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REVIEW

Current views on the potentials of convalescent plasma therapy (CPT) as Coronavirus disease 2019 (COVID-19) treatment: A systematic review and meta-analysis based on recent studies and previous respiratory pandemics

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Summary

Convalescent plasma therapy (CPT) has been investigated as a treatment for COVID-19. This review evaluates CPT in COVID-19 and other viral respiratory diseases, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and influenza. PubMed and Google scholar databases were used to collect eligible publications until 8 December 2020. Meta-analysis used Mantel–Haenszel risk ratio (RR) with 95% confidence interval (CI) and pooled analysis for individual patient data with inverse variance weighted average. The study is registered at PROSPERO with the number of CRD4200270579. Forty-four studies with 36,716 participants were included in the pooled analysis and 20 studies in the meta-analysis. Meta-analysis showed reduction of mortality (RR 0.57, 95% CI [0.43, 0.76], $z = 3.86$ [$p < 0.001$], $I^2 = 44\%$ [$p = 0.03$]) and higher number of discharged patients (RR 2.53, 95% CI [1.72, 3.72], $z = 4.70$ [$p < 0.001$], $I^2 = 3\%$ [$p = 0.39$]) in patients receiving CPT compared to standard care alone. A possible mechanism of action is prompt reduction in viral titre. Serious transfusion-related adverse events were reported to be less than 1% of cases, suggesting the overall safety of CPT; nevertheless, the number of patients participating in the studies was still limited. It is also important to notice that in all the studies, the majority of patients were also given other medications, such as antivirals, antibiotics and corticosteroid; furthermore, randomized controlled studies involving more patients and in combination with other treatment modalities are urgently needed.

KEYWORDS
convalescent plasma therapy, COVID-19, influenza, MERS, meta-analysis, SARS

Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory disease syndrome; AST, aspartate aminotransferase; CPT, convalescent plasma therapy; IL-6, interleukin 6; LDH, lactate dehydrogenase; MERS, Middle East respiratory syndrome; MERS-CoV, MERS-coronavirus; nAb, neutralizing antibody; PaO_2/FiO_2, partial arterial oxygen pressure to fractional inspired oxygen ratio; RR, risk ratio; S/Co, Signal to cut-off ratio; SARS, severe acute respiratory syndrome; SARS-CoV, SARS-coronavirus; SARS-CoV-2, SARS-coronavirus-2; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

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1 | INTRODUCTION

Severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) infections emerged at the end of January 2020, leading World Health Organization (WHO) to declare COVID-19 as a Public Health Emergency of International Concern, and later updated the status into pandemic. Up to 2 October 2020, 216 countries were affected with 1,023,522 (4%) deaths and 25,634,071 (96%) recovered among 26,657,593 confirmed cases.[1] The disease, later known as COVID-19, is mainly characterized by myalgia, fever, cough, dyspnoea, sore throat, dizziness and confusion. Laboratory and radiological examinations often reveal decreased albumin, high C-reactive protein (CRP), lymphopenia and pneumonia.[2] These clinical symptoms are similar with the previous cases of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and influenza.[3] Further genetic findings confirmed that a significant proportion of genetic sequences in SARS-CoV (79%) and MERS–coronavirus (MERS-CoV) (50%) are identical with SARS-CoV-2.[4]

Up until now, no specific and efficient pharmacological therapy has been validated. Chloroquine, a drug commonly used to treat malaria, is suggested to be effective against SARS-CoV-2 in vitro.[5] Hydroxychloroquine, one of the chloroquine derivatives, is suggested to be more potent than chloroquine, with less toxicity[6]; however, recent systematic reviews based on 19 studies have shown antiviral treatments, including ribavirin, favipiravir, lopinavir/ritonavir, umifenovir, interferon and hydroxychloroquine, which exhibit no beneficial effects in both mild and severe COVID-19 patients when compared to control.[7] Remdesivir, a monophosphoramidate prodrug, has a broad antiviral activity against human coronaviruses, including SARS-CoV, MERS-CoV, CoV-OC43, CoV-229E and SARS-CoV-2 in vitro. Remdesivir reduces viral titre, thus improving pulmonary lesions and respiratory function in SARS-CoV MA15-infected mice and SARS-CoV-2-infected rhesus macaques.[8] Two meta-analyses showed that remdesivir is associated with better overall clinical recovery[9,10]; however, no evidence suggests any differences in terms of mortality between remdesivir versus standard care.[10,11]

Another therapeutic approach having been intensively investigated is immunotherapies. Immunotherapies, such as convalescent plasma therapy (CPT) (polyclonal antibody), monoclonal antibodies, hormone for T-cell maturation and ACE2 immunoadhesins, focus on promoting patients' immune system against viral infection.[12] In CPT, blood plasma from recovered individuals is expected to contain high titre of neutralizing antibody, thus transplanted into newly infected patients.[13,14] CPT has been used in previous outbreaks of viral infections, such as Ebola virus,[15] Lassa fever,[16] Junin virus of Argentinian haemorrhagic fever,[17] Spanish flu influenza,[18] H1N1 influenza,[19] H5N1 avian influenza,[20] SARS[21] and MERS[22] cases. Encouraging results from CPT application in other severe acute respiratory infection cases suggest the potential of this therapy in COVID-19 patients.[13]

This study aims to evaluate the potentials of CPT to COVID-19 patients by performing systematic review and meta-analysis on the published application of CPT in COVID-19, influenza, SARS and MERS patients. Since the data on CPT in COVID-19 patients are not abundant yet, the inclusion of studies in other viral respiratory diseases is important to obtain an objective overview of this treatment method, including patients' characteristics, infection states, adverse effects and outcomes.

2 | METHODS

2.1 | Literature search and identification

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[23] PubMed and Google Scholar databases were used to collect publications up to 8 December 2020. The following search term were used in searches: convalescent plasma (title) AND (influenza OR SARS OR MERS OR Coronavirus OR SARS-CoV-2 OR COVID-19).

2.2 | Inclusion and exclusion criteria

Studies are included if they have (a) reported clinical evaluations of convalescent plasma or hyper-immune plasma; (b) reported viral respiratory diseases; and (c) reported response in severe to critically ill patients.

Studies are excluded if they are (a) not fully accessible; (b) not including original data, such as reviews, systematic reviews, comments or editorial letters; (c) not written in English; (d) using monoclonal antibody therapy or manufactured immunoglobulin; (e) using vaccination to enhance immune response; (f) using other intervention other than standard care as control; and (g) performed on animals. For meta-analysis synthesis, case reports, case series or studies which were not reporting comparison standard care group were excluded.

2.3 | Data collection and analysis

Two authors (JKA and DH) independently reviewed all titles and abstracts. Abstracts fulfilling the inclusion criteria underwent full-text screening. The following information were obtained: authors, country, publication year, number of patients, diseases, type of study, patients' ages, gender, plasma dose, comorbidities and clinical outcomes. Cochrane Collaboration's tool was used for assessing risk of bias for the included randomized clinical trials (RCTs),[24] while Risk of Bias in Non-Randomized Studies (ROBINS-I) was used for non-RCTs.[25]

2.4 | Data synthesis

Baseline characteristics were compared with primary outcomes describing the efficacy and safety of CPT in patients. For pooled

analysis, the parameters considered as primary outcomes included status at 7 and 30 days after intervention and serious transfusion-related adverse effects. Status after intervention is classified into four groups: discharged, hospitalized, deceased and alive. Outcomes are defined as additional data used to assess patients' improvement after intervention, including laboratory findings, time to negative viral titre and oxygenation.

