ORIGINAL ARTICLE

Convalescent Plasma for Covid-19–Induced ARDS in Mechanically Ventilated Patients

Benoît Misset, M.D., Michael Piagnerelli, M.D., Ph.D., Eric Hoste, M.D., Ph.D., Nadia Dardenne, M.Sc., David Grimaldi, M.D., Ph.D., Isabelle Michaux, M.D., Ph.D., Elisabeth De Waele, M.D., Ph.D., Alexander Dumoulin, M.D., Philippe G. Jorens, M.D., Ph.D., Emmanuel van der Hauwaert, M.D., Frédéric Vallot, M.D., Stoffel Lamote, M.D., Walter Swinnen, M.D., Nicolas De Schryver, M.D., Vincent Fraipont, M.D., Nathalie de Mey, M.D., Nicolas Dauby, M.D., Ph.D., Nathalie Layios, M.D., Jean-Baptiste Mesland, M.D., Ph.D., Geert Meyfroidt, M.D., Ph.D., Michel Moutschen, M.D., Ph.D., Veerle Compernolle, M.D., Ph.D., André Gothot, M.D., Ph.D., Daniel Desmecht, D.V.M., Ph.D., Maria I. Taveira da Silva Pereira, M.D., Ph.D., Mutien Garigliany, D.V.M., Ph.D., Tome Najdovski, Ph.D., Axelle Bertrand, M.Sc., Anne-Françoise Donneau, Ph.D., and Pierre-François Laterre, M.D.

ABSTRACT

BACKGROUND

Passive immunization with plasma collected from convalescent patients has been regularly used to treat coronavirus disease 2019 (Covid-19). Minimal data are available regarding the use of convalescent plasma in patients with Covid-19–induced acute respiratory distress syndrome (ARDS).

METHODS

In this open-label trial, we randomly assigned adult patients with Covid-19–induced ARDS who had been receiving invasive mechanical ventilation for less than 5 days in a 1:1 ratio to receive either convalescent plasma with a neutralizing antibody titer of at least 1:320 or standard care alone. Randomization was stratified according to the time from tracheal intubation to inclusion. The primary outcome was death by day 28.

RESULTS

A total of 475 patients underwent randomization from September 2020 through March 2022. Overall, 237 patients were assigned to receive convalescent plasma and 238 to receive standard care. Owing to a shortage of convalescent plasma, a neutralizing antibody titer of 1:160 was administered to 17.7% of the patients in the convalescent-plasma group. Glucocorticoids were administered to 466 patients (98.1%). At day 28, mortality was 35.4% in the convalescent-plasma group and 45.0% in the standard-care group (P=0.03). In a prespecified analysis, this effect was observed mainly in patients who underwent randomization 48 hours or less after the initiation of invasive mechanical ventilation. Serious adverse events did not differ substantially between the two groups.

CONCLUSIONS

The administration of plasma collected from convalescent donors with a neutralizing antibody titer of at least 1:160 to patients with Covid-19–induced ARDS within 5 days after the initiation of invasive mechanical ventilation significantly reduced mortality at day 28. This effect was mainly observed in patients who underwent randomization 48 hours or less after ventilation initiation. (Funded by the Belgian Health Care Knowledge Center; ClinicalTrials.gov number, NCT04558476.)

The authors' affiliations are listed in the Appendix. Dr. Misset can be contacted at benoit.misset@chuliege.be or at the Department of Intensive Care Medicine, University Hospital of Liège, Domaine Universitaire du Sart Tilman, 4000 Liège, Belgium.

N Engl J Med 2023;389:1590-600.
DOI: 10.1056/NEJMoa2209502

The coronavirus disease 2019 (Covid-19) pandemic spread from Asia to Europe in 2020. As of March 2023, more than 670 million cases, including more than 6.8 million deaths, had been confirmed around the world.[1] Patients admitted to intensive care units (ICUs) have represented 20 to 25% of hospitalizations, and 70% have received invasive mechanical ventilation for acute respiratory distress syndrome (ARDS).[2] Older age and direct injury to the lung are associated with higher mortality among patients with ARDS.[3] Mortality in the ICU among patients with Covid-19 receiving invasive mechanical ventilation was more than 45% in 2020–2021 in the U.K. Intensive Care National Audit and Research Centre register[4] and 45% (95% confidence interval [CI], 39 to 52) in a meta-analysis[5]; these values correlate with the delayed kinetics of neutralizing antibody production.[6] Patients with ARDS can shed live virus for more than 20 days.[7,8] In plasma obtained from donors who have recovered from Covid-19, neutralizing antibodies can be detected up to 10 months after infection.[9] Convalescent plasma has been proposed to provide passive immunization to patients presenting with Covid-19.[10] Transfusion of convalescent plasma in this context has been given without obvious safety concerns.[11] Multiple trials have tested convalescent plasma since the onset of the pandemic,[12] but there are few data on the use on convalescent plasma in patients with Covid-19–induced ARDS receiving invasive mechanical ventilation.

