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The Effect of Convalescent Plasma Therapy on Mortality Among Patients With COVID-19: Systematic Review and Meta-analysis

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Abstract

To determine the effect of COVID-19 convalescent plasma on mortality, we aggregated patient outcome data from 10 randomized clinical trials, 20 matched control studies, 2 dose-response studies, and 96 case reports or case series. Studies published between January 1, 2020, and January 16, 2021, were identified through a systematic search of online PubMed and MEDLINE databases. Random effects analyses of randomized clinical trials and matched control data demonstrated that patients with COVID-19 transfused with convalescent plasma exhibited a lower mortality rate compared with patients receiving standard treatments. Additional analyses showed that early transfusion (within 3 days of hospital admission) of higher titer plasma is associated with lower patient mortality. These data provide evidence favoring the efficacy of human convalescent plasma as a therapeutic agent in hospitalized patients with COVID-19.

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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] At the onset of the pandemic, human convalescent plasma was used worldwide as it represented the only antibody-based therapy for coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2-5] Despite the emerging availability of monoclonal antibody therapies and vaccines for use in nonhospitalized patients through federal emergency authorization routes, convalescent plasma use has persisted (~100,000 units per month in the United States in early

2021) during subsequent waves of the COVID-19 pandemic because of surging hospitalizations and mortality rates.[6-9] However, evidence for the efficacy of therapeutic COVID-19 convalescent plasma still requires definitive support from large randomized clinical trials (RCTs). As a result, there remains a lack of consensus on convalescent plasma use in hospitalized patients with COVID-19.[10,11] Smaller RCTs, matched control studies, and case series studies investigating convalescent plasma therapy for COVID-19 have emerged and provided a positive efficacy signal.[12-18] Most of these studies, however, lacked appropriate statistical power or were terminated early. Also, many studies have transfused patients only

after clinical progression to severe COVID-19 respiratory distress, which opposes historical data highlighting the efficacy of early convalescent plasma transfusion and overlooks viral neutralization as the fundamental mechanism for convalescent plasma therapy.[1,2]

There is an urgent need to determine the efficacy of potential treatments amid the ongoing COVID-19 pandemic. Although a "living" systematic review has summarized a broad-ranging clinical experience with convalescent plasma,[10,11] this approach may be limited because it employed stringent inclusion criteria for aggregating patient outcomes, which prevented a preliminary assessment of convalescent plasma efficacy. Given the insufficient patient outcome data available from RCTs, we used a pragmatic approach for study selection to aggregate COVID-19 clinical outcomes, focusing solely on mortality data from RCTs, matched control studies, dose-response investigations, and case series or case reports in real time. Our primary objective was to derive an aggregate estimate of the mortality rates from transfused and nontransfused cohorts of contemporaneous COVID-19 studies. As an exploratory objective, we assessed whether the time from hospital admission to convalescent plasma transfusion was associated with mortality of patients.

METHODS

Eligibility
We included RCTs, matched control trials, dose-response studies, and case series or case reports published on preprint servers or peer-reviewed journals that investigated the impact of human convalescent plasma therapy on mortality of patients with COVID-19.

Literature Search and Data Extraction
We performed a systematic search of the on-line PubMed and MEDLINE databases from January 1, 2020, through January 16, 2021. Keywords used in the search included ((convalescent plasma) OR (convalescent serum)) AND COVID-19 (and medical

ARTICLE HIGHLIGHTS

- There remains a lack of consensus on convalescent plasma use in hospitalized patients with COVID-19.
- Meta-analyses of randomized clinical trials and matched control data demonstrated that patients with COVID-19 transfused with convalescent plasma exhibited a lower mortality rate compared with patients receiving standard treatments.
- Additional analyses showed that early transfusion (within 3 days of hospital admission) of high-titer plasma is associated with lower mortality.
- These data provide evidence favoring the efficacy of human convalescent plasma as a therapeutic agent in hospitalized patients with COVID-19.

