outcomes of concern are presented via forest plots, which can simultaneously show the effect parameters of RR and its 95% CIs for each included study. Publication bias is rated using visual qualitative funnel plot inspection if enough eligible studies are included.

10. The Quality of Evidence and Recommendation

A recommendation on CP infusion in COVID-19 patients is made based on the guideline of GRADE23after the quality of evidence is adjudged as high, moderate, low or very low level according to the another guideline24.

11. Role of the Funding Source

There was not any financial support for the design, data retrieval and extraction, data synthesis, interpretation in ultimate results, and writing of original article associated with this meta-analysis. Each author has full access to the data associated with the meta-analysis and finally decides to publish it.

12. Results

The systematic review and meta-analysis on efficacy and safety of CP infusion in COVID-19 patients is registered at PROSPERO with the registration code of CRD42022324324.

A total of 697 articles (173 in PubMed, 392 in Embase and 132 in Web of Science)were obtained viaretrievalsearchin medical electronic databases of concern with the similar search strategy described above.197 and 54 articles were deleted for duplication in the fields of authors, headline, abstract and publish journal via EndNote or by hand, respectively. Sub-sequentially, the rest of 33 articles, following discarding 413 articles because of contradiction with inclusion criteria or accordance with exclusion criteria by inspecting the title and abstract, are assessed as preliminary eligibility. Finally, 9 articles [2, 14, 15, 18, 25-29], after eliminating 24 articles with such specific removal causes as 21 open-label RCTs, 2 single-blinded RCTs and one prophylactic RCT by reading full-text, were included in this quantitative meta-analysis. All operation procedures follow the flow diagram of search and selection displayed in Figure 1.Of 9 studies included in the quantitative synthesis (meta-analysis),a total of 3594 participants were randomized to the intervention group (n=1898) using CP infusion plus local standard care and the control group (n=1696) using either NS or non-convalescent plasma plus local standard care or merely local standard care.

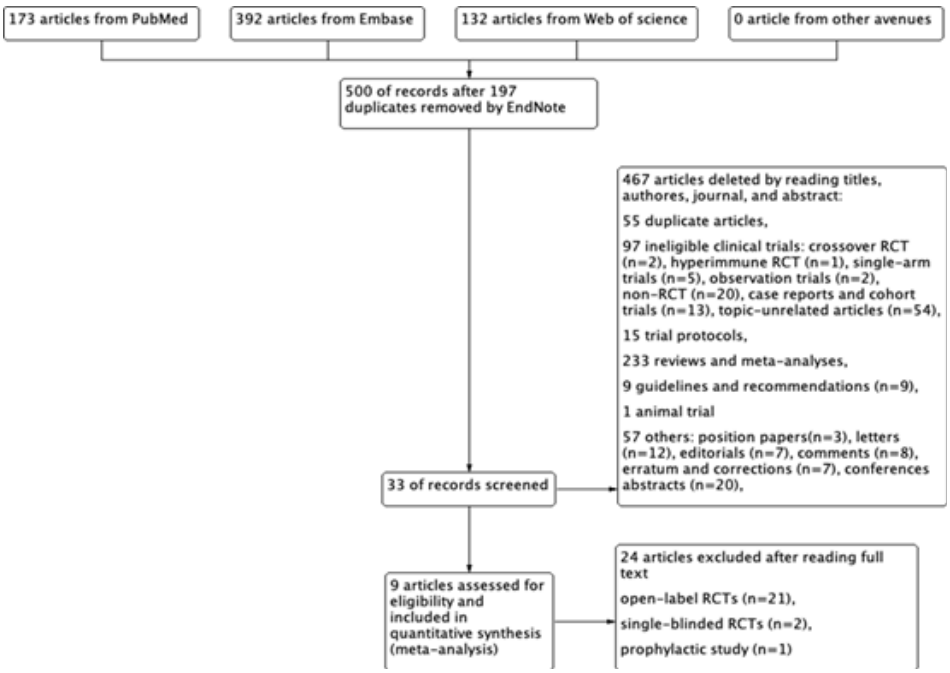

Figure 1: Study flow diagram of search and selection

13. The ROB Assessment for all Included Studies

The ROB assessments were performed using RevMan5.4.1 software and ROB 1.0 tool for the included clinical trials. RevMan5.4.1 software was utilized to create ROB summary in each domain-level evaluation for each inclusion study. Of 9 eligible included studies, 7 studies 2, 15, 18, 25, 26, 28, 29 on mortality, 3 studies 2, 26, 29 on invasive mechanical ventilation, 4 studies 2, 15, 26, 29 on hospitalization rate, 3 studies15, 25, 26 on AEs and 3 studies18, 26, 28 on serious AEs were judged as low ROB, and the study with at least one high risk or ≥ 3 unclear risks in all 7 domains were identified as high ROB. The results of overall ROB on all outcomes of concern are high risk presented in Figure 2.1-2.5.

