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COMMENTARY

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COVID-19 convalescent plasma therapy: hit fast, hit hard!

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COVID-19 convalescent plasma (CCP) is an investigational treatment for SARS-CoV-2 infection. Several lines of evidence, ranging from expanded access programmes (EAP) to clinical trials employing randomized controls (RCT) (summarized in Table 1) or propensity score-matched (PSM) controls (summarized in Table 2), are now indicating how CCP should be used. Such evidence is supporting the initiation of CCP treatment as early as 44-72 h after hospitalization (or anyway within 7 days from the onset of symptoms) and the use of CCP units with a high neutralizing antibody (nAb) titre. There seems to be no clinical benefit if the CCP units are administered later or with a low nAb titre.

Why you should treat fast

Timeliness of treatment can be defined in various ways: median duration of symptoms before randomization or transfusion, time between hospital admission and transfusion and time between final diagnosis and transfusion, or can be inferred from the disease stage.

The rationale for administering CCP as early as possible lies in the neutralization stoichiometry itself. The more actively replicating virions there are within the body, the higher the nAb dose needs to be to neutralize them all.

At the very beginning, many historically or internally controlled phase II studies showed clinical benefit from CCP. The largest of them is likely the one by Joyner *et al.*, who showed, in a post hoc analysis from the US open-label EAP (NCT04338360), that 7-day mortality in non-intubated patients younger than 80 years of age and treated within 72 h after diagnosis was 6·3% in those receiving high-titre CCP and 11·3% in those receiving low-titre CCP [1]. Of the 3,082 patients included in a later analysis, death within 30 days after CCP transfusion occurred in 22·3% in the high-titre group, 27·4% in the medium-titre group and 29·6% in the low-titre group; no effect of CCP titre on the risk of death was observed among patients who had received mechanical ventilation [2].

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In a post hoc subgroup analysis of 35,322 transfused patients from the Mayo Clinic (including 52·3% in the intensive care unit and 27·5% receiving mechanical ventilation), the 7-day mortality rate was 8·7% in patients transfused within 3 days of diagnosis but 11·9% in patients transfused ≥ 4 days after diagnosis. Similar findings were observed in 30-day mortality (21·6% vs. 26·7%) in the US EAP [3]. Unfortunately, the main bias of those studies is that controls were neither randomized nor PSM; hence, differences in the treatment outcome between treated and untreated groups may have been caused by a factor that predicted treatment rather than by the treatment itself.

PSM studies balance treatment and control groups on a large number of covariates without losing a large number of observations. In two retrospective PSM studies from two different hospitals in New York, trends for improved outcomes were observed in non-intubated patients and in those treated within 7 days of hospitalization (hazard ratio, 0·33) [4,5]. These findings were later confirmed in a prospective PSM study from Houston [6,7]. Of interest, a retrospective PSM study from Providence in which patients were treated at a median of 7 days after onset of symptoms did no show any benefit [8].

Since PSM only accounts for observed (and observable) covariates and not latent characteristics, RCTs remain the gold standard for highest level evidence (Table 1). In the PlasmAr RCT, the primary and secondary outcomes in the small number of early arrivals (within 72 h) were better in the CCP arm (n = 28) than in the placebo arm (n = 11), but the minimal contribution of this group to the overall cohort (228 CCP and 105 placebo) made the advantage disappear in the final outcomes at day 30 [9]. In another Argentinean RCT on 160 patients older than 65 years of age with mild COVID-19 who were treated with CCP within 72 h, progression to severe COVID-19 was halved at day 30 [10]. In another RCT from India, patients younger than 67 years of age treated at a median of 4 days after hospital admission showed superior mitigation of hypoxia and survival in the CCP arm [11]. Another RCT in Spain enrolling patients at less than 7 days of hospitalization showed benefit [12]. Many more RCTs are ongoing.