subject headings) using the following limits: Humans. No language restrictions were imposed. The references of all eligible studies were reviewed to identify other potentially eligible studies. To be considered eligible for inclusion, studies must have included patients with confirmed diagnosis of COVID-19, used convalescent plasma treatment, and reported mortality. Randomized clinical trials, matched control studies, dose-response studies, case series, and case reports were included. Two reviewers (S.A.K. and J.W.S.) independently screened the titles and abstracts of all studies identified by the search to determine eligibility. Studies that were deemed potentially eligible had their full text reviewed (S.A.K. and J.W.S.) to determine whether they met the criteria for inclusion in the review. Disagreement was resolved by consensus. Two reviewers (S.A.K. and J.W.S.) extracted study and patient characteristics as well as clinical information (additional information for each study is available in in Supplemental Tables 1-6, available online at http://www.mayoclinicproceedings.org).

Two reviewers (S.A.K. and J.W.S.) independently assessed the risk of bias for mortality data of each included study using the Cochrane risk of bias criteria (for RCTs; Supplemental Table 1, available online at http://www.mayoclinicproceedings.org) and the Newcastle-Ottawa Scale (for matched

control studies; Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).[19-21] Dose-response studies were evaluated with the Newcastle-Ottawa Scale. The criteria developed by the Mayo Clinic Evidence-Based Practice Research Program informed our assessment of bias in the mortality data reported by case series and case reports.[22]

Data Synthesis

For RCTs and matched control studies, we recorded the number of survivors and non-survivors in transfused and nontransfused cohorts to calculate odds ratios (ORs) with 95% CIs. For dose-response studies, we recorded the number of survivors and non-survivors among patients who were transfused with higher titer and lower titer convalescent plasma units to calculate ORs with 95% CIs. Aggregate mortality rates were calculated for transfused and, if applicable, nontransfused patients at the longest reported vital status for each study.

Using the DerSimonian-Laird random effects method,[23] we computed aggregate ORs with 95% CIs separately for RCTs and matched control studies. We also computed aggregate ORs with 95% CIs for RCTs and matched control studies combined. Simple random effects meta-regression analyses evaluated the moderator variables (ie, cohort age, proportion of cohort receiving mechanical ventilation, and duration of study follow-up) on mortality for all clinical studies. The I^2 statistic was used to quantify heterogeneity. On the basis of historical data,[1] we performed an exploratory subgroup analysis to assess the impact of early transfusion (within 3 days of hospital admission) compared with late transfusion (>3 days after hospital admission) on mortality of patients with COVID-19. All analyses were performed with Comprehensive Meta-analysis software (Biostat, version 3.3.070). Tests were 2 tailed, and α was .05. Figures were made with R software (R Foundation for Statistical Computing). The number needed to treat was calculated using aggregate data from controlled studies.[24] Dose-response studies, case series, and case reports were not included in the meta-analysis but were described in a narrative.

Certainty of Evidence Assessment

We used the Grading of Recommendations Assessment, Development, and Evaluation approach to assess the certainty of evidence regarding the impact of convalescent plasma on mortality of patients with COVID-19.[25] The risk of bias assessments for RCT and matched control data informed our certainty of evidence assessment.

RESULTS

Search Results

The literature search yielded 780 studies, of which 128 studies met the eligibility criteria and were included in the systematic review (Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org). The analyses included a total of 10 RCTs,[13,17,18,26-31] 20 matched control studies,[14,16,32-50] 2 dose-response studies,[51,52] and 96 case series or case reports.[3,14,15,43,53-143] Overall, these studies reported outcomes from 35,055 patients with COVID-19 in 31 countries (Tables 1 and 2; Supplemental Table 3, available online at http://www.mayoclinicproceedings.org). The age of patients enrolled in these studies ranged from 4 to 100 years, with a greater proportion of men than of women in most studies (proportion of women, 0%-100%; Supplemental Tables 4-6). All studies included patients with diagnosed COVID-19, with most studies including hospitalized 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 100%. The duration of follow-up ranged from 2 to 118 days (Supplemental Tables 4-6). In most studies, patients were eligible to receive concomitant and experimental therapies, such as antivirals, steroids, and chloroquine or hydroxychloroquine.

