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Review

Convalescent plasma may be a possible treatment for COVID-19: A systematic review

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) pandemic has spread globally. Therapeutic options including antivirals, anti-inflammatory compounds, and vaccines are still under study. Convalescent plasma(CP) immunotherapy was an effective method for fighting against similar viral infections such as SARS-CoV, and MERS-CoV. In the epidemic of COVID-19, a large number of literatures reported the application of CP. However, there is controversy over the efficacy of CP therapy for COVID-19. This systematic review was designed to evaluate the existing evidence and experience related to CP immunotherapy for COVID-19.

Methods: A literature search was conducted on Pubmed, Cochrane Library, Clinical Key, Wanfang Database; China National Knowledge Infrastructure(CNKI) were used to search for the proper keywords such as SARS-CoV-2, COVID-19, plasma, serum, immunoglobulins, blood transfusion, convalescent, novel coronavirus, immune and the related words for publications published until 15.10.2020. Other available resources were also used to identify relevant articles. The present systematic review was performed based on PRISMA protocol. Data extraction and risk of bias assessments were performed by two reviewers.

Results: Based on the inclusions and exclusions criteria, 45 articles were included in the final review. First, meta-analysis results of RCTs showed that, there were no statistically significant differences between CP transfusion and the control group in terms of reducing mortality(OR 0.79, 95% CI 0.52–1.19, $I^2 = 28\%$) and improving clinical symptoms(OR 1.21, 95%CI 0.68–2.16; $I^2 = 0\%$). The results of controlled NRSIs showed that CP therapy may reduce mortality in COVID-19 patients(RR 0.59, 95% CI 0.53–0.66, $I^2 = 0\%$). Second, limited safety data suggested that CP is a well-tolerated therapy with a low incidence of adverse events. But, due to lack of safety data for the control group, it is really not easy to determine whether CP transfusion has an impact on moderate to serious AEs. Thirdly, for children, pregnant, elderly, tumor and immunocompromised patients, CP may be a well-tolerated therapy, if the disease cannot be controlled and continues to progress. Studies were commonly of low or very low quality.

Conclusions: Although the results of limited RCTs showed that CP cannot significantly reduce mortality, some non-RCTs and case report(series) have found that CP may help patients improve clinical symptoms, clear the virus, and reduce mortality, especially for patients with COVID-19 within ten days of illness. We speculate that CP may be a possible treatment option. High-quality studies are needed for establishing stronger quality of evidence and pharmacists should also be actively involved in the CP treatment process and provide close pharmaceutical care.

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1. Introduction

The coronavirus disease 2019 (COVID-19), an outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread, and as per the World Health Organization (WHO) data on November 10, 2020, it has reported cumulative numbers to over 49.7 million confirmed cases and over 1.2 million deaths [1]. The case fatality rate in COVID-19 may be as high as 2.3% overall and from 10% to 40% among severely affected individuals [2]. Very few effective antiviral treatments exist [3], although hundreds of registered clinical trials are still ongoing, including several phase III vaccine trials [4]. In addition, we have to face an extremely challenge that some drugs are not widely available across the world [5]. Therefore, affordable, effective, and available therapies are in need. Over the past two decades, convalescent Plasma (CP) therapy was successfully used in the treatment of severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), avian influenza A (H5N1), and 2009 H1N1 pandemic [6–9]. Since the virological and clinical characteristics share similarity among SARS, MERS, and COVID-19 [10]. Given the absence of effective drugs, CP therapy may be one of a few promising treatments for COVID-19 [11]. The experiences of CP therapy are gradually enriched with the increasing number of patients. However, there is controversy over the efficacy of convalescent plasma therapy for COVID-19. Some recent systematic reviews on the efficacy of CP therapy for the COVID-19 patients reported a potential reduction in mortality and significant improvement in clinical symptoms, whether in addition to antiviral drugs or not [12,13]. Another systematic review and meta-analysis found that whether CP decreases mortality (hazard ratio (HR) 0.64, 95% CI 0.33–1.25) and improvement of clinical symptoms at seven days (RCT: risk ratio (RR) 0.98, 95% CI 0.30–3.19) were very uncertain [14]. Hence, we conducted this study to systematically analyze the latest evidence of the effect and safety of CP therapy in COVID-19 patients.

2. Method

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] (Table S1). The study protocol was registered with the National Institute for Health Research international prospective register of systematic reviews [16].

The study population of interest was patients who are diagnosed with COVID-19. The intervention of interest was CP, convalescent serum or hyperimmune immunoglobulin. Comparator treatments included placebo, sham therapy, or no intervention; studies with no comparator group were also included. Outcome measures were derived from the protocol research questions to ascertain the clinical effectiveness of therapy. Any other outcome associated with the intervention.

2.1. Types of study to be included

Studies will be included if the cases considered are positive for COVID-19, and have been diagnosed using any established protocol for case confirmation. Systematic reviews, meta-analyses, randomized clinical trials (RCTs), quasi-experimental studies, cohort studies, case series, case reports, clinical guidelines, protocols for clinical trials, any other grey literature will be included. Languages will include Chinese and English.

The following study types will not be included: studies without an available full text, posters, commentaries, opinion articles, and in vitro studies.

2.2. Search strategy and study selection

Pubmed, Cochrane Library, Clinical Key, Wanfang Database; China National Knowledge Infrastructure (CNKI) were used to search for the proper keywords such as SARS-CoV-2, COVID-19, plasma, serum,

immunoglobulins, blood transfusion, convalescent, novel coronavirus, immune and the related words for publications published until 15.10.2020. The search strategies are available in the [supplementary data](#) (Table S2). Following the removal of duplicate entries, a three-stage screening process was followed to identify eligible records through the sequential examination of each title, abstract, and full text. Two reviewers (Y.W and K.Z) screened each record, with provision for arbitration from a third reviewer (Q.Y).

2.3. Data extraction

The studies retrieved during the searches will be screened against the eligibility criteria, and those meeting the criteria will be selected for inclusion. Data will then be extracted from the eligible studies using a template by two independent authors (Y.W and K.Z) and validated by a third (Q.Y). The following information will be extracted: authors and country of the study, study design, number of participants, patients condition, time of administration, titers and dosages of CP, concomitant therapy, conclusion of authors, adverse events (AEs) and other results. The review will be constantly updated during the pandemic.

2.4. Risk of bias (quality) assessment

Two researchers (Y.W and R.L.D) assessed the potential bias in each selected study independently. The third researcher (X.L) was consulted for resolving any difference of opinion.

The 'Risk of Bias' 2.0 tool [17] was used to assess the randomized clinical trials, which includes five domains: 'randomization process', 'deviations from intended interventions', 'missing outcome data', 'measurement of the outcome', and 'selection of the reported results'. The 'Risk of Bias In Non-randomized studies-of Interventions (ROBINS-I)' [18] tool was applied to assess the risk of bias in controlled non-randomized studies of interventions (NRSIs). It comprises of seven domains: 'bias due to confounding', 'selection of participants, classification of intervention', 'deviations from intended interventions', 'missing data', 'measurement of outcomes' and 'selection of the reported results'. Each domain is judged as 'low', 'moderate', 'serious' and 'critical'. The 'Risk of bias' assessment criteria tool for observational studies provided by Cochrane Childhood Cancer [19] was used to assess the methodological quality and risk of bias for included non-controlled NRSIs. It comprises of following domains: 'Unrepresentative study group (selection bias)', 'Incomplete outcome assessment/follow-up (attrition bias)', 'Outcome assessors unblinded to investigated determinant (detection bias)', 'Important prognostic factors or follow-up not taken adequately into account (confounding)', 'Poorly defined study group (reporting bias)', 'Poorly defined follow-up (reporting bias)', 'Poorly defined outcome (reporting bias)', 'Poorly defined risk estimates (analyses)'. For every criterion, risk of bias judgements are 'high', 'unclear' or 'low'.

The National Institute for Health and Care Excellence's Quality Assessment for Case Series will be used to evaluate the quality of case series. The total score is 8 points, in which a score of 4–8 is high quality, and a score less than 4 is low quality.

2.5. Quality of the evidence

Two researchers (Y.W and R.L) assessed the quality of evidence by using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE)' tool [20]. We used 'GRADEpro GDT' software to create a 'Summary of findings' table, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions. The quality of evidence of each outcome is classified as 'high', 'moderate', 'low' or 'very low'.

2.6. Statistical analysis

The Review Manager version 5.3 software was used for analyses. One

Table 1
Summary of included studies (RCTs, controlled NRSIs, and non-controlled NRSIs) on CP for COVID-19 patients.

