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Effect of convalescent blood products for patients with severe acute respiratory infections of viral etiology: A systematic review and meta-analysis

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ABSTRACT

Objectives: The aim of this study was to determine whether convalescent blood products (CBPs) offer a survival advantage for patients with severe acute respiratory infections of viral etiology.
Methods: Up-to-date trials were identified by the authors through searches of the MEDLINE, Embase, Cochrane Library, Web of Science, ClinicalTrials.gov, and medRxiv databases from inception up to September 14, 2020. Meta-analyses were performed using a random-effects model.
Results: According to the observational studies, patients who received CBPs showed a decline in all-cause mortality compared with patients who did not receive CBPs (odds ratio (OR) 0.36, 95% confidence interval (CI) 0.23–0.56; $p < 0.00001$). However, the randomized controlled trials (RCTs) showed no difference between the intervention group and the control group regarding all-cause mortality (OR 0.82, 95% CI 0.57–1.19; $p = 0.30$). The use of CBPs did not increase the risk of adverse events (OR 0.88, 95% CI 0.60–1.29; $p = 0.51$). Using CBPs earlier compared with using CBPs later was associated with a significant reduction in all-cause mortality (OR 0.18, 95% CI 0.08–0.40; $p < 0.0001$).
Conclusions: Based on the outcomes of RCTs, CBPs may not decrease all-cause mortality. Furthermore, compared with later initiation of CBP therapy, earlier initiation of this therapy may decrease the rate of mortality.

Introduction

At the time of writing, more than 29 million people had been diagnosed with coronavirus disease 2019 (COVID-19) worldwide in the ongoing pandemic, which started in December 2019, and the overall mortality was 3.1% (Maps & Trends, 2020). The disease progresses rapidly in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and affected patients may suffer from acute respiratory distress syndrome (ARDS), acute respiratory failure, multi-organ dysfunction, and even death within a short period (Chen et al., 2020; Guan et al., 2020; Wang et al., 2020; Yang et al., 2020).

To date, only dexamethasone has been indicated to decrease the mortality of patients with COVID-19 (Horby et al., 2020). Current management consists of supportive therapy, including oxygen supplementation, antibiotics, antifungal treatment, and extracorporeal membrane oxygenation (ECMO) (Poston et al., 2020; Onder et al., 2020). Despite these treatments, hospitalized patients with COVID-19 are still at a high risk of mortality, with rates ranging from 10% to 80% (Guan et al., 2020; Richardson et al., 2020; Zeng et al., 2020; Zhou et al., 2020).

Convalescent plasma (CP) therapy is currently a treatment option proposed for severely affected COVID-19 patients who are experiencing a more rapid and concerning disease progression. This therapy has been one of the central interventions against COVID-19 in the absence of a vaccine and pharmacological interventions (Roback and Guarner, 2020; Piechotta et al., 2020). The transfusion of convalescent blood products (CBPs) is a type of passive antibody therapy that has been used among patients since the time of the Spanish flu (1917–1918) (Bloch et al., 2020). Antibody-rich CBPs represent the only treatment that can be applied immediately among patients with infections of viral etiology, allowing them to obtain antibodies and generate passive immunity. The antibodies from CBPs can bind to the virus directly

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and neutralize it. At the same time, the antibodies can also clear the virus through opsonization or antibody-dependent cell-mediated cytotoxicity (ADCC).

Recently, several observational studies have suggested that CP could decrease the risk of mortality among patients with COVID-19 (Abolghasemi et al., 2020; Duan et al., 2020). However, this clinical benefit was not found in a randomized controlled trial (RCT) (Li et al., 2020). Many previous studies have tested the safety and clinical treatment effect of CP among patients with other viral diseases, such as severe acute respiratory syndrome (SARS), influenza, and Ebola hemorrhagic fever (EBHF) (Anon., 2020).

Due to the urgency of the epidemic, people urgently want to know whether CBPs are effective for patients with severe acute respiratory infections (SARI) of viral etiology, especially for patients with COVID-19. However, in order to develop suggestions for doctors regarding the transfusion of CBPs in patients with COVID-19, there is a need to collect and pool the results of eligible studies comprehensively. Therefore, a series of systematic reviews was performed. There is currently little direct evidence to assess the efficacy and safety of CBPs among patients with COVID-19. As the route of disease transmission and clinical features are similar in COVID-19, SARS, Middle East respiratory syndrome (MERS), and influenza, related eligible studies on these SARI were comprehensively included to provide new evidence for the clinical treatment of COVID-19 patients.

Methods

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, developed by the Equator Network (**Supplementary Material File S1**). This work was registered in the International Prospective Register of Systematic Reviews (CRD42020172940). Ethical approval was not required.

Search strategy

A systematic search for relevant studies published between January 1, 1918 and September 14, 2020 was performed in the MEDLINE, Embase, Cochrane Library, Web of Science, ClinicalTrials.gov, and medRxiv databases. The search strategy combined concepts related to respiratory diseases of viral etiology (i.e., MERS coronavirus (MERS-CoV), SARS coronavirus (SARS-CoV), and SARS-CoV-2, influenza, human) and CBPs (i.e., CP, convalescent serum, convalescent blood, and immunization, passive) (**Supplementary Material File S2**). No filter was applied for the type of study or language.

Eligibility criteria

The inclusion criteria were as follows: (1) RCTs or observational studies; (2) patients of any age and sex who had a laboratory-confirmed or clinically suspected SARI (the definitions of influenza-like illness and severe acute respiratory infection issued by the World Health Organization (WHO) (Fitzner et al., 2018); (3) intravenous CP or convalescent serum or convalescent blood or hyperimmune intravenous immunoglobulin (H-IVIG) or a mixture was used in the intervention group; (4) a control group was included, with placebo, no treatment, other treatment, or later initiation of CBPs applied; (5) the donors had to have been diagnosed previously with the corresponding disease.

Study selection

First, the search results were manually screened by two authors (SS, YSW) independently to identify eligible studies for further analysis. The citations of each included study were also reviewed carefully. Any disagreement was resolved by discussion with a third author (ZHT).

Data extraction and quality assessment

The data extraction was performed by two authors using a double-entry procedure (SS, HYJK). In addition, the results of the data extraction were verified by a third author (YSW). The following data were extracted: author, publication year, country, the number of centers, study method, viral etiology, diagnostic criteria, type of CBP, treatment strategy with CBP, transfusion-related adverse events, number of patients in each group, quality score, outcome data, and treatment strategy in the intervention and control groups. The risk of bias in eligible RCTs was examined using the Cochrane Collaboration risk of bias tool (Higgins et al., 2011; Cochrane Training, 2020). The quality of observational studies was assessed using the Newcastle–Ottawa Scale (NOS) (range 0 – 9 stars) (Ottawa Hospital Research Institute, 2020).

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes included the timing of initiation of CBPs (earlier versus later), adverse events, length of intensive care unit (ICU) stay, length of hospital stay, and days on mechanical ventilation (MV).

Statistical synthesis and analysis

Continuous variables were recorded as the mean ± standard deviation (SD). Values for categorical variables were recorded as the odds ratio (OR) with 95% confidence interval (CI). The meta-analyses were performed using random-effects models. A two-tailed p-value of less than 0.05 was considered statistically significant for all results. A correction factor (1.0) was applied to zero-event trials to enforce the effect of the OR (Sweeting et al., 2004). The I^2 derived from Chi-square tests was applied to assess the heterogeneity between trials, with a value of >50% regarded as indicating high heterogeneity. Univariate meta-regression using a random-effects model analysis was used to reveal the potential sources of heterogeneity. The publication bias for the outcome, in analyses that included more than five studies, was judged by funnel plot and Egger's test (Song and Gilbody, 1998). The quality of evidence for the outcomes was further assessed according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. A trial sequential analysis (TSA) was also performed, in which it was chosen to calculate the required information size by using an 18% relative risk reduction (RRR) for falls (calculated from the eight RCTs (Li et al., 2020; Beigel et al., 2019; Beigel et al., 2017; Davey et al., 2019; Hung et al., 2013; Avendano-Sola et al., 2020; Agarwal et al., 2020)). The control group rate was assumed to be 10.3%. The TSA was performed with a two-sided alpha of 0.05 and a beta of 0.20 (power 80%) to limit type I errors and type II errors. The statistical analyses were completed using Review Manager version 5.3, Stata version 15.1, GRADE Profiler version 3.6, and TSA 0.9.5.10 Beta.

Subgroup and sensitivity analysis

The following variables were selected before the subgroup analysis was undertaken to explore the potential sources of heterogeneity: the type of CBP, the different types of viral disease, and the study quality score. A test of interaction was performed to judge the differences in treatment effect across these subgroups (Sun et al., 2014; Lee et al., 2018; Udell et al., 2013). When $I^2 \geq 50\%$, sensitivity analyses were performed by sequentially removing one

study at a time to identify the studies that influenced the results significantly.

Results

Study selection and characteristics

A flow chart of the literature search and selection process is shown in Figure 1. The Insight Flu 005 trial was not included in the present exploratory meta-analysis due to the lack of sufficient data for the outcomes that were required (Anon., 2020).