TABLE 1. Mortality Rates Among COVID-19 Patients: Randomized Clinical Trials and Matched Control Studies[a]

Study	Location	Convalescent plasma			Control			Statistics		
		Survivor	Nonsurvivor	Mortality (%)	Survivor	Nonsurvivor	Mortality (%)	OR	P	95% CI
Randomized clinical trials										
Avendano-Sola et al[18]	Spain	38	0	0	39	4	9	0.11	.15	0.01-2.19
Rasheed et al[17]	Iraq	20	1	5	20	8	29	0.13	.06	0.01-1.09
Gharbharan et al[13]	The Netherlands	37	6	14	32	11	26	0.47	.18	0.16-1.42
AlQahtani et al[26]	Bahrain	19	1	5	18	2	10	0.47	.56	0.04-5.69
Libster et al[27]	Argentina	78	2	3	76	4	5	0.49	.41	0.09-2.74
Li et al[12]	China	43	8	16	38	12	24	0.59	.30	0.22-1.59
Ray et al[28]	India	30	10	25	26	14	35	0.62	.33	0.24-1.63
Simonovich et al[29]	Argentina	197	25	11	93	12	11	0.98	.96	0.47-2.04
Agarwal et al[30]	India	201	34	14	198	31	14	1.08	.77	0.64-1.83
Bajpai et al[31]	India	11	3	21	14	1	7	3.82	.27	0.35-41.96
Random effects model		674	90	12	554	99	15	0.76	.14	0.54-1.09
Random effects model excluding Agarwal et al		473	56	11	356	68	16	0.65	.04	0.43-0.98
Matched control studies										
Duan et al[32]	China	10	0	0	7	3	30	0.10	.15	0.01-2.28
Perotti et al[42]	Italy	43	3	7	16	7	30	0.16	.01	0.04-0.69
Omrani et al[44]	Qatar	39	1	3	35	5	13	0.18	.13	0.02-1.61
Hegerova et al[45]	Washington	18	2	10	14	6	30	0.26	.13	0.05-1.49
Salazar et al[33]	Texas	146	6	4	235	34	13	0.28	.01	0.12-0.69
Alsharidah et al[46]	Kuwait	111	24	18	143	90	39	0.34	<.001	0.21-0.57
Zeng et al[47]	China	1	5	83	1	14	93	0.36	.50	0.02-6.85
Donato et al[48]	New York	36	11	23	775	565	42	0.42	.01	0.21-0.83
Salazar et al[49]	Argentina	647	221	25	1288	1010	44	0.44	<.001	0.37-0.52
Liu et al[50]	New York	34	5	13	118	38	24	0.46	.13	0.17-1.25
Xia et al[34]	China	135	3	2	1371	59	4	0.52	.27	0.16-1.67
Abolghasemi et al[16]	Iran	98	17	15	56	18	24	0.54	.10	0.26-1.13
AlShehry et al[35]	Saudi Arabia	30	10	25	78	46	37	0.57	.16	0.25-1.26
Budhiraja et al[36]	India	248	85	26	241	120	33	0.69	.03	0.50-0.96
ah Yoon et al[37]	New York	50	23	32	45	28	38	0.74	.39	0.37-1.46
Rogers et al[38]	Rhode Island	56	8	13	149	28	16	0.76	.52	0.33-1.77
Altuntas et al[39]	Turkey	669	219	25	642	246	28	0.85	.15	0.69-1.06
Klapholz et al[40]	New Jersey	37	10	21	38	9	19	1.14	.80	0.42-3.13
Klein et al[41]	Maryland	25	9	26	26	8	24	1.17	.78	0.39-3.51
Moniuszko-Malinowska et al[43]	Poland	49	6	11	672	43	6	1.91	.16	0.78-4.72
Random effects model		2482	668	21	5950	2377	29	0.57	<.001	0.45-0.72
Overall random effects model[b]		2955	724	20	6306	2445	28	0.58	<.001	0.47-0.71

[a]OR, odds ratio.
[b]Random effects model excludes trial by Agarwal et al.