Author	Country	Study design	No. of participants	Patients Condition	CPT dose	Time of Administration	Antibody titer(s)	Concomitant therapy	Conclusion of authors	AEs
Gharbharan et al. [21]	Netherlands	Open-label RCT, MC	Intervention 43; control 43	Mild moderately ill	300 ml	9 days(IQR7-13)	Nabs titers > 1:80	CHQ;LPVr; AZM; tocilizumab, anakinra as appropriate.	No statistically significant differences in mortality or improvement in the day-15 disease severity	No serious AEs.
Li et al [22]	China	Open-label RCT, MC	Intervention 52; control 51	Critically ill	4–13 ml/kg. 200 ml(IQR 200–300 ml)	27 days(IQR 22–39)	IgG > 1:640	antivirals, steroid, immunoglobulin, antibiotics and Chinese herbal medicines,as appropriate	Compared with standard treatment alone,CPT did not statistically reduce mortality or the time to clinical improvement within 28 days.	N = 3(in 2 patients)0.1 possible severe transfusion-associated dyspnoea.1 non-severe allergic transfusion reaction and 1 probable non-severe febrile
C Avendaño-Solà et al [23]	Spanish	RCT,MC	Intervention 38; control 43	Less severe	250–300 ml	Median time was 8 days.	Nabs titers > 1:80	–	No significant differences were found in mortality, but CPT could be superior to SOC in avoiding disease progression.	16 serious or grade 3–4 AEs were reported in 13 patients, 6 in the CP group and 7 in the SOC group.
Anup Agarwal et al [24]	Indian	Open-label RCT, MC	Intervention 235; control 229	Moderately ill	2 doses of 200 ml	–	Nabs titers 1:90 (1:30 to 1:240).	Antivirals, antibiotics, immunomodulators and supportive management	CP was not associated with reduction in mortality or progression to severe COVID-19.	Minor AEs of pain in local infusion site, chills, nausea, bradycardia and dizziness was reported in one patient each. Fever and tachycardia were reported in three patients each.
Duan et al [25]	China	Pilot prospective cohort with a historical control group, MC	Intervention 10; control 10.	Severely ill.	200 ml single dose	Median time from onset of illness to CPT was 16.5 days (IQR 11–19)	Nabs titers > 1:640	Antivirals, antimicrobials	CPT was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases.	Self-limited facial erythema in 2/10 patients. No major AEs.
Liu et al [26]	USA	Matched control study,SC	Intervention 39;control 156	Moderate-critically ill	2 units. Each unit of 250 ml	Median time 4 days (IQR 1–7)	antispik antibody titer of \geq 1:320	antivirals, antibiotics, steroid and immunoglobulin, as appropriate	CPT is a potentially efficacious treatment option for inpatients, and non-intubated patients may benefit more.	No serious AEs.
Zeng et al [27]	China	Retrospective controlled study,MC	Intervention 6, control 15	Critically ill	300 ml(IQR 200–600 ml)	21.5 days(IQR 17.8–23)	–	Antivirals, steroid and immunoglobulin, as appropriate	CPT can discontinue SARS-CoV-2 shedding but cannot reduce mortality in critically end stage patients.	No serious AEs.
Donato et al [28]	USA	Prospective controlled study, SC	Intervention 47; control 1340	Moderate-critically ill	500 ml(n = 36); 400 ml(n = 10); 200 ml(n = 1)	Median time 8–15 days	IgG Spike RBD > 1:500	HCQ,AZM,Steroids, Tocilizumab,Remdesivir	CPT was safe and conferred effective transfer of immunity while preserving endogenous immune response	Mild rash(n = 1)
Ralph Rogers et al. [29]	USA	A matched cohort analysis, SC	Intervention 64,control 177	Severe ill	One or two units	7 days after symptom onset	SARS-CoV-2 IgG antibody index > 1.4	Remdesivir, corticosteroids	No overall significant reduction of in-hospital mortality or increased rate of hospital discharge associated with the use of CP in this	Two patients who received CP were judged to have a TRALI reaction. ONE have transfusion-associated circulatory overload (TACO)

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Table 1 (continued)

Author	Country	Study design	No. of participants	Patients Condition	CPT dose	Time of Administration	Antibody titer(s)	Concomitant therapy	Conclusion of authors	AEs
Martin R Salazar et al [30]	Argentina	Retrospective cohort, MC	Intervention 868, control 2298	–	200–250 ml	–	Ig-G antibody titer \geq 1:400	–	study, although there was a signal for improved outcomes among the elderly. CP might be beneficial in COVID-19 and independently associated with decreased mortality.	No major adverse effects occurred.
Eric Salazar et al [31]	USA	Prospective, propensity score-matched study, MC	Intervention 321, control 582	Severe and/or critically ill	One or two units	\leq 72 h (n = 321)	Anti-RBD IgG titer \geq 1:1350 (n = 321)	Steroids, AZM, and tocilizumab	Transfusion of COVID-19 patients soon after hospitalization with high titer anti-spike protein RBD IgG present in convalescent plasma significantly reduces mortality.	7 CP-related AEs, 2 of which were serious AEs
Livia Hegerova et al [32]	Swedish	Matched study, MC	Intervention 20, control 20	Severe or life-threatening	1 unit	Median time from hospitalization to CP was early at 2 days	–	Remdesivir	CP use in severe and critically ill patients with COVID-19 may improve survival if given early in the course of disease.	No AEs with CP were reported.
Abolghasemi et al [33]	Iran	Non-randomized study, MC	Intervention 115, control 74	Moderate to severely ill	1 unit(500 cc)	less than 3 days of hospital admission	Antibody titer cut off index $>$ 1.1	LPVr and HCQ	CPT substantially improved patients' survival, significantly reduced hospitalization period and needs for intubation in COVID-19 patients in comparison with control group.	No AEs
Rasheed et al [34]	Iraq	Matched study, MC	Intervention 21, control 28	Critically-ill	400 ml	–	IgG index equal or more than 1.25	HCQ + AZM	CP therapy is an effective therapy if donors with high level of SARS-Cov2 antibodies are selected and if recipients are at their early stage of critical illness, being no more than three days in RCUs.	A single case developed mild skin redness. No serious AEs
Xia et al [35]	China	Retrospective cohorts, SC	Intervention 138, control 1430	Severe or critical	200–1200 ml	More than 14 days	Antibody titers \geq 1:160	antivirus therapy, traditional Chinese medicine, and respiratory support	CP transfused even after 2 weeks of symptom onset, could improve the symptoms and mortality in patients with severe or critical cases.	3 patients had minor allergic reactions, no serious AEs
Joyner et al(a) [36]	USA	Open-label, EAP, MC	Intervention 35,322	High proportion of critically-ill patients	One unit (approximately 200 ml)	0 days (n = 1364), 1–3 days (n = 14043), 4–10 days (n = 14358), and 11 + days (n = 5557)	Antibody levels over 18.45 S/Co or less than 4.62 S/Co	HCQ, CHQ, AZM, remdesivir and steroids	Earlier time to transfusion and CP with high antibody titers may reduce patient mortality	–
Perotti et al [37]	Italy	Single-arm, open-label, MC	Intervention 46	Severe	Approximate 330 ml	–	NAbs titer $>$ 1:160	antibiotics, HCQ and anticoagulants	Hyperimmune plasma in Covid-19 shows promising benefits.	5 serious AEs occurred in 4 patients (2 likely, 2 possible treatment related).
	USA				200–500 ml	–	–	–		

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Table 1 (continued)

Author	Country	Study design	No. of participants	Patients Condition	CPT dose	Time of Administration	Antibody titer(s)	Concomitant therapy	Conclusion of authors	AEs
Joyner et al(b) [38]		Open-label, EAP, MC	Intervention 20,000	Critically illness.					CPT is safe in hospitalized patients with COVID-19, and earlier administration is more likely to reduce mortality.	The incidence of all serious AEs was low; these included transfusion reactions (n = 78; <1%), thromboembolic or thrombotic events (n = 113; <1%), and cardiac events (n = 677, ~3%).
Valentini et al [39]	Argentina	Open label trial, MC	Intervention 87	Severe or critical	300–600 ml.	Median of three days after hospital admission	Index values ranged between 0 and 10 (mean 5.7)	LPVr	CPT are feasible, safe, and potentially effective, especially before requiring MV.	No serious AEs attributed to plasma.
Olivares-Gazca et al [40]	Mexico	Prospective, longitudinal, single arm, and quasi experimental, MC	Intervention 10	Critically-ill	200 ml	Median time 6 days	–	HCQ,AZM,Steroids, Tocilizumab, LPVr	The addition of CP to other therapies improved pulmonary function	–
Bradfute et al [41]	USA	Single arm trial	Intervention 12	Severe or life-threatening	200 ml	Median time: 8.5 days	Median Nabs titer is 1:40	–	CP infusion did not alter recipient NAB titers. Pre-screening of CP may be necessary for selecting donors with high levels of neutralizing activity for infusion into patients with COVID-19.	No study-related serious AEs
Madariaga MD et al [42]	USA	Open label clinical study	Intervention 10	Severe or life-threatening	~300 ml	Within 21 days	RBD range from 0 to 1:3289	Remdesivir, tocilizumab, anakinra and HCQ.	Despite variability in donor titer, 80% of recipients showed significant increase in antibody levels post-transfusion.	–

Abbreviations: M, male; F, female. CPT:convalescent plasma transfusion; ICU:Intensive care Unit; IQR:Inter quartile range; MC:multi center; SC:single center; RCT:randomized controlled trial; OR: odds ratio; CHQ: Chloroquine; HCQ: hydroxychloroquine; LPVr: lopinavir/ritonavir; AZM: azithromycin; MV:mechanical ventilation; TACO:transfusion-associated circulatory overload; TRALI:transfusion-related acute lung injury. NAbs, Neutralizing antibodies; SOC: standard of care; AEs:adverse events; EAP, Expanded Access Program

Table 2
Summary of included studies(case reports or case series) on CP for COVID-19 patients.

