Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy

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Abstract

To determine the effect of COVID-19 convalescent plasma on mortality, we aggregated patient outcome data from randomized clinical trials, matched control, and case-series studies. Fixed-effects analyses demontrated that hospitalized COVID-19 patients transfused with convalescent plasma exhibited a ~57% reduction in mortality rate (13%) compared to matched-patients receiving standard treatments (25%; OR: 0.43, $P < 0.001$). These data provide evidence favouring the efficacy of human convalescent plasma as a therapeutic agent in hospitalized COVID-19 patients.

Brief Communication

Convalescent plasma is a century-old passive antibody therapy that has been used to treat outbreaks of novel infectious diseases, including those affecting the respiratory system[1,2]. Due to the lack of vaccines or monoclonal antibody therapies, human convalescent plasma is currently being used wordwide to treat coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2–5]. However, evidence for therapeutic COVID-19 convalescent plasma efficacy still requires definitive support from large randomized clinical trials (RCT). As a result, there remains a lack of consensus on convalescent plasma use in hospitalized COVID-19 patients[6]. Several smaller RCTs, matched-control studies, and case series studies investigating convalescent plasma therapy for COVID-19 have emerged and provided a positive efficacy signal[7–17]. Most of these studies, however, lacked appropriate statistical power or were terminated early.

There is an urgent need to determine the efficacy of potential treatments amidst the ongoing COVID-19 pandemic. Thus, we used a practical approach to pool patient cohort data from RCTs, matched control, and case-series studies in real time. Our primary objective was to derive an aggregate estimate of mortality rate estimates from case and control cohorts of contemporaneous COVID-19 studies.

Data were extracted from studies published on pre-print servers or peer-reviewed journals that investigated human convalescent plasma therapy among hospitalized COVID-19 patients. Mortality rates were calculated at the longest reported vital status for each study and compared between cohorts using odds ratios (OR) determined by fixed effect meta-analysis models. Fixed effect meta-regression analyses evaluated the contribution of moderator variables (i.e., mean or median cohort age, proportion of cohort receiving mechanical ventilation, and duration of study follow up) on the aggregate OR computed for all controlled studies. All analyses were performed with Comprehensive Meta-analysis Software (Biostat, version 3.3.070). Alpha (α) was 0.05.

The present analyses included a total of twelve studies including three RCTs, five matched-control studies, and four case series studies containing 804 COVID-19 patient outcomes[7–17] from around the world (**Table 1**). The mean or median age of patients enrolled in these studies ranged from 48 to 70 years, with a greater proportion of men than women in most studies (proportion of women: 25% to 56%). All studies included patients with severe or life-threatening COVID-19. At the time of plasma transfusion, the proportion of patients on mechanical ventilation varied by study from 0% to 81%. The duration of follow up ranged from 7 to 30 days. All case-series studies demonstrated relatively low mortality rates for COVID-19 patients transfused with convalescent plasma (0% to 13%). Among RCTs, patients transfused with convalescent plasma exhibited a reduced mortality rate (13%) compared to non-transfused COVID-19 patients (26%; OR: 0.46, P = 0.03). Among matched control studies, patients transfused with convalescent plasma exhibited a reduced mortality rate (12%) compared to non-transfused COVID-19 patients (25%; OR: 0.41, P = 0.001). When patient outcomes from controlled studies were aggregated, patients transfused with convalescent plasma exhibited a reduced mortality rate (13%) compared to non-transfused COVID-19 patients (25%; OR: 0.43, P < 0.001). Meta-regression analysis indicated that mean or median cohort age, proportion of cohort receiving mechanical ventilation, and duration of study follow up did not affect the aggregate OR computed for all controlled studies (all coefficients P > 0.22). The fixed effect OR (OR: 0.44, P<0.001) was not different when *outlier* mortality rates from the matched control study by Xia and colleagues[18] were included in analyses (case mortality rate: 2%, control mortality rate: 4%).

In this outcomes analysis of contemporaneous COVID-19 convalescent plasma studies, the aggregate mortality rate of transfused COVID-19 patients was substantially lower than that of non-transfused COVID-19 patients. These results favour the efficacy of convalescent plasma as a COVID-19 therapeutic agent. The primary biological hypothesis for the efficacy of convalescent plasma is antibody-mediated SARS-CoV-2 viral neutralization, though other biological mechanisms may also contribute to the mitigation of symptoms[2]. These results align with similar analyses of historical data from convalescent plasma trials for viral diseases such as the 1918 flu epidemic[1], Severe acute respiratory syndrome[19], and H1N1 influenza[20].

There are several limitations to this analysis including aggregating mortality data across study populations that varied by: 1) the nation of data origin, 2) timing relative to worldwide progression of the pandemic, 3) clinical diagnostic and treatment algorithms, 4) plasma antibody titer and administration volume, 5) the latency between COVID-19 diagnosis and transfusion and 6) the duration of follow up after transfusion. We note that the reports cited in **Table 1** include positive results from different countries, suggesting that efficacy is robust across different health systems. Given the safety of plasma administration in COVID-19 patients[3,4], the results of this real-time data aggregration provide encouragement for its continued used as a therapy and may have broad implications for the treatment of COVID-19 and design of RCTs. Importantly, many of the patients enrolled in the studies included in the present analyses received convalescent plasma transfusions later in their disease course. In this context, prior to antibiotics and effective vaccinations, convalescent plasma therapy for streptococcal pneumonia and bacterial meningitis was widely understood to be most efficaceous very early in the course of hospitalizations[2]. As a result, our analysis may underestimate the mortality reduction acheivable through timely administration of convalescent plasma for COVID-19.