Characteristics of eligible studies

The characteristics of the included studies are shown in Table 1. The viral diseases that were studied included Spanish influenza A (H1N1) (Gould, 1919; Kahn, 1919; O'Malley and Hartman, 1919; Ross and Hund, 1919; Sanborn, 1920; Stoll, 1919), SARS (Cheng et al., 2005; Soo et al., 2004; Zhou et al., 2003), EBHF (Sahr et al., 2017; van Griensven et al., 2016), influenza A (H1NI) pdm09 (Chan et al., 2010; Hung et al., 2011; Hung et al., 2013), avian influenza A (H5N1) (Yu et al., 2008), multiple viral etiologies (Yu et al., 2008) (e.g., patients with influenza A(H1N1) and patients with influenza A(H3N2) at the same time (Beigel et al., 2019)), and COVID-19 (Abolghasemi et al., 2020; Avendano-Sola et al., 2020; Zeng et al., 2020). The median age of the patients in all studies was 53.0 years (interquartile range (IQR) 44.3–60.2 years) (Duan et al., 2020; Hung et al., 2011; Hung et al., 2013; Soo et al., 2004; van Griensven et al., 2016; Yu et al., 2008) (Tables 2a and 2b).

Risk of bias and quality assessment

In terms of the risk of bias of the nine RCTs included, seven RCTs were categorized as having a high risk of bias (Li et al., 2020; Beigel et al., 2017; Davey et al., 2019; Hung et al., 2013; Avendano-Sola et al., 2020) and the other two as having an unclear risk of bias (Anon., 2020; Beigel et al., 2019) (**Supplementary Material File S3 and File** S4). More details are shown in Table 3. The quality of the 19 observational studies was assessed according to the NOS. Seven studies (Abolghasemi et al., 2020; Duan et al., 2020; Cheng et al., 2005; Sahr et al., 2017; Soo et al., 2004; van Griensven et al., 2016; Zeng et al., 2020) were classified as high quality and 12 studies (Chan et al., 2010; Gould, 1919; Hung et al., 2011; Kahn, 1919; O'Malley and Hartman, 1919; Ross and Hund, 1919; Sanborn, 1920; Stoll, 1919; Yu et al., 2008; Zhou et al., 2003) were classified as moderate quality (**Supplementary Material** File S5).

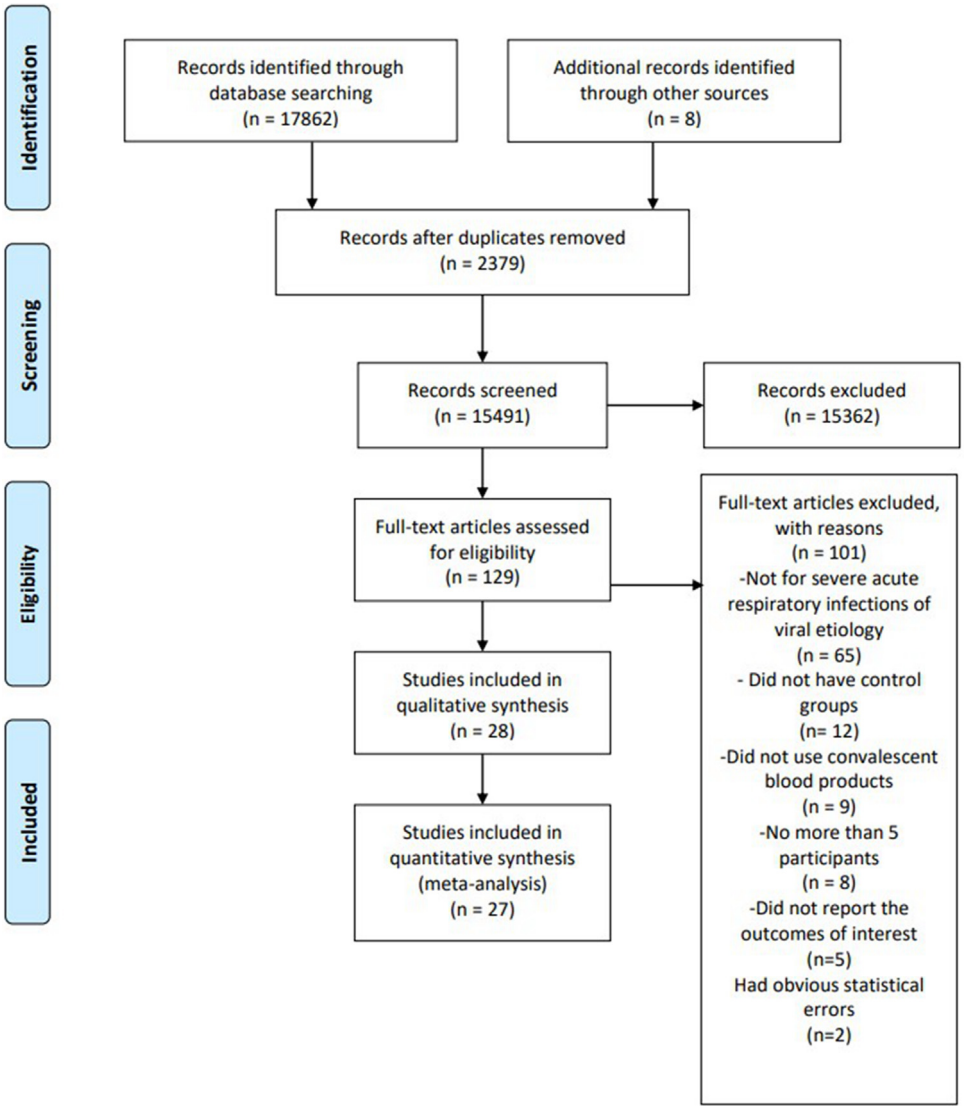

Figure 1. Flow chart of the search and study selection process.

Table 1
Characteristics of the included studies.

Source Year	Country	Center(s)	Method	Viral etiology	Diagnostic criteria	Type of CBP	Treatment strategy	Sample size I/C	Intervention group	Control group	Transfusion-related adverse events	Quality score
Beigel 2017	USA	29 ICUs	RCT	Influenza A(H1N1), A(H3N2), or B virus	Rapid antigen or PCR	Plasma	IV; two units of ABO-compatible plasma (volume range 225–350 ml/unit or 8 ml/kg pediatric equivalent) on study day 0 (HI titer of at least 1:40)	42/45	Anti-influenza plasma plus standard care (included a NAI)	Standard care alone (included a NAI)	ARDS, stroke, hyperglycemia, increased AST, diarrhea, anemia, and fever	High risk of bias
Beigel 2019	USA	41 ICUs	RCT	Influenza A(H1N1), A(H3N2) virus	Rapid antigen or PCR	Plasma	IV; infusion rate ≤500 ml/h; pediatric patients weighing <30 kg received 8 ml/kg plasma in one infusion, and those weighing ≥30 kg received two infusions of 4 ml/kg	91/47	High-titer anti-influenza plasma (antibody titer ≥1:80) plus standard care (a licensed anti-influenza antiviral drug)	Low-titer anti-influenza plasma (antibody titer ≤1:10) plus standard care (a licensed anti-influenza antiviral drug)	ARDS, allergic transfusion reactions, anemia, and respiratory distress	Unclear risk of bias
Davey 2019	USA	34 ICUs	RCT	Influenza A (i.e., A (H1N1) pdm09, A (H3N2)) or B virus	Nucleic acid testing or by rapid antigen test	H-IVIG	IV; 500 ml; one dose of 0.4 g/kg of H-IVIG was given after randomization over a period of approximately 2 h	156/152	Received 500 ml H-IVIG and standard care (95% patients received oseltamivir)	Received 500 ml saline and standard care (95% patients received oseltamivir)	Adverse events always found in respiratory system and mediastinum	High risk of bias
Insight Flu 005 2015	USA	8 ICUs	RCT	Influenza A or B	RT-PCR or rapid antigen testing of upper respiratory tract specimens	H-IVIG	IV; 500 ml; one dose of 0.25 g/kg of H-IVIG	16/15	Received 500 ml H-IVIG and standard care	Received 500 ml placebo and standard care	One patient had elevated bilirubin level, elevated platelet count, and renal failure; the other two experienced hyperkalemia and worsened dysthymic disorder, respectively	Unclear risk of bias
Li 2020	China	7 ICUs	RCT	SARS-CoV-2	RT-PCR	Plasma	IV; approximately 4–13 ml/kg of recipient body weight; plasma units with an S-RBD-specific IgG titer of ≥1:640; the median plasma infusion volume was 200 ml (IQR 200–300 ml), and 96% of patients received a single dose of plasma infusion	51/50	CP plus standard care (antiviral drug, antibacterial drug, steroids, human Ig, Chinese herbal medicines)	Standard care alone (antiviral drug, antibacterial drug, steroids, human Ig, Chinese herbal medicines)	One patient in the severe COVID-19 group had chills and rashes within 2 h of transfusion; the other one in the life-threatening group presented with shortness of breath, cyanosis, and severe dyspnea within 6 h of transfusion	High risk of bias
Hung 2013	China (Hong Kong)	5 ICUs	RCT	Influenza A(H1N1) pdm09 virus	RT-PCR	H-IVIG	IV; one dose of 0.4 g/kg of H-IVIG	17/17 12/5	Received 0.4 g/kg H-IVIG (NAT >1:40) plus oseltamivir Received 0.4 g/kg H-IVIG within 5 days of symptom onset	Received 0.4 g/kg normal IV Ig (NAT <1:10) plus oseltamivir Received 0.4 g/kg H-IVIG after 5 days of symptom onset	None	High risk of bias
Gharbharan 2020 (medRxiv)	Holland	14 ICUs	RCT	SARS-CoV-2	RT-PCR	Plasma	IV; 300 ml of plasma with anti-SARS-CoV-2 NAT of ≥1:80	43/43	CP plus standard care (e.g. chloroquine, azithromycin, LPV/r, tocilizumab, anakinra)	Standard care alone (e.g. chloroquine, azithromycin, LPV/r, tocilizumab, anakinra)	None	High risk of bias
Avendaño-Solà 2020 (medRxiv)	Spain	14 ICUs	RCT	SARS-CoV-2	RT-PCR	Plasma	IV; received one dose (250–300 ml) of plasma from donors with IgG anti-SARS-CoV-2	38/43	CP plus standard care (e.g. chloroquine, azithromycin, LPV/r, tocilizumab, anakinra)	Standard care alone (e.g. chloroquine, azithromycin, LPV/r, tocilizumab, anakinra)	Sixteen serious or grade 3–4 adverse events were reported in 13 patients, 6 in the intervention group and 7 in the control group	High risk of bias
Agarwal 2020 (medRxiv)	India	39 ICUs	RCT	SARS-CoV-2	RT-PCR	Plasma	IV; two doses of 200 ml CP was transfused 24 h apart in the intervention arm	235/229	CP plus standard care (including antiviral drug, broad-spectrum antibiotics, immuno-modulators and supportive management)	Standard care alone (including antiviral drug, broad-spectrum antibiotics, immuno-modulators and supportive management)	Chills, nausea, bradycardia, dizziness, fever, tachycardia, dyspnea, and intravenous catheter blockage	High risk of bias
Hung IF 2010	China (Hong Kong)	7 ICUs	OS	Influenza A(H1N1) pdm09 virus	RT-PCR	Plasma	IV; infused 500 ml of CP with NAT of >1:160 or >1:320	20/73	Received CP plus standard care alone (including antiviral drug, stress steroid treatment)	Standard care alone (included antiviral drug, stress steroid treatment)	None	6
Soo 2004		1 ICU	OS	SARS-CoV	CDC case definition	Plasma	IV; CP 200–400 ml at 11–42 days after onset	19/21	Received CP (including	Standard care alone (included	None	7

