ORIGINAL ARTICLE

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

M.J. Joyner, R.E. Carter, J.W. Senefeld, S.A. Klassen, J.R. Mills, P.W. Johnson, E.S. Theel, C.C. Wiggins, K.A. Bruno, A.M. Klompas, E.R. Lesser, K.L. Kunze, M.A. Sexton, J.C. Diaz Soto, S.E. Baker, J.R.A. Shepherd, N. van Helmond, N.C. Verdun, P. Marks, C.M. van Buskirk, J.L. Winters, J.R. Stubbs, R.F. Rea, D.O. Hodge, V. Herasevich, E.R. Whelan, A.J. Clayburn, K.F. Larson, J.G. Ripoll, K.J. Andersen, M.R. Buras, M.N.P. Vogt, J.J. Dennis, R.J. Regimbal, P.R. Bauer, J.E. Blair, N.S. Paneth, D.L. Fairweather, R.S. Wright, and A. Casadevall

ABSTRACT

BACKGROUND
Convalescent plasma has been widely used to treat coronavirus disease 2019 (Covid-19) under the presumption that such plasma contains potentially therapeutic antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can be passively transferred to the plasma recipient. Whether convalescent plasma with high antibody levels rather than low antibody levels is associated with a lower risk of death is unknown.

METHODS
In a retrospective study based on a U.S. national registry, we determined the anti–SARS-CoV-2 IgG antibody levels in convalescent plasma used to treat hospitalized adults with Covid-19. The primary outcome was death within 30 days after plasma transfusion. Patients who were enrolled through July 4, 2020, and for whom data on anti–SARS-CoV-2 antibody levels in plasma transfusions and on 30-day mortality were available were included in the analysis.

RESULTS
Of the 3082 patients included in this analysis, death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group. The association of anti–SARS-CoV-2 antibody levels with the risk of death from Covid-19 was moderated by mechanical ventilation status. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before transfusion (relative risk, 0.66; 95% confidence interval [CI], 0.48 to 0.91), and no effect on the risk of death was observed among patients who had received mechanical ventilation (relative risk, 1.02; 95% CI, 0.78 to 1.32).

CONCLUSIONS
Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the Department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Joyner at the Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at joyner.michael@mayo.edu.

Drs. Joyner, Carter, and Senefeld and Drs. Paneth, Fairweather, Wright, and Casadevall contributed equally to this article.

Passive antibody transfer has been used to treat infections of the respiratory system for more than a century.[1-3] During the 1918 influenza pandemic, this therapeutic approach involved the widespread use of convalescent plasma or serum.[4] The coronavirus disease 2019 (Covid-19) pandemic has revived interest in the use of convalescent plasma for the treatment of patients with Covid-19. Despite this substantial interest, the efficacy signals are preliminary,[5,6] and the published results of randomized trials or matched treatment–control studies have been inconclusive.[7-23]

In response to the Covid-19 pandemic, the Mayo Clinic initiated the Covid-19 Convalescent Plasma Expanded-Access Program. The charter of the program was to provide access to and to assess the safety profile of convalescent plasma in patients with this illness, and additional exploratory analyses were performed. In a retrospective cohort study, we tested the hypothesis that the administration of convalescent plasma with high antibody levels would be associated with a lower risk of death than the administration of convalescent plasma with low antibody levels. To address this hypothesis, we evaluated mortality among a subgroup of hospitalized adults with Covid-19 who received transfusions of convalescent plasma and for whom data on anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG antibody levels in those transfusions were available.

METHODS

STUDY DESIGN AND OVERSIGHT

As described previously,[24,25] the expanded-access program was a national registry of hospitalized adults with Covid-19. All hospitals or acute care facilities in the United States and any physician licensed in the United States were eligible to participate, provided they agreed to adhere to the protocol (available with the full text of this article at NEJM.org) as well as to both federal and state regulations. The protocol was approved by the institutional review board of the Mayo Clinic, and the study was overseen by an independent data and safety monitoring board. Written informed consent was obtained from the patients or legally authorized representatives of the patients, or by means of an emergency consent process for patients with a medical condition that warranted this process. Full details of the study design, conduct,

oversight, and analyses are provided in the protocol and statistical analysis plan (also available at NEJM.org).

Eligible patients were 18 years of age or older and were hospitalized with a laboratory-confirmed diagnosis of SARS-CoV-2 infection. These patients also had or were at high risk for progression to severe or life-threatening Covid-19, with high risk defined as the presence of at least one risk factor for severe Covid-19 (see Table 1). The primary outcome of the study was mortality at 30 days after the transfusion of convalescent plasma.

TREATMENT

Convalescent plasma was obtained according to the standardized procedures of blood-collection centers.[26] These procedures included the assignment of a standardized identifying number (an International Society of Blood Transfusion [ISBT] 128 code) specific to the donor, and these numbers were used to link anti–SARS-CoV-2 IgG antibody levels with study outcomes corresponding to the plasma recipient or recipients.

One or more units of convalescent plasma were administered intravenously according to individual institutional protocols. The anti–SARS-CoV-2 IgG antibody levels corresponding to plasma units were unknown to the blood-collection centers, investigators, and patients at the time of transfusion.

PROCEDURES

We retrospectively surveyed and solicited blood-collection centers for aliquots of serum from remnant samples retained from the donation process. The shipment of biospecimens to the laboratory at the Mayo Clinic for analysis of antibodies was a voluntary act that was authorized by the institutional review board of the Mayo Clinic, but the shipment was not required. A total of 54 blood-collection centers agreed to ship biospecimens for analysis (Fig. 1).

Levels of binding antibodies from serum were assessed with the use of the VITROS Anti–SARS-CoV-2 IgG chemiluminescent immunoassay (Ortho-Clinical Diagnostics) in accordance with the manufacturer's instructions.[27] Although this assay does not differentiate binding IgG antibodies from virus-neutralizing IgG antibodies, a strong correlation has been shown between the amount of antispike protein IgG and in vitro virus neutralization.[28,29] This IgG chemilumines-

cent immunoassay is a qualitative assay that is based on the detection of IgG antibodies against a recombinant form of the SARS-CoV-2 spike subunit 1 protein. Numerical results of the assay correspond to the ratio of the sample signal to a calibrator-assigned cutoff signal (the signal-to-cutoff ratio).

