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Review

What convalescent plasma in treating severe acute respiratory infections of viral aetiology can hint for COVID-19? Evidence from a meta-analysis

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ABSTRACT

Objective. – To explore whether convalescent plasma therapy is beneficial to patients with severe acute respiratory infections and gave hints to the management of COVID-19.

Methods. – A comprehensive literature search of PubMed, Web of Science, Embase, and Cochrane library was conducted for all eligible studies range from inception to February 29, 2020. Studies with control group were included. Treatment group received convalescent plasma therapy, and control group may receive any therapy other than convalescent plasma therapy. Odds ratios (ORs), mean differences (MDs) and 95% confidence intervals (CIs) were pooled for categorical and continuous outcomes.

Results. – A total of 1997 patients from 13 studies were included, and seven studies were prospectively designed. Pooled analysis indicated convalescent plasma treatment significantly reduced the mortality by 51% (OR = 0.49, 95% CI: 0.36 to 0.67). Subgroup analyses by publication time, study design, and influenza A revealed similar results. Sensitivity analyses suggested that the results were stable. In addition, convalescent plasma therapy reduced mechanical ventilation requirement (OR: 0.35, 95% CI: 0.21 to 0.59), while it was not associated with less use of extracorporeal membrane oxygenation (OR: 2.0, 95% CI: 0.83 to 4.83) and shorter length of hospital stay (MD: –2.20, 95% CI: –4.98 to 0.57 days). Pooled estimates showed there was no difference in serious adverse effects between the convalescent plasma treatment and control groups (OR: 0.75, 95% CI: 0.50 to 1.13).

Conclusion. – Convalescent plasma therapy significantly reduced the mortality and mechanical ventilation requirements of patients with virus-induced severe acute respiratory infections, without serious adverse effects. More studies are needed to explore whether this treatment can be extrapolated into COVID-19.

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1. Abbreviations

COVID-19 Coronavirus disease 2019
SARS-COV severe acute respiratory syndrome coronavirus
MERS-COV Middle East respiratory syndrome coronavirus
ICU intensive care unit
ECMO extracorporeal membrane oxygenation
RCT randomized controlled trial
RT-PCR reverse transcription polymerase chain reaction

hIVIG hyperimmune intravenous immunoglobulin
CWB convalescent whole blood
ARDS acute respiratory distress syndrome
TRALI transfusion-related acute lung injury
ADE antibody-dependent enhancement
H1N1/H3N2/H5N1/H7N9 influenza A
OR odds ratio
HR hazard ratio
MD mean difference
CI confidence interval

2. Introduction

The ongoing outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) which started in Wuhan

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city of China, in December 2019 caused by the 2019 novel coronavirus (COVID-19), now developed into a world pandemic, poses a global public health emergency. By September 28, 2020, this virus has affected 33,315,890 people worldwide and caused more than 998,548 deaths [1]. Similar to SARS-COV [2] and Middle East respiratory syndrome (MERS-COV) [3], COVID-19 is lethal with many uncertainties concerning its origins, nature, and course. To date, as no specific anti-viral treatment is developed, clinical management focuses on supportive care, such as symptom alleviation in mild cases and organ support for seriously ill patients, and the mortality rate is about 4%. Of note, using WHO data on the cumulative number of deaths to March 1, 2020, Baud et al. estimated the mortality rates would be 5.6% (95% CI: 5.4–5.8) for China and 15.2% (12.5–17.9) outside of China [4], indicating the real mortality of COVID-19 is under-estimated. Although remdesivir [5] and lopinavir [6] are reported to be effective in viral clearance from sporadic cases, larger sample cohort study [7] and randomized controlled trial (RCT) [8] yielded controversial results, and no benefit was observed with lopinavir–ritonavir treatment beyond standard care [9]. Future trials in patients with severe illness should conduct to confirm the possibility of a treatment benefit.

Recently, the administration of convalescent plasma or hyperimmune immunoglobulin (hIVIg, extracted from convalescent plasma) has been raised as one of the treatment options. A latest research reported that host cell entry of SARS-COV-2 depends on SARS-COV-2-spike protein combining with the receptor ACE2 of the target cells. Of interest, convalescent SARS patients exhibit a neutralizing antibody response, which is largely directed against the spike protein [10]. Previous experience in treating patients with SARS coronavirus (SARS-COV) whose condition continued to deteriorate despite treatment with ribavirin plus pulsed methylprednisolone, the convalescent plasma or hyperimmune immunoglobulin is the last resort and proved to be effective in lower mortality and shorten length of hospital stay [11]. Hence, administration of convalescent plasma may be of clinical benefit for treatment of COVID-19. Initial trial of 5 critical COVID-19 patients receiving convalescent plasma treatment also indicated improvement in their clinical status [12]. Further evidence in the battle against Ebola [13], MERS-COV [14], and pandemic 2009 influenza A H1N1 [15] supports the use of convalescent plasma in the treatment protocol of COVID-19 as well. Additionally, a meta-analysis showed a significant reduction in the pooled odds of mortality following convalescent plasma therapy, compared with placebo or no plasma therapy in treating SARS-COV and severe influenza A (H1N1, H5N1) [16]. However, several recently published clinical trials reported conflicted data that convalescent plasma was not associated with a significant improvement in survival of patients infected with Ebola virus [17] and severe influenza A [18]. These results may undermine our confident perception of utilizing convalescent plasma in the treatment of severe COVID-19 cases.