The effect of convalescent plasma is attributed to its content of neutralizing antibodies, but in most trials, neutralizing antibodies have been estimated indirectly, through total antibody assessment.[12] Early in the pandemic, the Red Cross, as the main provider of blood in Belgium, initiated a campaign for donations by persons who had recovered from Covid-19 and made an agreement with two university laboratories to have them measure neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in convalescent plasma. We conducted a trial (CONFIDENT) to test the hypothesis that passive immunization with convalescent plasma with a neutralizing antibody titer of at least 1:320 would reduce mortality when administered early after the initiation of invasive mechanical ventilation among patients with Covid-19–induced ARDS.

Methods

Trial Design

This randomized, two-group, open-label trial was conducted at 17 sites in Belgium and coordinated by the University Hospital of Liège. We encouraged inclusion soon after the initiation of invasive mechanical ventilation and stratified the randomization according to the delay between invasive mechanical ventilation and inclusion (≤48 hours vs. >48 to 120 hours). We assigned patients in a 1:1 ratio to receive either convalescent plasma with a neutralizing antibody titer against SARS-CoV-2 of at least 1:320 or standard care. The protocol, which was approved by the institutional review board at each center, was published previously[13] and is available with the full text of this article at NEJM.org.

Trial Patients

Adult patients who had a score on the Clinical Frailty Scale of less than 6 (range, 1 to 9, with higher scores indicating greater frailty),[14] who had been admitted to a participating ICU with a diagnosis of Covid-19–induced ARDS (corresponding to a score of 7, 8, or 9 on the World Health Organization [WHO] Clinical Progression Scale, with scores ranging from 0 to 10 and higher scores indicating more severe disease[15]), and who had received invasive mechanical ventilation for a maximum of 5 days were assessed for eligibility. ARDS was classified according to the Berlin definition.[16] Covid-19–induced ARDS was defined as extended interstitial pneumonia on a computed tomographic scan or a chest radiograph within 10 days before inclusion and a positive result of a clinical SARS-CoV-2 nasopharyngeal polymerase-chain-reaction (PCR) test within 15 days before inclusion. Exclusion criteria were pregnancy, a previous episode of transfusion-related side effects, a medical decision to limit therapy, and participation in another Covid-19 trial.

Before requesting consent, the local investigator contacted a physician at the coordinating center, who checked the inclusion criteria. At the same time, the availability of convalescent plasma with an ABO group identical to the eligible patient's group was checked on the Web site of the Belgian Red Cross. The capability of the patient to give consent was then assessed. If consent could not be obtained from the patient, it was asked of

a relative. When patients became able to give consent, they were asked to do so.

CONVALESCENT DONORS AND NEUTRALIZING ANTIBODY ASSESSMENT

Donors were recruited by the Belgian Red Cross among adults who had been infected with SARS-CoV-2 and who had fully recovered between 28 days and 10 months earlier.[13] Neutralizing antibody titers were determined with SARS-CoV-2 Nextstrain clade 20B (Wuhan-like, B.1.1), isolated from a Belgian patient, in 96-well plates containing confluent Vero E6 cells (ATCC CRL-1586)[17] and were reported as 50% virus neutralization titer (NT50). The NT50 was the highest dilution of serum that neutralized the cytopathic effect in 50% of the cells (see the protocol).[13,18] A neutralizing antibody titer of at least 1:320 was requested for the trial, and a titer of 1:160 was accepted in case of a shortage of plasma.

TRIAL GROUPS

Randomization was stratified according to the delay from the initiation of invasive mechanical ventilation and performed with the use of a Web-based program. Patients in the convalescent-plasma group were assigned to receive an infusion of 2 units (400 to 500 ml in total) of convalescent plasma of the identical ABO group within 24 hours after inclusion. No crossover was allowed between the convalescent-plasma group and the standard-care group. Investigators were aware of the trial-group assignments.

OUTCOMES

The primary outcome was death by day 28 after randomization. Secondary outcomes included adverse events, inflammatory and anti–SARS-CoV-2 antibody responses, the Sequential Organ Failure Assessment (SOFA) score, the use of organ support, the length of hospital stay, and death by day 90 and 365.

STATISTICAL ANALYSIS

We anticipated a day 28 mortality of 40% in the standard-care group. We estimated that a relative difference of one third in day 28 mortality was realistic and relevant. With a two-sided alpha level of 0.05 and a beta level of 0.20, the number of patients to include for an absolute difference of –13.5 percentage points (convalescent plasma minus standard care) in day 28 mortality was 250 for each group. Because our estimate of the between-group difference was empirical, we performed sequential blinded interim analyses. For these analyses, two Lan–Demets spending functions were used to adjust the type I error. The analysis was performed on an intention-to-treat basis. For the primary analysis, there were no missing values. No imputation was made for secondary outcomes because the pattern of missing data was completely at random, and missing data were either very infrequent or not used for statistical analyses. The results are expressed as median (interquartile range) and as number (percent). The primary outcome was compared with the chi-square test and adjusted for the stratification factor with a binary logistic regression. The two-sided level of significance was 5%. We summarized secondary analyses with point estimates for differences between the two groups and 95% confidence intervals using the Hodges–Lehmann estimation of location shift and a Wald asymptotic confidence interval for quantitative and binary variables, respectively. The confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The Fine–Gray model was used to analyze competing risks data. The secondary analyses should be considered exploratory. Statistical analyses were performed with the use of SAS software for Windows, version 9.4, and R software for Windows, version 4.0.2.