In meta-analysis, primary outcomes included mortality and discharge rates, while secondary outcomes included clinical improvement and viral nucleic acid negative rates in the treated groups (CPT-receiving patients) versus control groups (standard care alone). Mortality is defined as a cumulative number of deaths after 30-day intervention. Discharge rate is defined as the number of patients discharged from the hospital after 7 or 28 days after intervention. Clinical improvement is defined as an increase by 6 or 8 points in WHO disease severity scale,[26] and improvement of oxygenation at 14 days after intervention. Viral nucleic acid negative rate is defined as the number of patients with undetectable viral load via polymerase chain reaction (PCR) assay during 1, 2, 3 or 7 days after intervention. The above-mentioned analysis was performed for all diseases severity, time-to-transfusion, and antibody titre; furthermore, we also did meta-analysis of possible confounding factors which might affect CPT outcomes, including diseases severity and convalescent plasma antibody titre. Disease severity was classified into mild, moderate, severe and critical based on its clinical manifestations. Mild symptoms in COVID-19 patients are characterized by fever <38°C, with or without cough, no dyspnoea, no gasping, no chronic disease and no imaging findings of pneumonia. Moderate symptoms of COVID-19 are when patients developed fever, respiratory symptoms, with imaging findings of pneumonia. Severe signs of COVID-19 in patients are characterized by respiratory distress, suggested by tachypnoea of ≥30 breaths per minute in resting state, oxygen saturation of 93% or less in room air, or arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) of 300 or less. Critical symptoms of COVID-19 are characterized by respiratory failure requiring mechanical ventilation, shock or other organ failure (apart from lung), leading to the necessity of intensive care unit (ICU) monitoring.[27,28] Subgroup analysis was also performed according to the types of diseases (COVID-19, influenza, SARS and MERS).

2.5 | Statistical analysis

Meta-analysis used Mantel–Haenszel risk ratio (RR) for dichotomous data and mean difference (Mean diff) for continuous data with 95% confidence interval (CI). RevMan version 5.3 software (Cochrane Collaboration) was used for these purposes. Pooled analysis for individual patient's data was performed with inverse variance-weighted average. Heterogeneity across studies was assessed using inconsistency index ($I2$) test, with p-value <0.10 indicating a significant heterogeneity. Risk of publication bias was evaluated with Egger's statistics. Habord's and Peter's statistics was used to assess small size bias. This study is registered to PROSPERO with the number of CRD4200270579.

3 | RESULTS

The literature searches identified 3710 studies, and an additional 20 studies were found through bibliographical search (Figure 1). After removing duplicates and filtering all titles and abstracts, 169 full-text articles were reviewed, of which only 53 articles met the inclusion criteria. There were only 44 studies eventually included in the qualitative synthesis and pooled analysis, including 7 RCTs,[19,29–34] 9 non-RCTs or matched-control observational studies,[27,35–42] 15 single-arm studies[21,43–55] and 14 case reports,[20,22,30,56–66] while 8 studies reporting the use of manufactured immunoglobulin as the main intervention[67–74] and 1 study reporting the use of fresh frozen plasma control[75] were excluded. Five studies were performed on influenza cases,[19,20,29,30,56] 4 studies were of SARS,[21,35,57,58] 2 case reports were of MERS,[22,76] and 33 studies reported trials in COVID-19 cases.[27,31–34,36–55,59–66] Data from studies in SARS and MERS were grouped together, and further termed as SARS and MERS group in the text since studies in MERS only consisted of two case reports. Only RCTs, match-control observational studies or single-arm studies with subgroup analysis were included for meta-analysis. One study, Joyner et al.(2020)[49] was excluded from the meta-analysis as there was duplication of data with Joyner et al..[48] Characteristics of the included studies are presented in Table S1.

4 | CHARACTERISTICS AND OUTCOMES OF CPT RECEIVING PATIENTS IN COVID-19, INFLUENZA, SARS AND MERS CASES

4.1 | Baseline characteristics

Baseline characteristics of patients receiving CPT are shown in Table 1. The majority of patients receiving CPT in COVID-19 group were 40–70 years old. There were more male patients compared to female ones, which were especially observable in COVID-19 cases (60.23% vs. 39.63%). Major comorbidities in the studies were hypertension and respiratory system diseases among COVID-19 and influenza patients, while diabetes and cardiovascular diseases were identified among COVID-19 patients. In addition to CPT, all patients received standard treatment of antiviral therapy and corticosteroid. The commonly used antiviral in influenza cases was oseltamivir, in SARS and MERS cases was ribavirin, while in COVID-19 cases was remdesivir. Hydroxychloroquine was only used in COVID-19 patients. Antibiotics and/or antifungal treatments were also given as secondary bacterial and/or fungal infections were indicated in the cases of 42.50% of COVID-19 patients and 76.64% of SARS and MERS patients. At the time of admission, the majority of patients were identified as having severe or critical illness.

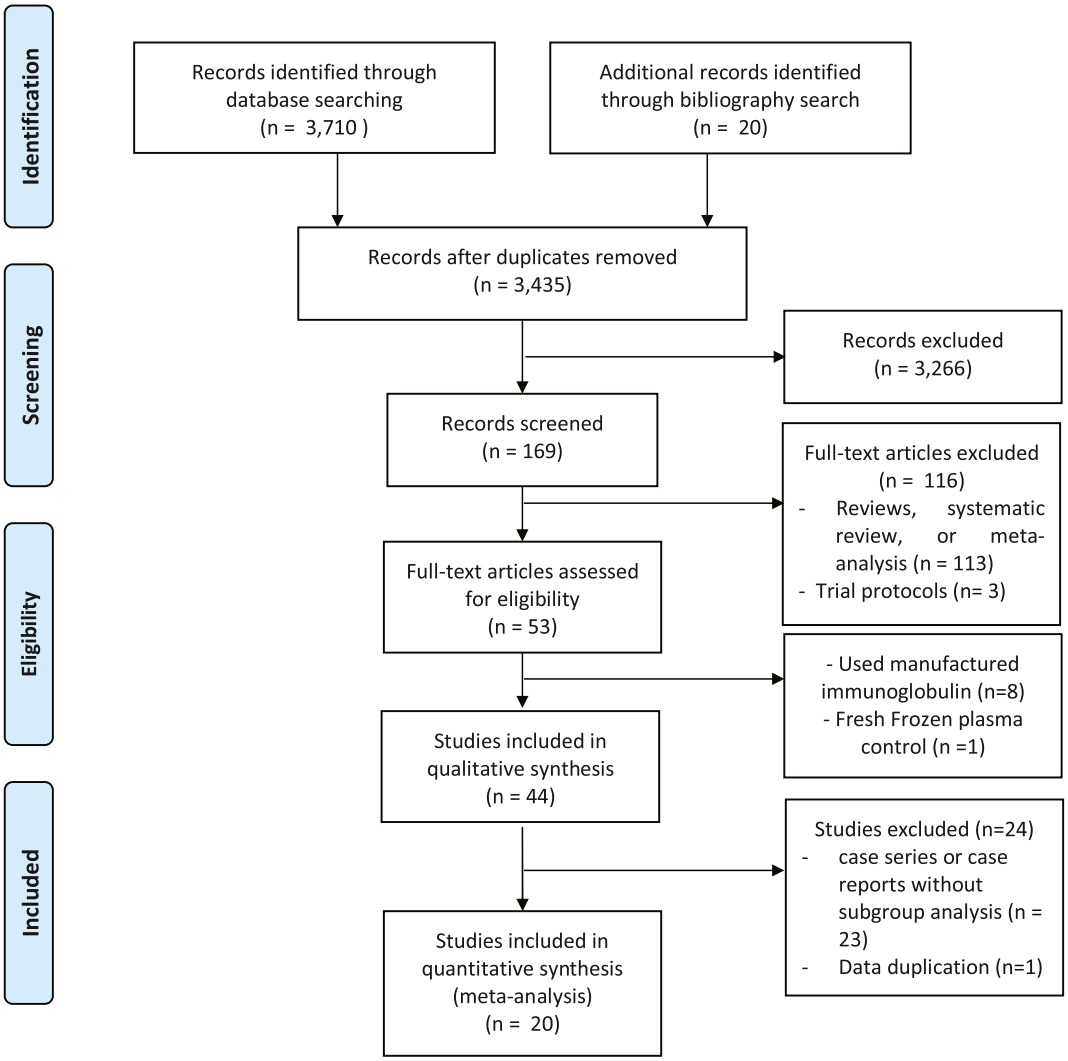

FIGURE 1 Study selection based on PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

4.2 | Primary outcomes of CPT in COVID-19, SARS and MERS and influenza patients

Mortality in COVID-19, SARS and MERS and influenza patients reached as high as 10.50% (n = 3725), 12.05% (n = 10) and 2.23% (n = 4) in 7 days after transfusion, and 24.26% (n = 8820), 0% (n = 0) and 7.69% (n = 15) in 30 days after transfusion, respectively. Serious transfusion-related adverse events are in the form of anaphylactic shock, deep vein thrombosis, sepsis, transfusion-related acute lung injury (TRALI), transfusion-related circulatory overload (TACO) and transfusion-related mortality were reported in ≤0.2% COVID-19 cases and only 1 reported in MERS cases (0.93%). Urticaria was reported in 9 (0.04%) COVID-19 and 4 (1.92%) influenza patients, while no SARS and MERS and influenza patients experienced this mild adverse effect. Febrile non-haemolytic transfusion reaction was reported in one COVID-19 case (<0.01%). Transfusion reaction symptoms of haematuria and dyspnoea were reported in two COVID-19 cases (<0.01) (Table 2).