Given the uncertainty of convalescent plasma therapy, we conducted a meta-analysis of available evidence to further explore the efficacy of convalescent plasma in treating severe acute respiratory infections of viral etiology, including Ebola Virus, SARS-COV, MERS-COV, severe influenza A (H1N1, H5N1, H7N9), to provide more solid evidence for management of COVID-19.

3. Methods

This meta-analysis was conducted following all aspects of the Cochrane Handbook for systematic review and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [19].

3.1. Search strategy

A comprehensive literature search of PubMed, Web of Science, Embase, and Cochrane library databases was conducted by two independent investigators (S. Y and J. Z) for all eligible articles published up to February 29, 2020. The key words included “convalescent plasma”, “hyperimmune immunoglobulin”, “Middle East respiratory syndrome (MERS)”, “severe acute respiratory syndrome (SARS)”, “Ebola”, “H1N1”, “H3N2”, “H5N1”, and “H7N9”. No time limit was set throughout the search process. We also searched the reference lists of two previous meta-analyses to avoid missing any publication [16,20]. Review of ClinicalTrials.gov was also performed until February 29, 2020.

3.2. Inclusion and exclusion criteria

We included studies that fulfilled the following criteria:

- clinical trials, cohort studies, case-control studies, or case series;
- participants diagnosed with any one of “MERS”, “SARS”, “H1N1”, “H3N2”, “H5N1”, “H7N9”, “Ebola” and severe influenza;
- studies with an intervention group receiving convalescent plasma therapy and a control group receiving treatment other than convalescent plasma therapy;
- number of patients in the intervention and control group > 3;
- studies reporting any outcome of interest;
- studies published in English or Chinese.

However, we excluded studies without sufficient statistics data, review articles, letters, and comments. If two or more studies were derived from the same dataset, only the study with more complete findings or longer follow-up was included. Two investigators (S.Y and J.Z) independently screened eligible studies. When there were discrepancies between S.Y and J.Z, Dr. T. R. Song will re-evaluate them and resolved by consensus.

3.3. Quality assessment

Quality assessment of observational articles was conducted using the Newcastle-Ottawa Quality Assessment Scale (NOS). NOS scores range from 0 to 9, and low quality was defined as score ≤ 5 , moderate quality scores 6 to 7, and high quality scores 8 to 9 [21]. Cochrane Collaboration’s tool was used to assess the risk of bias of randomized controlled trials [22].

3.4. Study outcomes and data extraction

The primary outcome was mortality. Secondary outcomes included length of stay in hospital, rate of admission to ICU, length of stay in ICU, rate and duration of mechanical ventilation, rate and duration of extracorporeal membrane oxygenation (ECMO), and viral load. Adverse effects were also assessed. Data was extracted from identified studies using a standardized extraction form. The following information was collected: the first author, publication year, study design, length of follow-up, and type of disease, study arm, number of participants, baseline characteristics, treatment, and clinical outcomes. For categorical outcomes (e.g. mortality), we extracted events and the total number of patients in both intervention and control group. For continuous outcomes (e.g. length of stay in hospital), we extracted the mean or median, and standard deviation, range or interquartile range. The process was independently performed by two reviewers (S. Y and J. Z), and any discrepancies were re-evaluated by Dr. T. R. Song and resolved by consensus.

3.5. Statistical analysis

We estimated the mean differences (MD) and 95% confidence intervals (CIs) for continuous outcomes. For categorical outcomes, the summarized odds ratios (ORs) and 95% CI are calculated. Fixed-effect or random-effect models were utilized, depending on the heterogeneity of the eligible studies. Heterogeneity across studies is determined by I^2 test. Significant heterogeneity is indicated by $P < 0.05$ and/or $I^2 > 50\%$. When heterogeneity is significant, a random-effect model is used; otherwise, a fixed-effect model is used. We conducted subgroup analysis to examine the possible modification effects of publication year (1919 vs. after 2004), study design (prospective vs. retrospective), and disease type (influenza A vs. Influenza A and B vs. Ebola vs. COV). In addition, to evaluate whether results of meta-analysis were affected by any individual study, we performed a sensitivity analysis by omitting one study once. Publication bias was assessed by funnel plots. Analyses were performed with R statistical software, version 3.4.3, using the Package “meta”.

4. Results

4.1. Search results

We identified 1289 publications from the initial database search and kept 784 for further review after removing the duplicates. Of these, 757 studies were discarded after screening the titles and abstracts. After assessing full text, 14 reports were further excluded and 13 studies [11,15,17,18,23–31] were included for data analysis. Details regarding the selection of studies are outlined in the flow diagram in Fig. 1.