Although the qualitative funnel plot test for publication bias is low power when a meta-analysis includes ten or fewer studies or the more confounding factors amongst inclusion trials, the publication bias test on mortality in this meta-analysis using a visual qualitative funnel plot presents somewhat asymmetry at the bottom of the funnel plot, indicating it is possible that some RCTs with small sample size or negative outcomes were not published showed in Figure 3; the publication bias test using funnel plot on the incidence of hospitalization, invasive mechanical ventilation, AEs and serious AEs in this meta-analysis were discarded owing to too few available studies.

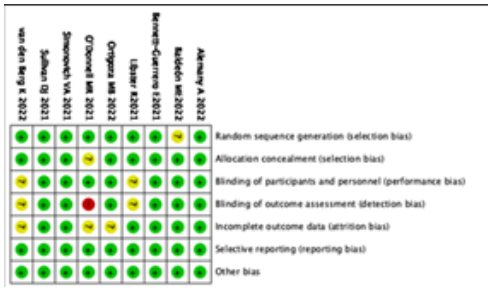

Figure 2.1: ROB summary on 28-day mortality

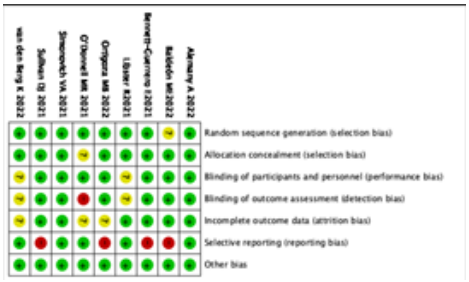

Figure 2.2: ROB summary on invasive mechanic ventilation

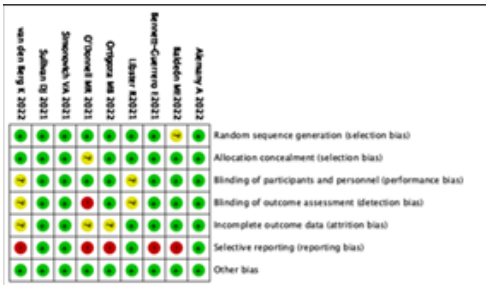

Figure 2.3: ROB summary on hospitalization rate

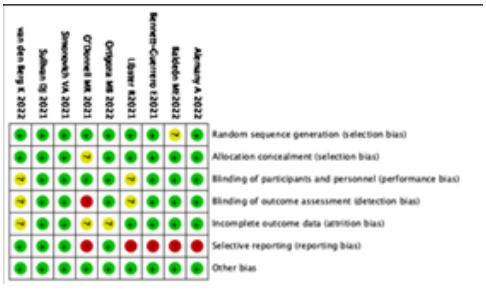

Figure 2.4: ROB summary on adverse events

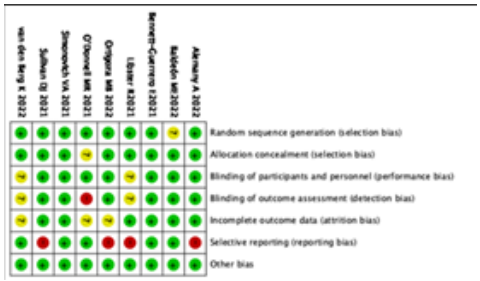

Figure 2.5: ROB summary on serious adverse events

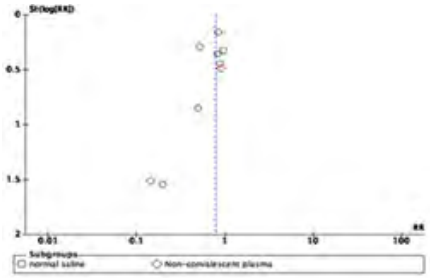

Figure 3: Funnel plot on 28-day mortality

14. General Characteristics and Key Information of the Included Studies

The general characteristics and critical information of a total of 9 eligible studies included in this meta-analysis are presented in Table 1. 9, 5, 4 and 5 studies are included in quantitative synthesis on mortality outcome 2, 14, 15, 18, 25-29 (137 deaths from1898 participants in the intervention group vs. 139 deaths from 1696 participants in the control group), invasive mechanical ventilation outcome 2, 14, 26, 27, 29 (36 sufferers from 1016 participants in the intervention group vs. 25 from 898 in the control group), AEs outcome 15, 25-27 (254 cases of 1358 participants in the intervention group vs. 175 of 1245 in the control group) and serious AEs outcome 14, 18, 26-28 (127 of 552 in the intervention group vs. 67 of 340 in the control group), respectively, and RE analysis model was applied owing tothe medium or low levels of heterogeneity amongst included clinical trials. The hospitalization rate outcome including 4 studies2, 15, 26, 29 (169 hospitalized cases from 1106participants in the intervention group vs. 130 from 989 in the control group) is dealt with via narrative analysis because of a high level of heterogeneity among inclusion studies.