Table 1 (*Continued*)

Source Year	Country	Center(s)	Method	Viral etiology	Diagnostic criteria	Type of CBP	Treatment strategy	Sample size I/C	Intervention group	Control group	Transfusion-related adverse events	Quality score
	China (Hong Kong)								antiviral drug, stress steroid treatment)	antiviral drug, stress steroid treatment)		
Zhou XZ 2003	China	1 ICU	OS	SARS-CoV	Diagnostic standard for SARS issued by the Ministry of Health	Plasma	IV; CP 1 × 50 ml (single dose) at 17 days after onset	1/28	Received CP plus standard care (antibiotic treatment, glucocorticoid, and oxygen support)	Standard care alone (antibiotic treatment, glucocorticoid, and oxygen support)	NA	5
Griensven 2016	Belgium	1 ETU	OS	Ebola virus	RT-PCR	Plasma	IV; received two consecutive transfusions of 200–250 ml of ABO-compatible CP	84/418	Anti-influenza plasma plus standard care	Standard care alone	Temporary increase, itching or skin rash, nausea, reaction requiring reduction in infusion rate	7
Kahn 1919	USA	1 ICU	OS	Spanish influenza A(H1N1) virus	Poor prognosis	CBPs (serum, plasma, and full blood)	IV; convalescent serum 100 ml (1–3 injections given)	25/18	CBPs plus standard care	Standard care alone	NA	5
Chan 2010	China (Hong Kong)	3 ICUs	OS	Influenza A(H1N1) pdm09 virus	RT-PCR	Plasma	IV; CP 500 ml	3/4	CP plus standard care	Standard care alone	NA	5
Yu 2008	China	Case reports from 12 provinces	OS	Avian influenza A(H5N1) virus	Virus isolation and RT-PCR	Plasma	IV; CP 1 or 3 × 200 ml (last 2 days)	2/24	CP plus standard care (antibiotic treatment, glucocorticoid, and oxygen support)	Standard care alone (antibiotic treatment, glucocorticoid, and oxygen support)	NA	5
O'Malley1 919	USA	1 ICU	OS	Spanish influenza A(H1N1) virus	Clinical diagnosis	Plasma	IV; CP average 125 ml; 1–4 doses every 12 h	46/111	CP plus standard care	Standard care alone	75% of treated patients experienced chills with a temporary increase	4
Stoll 1919	USA	1 ICU	OS	Spanish influenza A(H1N1) virus	Clinical diagnosis	Serum, plasma, or blood	IV; convalescent serum, 100–150 ml; convalescent blood, 300–400 ml; 1–6 doses	56/379 31/25	CBPs plus standard care Treated within 48 h after the development of the pneumonia	Standard care alone Treated at >48 h after the development of the pneumonia	16% of treated patients had chills, shakes, and temporary increase; transfusion reaction may have hastened death in 4 seriously ill patients	5
Gould 1918	USA	1 ICU	OS	Spanish influenza A(H1N1) virus	Clinical diagnosis	Serum	IV; convalescent serum 100 ml; 1–3 doses every 24 h	30/290	Convalescent serum plus standard care	Standard care alone	NA	5
Ross 1919	USA	1 ICU	OS	Spanish influenza A(H1N1) virus	Clinical diagnosis	Blood	IV; convalescent blood 250–500 ml; 1–3 doses every 12–24 h	28/21 21/7	Convalescent blood plus standard care (e.g. sodium salicylate) Transfusion within 7 days of symptom onset	Standard care alone (e.g. sodium salicylate) Transfusion after 7 days of symptom onset	Slight chills followed by profuse perspiration and drop in temperature; a feeling of constriction in the chest and slight respiratory distress occurred	5
Sanborn 1920	USA	NA	OS	Spanish influenza A(H1N1) virus	Clinical diagnosis	Serum	IV; convalescent serum 100 ml for adults, 50 ml for children (8–24-h intervals); 1–6 doses every 24 h	55/46	Received convalescent serum within the second day of pneumonia onset	Received convalescent serum after the second day of pneumonia onset	10% of the treated patients experienced a mild chill reaction	5
Maclachlan 1918	USA	1 ICU	OS	Spanish influenza A(H1N1) virus	Clinical diagnosis	Blood	IV; convalescent blood 75–100 ml; 1–4 doses	40/7	Received convalescent blood within 2.5 days of pneumonia onset	Received convalescent blood after 2.5 days of pneumonia onset	Some treated patients developed a chill reaction with a body temporary increase	5
Cheng2005	China (Hong Kong)	1 ICU	OS	SARS-CoV	CDC case definition and serology	Plasma	IV; 200–400 ml (4–5 ml/kg)	48/32	Received CP before day 14 of illness onset	Received CP after day 14 of illness onset	None	7
McGuire and Redden 1919	United Kingdom	1 ICU	OS	Spanish influenza A(H1N1) virus	Clinical diagnosis	Serum	IV; 100–250 ml; 1–7 doses every 8–16 h	151/400	Convalescent serum plus standard care	Standard care alone	Experienced chills and temporary increase; jaundice and phlebitis	5
Duan 2020	China	1 ICU	OS	SARS-CoV-2	RT-PCR	Plasma	IV; 200 ml; one dose of inactivated plasma with neutralization activity of >1:640 within 4 h	10/10	CP plus standard care (antibiotic treatment, antifungal treatment, glucocorticoid, and oxygen support)	Standard care alone (antibiotic treatment, antifungal treatment, glucocorticoid, and oxygen support)	Just one patient showed an evanescent facial red spot	7
Sahra2016	Sierra Leone (Freetown)	2 ICUs	OS	Ebola virus	RT-PCR	Blood	IV; 450 ml of ABO-compatible blood; transfusion over a period of 1–4 h	43/25	Convalescent blood plus standard care (multivitamins,	Standard care alone (multivitamins, antipyretics,	None	7

Table 1 (*Continued*)

Source Year	Country	Center(s)	Method	Viral etiology	Diagnostic criteria	Type of CBP	Treatment strategy	Sample size I/C	Intervention group	Control group	Transfusion-related adverse events	Quality score
									antipyretics, analgesics, antibiotics, anthelmintics, and antimalarial drugs)	analgesics, antibiotics, anthelmintics, and antimalarial drugs)		
Abolghasemi 2020	Iran	6 ICUs	OS	SARS-CoV-2	RT-PCR	Plasma	IV; 500 ml was infused within 4 h	115/74	CP plus standard care (antiviral drug)	Standard care alone (antiviral drug)	Only one patient had transient mild fever and chills after transfusion	7
Zeng 2020	China	2 ICUs	OS	SARS-CoV-2	RT-PCR	Plasma	IV; median volume 300 ml	6/15	CP plus standard care (antiviral drug, antibacterial drug, steroids, human Ig, Chinese herbal medicines)	Standard care alone (antiviral drug, antibacterial drug, steroids, human Ig, Chinese herbal medicines)	None	8

ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; C, control; CBP, convalescent blood product; CDC, US Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CP, convalescent plasma; ETU, Ebola treatment unit; HI, hemagglutination inhibition; H-IVIG, hyperimmune intravenous immunoglobulin; I, intervention; ICU, intensive care unit; Ig, immunoglobulin; IQR, interquartile range; IV, intravenous; LPV/r, lopinavir/ritonavir; NA not available; NAI, neuraminidase inhibitor; NAT, neutralizing antibody titer; OS, observational study; RCT, randomized controlled trial; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-RBD, USA, .