4.3 | Secondary outcomes of CPT in COVID-19 patients

Secondary outcomes are measured as time to hospital discharge, time to negative viral titre, improvement of oxygenation and laboratory findings. None of the influenza, SARS and MERS studies included in this systematic review reported any secondary outcomes. The mean time to discharge after CPT in COVID-19 patients was 14.78 days, while the mean time to negative viral titre was 3.04 days. Oxygenation baseline indicated that patients experienced moderate level of ARDS (P/F ratio 100–200 mmHg),[77] while oxygenation improved to mild ARDS (P/F ratio 200–300 mmHg)[77] within median time of 7 days after CPT transfusion. Lymphocytopenia was identified before CPT transfusion, and the increase of lymphocyte count to normal value was observed at median time of 3 days after transfusion. Baseline levels of CRP and interleukin-6 (IL-6) as inflammatory markers were remarkably high and resolved to nearly normal levels within 7 and 14 days. Alanine aminotransferase (ALT),

TABLE 1 Baseline characteristics of CPT-treated patients admitted to the studies

Characteristics	COVID-19 (n = 36,401) (%)	SARS and MERS (n = 107) (%)	Influenza (n = 208) (%)
Age			
≤ 40	3486 (9.58)	5 (4.67)	0
40–60	12,209 (33.54)	3 (2.8)	1 (0.48)
60–70	8,984 (24.68)	0	0
≥70	10,841 (29.78)	0	0
Not stated or uncategorized	881 (2.42)	99 (99.52)	207 (99.52)
Gender			
Male	21,874 (60.23)	5 (4.67)	108 (51.92)
Female	14,395 (39.63)	3 (2.80)	100 (48.08)
Not stated	51 (0.14)	99 (2.52)	0
Comorbidities			
Diabetes	318 (0.87)	1 (0.93)	9 (4.33)
Hypertension	352 (0.97)	0	22 (10.58)
Cardiovascular diseases	102 (0.28)	0	10 (4.81)
Respiratory system diseases	86 (0.24)	0	22 (10.58)
Chronic kidney diseases	43 (0.12)	0	8 (3.85)
Immunocompromised	19 (0.05)	0	0
Obesity	79 (0.22)	0	19 (9.13)
Others[a]	87 (0.24)	0	24 (11.54)
Not stated	35,403 (97.26)	106 (99.07)	138 (66.35)
Management before CPT			
Medications			
Antibiotics/antifungal[b]	15,472 (42.50)	82 (76.64)	10 (4.81)
Antiviral therapy	10,999 (30.22)	107 (100)	166 (79.81)
Arbidol	31 (0.09)	0	0
Lopinavir-ritonavir	220 (0.60)	3 (2.80)	0
Oseltamivir	7 (0.02)	0	127 (61.06)
Ribavirin	8 (0.02)	104 (97.20)	0
Favipavir	28 (0.08)	0	0
Remdesivir	10,672 (29.32)	0	0
Unspecified/others[c]	33 (0.09)	0	39 (18.75)
Hydroxychloroquine/chloroquine	7597 (20.87)	0	0
Corticosteroid	17,933 (49.27)	102 (95.33)	0
Immunosuppresive drugs	140 (0.38)	0	9 (4.33)
Immunotherapy[d]	77 (0.21)	3 (2.80)	0
Not stated	96 (0.26)	2 (1.87)	0
Oxygenation			
Low-flow nasal cannula	89 (0.24)	0	65 (31.25)
High-flow nasal cannula	156 (0.43)	0	24 (11.54)
Mechanical ventilation	9778 (26.86)	3 (2.80)	70 (33.65)

(Continues)

TABLE 1 (Continued)

Characteristics	COVID-19 (n = 36,401) (%)	SARS and MERS (n = 107) (%)	Influenza (n = 208) (%)
Extracorporeal membrane oxygenation	14 (0.04)	1 (0.93)	10 (4.81)
No requirement on oxygen supplement	8 (0.02)	0	34 (16.35)
Not stated	26,344 (72.37)	103 (96.26)	0
Renal replacement therapy	13 (0.04)	0	0
Severity before CPT			
Mild	1 (<0.01)	0	0
Moderate	13 (0.04)	0	34 (16.35)
Severe	25,935 (71.25)	0	89 (42.79)
Critical	9889 (27.17)	8 (7.48)	82 (39.42)
Severe or critical		99 (92.52)	

Abbreviations: CPT, convalescent plasma therapy; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

[a]Other comorbidities including gastro-oesophageal reflux disease, sleep apnoea, cancer, mental disorders and other neurological diseases.

[b]Antibiotics or antifungal used were azithromycin, trazodone, moxifloxacin, cefoxatime, levofloxacin, clarithromycin, meropenem, cefoperazone sodium, linezolid, imipenem-sitastatin sodium, cefoperagone sodium, tazobactam sodium, fluconazole and caspofungin.

[c]Other antivirals used including peremivir, zanamivir and darunavir.

[d]Immunotherapy used including interferon (IFN)-alpha-2b, IFN-alpha-1b, IVIG (intravenous immunoglobulin) and monoclonal antibodies.

aspartate aminotransferase (AST) and total bilirubin levels were normal prior to and after CPT transfusion. Lactate dehydrogenase (LDH) and ferritin levels were elevated above normal range before and after transfusion; however, the levels were decreased within 7–14 days after transfusion (Table 3).

5 | META-ANALYSIS OF COVID-19, INFLUENZA, SARS AND MERS PATIENTS RECEIVING CPT COMPARED TO STANDARD CARE ALONE

Meta-analysis was performed on studies comparing patients receiving CPT with patients treated with standard care (control). Risks of bias in RCTs are presented on Table S2 and Figure S1, while the risks of bias in non-RCTs are presented on Table S3 and Figure S2.

5.1 | Meta-analysis on mortality in CPT-treated patients

Comparison of mortality was reported in 14 studies[19,29,31–36,38–42,44] with 4526 participants. CPT transfusion was associated with significantly reduced mortality in COVID-19 (RR 0.62, 95% CI [0.46, 0.82], $z = 3.31$ [$p < 0.001$], $I^2 = 44\%$ [$p = 0.05$]) and influenza (RR 0.33, 95% CI [0.15, 0.76], $z = 2.62$ [$p = 0.009$], $I^2 = 0\%$ [$p = 0.65$]), while the effect was not significant in SARS patients (RR 0.10, 95% CI [0.01, 1.70], $z = 1.59$ [$p = 0.11$]) because of small sample size. No small study effect or publication bias were detected in COVID-19 cases, while the effect cannot be estimated in influenza and SARS cases. CPT seemed to be more effective in influenza compared to COVID-19; nevertheless, there were only two studies analysed for CPT application in influenza patients. Pooled analysis was done to show overall effect of CPT regardless of the types of diseases. There was lower risk of mortality in patients receiving CPT treatment (RR 0.57, 95% CI [0.43, 0.76], $z = 3.86$ [$p < 0.001$], $I^2 = 44\%$ [$p = 0.03$]) (Figure 2). No significant publication bias or risk of small-size bias were acknowledged in the pooled analysis (p-Egger = 0.115, p-Habord = 0.158, p-Peter = 0.371) (Table S4). Subgroup analysis was also performed based on the disease's severity and antibody titre. In COVID-19 cases, CPT is suggested to be effective when applied to patients with severe COVID-19 symptoms (RR 0.61, 95% CI [0.39, 0.95], $z = 2.17$ [$p = 0.03$], $I^2 = 27\%$ [$p = 0.24$]) (Figure 3a), but had no significant effects in patients with critical symptoms when compared to control group (RR 0.72, 95% CI [0.46, 1.12], $z = 1.45$ [$p = 0.15$], $I^2 = 0\%$ [$p = 0.74$]) (Figure 3b). The insignificant results persisted even when they were treated with plasma containing high neutralizing antibody titre (>1:640). No significant publication bias or risk of small-size bias were detected in the pooled analysis (p-Egger = 0.357, p-Habord = 0.551, p-Peter = 0.694). Further analysis showed that only CPT with high antibody titre (≥1:640) reduced mortality more significantly (RR 0.42, 95% CI [0.22, 0.78], $z = 2.75$ [$p = 0.006$], $I^2 = 0\%$ [$p = 0.77$]) than to lower antibody titre (neutralizing titre ≤ 1:320) (RR 0.80, 95% CI [0.47, 1.34], $z = 0.86$ [$p = 0.39$]) in patients with severe COVID-19 symptoms (Figure 3a).