Signal-to-cutoff ratios for anti–SARS-CoV-2 IgG antibody levels were categorized as low (<4.62), medium (4.62 to 18.45), or high (>18.45). The cutoff points corresponded approximately to the 20th and 80th percentiles of the distribution for the signal-to-cutoff ratio. The upper threshold for the IgG antibody signal-to-cutoff ratio was selected to provide 90% specificity for the detection of a dilution of the sample of 1:2560 or greater with the use of a new semiquantitative assay developed at the Mayo Clinic (in Rochester, MN). That assay measured the capacity to neutralize a pseudovirus bearing the SARS-CoV-2 spike protein. The 90% specificity was prespecified without knowledge of how the threshold would relate to survival and was selected on the basis of an a priori definition of a "high" antibody concentration (1:2560 was the maximum dilution for the assay). The lower threshold was selected to provide 90% sensitivity to detect neutralizing antibody titers of 1:160 or higher. Since the lower limit of detection of the pseudovirus assay was 1:80, the 1:160 titer was one dilution above the minimal detectable value. Web-based, standardized data-reporting surveys entered into the Research Electronic Data Capture system (REDCap, version 9.1.15; Vanderbilt University)[30,31] were used to assess the clinical and vital status of the patients, as previously described.[24,25]

STATISTICAL ANALYSIS

The sample size for this retrospective cohort study could not be determined a priori because of the uncertain number of available remnant samples linked to patient data in the registry. Patients who were enrolled through July 4, 2020, or during the first 3 months of the expanded-access program and for whom data on anti–SARS-CoV-2 antibody levels in plasma transfusions and on 30-day mortality were available were included in this analysis. An imputation program was not applied to the data; differences in sample size because of missing data are reported.

In order to mitigate the potentially confounding effects of the plasma volume transfused and to address the uncertainty of how to classify the antibody levels when more than one unit (potentially from different donors) was transfused, the analyses were restricted to patients who received a single unit of convalescent plasma. The database was maintained by the Mayo Clinic and was locked for this retrospective cohort study report on August 5, 2020.

In the primary analysis, we used a regression approach to estimate the relative risk of death at 30 days as a function of the relative anti–SARS-CoV-2 IgG antibody level (low, medium, or high), with or without adjustment for putative confounding variables and known risk factors for death (e.g., advanced age), particularly those that may have been imbalanced across the antibody levels. In this relative-risk regression model, we used a generalized linear model framework that included a log link and the robust variance estimator to correct for the misspecified variance structure (a Poisson distribution was used to improve convergence). This analysis assumed that all patients who were discharged were alive at day 30. To assess the sensitivity of that assumption, we used a Cox model that included patients who were excluded at discharge. To support these two model-based approaches, a classic stratified analysis based on the pooled Mantel–Haenszel estimator for relative risk was constructed. This approach allowed for stratum-by-stratum estimates of the association to be formed while providing a means to estimate the overall (pooled) association.

In addition, we used a gradient-boosting machine, a type of modern machine-learning algorithm that works on the principle of "weak learners" (i.e., the boosting algorithm begins with a simple classification algorithm and then extends the algorithm through the addition of decision trees to generate a single, comprehensive algorithm with a low error rate). Instead of trying to develop a singular prediction equation to link the antibody levels and adjustment variables with survival, we used an algorithm that builds a series of relatively simple decision trees. This series of trees is differentiated from a method such as random forests in that the trees are not independent — specifically, as the gradient-boosting machine builds a network of relatively simple classification algorithms, the observations that remain incorrectly classified are weighted differentially so that the model can learn subtleties that may be present in the data. Although each

Table 1. Characteristics of Patients with Covid-19 Who Received Convalescent Plasma, According to Anti–SARS-CoV-2 IgG Level.*

Variable	Low Titer (N=561)	Medium Titer (N=2006)	High Titer (N=515)	All Patients (N=3082)	P Value†
	number/total number (percent)				
Age category at enrollment					0.08
18–39 yr	59/561 (10.5)	155/2006 (7.7)	53/515 (10.3)	267/3082 (8.7)	
40–59 yr	185/561 (33.0)	689/2006 (34.3)	183/515 (35.5)	1057/3082 (34.3)	
60–69 yr	152/561 (27.1)	503/2006 (25.1)	143/515 (27.8)	798/3082 (25.9)	
70–79 yr	102/561 (18.2)	418/2006 (20.8)	86/515 (16.7)	606/3082 (19.7)	
≥80 yr	63/561 (11.2)	241/2006 (12.0)	50/515 (9.7)	354/3082 (11.5)	
Sex					0.14
Female	201/559 (36.0)	774/2002 (38.7)	221/515 (42.9)	1196/3076 (38.9)	
Male	357/559 (63.9)	1227/2002 (61.3)	293/515 (56.9)	1877/3076 (61.0)	
Undisclosed	1/559 (0.2)	1/2002 (<0.1)	1/515 (0.2)	3/3076 (0.1)	
Weight status					0.06
Underweight	7/511 (1.4)	32/1891 (1.7)	3/490 (0.6)	42/2892 (1.5)	
Normal weight	87/511 (17.0)	334/1891 (17.7)	84/490 (17.1)	505/2892 (17.5)	
Overweight	154/511 (30.1)	545/1891 (28.8)	115/490 (23.5)	814/2892 (28.1)	
Obese	263/511 (51.5)	980/1891 (51.8)	288/490 (58.8)	1531/2892 (52.9)	
Race or ethnic group‡					0.38
White	266/561 (47.4)	967/2006 (48.2)	234/515 (45.4)	1467/3082 (47.6)	
Black	125/561 (22.3)	443/2006 (22.1)	135/515 (26.2)	703/3082 (22.8)	
Other race	170/561 (30.3)	596/2006 (29.7)	146/515 (28.3)	912/3082 (29.6)	
Hispanic or Latino	223/561 (39.8)	747/2006 (37.2)	179/515 (34.8)	1149/3082 (37.3)	
Not Hispanic or Latino	338/561 (60.2)	1259/2006 (62.8)	336/515 (65.2)	1933/3082 (62.7)	
Clinical status					
Severe or life-threatening Covid-19	382/561 (68.1)	1286/2006 (64.1)	341/515 (66.2)	2009/3082 (65.2)	0.19
ICU care before infusion	344/561 (61.3)	1226/2006 (61.1)	298/515 (57.9)	1868/3082 (60.6)	0.38
Mechanical ventilation before infusion	183/548 (33.4)	666/1963 (33.9)	158/510 (31.0)	1007/3021 (33.3)	0.45
Risk factors for severe Covid-19 in subgroup of patients with severe or life-threatening Covid-19					
Respiratory failure	265/382 (69.4)	919/1286 (71.5)	231/341 (67.7)	1415/2009 (70.4)	0.36
Dyspnea	265/382 (69.4)	910/1286 (70.8)	241/341 (70.7)	1416/2009 (70.5)	0.87
Blood oxygen saturation ≤93%	269/382 (70.4)	909/1286 (70.7)	233/341 (68.3)	1411/2009 (70.2)	0.70
Lung infiltrates >50% within 24 to 48 hr	194/382 (50.8)	588/1286 (45.7)	147/341 (43.1)	929/2009 (46.2)	0.10
Respiratory rate ≥30 breaths/min	177/382 (46.3)	580/1286 (45.1)	157/341 (46.0)	914/2009 (45.5)	0.89
P_{AO_2}:F_{IO_2}<300	137/382 (35.9)	451/1286 (35.1)	93/341 (27.3)	681/2009 (33.9)	0.02
Multiple organ dysfunction or failure§	65/382 (17.0)	227/1286 (17.7)	48/341 (14.1)	340/2009 (16.9)	0.29
Septic shock§	56/382 (14.7)	188/1286 (14.6)	44/341 (12.9)	288/2009 (14.3)	0.71
Lung infiltrates or low P_{AO_2}:F_{IO_2}§	223/382 (58.4)	725/1286 (56.4)	175/341 (51.3)	1123/2009 (55.9)	0.14