Table 1 Randomized controlled trials of COVID-19 convalescent plasma reported to date

RCT identifier	Country	Recruitment (out of expected) (randomization strategy)	Control arm components	Median days from symptoms or hospital admission	Baseline recipient WHO score*	Median nAb in CCP units	Median nAb in recipient	Transfused CCP volume (ml)	Outcome	Refs
ChiCTR2000029757	China	103 (out of 200) (1:1)	BSC	30 (from symptoms)	5–6	not assessed	not assessed	200	Reduced mortality at day 28 only in WHO score 5 patients (HR 2·5)	[21]
NCT04342182 (ConCOVID)	Netherlands	86 (out of 426) (1:1)	BSC	10 (from symptoms)	5–6	1:160	1:160 in 79% of recipients	300	No benefit at day 15	[14]
CTRI/2020/04/024775 (PLACID)	India	464 (1:1)	BSC	6 (from symptoms)	4–5	1:40	1:90	200 + 200	No benefit at day 28	[13]
NCT04345523 (ConPlas-19)	Spain	81 (out of 278, still recruiting) (1:1)	BSC	8 (from symptoms)	3 (25%) 4 (75%)	1:292	not assessed	250–300	Reduced mechanical ventilation or death (0% vs. 14%). Mortality rates were 0% vs. 9·3% at days 15 and 29 for the active and control groups, respectively.	[12]
NCT04375098	Chile	58 (1:1)	late CCP	6 (from symptoms)	3-4	≥1:160	59% <1:160 (16% of patients enrolled before day 5 were ≥1:160 vs. 60% of those enrolled after day 6	200 + 200	NO benefit at day 30 in death, mechanical ventilation or prolonged hospitalization compared to CCP administration only in case of clinical worsening or >7 days after enrolment	[22]
NCT04479163	Argentina	160 (out of 210) (1:1)	normal saline	≤3 (from symptoms; and > 65 yrs)	3	Not assessed	Not assessed	250	Progression to severe COVID-19 halved at day 30	[10]
NCT04383535 (PlasmAr)	Argentina	333 (2:1)	normal saline	8 (from symptoms)	5	1:300 IC_{80}	Not assessed	500	No benefit at day 30 (16·2% vs. 31·2%)	[9]
CTRI/2020/05/025209	India	80 (1:1)	BSC	4·2 (from hospital admission)	5	Not assessed	Not assessed	200 + 200	Immediate mitigation of hypoxia, reduction in hospital stay as well as survival benefit was recorded in severe COVID-19 patients with ARDS aged less than 67 years	[11]
NCT04356534	Bahrain	40 (1:1)	BSC	n.a.	4 (95%) 5 (5%)	Not assessed	Not assessed	200 + 200	No difference in requirement for ventilation, white blood cell count, LDH, CRP, troponin, ferritin, D-dimer, procalcitonin, mortality rate at 28 days	[23]
NCT04346446	India	29 (1:1)	FFP	<3 (from symptoms)	4-5	not assessed	not assessed	250 + 250	Better median improvement in PaO_2/FiO_2 at 48-h [42 vs. 231] and at day 7	[24]

Table 1 (Continued)

RCT identifier	Country	Recruitment (out of expected) (randomization strategy)	Control arm components	Median days from symptoms or hospital admission	Baseline recipient WHO score*	Median nAb in CCP units	Median nAb in recipient	Transfused CCP volume (ml)	Outcome	Refs
BKH-CT-012	Iraq	49 (1:1)	BSC	<3 (from ICU admission)	5	not assessed	not assessed	400	Duration of infection reduced by 4 days; mortality 1/21 in CCP arm vs. 8/28	[25]

RCT, randomized controlled trial; WHO, World Health Organization; nAb, neutralizing antibodies; CCP, COVID-19 convalescent plasma; Ref, reference; BSC, best supportive care; FFP, fresh-frozen plasma; n.a., not assessed; HR, hazard ratio; ARDS, acute respiratory distress syndrome; LDH, lactate dehydrogenase; CRP, C-reactive protein; PaO_2/FiO_2, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; ICU, intensive care unit. 'Not assessed' means that antivirus antibodies were assessed only using high-throughput serology.