Table 1: General characteristics and key information of included clinical trials

Author and year	Alemany2022	Baldeón 2022	Bennett-Guerrero 2021	Libster2021	Ortigoza2022	O'Donnell 2021	Simonovich 2021	Sullivan 2021	van den Berg 2022
T-assess	Day 28	Day 28	Day 28	Day 28	Day 28	Day 28	Day 30	Day 28	Day 28
Severity	mild and moderate	NA	moderate to severe	mild	noninvasive oxygen supplementation	severe and critical	severe	Mild moderate or severe	moderate to severe
Age(int)	Median (IQR) 56 (52–62)	mean (SD) 56.3 ± 12.7	mean (SD): 67 (15.8)	mean (SD) 76.4±8.7	Median (IQR) 62.0 (51.0-72.0)	Median (IQR) 60 (48–71)	Median (IQR) 62.5 (53–72.5)	Median (IQR) 42 (31.5-54)	Median (IQR) 54 (46–62)
Age(con)	Median (IQR) 56 (53–63)	mean (SD) 55.0 ± 13.3	mean (SD) 64 (17.4)	mean (SD) 77.9±8.4	Median (IQR) 64.0 (54.0-74.0)	Median (IQR) 63 (49–72)	Median (IQR) 62 (49–71)	Median (IQR) 44 (33–55)	Median (IQR) 57 (47–64)
Nitt(int)	188	63	59	80	468	150	228	610	52
Nitt(con)	188	95	15	80	473	73	106	615	51
Nmitt(int)	188	63	58	76	462	147	228	592	47
Nmitt(con)	188	95	14	78	462	72	105	589	50
M/F(int)	105/83	42/21	36/23	26/54	284/184	96/54	161/67	269/323(Mitt)	21/31
M/F(con)	98/90	65/30	7-Aug	34/46	272/201	51/22	64/41	237/352(Mitt)	21/30
T-int-symptoms	≤7d	NA	Median (IQR): 9 (6–18)	≤3d	Median (IQR): 7(4-9)	Median: 9d	Median (IQR):8 (5–10)	≤8d	Median (IQR): 9 (6–11)
T-con-symptoms	≤7d	NA	Median (IQR): 9 (6–15)	≤3d	7(4-9)	Median: 9d	Median (IQR): 8 (5–10)	≤8d	Median (IQR): 9 (6–11)
Pr-PLB (ml)	NS 250ml or 5 ml/kg	Non-convalescent pasma 5 ml/kg	Standard plasma 480ml	NS 250	NS 250ml	control plasma 200-250ml	NS500	Standard plasma ≥175	NS 200
Pr-CP (ml)	250–300ml or 5 ml/kg	5 ml/kg	480ml	250ml	250ml	CP 200-250ml	Median (IQR) 500(415-600)	≥175ml	200–250ml

Death toll(int)	0	7	14	2	59	19	25	0	11
Death toll(con)	2	12	4	4	71	18	12	3	13
N in-venti(int)	2	NA	NA	2	NA	12	19	NA	1
N in-venti(con)	4	NA	NA	4	NA	4	10	NA	3
N int-hosp	22	NA	NA	7	NA	NA	123	17	NA
Ncon-hosp	21	NA	NA	12	NA	NA	63	37	NA
N_{AE}(int)	NA	NA	NA	NA	44	NA	153	34	23
N_{AE}(con)	NA	NA	NA	NA	39	NA	66	53	17
N_{SAE}(int)	NA	0	16	NA	NA	39	54	NA	18
N_{SAE}(con)	NA	0	4	NA	NA	26	19	NA	18

Abbreviations: T-assess = Time at assessing outcome; Age (int) = age in intervention group; Age (con) = age in control group; IQR = interquartile range; SD = standard deviation; Niit(int) = the number of intention-to-treat participants in intervention group; Niit(con) = the number of intention-to-treat participants in control group; Nmiit(int) = the number of modified intention-to-treat participants in intervention group; Nmiit(con) = the number of modified intention-to-treat participants in control group; M/F(int) = male/female inintervention group; M/F(con) = male/female in control group; T-int-symptoms = intervention timing after the onset of symptoms in intervention group; T-con-symptoms = intervention timing after the onset of symptoms in control group; Pr-PBO = Prescription of placebo in control group; Pr-CP = Prescription of convalescent plasma in intrvention group; NS = normal saline; int = intervention group; con = control group; ml = milliliters; kg = kilogram; N in-venti(int) = the number of cases using invasive mechanic ventilation in intervention group; N in-venti(con) = the number of cases using invasive mechanic ventilation in control group; N int-hosp = the number of hospitalized cases in intervention group; N con-hosp = the number of hospitalized cases in control group; NAE (int) = the number of cases with any adverse events in intervention group; NAE (con) = the number of cases with any adverse events in control group; NSAE (int) = the number of cases with serious adverse events in intervention group; NSAE (con) = the number of cases with serious adverse events in control group; NA = not available.