Definition of 'earlier' versus 'later'

Six studies compared 'earlier' treatment with 'later' treatment in SARI patients (Cheng et al., 2005; Hung et al., 2013; Maclachlan and Fetter, 1918; Ross and Hund, 1919; Sanborn, 1920; Stoll, 1919). All of them used a time-point to define 'earlier' and 'later,' but the specific time-point cut-offs were not the same among the studies. Specifically, the median time-point of 'earlier' treatments when patients received CBPs after symptom onset was 3.8 days (IQR 2.1–6.5 days) (Cheng et al., 2005; Hung et al., 2013; Maclachlan and Fetter, 1918; Ross and Hund, 1919; Sanborn, 1920; Stoll, 1919). As a result, earlier treatment was defined as receiving CBPs within 4 days of illness onset and later treatment was defined as receiving CBPs at $\geq$4 days following illness onset.

Definition of 'high dose of CBPs' versus 'low dose of CBPs'

Two studies provided the mean total volume of CBP transfusion (125 ml (O'Malley and Hartman, 1919) and 400 ml (Yu et al., 2008)). The other six studies described the protocol of CBP transfusion clearly in the methods section (Abolghasemi et al., 2020; Duan et al., 2020; Chan et al., 2010; Davey et al., 2019; Hung et al., 2011; Sahr et al., 2017; Zhou et al., 2003; Gharbharan et al., 2020; Agarwal et al., 2020). The median volume of CBP was 400 ml (IQR 200–500 ml). A low dose was defined as a total volume of less than 200 ml, because one unit of CBP was almost 200 ml. Greater volumes were considered a high dose.

Synthesis of results

Primary outcome

The pooled data extracted from the RCTs revealed that there was no significant reduction in all-cause mortality in the intervention group when compared with the control group (OR 0.82, 95% CI 0.57–1.19; $p = 0.30$; $I^2 = 0\%$) (Figure 2A) (Li et al., 2020; Beigel et al., 2019; Beigel et al., 2017; Davey et al., 2019; Hung et al., 2013; Avendano-Sola et al., 2020; Agarwal et al., 2020). After the eight studies were divided into COVID-19 and influenza subgroups, CBPs did not significantly reduce all-cause mortality either in patients with COVID-19 (Li et al., 2020; Avendano-Sola et al., 2020; Agarwal et al., 2020) (OR 0.72, 95% CI 0.41–1.25; $p = 0.25$; $I^2 = 25\%$) or in those with influenza (Beigel et al., 2019; Beigel et al., 2017; Davey et al., 2019; Hung et al., 2013) (OR 0.87, 95% CI 0.42–1.80; $p = 0.71$; $I^2 = 0\%$) when compared to the control group (Supplementary Material **File S6**). However, the data on all-cause mortality extracted from the observational studies revealed a significant decrease in mortality in the intervention group when compared with the control group (OR 0.36, 95% CI 0.23–0.56; $p < 0.00001$; $I^2 = 52\%$) (Figure 2B) (Abolghasemi et al., 2020; Duan et al., 2020; Chan et al., 2010; Gould, 1919; Hung et al., 2011; Kahn, 1919; McGuire and Redden, 1919; Sahr et al., 2017; Soo et al., 2004; Zhou et al., 2003; Zeng et al., 2020).

A sensitivity analysis was then performed by sequentially omitting each trial. After excluding the trial of McGuire et al. (McGuire and Redden, 1919; McGuire and Redden, 1918), the results revealed that the heterogeneity decreased from 52% to 14% (OR 0.48, 95% CI 0.35–0.66; $p < 0.00001$; $I^2 = 14\%$) (**Supplementary Material File S7**). This may be because the patients in the intervention group and the patients in the control group did not come from the same time period, although they all came from the same hospital. As a result, it was best to exclude this trial to ensure the robustness of the outcome of all-cause mortality (Table 4).

Potential sources of heterogeneity were explored by subgroup analysis (Figure 3). The results of the subgroup analysis revealed that CP (OR 0.43, 95% CI 0.25–0.71; $p = 0.001$; $I^2 = 28\%$), convalescent serum (OR 0.11, 95% CI 0.05–0.23; $p < 0.00001$; $I^2 = 0\%$), and convalescent blood (OR 0.41, 95% CI 0.18–0.90; $p = 0.03$; $I^2 = 0\%$) could decrease all-cause mortality when compared with the control group. The interaction test showed that there might be differences between the subgroups of the various types of CBP compared with control group for this outcome ($p = 0.002$). The type of viral etiology and the quality of the study were not the source of heterogeneity (**Supplementary Material** File S8).

The meta-regression regarding all-cause mortality of observational studies observed that the treatment effect was not affected by the dose of CBP (high or low dose) ($p = 0.697$), publication year ($p = 0.329$), study sample size ($p = 0.945$), race ($p = 0.896$), mean age ($p = 0.324$), proportion of males (%) ($p = 0.117$), proportion of pregnant women (%) ($p = 0.866$), or the proportion of patients under 18 years old (%) ($p = 0.535$). The funnel plot for RCTs, which

Table 2a
Characteristics of patients at inclusion.

Source/year	Male (%)	Mean age (years)	Mean APACHE II score	Sample size	Positive pregnancy status (%)	Participants <18 years old (%)	Hypertension (%)	COPD (%)	Diabetes (%)	Coronary artery disease (%)	Mean days of influenza illness before admission
Beigel/2017	48	53	13	98	4	11.2	50	24	15	13	4
Beigel/2019	51.4	59.7	–	138	0.7	9.4	–	–	–	–	3
Hung/2013	55.9	49	12.5	34	0	0	29.4	2.9	23.5	2.9	–
Hung IF/2010	68.8	52.7	12.8	93	0	0	–	–	–	9.6	3.1
Soo/2004	–	43.53	–	40	0	0	10	–	–	–	–
Zhou XZ/2003	37.9	–	–	29	0	0	–	–	–	–	–
Griensven/2016	48.6	28.17	–	502	1.59	17.72[a]	–	–	–	–	–
Kahn/1919	–	–	–	43	0	0	–	–	–	–	–
Chan/2010	28.6	42	17	7	0	0	29	14	14	–	5
Yu/2008	42.3	29	–	26	7.6	23	–	–	–	–	
O'Malley/1919	–	–	–	157	–	–	–	–	–	–	–
Stoll/1919	–	–	–	435	–	–	–	–	–	–	–
Gould/1918	–	–	–	320	–	–	–	–	–	–	–
Ross/1919	–	–	–	49	0	6.12	–	–	–	–	3.6
Sanborn/ 1920	–	–	–	101	8.91	–	–	–	–	–	–
Maclachlan/1918	–	–	–	47	–	–	–	–	–	–	–
Cheng/2005	46.3	45	–	80	–	–	–	–	–	–	–
McGuire and Redden/1919	–	–	–	551	–	–	–	–	–	–	–
Davey/2019	45	57	–	308	0	0	–	–	–	–	3.5
Duan/2020	60	52.75	–	20	0	0	–	–	–	–	–
Insight Flu 005/2015	38.7	53	–	31	0	0	–	–	–	–	≤6
Li/2020	58.3	69.5	–	103	0	0	54.4	–	20.4	25.2	11
Sahra/2016	46.4	30.3	–	69	0	20.3	–	–	–	–	1.8
Abolghasemi/2020	55.0	55.36	–	189	–	0	21.7	–	22.8	–	–
Zeng/2020	76.2	69.7	–	21	0	0	19.0	–	28.6	4.8	–
Gharbharan/2020 (medRxiv)	72.1	62	–	86	0	0	25.6	–	24.4	23.3	10
Avendaño-Solà/2020 (medRxiv)	54.3	60.8	–	81	0	0	39.5	12.3	21.0	18.5	5.2
Agarwal/2020 (medRxiv)	51.2	76.3	–	464	0	0	37.3	3.2	43.1	6.9	4.7

APACHE, Acute Physiology and Chronic Health Evaluation score; COPD, chronic obstructive pulmonary disease; '-', not available.
[a] Only participants under the age of 14 years were covered.

Table 2b
Characteristics of patients at inclusion.

