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Meta-analysis

Convalescent plasma a tool to treat or a reason to retreat in COVID-19 infection: a systematic review and meta-analysis

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ABSTRACT

For management of Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, different therapeutic approaches are being given for mitigating symptoms that reduce hospital and intensive care unit (ICU) stay and decreasing the mortality. Convalescent plasma therapy is among one of the therapeutic approaches and to determine its effect on COVID-19, we aggregated patient outcome data from 8 randomized clinical trials (RCT). Studies published between 01 January 2020 to 28 February 2021 were identified via a thorough systematic search of PubMed, Embase, Medline and preprint platforms MedRxiv databases and data was analysed for its efficacy. Random-effects analyses of RCT demonstrated that COVID-19 patients who received convalescent plasma therapy along with standard of care showed a similar mortality rate when compared to patients receiving only standard of care treatments. Additional data showed that these data doesn't provide evidence favoring the efficacy of human convalescent plasma as a therapeutic agent in hospitalized COVID-19 patients.

Keywords: Convalescent plasma, COVID-19, Randomized control trials, SARS-CoV-2, Standard of care, Mortality, Efficacy

INTRODUCTION

COVID-19 is corona virus disease named after a novel virus discovered in 2019 also known as severe acute respiratory syndrome corona virus 2 (SARS CoV-2).

Till date there is no definitive treatment of this infection, although vaccine has been developed which has only preventive role. Around 81% of infected people have asymptomatic to mild course of disease and 15% of people have severe disease and around 5% of them require invasive ventilation.[1]

COVID associated mortality is around 2-3%.[2] Those experiencing mild to moderate course of disease usually require supportive treatment at home without any need of hospital care, but those with severe disease require hospitalization and intensive care. Since there is no proven treatment is available attempts have been made to treat these patients with supportive therapy and off-label use of already known drugs like antivirals, antimalarial drugs and immunomodulatory drugs.[3]

Another treatment modality which brought hope was use of convalescent plasma (CP).[4]

It was thought that antibodies present in plasma of patients recovered from COVID-19 will bind to SARS-CoV-2 and thus will block its access to cells. CP was used successfully in past for treatment of other viral diseases.[5]

Initial encouraging reports regarding effective passive immunization in COVID-19 came from China and after that various author in their case series and case reports reported efficacy of convalescent plasma to treat severe COVID-19 infections, also meta-analysis conducted based on these studies showed curative role of CP treatment, but all these studies included in this meta-analysis were of low quality and had moderate to high risk of bias.[6-11]

Meta-analysis of randomized control trial (RCT) done in confirmed COVID-19 patients only, which has high level of evidence is still limited in literature to best of our knowledge. Thus, we planned to do meta-analysis of all the available RCT testing efficacy of CP therapy over control group and systematically analyze the current evidence on efficacy and safety of CP therapy in COVID-19 patients to prevent and control this pandemic. This study was done in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA-P) guidelines.

Study rationale

To date, no therapeutics has yet been proven effective for the treatment of the critical illness in COVID-19 except for supportive care, including treatment with antiviral drugs, corticosteroids, immunoglobulins, and noninvasive or invasive mechanical ventilation. The efficacy of CP in critically ill patients with SARS CoV-2 infection remains unclear and data is scarce regarding the same.

METHODS

Search strategy and eligibility

A through online systematic search was conducted using major electronic databases (PubMed, Medline and Embase), Cochrane central registrar of controlled trials and preprint platforms MedRxiv from 01 January 2020 to 28 February 2021, independently by two researchers. Key words used for search included COVID-19 or SARS-CoV-2 and plasma or convalescent plasma.

The search was limited to human studies with no language restriction. RCTs were searched for data search and extraction. The references of all eligible articles were then searched to identify other potentially eligible articles. Those RCTs studies were eligible, if having: confirmed diagnosis of COVID-19, patients randomly distributed to receive CP and other group given only standard of care.

Inclusion and exclusion criteria

We included RCT for confirmed COVID-19 patients. Our primary outcome of interest was mortality, and secondary outcomes were need of invasive mechanical ventilation and 30-day patient discharge. We excluded cohort studies, case-control studies, cross-sectional studies, case reports, case series, press releases and studies without retrievable full text.

Study selection

Two reviewers (RK and VK) independently screened the titles and abstracts of all studies to determine eligibility of the studies. Potentially eligible studies then had their full text reviewed (RK and VK) to determine if they met the criteria for inclusion in the review. Disagreement when faced was resolved by mutual consensus and opinion of third and fourth reviewer (VKK and MP).

Data extraction

Three reviewers (RK, VK and VKK) extracted the data independently from all included studies using data extraction sheet. The extracted information contained details of the intervention and control groups, mortality, ventilator support requirements, 30-day discharge data.

Risk of bias assessment

Two reviewers (MKG and VKK) independently assessed the risk of bias for data of each included study using the Cochrane risk of bias criteria.