The statistical analysis plan[13] included prespecified analyses of subgroups defined according to the median of C-reactive protein level, SOFA score, and time from admission to inclusion. Exploratory post hoc analyses addressed subgroups based on the periods determined by the predominant variant in Belgium during the trial and subgroups defined according to the median total antibody IgG and neutralizing antibody titers against SARS-CoV-2 at the time of inclusion.

RESULTS

PATIENTS

Between September 10, 2020, and March 9, 2022, a total of 1034 patients with Covid-19–induced ARDS were screened and 475 (45.9%) were included (Fig. S6 in the Supplementary Appendix, available at NEJM.org). We decided to end recruitment prematurely, on April 9, 2022, because no new case had been screened in 1 month,

presumably owing to reduced virulence of the omicron BA.2 variant.[19] At inclusion, 47 patients (9.9%) had mild ARDS, 274 (57.7%) had moderate ARDS, and 154 (32.4%) had severe ARDS[16]; 342 (72.0%) underwent randomization 48 hours or less after the initiation of invasive mechanical ventilation, and 133 (28.0%) underwent randomization more than 48 hours after the initiation of invasive mechanical ventilation. A total of 237 patients were assigned to receive convalescent plasma, and 238 patients were assigned to receive standard care. These numbers were 171 and 171, respectively, among patients who underwent randomization 48 hours or less after ventilation initiation and 66 and 67, respectively, among those who underwent randomization more than 48 hours after ventilation initiation. Relatives provided consent for all the patients. Four patients declined to continue participation after recovery; with the exception of data on vital status, subsequent data for these patients were not collected. No patient was lost to follow-up regarding vital status.

All the patients in the convalescent-plasma group received convalescent plasma except 1 who died before infusion, and none in the standard-care group received convalescent plasma. Adherence to the standard of care for invasive mechanical ventilation was similar in the two groups (Table S2). No patient received polyvalent immunoglobulins between inclusion and day 28. The inclusion rate followed the pandemic waves in Belgium (Fig. S1). We included 197, 163, 99, and 16 patients during periods when the ancestral virus and B.1.1.7 (alpha), B.1.617.2 (delta), and B.1.1.529 (omicron) variants, respectively, were predominant in Belgium.[20] The data and safety monitoring board recommended that the trial be continued after each interim analysis (see the Supplementary Appendix).

The baseline characteristics are shown in Table 1 and Table S1 and include some imbalance in hypertension and diabetes between the two groups. In the convalescent-plasma group, convalescent plasma with a neutralizing antibody titer of 1:160, 1:320, 1:640, and more than 1:640 was administered in 17.7%, 38.8%, 31.9%, and 11.6%, respectively, of the patients. Glucocorticoids were administered to 466 patients (98.1%).

PRIMARY OUTCOME

At day 28, mortality was 35.4% (84 of 237 patients) in the convalescent-plasma group and 45.0% (107 of 238) in the standard-care group ($P=0.03$, before and after adjustment for the stratification factor). These values were 32.7% (56 of 171) and 46.8% (80 of 171), respectively, among patients who underwent randomization 48 hours or less after ventilation initiation and 42% (28 of 66) and 40% (27 of 67), respectively, among those who underwent randomization more than 48 hours after ventilation initiation (Table 2). The survival curves in the convalescent-plasma and standard-care groups separated at approximately day 17 (Fig. 1), and the difference in restricted mean survival time (convalescent plasma minus standard care) at day 28 was 0.33 days (95% CI, −1.27 to 1.92). The neutralizing antibody titer of the infused convalescent plasma was not associated with mortality. The direction of the effect was opposite in Center 105 (Fig. 2). In this center, the standard-care group had a shorter time from ICU admission to inclusion than the convalescent-plasma group (Fig. S8).

SECONDARY OUTCOMES AND SUBGROUP ANALYSES

The investigators reported 711 adverse events and classified 209 of these as serious (Table 3 and Table S7). Of the 209 serious adverse events, 184 (88.0%) were fatal. All 711 events were attributed to Covid-19 or complications of organ support, and none was directly attributed to convalescent plasma. The occurrence of secondary bacteremia and pneumonia, duration of organ support, and length of hospital stay were similar in the two groups. Mean neutralizing antibody and total IgG titers to SARS-CoV-2 increased in both groups after inclusion.