Source/year	ARDS (%)	ECMO (%)	MV (%)	Mean WBC count ($\times 10^9$/l)
Beigel/2017	38	–	43	–
Beigel/2019	13	0.72	28.2	–
Hung/2013	–	–	94.1	–
Hung IF/2010	55.9	12.9	93.5	–
Soo/2004	–	–	–	–
Zhou XZ/2003	–	–	–	–
Griensven/2016	–	–	–	–
Kahn/1919	–	–	–	–
Chan/2010	–	100	–	–
Yu/2008	80.8	–	–	4.3
O'Malley/1919	–	–	–	–
Stoll/1919	–	–	–	–
Gould/1918	–	–	–	–
Ross/1919	–	–	–	4.93
Sanborn/ 1920	–	–	–	–
Maclachlan/ 1918	–	–	–	–
Cheng/2005	–	–	–	–
McGuire and Redden/1919	–	–	–	–
Davey/2019	–	–	–	–
Duan/2020	–	–	–	–
Insight Flu 005/2015	–	–	–	–
Li/2020	–	–	–	7.38
Sahra/2016	–	–	–	–
Abolghasemi/2020	–	–	–	7.67
Zeng/2020	–	76.2	85.7	6.69
Gharbharan/2020 (medRxiv)	–	–	36.0	–
Avendaño-Solà/2020 (medRxiv)	–	0	0	–
Agarwal/2020 (medRxiv)	–	0	–	8.71

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; WBC, white blood cell; '-', not available.

Table 3
Assessment of study quality (RCTs).

Source	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Beigel/2017	Low	Low	High[a]	Low	Low	Low	High[b]
Beigel/2019	Low	Low	Low	Low	Low	Low	Unclear[c]
Davey/2019	Low	Low	Low	Low	High[d]	Low	High[e]
Hung/2013	Low	Low	Low	Low	Low	Low	High[f]
Insight Flu 005/2015	Unclear[c]	Low	Low	Unclear[c]	Low	Low	Unclear[c]
Li/2020	Low	Low	High[a]	Low	High[h]	Low	Unclear[c]
Gharbharan/2020 (medRxiv)	Low	Low	Unclear[c]	Low	Low	Low	High[i]
Avendaño-Solà/2020 (medRxiv)	Low	Low	High[a]	Low	Low	Low	High[i]
Agarwal/2020 (medRxiv)	Low	Low	Low	Low	Low	Low	High[j]

[a] Study used an unblinded design.
[b] The losses to follow-up appeared to be higher in the control group compared to the intervention group, although the authors did not think it would affect the outcomes.
[c] Insufficient information to judge.
[d] Seventeen patients from one site were excluded as their eligibility could not be confirmed. According to the sensitivity analyses, their exclusion had little impact on estimated odds ratios for the primary endpoint.
[e] The subgroup with influenza B only included 27% of all participants in the trial (84 patients).
[f] The sample size was small (34 patients).
[h] Missing data for secondary outcomes and adverse events were not imputed.
[i] The study was stopped prematurely.
[j] The antibody titers in convalescent plasma could not be measured before transfusion.

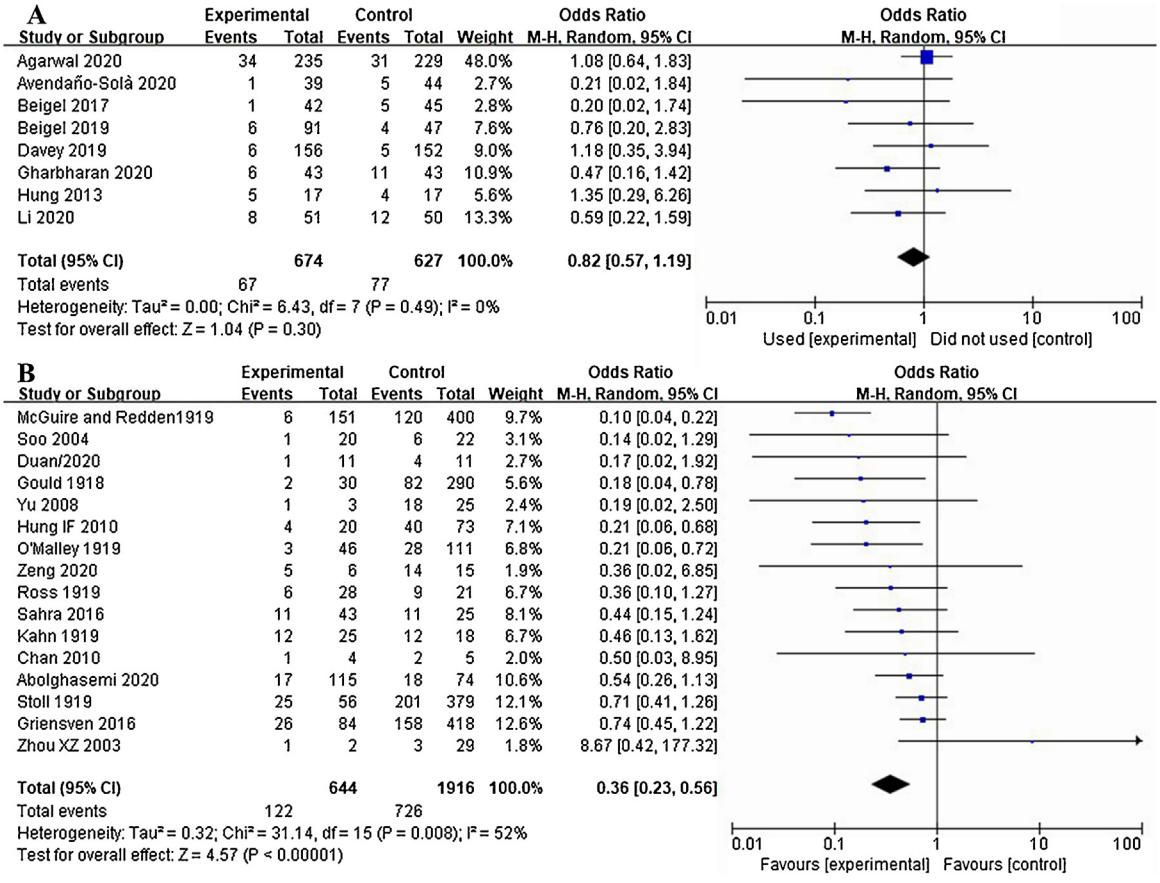

Figure 2. Primary outcome: all-cause mortality. (A) All-cause mortality in RCTs. (B) All-cause mortality in observational studies.

Table 4
Outcomes or subgroup analysis of included studies [Au?19].

Outcomes or subgroup analysis or sensitivity analysis		Studies	Study reference numbers	Patients	OR/MD (95% CI)	I^2	*p*-Value
Primary outcomes							
All-cause mortality in RCTs		8	(Li et al., 2020; Beigel et al., 2019; Beigel et al., 2017; Davey et al., 2019; Hung et al., 2013; Avendano-Sola et al., 2020; Gharbharan et al., 2020; Agarwal et al., 2020)	1301	0.82 (0.57, 1.19)	0%	0.30
All-cause mortality in observational studies		16	(Abolghasemi et al., 2020; Duan et al., 2020; Chan et al., 2010; Gould, 1919; Hung et al., 2011; Kahn, 1919; McGuire and Redden, 1919; McGuire and Redden, 1918; O'Malley and Hartman, 1919; Ross and Hund, 1919; Sahr et al., 2017; Soo et al., 2004; Stoll, 1919; van Griensven et al., 2016; Yu et al., 2008; Zhou et al., 2003; Zeng et al., 2020)	2560	0.36 (0.23, 0.56)	52%	<0.00001
Secondary outcomes							
Earlier versus later		6	(Cheng et al., 2005; Hung et al., 2013; Maclachlan and Fetter, 1918; Ross and Hund, 1919; Sanborn, 1920; Stoll, 1919)	331	0.18 (0.08, 0.40)	39%	<0.0001
Adverse events		7	(Li et al., 2020; Beigel et al., 2019; Beigel et al., 2017; Davey et al., 2019; Hung et al., 2013; Avendano-Sola et al., 2020; Gharbharan et al., 2020)	850	0.88 (0.60, 1.29)	0%	0.51
Length of ICU stay		4	(Beigel et al., 2019; Beigel et al., 2017; Hung et al., 2013; Agarwal et al., 2020)	723	0.35 (−0.70, 1.40)	0%	0.51
Length of hospital stay		3	(Beigel et al., 2019; Beigel et al., 2017; Hung et al., 2013)	259	−1.52 (−3.53, 0.49)	0%	0.14
Days on mechanical ventilation		2	(Beigel et al., 2019; Beigel et al., 2017)	225	−4.20 (−7.45, −0.94)	19%	0.01
Subgroup analysis of all-cause mortality in RCTs							
COVID-19		4	(Li et al., 2020; Avendano-Sola et al., 2020; Gharbharan et al., 2020; Agarwal et al., 2020)	734	0.72 (0.41, 1.25)	25%	0.25
Influenza		4	(Beigel et al., 2019; Beigel et al., 2017; Davey et al., 2019; Hung et al., 2013)	568	0.87 (0.42, 1.80)	0%	0.71
Subgroup analysis of all-cause mortality in observational studies							
Different types of viral etiology	COVID-19	3	(Abolghasemi et al., 2020; Duan et al., 2020; Zeng et al., 2020)	211	0.48 (0.24, 0.96)	0%	0.31[a]
	Influenza A (H1N1) pdm09	2	(Chan et al., 2010; Hung et al., 2011)	102	0.23 (0.08, 0.70)	0%	
	SARS	2	(Soo et al., 2004; Zhou et al., 2003)	73	0.97 (0.02, 57.63)	79%	
	Spanish influenza A (H1N1)	6	(Gould, 1919; Kahn, 1919; McGuire and Redden, 1919; McGuire and Redden, 1918; O'Malley and Hartman, 1919; Ross and Hund, 1919; Stoll, 1919)	1555	0.28 (0.13, 0.63)	72%	
	EBHF	2	(Sahr et al., 2017; van Griensven et al., 2016)	570	0.67 (0.42, 1.05)	0%	
	Avian influenza A (H5N1)	1	(Yu et al., 2008)	28	0.19 (0.02, 2.50)	–	
Type of convalescent blood products	Convalescent plasma	10	(Abolghasemi et al., 2020; Duan et al., 2020; Chan et al., 2010; Hung et al., 2011; O'Malley and Hartman, 1919; Soo et al., 2004; van Griensven et al., 2016; Yu et al., 2008; Zhou et al., 2003; Zeng et al., 2020)	1094	0.43 (0.25, 0.71)	28%	0.002[a]
	Convalescent serum	2	(Gould, 1919; McGuire and Redden, 1919; McGuire and Redden, 1918)	871	0.11 (0.05, 0.23)	0%	
	Convalescent whole blood	2	(Ross and Hund, 1919; Sahr et al., 2017)	117	0.41 (0.18, 0.90)	0%	
	Mixture	2	(Kahn, 1919; Stoll, 1919)	478	0.66 (0.40, 1.11)	0%	
The quality of study	Moderate quality	10	(Chan et al., 2010; Gould, 1919; Hung et al., 2011; Kahn, 1919; McGuire and Redden, 1919; McGuire and Redden, 1918; O'Malley and Hartman, 1919; Ross and Hund, 1919; Stoll, 1919; Yu et al., 2008; Zhou et al., 2003)	1713	0.31 (0.16, 0.60)	61%	0.11[a]
	High quality	6	(Abolghasemi et al., 2020; Duan et al., 2020; Sahr et al., 2017; Soo et al., 2004; van Griensven et al., 2016; Zeng et al., 2020)	844	0.58 (0.40, 0.84)	0%	