The RK and MP were consulted for resolving any difference of opinion. The RoB 2.0 tool was used for RCTs, which includes five domains: ‘randomization process’, ‘deviations from intended interventions’, ‘missing outcome data’, ‘measurement of the outcome’, and ‘selection of the reported result’.[12] The risk of bias assessments for RCT informed our certainty of evidence assessment.

Data synthesis

For RCTs we recorded events in those receiving or not receiving convalescent plasma therapy to calculate odds ratios with 95% confidence intervals. After extraction, relevant data was entered into Microsoft word and excel sheet whichever relevant. Simple random-effects meta-regression analyses evaluated the variables i.e. mortality, proportion of patients receiving mechanical ventilation, 30-day discharge data for all clinical studies. The I^2 statistic was used to quantify heterogeneity. All analyses were performed with comprehensive meta-analysis software. Tests were two-tailed and alpha was 0.05.

RESULTS

Search results

A total of 471 records were identified in all the searched databases from 01 January 2020 to 28 February 2021.

There were 5 RCTs published in peer-reviewed journals and 5 RCTs published as preprints were included.[13-22]

So, a total of 10 RCTs which met the eligibility criteria were included in the metanalysis. Of the 10 included RCTs, 3 were conducted in India, 2 in Argentina, and 1 each in Bahrain, China, the Netherlands, Iraq and Spain (Table 1). Four RCTs were terminated early; 1 was terminated early due to futility (CP as therapy for COVID-19 severe SARS-CoV-2 disease and 3 trials were terminated early due to slow recruitment.[16,17,19,21]

There were 2 double-blind RCTs whereas the other 8 were open-label RCTs (Table 1).[15,16]

From the 5 RCTs published in peer-reviewed journals, there were 1049 patients (616 randomized to convalescent plasma and 393 to only standard of care). From the 5 RCTs published as preprints, there were 276 patients (155 randomized to convalescent plasma and 161 to standard of care).

All studies included patients with confirmed COVID-19, most of the studies included hospitalized patients with severe or life-threatening COVID-19. 5 RCTs included mild- moderate ill COVID-19 positive patients. Rest 5 RCTs studies included severe to critically ill COVID-19 positive patients. Patients in the convalescent plasma group were administered a single CP transfusion in 5 of the RCTs and were administered 2 transfusions at least 24 hours apart in the other 5 RCTs. Detailed information on patient characteristics was available for 7 of the 10 RCTs (Table 2). The mean age of patients was younger than 80 years and there was greater proportion of men than women in most studies (>50% males; except for Libster et al).[16]

Common comorbidities reported were diabetes, hypertension, pulmonary, cardiac and renal failure (Table 2).

As per Cochrane risk of bias assessment (RoB 2.0) for RCT, out of 10 studies, 06 had few concerns for bias while rest 04 studies had low bias (Table 3).

Meta-analysis

Out of the total 10 studies chosen for meta-analysis, 9 studies reported data on mortality, of which 7 studies favored the administration of convalescent plasma; as the mortality rate are comparatively lesser in the CP group while one study had equivocal results and 1 study was not estimatable.[13]

Overall mortality rate was 10.75% (77/716) in group receiving convalescent plasma therapy compared to 14.04% (84/598) in standard of care group [odd's ratio: 0.74, 95% CI: 0.50, 1.14]. Results were statistically insignificant (p value 0.13) with heterogeneity of I^2: 10%. Although statistically insignificant results, still it favors to administer CP therapy, owing to some evidence of decreased mortality in CP recipients but further high-quality studies addressing the role of CP in reducing mortality in such patients would be beneficial (Figure 2).

Subgroup analysis of mortality in peer reviewed articles only showed similar results with mortality of 11.38% (70/615) in CPP group versus 13.61% (67/492) in standard of care group with overall odd's ratio of 0.95 and 95% CI of 0.46-1.98 (I^2=18%, p value=0.30) (Figure 3).

8 RCTs had data of patients requiring invasive mechanical ventilatory support; out of which 4 studies favored infusion of CP while one study gave equivalent results in both the groups.[13,15,16,18,21]

The aggregated results indicated equal chances of requirement of invasive mechanical ventilation in both CP and SOC group. Meta-analysis showed important heterogeneity in the assessment of administering CP suggesting the existence of potential moderators like viral load, and immunity status.

Data showed overall statistically insignificant difference (p value 0.25); overall in CPP group 11.27% (75/665) patients and, in group SOC 13.09% (72/550) needed invasive mechanical ventilator support [odd's ratio: 0.98, 95% CI: 0.61, 1.58] with heterogeneity of I^2: 23%. Only 2 RCTs in the study didn't favor administering CPP as the requirement of invasive ventilation was low in the SOC group in these studies while 1 study was not estimable.