*The WHO score [20] ranges from 0 to 8: 0: no clinical or virological evidence of infection; 1: no limitations of activities; 2: limitations of activities; 3: hospitalized, no oxygen therapy; 4: oxygen by mask or nasal prongs; 5: non-invasive ventilation or high-flow oxygen; 6: intubation and mechanical ventilation; 7: ventilation + additional organ support - pressors, renal replacement therapy, extracorporeal membrane oxygenation; and 8: death.

Here below, an alternative layout/adaptation of Table 1.

RCT identifier [Country]	Recruited (out of expected) [randomization strategy]	Control arm components	Median days from symptoms or hospital admission	Baseline recipient WHO score*	Median nAb in CCP units	Median nAb in recipient	Volume of CCP transfused (ml)	Outcome	Refs
ChiCTR2000029757 [China]	103 (of 200) [1:1]	BSC	30 (from symptoms)	5–6	n.a.	n.a.	200	Reduced mortality at day 28 only in WHO score 5 patients (HR 2·5)	[21]
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NCT04345523 (ConPlas-19) [Spain]	81 (of 278, still recruiting) [1:1]	BSC	8 (from symptoms)	3 (25%) 4 (75%)	1:292	n.a.	250–300	Reduced mechanical ventilation or death (0% vs. 14%). Mortality rates were 0% vs. 9·3% at days 15 and 29 for the active and control groups, respectively.	[12]
NCT04375098 [Chile]	58 [1:1]	late CCP	6 (from symptoms)	3–4	≥1:160	59% <1:160 (16% of patients enrolled before day 5 had ≥1:160 vs. 60% of those enrolled after day 6	200 + 200	No benefit at day 30 in death, mechanical ventilation or prolonged hospitalization compared to CCP administration only in case of clinical worsening or >7 days after enrolment	[22]

Table 1 (Continued)

RCT identifier [Country]	Recruited (out of expected) [randomization strategy]	Control arm components	Median days from symptoms or hospital admission	Baseline recipient WHO score*	Median nAb in CCP units	Median nAb in recipient	Volume of CCP transfused (ml)	Outcome	Refs
NCT04479163 [Argentina]	160 (of 210) [1:1]	Normal saline	≤ 3 (from symptoms; and >65 years)	3	n.a.	n.a.	250	Progression to severe COVID-19 was halved at day 30	[10]
NCT04383535 (PlasmAr) [Argentina]	333 [2:1]	normal saline	8 (from symptoms)	5	1:300 IC_{80}	n.a.	500	No benefit at day 30 (16·2% vs. 31·2%)	[9]
CTRI/2020/05/025209 [India]	80 [1:1]	BSC	4·2 (from hospital admission)	5	n.a.	n.a.	200 + 200	Immediate mitigation of hypoxia, reduction in hospital stay as well as survival benefit in severe COVID-19 patients with ARDS aged < 67 years	[11]
NCT04356534 [Bahrain]	40 [1:1]	BSC	n.a.	4 (95%) 5 (5%)	n.a.	n.a.	200 + 200	No difference in requirement for ventilation, white blood cell count, LDH, CRP, troponin, ferritin and D-dimer, procalcitonin, mortality rate at 28 days	[23]
NCT04346446 [India]	29 [1:1]	FFP	<3 (from symptoms)	4–5	n.a.	n.a.	250 + 250	Better median improvement in PaO_2/FiO_2 at 48 h (42 vs. 231) and at day 7	[24]
BKH-CT-012 [Iraq]	49 [1:1]	BSC	<3 (from ICU admission)	5	n.a.	n.a.	400	Duration of infection reduced by 4 days; mortality 1/21 in CCP arm vs. 8/28	[25]