Meta-analysis

Randomized Clinical Trials. When data from the 10 RCTs were aggregated, there was no association between convalescent plasma therapy and mortality (OR, 0.76; 95% CI, 0.54 to 1.09; $P=.14$; $I^2=7\%$; Table 1; Figure). Although the heterogeneity was low, 1 RCT (Agarwal et al[30]) demonstrated a directionally different effect, had a large statistical weight (34.2), and represented the primary source of heterogeneity ($\Delta I^2=7\%$). In addition, in the context of COVID-19,

TABLE 2. Mortality Rates Among COVID-19 Patients: Dose-Response Studies							
		Convalescent plasma higher titer			Convalescent plasma lower titer		
Study	Location	Survivor	Nonsurvivor	Mortality (%)	Survivor	Nonsurvivor	Mortality (%)
Dose-response studies							
Joyner et al[51]	Minnesota	400	115	22	395	166	30
Maor et al[52]	Israel	17	2	11	23	7	23
Dose-response total		417	117	22	418	173	29

neutralizing antibodies are hypothesized to represent the primary active agent in convalescent plasma and the marker of plasma potency.[144,145] In this regard, as mentioned later, 2 studies reported a dose-response relationship between convalescent plasma antibody level and mortality, suggesting the need for a sufficient amount of antibody for therapeutic success.[144,145] The trial of Agarwal et al[30] included a large proportion of patients (~70%) in the convalescent plasma arm who received plasma with low levels of SARS-CoV-2 antibodies less than 1:80, with approximately 30% receiving plasma with no detectable antibodies.[30] Thus, there were strong analytical and biologic rationales to exclude this study from statistical models.