15. Primary and Secondary Outcomes

Meta-analysis using quantitative synthesis on hospitalization rate is rejected because heterogeneity (I2 = 92%, P<0.00001) amongst the included trials are significant. Heterogeneity tests on 28- day mortality, invasive mechanical ventilation, AEs and serious AEs amongst the included trials shown in Figure 4.1-4.4 reveal homogeneity. 28-day mortality outcome presented in Figure 4. 1 shows a significant statistical difference between the two groups (RR 0.78 [95% CI 0•62–0.97], I2 0%, P=0.03), which indicates that the CP infusion is effective for COVID-19 patients in reducing the 28-day mortality by approximately 22%. However, the incidences of invasive mechanical ventilation, AE and serious AE are no statistical significance between the intervention group and the control group, which indicate that CP infusion in COVID-19 patients is safe and does not decrease usage of invasive mechanical ventilation for COVID-19 patients.

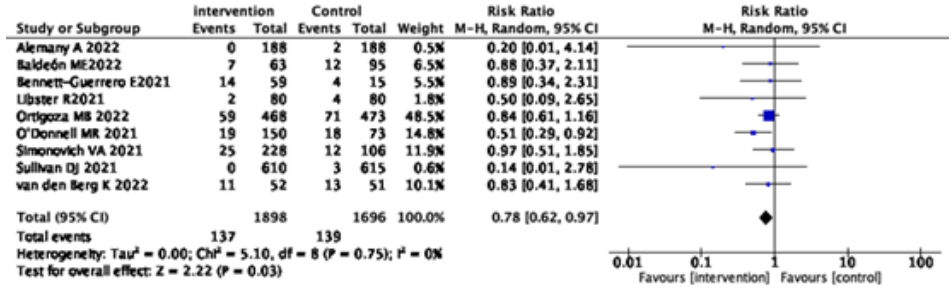

Figure 4.1: the forest plots of 28-day mortalitybetween the CP and control group.

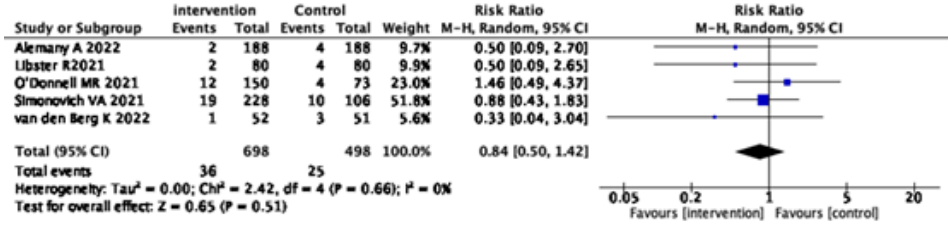

Figure 4.2: the forest plots of the rate of invasive mechanic ventilation between the CP and control group.

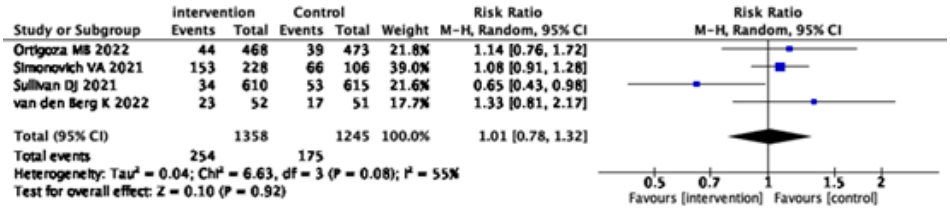

Figure 4.3: The forest plots of the rate of any AE between the CP and control group.

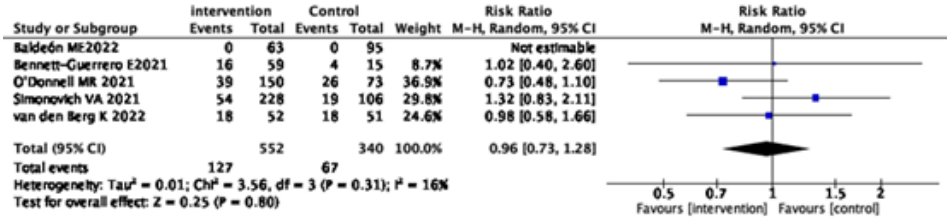

Figure 4.4: The forest plots of the rate of serious AE between the CP and control group.