Author	Country	Study design	Study population	CPT dose	titers	Time of administration	Status during CPT	Outcomes	Sever events and treatment complications
Salazar E et al. [43]	USA	Case series (n = 25)	Age (23–67),14F:11 M,16 patients had one or more underlying chronic conditions:DM2(n = 10), HTN(n = 9),HLD (n = 5),GERD(n = 4)	300 ml single dose	Ranged from 0 to 1350 for the RBD and ECD domains.	Median time from symptoms onset to CPT was 10 days (IQR,7.5 to 12.5 days)	ARDS(n = 11);ARDS,CRRT(n = 1);ARDS, CRRT, ECMO (VV)(n = 1);None(n = 12)	At 7 days after transfusion, 9 of 25 patients (36%) had improvement. By 14 days after transfusion, 19 patients (76%) had improved or been discharged.	No AEs
Ye et al. [44]	China	Case series (n = 6)	Age (28–75),3M:3F, Bronchitis(n = 1) and Sjogren syndrome(n = 1)	200–250 ml two consecutive transfusions	–	Average interval between symptom onset and CPT is 34.8 days (range from 22 to 48 days)	Clinical deterioration	Clinical symptoms improved	No severe AEs
Shen et al. [45]	China	Case series (n = 5)	Age(36–65),2F:3M, HTN;mitral insufficiency(n = 1)	200 ml two consecutive transfusions	NAbs > 40	Average interval between symptom onset and CPT is 20.8 days (range from 14 to 24 days)	All 5 critical severe ARDS on MV, ECMO (n = 1)	Viral loads decreased,NAbs increased and clinical symptoms improved.	No severe adverse reactions
Zhang et al. [46]	China	Case series (n = 4)	Age (31–73),2F:2M, HTN(n = 2,&CRF n = 1),COPD (n = 1), pregnant(35 week and 2 days of gestation)	200–400 ml in one or two consecutive transfusions. A patient received 2400 ml divided in eight consecutive transfusions	–	Average interval between admission and CPT is 16.2 days (range from 11 to 22 days)	Critically ill invasive MV	Clinical symptoms and lung imaging improved. All patients discharged.	No severe adverse reactions
Anh et al. [47]	South Korea	Case series (n = 2)	Age(67,71),1M:1F, HTN(n = 1)	250 ml two consecutive transfusions.	Optional density ratio for IgG:0.532&0.586	Interval between symptom onset and CPT was 22 days and 6 days	Severe ARDS, MV	Favourable clinical outcome in critically ill patients with ARDS.	No adverse reactions
Kong,et al [48]	China	Case report	A 100-year-old male	200 ml,100 ml	IgG titer of >1:640	More than 60 days	High-flow oxygen; a 30-year record of HTN, abdominal aortic aneurysm, cerebral infarction, prostate HLD, and complete loss of cognitive function for the preceding 3 years.	Laboratory indicators and clinical symptoms recovered, discharged from hospital.	No adverse reactions
Anderson, et al. [49]	United States	Case report	A 35-year-old critically ill obstetric patient(22 weeks and 2 days of gestation).	One unit	–	14 days	Worsening dyspnea and hypoxia. acute respiratory distress syndrome.high-flow non-invasive positive-pressure ventilation	After the combination of remdesivir.Clinical recovery and discharge from hospital.	No adverse reactions
Çınar,et al. [50]	Turkey	Case report	A 55-year-old male with a history of myelodysplastic syndrome complicated by disseminated systemic tuberculosis and associated kidney disease.	200 ml,twice	Titer of anti-SARS-CoV-2 IgG was 6.6(<0.8 negative,≥0.8 to < 1.1 borderline,≥1.1 positive)	Interval between admission and CPT is 5 days	ICU,oxygen supplementation of 2 L/min with nasal cannula.	Clinical recovery and discharge from hospital.	No adverse reactions
Abdullah HM et al [51]	Iraq	Case series (n = 2)	46y/M; 56y/M	200 ml	–	case1:10 days; case2: not reported	Severe illness	Clinical recovery and discharge from hospital	No AEs
	China		66y/F	200 ml,twice	Greater than 1:160.	10 days	Severe illness		No AEs

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Table 2 (continued)

Author	Country	Study design	Study population	CPT dose	titers	Time of administration	Status during CPT	Outcomes	Sever events and treatment complications
Peng H et al [52]		Case report						On the fourth day after CPT, the absolute lymphocyte count returned to normal. After 2 weeks, she recovered and discharged.	
Al Helali AA et al [53]	Abu Dhabi, UAE	Case report	55y/M	300 ml	–	9 days	Severe illness	There was a significant radiological and clinical improvement in a few days' post CPT.	No significant AEs were observed.
Jafari R et al [54]	Iran	Case report	26y/F, pregnant(36 w)	–	–	12 days	–	Her clinical course during hospitalization improved, particularly during the second week.	No AEs
Im JH et al [55]	Korea	Case report	68y/M	250 ml,twice	1:32	16 days	Critical illness	The patient showed clear improvement in respiratory distress and fever symptoms for 3 days after CPT. However, 4 days after CPT, he presented respiratory distress again. It was difficult to assess the effects of CP clearly.	4 days after the CPT, the patient presented respiratory distress.
Figlerowicz M ey al [56]	Poland	Case report	6y/F	200 ml	1:700	–	Severe and severe aplastic anemia	The patient's SARS-CoV-2 RNA in nasopharyngeal swabs was tested seven times in next three weeks. All these results were negative.	No AEs
Xu TM et al [57]	China	Case report	65y/M	–	–	–	Severe illness	On day 4 after CPT, the lactic acid and CRP levels remained high. The arterial oxyhemoglobin saturation decreased to 86%, and mv was administered.	No AEs
Karataş A et al [58]	Turkey	Case report	61y/M	–	13.3 (≥1.1 positive)	–	Mixed cellularity classical Hodgkin lymphoma, autologous stem cell transplantation (ASCT, 6 months ago)	After the CPT, his fever resolved after 3 days.He was discharged from the hospital on the 78th day of hospitalization.	No AEs
Naeem S et al [59]	USA	Case series (n = 3)	65y/F;35y/F;36y/F	Case1: 1 unit case2: 2 units case3: 3 unit	Case1:antibody Levels in plasma (index):8.68. case2:antibody index:5.70,8.15 case3: antibody index:5.67.	–	3 kidney transplant (KT) recipients	They all successful recovery from COVID-19.	No AEs
Zeng H et al [60]	China	Case series (n = 8)	F:4;M:4;median age 65.0	5/8 cases received two doses of 100–200 ml of CP within 24 h (totally 300 or 400 ml), 3 cases received one dose of 200 ml	1:320–1:2560(Anti-S-RBD specific IgG ELISA titer)	–	Critical or severe illness;5 patients had coexisting chronic diseases.	After CPT, patients' oxygen support status and chest CT improved, and viral load was decreased.	No AEs
Wang M et al [61]	China	Case series (n = 5)	56y/M;66y/F;46y/F;51y/F;61y/M	200 ml of CP was transfused at a time,3 received	above 1:640	Median and IQR: 34, 44 days	All patients were critically ill and had underlying chronic comorbidities,	2 patients were cured and subsequently discharged, 3	None of the patients developed

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Table 2 (continued)