In the prespecified subgroup analysis, a higher SOFA score at inclusion was associated with a greater effect. The effect appeared similar in the four periods defined a posteriori by the predominance of the successive variants[20] and in the subgroups defined according to the median total antibody IgG and neutralizing antibody titers against SARS-CoV-2 at the time of inclusion.

DISCUSSION

In this trial involving patients admitted to the ICU with Covid-19–induced ARDS, administration of convalescent plasma with neutralizing antibody titers of at least 1:160 against SARS-CoV-2 early after the initiation of invasive mechanical ventilation reduced mortality at day 28. This effect was observed mainly in the patients

who underwent randomization 48 hours or less after the initiation of invasive mechanical ventilation. The survival curves in both the overall population and the patients who underwent randomization 48 hours or less after ventilation initiation separated near day 17. Among the secondary outcomes, the results for inflammation, vasopressor support, and the number of adverse events tended to be better in the convalescent-plasma group. In prespecified subgroup analyses, we observed a greater effect in patients with a higher illness severity at inclusion.

Our trial differs from previous trials of convalescent plasma in Covid-19 in three significant ways. First, we used convalescent plasma selected for higher neutralizing antibody titers as determined by a virus neutralization test. Plasma with higher titers is recommended by most experts and the Food and Drug Administration[21,22] because low titers have been incriminated in several treatment failures.[23,24] We used convalescent plasma with a neutralizing antibody titer of 1:320 in 82.3% of the patients and a titer of 1:160 in the remaining 17.7%. We used this lower titer owing to a shortage of donors in the early phase of the pandemic, and we accepted it be-

Table 1. Characteristics of the Patients at Inclusion.*

Characteristic	Convalescent Plasma (N=237)	Standard Care (N=238)
Median age (IQR) — yr	64 (55–71)	64 (56–70)
Male sex — no. (%)	158 (66.7)	165 (69.3)
Vaccinated against SARS-CoV-2 — no. (%)†	27 (11.4)	19 (8.0)
Median body-mass index (IQR)‡	30.5 (26.5–34.9)	29.7 (26.5–34.3)
Median time since first reported symptoms (IQR) — days	12 (8–14)	12 (8–15)
Median time since hospital admission (IQR) — days	5 (3–7)	5 (3–8)
Median time since ICU admission (IQR) — days	3 (2–5)	3 (2–5)
Median time since positive nasopharyngeal PCR test for SARS-CoV-2 (IQR) — days	7 (4–10)	7 (5–10)
Median APACHE II score (IQR)§	13.0 (9.0–18.0)	13.0 (9.0–17.0)
Median SOFA score (IQR)¶	6.0 (4.0–8.0)	6.0 (4.0–8.0)
Median positive end-expiratory pressure (IQR) — cm of water	10 (10–12)	10 (10–12)
Median Pao_2:FIo_2 ratio (IQR)	117 (90–162)	128 (93–160)
Median cycle-threshold value on nasopharyngeal PCR test for SARS-CoV-2 (IQR)‖	22 (18–26)	20 (17–26)
Median total IgG antibodies against SARS-CoV-2 (IQR) — BAU/ml**	249 (29–928)	288 (36–877)
Median neutralizing antibodies against SARS-CoV-2 (IQR) — NT50**††	20 (<20–80)	40 (<20–80)
Median C-reactive protein level (IQR) — mg/liter	126 (67–191)	110 (55–188)
Median score on WHO Clinical Progression Scale (IQR)‡‡	8 (8–8)	8 (8–8)
Coexisting conditions — no. (%)		
Hypertension	145 (61.2)	129 (54.2)
Congestive heart failure	19 (8.0)	11 (4.6)
Diabetes	81 (34.2)	92 (38.7)
COPD	27 (11.4)	24 (10.1)
Asthma	22 (9.3)	17 (7.1)
Chronic renal failure	32 (13.5)	30 (12.6)
Hematologic cancer	6 (2.5)	11 (4.6)
Solid tumor	6 (2.5)	12 (5.0)
Missing data	0	1 (0.4)

Table 1. (Continued.)

Characteristic	Convalescent Plasma (N=237)	Standard Care (N=238)
Concomitant therapy against SARS-CoV-2 — no. (%)		
Hydroxychloroquine	1 (0.4)	0
Azithromycin	10 (4.2)	4 (1.7)
Remdesivir	13 (5.5)	14 (5.9)
Anti–interleukin-6 or anti–interleukin-6 receptor agent	12 (5.1)	7 (2.9)
Glucocorticoids	233 (98.3)	233 (97.9)
Dexamethasone	216 (91.1)	225 (94.5)
Other	15 (6.3)	8 (3.4)

* Unless otherwise indicated, the numbers of patients with missing data were as follows: for time since first reported symptoms, 11 in the convalescent-plasma group and 8 in the standard-care group; for time since hospital admission, 3 in the convalescent-plasma group and 7 in the standard-care group; for time since intensive care unit (ICU) admission, 1 in the convalescent-plasma group and 5 in the standard-care group; for positive end-expiratory pressure, 3 in each group; for ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FIO_2), 1 in the standard-care group; and for C-reactive protein level, 1 in the standard-care group. BAU denotes binding antibody units, COPD chronic obstructive pulmonary disease, IQR interquartile range, NT50 50% virus neutralization titer, PCR polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† The vaccination status had not been specified in the protocol because the trial started in September 2020 — 3 months before the beneficial effects of vaccination were shown[35] and 5 months before vaccination was routine in Belgium. Therefore, the collection of the data was heterogeneous across centers.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 26 patients in the convalescent-plasma group and 20 patients in the standard-care group owing to the lack of reporting by some investigators.

§ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater disease severity and a higher risk of death. Data were missing for 3 patients in the standard-care group.

¶ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating more severe organ failure. Data were missing for 3 patients in the standard-care group.

‖ Quantitative cycle-threshold values on the nasopharyngeal PCR test for SARS-CoV-2 were missing for 82 patients (34.6%) in the convalescent-plasma group and 90 patients (37.8%) in the standard-care group because the laboratory at several centers provided a binary result (positive or negative) or semiquantitative result.

** Titers for total IgG antibodies were missing for 47 patients (19.8%) in the convalescent-plasma group and 52 patients (21.8%) in the standard-care group. Collection of these data was added as an amendment to the protocol after the trial had begun.

†† The SARS-CoV-2 strain that was used for neutralization assessment was the one that was prevalent in Belgium at the time of inclusion of the patient.

‡‡ Scores on the World Health Organization (WHO) Clinical Progression Scale range from 0 to 10, with higher score indicating a worse clinical condition. Data were missing for 3 patients in the standard-care group.

Table 2. Mortality at Day 28.*

Population	Convalescent Plasma	Standard Care	P Value
	no. of deaths/no. of patients (%)		
Total	84/237 (35.4)	107/238 (45.0)	0.03†
Randomization stratum			
≤48 Hr after IMV initiation	56/171 (32.7)	80/171 (46.8)	
>48 Hr after IMV initiation	28/66 (42.4)	27/67 (40.3)	

* IMV denotes invasive mechanical ventilation.

† The P value was the same before and after adjustment for the stratification factor.

cause it still exceeded the titer that has been recommended.[21,25] In our trial, convalescent plasma was assessed for NT50 in two academic centers, which ensured that a similar technique was used to assess all plasma.[21]

Second, our trial focused on patients with ARDS, corresponding to a score of 7, 8, or 9 on the WHO Clinical Progression Scale.[15] Such a high severity was chosen because no antiviral treatment was available and the virus is often