Variable	Low Titer (N=561)	Medium Titer (N=2006)	High Titer (N=515)	All Patients (N=3082)	P Value†
			number/total number (percent)		
Medications received during hospital stay					
ARB	27/489 (5.5)	107/1733 (6.2)	24/425 (5.6)	158/2647 (6.0)	0.83
ACEI	40/489 (8.2)	175/1733 (10.1)	35/425 (8.2)	250/2647 (9.4)	0.29
Azithromycin	277/489 (56.6)	923/1733 (53.3)	226/425 (53.2)	1426/2647 (53.9)	0.40
Remdesivir	164/489 (33.5)	538/1733 (31.0)	130/425 (30.6)	832/2647 (31.4)	0.53
Corticosteroids	251/489 (51.3)	899/1733 (51.9)	209/425 (49.2)	1359/2647 (51.3)	0.61
Chloroquine	4/489 (0.8)	4/1733 (0.2)	1/425 (0.2)	9/2647 (0.3)	0.13
Hydroxychloroquine	174/489 (35.6)	595/1733 (34.3)	99/425 (23.3)	868/2647 (32.8)	<0.001
Study time period					0.08
April 4 to May 14	245/561 (43.7)	980/2006 (48.9)	253/515 (49.1)	1478/3082 (48.0)	
May 15 to July 4	316/561 (56.3)	1026/2006 (51.1)	262/515 (50.9)	1604/3082 (52.0)	

Table 1. (Continued.)

* Percentages may not total 100 because of rounding. ACEI denotes angiotensin-converting-enzyme inhibitor, ARB angiotensin-receptor blocker, ICU intensive care unit, $P_{AO_2}:F_{IO_2}$ ratio of the partial pressure of alveolar oxygen to the fraction of inspired oxygen, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† P values should be interpreted as summary statistics that quantify empirical variation of multilevel variables across multiple groups, and they should not be interpreted as results of hypothesis tests. In particular, the P values are compared with a type I error threshold to test specific hypotheses.

‡ Race and ethnic group were reported by the investigators. In the "other race" category, 115 patients were Asian, 24 were multiracial, and 773 had race that was reported as "unknown" by the study site.

§ Life-threatening Covid-19 was defined as the development of respiratory failure, septic shock, or multiple organ dysfunction or failure.

method was distinct in approach, each attempted to account for potential confounding and risk modification with the use of different statistical techniques.

We also examined patient subgroups that were selected on the basis of historical experience with convalescent plasma, and in adjusted models we chose variables that were similar to those in trials of other therapeutic agents for Covid-19.[32,33] Mechanical-ventilation status has emerged as a key factor in determining the effectiveness of leading therapeutic agents for Covid-19, including dexamethasone[34] and remdesivir,[32] and we used it to dichotomize the cohort for subgroup analyses.
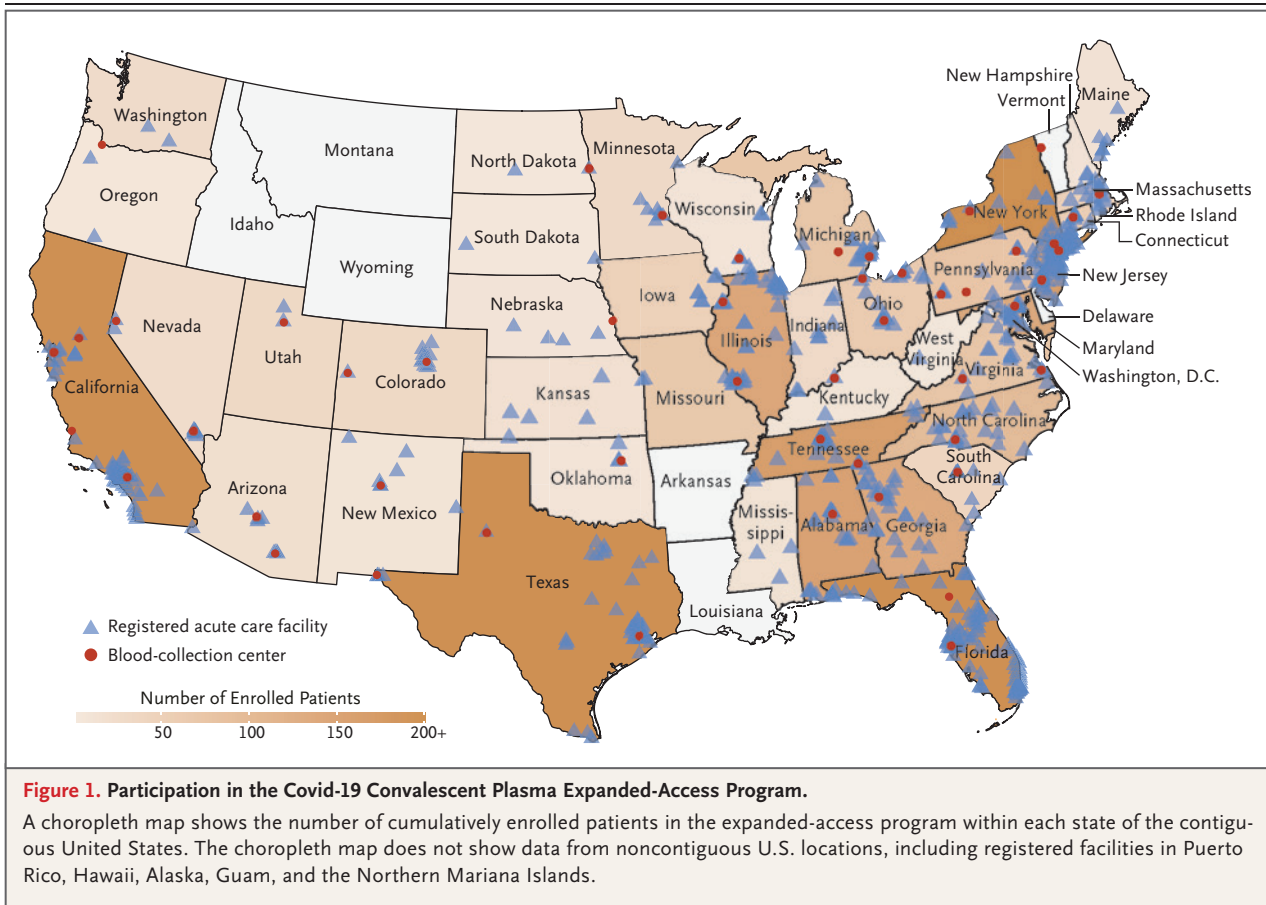
Analyses were performed with the use of R software (R Core Team).[35] Descriptive statistics are presented as frequencies and percentages. The interpretation of the findings was based on the 95% confidence intervals for the estimated measures of association. For analyses of time to transfusion, the point estimates for mortality were estimated at day 30 on the basis of crude mortality and confidence intervals for binomial proportions calculated with the use of the Wilson method. The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects. Reported P values are two-sided. Additional details about the statistical analyses are provided in the Supplementary Statistical Methods section of the Supplementary Appendix (available at NEJM.org).