When analyses were performed on data from 9 RCTs excluding the study of Agarwal et al,[30] patients transfused with convalescent plasma exhibited a lower mortality rate compared with nontransfused patients with COVID-19 (11% vs 16% mortality; OR, 0.65; 95% CI, 0.43 to 0.98; $P=.04$; $I^2=0\%$; Table 1; Figure). The aggregate OR (0.65) indicates that convalescent plasma was associated with a 35% reduction in the odds of mortality among patients with COVID-19.
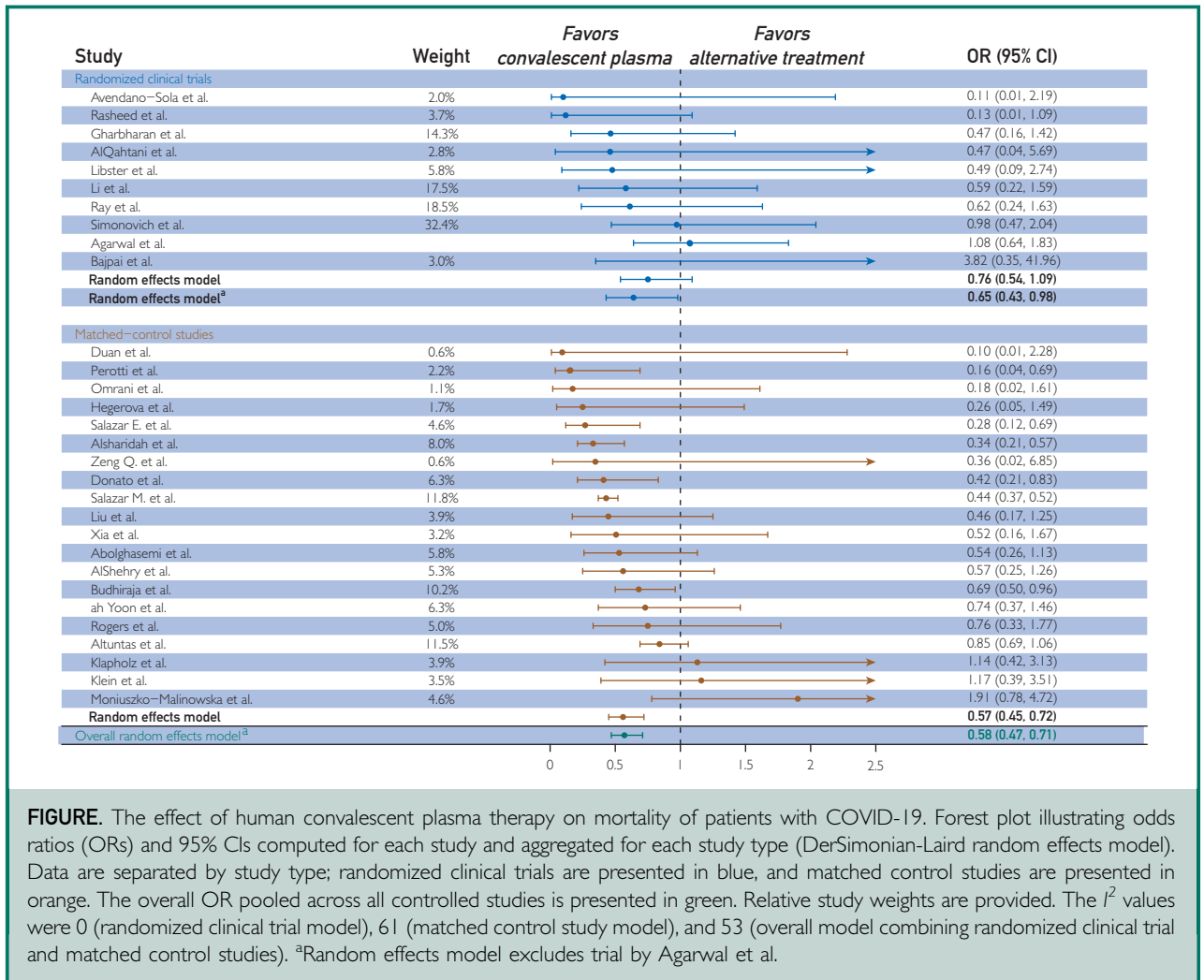
Matched Control Studies. When we aggregated mortality data from the 20 matched control studies, patients transfused with convalescent plasma exhibited a lower mortality rate compared with nontransfused patients (21% vs 29% mortality; OR, 0.57; 95% CI, 0.45 to 0.72; $P<.001$; $I^2=61\%$; Table 1; Figure).

Randomized Clinical Trials and Matched Control Studies. Aggregation of mortality data from all controlled studies including RCTs and matched control studies indicated that patients transfused with convalescent plasma exhibited a 42% reduction in mortality rate compared with patients receiving standard treatments (20% vs 28% mortality; OR, 0.58; 95% CI, 0.47 to 0.71; $P<.001$; $I^2=53\%$; Table 1; Figure). Simple random effects meta-regression analyses indicated that cohort age ($P=.23$), proportion of cohort receiving mechanical ventilation ($P=.51$), and duration of study follow-up ($P=.29$) did not affect the aggregate OR computed for all controlled studies.

Subgroup Analysis: Effect of Days Between Hospital Admission and Plasma Transfusion. Sixteen studies (n=6 RCTs, n=10 matched control studies) reported the number of days between hospital admission and convalescent plasma transfusion (Supplemental Table 4). Exploratory analysis revealed that the mortality reduction associated with convalescent plasma transfusion was greater in studies that transfused patients within 3 days of hospital admission (OR, 0.44; 95% CI, 0.32-0.61) compared with studies that transfused patients more than 3 days after hospital admission (OR, 0.79; 95% CI, 0.62 to 0.98; random effects test of heterogeneity between subgroups, $P=.005$). However, this analysis was strongly influenced by the study by Altuntas et al,[39] which transfused patients more than 3 days after admission (relative weight, 73%). On removal of the study by Altuntas et al,[39] the number of days from hospital admission to transfusion no longer affected the mortality reduction associated with convalescent plasma transfusion (transfusion within 3 days of hospitalization, 0.44 [0.32-0.60]; transfusion >3