Rasheed et al showed 80.95% and 57.14% patients requiring invasive ventilatory support, in CP and SOC group, respectively [odd's ratio 3.19, 95% CI: 0.85, 11.95], study by Ling et al also favored SOC group with 27.45% in CPP group and 22% patients requiring invasive ventilation (Odd's ratio 1.34, 95% CI: 0.54, 3.33) (Figure 4).

Subgroup analysis of invasive mechanical ventilator support in peer–reviewed articles only showed similar trends with 11.69% (71/607) versus 12.32% (60/487) patients requiring invasive mechanical ventilator support in CPP and SOC groups respectively; with overall odd's ratio of 1.09 and 95% CI of 0.72-1.65 (I^2=0%, p value=0.68) (Figure 5).

Only 3 studies provided data on 30-day discharge summary among two groups, out of which one study favored CPP therapy while one didn't favor CPP therapy whereas one study had equivocal results.[15,17,19]

Overall, at 30 days, 59.81% (192/321) in CP therapy and 58.08% (115/198) in SOC group were discharged at 30 days (Odd's ratio: 1.04; 95% CI: 0.61, 1.78) with heterogeneity of I^2: 44%.

Results were statistically insignificant with p value of 0.88 (Figure 6).

Table 1: Data of all RCTs.

S. no.	Studies	Country	Type of study (centre)	No. of patients	Patient condition	Dose of CPP	CPP: SOC patients	Remarks
1	Agarwal et al	India	Open label, phase II, MC, RCT	464	Moderate	2 doses of 200 ml	235 CPP: 229 soc	Mortality within 28 days of enrolment: 34 (15%) in the CPP arm and 31 (14%) in soc arm (risk ratio1.04, 0.66 to 1.63). Progression to severe disease: 17 pts from each arm (risk ratio 1.04, 0.54 to 1.98)
2	Al Qahtani et al	Bahrain	Controlled open label, RCT	40	Severe, life threatening COVID	400 ml (200 ml over 2 days)	20 patients/group	6 SOC (30%) and 4 CPP patients (20%) were ventilated (risk ratio 0.67 95% CI 0.22 –2.0, p=0.72). time to ventilation not different (p=0.52, logrank test; 177); time on ventilation did not differ (10.5 days control; 8.25 days CPP, p=0.809)
3	Bajpai et al	India	Open label, single centre, RCT	29	Severe	500 ml in 2 divided doses	CPP14: SOC 15	Median improvements in % O_2 saturation at 48-hours were 6.5 and 2 respectively [p=0.001] and at day seven were 10 and 7.5 respectively (p=0.026). We did not find significant differences in hospitalization duration between the groups (0.08)
4	Gharbharan et al	Nether-lands	Open label RCT, MC	86	Mild-moderately ill	300 ml of CPP, 2nd dose at 5 days	SCC 43: SOC 43	No statistically significant differences in mortality (OR, 0.95, CI, 0.20-4.67; p=0.95) or improvement in the day-15 disease severity (OR, 1.30; CI, 0.52-3.32; p=0.58) was observed when the study was suspended
5	Li et al	China	Open label RCT, MC	103	Critically ill	4-13 ml/kg 200 ml (IQR, 200-300)	CPP 52: SOC 51	In severe or life-threatening COVID-19 patients, in addition to standard treatment, CPP did not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial
6	Libster et al	Argentina	Double-blind, placebo-RCT	160	Mild-moderate	250 ml	CPP 80: SOC 80	Severe disease developed in 16% patients who received CPP and 31% patients who received placebo (RR 0.52; 95% CI, 0.29 to 0.94; p=0.03). No solicited adverse events were observed
7	Rasheed et al	Iraq	MC, RCT	49	Critically-ill	400 ml	CPP 21: SOC 28	Mortality in CPP much lower than SOC. 1/21 (4.8%) in CP versus 8/28 (28.5%) in SOC (p<0.05); No significant difference in % of pts on ventilators, 81% in CP versus 57% in SOC (p>0.05)
8	Ray et al	India	Single center open label phase II RCT		Severe	2 doses of 200 ml	40: CPP, 40: SOC	Mortality at 30 days, no significant diff, (hazard ratio 0.6731, 95% CI 0.3010-1.505, p value: 0.3424), duration of hospital stay since enrolment (median 17 days for SOC versus 13 days for CPP arm, p value 0.098) or duration of hospital stay since admission (median 23 days for SOC versus 17 days for CPP arm, p value: 0.0797)
9	Solà et al	Spain	MC, RCT	81	Moderate	One dose (250-300 ml)	38: CPP, 43: SOC	Mortality was 0% versus 9.3% CPP and SOC, respectively. No significant difference was found in secondary endpoints. CPP could be superior to SOC in avoiding mechanical ventilation or death
10	Simonov-ich et al	Argentina	Double blind placebo-	233	Moderate	500 ml	CPP: 228, SOC: 105	Median time from intervention (IQR) - days to hospital discharge CPP:13 (8-30) SOC: 12 (7- ND); clinical status at 30 days- no. of

Continued.