RESULTS

PATIENTS

The cohort consisted of 3082 patients from 680 acute care facilities across the United States (Fig. 1). Table 1 shows key characteristics of the patients, stratified into three groups according to anti–SARS-CoV-2 IgG antibody levels (based on signal-to-cutoff ratios). Overall, 61% of the patients were men, 23% were Black, 37% were

Figure 1. Participation in the Covid-19 Convalescent Plasma Expanded-Access Program.
A choropleth map shows the number of cumulatively enrolled patients in the expanded-access program within each state of the contiguous United States. The choropleth map does not show data from noncontiguous U.S. locations, including registered facilities in Puerto Rico, Hawaii, Alaska, Guam, and the Northern Mariana Islands.

Hispanic, 69% were younger than 70 years of age, and two thirds had received transfusions before invasive mechanical ventilation. The median number of patients per site was 2 (interquartile range, 1 to 6). The maximum number of patients from any single site was 59. As shown in Table 1, the three groups (patients who received plasma transfusions with high, medium, and low IgG antibody levels) were generally similar in terms of demographic characteristics, risk factors associated with severe Covid-19, and concomitant use of therapeutic agents for Covid-19. The percentages of patients with hypoxemia and concomitant use of hydroxychloroquine (both of which were variables that were included in adjustment models) were lower in the high-titer group than in the other two groups.

PRIMARY OUTCOME

Death within 30 days after plasma transfusion occurred in 26.9% of all the patients (830 of

3082 patients; 95% confidence interval [CI], 25.4 to 28.5). This primary-outcome event occurred in 29.6% (166 of 561 patients) in the low-titer group, 27.4% (549 of 2006 patients) in the medium-titer group, and 22.3% (115 of 515 patients) in the high-titer group. Patients in the high-titer group had a lower relative risk of death within 30 days after transfusion than patients in the low-titer group (relative risk, 0.75; 95% CI, 0.61 to 0.93) (Table 2). Additional analyses with adjustment for patient demographic characteristics (age, weight status, and race) and clinical characteristics (receipt of invasive mechanical ventilation, use of concomitant therapeutics, and hypoxemia) were conducted to evaluate the overall effect of the anti–SARS-CoV-2 IgG antibody level on the risk of death within 30 days after transfusion (Table S1 in the Supplementary Appendix). The adjusted models (as defined in Table 2) generally showed a similar association — a lower relative risk of death among patients who received plasma trans-

fusions with high anti–SARS-CoV-2 IgG antibody levels (model 2, relative risk, 0.79 [95% CI, 0.65 to 0.96], and model 3 [with additional adjustment], relative risk, 0.82 [95% CI, 0.67 to 1.00]) (Table 2). The findings of the sensitivity analysis in which patients were excluded at discharge were qualitatively similar to each of these findings.

SUBGROUP ANALYSIS

In the cohort of 3082 patients, 2014 patients did not receive mechanical ventilation before transfusion. Table 3 shows key patient characteristics of the subgroup of patients who were not receiving mechanical ventilation, stratified according to anti–SARS-CoV-2 IgG antibody levels. In the subgroup of patients who were not receiving mechanical ventilation, death within 30 days after plasma transfusion occurred in 81 of 365 patients (22.2%; 95% CI, 18.2 to 26.7) in the low-titer group, 251 of 1297 patients (19.4%; 95% CI, 17.3 to 21.6) in the medium-titer group, and 50 of 352 patients (14.2%; 95% CI, 10.9 to 18.2) in the high-titer group; Table S4 shows these results in the subgroup of patients who were receiving mechanical ventilation. In the subgroup of patients who were receiving mechanical ventilation, death within 30 days after plasma transfusion occurred in 80 of 183 patients (43.7%; 95% CI, 36.7 to 51.0) in the low-titer group, 277 of 666 patients (41.6%; 95% CI, 37.9 to 45.4) in the medium-titer group, and 64 of 158 patients (40.5; 95% CI, 33.2 to 48.3) in the high-titer group. In both subgroups, the characteristics of the patients were well balanced across the three antibody-titer groups.

In the fully adjusted relative risk regression model, the lower risk of death within 30 days after plasma transfusion in the high-titer group than in the low-titer group was observed among patients who were not receiving mechanical ventilation before transfusion (relative risk, 0.66; 95% CI, 0.48 to 0.91). No effect on mortality was observed among patients who received mechanical ventilation before transfusion (relative risk, 1.02; 95% CI, 0.78 to 1.32).

Table S2 shows relative-risk regression with or without full adjustment for patient demographic characteristics, anti–SARS-CoV-2 IgG antibody levels, clinical characteristics, and study time period, including all three models (the base model, model 2, and model 3), for the subgroup of patients who were not receiving mechanical venti-

Table 2. Models of the Association between Anti–SARS-CoV-2 Antibody Levels in Transfused Plasma and the Risk of Death.*

Cohort, Model, and Titer Level	No. of Patients	Estimated Relative Risk (95% CI)
Entire cohort		
Base model	3082	
Low titer		Reference
Medium titer		0.92 (0.80–1.07)
High titer		0.75 (0.61–0.93)
Model 2	3021	
Low titer		Reference
Medium titer		0.89 (0.77–1.02)
High titer		0.79 (0.65–0.96)
Model 3	2858	
Low titer		Reference
Medium titer		0.90 (0.78–1.05)
High titer		0.82 (0.67–1.00)
Patients not receiving mechanical ventilation		
Base model	2014	
Low titer		Reference
Medium titer		0.87 (0.70–1.09)
High titer		0.64 (0.46–0.88)
Model 2	2014	
Low titer		Reference
Medium titer		0.86 (0.69–1.06)
High titer		0.67 (0.49–0.91)
Model 3	1936	
Low titer		Reference
Medium titer		0.87 (0.71–1.08)
High titer		0.66 (0.48–0.91)
Patients receiving mechanical ventilation		
Base model	1007	
Low titer		Reference
Medium titer		0.95 (0.79–1.15)
High titer		0.93 (0.72–1.19)
Model 2	1007	
Low titer		Reference
Medium titer		0.94 (0.78–1.13)
High titer		0.93 (0.73–1.19)
Model 3	922	
Low titer		Reference
Medium titer		0.99 (0.81–1.21)
High titer		1.02 (0.78–1.32)

* Anti–SARS-CoV-2 IgG signal-to-cutoff ratios were used to stratify samples into three groups (low, <4.62; medium, 4.62 to 18.45; and high, >18.45). The base model was adjusted for anti–SARS-CoV-2 IgG levels; model 2 was adjusted for age, anti–SARS-CoV-2 IgG levels, and time period; and model 3 was adjusted for age, body-mass index, receipt of hydroxychloroquine, anti–SARS-CoV-2 IgG levels, hypoxemia, race or ethnic group, and time period. CI denotes confidence interval.