4.2. Study characteristics

The characteristics of included studies were summarized in Table 1. The 13 studies contained 1997 patients from five countries, including China, United States, South Korea, Belgium and Sierra Leone. Seven studies were conducted prospectively, including 4 RCTs, 2 non-randomized clinical trials, and 1 cohort study. For all included studies, sample size varied from 7 to 502 with a follow-up period of 7 days to 5 months. Of included studies, 3 reported Spanish influenza A (H1N1) and were published in 1919. Ten studies were published between 2004 and 2019, with 4 for severe influenza A, 2 for both influenza A and influenza B, 2 for Ebola, 1 for MERS-COV and 1 for SARS-COV. The mean age of all included patient was 43.1 years and 56.1% were male. However, patients in two studies focusing on Ebola was younger (about 30 years). Patients were treated with standard care plus convalescent plasma or high-titer hIVIG, and were compared with those receiving standard care only, or standard plus placebo, or not receiving plasma therapy.

4.3. Quality assessment

Quality of 4 RCTs was evaluated by Cochrane Collaboration's tool (Fig. S1A, Table S1A). All studies exhibited an adequate random sequence generation process, 3 trials described the methods used for allocation concealment, except for the high risk of allocation concealment by Beigel et al. [18]. The risk of bias assessments about 9 observational studies were summarized by Newcastle-Ottawa scale (Table S1B, Fig. S1B). Only 2 studies scored 6, whereas 6 scored below 5. Studies reported 27 outcomes that were moderate risk of selection bias. Most of them lacked a comparator group, and most studies were at high risk of reporting bias. In a short, the study included was at moderate to high risk of bias.

4.4. Primary outcomes

The primary outcome of interest was all-cause mortality. A total of 78 (13.7%) patients died in the convalescent plasma therapy group compared with 293 (20.9%) in the control group. Pooled analysis indicated convalescent plasma treatment significantly reduced the mortality by 51% (OR = 0.49, 95% CI: 0.36–0.67) with low heterogeneity ($I^2 = 18\%$) (Fig. 2). We had made the subgroup analyses about study design, publication year, and disease type in Table 2. Similar results were observed in subgroup analyses of study design, for 7 prospective studies (OR: 0.63, 95% CI: 0.44–0.90, $I^2 = 16\%$) (Fig. S2A); for 6 retrospective studies (OR: 0.25, 95% CI: 0.13–0.50, $I^2 = 0\%$) (Fig. S2B) and publication year, for 10 studies published after 2004 (OR: 0.60, 95% CI: 0.42–0.84, $I^2 = 3\%$) (Fig. S2C); for 3 studies published in 1919 (OR: 0.25, 95% CI: 0.12–0.52, $I^2 = 0\%$) (Fig. S2D). Additionally, pooled analysis from 7 studies showed that convalescent plasma therapy was associated with reduced mortality in patients infected with influenza A (OR: 0.33, 95% CI: 0.20–0.55, $I^2 = 12\%$) (Fig. S2E). However, this therapy did not show extra benefit in patients with Influenza A and B (OR: 0.69, 95% CI: 0.26–1.86, $I^2 = 51\%$) (Fig. S2F), Ebola (OR: 0.68, 95% CI: 0.44–1.08, $I^2 = 0\%$) (Fig. S2G), and SRAS-COV (OR: 0.28, 95% CI: 0.05–1.47, $I^2 = 37\%$) (Fig. S2H). A sensitivity analysis revealed no significant change in the pooled OR by eliminating any single study, indicating that the results were stable (Fig. S3).

4.5. Secondary outcomes

Four prospective studies reported mechanical ventilation use in these patients, and 45.3% (77/170) of patients used the mechanical ventilation in the convalescent plasma therapy compared with 77.5% (141/182) in the control group. These studies showed that convalescent plasma therapy was associated with reduced mechanical ventilation requirement (OR: 0.35, 95% CI: 0.21–0.59, $I^2 = 12\%$) (Fig. 3A). The mean difference in length of stay in ICU was recorded in 3 prospectively-designed studies, plasma treatment group seemed to reduce the length of ICU stay, without any significant difference (MD: -2.20, 95% CI: -4.98 to 0.57 days, $I^2 = 34\%$) (Fig. 3B). In addition, a total of 16 (12.5%) patients needed ECMO support in the convalescent plasma therapy group compared with 14 (10.2%) in the control group. Convalescent plasma therapy was not associated with the use of ECMO (OR: 2.0, 95% CI: 0.83–4.83, $I^2 = 0\%$) (Fig. 3C).