5.2 | Meta-analysis on 7- and 28-day discharge rate

The comparison of number of discharged CPT-treated patients to untreated patients was reported during 7 and 28 days after transfusion in five[27,29,31,35,36] and six studies,[29,31,32,36,38,42]

TABLE 2 Primary outcome of patients receiving CPT

Outcomes	COVID-19 (*n*, %)	SARS and MERS (*n*, %)	Influenza (*n*, %)
Status during 30 days after transfusion			
Discharged	528 (1.46)	19 (79.17)	154 (78.97)
Hospitalized	75 (0.21)	5 (20.83)	26 (13.33)
Deceased	8802 (24.26)	0	15 (7.69)
Lived, not specified	26,875 (74.08)	0	0
Total	**36,280 (100.00)**	**24 (100.00)**	**195 (100.00)**
Status during 7 days after transfusion			
Discharged	20 (0.06)	33 (39.76)	94 (51.51)
Hospitalized	43 (0.12)	40 (48.19)	81 (45.25)
Deceased	3725 (10.50)	10 (12.05)	4 (2.23)
Lived, not specified	31,679 (89.32)	0	0
Total	**35,467 (100.00)**	**83 (100.00)**	**179 (100.00)**
Transfusion-related adverse effects[a]			
Anaphylatic shock	28 (0.13)	0	0
Urticaria, mild effects	9 (0.04)	0	4 (1.92)
Deep vein thrombosis	42 (0.20)	0	0
Febrile non-haemolytic	1 (<0.01)	0	0
Haematuria	1 (<0.01)	0	0
Transfusion-associated dyspnoea	1 (<0.01)	0	0
Sepsis	3 (0.01)	0	0
TRALI[b]	23 (0.11)	1 (0.93)	0
TACO[c]	37 (0.18)	0	0
Transfusion-related mortality	16 (0.08)	0	0

Abbreviations: MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; .

[a]Transfusion-related adverse effects were reported for 21,079 Covid-19 patients, 107 SARS and MERS patients and 208 influenza patients

[b]TRALI, Transfusion related acute lung injury

[c]TACO, Transfusion-associated circulatory overload

respectively. The 7-day discharge rate was significant in COVID-19 (RR 2.32, 95% CI [1.10, 4.89], $z = 2.20$ [$p = 0.03$], $I^2 = 33\%$ [$p = 0.22$]), influenza (RR 2.62, 95% CI [1.37,5.03], $z = 2.90$ [$p = 0.004$]), and SARS (RR 3.87, 95% CI [1.54, 9.72], $z = 2.88$ [$p = 0.004$]) cases. Pooled analysis showed significantly higher discharge rate in CPT patients (RR 2.65, 95% CI [1.82, 3.87], $z = 5.05$ [$p < 0.001$], $I^2 = 3\%$ [$p = 0.39$]) (Figure 4a). No publication bias or small-study effects were detected (p-Egger = 0.577, p-Habord = 0.486, p-Peter = 0.323) (Table S4). The 28-day discharge rate was not significant in the reported COVID-19 cases (RR 1.11, 95% CI [1.00, 1.23], $z = 1.90$ [$p = 0.06$], $I^2 = 0\%$ [$p = 0.79$]), while it was reported that there was only one influenza case with significant result (RR 1.50, 95% CI [1.02, 2.22], $z = 2.04$ [$p = 0.04$]). The pooled analysis of the two groups shows higher rates of discharged patients in CPT groups during 28 days (RR 1.13, 95% CI [1.23, 1.25], $z = 2.36$ [$p = 0.02$], $I^2 = 0\%$ [$p = 0.54$]) (Figure 4b). No publication bias or small size was detected in the pooled analysis (p-Egger = 0.954, p-Habord = 0.361, p-Peter = 0.544) (Table S4). Subgroup analysis for diseases severity and antibody titre was not possible for these particular outcomes as very limited studies reported the subgroup analysis.

5.3 | 14-day clinical improvement

Clinical improvement was assessed in 14 days post-transfusion in five studies.[29,31,32,38,42] In subgroup analysis, no significant difference was found both in COVID-19 (RR 1.15, 95% CI [0.99, 1.34], $z = 1.89$ [$p = 0.06$], $I^2 = 0\%$ [$p = 0.47$]) and influenza (RR 1.61, 95% CI [0.95, 2.73], $z = 1.76$ [$p = 0.08$]) (Figure 5); however, the pooled analysis showed significant difference (RR 1.20, 95% CI [1.02, 1.42], $z = 2.19$ [$p = 0.03$], $I^2 = 8\%$ [$p = 0.36$]). No publication bias or small size was

TABLE 3 Laboratory findings of COVID-19 patients before and after receiving CPT

Outcome	*N* studies	*N* patients	Effect estimate	Heterogeneity I^2	CI lower	CI upper
Time to discharge post-transfusion (days)	14	401	14.78	98%	10.23	19.32
Time to negative viral titre (days)	10	99	3.04	70%	1.98	4.10
Oxygenation improvement (PaO_2/FiO_2)						
Before CPT transfusion	9	307	158.19	99%	86.55	229.84
After CPT transfusion	7	68	251.80	99%	173.03	330.57
Median time of improvement (days)	7	68	7 (3– 12)			
Laboratory findings						
Lymphocyte (10^9/L, normal range 1.1–3.2)						
Before CPT transfusion	11	181	0.86	89%	0.66	1.06
After CPT transfusion	6	44	1.01	77%	0.67	1.35
Median time of improvement (days)	6	44	3 (1–7)			
C-reactive protein (mg/L, normal range ≤ 8)						
Before CPT transfusion	21	586	65.92	96%	53.67	78.17
After CPT transfusion	11	129	8.23	79%	4.89	11.56
Median time of improvement (days)	11	129	7 (1–12)			
IL-6 (ng/L, normal range 0–7)						
Before CPT transfusion	8	155	45.42	84%	10.38	80.47
After CPT transfusion	6	70	7.36	76%	0.01	14.71
Median time of improvement (days)	6	70	14 (1–14)			
ALT (alanine aminotransferase) (U/L, normal range 5–50)						
Before CPT transfusion	7	268	36.21	84%	27.02	45.40
After CPT transfusion	4	167	37.04	76%	19.08	55.01
Median time of improvement (days)	4	167	14 (3–14)			
AST (aspartate aminotransferase) (U/L, normal range 10–35)						
Before CPT transfusion	5	228	31.52	94%	21.83	41.21
After CPT transfusion	4	166	30.13	85%	16.98	43.28
Median time of improvement (days)	4	166	14 (3–14)			
LDH (lactate dehydrogenase) (U/L, normal range 140–280)						
Before CPT transfusion	9	498	398.17	98%	273.12	523.22
After CPT transfusion	4	209	356.22	99%	219.48	492.96
Median time of improvement (days)	4	209	14 (1–14)			
Total bilirubin (mg/L, normal range 3–12)						
Before CPT transfusion	5	212	11.84	98%	4.73	18.94
After CPT transfusion	4	166	8.89	95%	8.39	9.40
Median time of improvement (days)	4	166	14 (3–14)			
Ferritin (mg/L, normal range 12–300)						
Before CPT transfusion	12	498	907.92	83%	717.80	1098.03
After CPT transfusion	5	101	881.68	71%	599.93	1163.43
Median time of improvement (days)	5	101	7 (1–8)			

Abbreviations: CPT, convalescent plasma therapy; CI, confidence interval.