Table 3. Characteristics of Patients with Covid-19 Who Were Not Receiving Mechanical Ventilation and Who Received Convalescent Plasma, According to Anti–SARS-CoV-2 IgG Level.*

Variable	Low Titer (N=365)	Medium Titer (N=1297)	High Titer (N=352)	All Patients (N=2014)	P Value†
	number/total number (percent)				
Age category at enrollment					0.07
18–39 yr	38/365 (10.4)	110/1297 (8.5)	41/352 (11.6)	189/2014 (9.4)	
40–59 yr	127/365 (34.8)	445/1297 (34.3)	122/352 (34.7)	694/2014 (34.5)	
60–69 yr	92/365 (25.2)	301/1297 (23.2)	95/352 (27.0)	488/2014 (24.2)	
70–79 yr	53/365 (14.5)	260/1297 (20.0)	57/352 (16.2)	370/2014 (18.4)	
≥80 yr	55/365 (15.1)	181/1297 (14.0)	37/352 (10.5)	273/2014 (13.6)	
Sex					0.57
Female	132/363 (36.4)	519/1294 (40.1)	140/352 (39.8)	791/2009 (39.4)	
Male	230/363 (63.4)	774/1294 (59.8)	211/352 (59.9)	1215/2009 (60.5)	
Undisclosed	1/363 (0.3)	1/1294 (0.1)	1/352 (0.3)	3/2009 (0.1)	
Weight status					0.20
Underweight	5/346 (1.4)	25/1251 (2.0)	1/339 (0.3)	31/1936 (1.6)	
Normal weight	67/346 (19.4)	246/1251 (19.7)	63/339 (18.6)	376/1936 (19.4)	
Overweight	104/346 (30.1)	358/1251 (28.6)	86/339 (25.4)	548/1936 (28.3)	
Obese	170/346 (49.1)	622/1251 (49.7)	189/339 (55.8)	981/1936 (50.7)	
Race or ethnic group‡					0.06
White	186/365 (51.0)	646/1297 (49.8)	171/352 (48.6)	1003/2014 (49.8)	
Black	65/365 (17.8)	279/1297 (21.5)	93/352 (26.4)	437/2014 (21.7)	
Other race	114/365 (31.2)	372/1297 (28.7)	88/352 (25.0)	574/2014 (28.5)	
Hispanic or Latino	152/365 (41.6)	479/1297 (36.9)	119/352 (33.8)	750/2014 (37.2)	
Not Hispanic or Latino	213/365 (58.4)	818/1297 (63.1)	233/352 (66.2)	1264/2014 (62.8)	
Clinical status					
Current severe or life-threatening Covid-19	203/365 (55.6)	648/1297 (50.0)	198/352 (56.2)	1049/2014 (52.1)	0.04
ICU care before infusion	153/365 (41.9)	534/1297 (41.2)	138/352 (39.2)	825/2014 (41.0)	0.74
Severe risk factors in subgroup of patients with severe or life-threatening Covid-19					
Respiratory failure	107/203 (52.7)	332/648 (51.2)	96/198 (48.5)	535/1049 (51.0)	0.69
Dyspnea	175/203 (86.2)	550/648 (84.9)	170/198 (85.9)	895/1049 (85.3)	0.87
Blood oxygen saturation ≤93%	173/203 (85.2)	526/648 (81.2)	158/198 (79.8)	857/1049 (81.7)	0.32
Lung infiltrates >50% within 24 to 48 hr	103/203 (50.7)	265/648 (40.9)	88/198 (44.4)	456/1049 (43.5)	0.04
Respiratory rate ≥30 breaths/min	101/203 (49.8)	294/648 (45.4)	96/198 (48.5)	491/1049 (46.8)	0.48
$Pa_{O_2}:F_{I_{O_2}}<300$	57/203 (28.1)	153/648 (23.6)	38/198 (19.2)	248/1049 (23.6)	0.11
Multiple organ dysfunction or failure	21/203 (10.3)	50/648 (7.7)	14/198 (7.1)	85/1049 (8.1)	0.41
Septic shock	14/203 (6.9)	29/648 (4.5)	9/198 (4.5)	52/1049 (5.0)	0.37
Lung infiltrates or low $Pa_{O_2}:F_{I_{O_2}}$	116/203 (57.1)	314/648 (48.5)	99/198 (50.0)	529/1049 (50.4)	0.10

Table 3. (Continued.)

Variable	Low Titer (N=365)	Medium Titer (N=1297)	High Titer (N=352)	All Patients (N=2014)	P Value†
	number/total number (percent)				
Medications received during hospital stay					
ARB	20/317 (6.3)	72/1119 (6.4)	22/288 (7.6)	114/1724 (6.6)	0.74
ACEI	29/317 (9.1)	108/1119 (9.7)	21/288 (7.3)	158/1724 (9.2)	0.46
Azithromycin	172/317 (54.3)	562/1119 (50.2)	150/288 (52.1)	884/1724 (51.3)	0.43
Remdesivir	125/317 (39.4)	397/1119 (35.5)	97/288 (33.7)	619/1724 (35.9)	0.30
Corticosteroids	146/317 (46.1)	521/1119 (46.6)	131/288 (45.5)	798/1724 (46.3)	0.94
Chloroquine	2/317 (0.6)	2/1119 (0.2)	1/288 (0.3)	5/1724 (0.3)	0.41
Hydroxychloroquine	88/317 (27.8)	278/1119 (24.8)	51/288 (17.7)	417/1724 (24.2)	0.01
Days to transfusion (range)	4 (0–33)	4 (0–38)	4 (0–34)	4 (0–38)	0.56
Study time period					0.05
April 4 to May 14	125/365 (34.2)	515/1297 (39.7)	151/352 (42.9)	791/2014 (39.3)	
May 15 to July 4	240/365 (65.8)	782/1297 (60.3)	201/352 (57.1)	1223/2014 (60.7)	

* Percentages may not total 100 because of rounding. Anti–SARS-CoV-2 IgG signal-to-cutoff ratios were used to stratify samples into three groups (low, <4.62; medium, 4.62 to 18.45; and high, >18.45).
† P values should be interpreted as summary statistics that quantify empirical variation of multilevel variables across multiple groups, and they should not be interpreted as results of hypothesis tests. In particular, the P values are not compared with a type I error threshold to test specific hypotheses.
‡ Race and ethnic group were reported by the investigators. In the "other race" category, 76 of the patients were Asian, 13 were multiracial, and 485 had race that was reported as "unknown" by the study site.

lation. Table S3 shows relative-risk regression for the subgroup of patients who were receiving mechanical ventilation.

These findings were further supported by a stratified-data analytic approach that provided direct analytic control for the key variables associated with the risk of death (age, receipt of invasive mechanical ventilation, and study time period) (Fig. 2). The pooled (or common) relative risk of death among all the patients within 30 days after plasma transfusion in the high-titer group, as compared with the low-titer group, was 0.80 (95% CI, 0.65 to 0.97) (Fig. 2). Figure S1 shows the risk of death within 7 days after transfusion of convalescent plasma, as determined with this stratified data analytic approach.