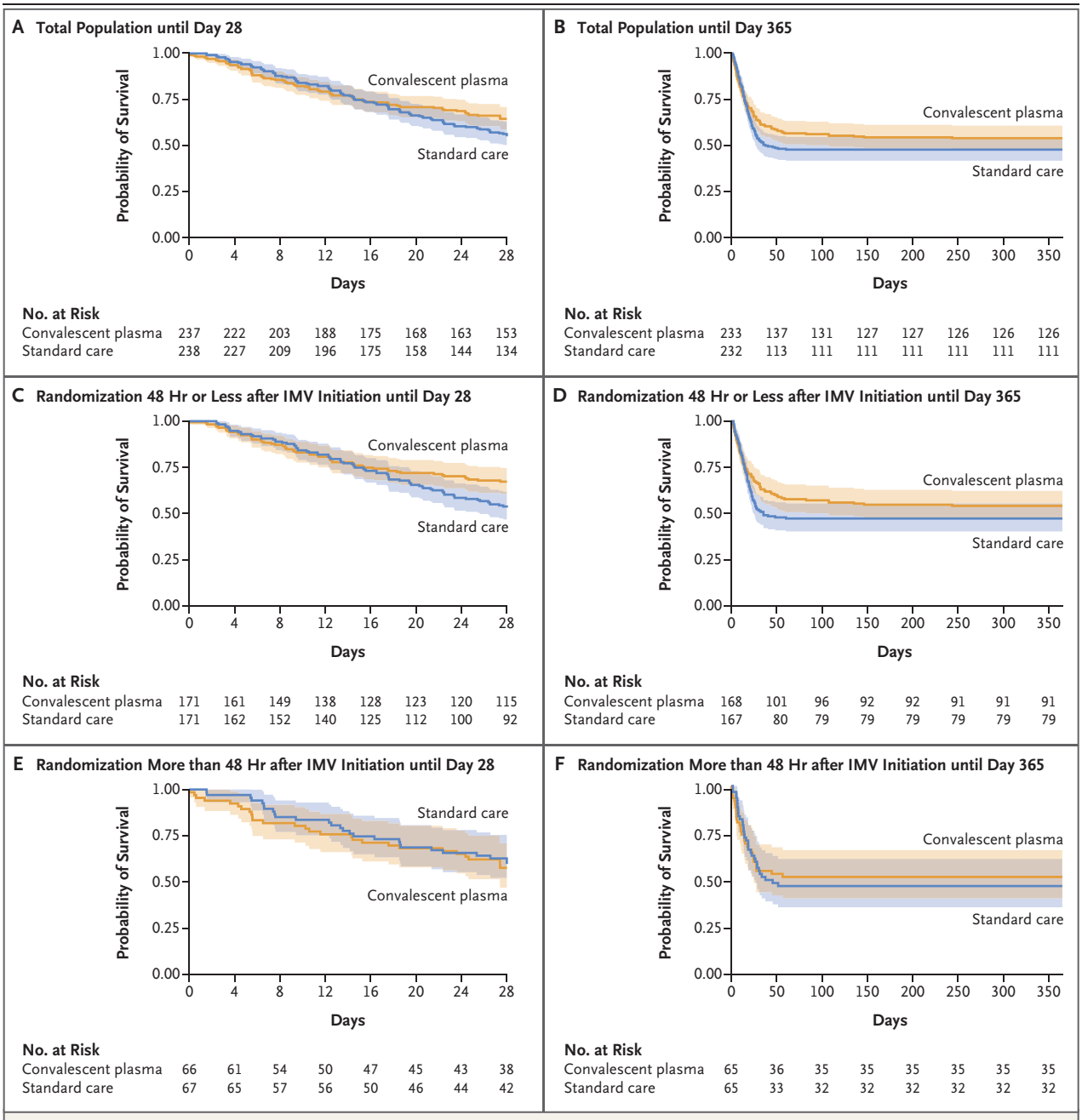

Figure 1. Survival Curves (Kaplan–Meier Estimates).

The shaded areas represent the pointwise 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to infer definitive treatment effects. IMV denotes invasive mechanical ventilation.

present for a prolonged period in most of these patients.[7,8] In our trial, as in most Belgian centers after the first wave of the pandemic,[26] invasive mechanical ventilation was initiated on the basis of statements by experts,[27] which favored the previous use of high-flow nasal oxygen in an attempt to prevent tracheal intubation and invasive mechanical ventilation. By contrast, in the other trials addressing the efficacy of convalescent plasma, patients receiving invasive mechanical ventilation were only subgroups of the included patients,[28,29] mortality was addressed as a secondary outcome,[24] or invasive mechanical ventilation was received by a low number of patients,[30] which led to inconclusive results.

Third, to ensure homogeneity of the cohort, we chose to include patients as early as possible after the initiation of invasive mechanical ventilation. Because several tertiary centers expected to receive patients transferred from other institutions, we included patients until the fifth day of invasive mechanical ventilation and stratified randomization to assess the treatment effect in the first 48 hours of invasive mechanical ventilation with the lowest risk of bias.

Mortality in the standard-care group was 45.0%, a finding consistent with those of previous studies. This high mortality may be due to the age of the population and the direct nature of the pulmonary injury.[3] Our interpretation of the benefit with respect to mortality is that convalescent plasma is directed against the cause of Covid-19–induced ARDS in patients receiving invasive mechanical ventilation. Convalescent plasma may reduce the quantity of virus alive in the lungs of patients who continue to shed the virus.[7,8] It may counteract the delayed kinetics of neutralizing antibody production in these patients,[6] a phenomenon that was observed in a placebo-controlled trial.[31] A decrease in viral load might reduce inflammation, as we observed in our convalescent-plasma group. The median time between viral infection and ARDS occurrence is 12 days.[32] This delay is close to the one we observed between the administration of convalescent plasma and the separation in survival curves between the two groups. This finding is consistent with our hypothesis that neutralizing antibodies act at the beginning of the cascade between infection and inflammation.

We believe our trial has a good potential for generalizability to most patients with Covid-19–induced ARDS because almost 50% of such patients were included in the centers during their participation in the trial. Our results should be confirmed in patients with ARDS with different Covid-19 variants than those we studied. Confirmation could be accomplished by continuing collection campaigns and delivering the most recently collected plasma available.

Our trial has limitations. First, it was not blinded. We chose this design intentionally, because the use of a placebo would have added an extra fluid volume of 500 ml, which is against the recommended conservative approach when treating ARDS.[33] To reduce the risk of bias due to the lack of blinding, we chose a nonsubjective primary outcome, death by day 28, that was not likely to be influenced by the knowledge of the trial-group assignment. The open design may have resulted in subtle differences in clinical decisions after ran-

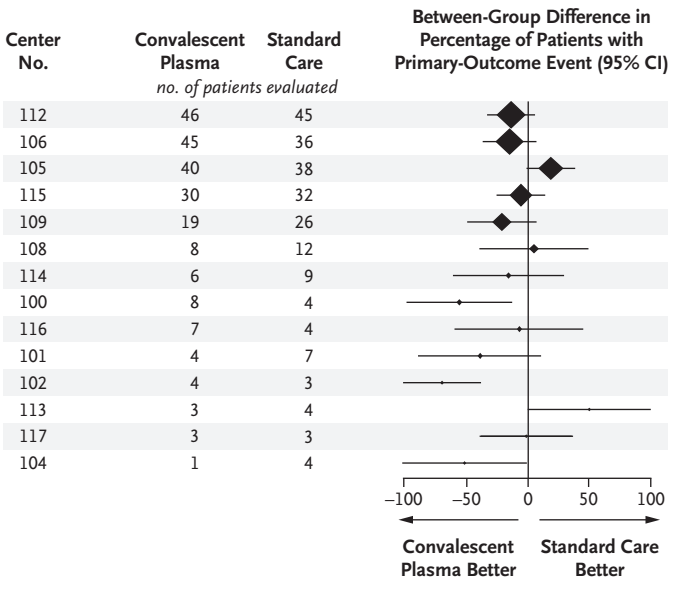

Figure 2. Primary Outcome across Centers.