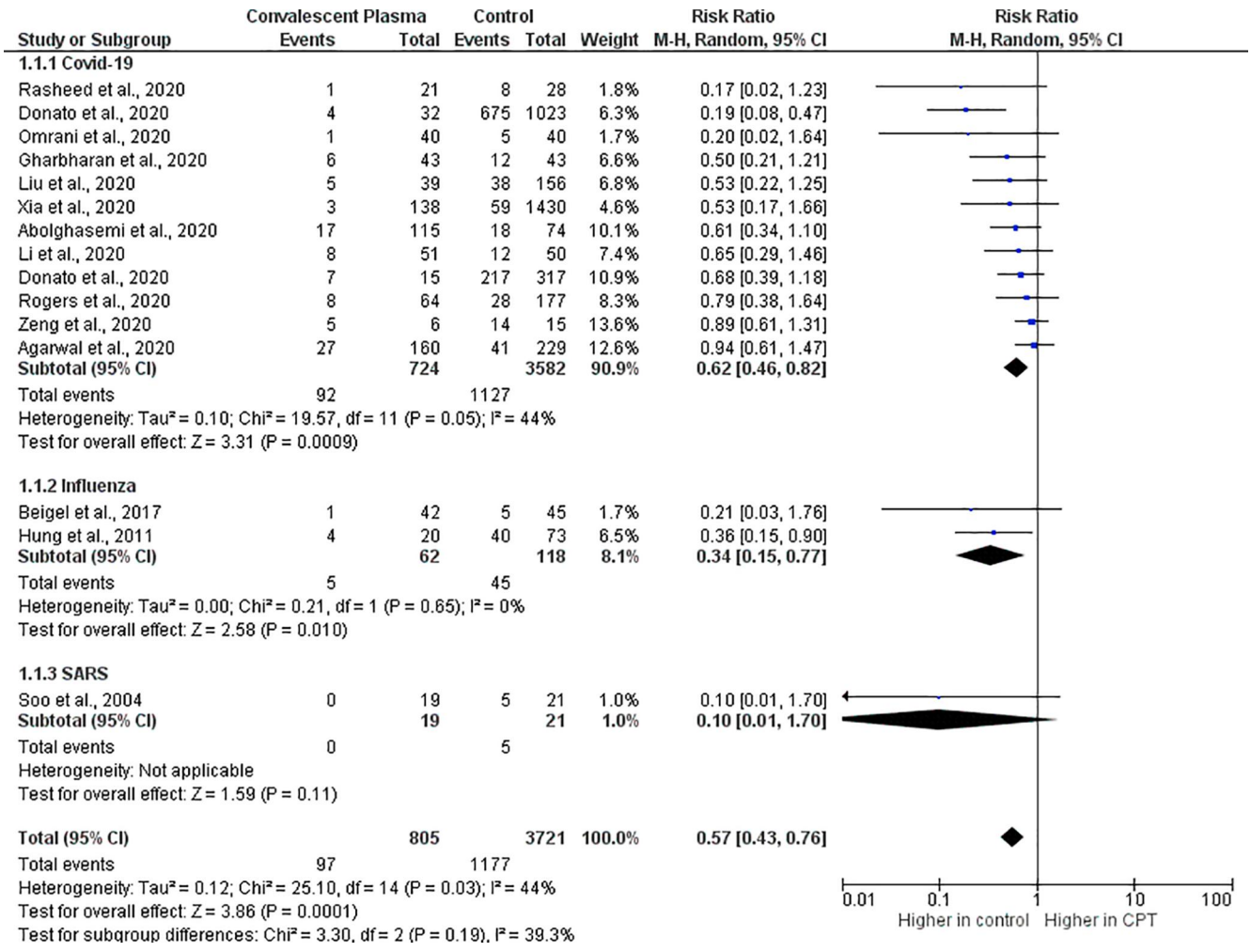

FIGURE 2 Meta-analysis of 30 days mortality in patients receiving convalescent plasma therapy compared to standard-care alone in COVID-19, influenza, and SARS cases

detected in the pooled analysis (p-Egger = 0.670, p-Habord = 0.659, p-Peter = 0.522) (Table S4). Subgroup analysis for diseases severity and antibody titre was not possible for these outcomes since only few studies reported the subgroup analysis.

5.4 | Rate to negative viral titre

The number of patients with negative viral titre was compared cumulatively within 1, 2, 3 and 7 days post-transfusion, which was reported in only three studies[29,32,34] of COVID-19 and influenza cases. The number of patients with negative viral titre was significantly higher in day 3 (RR 1.51, 95% CI [1.05, 2.18], $z = 2.22$ [$p = 0.03$], $I^2 = 74\%$ [$p = 0.02$]) and day 7 (RR 1.23, 95% CI [1.04, 1.46], $z = 2.36$ [$p = 0.02$]); however, these results were reported on very limited number of studies. Overall, more patients were found to have negative viral titre in the CPT-receiving group compared to control group (RR1.48, 95% CI [1.22, 1.81], $z = 3.91$ [$p < 0.001$], $I^2 = 57\%$ [$p = 0.02$]) (Figure 6). No publication bias or small-study effect was found (Table S4). Subgroup analysis for disease severity and antibody titre was not possible for these outcomes as subgroup analysis was reported in very few of the studies.

6 | META-ANALYSIS ON FACTORS AFFECTING CPT OUTCOMES

There were some known conditions affecting the effect of CPT effectiveness including disease severity and antibody titre. Subgroup analysis for the comparison of outcomes in critical versus severe patients could only be carried out in COVID-19 cases which were reported in five studies.[32,44,46,53,55] Mortality was significantly lower in patients with severe symptoms compared to the group of patients with critical symptoms (RR 4.62, 95% CI [2.15, 10.03], $z = 3.90$ [$p < 0.001$], $I^2 = 0\%$ [$p = 0.77$]) (Figure 7a1). The mean time of hospitalization was 11.31 days longer for critical patients (Mean diff 11.31, 95% CI [6.35, 16.26], $z = 4.47$ [$p < 0.001$], $I^2 = 59\%$ [$p = 0.06$]) (Figure 7a2). The comparison of antibody titre was reported in only three studies.[29,34,49] High antibody titre is defined as neutralizing titre of ≥1:80 by neutralizing antibody (nAb) assay[29,34] or S/Co ratio