Four studies reported viral load decreased in the therapy group after receiving convalescent plasma therapy (Table S2). Davey et al. [24] showed the viral load decreased by 1.99 lg copies/mL in the hIVIG group and 2.32 lg copies/mL in the control group during the first 3 days ($P = 0.49$). Sahr et al. [17] reported the Ebola viral load in those receiving convalescent whole blood (CWB) was significantly lower than that in non-convalescent whole blood (non-CWB) group after the first 24 h ($P < 0.01$). Hung et al. [26] showed the Influenza A (H1N1) viral load on day 5 after treatment was significantly lower in the hIVIG than the IVIG group (3.3 vs. 4.67 lg copies/mL; $P = 0.04$). In a prospective cohort study [15], a subgroup analysis of 44 patients with influenza A (H1N1) infection found that SARS-COV load decreased more rapidly in patients receiving convalescent plasma therapy than those in the control group at 3, 5 and 7 days after admission in the ICU ($P < 0.001$, $P = 0.02$, and $P = 0.04$, respectively). In order to show the decreasing trend of viral load more clearly, we made a trend chart to illustrate them (Fig. S4). No detail data on the change of viral load were reported by Sahr et al. [17]. These results suggest that early use of convalescent plasma therapy may be of critical importance in reducing viral load.

Table 1
Key characteristics of included studies.

Author, year	Country	Study type	Sample size	Viral aetiology	Diagnosis	Follow-up	Group	Size	Age (year)	Sex (male, %)	ARDS (initial)	Co-morbidities	Treatment
Davey, 2019 [24]	USA	RCT	308	Influenza A (H1N1, H3N2, subtype unknown) and B (Victoria, Yamagata)	RT-PCR	28 days	Intervention	156	55	76	NR	NR	Standard care + hyperimmune intravenous immunoglobulin (0.25 g/kg bodyweight, 24.75 g maximum)
Beigel, 2019 [31]	USA	RCT	140	Severe influenza A (H1N1, H3N2)	RT-PCR	28 days	Control	152	57	64	NR	NR	Standard care + saline Standard care + high-titre anti-influenza plasma (haemagglutination inhibition antibody titre \geq 1:80) (500 mL/h for adults, 8 mL/kg plasma for children)
							Intervention	92	58	55	15	NR	
Sahr, 2017 [17]	Sierra Leone	Non-RCT	69	Ebola	PCR	5 months	Control	48	63	45	3	NR	Standard care + low-titre plasma (\leq 1:10) Routine care + convalescent whole blood Routine care
							Intervention	44	28	48	NR	NR	
Beigel, 2017 [18]	USA	RCT	98	Severe influenza A (H1N1, H3N2) or B	PCR	28 days	Control	25	34	52	NR	NR	Standard care + anti-influenza plasma (haemagglutination inhibition antibody titre \geq 1:80) (500 mL/h for adults, 8 mL/kg plasma for children)
							Intervention	49	50	51	16	Chronic medical condition 87 (89%)	
Van, 2016 [23]	Belgium	Non-RCT	502	Ebola	RT-PCR	16 days	Control	49	57	45	20	Chronic medical condition 45 (92%)	Standard care + convalescent plasma (two consecutive transfusions of 200 to 250 mL) Standard Care Convalescent plasma Others
							Intervention	84	29	43	9	Chronic medical condition 2 (2%) 5 (1%)	
Choi, 2016 [25]	South Korea	Retrospective cohort study	186	MERS	RT-PCR	28 days	Intervention	7	28	NR	7	NR	Standard Care
Hung, 2013 [26]	Hong Kong	RCT	34	Influenza A (H1N1)	RT-PCR	21 days	Control	179	NR	NR	NR	NR	Hyperimmune IV Immunoglobulin (HIVIG) (a neutralizing antibody titer (NAT) to H1N1 > 1:40, 0.4 g/kg) IV immunoglobulin (IVIG) (0.4 g/kg) Convalescent plasma > 1:160 Non-Convalescent Plasma Convalescent plasma Others
							Intervention	17	43	71	9	13 (76%)	
Hung, 2011 [15]	Hong Kong	Prospective cohort study	93	Influenza A (H1N1)	RT-PCR	9 days	Intervention	20	52	41	7	17 (100%)	Convalescent plasma
Chan, 2010 [27]	Hong Kong	Case series with control	7	Influenza A (H1N1)	RT-PCR	70 days	Control	73	48	55	14	NR	Non-Convalescent Plasma Convalescent plasma Others
							Intervention	3	NR	NR	NR	NR	
Soo, 2004 [11]	Hong Kong	Retrospective cohort study	40	SARS	CDC case definition	22 days	Control	4	NR	NR	NR	NR	Convalescent plasma Methylprednisolone Convalescent plasma Non-convalescent plasma Convalescent serum Convalescent serum Others
							Intervention	19	39	NR	NR	1 (5%)	
O'Malley, 1919 [28]	USA	Case series with control	157	Spanish influenza A (H1N1)	Clinical diagnosis	NR	Intervention	46	NR	NR	NR	NR	Convalescent plasma
Kahn, 1919 [29]	USA	Case series with control	43	Spanish influenza A (H1N1)	Clinical diagnosis	NR	Control	111	NR	NR	NR	NR	Non-convalescent plasma Convalescent serum Non-convalescent plasma Convalescent serum Convalescent serum Others
							Intervention	25	NR	NR	NR	NR	
Gould, 1919 [30]	USA	Case series with control	320	Spanish influenza A (H1N1)	Clinical diagnosis	NR	Control	18	NR	NR	NR	NR	Convalescent serum Convalescent serum Others
							Intervention	30	NR	NR	NR	NR	
							Control	290	NR	NR	NR	NR	

RCT: randomized controlled trial; RT-PCR: reverse transcription polymerase chain reaction; CDC: Centers for Disease Control; ARDS: acute respiratory distress syndrome; NR: not reported.