EXPLORATORY ANALYSES

Among patients who received mechanical ventilation before transfusion, the mean (±SD) number of days between the diagnosis of Covid-19 and the transfusion of convalescent plasma was 10.0±7.7; this was nearly double the mean number of days among patients who were not receiving

mechanical ventilation (5.4±4.8). The unadjusted mortality within 30 days after transfusion was lower among patients who received a transfusion within 3 days after receiving a diagnosis of Covid-19 (point estimate, 22.2%; 95% CI, 19.9 to 24.8) than among those who received a transfusion 4 or more days after receiving a diagnosis of Covid-19 (point estimate, 29.5%; 95% CI, 27.6 to 31.6). In model 3, the replacement of ventilation status with a binary classification of days to transfusion resulted in a relative risk of death of 1.18 (95% CI, 1.04 to 1.35) among patients who received a transfusion 4 or more days after receiving the diagnosis. This effect size was lower than that observed in patients who had previously received mechanical ventilation in model 3 (relative risk, 2.16; 95% CI, 1.90 to 2.46).

The trained gradient-boosting machine was used to estimate the relationship between key variables associated with risk of death within 30 days after plasma transfusion and mortality at 30 days. Two methods were used to explore how this machine-learning technique linked the key variables with the mortality predictions.
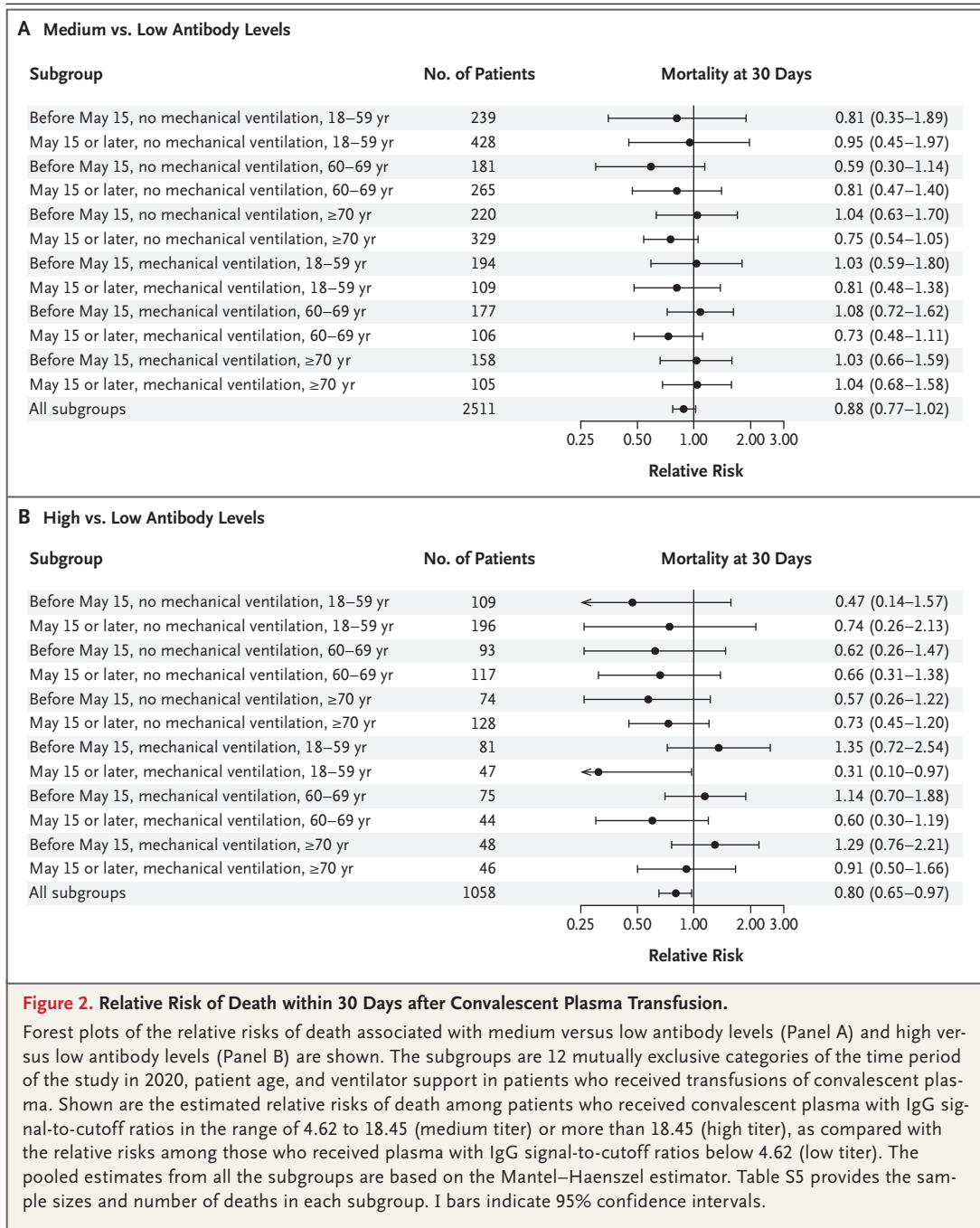
A Medium vs. Low Antibody Levels

Subgroup	No. of Patients	Mortality at 30 Days	
Before May 15, no mechanical ventilation, 18–59 yr	239		0.81 (0.35–1.89)
May 15 or later, no mechanical ventilation, 18–59 yr	428		0.95 (0.45–1.97)
Before May 15, no mechanical ventilation, 60–69 yr	181		0.59 (0.30–1.14)
May 15 or later, no mechanical ventilation, 60–69 yr	265		0.81 (0.47–1.40)
Before May 15, no mechanical ventilation, ≥70 yr	220		1.04 (0.63–1.70)
May 15 or later, no mechanical ventilation, ≥70 yr	329		0.75 (0.54–1.05)
Before May 15, mechanical ventilation, 18–59 yr	194		1.03 (0.59–1.80)
May 15 or later, mechanical ventilation, 18–59 yr	109		0.81 (0.48–1.38)
Before May 15, mechanical ventilation, 60–69 yr	177		1.08 (0.72–1.62)
May 15 or later, mechanical ventilation, 60–69 yr	106		0.73 (0.48–1.11)
Before May 15, mechanical ventilation, ≥70 yr	158		1.03 (0.66–1.59)
May 15 or later, mechanical ventilation, ≥70 yr	105		1.04 (0.68–1.58)
All subgroups	2511		0.88 (0.77–1.02)

0.25 0.50 1.00 2.00 3.00
Relative Risk

B High vs. Low Antibody Levels

Subgroup	No. of Patients	Mortality at 30 Days	
Before May 15, no mechanical ventilation, 18–59 yr	109		0.47 (0.14–1.57)
May 15 or later, no mechanical ventilation, 18–59 yr	196		0.74 (0.26–2.13)
Before May 15, no mechanical ventilation, 60–69 yr	93		0.62 (0.26–1.47)
May 15 or later, no mechanical ventilation, 60–69 yr	117		0.66 (0.31–1.38)
Before May 15, no mechanical ventilation, ≥70 yr	74		0.57 (0.26–1.22)
May 15 or later, no mechanical ventilation, ≥70 yr	128		0.73 (0.45–1.20)
Before May 15, mechanical ventilation, 18–59 yr	81		1.35 (0.72–2.54)
May 15 or later, mechanical ventilation, 18–59 yr	47		0.31 (0.10–0.97)
Before May 15, mechanical ventilation, 60–69 yr	75		1.14 (0.70–1.88)
May 15 or later, mechanical ventilation, 60–69 yr	44		0.60 (0.30–1.19)
Before May 15, mechanical ventilation, ≥70 yr	48		1.29 (0.76–2.21)
May 15 or later, mechanical ventilation, ≥70 yr	46		0.91 (0.50–1.66)
All subgroups	1058		0.80 (0.65–0.97)

0.25 0.50 1.00 2.00 3.00
Relative Risk

Figure 2. Relative Risk of Death within 30 Days after Convalescent Plasma Transfusion.