Figure 4: the forest plots of primary and secondary outcomes

16. Sensitivity Analysis

Sensitivity analyses are performed for all outcomes of interest and their information is presented in Table 2. From sensitivity analyses on hospitalization rate, the striking heterogeneities showed in Table 2 Cmay indicate more confounders or baseline imbalance amongst inclusion trials and make quantitative synthesis on this outcome be abandoned. After deleting the study by O'Donnell, the combining effect measure on mortality (RR 0.83 [0.66, 1.06], I2 0%, Z-value 1.46, P = 0.14) is different from the total effect measure in advance of deleting the study, hinting that the deleted study may be more efficacious in reducing mortality or exist additional confounders (e.g.: severe or critical illness); this marked impact on the total effect may require more identical clinical trials to check this effect and explore confounders of concern. Sensitivity analyses on invasive mechanical ventilation, any AEs, and serious AEs presented in Table 2B, 2D, 2E show that all statistical results are not altered after deleting any trial, which corroborate that the results are robust accompanying with the low to medium levels of heterogeneity amongst inclusion trials.

Table 2: Sensitivity analysis

Deleted article	RR and 95%CI	I^2(%)	Z-value	*P*-value
A: 28-day mortality and overall effect RR (0.78 [0.62, 0.97], I^2=0%, Z=2.22, *P*=0.03				
Alemany 2022	0.78 [0.63, 0.98]	0	2.14	0.03
Baldeón 2022	0.77 [0.61, 0.97]	0	2.22	0.03
Bennett-Guerrero 2021	0.77 [0.61, 0.97]	0	2.22	0.03
Libster 2021	0.78 [0.63, 0.98]	0	2.13	0.03
Ortigoza 2022	0.72 [0.53, 0.99]	0	2.05	0.04
O'Donnell 2021	0.83 [0.66, 1.06]	0	1.46	0.14
Simonovich 2021	0.75 [0.59, 0.96]	0	2.32	0.02
Sullivan 2021	0.78 [0.63, 0.98]	0	2.13	0.03
Van den Berg 2022	0.77 [0.61, 0.98]	0	2.16	0.03
B: Invasive mechanical ventilation and effect RR (0.84[0.50, 1.42], I^2=0%, Z=0.65, *P*=0.51				
Alemany 2022	0.89 [0.51, 1.54]	0	0.42	0.67
Libster 2021	0.89 [0.51, 1.55]	0	0.42	0.67
O'Donnell 2021	0.71 [0.39, 1.29]	0	1.12	0.26
Simonovich 2021	0.79[0.37, 1.69]	0	0.6	0.55
Van den Berg 2022	0.89[0.52, 1.52]	0	0.44	0.66
C: Hospitalization rate and overall effect RR (1.11 [0.33, 3.67], I^2=92%, Z=0.16, *P*=0.87				
Alemany 2022	1.09 [0.17, 6.84]	94	0.09	0.93
Libster 2021	1.32[0.34, 5.18]	94	0.4	0.69
Simonovich 2021	0.67 [0.35, 1.26]	52	1.24	0.22
Sullivan 2021	1.55 [0.24, 5.76]	89	0.66	0.51

D: Any AEs and overall effect RR (1.01 [0.78, 1.32], I^2=55%, Z=0.10, P=0.92				
Ortigoza 2022	0.98 [0.67, 1.42]	70	0.13	0.9
Simonovich 2021	0.98 [0.64, 1.52]	66	0.08	0.93
Sullivan 2021	1.11 [0.95, 1.29]	0	1.32	0.19
Van den Berg 2022	0.95[0.69, 1.31]	65	0.31	0.76
E: Serious AEs and overall effect RR (0.96 [0.73, 1.28], I^2=16%, Z=0.25, P=0.80				
Baldeón 2022	0.96 [0.73, 1.28]	16	0.25	0.8
Bennett-Guerrero 2021	0.97 [0.68, 1.38]	44	0.18	0.85
O'Donnell 2021	1.14 [0.82, 1.58]	0	0.78	0.43
Simonovich 2021	0.84 [0.62, 1.13]	0	1.15	0.25
Van den Berg 2022	0.97 [0.64, 1.48]	44	0.13	0.9