S. no.	Studies	Country	Type of study (centre)	No. of patients	Patient condition	Dose of CPP	CPP: SOC patients	Remarks
			controlled MC, RCT					patients (%) discharged with full return to baseline physical function CPP: 141 (61.8) SOC: 72 (68.6)

MC: multicentred, CPP: convalscent plasma, Pt: patient, SOC: standard of care, RCT: randomized controlled trial, RR: risk ratio, OR: odds ratio, CI: confidence interval

Table 2: Demographic data of RCTs.

Data	CPP therapy										Standard of care therapy									
	Ghar-baran n=43	Agrw-al n=235	Ling n=52	Al-Khtni n=20	Simo-novic-h n=228	Rash-eed n=21	Ray n=40	Sola n=38	Bajp-ai n=14	Li-bster n=80	Gha-rbar-an n=43	Ag-rw-al n= 229	Ling n=5	Al-Khtni n=20	Simo-novic-h n=105	Ras-heed n=28	Ray n=40	Sola n= 43	Bajp-ai n= 15	Libst-er n=80
Median (IQ) age (years)	61 (56-70)	52 (42-60)	70 (62-80)	52.6	62.5 (53-72.5)	Mean 55.6± 17.8	-	-	48.1± 9.1	76.4± 8.7	63 (55-77)	52 (41-60)	69 (63-76)	50.7	62 (49-71)	Mean 47.8± 15.3	-	-	48.3± 10.8	77.9± 8.4
Male sex, N (%)	29 (67)	177 (75)	27 (52)	17 (85)	161 (70.6)	-	30 (75)	-	11 (78)	26 (32)	33 (77)	177 (77)	33 (65)	15 (75)	64 (61)	-	27 (67.5)	-	11 (73)	34 (42)
N (%) Diabetes	13 (30)	113 (48)	9 (17)	7 (35)	40 (17.5)	8 (38)	-	-	-	23 (29)	8 (19)	87 (38)	12 (23.5)	9 (45)	21 (20)	9 (32.1)	-	-	-	13 (16)
HTN	11 (26)	92 (39)	29 (56)	5 (25)	111 (49)	7 (33)	-	-	-	62 (78)	11 (26)	81 (35)	27 (53)	5 (25)	48 (45.7)	10 (35.7)	-	-	-	52 (65)
Cardiac	9 (21)	15 (6)	14 (27)	2 (10)	8 (3.5)	5 (24)	-	-	-	14 (18)	11 (26)	17 (7)	12 (23.5)	2 (10)	3 (3)	5 (17.8)	-	-	-	7 (9)
Respi	12 (28)	8 (3)	-	3 (15)	11	-	-	-	-	5 (6)	11 (26)	7 (3)	-	0	7	-	-	-	-	8 (10)
CKD	1 (2)	8 (3)	2 (4)	1 (5)	10 (4.4)	-	-	-	-	1 (1)	6 (14)	9 (4)	4 (8)	1(5)	4 (3.8)	-	-	-	-	3 (4)

IQ: Interquartile, HTN: hypertension, Respi: respiratory, CKD: chronic kidney disease

Table 3: Cochrane risk of bias assessment (RoB 2.0) for randomized clinical trials.

Domain study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bas
Agarwal et al	Low	Some concerns	Low	Low	Low	Some concerns
Al Qahtani et al	Low	Low	Low	Low	Some concerns	Some concerns
Sola et al	Low	Some concerns	Low	Low	Low	Some concerns
Bajpai et al	Low	Low	Low	Low	Low	Low
Gharbhara et al	Low	Some concerns	Low	Low	Low	Some concerns
Li et al	Low	Some concerns	Low	Low	Low	Some concerns
Libster et al	Low	Low	Low	Low	Low	Low
Rasheed et al	Low	Low	Low	Low	Low	Low
Ray et al	Low	Some concerns	Low	Low	Some concerns	Some concerns
Simonovichet al	Low	Low	Low	Low	Low	Low

