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, case series, and case report studies. Fixed-effects analyses demonstrated that hospitalized COVID-19 patients transfused with convalescent plasma exhibited a ~57% reduction in mortality rate (10%) compared to matched-patients receiving standard treatments (22%; 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]. Smaller RCTs, matched-control studies, and case series studies investigating convalescent plasma therapy for COVID-19 have emerged and provided a positive efficacy signal[7–27]. 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 or case report studies in real time. Our primary objective was to derive an aggregate estimate of mortality rates from case and control cohorts of contemporaneous COVID-19 studies.

Studies published on pre-print servers or peer-reviewed journals that investigated human convalescent plasma therapy among hospitalized COVID-19 patients were identified from a search of the online PubMed database through August 25, 2020. Keywords used in the search included: ((convalescent plasma) OR (convalescent serum)) AND COVID-19 using the following limits: Humans. The references of all eligible studies were also reviewed to identify other potentially eligible studies. In order to be considered eligible for inclusion, studies must have: 1) included hospitalized patients with COVID-19, 2) used convalescent plasma treatment, and 3) reported mortality.

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). Tests were two-tailed and alpha was 0.05.

The literature search yielded 113 studies, of which 21 studies met the eligibility criteria. The present analyses included a total of twelve controlled studies including two RCTs and 9 case series or case reports containing 4,173 COVID-19 patient outcomes[7–27] from around the world (**Table 1**). The mean or median age of patients enrolled in these studies ranged from 52 to 70 years, with a greater proportion of men than women in most studies (proportion of women: 0% to 53%). 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. The mortality rates for COVID-19 patients transfused with convalescent plasma in case series or case reports ranged from 0% to 20%. Among controlled studies, patients transfused with convalescent plasma exhibited a reduced mortality rate (10%) compared to non-transfused COVID-19 patients (22%; OR: 0.43, $P < 0.001$). The aggregate OR of 0.43 indicates that convalescent plasma was associated with a 57% reduction in the odds of mortality among hospitalized COVID-19 patients. 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 $P > 0.24$). Both Fixed and Random effects models provided similar results for the aggregate OR and meta-regression.

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 and interference with viral replication, 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[28], and H1N1 influenza[29].

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[2,30]. As a result, our analysis may underestimate the mortality reduction acheivable through early administration of convalescent plasma for COVID-19.

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Competing Interests: The authors declare no competing interests.

Data availability: The data supporting the study findings are available within the paper.

Table

Table 1 | Mortality Rates in Hospitalized COVID-19 Patients

		Convalescent Plasma			Control			Statistics	
Study	**Location**	**Survivor**	**Non-Survivor**	**Mortality**	**Survivor**	**Non-Survivor**	**Mortality**	***OR***	***P***
Controlled Studies									
Duan et al. [26]	CHN	10	0	0%	7	3	30%	0.10	0.15
Rasheed et al. [19]	IRQ	20	1	5%	20	8	29%	0.13	0.06
Perotti et al. [23]	ITA	43	3	7%	16	7	30%	0.16	0.01
Hegerova et al. [21]	Washington, USA	18	2	10%	14	6	30%	0.26	0.13
Zeng et al. [9]	CHN	1	5	83%	1	14	93%	0.36	0.50
Donato et al. [10]	New York, USA	36	11	23%	775	565	42%	0.42	0.01
Liu et al. [22]	New York, USA	35	5	13%	118	38	24%	0.44	0.11
Salazar et al. [11]	Texas, USA	131	5	4%	232	19	8%	0.47	0.14
Gharbharan et al. [8]	NLD	37	6	14%	32	11	26%	0.47	0.18
Xia et al. [12]	CHN	135	3	2%	1371	59	4%	0.52	0.27
Abolghasemi et al. [24]	IRN	98	17	15%	56	18	24%	0.54	0.10
Li et al. [7]	CHN	43	8	16%	38	12	24%	0.59	0.30
Fixed Effect Model [a]		607	66	10%	2680	760	22%	0.43	<0.001
Case Series or Reports									
Martinez-Resendez et al. [27]	MEX	8	0	0%	--	--	--	--	--
Zhang et al. [13]	CHN	4	0	0%	--	--	--	--	--
Ahn et al. [14]	KOR	2	0	0%	--	--	--	--	--
Bobek et al. [15]	HUN	2	0	0%	--	--	--	--	--
Im et al. [16]	KOR	1	0	0%	--	--	--	--	--
Peng et al. [17]	CHN	1	0	0%	--	--	--	--	--
Xu et al. [18]	CHN	1	0	0%	--	--	--	--	--
Hartman et al. [25]	Wisconsin, USA	27	4	13%	--	--	--	--	--
Olivares-Gazca et al. [20]	MEX	8	2	20%	--	--	--	--	--
Total		54	6	10%	--	--	--	--	--