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Table

Table 1 | Case Fatality Rates in Hospitalized COVID-19 Patients

		Convalescent Plasma			Control			Statistics	
Study	**Location**	**Survivor**	**Non-Survivor**	**Mortality**	**Survivor**	**Non-Survivor**	**Mortality**	***OR***	***P***
Randomized Clinical Trials (RCT)									
Li et al. [7]	Wuhan, CHN	43	8	16%	38	12	24%	0.59	0.30
Gharbharan et al. [8]	NLD	37	6	14%	32	11	26%	0.47	0.18
Rasheed et al. [10]	IRQ	20	1	5%	20	8	29%	0.13	0.06
Fixed Effect Model [a]		100	15	13%	90	31	26%	0.46	0.03
Matched Controls									
Hegerova et al. [11]	Washington, USA	18	2	10%	14	6	30%	0.26	0.13
Liu et al. [17]	New York, USA	35	5	13%	118	38	24%	0.44	0.11
Perotti et al. [13]	Pavia, ITA	43	3	7%	16	7	30%	0.16	0.01
Abolghasemi et al. [14]	IRN	98	17	15%	56	18	24%	0.54	0.10
Fixed Effect Model [b]		194	27	12%	204	69	25%	0.41	0.001
Controlled studies Fixed Effect Model [c]		294	42	13%	294	100	25%	0.43	<0.001
Case Series									
Salazar et al. [15]	Texas, USA	24	1	4%	--	--	--	--	--
Hartman et al. [16]	Wisconsin, USA	27	4	13%	--	--	--	--	--
Duan et al. [17]	Wuhan, CHN	10	0	0%	--	--	--	--	--
Martinez-Resendez et al. [9]	Monterrey, MEX	8	0	0%	--	--	--	--	--
Total		69	5	7%	--	--	--	--	--

OR, odds ratio

[a] Relative weight (%): Li et al. (49.3), Gharbharan et al. (40.3), Rasheed et al. (10.4).

[b] Relative weight (%): Hegerova et al. (9.1), Liu et al. (27.4), Perotti et al. (12.8), Abolghasem et al. (50.7).

[c] Relative weight (%): Li et al. (17.8), Gharbharan et al. (14.6), Rasheed et al. (3.8), Hegerova et al. (5.8), Liu et al. (17.5), Perotti et al. (8.2), Abolghasem et al. (32.3).

Figure legend

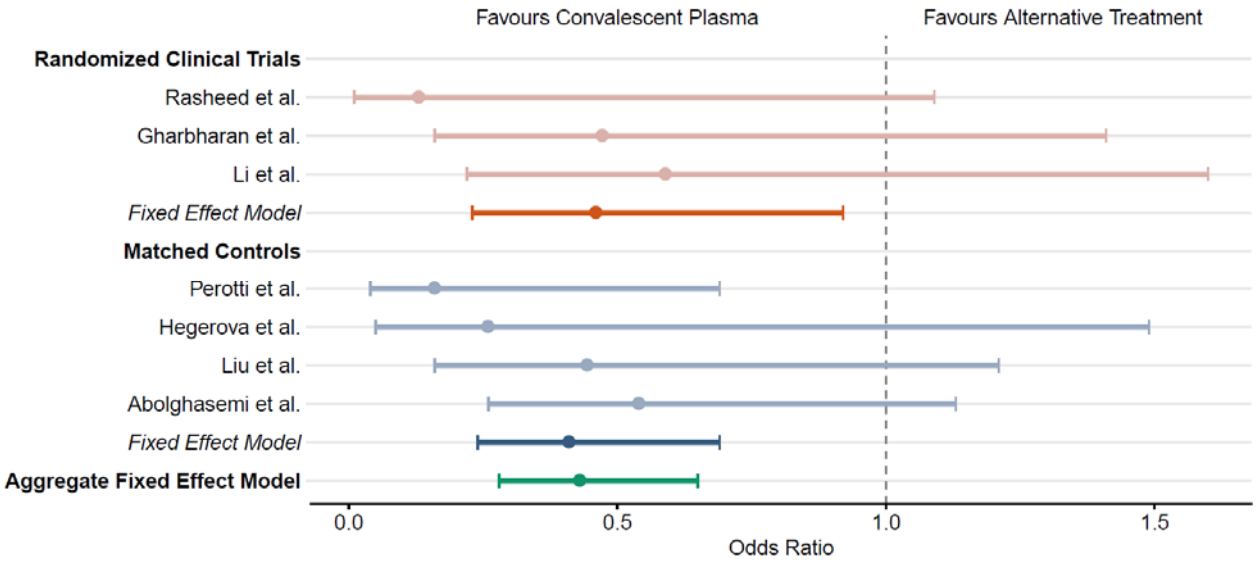

Figure 1. The impact of human convalescent plasma therapy on COVID-19 patient mortality. Forest plot illustrating odds ratios (OR) and 95% confidence intervals for controlled studies and aggregate fixed effect models. Randomized clinical trials including Rasheed et al.[10], Gharbharan et al.[8], and Li et al.[7] are represented in orange. Matched controlled studies including Perotti et al.[13], Hegerova et al.[11], Liu et al.[12], and Abolghasemi et al.[14] are represented in blue. Aggregate fixed effect models for each study type are represented by shaded hues. The overall aggregate fixed effect model is represented in teal.