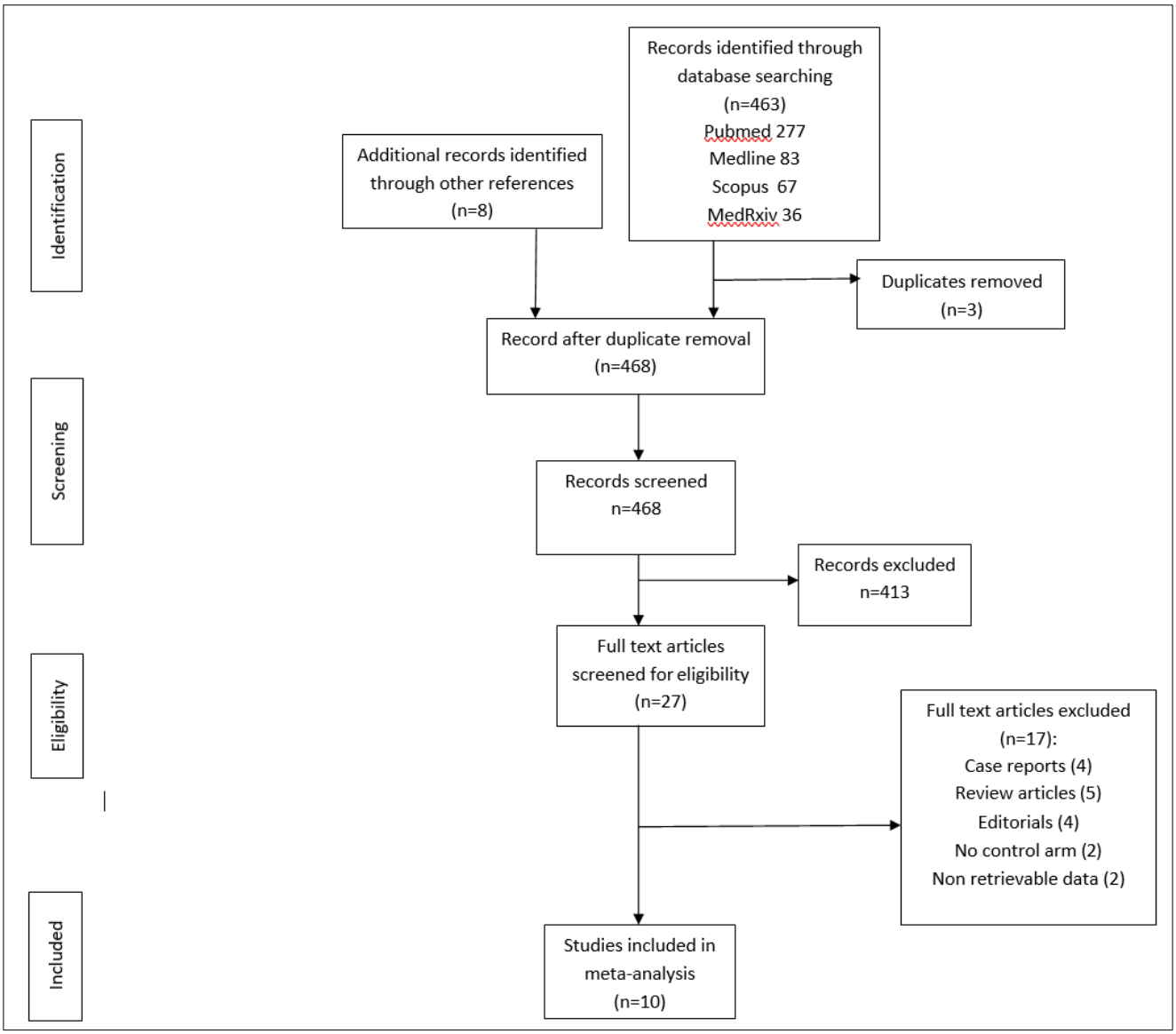

Figure 1: PRISMA flow diagram demonstrating identification and selection of eligible studies for meta-analysis.