The outcome data according to center are provided in Table S3 in the Supplementary Appendix. A center effect is apparent for the primary outcome. The result in Center 105 was the reverse of the other centers. This finding was associated with a shorter time from intensive care unit admission to inclusion in the standard-care group than in the convalescent-plasma group (Fig. S7). In this center, the standard-care group had a very low mortality (13%) as compared with the rest of the population. Because randomization was not stratified according to center, the difference in disease severity at patients' inclusion may be due to chance. Owing to centers with low numbers of patients, we could not assess an interaction between treatment and center.

Table 3. Secondary Outcomes in the Total Population.*

Outcome	Convalescent Plasma (N=237)	Standard Care (N=238)	Difference (95% CI)†
≥1 Adverse event — no. (%)	158 (66.7)	173 (72.7)	−6.0 (−14.7 to 1.7)‡
Total adverse events — no.	324	387	
Total serious adverse events — no.	93	116	
Fatal	78	106	
Nonfatal	15	10	
Related to convalescent plasma	0	NA	
Decision to limit therapy before day 28 — no. (%)	21 (8.9)	32 (13.4)	−4.6 (−10.2 to 1.1)‡
Median time to decision to limit therapy (IQR) — days	17 (11 to 20)	13 (7 to 21)	−3.0 (−8.0 to 2.0)
Bacteremia			
≥1 Episode — no./total no. (%)	62/232 (26.2)	69/232 (29.0)	−2.8 (−10.9 to 5.2)‡
Episodes per 10,000 ICU days — no.	10	12	
Ventilator-associated pneumonia			
≥1 Episode — no./total no. (%)	182/232 (76.8)	188/232 (79.0)	−2.2 (−9.5 to 5.0)‡
Episodes per 10,000 IMV days — no.	73	75	
Values at day 7 among survivors			
No. of patients evaluated	215	217	
Median C-reactive protein level (IQR) — mg/liter	85 (37 to 182)	120 (59 to 203)	−17.3 (−35.5 to −0.50)
Median SOFA score (IQR)	4 (3 to 7)	5 (4 to 8)	−1.0 (−1.0 to 0)
Use of organ support — no./total no. (%)			
Vasopressors	192/233 (81.0)	204/235 (85.7)	−4.7 (−11.2 to 1.8)‡
Renal-replacement therapy	31/233 (13.1)	42/233 (17.6)	−4.5 (−11.0 to 1.8)‡
ECMO	45/235 (19.0)	47/235 (19.7)	−0.7 (−7.9 to 6.5)‡
Median time alive and free of support at day 28 (IQR) — days§			
IMV	0 (0 to 14)	0 (0 to 10)	0 (0 to 0)
Vasopressors	19 (4 to 27)	14 (2 to 26)	1.0 (0 to 2.5)
Renal-replacement therapy	28 (12 to 28)	28 (10 to 28)	0 (0 to 0)
Median duration of IMV (IQR) — days¶	15 (9 to 27)	17 (10 to 25)	−1.0 (−3.0 to 1.0)
Median duration of ICU stay (IQR) — days‖	20 (12 to 37)	21 (13 to 34)	0.0 (−3.0 to 2.0)
Median duration of hospital stay (IQR) — days**	28 (18 to 53)	27 (17 to 46)	−1.0 (−2.0 to 4.0)
Death at day 90 — no. (%)	102 (43.0)	121 (50.8)	−7.8 (−16.8 to 1.2)
Death at day 365 — no./total no. (%)	107/233 (45.9)	123/234 (52.6)	−6.7 (−15.7 to 2.4)‡

* ECMO denotes extracorporeal membrane oxygenation, and NA not applicable.
† Differences between groups are provided with point estimates for differences, and 95% confidence intervals were determined with the use of the Hodges–Lehmann estimation of location shift and a Wald asymptotic confidence interval for quantitative and binary variables, respectively. The widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to infer definitive treatment effects.
‡ The difference is in percentage points.
§ For IMV, data were missing for 1 patient in the convalescent-plasma group and 3 patients in the standard-care group. For vasopressors, data were missing for 4 patients and 3 patients, respectively. For renal-replacement therapy, data were missing for 4 patients and 5 patients, respectively.
¶ Data were missing for 1 patient in the convalescent-plasma group and 3 patients in the standard-care group.
‖ Data were missing for 2 patients in the convalescent-plasma group and 4 patients in the standard-care group.
** Data were missing for 5 patients in the convalescent-plasma group and 6 patients in the standard-care group.