OR, odds ratio; MD, mean difference; CI, confidence interval; RCT, randomized controlled trial; ICU, intensive care unit; COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome; EBHF, Ebola hemorrhagic fever.
[a] Values of the test of interaction between subgroups.

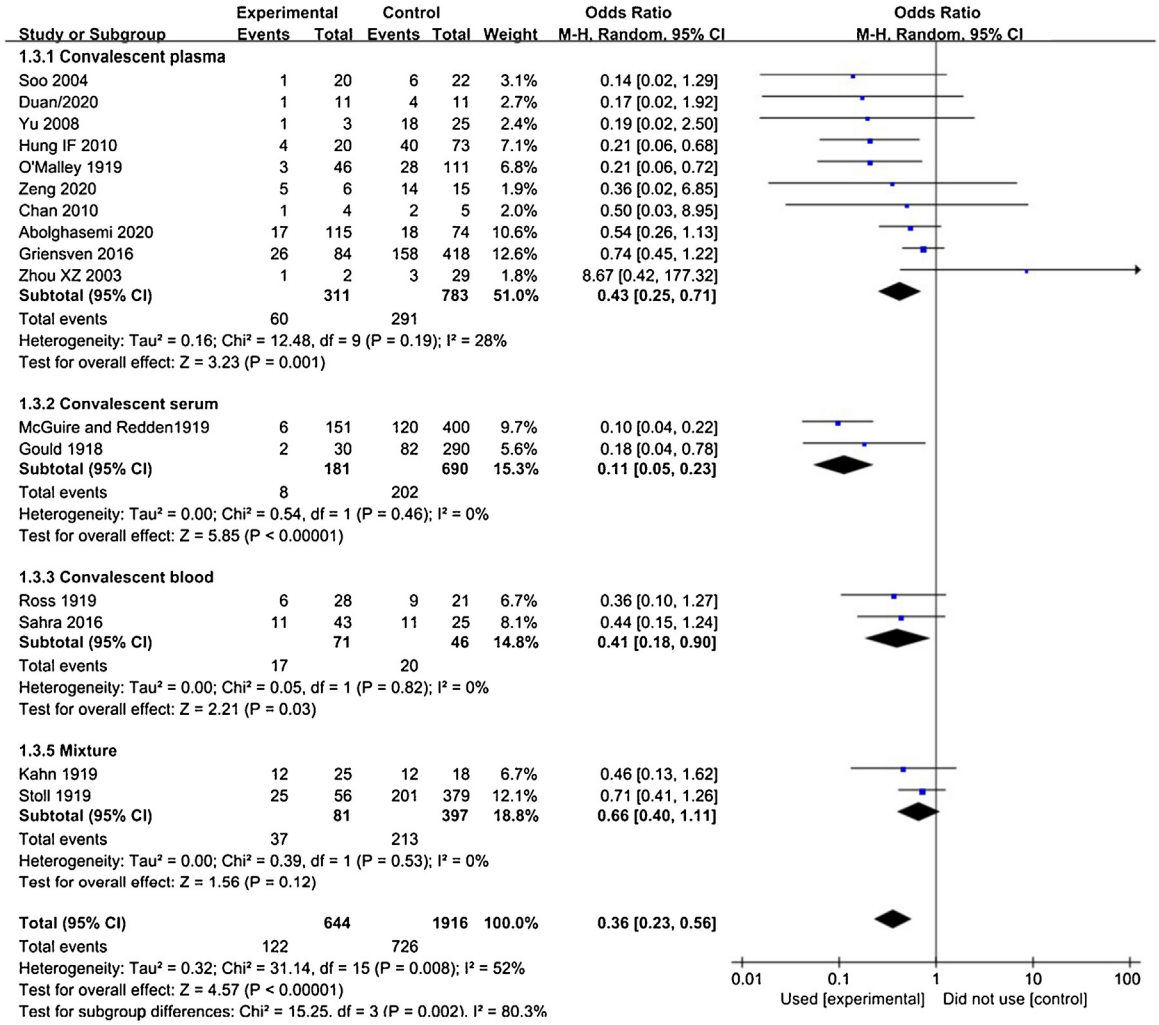

Figure 3. Subgroup analysis of all-cause mortality according to the types of convalescent blood products.

compared the CBPs with placebo (or no treatment), showed an absence near the bottom right, but the Egger linear regression test did not show any evidence of potential publication bias ($p = 0.077$) (Figure 4A). The same situation was found for the results of all-cause mortality in the observational studies, and the Egger linear regression test did not find any evidence of substantial publication bias ($p = 0.195$) (Figure 4B).

Secondary outcomes

In terms of the optimal timing of initiation of CBPs, the pooled results revealed that there might be an improvement in the 'earlier' group when compared with the 'later' group (OR 0.18, 95% CI 0.08–0.40; $p < 0.0001$; $I^2 = 39\%$) (Figure 5) (Cheng et al., 2005; Hung et al., 2013; Maclachlan and Fetter, 1918; Ross and Hund, 1919; Sanborn, 1920; Stoll, 1919).

The pooled analysis revealed no significant difference between the groups in the length of ICU stay (mean difference (MD) 0.35, 95% CI − 0.70 to 1.40; $p = 0.51$; $I^2 = 0\%$) (Beigel et al., 2019; Beigel et al., 2017; Hung et al., 2013; Agarwal et al., 2020), length of hospital stay (MD − 1.52, 95% CI − 3.53 to 0.49; $p = 0.14$; $I^2 = 0\%$) (Beigel et al., 2019; Beigel et al., 2017; Hung et al., 2013) (**Supplementary Material File S9), or** adverse events (OR 0.88, 95% CI 0.60–1.29; $p = 0.51$; $I^2 = 0\%$) (Li et al., 2020; Beigel et al., 2019; Beigel et al., 2017; Davey et al., 2019; Hung et al., 2013; Avendano-Sola et al., 2020; Gharbharan et al., 2020) (Figure 6). However, there was a significant improvement in the intervention group versus the control group regarding days on MV (MD − 4.20, 95% CI − 7.45 to −0.94; $p = 0.01$; $I^2 = 19\%$) (Beigel et al., 2019; Beigel et al., 2017) (**Supplementary Material File** S9C) (Beigel et al., 2019; Beigel et al., 2017).

Visual inspection indicated symmetry in the funnel plots of the secondary outcomes of the optimal timing of initiation of CBPs and adverse events, and the p-value of Egger linear regression was 0.768 and 0.679, respectively (**Supplementary Material File S10**).

Quality of the evidence in this meta-analysis

The quality of the evidence for the five outcomes ranged from very low to moderate. The quality of the evidence for all-cause mortality in RCTs was assessed as low (Table 5). Furthermore, the quality of evidence for all-cause mortality in the observational studies was assessed as very low (Table 5). Details for the secondary outcomes can be found in **Supplementary Material File S**11.