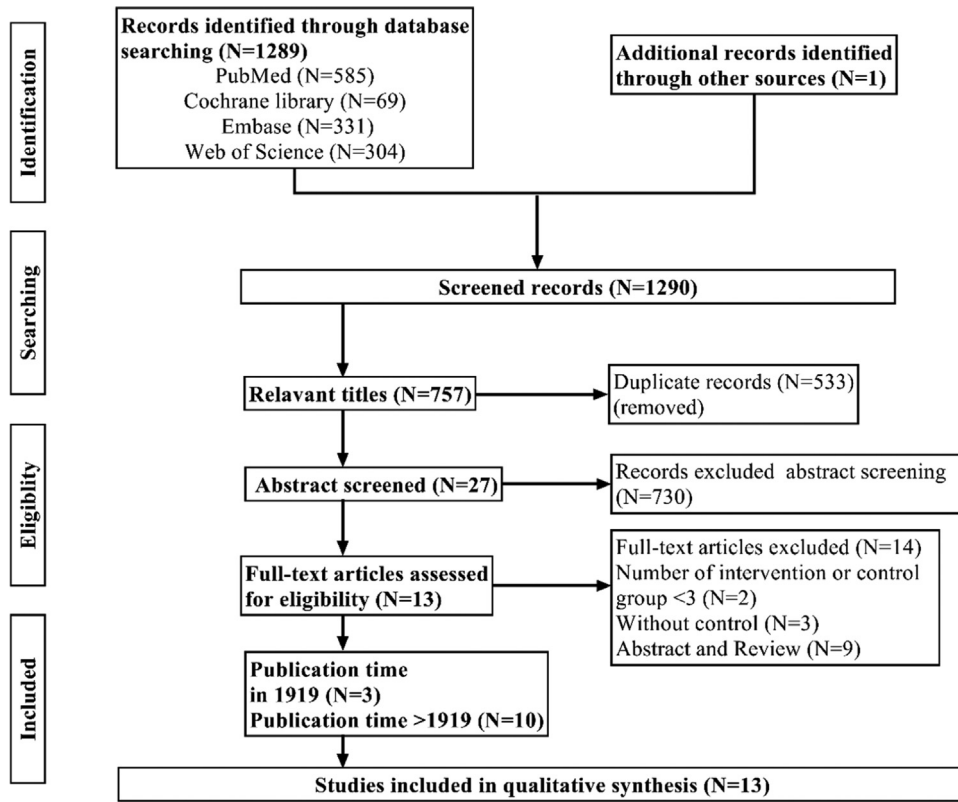


Fig. 1. PRISMA diagram of study flow.

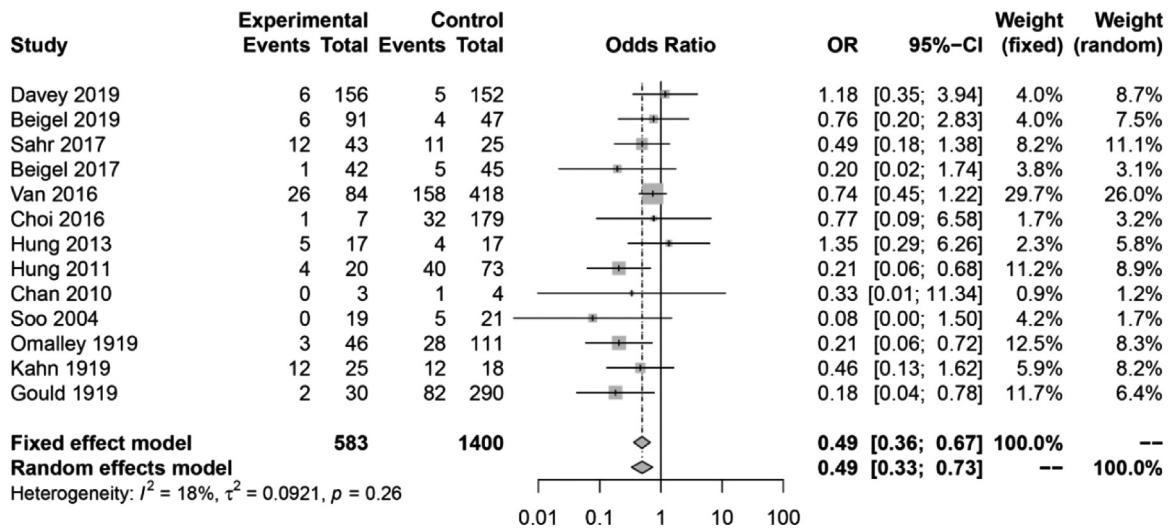


Fig. 2. Forest plot of convalescent plasma therapy vs. control for reducing mortality.