Table 2 Propensity score-matched studies reported to date

Type of study	Country	Patients + control	Median days after hospitalization	Baseline recipient WHO score*	CCP volume transfused (ml)	Statistically significant outcomes	Refs
Retrospective	Mount Sinai, NY, USA	39 + 156	4	5 (87%) 6 (10%)	250 + 250	On day 14 oxygen requirements worsened in 17·9% of plasma recipients vs. 28·2% of controls (aOR 0·86). Survival improved in plasma recipients (aHR 0·34)	[5]
	Providence, RI, USA	64 + 177	>2 (<10 from onset of symptoms: median 7)	4 (70%) 5 (30%)	n.a. (2 units)	No significant differences in incidence of in-hospital mortality (12·5% and 15·8%; aHR 0·93) or overall rate of hospital discharge (RR 1·28, although increased among patients > 65 years)	[8]
	Montefiore Medical Center, NY, USA	90 + 258	<3 (3–7 days from onset of symptoms)	5–6 (<24 h mechanical ventilation)	200	Anti-S IgG titre ≥ 1:2,430 (median 1:47,385) recipients < 65 years had fourfold lower mortality and fourfold lower deterioration in oxygenation or mortality at day 28	[4]
	Washington, USA	263 + 263	n.a.	n.a.	245 (median)	Reduced 7-day (9·1 vs. 19·8%) and 14-day mortality (14·8 vs. 23·6%), but not 28-day mortality, and longer hospital stay	[26]
	China	163 + 163	n.a.	n.a.	300	Hospital stay in the CCP group was significantly longer than in the matched control group ($P < 0·0001$).	[27]

Table 2 (Continued)

Type of study	Country	Patients + control	Median days after hospitalization	Baseline recipient WHO score*	CCP volume transfused (ml)	Statistically significant outcomes	Refs
Prospective	Houston, USA	136 + 251	n.a.	3 (9%) 4 (63%) 5 (18%) 6 (10%) 7 (1%)	300 (1–2 units)	Reduction in mortality within 28 days, specifically in patients transfused < 72 h of admission with CCP with an anti-RBD titre ≥ 1:1350 (i.e. ~80% probability of a live virus *in vitro* neutralization titre of ≥1:160 [28])	[6]
		341 + 594	n.a.		300 (1-2 units)	Reduced 28-day (aHR = 2·09 for controls) and 60-day (5·7% vs. 10·7%; aHR = 1·82 for controls) mortality in those transfused with anti-RBD ≥ 1:1350 within 72 h post-hospitalization. Optimal window of 44 h to maximize benefit in 60-day mortality (4% vs. 12·3%). 91% received CCP with an anti-RBD titre ≥ 1:1350. Median S/CO ratio = 24 using Ortho Vitros.	[7]

None of these studies tittered neutralizing antibodies in either the donors or recipients using the plaque reduction neutralization test.

WHO, World Health Organization; CCP, COVID-19 convalescent plasma; Refs, references; aOR, adjusted odds ratio; aHR, adjusted hazard ratio; RR, relative risk; RBD, receptor binding domain; S/CO, significant cut-off.

*The WHO score [20] ranges from 0 to 8: 0: no clinical or virological evidence of infection; 1: no limitations of activities; 2: limitations of activities; 3: hospitalized, no oxygen therapy; 4: oxygen by mask or nasal prongs; 5: non-invasive ventilation or high-flow oxygen; 6: intubation and mechanical ventilation; 7: ventilation + additional organ support - pressors, renal replacement therapy, extracorporeal membrane oxygenation; and 8: death.

Why you should treat hard

In the previously mentioned subgroup analysis on the EAP, a gradient of mortality was seen in relation to IgG antibody levels in the transfused CCP: 7-day mortality was 8·9% for patients who received high IgG plasma (>18·45 signal cut-off [S/CO]), 11·6% for recipients of medium IgG plasma (4·62 to 18·45 S/CO) and 13·7% for recipients of low IgG plasma (<4·62 S/CO). This unadjusted dose–response relationship with IgG was also observed in 30-day mortality. The pooled relative risk of mortality among patients transfused with plasma units containing high levels of antibodies was 0·65 for 7 days and 0·77 for 30 days compared to units containing low levels [3].

The lack of utility from low-titre (1:40) CCP in moderate COVID-19 was confirmed by the PLACID trial [13]. Similarly, the ConCOVID RCT proved that CCP units with nAb titres similar to those of the recipients (1:160) were useless [14].