Forest plots of the relative risks of death associated with medium versus low antibody levels (Panel A) and high versus low antibody levels (Panel B) are shown. The subgroups are 12 mutually exclusive categories of the time period of the study in 2020, patient age, and ventilator support in patients who received transfusions of convalescent plasma. Shown are the estimated relative risks of death among patients who received convalescent plasma with IgG signal-to-cutoff ratios in the range of 4.62 to 18.45 (medium titer) or more than 18.45 (high titer), as compared with the relative risks among those who received plasma with IgG signal-to-cutoff ratios below 4.62 (low titer). The pooled estimates from all the subgroups are based on the Mantel–Haenszel estimator. Table S5 provides the sample sizes and number of deaths in each subgroup. I bars indicate 95% confidence intervals.

In the first method, a variable importance plot was generated for each variable included in the model (Fig. S2). The "importance" of the variable is the relative amount by which it improves the prediction, both in terms of location in the decision trees (where more observations are classified higher up in the decision tree) and in the number of times it is used in the collection of trees. The primary variables associated with a risk of death at 30 days were age; evidence of an advanced clinical course of Covid-19, such as the receipt of invasive mechanical ventilation and admission to an intensive care unit (ICU); and the anti–SARS-CoV-2 antibody level, in order of variable importance.

The second method used to explore the asso-

ciation between a given variable and prediction of mortality was by means of a partial dependence plot. The partial dependence plot shows that after adjustment for all other variables included in the model, anti–SARS-CoV-2 IgG antibody levels maintained an inverse relationship with the risk of death. Figure S3 shows similar partial dependence plots for the primary analysis model in which the antibody levels were treated as a continuous variable with the use of a natural spline with four evenly spaced knots. In this model, the partial dependence plot for the overall sample aligned closely with the pattern observed in the gradient-boosting machine model. The inverse relationship with antibody levels was again observed in the patients who were not receiving mechanical ventilation, and there was a general lack of a clear association in these patients.

DISCUSSION

In a retrospective study based on a national registry, convalescent plasma was identified as a potentially beneficial therapy in hospitalized patients with Covid-19. Our principal finding was that among patients with Covid-19 who were not receiving mechanical ventilation, the transfusion of plasma with high antibody levels was associated with a lower risk of death than the transfusion of plasma with low antibody levels. We found no such relationship (between antibody level and the risk of death) among patients with Covid-19 who were receiving mechanical ventilation. In addition, patients who received plasma within 3 days after receiving a diagnosis of Covid-19 had a lower risk of death than those who received transfusions later in the disease course.

These data were consistent with a mortality benefit associated with high-titer plasma administered earlier in the course of the disease. Our findings parallel the recent findings from a trial of the antiviral agent remdesivir in which clinical benefit was evident among patients who were not receiving advanced respiratory support and absent among patients who were receiving noninvasive high-flow oxygen or mechanical ventilation.[32,36,37] Our findings are also consistent with aggregate data from observational studies and randomized trials of convalescent plasma,[7,9,38,39] as well as with historical evidence regarding antibody therapy for infectious diseases.[3] Our data and those from other studies provide support for the use of anti–SARS-CoV-2 antibody assays as an indicator of the potency of Covid-19 convalescent plasma.

Although patient age was not the primary focus of these analyses, it was estimated to be the most important variable in predicting the risk of death within 30 days after plasma transfusion. The next two most important correlates of this risk — receipt of invasive mechanical ventilation and admission to the ICU — occur late in the course of the disease, when the level of antibodies in the transfused plasma does not appear to affect the risk of death.

Numerous challenges that were encountered during this program were similar to those enumerated elsewhere.[32] To overcome these contextual challenges during a pandemic,[40] we developed a streamlined registration and data-collection system with oversight from a centralized institutional review board. However, several limitations resulted from this design, including limited participation in this retrospective cohort study, limited availability of data owing to the use of abbreviated data-collection forms, the lack of precision in details regarding the temporal relationship between concomitant medication use and transfusion, and missing data (a problem inherent to a national registry). We determined a priori that the low-titer group may have been at higher risk for death than the high-titer group. In addition, the interpretation of these results is limited by the open-label design and the lack of a randomized placebo (control) group. Finally, the study enrollment progressed quickly, and this article was prepared before the second surge of patients had been entered into the expanded-access program (Fig. S4). Although the overall program eventually enrolled more than 105,000 patients — including nearly 94,000 patients who received transfusions — only one third of the data were available for these analyses. Further efforts to obtain antibody data on a larger cohort of patients in the expanded-access program are under way.

These findings were an important component of the scientific evidence considered by the Food and Drug Administration in the decision on August 23, 2020, to issue an emergency-use authorization for convalescent plasma in the treatment of hospitalized adults with Covid-19.[41] Convalescent plasma has also received full or conditional approval in several other countries since that time.

Our analyses show that among patients with Covid-19 who were not receiving mechanical ventilation, the transfusion of plasma with high antibody levels was associated with a lower risk of death than the transfusion of plasma with low antibody levels. In addition, patients who received plasma within 3 days after the diagnosis of Covid-19 had a lower risk of death than those who received a transfusion later in the disease course. These data show that the benefit of convalescent plasma was most apparent in patients who received plasma transfusions containing higher levels of anti–SARS-CoV-2 IgG antibodies early in the disease course.

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of Health and Human Services and its agencies, including the Biomedical Advanced Research and Development Authority (BARDA) and the Food and Drug Administration, as well as any other agency of the U.S. Government. Assumptions made within and interpretations from the analysis do not necessarily reflect the position of any U.S. Government entity.