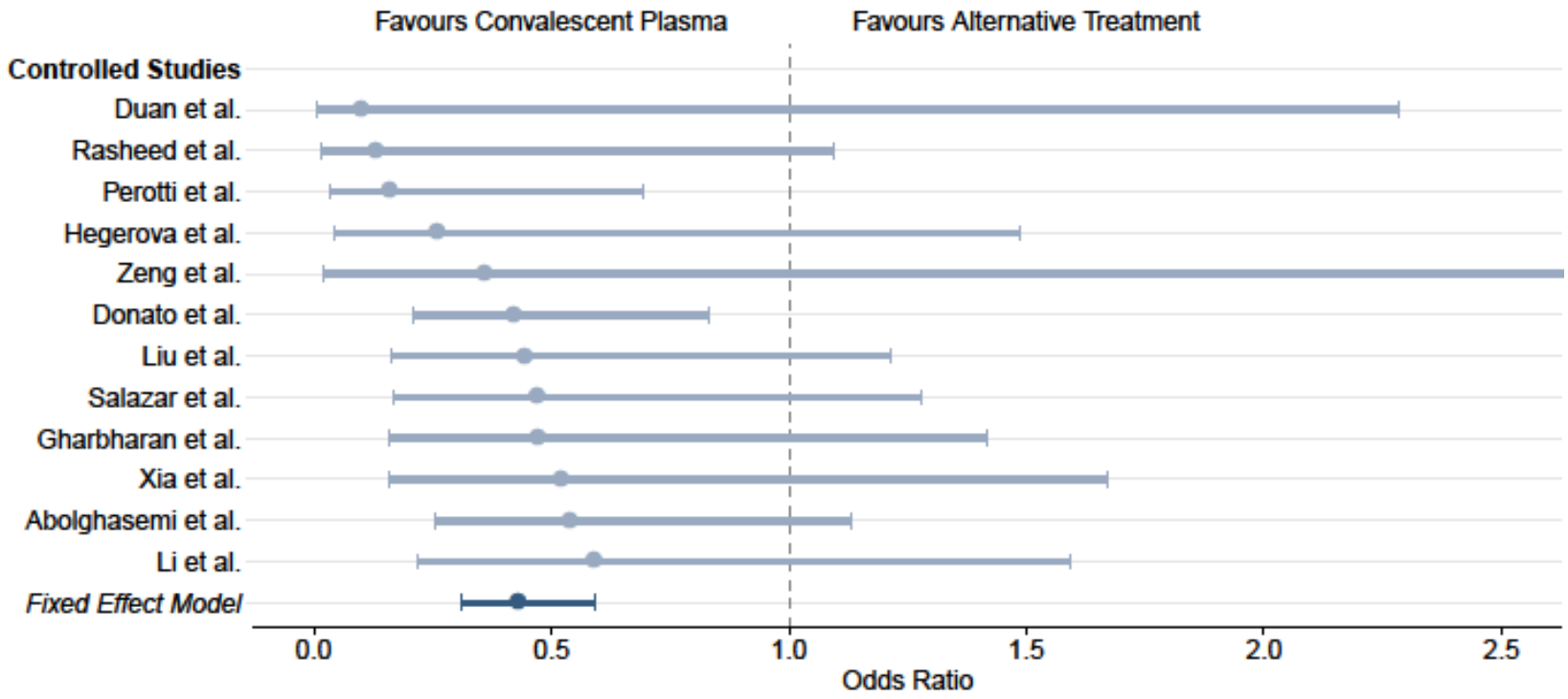
OR, odds ratio

[a] Relative weight (%): Duan et al. (1.1), Rasheed et al. (2.2), Perotti et al. (4.7), Hegerova et al. (3.4), Zeng et al. (1.2), Donato et al. (22.0), Liu et al. (10.1), Salazar et al. (10.1), Gharbharan et al. (8.5), Xia et al. (7.5), Abolghasemi et al. (18.8), Li et al. (10.4).

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. Fixed effect ORs for Duan et al.[26], Rasheed et al.[19], Perotti et al.[23], Hegerova et al.[21], Zeng et al.[9], Donato et al.[10], Liu et al.[22], Salazar et al.[11], Gharbharan et al.[8], Xia et al.[12], Abolghasemi et al.[24], and Li et al.[7] are represented in blue. The aggregate fixed effect model OR is represented in shaded blue.

Figure


Favours Convalescent Plasma
Favours Alternative Treatment
Controlled Studies
Duan et al.
Rasheed et al.
Perotti et al.
Hegerova et al.
Zeng et al.
Donato et al.
Liu et al.
Salazar et al.
Gharbharan et al.
Xia et al.
Abolghasemi et al.
Li et al.
Fixed Effect Model
0.0
0.5
1.0
1.5
2.0
2.5
Odds Ratio