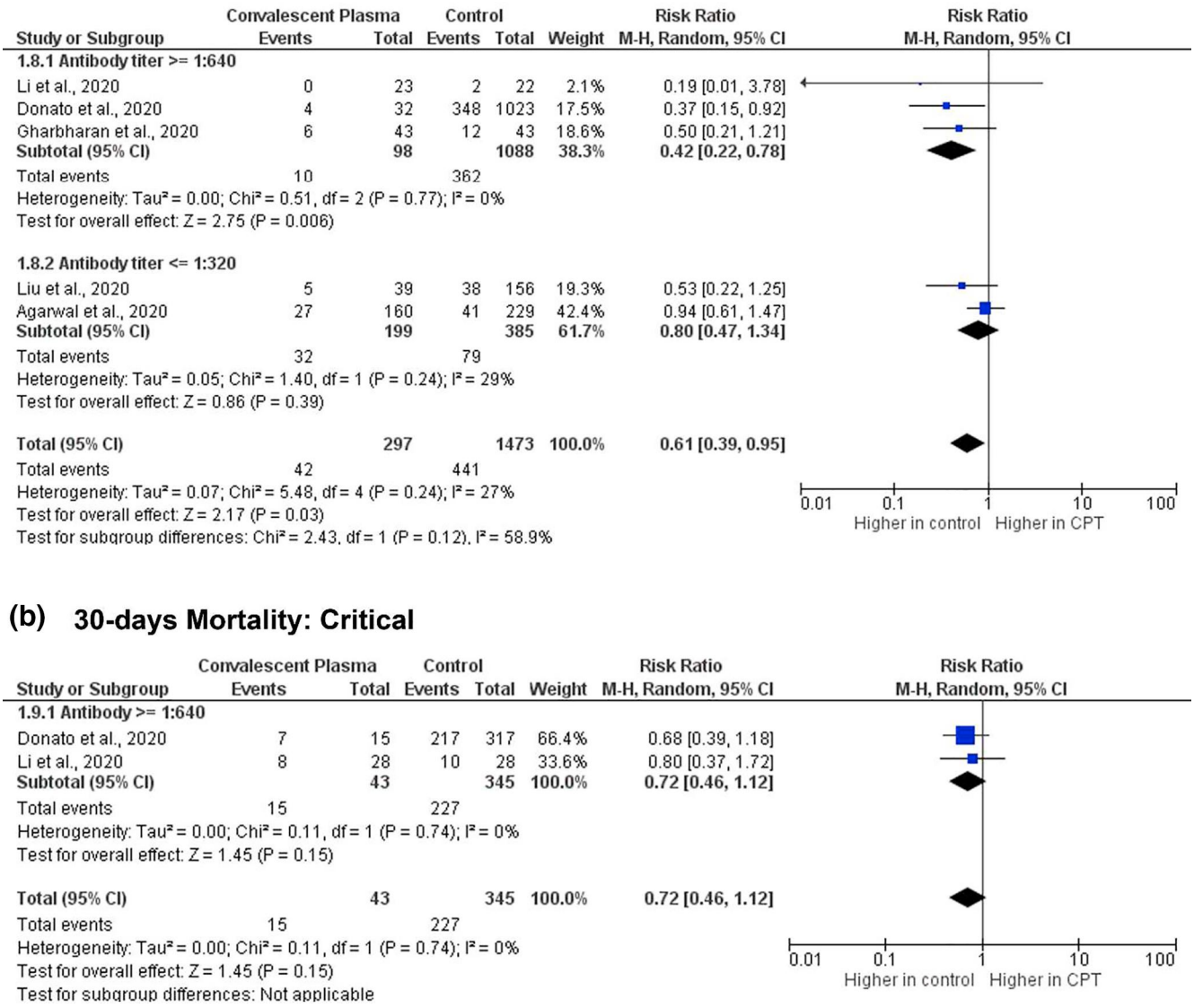

FIGURE 3 Meta-analysis of 30 days mortality in COVID-19 patients receiving convalescent plasma therapy with (a) severe condition and (b) critical condition. Subgroup analysis was also done for antibody titre: neutralizing titre ≥1:640 and neutralizing titre ≤1:320 on each disease severity

>18.45 in Ortho Clinical Diagnostic VITROS anti-SARS-CoV-2 total.[49] Low antibody titre is defined as undetectable neutralizing titre of <1:20 nAb[29,34] or S/Co ratio <4.62 in Ortho Diagnostic tools.[49] Pooled analysis showed that plasma with high antibody titre could significantly reduce mortality compared to plasma with low antibody titre (RR 0.76, 95% CI [0.63, 0.93], $z = 2.71$ [$p = 0.007$], $I^2 = 0\%$ [$p = 0.92$]) (Figure 7b).

7 | DISCUSSION

CPT has been used since the 20th century whenever new viral diseases emerge, particularly when neither vaccine nor drugs are available, but often without placebo-controlled RCTs. Conceptually, CPT consists of three major steps: (a) isolation of whole blood from the donor; (b) isolation of plasma from donor whole blood; (c) transfusion of donor plasma into the recipient. The donor in CPT is a person who has already recovered from a severe viral infection; therefore, their plasma is expected to contain rich amount of immunoglobulin reacting specifically against the virus. CPT also contains anti-inflammatory cytokines which could be useful to modulate severe immune responses against the virus.[4]

This systematic review and meta-analysis are intended to analyse all aspects of the potential of CPT as a COVID-19 treatment. Owing to the limited data in COVID-19 patients and similarities between COVID-19 and past viral respiratory diseases, we also included studies in SARS, MERS and influenza patients as a comparison.

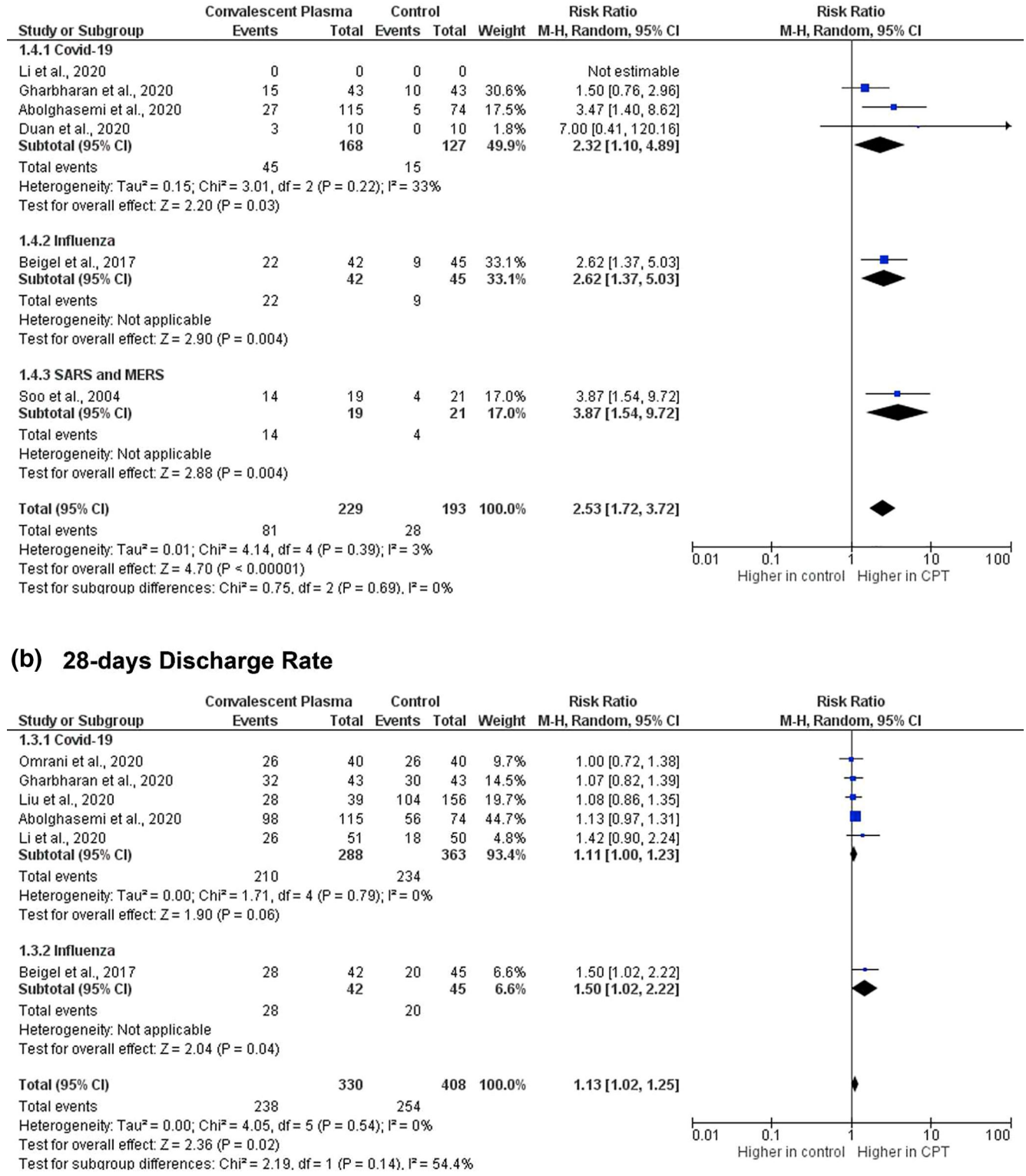

FIGURE 4 Meta-analysis of number of discharged patients after convalescent plasma therapy compared to standard care alone during (a) 7-day post-transfusion and (b) 28-day post-transfusion in COVID-19, influenza and SARS cases

This study identified hypertension, diabetes, cardiovascular disease, obesity and respiratory system diseases as major comorbidities in COVID-19 and influenza patients, while only one study reported diabetes as a comorbidity in SARS cases. These results are in line with previous findings reporting hypertension, diabetes and obesity as major comorbidities in COVID-19 patients.[78] Another