17. Subgroup Analysis

Subgroup analyses are performed based on age≤ 60 years old or >60 years old. The subgroup analysis on mortality presented in Figure 5.1 indicates that CP infusion develops more beneficial reduction in mortality by 36% than that in the control group in ≤ 60 years old subgroup. The incidences of hospitalization and invasive mechanical ventilation remain their robustness whether ≤ 60 years old or >60 years old subgroup, indicating that CP infusion does not reduce the rates of hospitalization and invasive mechanical ventilation no matter ≤ 60 years old or >60 years old subgroup observed in Figure 5.2 and 5.3. CP infusion develops similar AEs compared with placebo regardless of ≤ 60 years old or >60 years old subgroup; although CP infusion can cause fewer serious AEs compared with control group in ≤ 60 years old subgroup than that in >60 years old subgroup recorded in Figure 5.4 and 5.5, there is no statistical difference in the incidence of serious AEs between the intervention group and the control groups whether ≤ 60 years old or >60 years old subgroup, which indicates that CP infusion possesses such remarkable safety.

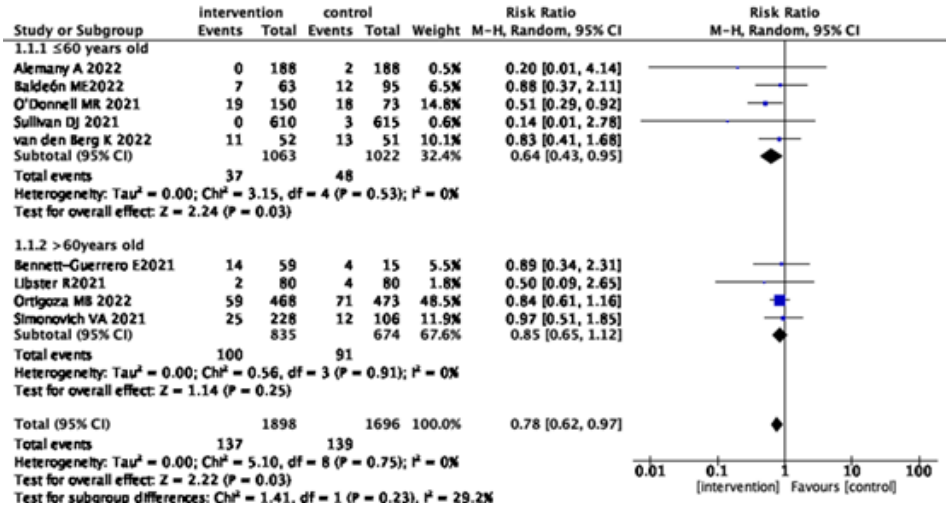

Figure 5.1: Forest plot of comparison of 28-day mortality in intervention group vs. control group.

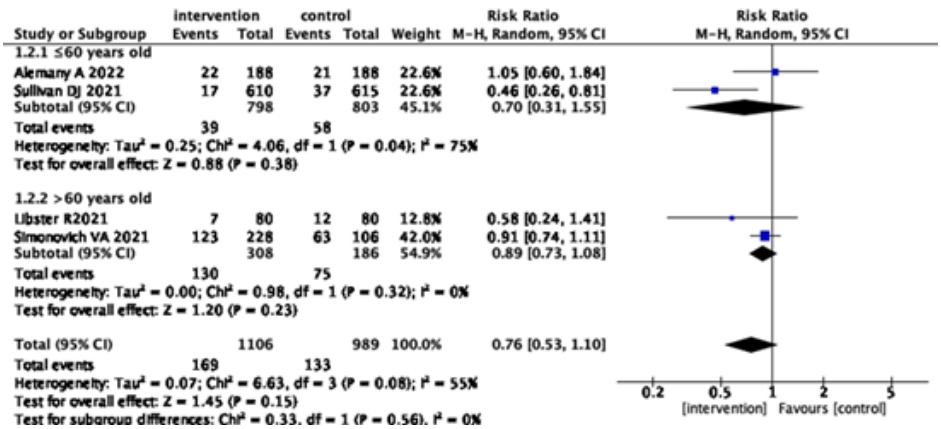

Figure 5.2: Forest plot of comparison of hospitalization rate in intervention group vs. control group.