4.6. Adverse effects

Four clinical trials studies [18,23,24,31] had evaluated the serious adverse effects (grade 3 and 4 adverse events) after receiving convalescent plasma therapy and reported an incidence of 0%–35% in treatment group compared with 0%–39% in the control group. Pooled estimates showed no significant difference between two groups (OR: 0.75, 0.50–1.13, $I^2 = 41\%$) (Table S3, Fig. 4). In Table S4, we described the specific adverse events in the treatment group and the control group in four articles, including ARDS, allergic transfusion reactions, respiratory distress, and nervous system disorders,

gastrointestinal disorders, metabolism and nutrition disorders. We found that there was no difference in most adverse events between the two groups except for increased temperature (5% vs. 0, $P < 0.01$) and skin rash (4% vs. 0, $P < 0.01$) between the two groups.

4.7. Publication bias

A funnel plot was generated to evaluate the possibility of publication bias. The results showed generally symmetrical distributions for mortality (Fig. 5), mechanical ventilation rate (Fig. S5A), length of stay in ICU (Fig. S5B), ECMO rate (Fig. S5C).

Table 2
Subgroup analysis of mortality.

Subgroup analyses	Model	Study number	OR (95% CI)	P-value	I ² , P-value
Study design	Prospective	7	0.63 (0.44–0.90)	0.01	16%, 0.31
	Fixed				
	Random	6	0.25 (0.13–0.5)	<0.001	
	Retrospective				
Fixed	3	0.27 (0.13–0.57)	<0.001		
Random					
Publication year	After 2004	10	0.60 (0.42–0.84)	0.003	3%, 0.41
	Fixed				
	Random	3	0.62 (0.43–0.90)	0.01	
	Before 2004				
Fixed	2	0.69 (0.26–1.86)	0.47		
Random					
Disease type	Influenza A	7	0.33 (0.20–0.55)	<0.001	12%, 0.34
	Fixed				
	Random	2	0.37 (0.21–0.66)	<0.001	
	Fixed				
	Random	2	0.61 (0.11–3.37)	0.57	
	Influenza A and B				
Fixed	2	0.68 (0.44–1.08)	0.1		
Random					
Fixed	2	0.28 (0.05–1.47)	0.13		
Random					
Fixed	2	0.68 (0.43–1.07)	0.09		
Random					
Fixed	2	0.28 (0.05–1.47)	0.13		
Random					
Fixed	2	0.3 (0.3–2.91)	0.3		
Random					