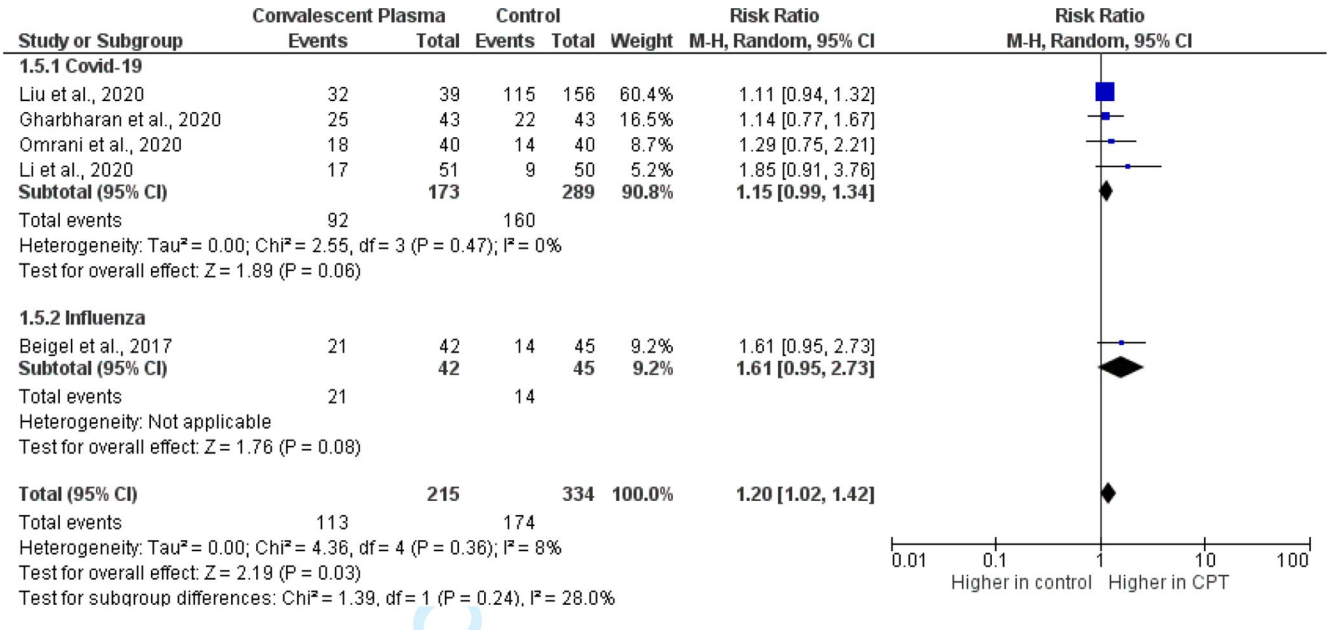

FIGURE 5 Meta-analysis of 14-day clinical improvement rate in COVID-19 and influenza patients after convalescent plasma therapy compared to standard care alone

study also acknowledged that patients with hypertension, diabetes, cardiovascular disease are at greater risk in acquiring more severe symptoms and mortality in COVID-19[79,80] and influenza[80] cases. Biologically, SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2), which is highly expressed in heart, lungs, kidney and gastrointestinal tract as an initial binding receptor for infection. Interestingly, patients with hypertension and cardiovascular diseases demonstrated elevated ACE2 expression; therefore, they could have a risk to acquire more severe symptoms of COVID-19.[81] In influenza cases, cardiovascular diseases, especially atherosclerosis, is associated with an increased risk of influenza infection since atherosclerosis plaque can function as carriers of influenza viruses for a long period of time.[82] Obesity had been known to be correlated with the COVID-19 and influenza infection as it reduced and delayed capacity to produce interferons, thereby allowing more viral RNA replication.[83] Obesity even impairs functions of the mucociliary cells, therewith reducing the clearance of the viruses.[84] Our results showed that diabetes is the second most common major comorbidity in COVID-19, but not in influenza. This might be related to the elevated circulating level of furin, a cellular protease involving in facilitating viral entry by cleaving S1 and S2 domains of SARS-CoV-2 spike protein in patients with diabetes mellitus.[85] Underlying respiratory disease is another major comorbidity aside from hypertension in influenza patients, but not in COVID-19 patients. Our results are in line with the previous study in which higher prevalence of asthma was found in patients hospitalized for influenza, but not for COVID-19.[86]

Serious transfusion-related adverse events were reported in <0.2% COVID-19 cases and MERS cases (0.93%). Urticaria and mild effects were reported in nine (0.04%) COVID-19 and four (1.92%) influenza patients, suggesting the overall safety of CPT.

The 7-day mortality rates among COVID-19 patients were similar with the rates in SARS and MERS cases; nevertheless, it was remarkably higher than mortality rates in influenza cases. Thirty-day mortality rates were reported just in COVID-19 and influenza cases. Mortality in COVID-19 cases was more than twofold higher compared to influenza cases. Our results are in line with previous reports where overall in-hospital mortality rates were higher in COVID-19 cases compared to influenza and SARS-CoV cases.[86–88]

Clinical improvements were seen in COVID-19 patients receiving CPT. Improvement of oxygenation was seen within 7-day post-transfusion. Reduced lymphocyte counts were noticed before transfusion which was significant in severe/critical patients.[89] The levels of IL-6 and CRP increased significantly in patients on admission. IL-6 is a pro-inflammatory cytokine elevated during bacterial or viral infection. It is the primary trigger for cytokine storms. CRP is induced by IL-6 in the liver whose level increases dramatically during acute inflammatory responses. A cohort study involving 140 patients showed patients with IL-6 >32.1 pg/ml or CRP >41.8 mg/L were more likely to have severe complications.[90] Ferritin levels were also elevated during admission. Ferritin is a key mediator of immune dysregulation contributing to cytokine storm which indicated the admitted patients had severe inflammatory conditions.[91] CPT transfusion was associated with resolved inflammatory conditions in 1–2 weeks mean time (Table 3). ALT, AST and total bilirubin levels were normal before and after CPT transfusion indicating that the majority of the patients did not experience kidney function impairment.[92] LDH level was elevated indicating that most of the patients were in severe to critical conditions.[93]

The meta-analyses showed that the differences in mortality between COVID-19 patients who did and did not receive CPT were significant (Figure 2). The same finding was also identified in influenza