Author	Country	Study design	Study population	CPT dose	titers	Time of administration	Status during CPT	Outcomes	Sever events and treatment complications
Shankar R et al [62]	India	Case report	4y/F	400 ml and remaining 2 received 1200 ml She received CP 15 ml/kg on Days 8 and 9 of illness.	–	8 days	including HTN and DM.2 Septic shock;1Coagulopathy;1Septicemia Standard-risk B Lineage Acute Lymphoblastic Leukemia in remission and on interim maintenance therapy	patients succumbed due to multiple organ failure. She showed remarkable improvement by day 10. And She was discharged after remaining asymptomatic for 5 days.	adverse reactions following the infusion of CPT. No transfusion reaction
Jiang J et al [63]	China	Case report	70y/F	200 ml,twice	SARS-CoV-2-specific ELISA antibody titer higher than 1:1000.	26 days	Renal transplant patient receiving immunotherapy, combined with chronic bronchitis, HTN, and HLD	The patient was discharged and the use of plasma was helpful for SARS-CoV-2 clearance and patient recovery.	No AEs
Zhang LB et al [64]	China	Case series (n = 2)	69y/F, 50y/F	Case1:400 ml, once. case2:200 ml	–	30 days, 10 days	Case1: recurrent gastrointestinal complaints of anorexia and mild diarrhea. case2: intermittent course of diarrhea, positive fecal occult blood; SLE, LI, and DM.	Case1:3 days after CPT, the patient's condition was much improved, and was discharged. case2:7 days after CPT, she showed complete recovery and was discharged.	No AEs
Diorio C et al [65]	USA	Case series (n = 4)	14–18 years	200–220 ml	2patients received CP with RBD-specific antibody titer (<1:160), and full-length IgG S titers(>1:1000). 1 patient received CP with RBD-specific antibody titer levels >1:6000	8–15 days	Critical illness	1 patient showed transient clinical improvement, decannulating from ECMO, however, died from cardiac.2patients remain in hospital and have had the placement of tracheostomies. 1patients has been discharged from the hospital after being critically ill and on ECMO.	No AEs

Abbreviations: M, male; F, female. CPT, convalescent plasma transfusion; CP, convalescent plasma; DM2, diabetes mellitus type 2; HTN, hypertension; GERD, gastrointestinal reflux disease; HLD, hyperlipidemia; RBD, receptor binding domain; ECD, ectodomain; ARDS, acute respiratory distress syndrome; CRRT, cardiac rapid response team; ECMO (VV), extracorporeal mechanical oxygenation(venovenous);AZM, azithromycin; HCQ, hydroxychloroquine; LPVr, lopinavir/ritonavir; RBV, ribavirin; ARB,arbidol; DRV, darunavir; IFN,interferon; NAbs, Neutralizing antibodies; HFNO, High-flow nasal oxygen therapy; LFNO, low-flow nasal cannula oxygenation; ICU, Intensive care unit; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; SLE, systemic lupus erythematosus; LI, lacunar infarction; AEs, adverse events; IQR:Inter quartile range; MV: mechanical ventilation;

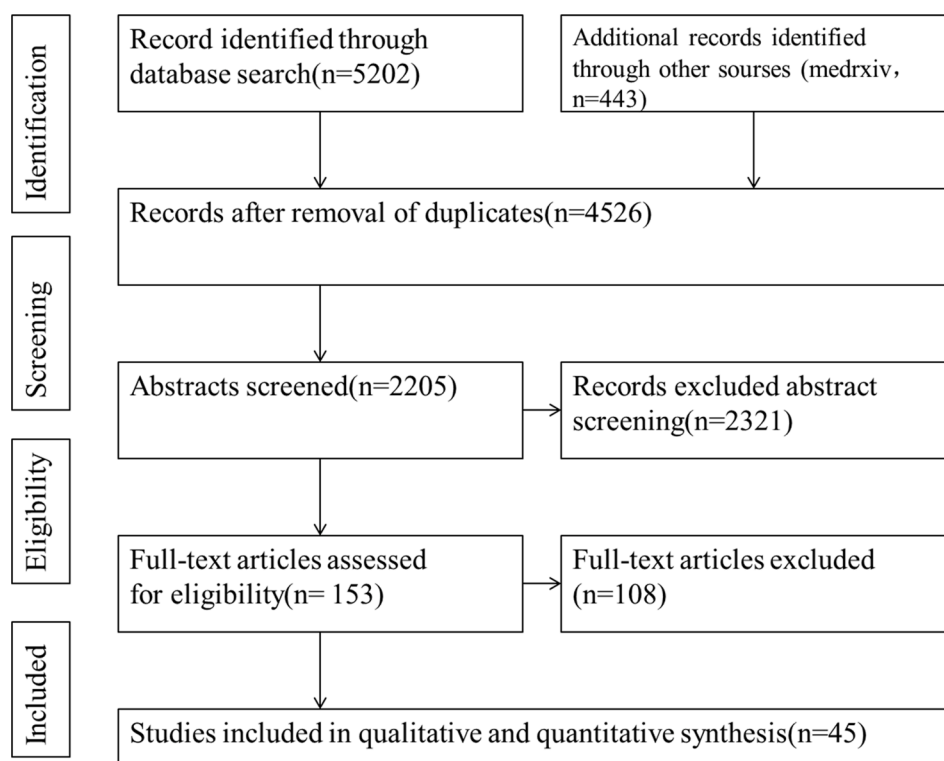


Fig. 1. PRISMA Flow chart of study selection.

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Li-mortality	+	+	+	+	-	+
Li-clinical improvement	+	+	+	+	-	+
Li-safety	+	+	+	X	+	X
Gharbharan-overall mortality	+	-	+	+	-	-
Gharbharan-clinical improvement	+	-	+	-	-	-
Gharbharan-safety	+	-	+	X	X	X
Avendano SC-mortality	-	-	+	+	+	-
Avendano SC-improvement	-	-	+	+	-	-
Avendano SC-safety	-	X	+	+	-	X
Agarwal A-mortality	+	+	+	-	+	-
Agarwal A-clinical improvement	+	+	+	-	-	-
Agarwal A-safety	+	X	+	X	X	X

Domains:
 D1: Bias arising from the randomization process
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 ● High
 ● Some concerns
 ● Low

Fig. 2a. Risk of bias summary for RCTs.