Analysis of published and ongoing trials has also revealed the importance of testing the antiviral activity of CCP units within clinical trials with the standard plaque reduction neutralization test (PRNT) rather than with the surrogate high-throughput serological tests [15]. Considering that the qualitative composition of CCP is due to the nAb titre (the higher, the better), its accurate evaluation is particularly critical and could make the difference between clinical efficacy and inefficacy. Thus, although most trials perform a correlation analysis between PRNT and high-throughput serological assays, in many cases, the CCP units are tested only with the latter tests (44% in the PlasmAr trial [3]), with the risk of an incorrect evaluation of the neutralizing CCP activity. One major cause could be that, despite IgM, IgG and IgA all being capable of mediating neutralization, virus neutralization test titres correlated better with binding levels of IgM and IgA_1 than IgG [16], which are the only class routinely measured in high-throughput serological assays. In addition, the quaternary structure of the Spike protein available on infected replication-competent cell lines is poorly replicated by recombinant antigens bound on solid substrates.

For the above reason, in the ongoing Italian RCT TSUNAMI (NCT04393727) nAb titration of CCP is mandatory. Only if and when CCP is formally shown to be an effective treatment within clinical trials, could CCP collection be driven by surrogate high-throughput serology, given the hurdles to PRNT scalability.

Finally, in order to collect CCP units with an adequate nAb titre (≥1:160), CCP should preferentially be collected from older male patients who have recovered from a previous symptomatic COVID-19 that required hospitalization, in accordance with the most recent literature data [17,18].

What are the hurdles to early treatment?

There are several logistical hurdles to early initiation of CCP treatment. First, during a pandemic, there is massive accrual of severely ill patients to emergency departments, and in collapsed health systems, the turnaround time between emergency room admission and admission to a ward can be relevant. Additionally, in the absence of quick (antigenic or molecular) tests for SARS-CoV-2, the turnaround time for final confirmation of diagnosis with polymerase chain reaction tests, usually run in batches, takes from 5 to 10 h. Then, bureaucracy also takes time when it comes to preparing the papers for recruiting a patient within a clinical trial, and there are challenges associated with outpatient transfusion of known infectious individuals. Finally, ABO-compatible CCP units may not be readily available at the local blood bank, and recruited patients are therefore left on the waiting list. All these variables are likely to affect the efficacy of CCP treatment. We suggest wide deployment of quick tests within emergency departments, where CCP could be safely administered even before the patient reaches the final ward.

As suggested by the recently revised European Commission guidelines on CCP, '*evidence suggests that studies should focus on early transfusion of convalescent plasma with high neutralizing antibody titres*'. [19]. In conclusion, CCP is emerging as a new time-sensitive, life-saving treatment.

Conflict of interest

We declare we have no conflict of interest to disclose.

Authors contributions

D.F. designed the paper, analysed the data and wrote the first draft. M.F. revised the final version.

References

1 Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc 2020;95:1888–95.

2 Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19 (published ahead of print on Jan 13, 2021). N Engl J Med https://doi.org/10.1056/NEJMoa2031893

3 Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of Convalescent Plasma on

Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. (published ahead of print on Aug 12, 2020) medRxiv. https://doi.org/10.1101/2020.08.12.20169359

4 Yoon HA, Bartash R, Gendlina I, et al. Treatment of Severe COVID-19 with Convalescent Plasma in the Bronx, NYC (published ahead of print on Jan 21, 2021). JCI Insight. https://doi.org/10.1172/jci.insight.142270

5 Liu STH, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study. Nat Med 2020;26:1708–13.

6 Salazar E, Christensen PA, Graviss EA, et al. Treatment of Coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. Am J Pathol 2020;190:2290–303.

7 Salazar E, Christensen PA, Graviss EA, et al. Significantly decreased mortality in a large cohort of Coronavirus disease 2019 (COVID-19) patients transfused early with convalescent plasma containing high-titer anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike protein IgG. Am J Pathol 2021;191:90–107.