TSA for 28-day mortality

A TSA was performed for all-cause mortality for the eight RCTs. The Z-curve of all-cause mortality between the intervention group and the control group did not cross the trial sequential monitoring

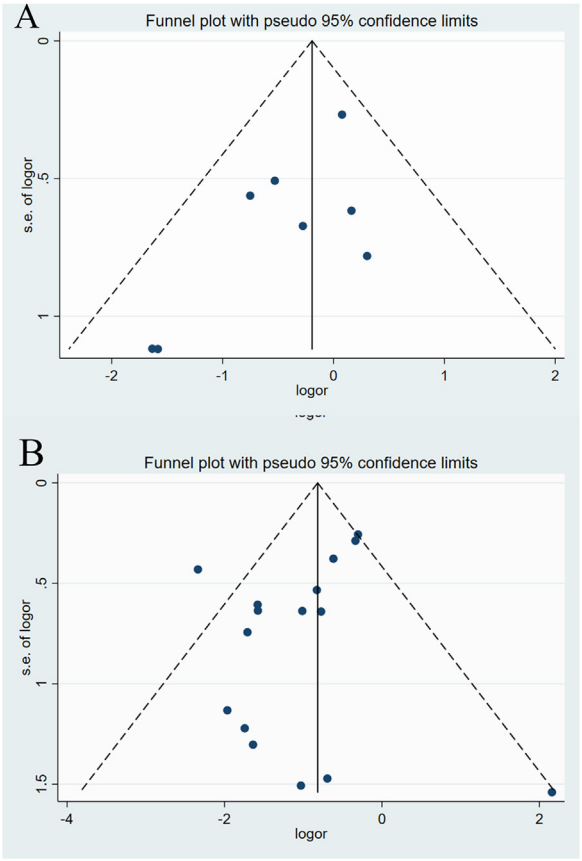

Figure 4. Funnel plots for all-cause mortality in RCTs and observational studies: (A) funnel plot for all-cause mortality in RCTs; (B) funnel plot for all-cause mortality in observational studies.

boundary, the conventional boundary, or the line of estimated information size, revealing that the result may be a false-negative and that more RCTs are needed to prove it (Figure 7).

Discussion

Main findings

In this meta-analysis, a reduction in all-cause mortality associated with CBPs was found for the observational studies but not for the RCTs. Moreover, the results indicate that earlier treatment, when compared with later treatment, might decrease the all-cause mortality of SARI patients. In terms of days on MV, the pooled results revealed that there might be an improvement for patients receiving CBPs when compared to those not receiving this treatment. The pooled estimates of eligible studies indicated that no significant difference could be found between the groups with regard to the length of ICU stay, length of hospital stay, or risk of adverse events.

Discussion of the important differences in the results

Compared with the previous meta-analyses (Luke et al., 2006; Mair-Jenkins et al., 2015), we completed an up-to-date and comprehensive meta-analysis by including studies published after 2013, especially RCTs published from 2013 to 2019 (Luke et al., 2006; Mair-Jenkins et al., 2015) and seven studies published in 2020 (Abolghasemi et al., 2020; Li et al., 2020; Avendano-Sola et al., 2020; Zeng et al., 2020).

A recent meta-analysis studied the efficacy and safety of CP (Devasenapathy et al., 2020). Compared with that study, we included an additional 19 observational studies (Abolghasemi et al., 2020; Duan et al., 2020; Chan et al., 2010; Gould, 1919; Hung et al., 2011; Kahn, 1919; McGuire and Redden, 1919; Sahr et al., 2017; Soo et al., 2004; Zhou et al., 2003; Zeng et al., 2020) and four

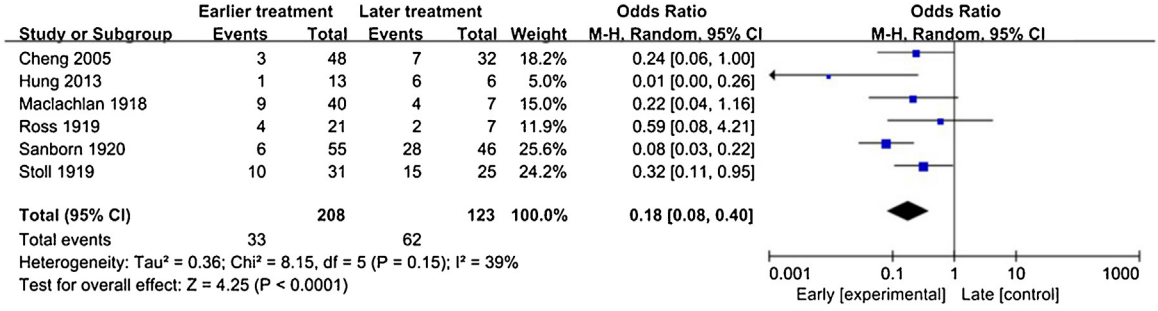

Figure 5. Secondary outcome: the timing of initiation of convalescent blood products—earlier versus later.

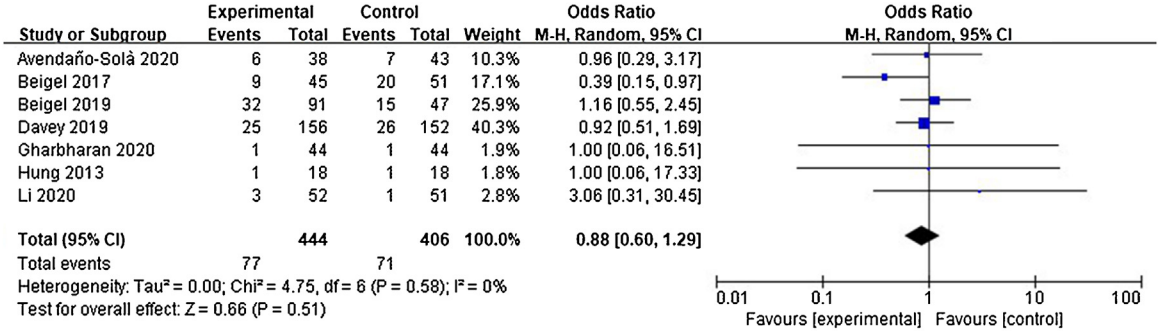

Figure 6. Secondary outcome: adverse events.

Table 5
Quality of evidence for primary outcomes by GRADE system.

Mortality following treatment with CBPs for severe acute respiratory infections of viral etiology						
Patient or population: patients with severe acute respiratory infections of viral etiology Intervention: Mortality following treatment with CBPs						
Outcomes	Illustrative comparative risk[a] (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)[b]	Comments
	Assumed risk Control	Corresponding risk Mortality following treatment with CBPs				
Mortality following treatment with CBPs – RCTs	Study population 123 per 1000 Moderate 111 per 1000	103 per 1000 (74–143) 87 per 1000 (54–146)	OR 0.82 (0.57–1.19)	1301 (8 studies)	⊕⊕⊖⊖ low[c,d]	
Mortality following treatment with CBPs – observational studies	Study population 379 per 1000 Moderate 378 per 1000	180 per 1000 (123–255) 180 per 1000 (123–254)	OR 0.36 (0.23–0.56)	2560 (16 studies)	⊕⊖⊖⊖ very low[e,f,g]	

CBPs, convalescent blood products; CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial.
[a] The basis for the assumed risk (e.g., the median control group risk across studies) is provided in the footnotes below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b] 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.
[c] Seven RCTs were categorized as having a high risk of bias. The other one was evaluated as having an unclear risk of bias, due to insufficient information to judge whether there was other bias in the RCT.
[d] Only 34 patients were included in the study of Hung et al., which was published in 2013, and only 21 patients were included in the study of Li et al., which was published in 2020.
[e] The quality of 16 observational studies was assessed according to the Newcastle–Ottawa Scale; six studies were classified as high quality and 10 studies were classified as moderate quality.
[f] The experimental results were inconsistent.
[g] Half of the eligible studies included fewer than 50 participants.