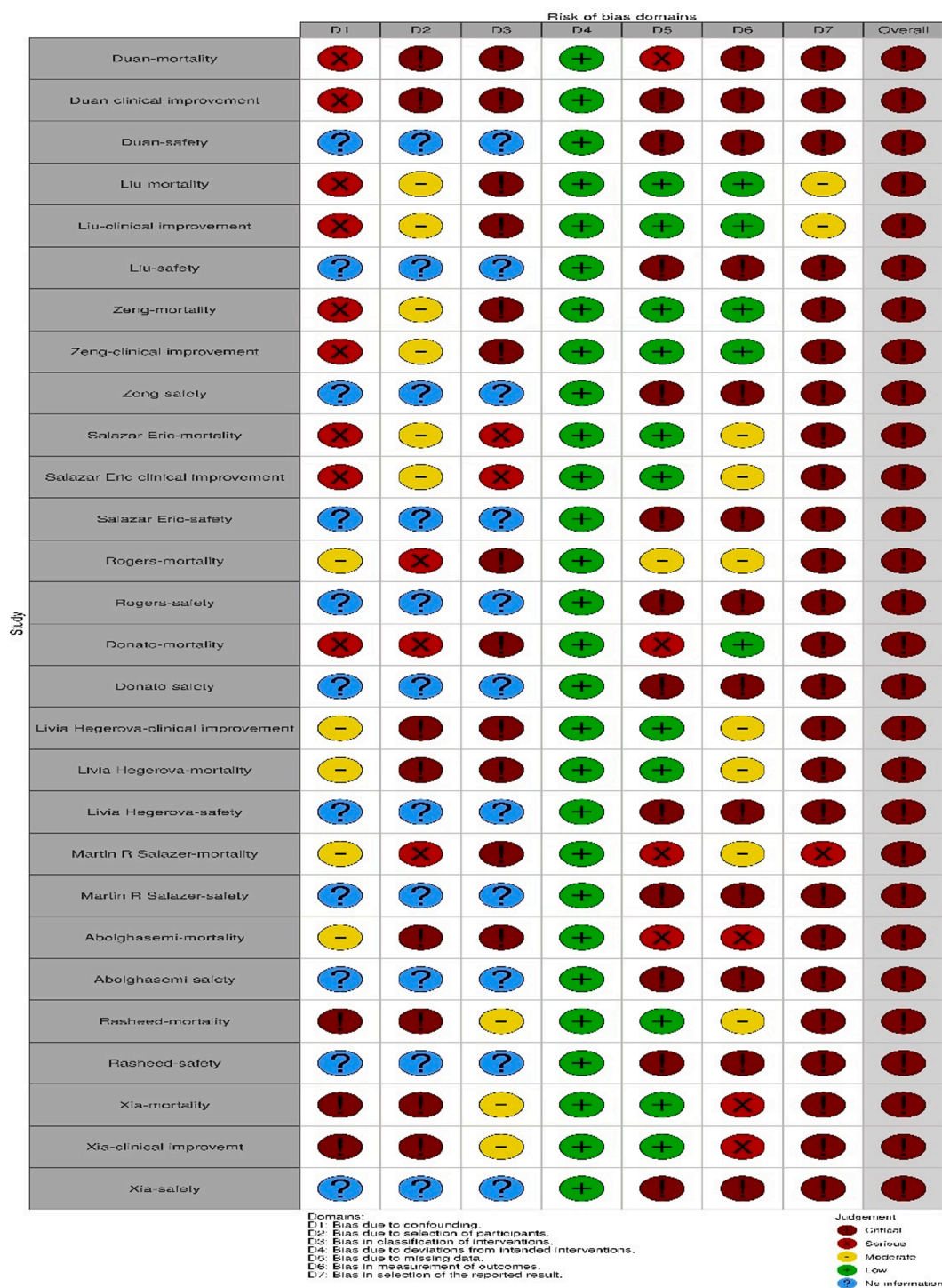


Fig. 2b. Risk of bias summary for controlled NRSIs.

researcher (Y.W) would have entered the data into the software, and a second researcher (K.Z) would have checked the data for accuracy.

For dichotomous outcomes, the number of events and total number of participants in two groups were recorded. Fixed-effects model was used if the result of the Q test was not significant ($p > 0.1$) or $I^2 < 50\%$. The different types of studies were analyzed separately (such as RCTs and controlled NRSIs). If we could not perform a meta-analysis, we had planned to comment on the results from all studies. The odd's ratio(OR) and the RR with 95% confidence intervals(CIs) was assessed for RCTs and controlled NRSIs respectively. A χ^2 test with a significance level at $P \leq 0.1$ was used to assess heterogeneity of treatment effects between

trials. The I^2 statistic was used to quantify possible heterogeneity (I^2 statistic: 30–60% may represent moderate heterogeneity, 75–100% considerable heterogeneity). If heterogeneity had been above 80%, we would explore potential causes through sensitivity and subgroup analyses. If we had not found a reason for heterogeneity, we would not have conducted a meta-analysis. Subgroup analyses will be performed, if appropriate based on the data retrieved.

3. Results

Because of insufficient evidence available from RCTs, we also

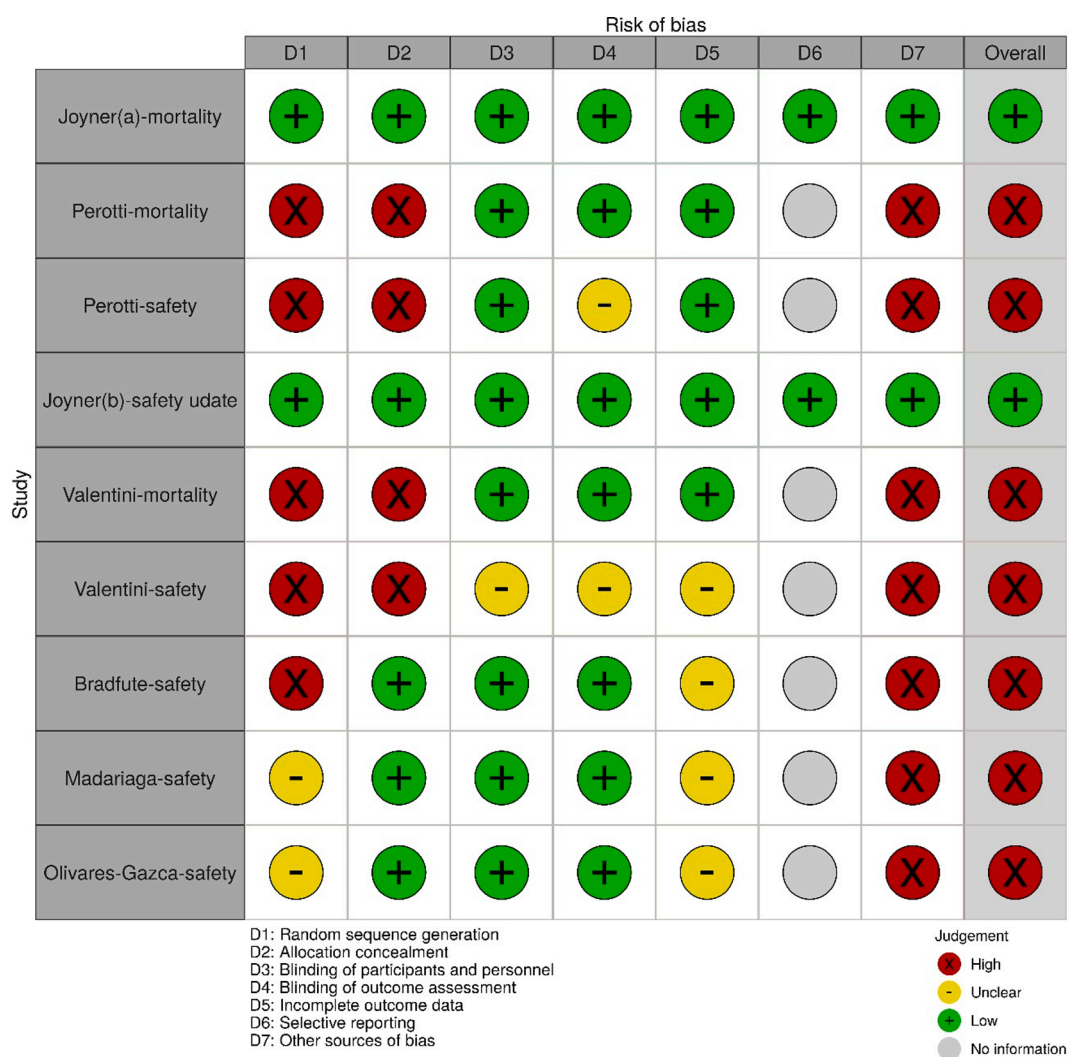


Fig. 2c. Risk of bias summary for non-controlled NRSIs.

included controlled NRSIs, non-controlled NRSIs and case reports(ser-ies). The search process yielded 5645 records. Following removing duplicates and screening of titles and abstracts, we evaluated 153 articles in full text. Among these, we found 45 relevant articles (4RCTs, 11 controlled NRSIs, 7 non-controlled NRSIs and 23 case reports) [21–65]. Extracted details are presented in Table 1(RCTs, controlled NRSIs, and non-controlled NRSIs) and table 2(case report(series)). A flow chart summarizing the inclusion and exclusion criteria of the searched studies is presented in Fig. 1.

The included 45 studies were identified and critically evaluated, which included 44,068 participants in this review, of whom 22,260 received CP. The patients included in the study had a wide range of age distribution, ranged from 4 to 100 years old. The patients' conditions were variable, two RCTs [21,24] and three controlled NRSIs [26,28,33] included moderate to severely ill patients, one RCT included less-severe patients, and the clinical symptoms of patients in the 6 controlled NRSIs met the definitions of severe or life-threatening disease [29,31,32,37,41,42]. One RCT [22] and 4 controlled NRSIs [27,34,35,40] evaluated CP therapy in critically ill individuals.

3.1. Risk of bias (quality) assessment

We assessed the methodological quality and risk of bias for RCTs,

controlled NRSIs and non-controlled NRSIs for different outcomes (such as mortality, clinical improvement, and safety) respectively, the results were summarized in Figs. 2a, 2b and 2c. Some studies reported only one or two of mortality, clinical improvement, or safety outcomes, and we assess the risk of bias for the results reported in the study. For example, bias in measurement of outcomes was not applicable for clinical improvement for Ralph Rogers, because they did not report this outcome.

The methodological quality evaluation results of the 2 researchers on the included case reports(series) showed that the quality was low to medium(Table 3).

3.2. Meta-analysis

3.2.1. Mortality

Mortality outcomes were reported in 21 of the included 22 controlled studies and non-controlled NRSIs [21–40,42]. The mortality outcome was evaluated from controlled studies: 4RCTs and 11NRSIs(Figs. 3a and 3b). Compared to the control group, the results of RCTs showed that the use of CP transfusion may reduce the mortality rate (OR 0.79, 95% CI 0.52–1.19, I² = 28%), but there was no significant difference between the two groups (Fig. 3a). The results of controlled NRSIs showed similar findings (RR 0.59, 95% CI 0.53–0.66, I² = 0%), but there is statistically

Table 3
Quality Assessment for Case Series.