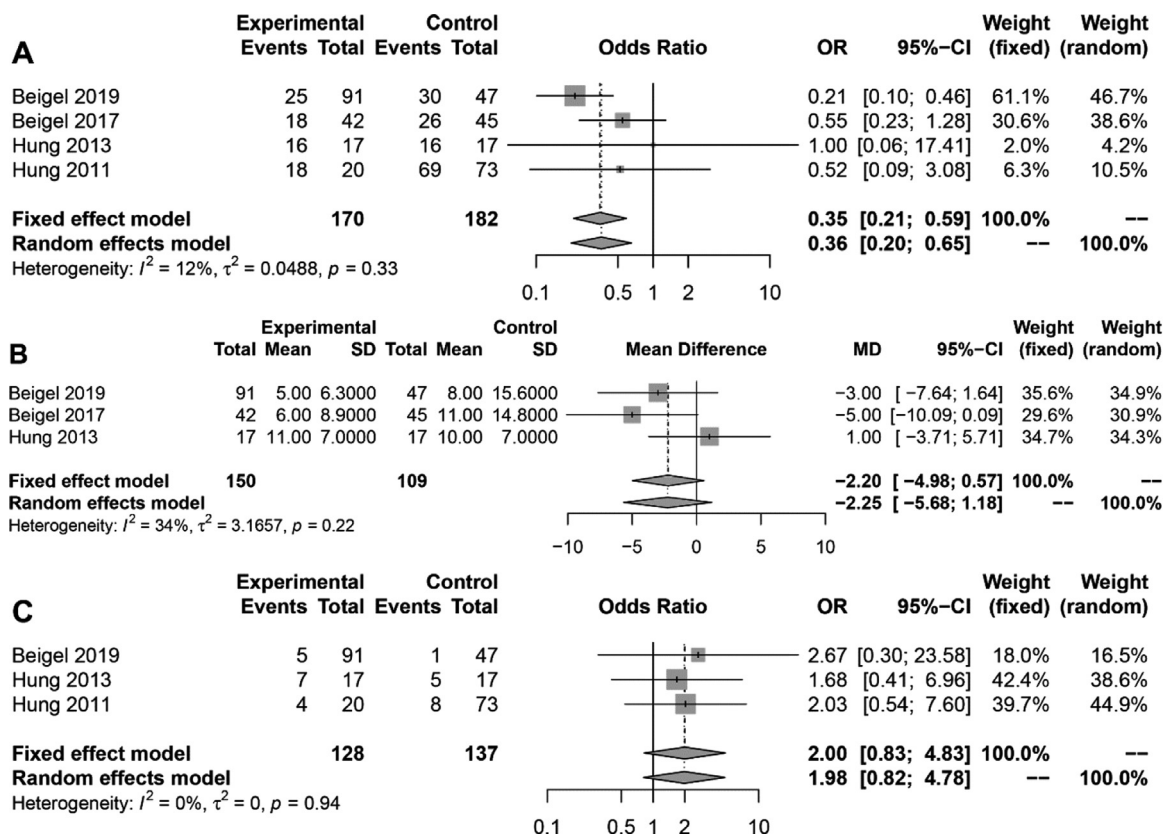


Fig. 3. Forest plot of convalescent plasma therapy vs. no plasma therapy for reducing mechanical ventilation rate (A), length of stay in intensive care unit (ICU) (B), and extracorporeal membrane oxygenation (ECMO) rate (C).

5. Discussion

To our knowledge, this meta-analysis is the most comprehensive one analyzing all available data of convalescent plasma in the treatment of a severe acute virus-induced respiratory disease. We

found that convalescent plasma therapy significantly reduced the mortality and mechanical ventilation requirements, without serious adverse effects. This treatment also seemed to decrease the viral load. However, it did not reduce the length of ICU stay and ECMO use.

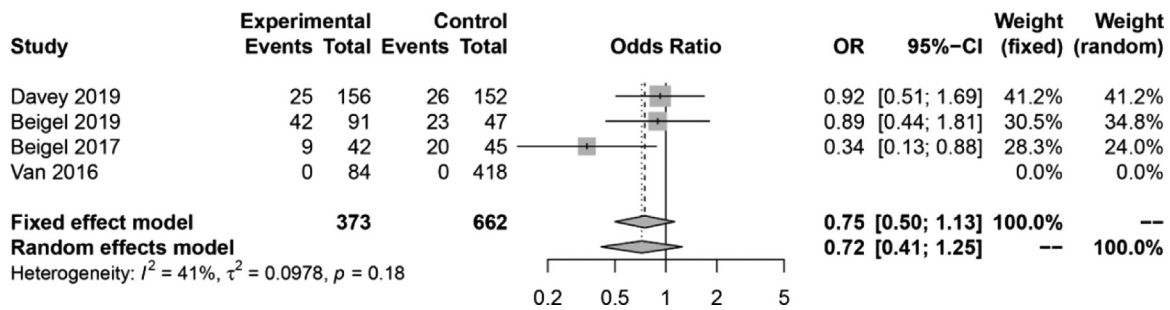


Fig. 4. Forest plot of convalescent plasma therapy vs. no plasma therapy for serious adverse effects.

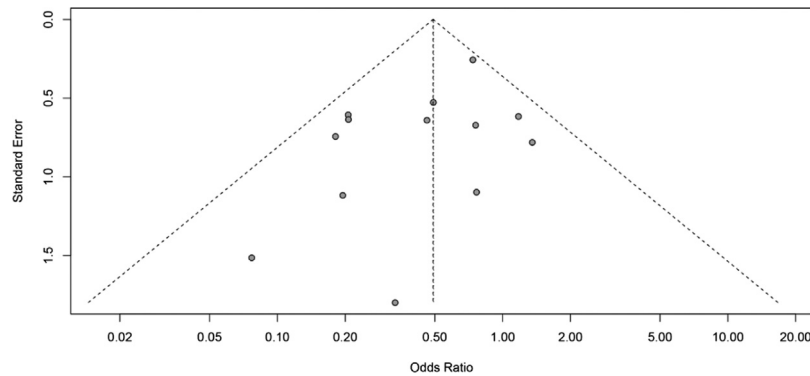


Fig. 5. Funnel plot of mortality.

Over last 100 years, convalescent plasma therapy has been considered in treating patients with severe infectious diseases when no specific anti-pathogen treatment is available. In the setting of a rapidly spreading epidemic, the number of cured and survivors will increase as well, that the hyper-immunologic plasma is a growing resource for specific passive immunity against a particular pathogen. This treatment has been used in Spanish influenza pneumonia in 1918 [29,30], Ebola [13], MERS-COV [14], and pandemic 2009 influenza A H1N1 [15]. Even presently, as no specific anti-viral treatment is developed, the use of immune plasma has been recommended as a primary therapy for severe respiratory infectious diseases of these viral etiology as well [32]. Thus, it is reasonable to utilize convalescent plasma in the treatment of severe cases when we are facing the same dilemma in deal with COVID-19 infection.