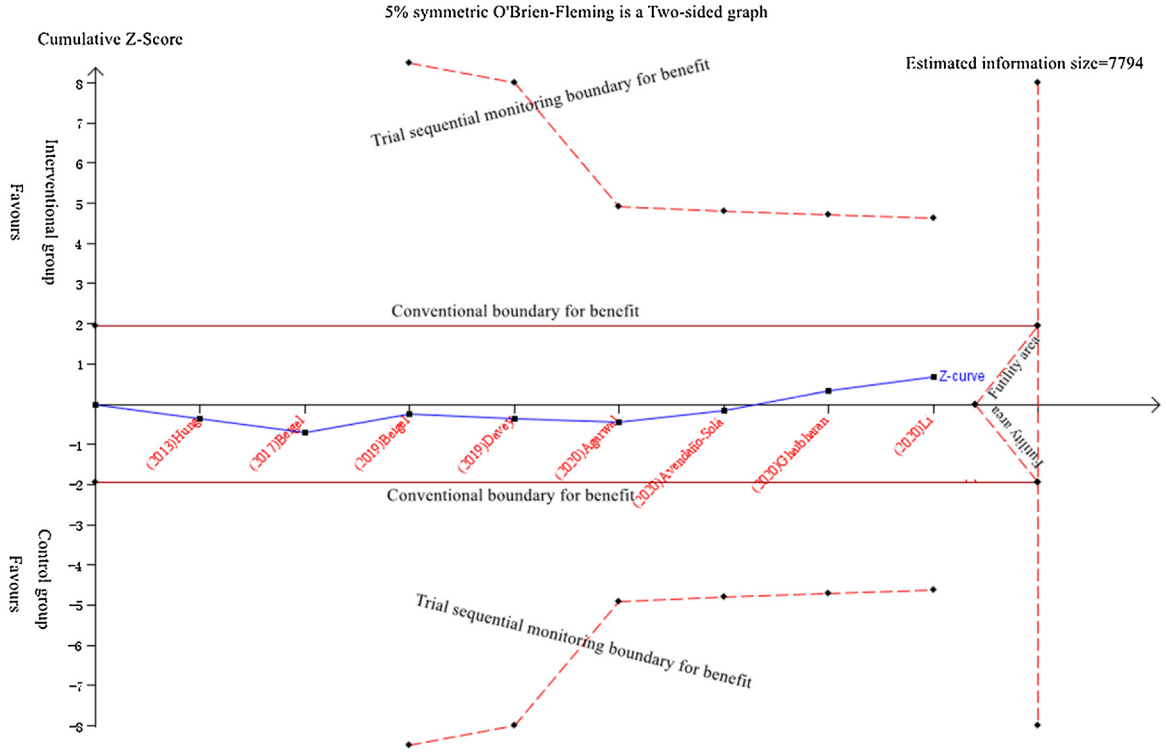

Figure 7. Trial sequential analysis of all-cause mortality.

RCTs focused on patients with SARS-CoV-2 infection (Li et al., 2020; Avendano-Sola et al., 2020; Agarwal et al., 2020); this enabled us to comprehensively evaluate the efficacy of CBPs in patients with SARI of viral etiology. Niveditha et al. (Devasenapathy et al., 2020) included four RCTs, and the pooled results showed that CP did not decrease mortality in the intervention group compared with the control group, which is similar to the result of the present study. However, this finding differs from that for all-cause mortality derived from observational studies. Possible reasons for this difference are as follows. According to the TSA, the RCT analysis might have led to false-negative results, and more patients are needed to clarify the therapeutic effect of CBPs. In addition, three RCTs used H-IVIG with a high hemagglutination inhibition titer (HAI) in the intervention groups (Beigel et al., 2019; Beigel et al., 2017; Davey et al., 2019). However, although the HAI can indicate the quantity of antibodies, it cannot determine the quality of antibodies very well. At the same time, the HAI in these three studies might not have been high enough to treat patients with SARI of viral etiology (Kanjilal and Mina, 2019). Also, standard care, including neuraminidase inhibitors, antibiotic treatment, antifungal treatment, etc., was used in both groups, but whether these concomitant therapies could have influenced the clinical outcomes was unclear. Although there might be several limitations in these RCTs, the limitations of observational studies, including the lack of randomization to contemporary control groups, is a far greater concern, and this cannot be ignored. As a result, more high quality and large sample size RCTs should be performed in the future.

In theory, CBPs might improve the clinical outcomes of patients by increasing antibody titers, decreasing the viral load, and reducing the levels of inflammatory factors in the patient's body. A recent study observed that five COVID-19 patients, after receiving CP, had higher antibody titers than did pre-transfusion patients (range 40–60 before transfusion and 80–320 on day 7 after transfusion) (Shen et al., 2020). A study by Zeng et al. observed that all COVID-19 patients had viral clearance by 3 days after they received CP (Zeng et al., 2020). A similar outcome was found in another study, which showed that 87.2% of the CP group was negative for viral nucleic acid at 72 hours after transfusion, while this rate was only 37.5% in the control group (Li et al., 2020). Moreover, several studies have found that the cytokine storm mediated by interleukin (IL)-2, IL-7, IL-10, G-SCF, IP10, MCP-1, MIP (macrophage inflammatory protein)-1A, and tumor necrosis factor alpha (TNF-α) was the crucial mechanism of disease progression in patients with severe COVID-19 (Huang et al., 2020; Vaninov, 2020; Mehta et al., 2020). In a cohort study that recruited patients with influenza A(H1N1) pdm09, a subgroup analysis of 44 patients revealed that the corresponding day 5 IL-6, day 5 IL-10, day 5 TNF-α, day 7 IL-10, and day 9 IL-10 levels were significantly lower in patients who received CP than in the patients in the control group (Hung et al., 2011).

Additionally, the present study results indicated that the earlier usage of CBPs could offer a greater improvement for patients with SARI when compared with the later usage of CBPs, which is consistent with the results of previous meta-analyses (Luke et al., 2006; Mair-Jenkins et al., 2015). The newest study focusing on COVID-19 patients showed that those who received CP before 14 days post-onset of illness had better treatment outcomes than those who received transfusions later (Duan et al., 2020). This may be because, in the early stage of infection, the body's immune response is not severe, and the tissues and organs are not severely damaged. At this time, the antibody could neutralize the virus' infectivity directly and bring clinical benefits to the patient through antibody-mediated pathways like complement activation and ADCC. Using CBPs later might allow the course of the illness to progress too far for the patient to benefit from the treatment. Although the neutralizing antibody could still bind to the pathogen through the mechanisms mentioned above, the tissues and organs of the patient might have been damaged irreversibly due to virus reproduction and a severe inflammatory reaction. Serious complications, such as sepsis and coagulation dysfunction, may have occurred at the same time.

According to the existing study results, CBPs seem to be safe in treating patients with SARI of viral etiology, and no study has reported life-threatening CBP-related adverse events. Joyner et al. analyzed safety metrics in 5000 hospitalized adults with severe or life-threatening COVID-19 after the transfusion of ABO-compatible CP (Joyner et al., 2020). Thirty-six patients (<1%) reported severe adverse events (SAEs), and half of them were transfusion-associated circulatory overload (TACO) (seven patients) or transfusion related acute lung injury (TRAIL) (11 patients). Simultaneously, according to the judgment of the treating physician, only two of 18 SAEs were directly related to the transfusion of CP. 'Antibody-dependent enhancement' (ADE) is another concern for the transfusion of CP in COVID-19 patients. This is largely a theoretical risk of severe COVID-19 patients experiencing ADE after previous exposure to one or more strains of the coronavirus with heterogeneity of the antigenic epitope (Tetro, 2020). In theory, if enough neutralizing antibodies are present in the CP from donors, and the patient who receives the CP is infected with the same SARS-CoV-2 strain of virus, the virus may be destroyed (Ulrich et al., 2020). However, if the protective neutralizing antibody titer in the CP is low or the recipient is infected with a different SARS-CoV-2 strain (e.g., RBD mutant), low levels of SARS-CoV-2/antibody complexes may be induced (Ulrich et al., 2020; Fu et al., 2020). This complex could bind to angiotensin-converting enzyme 2 (ACE2), and ADE can subsequently be observed through internalization of the complex and IgG-induced stimulation (Ulrich et al., 2020; Fu et al., 2020). However, most descriptions of ADE have been in relation to experimental settings without strong clinical support (de Alwis et al., 2020). The potential threat of ADE needs to be investigated further, especially given the many survivors who have developed immunity.

Strengths and limitations of this study

To our knowledge, this meta-analysis recruited the largest number of relevant studies by far, and seven studies on patients with COVID-19 were included (Abolghasemi et al., 2020; Avendano-Sola et al., 2020; Zeng et al., 2020). We updated the outcomes, such as the optimal timing of CBP initiation. TSA software was applied in the present study to assess the robustness of the relevant results. However, there are some limitations. First, several eligible studies involved very few patients, so we cannot ignore the possibility of a 'small sample effect,' and their sampling error should be fully considered (Lin, 2018). In addition, the current results may not be conclusive. The TSA analysis revealed that more patients were required to validate the use of CBPs in patients with SARI. Moreover, three of the RCTs have not been peer-reviewed, which might affect the robustness of the result (Avendano-Sola et al., 2020). Although this meta-analysis recruited studies including multiple types of viral CBP, which might be non-specific for any viral disease, subgroup analyses were performed to resolve this problem. As we know little about the treatment effects of CP in COVID-19, more high-quality RCTs with a larger sample size are needed to assess the efficacy, safety, optimal time of initiation, and best dose of CP in COVID-19 patients.

Conclusions

Taken together, the low-quality evidence in this study shows that the transfusion of CBPs may not reduce all-cause mortality.

Although the transfusion of CP is associated with a low rate of adverse events, the widespread use of CP in patients should be based on high-quality RCTs. If clinicians decide to transfuse CP to patients, earlier initiation might be better.

Author contributions

Shuai Shao developed the initial idea for this study and conducted a comprehensive search of the databases. Shuai Shao and Yishan Wang were responsible for the study selection. Shuai Shao extracted the data. All authors made contributions to the research design, interpretation of results, and ideas for writing studies. Shuai Shao synthesized and analyzed the data and drafted the manuscript. Yishan Wang, Hanyujie Kang, and Zhaohui Tong reviewed the study and provided suggestions. All authors carefully examined this manuscript and agreed with the ideas presented in the study.

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the MEDLINE, Embase, Cochrane Library, Web of Science, ClinicalTrials.gov, and medRxiv databases.

Conflict of interest

None of the authors has any competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.09.1443.

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