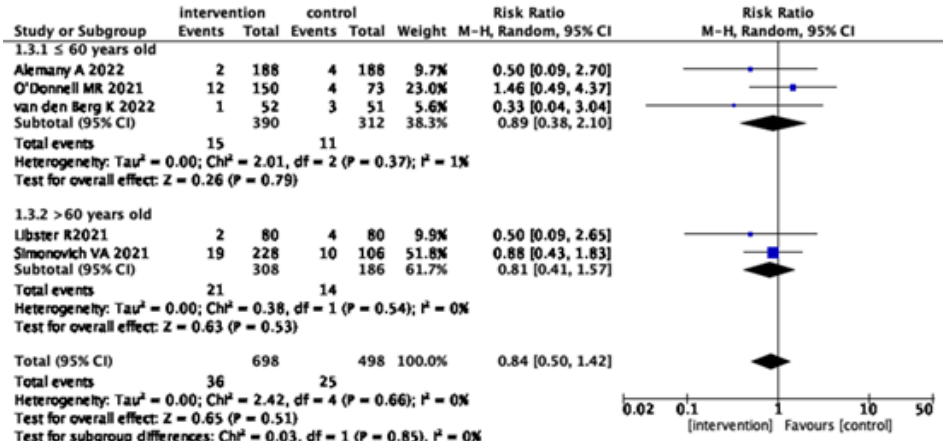

Figure 5.3: Forest plot of comparison of invasive mechanical ventilation in intervention group vs. control group.

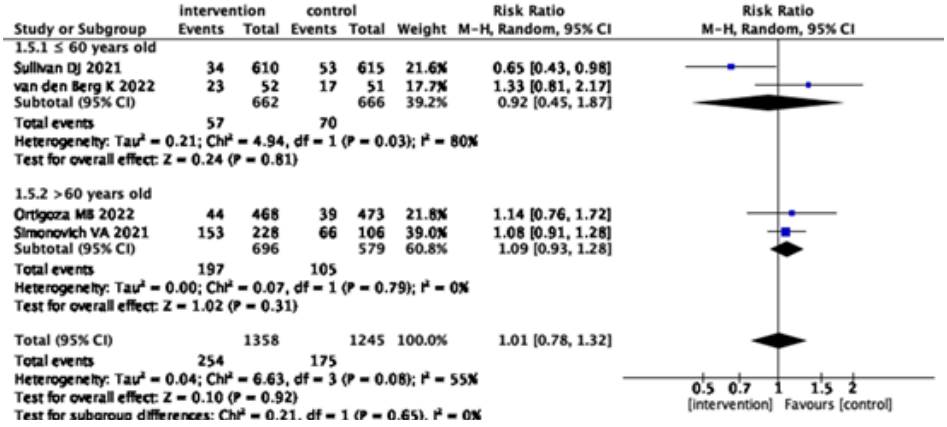

Figure 5.4: Forest plot of comparison of any adverse events in intervention group vs. control group.

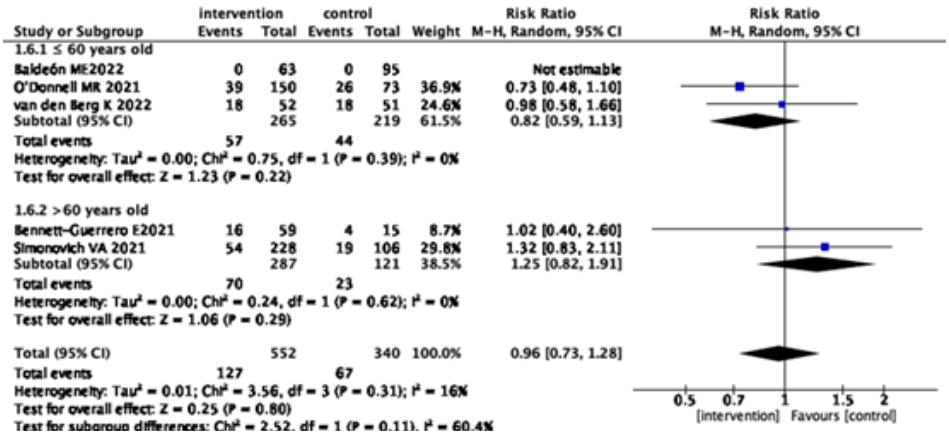

Figure 5.5: Forest plot of comparison of severe adverse events in intervention group vs. control group.

Figure 5: Forest plot of comparison in intervention group vs. control group.

18. Quality of Evidence and Strength of Recommendation

The quality of evidence on the CP infusion in COVID-19 patients is high level. Based on current information, a strong recommendation of CP infusion is made for patients with COVID-19 if necessary, especially for COVID-19 patients with ≤ 60 years old.

19. Discussion

As far as we know, this meta-analysis is the most all-round systematic review and meta-analysis, based on double-blind, parallel-arm, placebo-control, randomized clinical trials, to probe the efficacy and safety of CP infusion in patients with COVID-19.Because current SARS-CoV-2 with high infectivity has been endangering global healthcare all over the world since the late of 2019, a specific drug targeted to COVID-19 is not available yet. CP, as an alternative passive immunotherapy option, once has been recommended to apply for multiple infectious diseases for more than one hundred years. Multiple study results displayed that CP infusion could significantly decrease the mortality caused by SARS virus10, MERS-CoV8, influenza virus9 infection. However, due to the low certainty of evidence on the beneficial effects of CP infusion in COVID-19 patients, the present meta-analysis is performed

to confirm its efficacy and safety for future clinical practice.