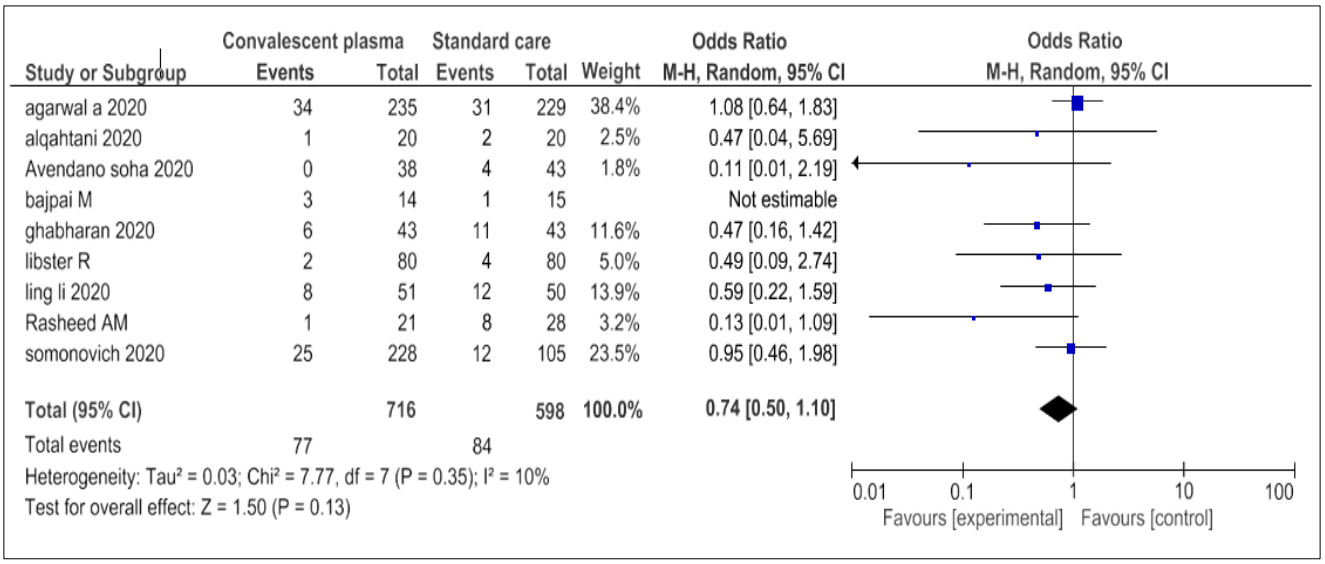

Figure 2: Overall mortality in all studies.

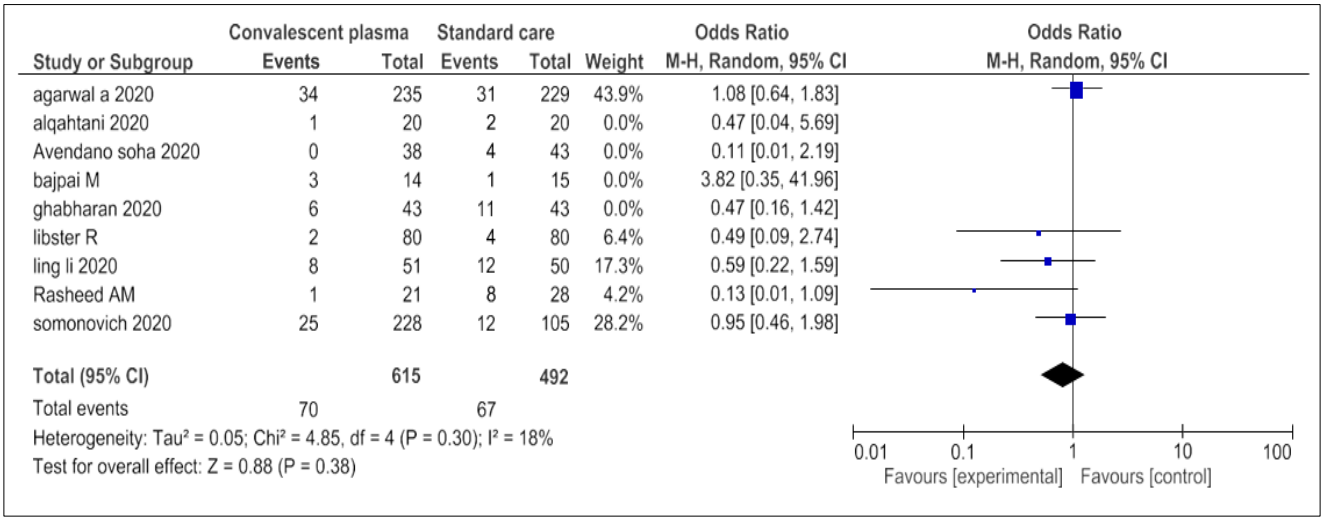

Figure 3: Mortality in peer reviewed studies.