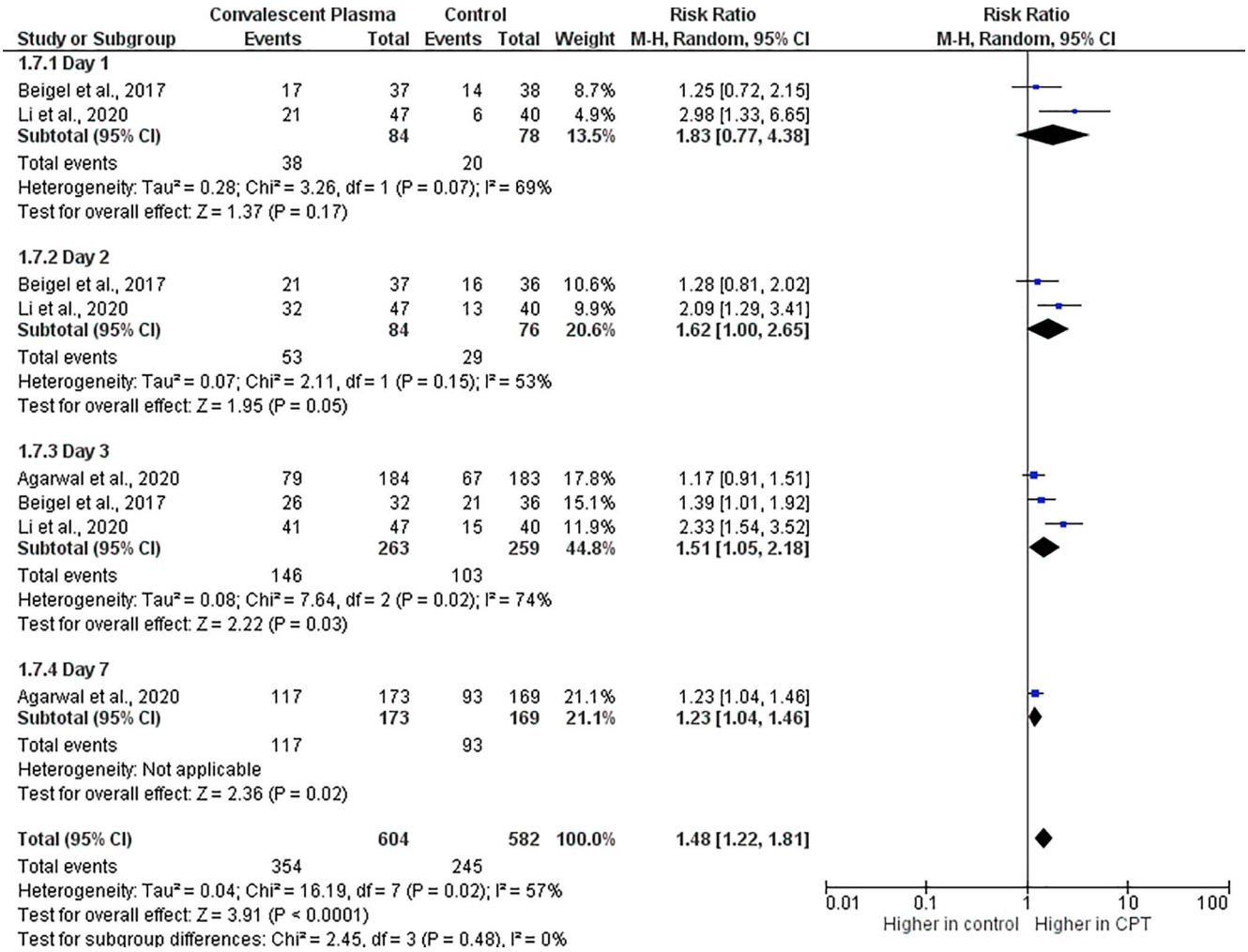

FIGURE 6 Meta-analysis of number of COVID-19 and influenza patients with negative viral titre during 1, 2, 3 and 7 days after transfusion

cases, thus the pooled analysis of COVID-19, influenza and SARS concluded that CPT transfusion leads to lower risks of mortality in patients.

Meta-analysis of studies on rates of hospital discharge among patients in three different groups showed that there were significantly higher numbers of discharged influenza, SARS and MERS, and COVID-19 patients after receiving CPT compared to patients who did not receive CPT in 7-day period. The pooled analysis concluded higher rates of discharged patients in CPT groups; however, after following up for 28 days, the effect was not significant. The follow-up in day 14 showed no significant improvement between patients receiving CPT compared to standard care alone. Pooled analysis showed significant differences both in 28-day discharge and 14-day improvement rates. We speculate that this might be due to high heterogeneity of the data and few reported cases. The source of heterogeneity is the severity of the diseases, which patients in critically end-stage infection possessed higher risk of mortality (Figure 7a1); moreover, technical considerations, such as antibody titre in the plasma, might also have affected the outcomes (Figure 7b). Another possibility was patient-specific responses which resulted in poor or good outcomes.[54] Our subgroup analysis based on diseases severity showed that CPT gave significant effect when transfused during early stage of the disease (severe stage) compared to standard care alone (Figure 3a), but not in critical stage of the disease (Figure 3b). Higher antibody titre >1:640 was also preferable compared to lower antibody titre to give significant effects (Figure 3a).

One of the possible mechanisms in CPT application is the direct inactivation of virus, thus one would expect a decrease of viral titre in patients after CPT. Unfortunately, of all the studies reviewed systematically, the decrease of viral titre was reported in just three studies, two in COVID-19 and one in influenza. The negative viral titres in CPT groups were acquired more rapidly.

Although recent trials reported no significant cumulative clinical improvement in COVID-19 patients receiving CPT,[29,31,32,36,38,42] the number of patients who participated in the study was still very limited. It is also important to notice that in all the studies, the majority of patients were also given other medications, such as

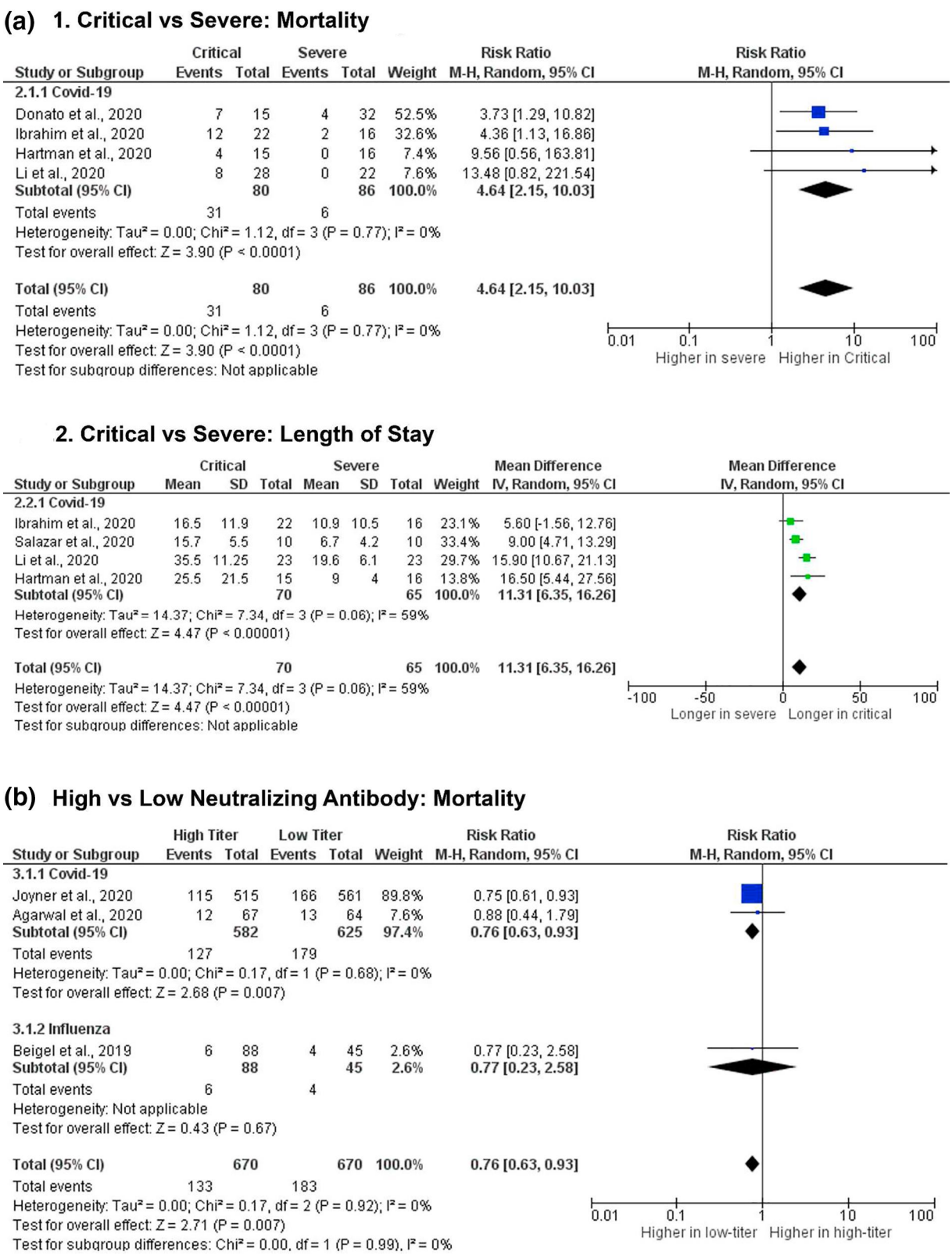

FIGURE 7 Meta-analysis of factors affecting convalescent plasma therapy outcomes as indicated with mortality rate and length of hospital stay. Only COVID-19 cases can be subgroup analysed for disease severity: severe versus critical. The outcome assessed here were comparison of (a1) mortality rate and (a2) length of hospital stays, while analysis of mortality for comparison of antibody titre was carried out for COVID-19 and influenza cases (b)

antivirals, antibiotics, corticosteroid and immunomodulatory or immunosuppressive agents; therefore, it remains plausible to assess the possibilities to use CPT in combination with other medications for patients with viral respiratory diseases, such as COVID-19.

8 | CONCLUSION

Based on the results from meta-analyses, it is safe to conclude that CPT is a potential therapy to accelerate the decrease of viral titres, thus expecting to increase the rates of hospital discharge and decrease the rates of mortality. Since CPT is used as a part of multimodality treatment for COVID-19 patients, development of other drugs included in the treatment will also affect the post-CPT outcomes.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available in the supplementary material of this article.

ETHICAL APPROVAL

Not required.

AUTHORS CONTRIBUTION

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