This meta-analysis identified and summarized up to 9randomized, double-blind, parallel-arm, placebo-controlled, clinical trials. This meta-analysis based on data recorded above shows that CP infusion could significantly lower the mortality, and that the similar results on mortality mentioned above are consistent with the results from RCT14 and meta-analysis based on RCTs30, 31;but, some RCTs2, 15, 18, 25-29 did not support this conclusion. Therefore, Although the conclusion is still controversial, the available evidence from this meta-analysis may provide a basis for an option of CP application for COVID-19 treatment until now. Secondary mortality caused by SARS-CoV-2 infection was reduced by CP transfusion, which might be attributable to such multiple complex known or unknown mechanisms of action as restraining complement activation, antagonizing cytokine effects, and down-regulating B- and T-cells functions5,and such other action mechanisms as controlling the attachment of the SARS-CoV-2 to angiotensin converting enzyme 2 receptors by strengthening neutralizing antibodies against the membrane spike protein of SARS-Cov-24 and the coupling of SARS-CoV-2 with its receptor by the IgG of anti-A isoagglutinin in O-type blood subjects6. Concrete and authentic mechanisms of action which are unclear yet need to be explored using more clinical trials and fundamental research on COVID-19. Sensitivity analysis on mortality after deleting O'Donnell14 showed that there are significantly different effects before and after deleting O'Donnell, which indicated that CP infusion might make more severe or critical COVID-19 patients keep from death in the deleted study. And subgroup analysis on mortality based on age≤ 60 years old or >60 years old showed that CP therapy for patients in ≤ 60 years old sub group might be more efficacious than that in >60 years old subgroup, which hinted that onset age might be one of the commonest confounding factors which led to significant heterogeneities, which suggested that CP infusion might be an extremely good alternative option to reduce mortality for COVID-19 patients, the more so as COVID-19 patients are ≤ 60 years old if other efficacious therapeutics aren't acquired.

Owing to the significant heterogeneities among included trials in terms of synthetizing hospitalization rate, which might be attributable to the difference in severity, sample size, age and so on. The outcome on hospitalization rate derived from the inclusion studies cannot be synthetized because of the significant heterogeneities. It is uncertain whether CP infusion can reduce the hospitalization rate or not, which must be verified by performing more homogenous and high-quality randomized controlled trials.

CP infusion cannot efficaciously reduce the utilization of invasive mechanic ventilation yet, which is consistent with the studies [2, 27, 29], sensitivity and subgroup analyses on the utilization of invasive mechanic ventilation exhibit this effect is robust and CP infusion did not make COVID-19 patients benefit from in terms of reduction in invasive mechanic ventilation, some inferred causes might be inappropriate timing and doses of administration.

Based on current limited safety data deriving from this meta-analysis, there are similar and no significant statistical differences in no matter general AEs or serious AEs in both groups, and that most of AEs are mild or moderate. Subgroup analysis displays CP infusion compared with placebo may develop fewer serious AEs in ≤ 60 years old subgroup than those in >60 years old subgroup and but there are no statistical differences. This meta-analysis authenticates CP infusion may be more safe and well-tolerated for COVID-19 patients, especially for patients aged less than 60 years old.

The participants in this meta-analysis merely involved in adults with or without underlying diseases and did not include children and pregnant women with COVID-19.Theefficacy and safety data of CP infusion for such special COVID-19 populations as children and pregnant women are lacking, CP infusion may be an optional therapy for children and pregnant women according to the principle of extrapolation, if the COVID-19 illness cannot be held back.

20. Strength and Limitation

Our ongoing study has several strengths and limitations. Primero Firstly, the main strength is that this meta-analysis deriving from high-quality randomized, double-blinded, placebo-control parallel-arm clinical trials is fewer biases and more high-quality; secondly, CP infusion can efficaciously and reasonably cut down the mortality outcome for COVID-19 patients, especial for COVID-19 patients with ≤ 60 years old. On limitations, this meta-analysis merely includes fewer eligible clinical trials and did not touch upon the optimal timing of infusion, titers and dosage of CP and the duration of administration, which can affect the efficacy and safety of CP transfusion. So, the optimal timing of infusion, dosage, titer of CP and duration of the administration still require more high-quality clinical trials to provide support.

21. Conclusions

CP therapy for patients with COVID-19, especially for COVID-19 patients aged less than 60 years old, might be more efficacious in reducing mortality outcome and safer. CP infusion is strongly recommended in order to reduce the mortality in patients with COVID-19 if necessary, especially for COVID-19 patients with ≤ 60 years old, based on high quality of evidence.

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