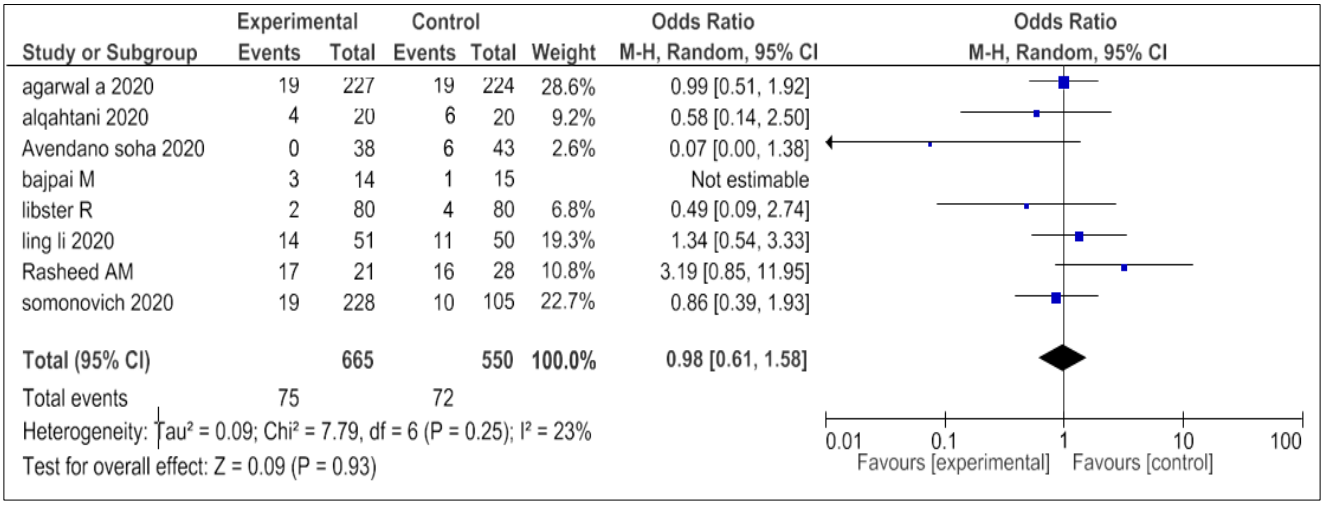

Figure 4: Overall invasive mechanical ventilator needs in all studies.

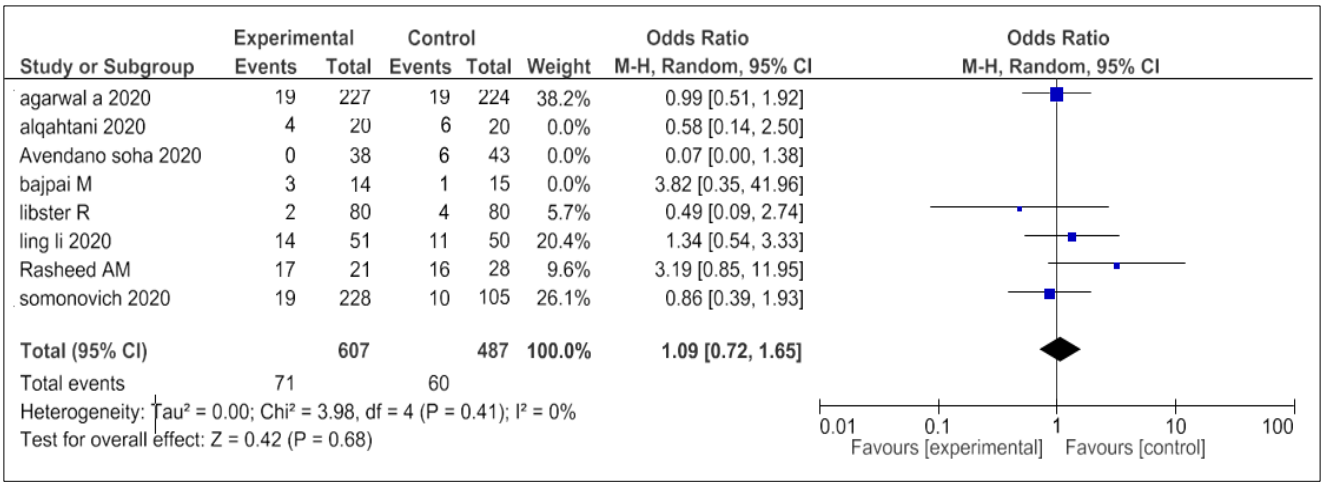

Figure 5: Subgroup analysis.

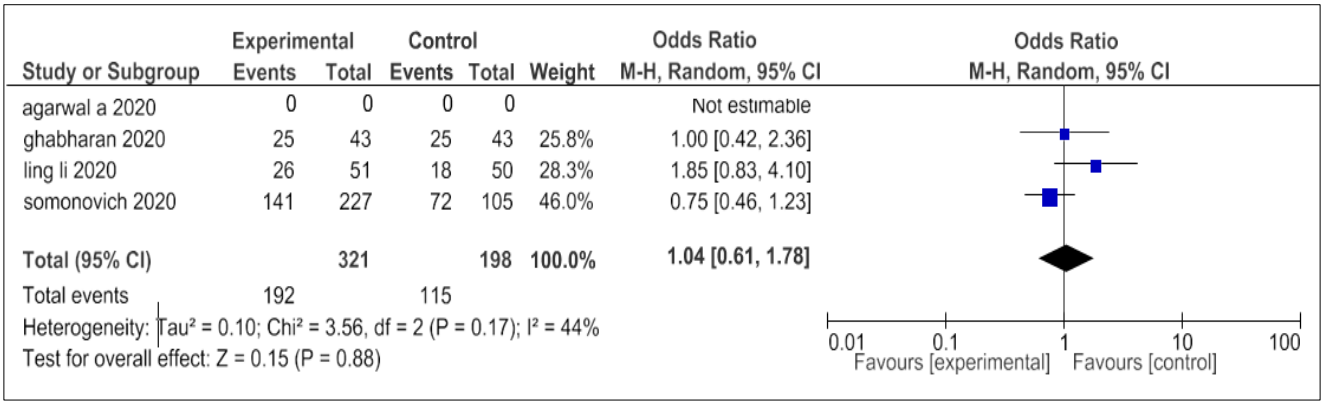

Figure 6: 30 days discharge data in various studies.