Author	Case series collected in more than one centre.	Is the hypothesis/aim/objective of the study clearly described?	Are the inclusion and exclusion criteria (case definition) clearly reported?	Is there a clear definition of the outcomes reported?	Were data collected prospectively?	Is there an explicit statement that patients were recruited consecutively?	Are the main findings of the study clearly described?	Are outcomes stratified?	scores
Salazar E et al. [43]	0	1	1	1	0	0	1	1	5
Ye et al. [44]	0	1	1	1	0	0	1	0	4
Shen et al. [45]	0	1	1	1	0	0	1	0	4
Zhang et al. [46]	1	1	1	1	0	0	0	0	4
Anh et al. [47]	0	1	1	1	0	0	0	0	3
Kong,et al [48]	0	1	1	1	0	0	1	0	4
Anderson, et al. [49]	0	1	1	1	0	0	0	0	3
Çınar et al. [50]	0	1	1	1	0	0	0	0	3
Abdullah HM et al [51]	0	1	1	1	0	0	0	0	3
Peng H et al [52]	0	1	1	1	0	0	1	0	4
Al Helali AA et al [53]	0	1	1	1	0	0	0	0	3
Jafari R et al [54]	0	1	1	1	0	0	0	0	3
Im JH et al [55]	0	1	1	1	0	0	1	0	4
Figlerowicz M ey al [56]	0	1	1	1	0	0	0	0	3
Xu TM et al [57]	0	1	1	1	0	0	0	0	3
Karataş A et al [58]	0	1	1	1	0	0	0	0	3
Naeem S et al [59]	0	1	1	1	0	0	0	0	3
Zeng H et al [60]	0	1	1	1	0	0	0	0	3
Wang M et al [61]	0	1	1	1	0	0	1	0	4
Shankar R et al [62]	0	1	1	1	0	0	0	0	3
Jiang J et al [63]	0	1	1	1	0	0	1	0	4
Zhang LB et al [64]	0	1	1	1	0	0	1	0	4
Diorio C et al [65]	0	1	1	1	1	0	1	0	5

Yes = 1, No = 0. The total score:8. High quality: 4–8. Low quality: < 4.

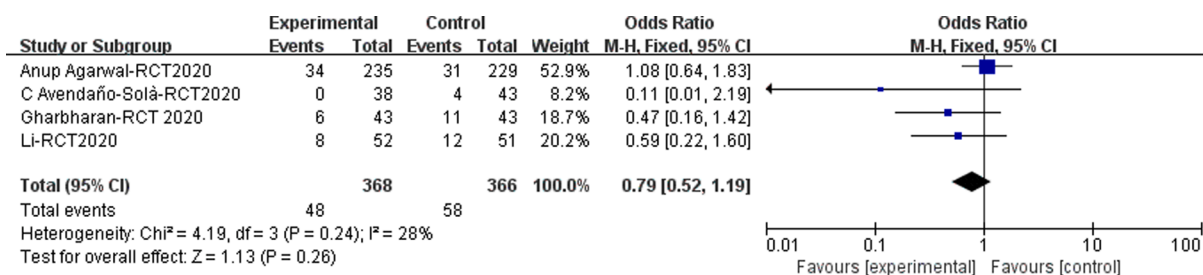


Fig. 3a. The mortality outcome of CP therapy on COVID-19 patients(results from RCTs).

significant (Fig. 3b). Evidence suggests that CP may have effect on reducing mortality in patients, but it is uncertain whether there is a statistical difference between CP and or not.

However, by far the largest study of CP transfusion -Expanded Access Program(EAP), which resulted in widespread use of CP to treat COVID-19 in the U.S.A. The authors reported 7 and 30-day mortality in 35,322

severe to critical hospitalized adults transfused with CP was 3706 (10.49%) and 8652(24.49%) respectively [36]. The case fatality rate in COVID-19 may be as high as 2.3% overall and from 10% to 40% among severely affected individuals [2]. Although the EAP program was designed to evaluate the safety of CP, overall data suggest that patients with severe to critical conditions who use CP have a lower mortality rate

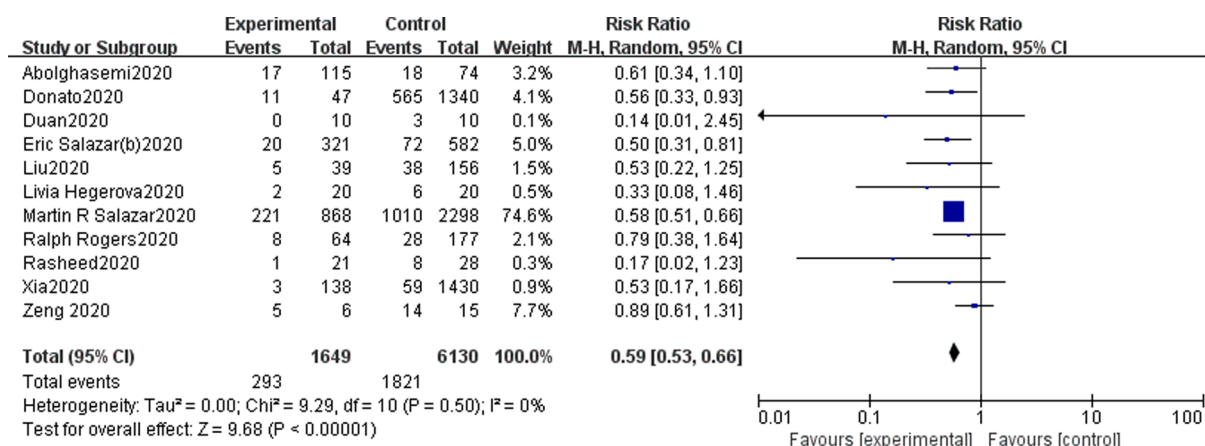


Fig. 3b. The mortality outcome of CP therapy on COVID-19 patients (results from controlled NRSIs).

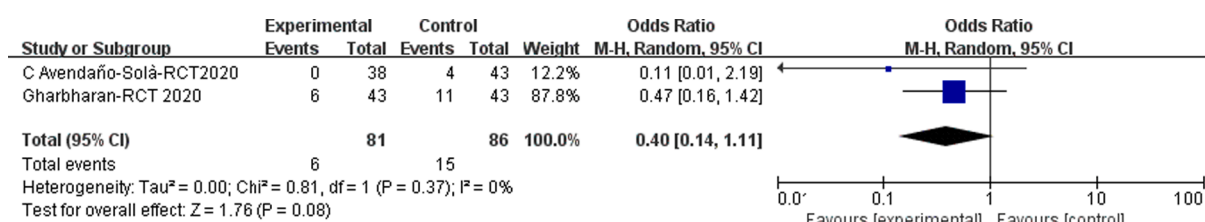


Fig. 4a. The mortality outcome of CP therapy on COVID-19 patients, which the treatment time point within 10 days (results from RCTs).

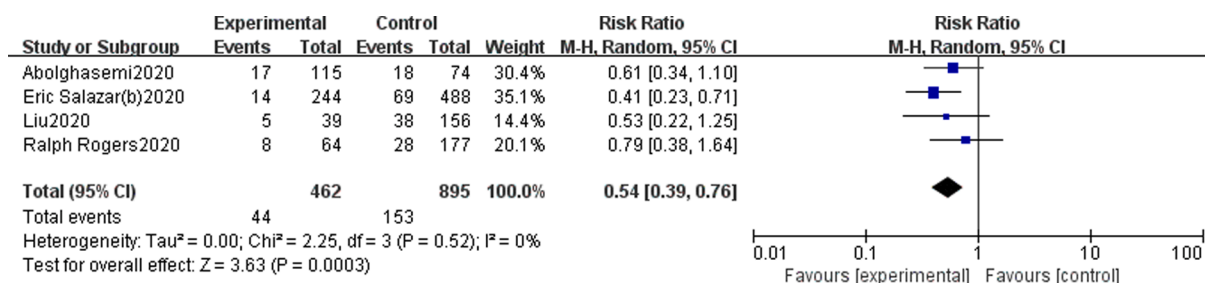


Fig. 4b. The mortality outcome of CP therapy on COVID-19 patients, which the treatment time point within 10 days (results from controlled NRSIs).

[36].

3.2.2. CP treatment time point on mortality

For most viral illnesses, viremia peaks in the first week of infection [66]. Studies have shown that viral loads are highly correlated with disease severity and progression [67,68]. In theory, the patient is at greater risk of virus-related damage. At this time, if CP is transfused, the patients may benefit more [69,70]. In this systematic review, 11 controlled studies reported the time from symptom onset (or hospitalization) to transfusion, and the treatment time point was different.