8 Rogers R, Shehadeh F, Mylona EK, et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study (published ahead of print on Oct 10, 2020). Clin Infect Dis https://doi.org/10.1093/cid/ciaa1548

9 Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in covid-19 severe pneumonia (published ahead of print on Nov 24, 2020). N Engl J Med 2021;384:619–29. https://doi.org/10.1056/NEJMoa2031304

10 Libster R, Pérez Marc G, Wappner D, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults (published ahead of print on Jan 6, 2021. N Engl J Med 2021;384:610–18. https://doi.org/10.1056/NEJMoa2033700

11 Ray Y, Paul SR, Bandopadhyay P, et al. Clinical and immunological benefits of convalescent plasma therapy in severe COVID-19: insights from a single center open label randomised control trial (published ahead of print on Nov 25, 2020). medRxiv. https://doi.org/10.1101/2020.11.25.20237883

12 Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, et al. Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial (published ahead of print on Aug 26, 2020). medRxiv. https://doi.org/10.1101/2020.08.26.20182444

13 Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate COVID-19 in India: open-label parallel-arm phase II multicentre randomized controlled trial (PLACID Trial). BMJ 2020;371:m3939.

14 Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Convalescent Plasma for COVID-19. A randomized clinical trial (published ahead of print on Jul 1, 2020). medRxiv https://doi.org/10.1101/2020.07.01.20139857

15 Focosi D, Maggi F, Mazzetti P, et al. Viral infection neutralization tests: a focus on SARS-CoV-2 with implications for convalescent plasma therapy. Rev Med Virol 2020:e2170.

16 Klingler J, Weiss S, Itri V, et al. Role of IgM and IgA Antibodies in the Neutralization of SARS-CoV-2 (published ahead of print on Aug 18, 2020). medRxiv. https://doi.org/10.1101/2020.08.18.20177303

17 Del Fante C, Franchini M, Baldanti F, et al. A retrospective study assessing the characteristics of COVID-19 convalescent plasma donors and donations (published ahead of print on Nov 24, 2020). Transfusion https://doi.org/10.1111/trf.16208

18 Mehew J, Johnson R, Roberts D, et al. Convalescent plasma for COVID-19: male gender, older age and hospitalisation associated with high neutralising antibody levels, England, 22 April to 12 May 2020. Euro Surveill 2020;25:2001754.

19 European Commission. An EU programme of COVID-19 convalescent plasma collection and transfusion. Guidance on collection, testing, processing, storage, distribution and monitored use. Version 3.0. 2020.

20 WHO. R & D Blueprint - Novel Coronavirus COVID19 Therapeutic Trial Synopsis. 2020. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf?ua=1 (Last accessed October 1 2020).

21 Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324:460–70.

22 Balcells ME, Rojas L, Le Corre N, et al. Early anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial (published ahead of print on Sep 17, 2020). medRxiv. https://doi.org/10.1101/2020.09.17.20196212

23 AlQahtani M, Abdulrahman A, Almadani A, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease (published ahead of print on Nov 2, 2020). medRxiv. https://doi.org/10.1101/2020.11.02.20224303

24 Bajpai M, Kumar S, Maheshwari A, et al. Efficacy of convalescent plasma therapy compared to fresh frozen plasma in severely ill COVID-19 patients: a pilot randomized controlled trial (published ahead of print on Oct 25, 2020). medRxiv. https://doi.org/10.1101/2020.10.25.20219337

25 Rasheed AM, Fatak DF, Hashim HA, et al. The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. Infez Med 2020;28:357–66.

26 Shenoy AG, Hettinger AZ, Fernandez SJ, et al. Early mortality benefit with COVID-19 convalescent plasma: a matched control study (published ahead of print on Jan 21, 2021). British J Haematol 2021;192:706–13. https://doi.org/10.1111/bjh.17272

27 Jiang W, Li W, Xiong L, et al. Clinical efficacy of convalescent plasma therapy on treating COVID-19 patients: Evidence from matched study and a meta-analysis. Clin Transl Med 2020;10:e259.

28 Salazar E, Kuchipudi SV, Christensen PA, et al. Convalescent plasma anti-SARS-CoV-2 spike protein ectodomain and receptor-binding domain IgG correlate with virus neutralization. J Clin Invest 2020;130:6728–38.