The benefit of convalescent plasma transfusion is largely dependent on the virus-specific neutralizing antibody. Administration of convalescent plasma or hIVIG immediately increase the titer of antibody and persist to 7 days [24,31]. As viral load of H1N1 is associated with the mortality [26] and that of Ebola plays an important part in patient recovery [33], suggesting a reduction of the viral load may lead to improved survival and enhanced recovery. Previous studies have indicated the faster and greater decrease of H1N1 load in 5–7 days since the administration of convalescent plasma [15]. Sahr et al. also reported a more observable reduction of viral load after the first 24 h of treatment with convalescent whole blood in Ebola infected patients [17]. All the rest of included studies did not report the viral load change. Of note, Hung et al. reported convalescent plasma, which significantly reduced the viral load was associated with reduced mortality [15]. In addition, one study found hIVIG treatment within 5 days of symptom onset was associated with significantly better survival than ordinary immunoglobulin treatment [26], suggesting early administration of convalescent plasma therapy may be better.

Marked increases in cytokine and chemokine levels in H1N1 induced severe cases are often associated with multiorgan dysfunction, vascular thrombosis, lymphoid atrophy, and reactive

hemophagocytosis [34]. Exuberant elevation of IP-10, MCP-3 and IL-1 α are also found in critical patients with SARS-COV-2 infection, and continuously high levels of CXCL10, CCL7 and IL-1 receptor antagonist were associated with increased viral load, loss of lung function, lung injury and a fatal outcome [35]. Hung et al. applied convalescent plasma with high-titre virus-specific antibody (1:160) in the treatment of severe H1N1 patients also found significantly decreased level of IL-6, IL-10 and TNF- α than standard care did [15], this might contribute to reduced mortality as well as mechanical ventilation requirements. However, the convalescent plasma therapy failed to reduce the length of ICU stay and ECMO use, probably due to inconsistent baseline, such as severity and co-morbidity, of included patients from different studies.

The expected benefits of a therapeutic must outweigh its potential risks to patients. Apart from the survival benefits, convalescent plasma therapy might have reduced the harmful effect of non-detected coexisting community-acquired infection in the treated patients and therefore contribute to decreasing the cytokine level and mortality. It has to be admitted that although convalescent plasma therapy has its unique effect, there is also a risk of related complications, such as transfusion-related acute lung injury (TRALI), circulatory overload, or allergic reactions associated with blood transfusion [36]. In these articles that were included in the analysis, few cases had an adverse reaction during or early after the transfusion. These reactions resolved spontaneously with treatment of the symptoms or a reduced rate of transfusion. Our pooled analysis also confirmed the safety of this treatment. In those patients with influenza B infection, the control group even had a significantly higher incidence of death and severe adverse events [24]. In addition, we need to consider the antibody-dependent enhancement (ADE) of viral entry, which results from the neutralizing antibody binding to the panicle protein of the virus, will lead to conformational changes in the panicle, and then the antibody can better entry into human cells through IgFc receptors [37–39]. Although this side effect has not been recognized, great attention should be paid to plasma therapy in the future.

Convalescent plasma therapy had a good effect on the treatment of viral infectious diseases with limited side effects. In view of this, some institutions had tried to use it to treat severe COVID-19 patients, and achieved favorable results. Shen et al. [12] and Duan et al. [40] reported clinical symptoms relief and viral load decreasing after convalescent plasma therapy in severe COVID-19 patient. Zhang et al. [41] also found decreasing of viral load and improvement of lung injury, indicating convalescent plasma is a promising treatment in treating critically ill patients with SARS-COV-2 infection. Taken together, the convalescent plasma may contribute to the clearance of the virus and improvement of symptoms. However, these were small case series without control, more well-designed studies with larger sample size is necessary to evaluate the safety and effectiveness of plasma therapy in the treatment of COVID-19.

This study has several limitations. First, some of the included studies are retrospectively designed, that selection bias is inevitable. Second, most studies are of limited patients and death events, which might undermine the statistical power. Third, patients from different studies had different causative agents, baseline characteristics and received various treatment. The overall effect is not in line with some of well-performed RCTs. Fourth, whether the beneficial effects of convalescent plasma therapy in H1N1, Ebola, MERS-COV and SRAS-COV can be extrapolated into COVID-19 remained to be tested, that more studies are needed.

6. Conclusion

Convalescent plasma therapy significantly reduced the mortality and mechanical ventilation requirements of patients with virus-induced severe acute respiratory infections, without serious adverse effects. More studies are needed to explore whether this treatment can be extrapolated into COVID-19.

Author contributions

Jun Zeng and Turun Song designed the study and wrote the manuscript. Saifu Yin performed the meta-analysis. Xinmiao Du did the data extraction and checked the results. Tao Lin designed the research strategy and revised the manuscript. All authors reviewed the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.tracli.2021.03.004>.

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