DISCUSSION

Our systematic review and meta-analysis are recent assemblage of all the randomized controlled trial comparing convalescent plasma and standard of care with or without placebo for the treatment of COVID-19.

Although most of the studies as per our review favored administration of CP, however meta-analysis revealed no edge of giving CP over SOC.

We ought to choose only randomized control trials and excluded other type of studies as RCT have higher level of evidence; we included 5 peer-reviewed RCT and 5 preprints RCT.

Sarkar et al in their systematic review and meta-analysis included 2 RCT and 5 cohort studies.[10] Their results were in contrast to ours. They assessed mortality in 5444 COVID-19 patients, as per them it was reduced to half with use of CP therapy and results being statistically significant. Clinical improvement was assessed in 259 patients in same study, and they stated that the majority of COVID-19 CP receivers showed clinical improvement although results were not statistically significant. They assessed viral clearance in 144 patients and found CP therapy helps in viral clearance with statistically significant results. However, quality of evidence for mortality and viral clearance was low and for clinical improvement it was very low.

Our results were in contrast to findings of meta-analysis done by Sun et al as per them CP is potentially effective for treating COVID-19 patients and it could reduce mortality and is a well-tolerated therapy.[11]

But their review was based on studies which were of very low quality with moderate to high risk of bias. Also, many of these studies were regarding treatment of viral diseases like Ebola, SARS, and influenza and not related to COVID-19. Although this review gave foresight for treatment of COVID-19 amid of pandemic.

Vegiviniti et al conducted meta-analysis and gave a concise review of studies done in COVID-19 patients.[23] They included 5 RCT, 1 non-RCT and 9 cohort studies. They found that mortality benefit from CP therapy is unclear as 2 key RCT's included by them did not support any mortality benefit, 8 studies supported it and 5 were inconclusive. Odds of clinical improvement was more with

CP treatment as results were statistically significant unlike our results. Length of stay was not reduced as per their analysis, and this was analogous to our results. But their study had several limitations as meta-regression was not performed due to limited number of studies and lack of patient-level data. Also, small study bias served limitation to their study.

Janiaud et al included 4 peer-reviewed RCT's, 5 preprints and 1 press release conducted on confirmed as well as non-confirmed COVID-19 patients in contrast to our study where only RCT's conducted on confirmed COVID-19 patients was taken.[24] Their results were similar to ours as they concluded that use of CP when compared to placebo or standard of care treatment was not associated with significant decrease in mortality. As per them no association was found between CP therapy and length of hospital stay and this result was similar to ours. Also, as per them there was no benefit in other clinical outcomes and same inference was drawn from our meta-analysis.

On 15 January 2021 there was a press release from chief trial investigators of recovery trial that recruitment is closed as there was no conclusive proof of worthwhile mortality benefit, as per them there was no significant difference in 28-day mortality in between two randomized groups, receiver and non-receivers of CP therapy however patients are being followed up and final results are awaited.[25] Recovery trial was not included in our review as it doesn't fit in our inclusion criteria.

Regarding safety of convalescent plasma as per our review majority of trials reported mild manageable side effects whereas Agarwal et al reported plasma therapy related death in 3 patients (1%), however a small percentage but side effect leading to mortality cannot be ignored. As per Gharbharan et al no plasma related serious adverse events were noted. In Ling et al 2 patients reported transfusion related adverse events one mild and other severe symptoms but both recovered fully.

In Simmonvich et al study 5 patients in CPP group and none in SOC group had nonhemolytic febrile reaction. Al-Qahatni et al reported 3 patients in CPP group having adverse events that were not related to therapy (1-dairrhoea and vomiting, 1-constipation, 1-desaturated transiently after infusion). Sola et al reported 16 serious or grade 3-4 adverse events in 13 patients; 6in CPP group, 7 in SOC group with 2 CPP infusion-related adverse events (both patients recovered without sequelae). None on the remaining events were considered to be related to CP. Agarwal et al study reported minimal non-life-threatening adverse events. They related possibility of 3 deaths in their study to transfusion which was comparable to other larger report on safety of convalescent plasma use to treat COVID-19. Rasheed et al reported one mild allergic reaction related to convalescent plasma. Bajpai et al reported 1 patient in both the groups showing mild urticaria during transfusion of convalescent plasma or FFP.

CONCLUSION

Meta-analyses of RCT demonstrated that COVID-19 patients who received convalescent plasma therapy along with standard of care showed a similar mortality rate when compared to patients receiving only standard of care treatments. Requirement of invasive ventilation doesn't decrease with plasma therapy. Plasma therapy does not shorten the duration of disease in COVID-19 patients.

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