FIGURE. The effect of human convalescent plasma therapy on mortality of patients with COVID-19. Forest plot illustrating odds ratios (ORs) and 95% CIs computed for each study and aggregated for each study type (DerSimonian-Laird random effects model). Data are separated by study type; randomized clinical trials are presented in blue, and matched control studies are presented in orange. The overall OR pooled across all controlled studies is presented in green. Relative study weights are provided. The I^2 values were 0 (randomized clinical trial model), 61 (matched control study model), and 53 (overall model combining randomized clinical trial and matched control studies). [a]Random effects model excludes trial by Agarwal et al.

days after hospitalization, 0.61 [0.36-0.68]; random effects test of heterogeneity between subgroups, *P*=.23).

Additional Evidence
Dose-Response Studies. Two studies investigated the association between convalescent plasma antibody levels and the risk of mortality from COVID-19.[3,52] Although different criteria were used to categorize convalescent plasma units as higher and lower antibody level, both studies found a dose-response association between antibody level and COVID-19 mortality, such that patient mortality was lower in the subgroups transfused with higher titer plasma. The aggregate mortality rate of patients with

COVID-19 transfused with higher titer convalescent plasma was less than that of patients transfused with lower titer plasma (22% vs 29% mortality; Table 2).

Case Series and Case Reports. The aggregate mortality rate among patients with COVID-19 transfused with convalescent plasma reported in uncontrolled studies was 13% (range, 0%-100%), which is comparable to the mortality rates exhibited by transfused cohorts from clinical trials and matched control studies (Supplemental Table 3). Case series and case report data included diverse cohorts of patients with varying inherent risk for COVID-19 complications. Several studies explored immunosuppressed

patients with suppressed antibody production due to hematologic malignant neoplasms, cancer-directed therapy, or X-linked agammaglobulinemia and provided an important "experiment of nature" to evaluate convalescent plasma efficacy for COVID-19.[84,92,124,146] For example, Jin et al[92] highlighted a series of 3 patients with X-linked agammaglobulinemia with severe COVID-19 who failed to respond to other supportive treatments but demonstrated strong improvements in oxygen requirements and viral clearance within days of receiving convalescent plasma transfusions.

Risk of Bias

Overall, we deemed the risk of bias for mortality data to be low to moderate for RCTs and low to moderate for matched control studies. We present the full judgment for each study in Supplemental Tables 1 and 2. The risk of bias for uncontrolled studies is inherently high. Visual inspection of the funnel plot to assess publication bias shows that 1 study falls below the 95% CI and 2 studies fall above the 95% CI (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org). The funnel plot shows symmetry in the effect sizes among studies with low standard error and asymmetry among studies with greater standard error, suggesting that smaller studies with larger standard error may be more likely to report an effect of convalescent plasma. However, the Egger regression test suggests that there is no significant asymmetry of the plot (intercept, -0.17; $P=.67$).

Certainty of Evidence

The certainty in the estimate of the effect of convalescent plasma on mortality is moderate to high.[147] This judgment was based on the consistency of the results between RCTs and matched control studies and the corroborating evidence from dose-response studies and other uncontrolled case data. In aggregating data from all controlled studies, the meta-analyses provided precise estimates, did not demonstrate substantial heterogeneity, and demonstrated no strong evidence of publication bias. The inherent limitations of the included studies rendered the certainty of evidence judgment to be moderate to high.

Number Needed to Treat

Based on the aggregate OR (0.58; 95% CI, 0.47 to 0.71) computed for all controlled studies and the aggregate mortality rate (28%) expressed by nontransfused cohorts among the controlled studies, to avoid 1 death, the number needed to be transfused with convalescent plasma rather than only to receive the standard of care is 11 (range, 8-16).