For the median time of patients from symptoms onset (or hospitalization) to transfusion, there was 6 studies reported less than 10 days, 4 studies reported 10–20 days, and only one study reported exceed 30 days. Meta-analysis was conducted for studies in which the time from symptom onset (or hospitalization) to transfusion was less than 10 days for RCTs and controlled NRSIs respectively. Compared to the control group, the results of RCTs showed that the use of CP transfusion may be reduce the mortality of patients, if the treatment time point was within 10 days (OR 0.4, 95%CI 0.14–1.11; I² = 0%). But there was no significant difference between the two groups (Fig. 4a). Similar results were found in controlled NRSIs (RR 0.54, 95%CI 0.39–0.76; I² = 0%), but there is statistically significant (Fig. 4b).

3.2.3. Clinical improvement

In this study, the clinical improvement was assessed by WHO 8-point disease severity scale (5–6 score) and/or oxygen status improvement. There are only two RCTs reported improvement of clinical symptoms and 8 controlled NRSIs reported clinical improvement or discharged outcomes at 14–30 days. However, due to the high heterogeneity of results from controlled NRSIs (I² = 82%), we abandoned the analysis. The clinical improvement outcome was evaluated from 2RCTs (Fig. 5). Compared to the control group, the results of RCTs showed that the use of CP transfusion may be beneficial to the improvement of patients' clinical symptoms (OR 1.21, 95%CI 0.68–2.16; I² = 0%). But there was no significant difference between the two groups (Fig. 5).

3.3. Safety

The safety data in the controlled studies was insufficient, we included non-controlled NRSIs to list information on adverse reactions. Due to the lack of safety outcomes data for the control group, we did not conduct a meta-analysis, but provided information in table 1 and 2. In the included studies, the reporting of safety results and the follow-up period were different. Only one RCT reported AEs and serious AEs in the control group, and none of the other controlled studies reported

safety data for the control group. Meanwhile, it is difficult to determine whether some (serious) AEs were related with CP transfusion, or due to underlying disease or other combination treatment, or above.

21 studies (43,990 participants) assessed AEs and/or serious AEs for 22,182 of its participants. 15 studies (1371 recipients) reported no serious AEs and 7 studies (541 recipients) reported 33 patients seemed major or non-severe reactions possibly attributed to CP transfusion. The majority of AEs were allergic, fever, rash, or respiratory events.

The EAP study reported on serious AEs within the 4 h and an additional 7 days after transfusion respectively [38]. There were 141 serious AEs within 4 h and 1247 serious AEs within 7 days after transfusion. These were mainly allergic or respiratory, thrombotic or thromboembolic and cardiac events. There were 78 non-mortality events occurring within 4 h after CP transfusion, of which 36 reports of transfusion-associated circulatory overload (TACO), 21 reports of transfusion-related acute lung injury (TRALI), and 21 reports of severe allergic transfusion reaction. There were 63 deaths occurring within 4 h of CP transfusion, of which 10 were possibly related to transfusion. Of these serious AEs reported within 7 days post-transfusion, only 38 thromboembolic or thrombotic events, 457 sustained hypotensive events, and 80 cardiac events were judged to be related to the plasma transfusion.

Combined with the included evidence, convalescent plasma therapy may be a well-tolerated therapy with a low incidence of AEs. However, because of the lack of safety data for the control group, it is really not easy to determine whether CP transfusion has an impact on AEs.

3.4. Dosage and titers of CP

In vivo studies showed that the effects of neutralizing antibodies in CP were not only limited to viral clearance, but also included acceleration of infected cell clearance, and have been considered essential in protecting against viral diseases [71,72]. The efficacy of this therapy has been associated with the titer of neutralizing antibodies in CP [73]. We found that the antibody titers of CP were significantly different in the included literatures. In addition, the detection methods and evaluation indexes of antibody titer were also different. All the four included RCTs reported titers, but the values were different. Among them, the titers in CP were greater than 1:80 in 2 RCTs [21,23] and a subgroup in 1 RCT [24]. However, due to the lack of subsets of data with titer greater than 1:80, we were unable to carry out meta-analysis. Similar trends were pronounced in controlled NRSIs. Only eight controlled NRSIs reported donors' CP titers, and the titers varied in scope, unit, and assay. We were also unable to perform a meta-analysis on titers.

However, there is not a standard transfusion dose of CP. The dosage range of CP commonly used in clinical practice is between 200 and 500 ml, with single or double regimen doses (Tables 1 and 2). We think that the optimal dose cannot be determined due to the different titers.

3.5. Special patients

Currently, there are not sufficiently randomized controlled trials for the treatment of COVID-19. Case reports and case series are the available clinical evidence particularly for the passive immunity transfer namely convalescent immune plasma therapy, especially among special groups.

Pregnant women, especially at the end of pregnancy, maybe more susceptible to COVID-19, probably due to changes in the immune system and physical stature [54]. A pregnant woman with COVID-19 received CP treatment six days after delivery, and her clinical course improved, particularly during the second week [54]. The other pregnant was extubated and her oxygen requirements were gradually decreased after receiving CP [49]. A pregnant woman with COVID-19 developed severe ARDS, after 8 days of CP treatment, continuous renal replacement therapy and extra-corporeal membrane oxygenation were removed

[46].

Treating transplant recipients with COVID-19 can be challenging given the need for ongoing immunosuppressive medications in these patients, such as kidney transplantation, bone marrow transplantation or stem cell transplantation. Çınar et al reported an immunocompromised patient due to myelodysplastic syndrome, and attacked by SARS-CoV-2 leading to COVID-19 syndrome, which was successfully managed via the administration of double CP transfusion [50]. Naeem S et al and Jiang J et al reported 4 cases of renal transplantation patients undergoing immunotherapy, two of them were 65 and 70 years old, they were discharged and the use of plasma was helpful for SARS-CoV-2 clearance and her recovery [59,63]. Karataş A et al reported a 61-year-old man with a history of mixed cellularity classical Hodgkin lymphoma, autologous stem cell transplantation (6 months ago) [58]. On After the CP transfusion, his fever resolved after 3 days and he was discharged from the hospital on the 78th day of hospitalization. But unfortunately, a week later, his sensor released and follow-up RT-PCR test was found to be positive. In patients with hematological malignancies or immunosuppression such as ASCT may lead to prolonged viral shedding [58].

As everyone known, the patient had an older age and coexisting chronic diseases, which were associated with severe clinical symptoms and poor prognosis. A male centenarian with cough and dyspnea for 2 months was diagnosed with COVID-19. Without effective treatments and with the increased risks of antiviral therapy for the elderly, this patient was given CP. The viral load and clinical symptoms improved after CP transfusion [48].

Few cases of severe and often fatal COVID-19 have been reported although the infection is mild in the large majority in children. Figlerowicz M et al reported the first case of CP transfusion in a child with COVID-19-associated severe aplastic anemia. Three weeks after CP treatment, although her hematologic parameters did not improve significantly, the results of sars-cov-2 RNA in 7 nasopharyngeal swabs were negative [56]. Shankar R et al reported the case of a 4-year-old girl with severe COVID-19 associated pneumonia who presented to us as febrile neutropenia. She is the first in a child with underlying malignancy [62]. The use of CP along with steroids and intravenous immunoglobulin showed dramatic results in this child and she recovered without the need for any specific treatment.

According to the findings of the present studies, clinical symptoms, laboratory results, and viral load were significantly improved in pregnant women, children, elderly, and immunocompromised COVID-19 patients after CP transfusion. No serious adverse reactions occurred during and after CP infusion.

3.6. Quality of evidence

The quality of evidence on the impact of CP transfusion on mortality in COVID-19 was of low and very low quality for RCTs and controlled NRSIs respectively. As for the median time of patients from symptoms onset (or hospitalization) to transfusion within 10 days, the similar results of quality were shown (low and very low quality for RCTs and controlled NRSIs respectively). In addition, the quality of evidence on the impact of CP transfusion on clinical improvement is of very low quality. The results were shown in table 4.