APPENDIX

The authors' full names and academic degrees are as follows: Michael J. Joyner, M.D., Rickey E. Carter, Ph.D., Jonathon W. Senefeld, Ph.D., Stephen A. Klassen, Ph.D., John R. Mills, Ph.D., Patrick W. Johnson, B.S., Elitza S. Theel, Ph.D., Chad C. Wiggins, Ph.D., Katelyn A. Bruno, Ph.D., Allan M. Klompas, M.B., B.Ch., B.A.O., Elizabeth R. Lesser, M.S., Katie L. Kunze, Ph.D., Matthew A. Sexton, M.D., Juan C. Diaz Soto, M.D., Sarah E. Baker, Ph.D., John R.A. Shepherd, M.D., Noud van Helmond, M.D., Nicole C. Verdun, M.D., Peter Marks, M.D., Ph.D., Camille M. van Buskirk, M.D., Jeffrey L. Winters, M.D., James R. Stubbs, M.D., Robert F. Rea, M.D., David O. Hodge, M.S., Vitaly Herasevich, M.D., Ph.D., Emily R. Whelan, B.S., Andrew J. Clayburn, B.S., Kathryn F. Larson, M.D., Juan G. Ripoll, M.D., Kylie J. Andersen, B.S., Matthew R. Buras, M.S., Matthew N.P. Vogt, M.D., Joshua J. Dennis, B.S., Riley J. Regimbal, B.S., Philippe R. Bauer, M.D., Ph.D., Janis E. Blair, M.D., Nigel S. Paneth, M.D., M.P.H., DeLisa Fairweather, Ph.D., R. Scott Wright, M.D., and Arturo Casadevall, M.D., Ph.D.

The authors' affiliations are as follows: the Departments of Anesthesiology and Perioperative Medicine (M.J.J., J.W.S., S.A.K., C.C.W., A.M.K., M.A.S., J.C.D.S., S.E.B., J.R.A.S., V.H., A.J.C., J.G.R., K.J.A., M.N.P.V., J.J.D., R.J.R.), Laboratory Medicine and Pathology (J.R.M., E.S.T., C.M.B., J.L.W., J.R.S.), and Cardiovascular Medicine (R.F.R., K.F.L., R.S.W.), the Human Research Protection Program (R.S.W.), and the Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine (P.R.B.), Mayo Clinic, Rochester, MN; the Departments of Health Sciences Research (R.E.C., P.W.J., E.R.L., D.O.H.) and Cardiovascular Medicine (K.A.B., E.R.W., D.F.), Mayo Clinic, Jacksonville, FL; the Department of Health Sciences Research (K.L.K., M.R.B.) and the Department of Internal Medicine, Division of Infectious Diseases (J.E.B.), Mayo Clinic, Phoenix, AZ; the Department of Anesthesiology, Cooper Medical School of Rowan University, Cooper University Health Care, Camden, NJ (N.H.); the Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring (N.C.V., P.M.), and the Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore (A.C.) — both in Maryland; and the Departments of Epidemiology and Biostatistics and of Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing (N.S.P.).

REFERENCES

1. Luke TC, Casadevall A, Watowich SJ, Hoffman SL, Beigel JH, Burgess TH. Hark back: passive immunotherapy for influenza and other serious infections. Crit Care Med 2010;38:4 Suppl:e66-e73.
2. Casadevall A, Scharff MD. Serum therapy revisited: animal models of infection and development of passive antibody therapy. Antimicrob Agents Chemother 1994;38:1695-702.
3. Casadevall A, Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. Clin Infect Dis 1995;21:150-61.

4. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med 2006;145:599-609.
5. Chai KL, Valk SJ, Piechotta V, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev 2020;10:CD013600.
6. Klassen SA, Senefeld JW, Johnson PW, et al. Evidence favoring the efficacy of convalescent plasma for COVID-19 therapy. October 29, 2020 (https://www .medrxiv.org/content/10.1101/2020.07.29 .20162917v3). preprint.
7. 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.
8. Salazar E, Perez KK, Ashraf M, et al. Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. Am J Pathol 2020;190:1680-90.
9. Rasheed AM, Fatak DF, Hashim HA, et al. The therapeutic potential of conva-

lescent 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.

10. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, et al. Convalescent plasma for COVID-19: a multicenter, randomized clinical trial. September 29, 2020 (https://www.medrxiv.org/content/10.1101/2020.08.26.20182444v3). preprint.

11. Gharbharan A, Jordans CCE, Geurts-vanKessel C, et al. Convalescent plasma for COVID-19: a randomized clinical trial. July 3, 2020 (https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1). preprint.

12. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020; 371:m3939.

13. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020;117:9490-6.

14. Perotti C, Baldanti F, Bruno R, et al. Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma: a proof of concept single arm multicenter trial. Haematologica 2020;105: 2834-40.

15. Omrani AS, Zaqout A, Baiou A, et al. Convalescent plasma for the treatment of patients with severe coronavirus disease 2019: a preliminary report. J Med Virol 2020 September 23 (Epub ahead of print).

16. Hegerova L, Gooley TA, Sweerus KA, et al. Use of convalescent plasma in hospitalized patients with COVID-19: case series. Blood 2020;136:759-62.

17. Zeng Q-L, Yu Z-J, Gou J-J, et al. Effect of convalescent plasma therapy on viral shedding and survival in patients with coronavirus disease 2019. J Infect Dis 2020;222:38-43.

18. Donato M, Park S, Baker M, et al. Clinical and laboratory evaluation of patients with SARS-CoV-2 pneumonia treated with high-titer convalescent plasma: a prospective study. August 4, 2020 (https://www.medrxiv.org/content/10.1101/2020.07.20.20156398v3). preprint.

19. Salazar MR, González SE, Regairaz L, et al. Effect of convalescent plasma on mortality in patients with COVID-19 pneumonia. October 9, 2020 (https://www.medrxiv.org/content/10.1101/2020.10.08.20202606v1). preprint.

20. Xia X, Li K, Wu L, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood 2020;136:755-9.

21. Abolghasemi H, Eshghi P, Cheraghali AM, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study. Transfus Apher Sci 2020;59: 102875.

22. Rogers R, Shehadeh F, Mylona EK, et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study. Clin Infect Dis 2020 October 10 (Epub ahead of print).

23. Altuntas F, Ata N, Yigenoglu TN, et al. Convalescent plasma therapy in patients with COVID-19. Transfus Apher Sci 2020 September 19 (Epub ahead of print).

24. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc 2020;95:1888-97.

25. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest 2020;130:4791-7.

26. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 2020;130:2757-65.

27. Theel ES, Harring J, Hilgart H, Granger D. Performance characteristics of four high-throughput immunoassays for detection of IgG antibodies against SARS-CoV-2. J Clin Microbiol 2020;58(8):e01243-20.

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.

29. Luchsinger LL, Ransegnola BP, Jin DK, et al. Serological assays estimate highly variable SARS-CoV-2 neutralizing antibody activity in recovered COVID-19 patients. J Clin Microbiol 2020;58(12): e02005-20.

30. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95: 103208.

31. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) — a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.

32. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 2020; 383:1813-26.

33. The RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;383:2030-40.

34. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2021436.

35. R Core Team. R: a language and environment for statistical computing. Vienna: Foundation for Statistical Computing, 2013.

36. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-78.

37. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020;324:1048-57.

38. 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.

39. 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.

40. Rojek AM, Horby PW. Modernising epidemic science: enabling patient-centred research during epidemics. BMC Med 2016;14:212.

41. Food and Drug Administration. Clinical memorandum for the Emergency Use Authorization of COVID-19 convalescent plasma. 2020 (https://www.fda.gov/media/141480/download).