DISCUSSION

This analysis represents the most current aggregation of mortality data from contemporaneous COVID-19 convalescent plasma studies. The aggregate mortality rate of transfused patients with COVID-19 was lower than that of nontransfused patients with COVID-19. Additional analyses demonstrated that early transfusion of high-titer plasma reduces mortality among patients with COVID-19. These results favor the efficacy of convalescent plasma as a COVID-19 therapeutic agent. The primary biologic hypothesis for the efficacy of convalescent plasma is antibody-mediated SARS-CoV-2 viral neutralization and interference with viral replication, although other biologic mechanisms may also contribute to the mitigation of symptoms.[2] The mortality reduction associated with convalescent plasma aligns with similar analyses of historical data from convalescent plasma trials for viral diseases, such as the 1918 influenza epidemic,[1] severe acute respiratory syndrome,[148] and H1N1 influenza.[149] Our findings are discordant with those of a previous living systematic review,[10,11] which concluded that there is insufficient evidence to determine the impact of convalescent plasma on all-cause mortality based on only 2 RCTs, including 1 prematurely terminated RCT (Li et al[12]). This discordance reflects differences in the studies included in the analysis. Our approach was pragmatic

and used less stringent study inclusion criteria, allowing the inclusion of 30 controlled studies, of which a majority found a directionally similar effect of convalescent plasma, and our analyses stratified by study design (eg, RCTs and matched control studies) revealed similar aggregate ORs.

Mechanistic and clinical data support the reduction in mortality associated with convalescent plasma administration. Importantly, convalescent plasma contains SARS-CoV-2–neutralizing antibodies.[150,151] Convalescent plasma administration increases SARS-CoV-2 clearance in patients with COVID-19,[12,32] including immunocompromised individuals,[84,92,107,118] indicating an antiviral effect. Viral neutralization is then posited to reduce the inflammatory response and thus to lessen the likelihood that an overexuberant immune response progresses to lung damage, interference with gas exchange, and death. Additional evidence arising from animal studies shows that administration of human convalescent plasma is protective against SARS-CoV-2 infection.[152,153] Antibody-mediated interference with viral replication may increase tissue repair and eventually be manifested as reduced mortality. In addition, convalescent plasma transfusion is associated with reductions in inflammatory markers, such as chemokines, cytokines, and C-reactive protein.[124,154] Concomitant reductions in inflammation and improved gas exchange may underlie the reductions in oxygen requirements associated with convalescent plasma, even in critically ill patients. These findings provide mechanistic evidence for the reduction in mortality observed in patients receiving convalescent plasma.

There are several limitations to this analysis, including the aggregation of mortality data across study populations that varied by the nation of data origin, the timing relative to worldwide progression of the pandemic, the clinical diagnostic and treatment algorithms, the plasma antibody titer and administration volume, the latency between COVID-19 diagnosis and transfusion,

and the duration of follow-up after transfusion. Also, we did not consult a librarian when constructing our search terms. However, high-quality evidence from large RCTs remains unavailable, and the continuing global health emergency related to COVID-19 necessitated a practical real-time aggregation of existing mortality data. We note that the reports cited herein include positive results from different countries, suggesting that efficacy is robust across different health care systems. Given the safety of convalescent plasma administered to patients with COVID-19,[3,4] the results of this real-time systematic review and meta-analysis provide encouragement for its continued use 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 analyses received convalescent plasma transfusions later in their disease course. In this context, before antibiotics and effective vaccinations, convalescent plasma therapy was widely understood to be most efficacious very early in the course of hospitalizations.[2,155] As a result, our analysis may underestimate the mortality reduction achievable through early administration of high-titer convalescent plasma for COVID-19.

CONCLUSION

This real-time systematic review and meta-analysis of contemporaneous studies highlights that the mortality rate of transfused patients with COVID-19 was lower than that of nontransfused patients with COVID-19 and suggests that early transfusion of high-titer plasma represents the optimal use scenario to reduce the risk of mortality among patients with COVID-19. These results favor the efficacy of convalescent plasma as a COVID-19 therapeutic agent.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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