4. Discussion

4.1. CP therapy

Currently, treatment strategies for COVID-19 patients are lacking [74,75]. There are few approved specific antivirals targeting the virus, while some drugs are still under investigation. To this end, there are urgent needs to develop COVID-19-specific treatment to alleviate the

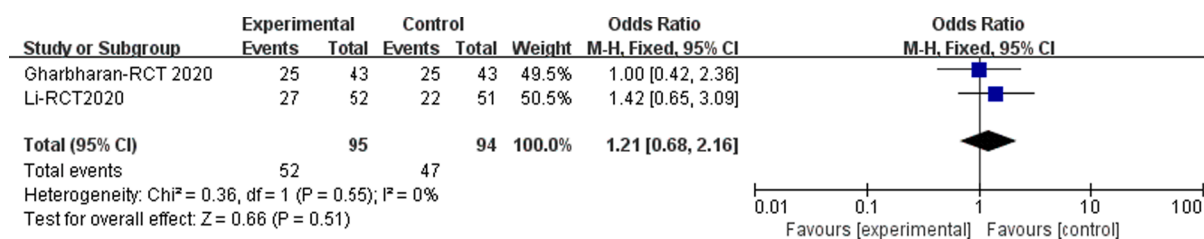


Fig. 5. The clinical improvement outcome of CP therapy on COVID-19 patients (results from RCTs).

symptoms and reduce the mortality.

CP therapy, a classic adaptive immunotherapy, has been applied to the prevention and treatment of many infectious diseases for more than one century. During the 2009 H1N1 infection outbreak, a study in Hong Kong showed that CP therapy with antibody titer $\geq 1:160$ could significantly reduce respiratory viral load and mortality [9]. Mair JJ et al analyzed 32 studies, the results showed that CP could significantly reduce the mortality of SARS, and the effect of early use is more obvious [76]. KO et al found that CP with antibody titer $\geq 1:80$ was effective in the treatment of MERS-CoV infection [7]. Luke TC et al performed a meta-analysis on the therapeutic effect of CP in patients with Spanish influenza, they identified eight studies involving 1703 patients with influenza pneumonia who received an infusion of influenza-convalescent human blood products, which showed the range of absolute risk differences in mortality between the treatment and control groups was 8–26% (pooled risk difference, 21% [95% CI, 15–27%]), suggesting that CP would be a possible treatment for H5N1 [77]. In 2014, the use of CP collected from patients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks [78]. The recent COVID-19 outbreak has refocused attention on the use of CP therapy. It has recently been suggested by Food and Drug Administration that administration and study of investigational CP treatment may provide a clinical effect for COVID-19 during the public health emergency [79]. CP therapy was mentioned in the “Diagnosis and Treatment Guidelines of COVID-19 (trial 6th, 7th, and 8th)” issued by NHC, especially for severe and critical cases with rapid disease progression [80–82].

This systematic review identified and summarized 4 RCTs, 11 controlled NRSIs, 7 non-controlled NRSIs and 24 case reports (series) to evaluate the effect and safety of CP treatment. First, because of the inadequacy of randomized controlled trials, we also conducted meta-analysis of the data from controlled NRSIs. Meta-analysis results of RCTs showed that, there were no statistically significant differences between CP transfusion and control group in terms of reducing mortality and improving clinical symptoms. However, the results of controlled NRSIs showed that CP therapy may reduce mortality in COVID-19 patients. There are not sufficiently RCTs for CP treatment for COVID-19 patients until now. Therefore, the available evidence from controlled NRSIs may also serve as an option for COVID-19 treatment. The evidence was commonly of low or very low quality. Second, limited safety data suggested that CP may be a well-tolerated therapy with a low incidence of AEs. But, due to lack of safety data for the control group, it is really not easy to determine whether CP transfusion has an impact on AEs. Third, for children, pregnant, elderly, tumor and immunocompromised patients, CP may be a well-tolerated therapy, if the disease cannot be controlled and continues to progress.

However, the optimal timing, titers and dosage of CP therapy is unknown. We found that there were significant differences in CP titers, duration of administration, and doses in the included studies, which were likely to affect the efficacy and safety of CP therapy. The optimal time, dose, and titer for CP therapy still require large, high-quality studies to provide data.

4.2. Pharmaceutical care

For normal adults, plasma volume ranges from 39 to 44 ml/kg [83]. CP infusion may have little influence on blood concentration in the recipient, but large amounts of plasma infusion (Zhang et al reported a maximum of 2400 ml of CP administered to a 73 years old male patient [46]) may affect the blood concentration and the therapeutic effect of the drugs. Pharmacists should develop individualized drug adjustment programs based on patient weight, plasma volume, infusion plasma dose, and plasma protein binding rate.

In addition, we should be concerned about the potential risks of drugs in donated plasma. Melanson et al reported, in the absence of drug declaration, 11% of blood donors had drug residues [84]. Medication taken by the donor in plasma for transfusion may cause an anaphylactic transfusion reaction in the recipient. In any case, the transfer of drugs from donors to recipients should be avoided, as these drugs may be allergic or potential harm to the recipients [85]. Both the relevant documents and the blood donation guidance manual have strict rules on the conditions of blood donation, including which drugs donors should not take before donating blood. However, COVID-19 patients have received antivirals, antibacterial drugs, glucocorticoids and treatment for virus-related complications due to medical need. It is conceivable that these drugs remained in the plasma donated by the convalescent COVID-19 patients. However, due to the urgency of the epidemic and the critical condition of the patients, most clinicians do not pay much attention to the risk that CP may contain drugs. To avoid these risks, pharmacists should conduct pharmaceutical care in CP patients, although the residual amount and effect of the drug are still uncertain.

4.3. Limitation

A lack of high-quality studies and a paucity in the volume of relevant literature limited our analyses. The confidence of the results from meta-analysis is limited by insufficient data of the RCTs. Due to the evidence from controlled studies was insufficient, we included case reports (series), and had a low to medium quality. Some articles that are not accessible to full texts and those in languages other than English were excluded from the analysis. This might have led to overlook some critical findings or observations.

5. Conclusion

Although the results of limited RCTs showed that CP cannot significantly reduce mortality, some non-RCTs and case report (series) have found that CP may help patients improve clinical symptoms, clear the virus, and reduce mortality, especially for patients with COVID-19 within ten days of illness. Therefore, we speculate that CP may be a possible treatment option, but this effect may be affected by the time of administration, dose, titer, population, and other aspects. However, high-quality studies are needed for establishing stronger quality of evidence along with the optimal initiation time, titers, and doses for the effective usage of CP. During CP therapy, pharmacists should also be actively involved in the treatment process and provide close pharmaceutical care to the recipients.

Table 4
GRADE evidence profile of CP for COVID-19 studies.

CP for COVID-19 patients						
Patient or population: patients with COVID-19 patients						
Settings: RCTs and controlled NRSIs						
Intervention: CP for COVID-19 patients						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
RCT-mortality mortality	Control	CP for COVID-19 patients	OR 0.79 (0.52 to 1.19)	734 (4 studies)	⊕⊕⊕⊖ low ¹	
	Study population 158 per 1000	130 per 1000 (89 to 183)				
< 10 days-RCT mortality mortality	Moderate		OR 0.4 (0.14 to 1.11)	167 (2 studies)	⊕⊕⊕⊖ low ¹	
	185 per 1000	152 per 1000 (06 to 213)				
controlled NRSIs-mortality mortality	Study population		RR 0.59 (0.53 to 0.66)	7779 (11 studies)	⊕⊕⊕⊖ very low ^{2,3,4}	
	297 per 1000	175 per 1000 (157 to 196)				
< 10 days controlled NRSIs mortality mortality	Moderate		RR 0.54 (0.39 to 0.76)	1357 (4 studies)	⊕⊕⊕⊖ very low ^{2,3,4}	
	286 per 1000	169 per 1000 (152 to 189)				
RCT clinical improvement clinical improvement	Study population		OR 1.21 (0.68 to 2.16)	189 (2 studies)	⊕⊕⊕⊖ very low ^{1,5}	
	500 per 1000	548 per 1000 (405 to 684)				
	Moderate					
	506 per 1000	553 per 1000 (411 to 689)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ There are too few randomized controlled studies to evaluate the information size and results, so we downgraded two point for imprecision.

² Controlled non-randomized studies.

³ We downgraded one points because the risk of bias within this study is critical.

⁴ There were too few studies to evaluate the information size and results, so we downgraded one point for imprecision.

⁵ Risk of bias within this study is some concerns, so we downgraded one point for risk of bias.

CRedit authorship contribution statement

Ying Wang: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Pengfei Huo:** Conceptualization, Data curation, Formal analysis, Writing - original draft. **Rulin Dai:** Data curation, Validation. **Xin Lv:** Resources, Software, Validation. **Shaofei Yuan:** Methodology. **Yang Zhang:** Methodology. **Yiming Guo:** Methodology. **Rui Li:** Methodology. **Kun Zhu:** Project administration, Supervision,

Writing - review & editing. **Qian Yu:** Project administration, Supervision, Validation.

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Declaration of Competing Interest

There is no potential conflict of interest for authors to disclose.

Appendix A. Supplementary material

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