domization. Such potential differences may have been in either direction, depending on the confidence of each investigator regarding convalescent plasma. In our trial, if one group had been treated with a lower intensity, we assume the survival curves would have diverged in the days immediately after the randomization process, which was not the case. In addition, the results were not driven by a particular center. Second, the convalescent plasma was obtained between April 2020 and May 2021, when the ancestral virus and then its alpha variant were predominant in Belgium, and their neutralizing antibodies might have been less active against subsequent variants. However, a difference in treatment effect was not apparent between the periods when the delta or omicron BA.1 variants were predominant in Belgium. Third, the trial ended prematurely because of the absence of new inclusion, presumably owing to the reduced virulence of the omicron BA.2 variant. We ultimately included 475 patients, representing 95% of the planned inclusions, and it is unlikely that the results would have been modified by including 25 patients more. The reduced virulence of new variants may limit the immediate effect of our results, but future SARS-CoV-2 variants with increased virulence may occur. Fourth, we have not standardized our in-house neutralizing antibody titers against an international standard. The quantitative results generated by this method are known to vary among laboratories because, as a reference standard, it is mostly used as a research tool. However, because the convalescent plasma that we selected for passive immunization had a higher NT50 than that measured in 85% of all the convalescent plasma we tested in a previous large-scale study,[34] we believe that, using this qualitative selection threshold, other investigators should approach the potency of our own convalescent-plasma preparations. Fifth, data were missing for a substantial number of quantitative nasopharyngeal PCR and antibody measurements, and the interpretation of the corresponding secondary results should be cautious.

The administration of plasma collected from convalescent donors and documented to have neutralizing antibody titers of at least 1:160 to patients with Covid-19–induced ARDS within 5 days after the initiation of invasive mechanical ventilation significantly reduced mortality at day 28. In a prespecified analysis, this effect was mainly observed in the patient group that underwent randomization 48 hours or less after the initiation of invasive mechanical ventilation.

Presented in part at the annual meetings of the Belgian Society of Intensive Care Medicine in Brussels on June 15, 2022, and of the French Intensive Care Society in Paris on June 23, 2022.

Supported by the Belgian Health Care Knowledge Center (KCE) through the KCE Trials Program.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Nelle Stocquart, appointed by the KCE, for her support in implementing the trial; Jean Chastre, Muriel Mauer, Jérôme Pugin, Tom Van der Poll, and Olivier Lesieur for their involvement in the data and safety monitoring board; Jean-Louis Vincent for his support and advice; Marc Buyse for his advice and review of the statistical plan; the teams at each participating center for their enthusiasm and involvement in the care of their patients; and Leslie Gielens, Marie-France Dujardin, Suzanne Renard, Caroline Berghe, and Stéphane Van Malderen for their role in monitoring and managing the database.

APPENDIX

The authors' affiliations are as follows: the Departments of Intensive Care Medicine (B.M., N.L., A.B.), Infectious Diseases (M.M.), Immunohematology (A.G.), and Microbiology (M.I.T.S.P.), University Hospital of Liège, the Biostatistics Unit, Public Health Department (N. Dardenne, A.-F.D.), and the Department of Animal Pathology (D.D., M.G.), Liège University, and the Department of Intensive Care Medicine, Citadelle General Hospital (V.F.), Liège, the Department of Intensive Care Medicine, Centre Hospitalier Universitaire (CHU) de Charleroi–Marie Curie Hospital, Université Libre de Bruxelles, Charleroi (M.P.), the Department of Intensive Care Medicine, Ghent University Hospital (E. Hoste), and the Faculty of Medicine and Health Sciences (V.C.), Ghent University, Ghent, the Department of Intensive Care Medicine, Cliniques Universitaires de Bruxelles–Erasme, Université Libre de Bruxelles (D.G.), the Division of Infectious Diseases, Saint-Pierre University Hospital (N. Dauby), and the Department of Intensive Care Medicine, Saint-Luc University Hospital (J.-B.M., P.-F.L.), Brussels, the Department of Intensive Care, Université Catholique de Louvain (UCL), CHU UCL Namur, Yvoir (I.M.), the Department of Intensive Care Medicine, Brussels University Hospital, Vrije Universiteit Brussel, Jette (E.D.W.), the Department of Intensive Care Medicine, Delta General Hospital, Roeselare (A.D.), the Department of Intensive Care Medicine, Antwerp University Hospital, University of Antwerp, Edegem (P.G.J.), the Department of Intensive Care Medicine, Imelda General Hospital, Bonheiden (E. Hauwaert), the Department of Intensive Care Medicine, Wallonie Picarde General Hospital, Tournai (F.V.), the Department of Intensive Care Medicine, Groeninge General Hospital, Kortrijk (S.L.), the Department of Intensive Care Medicine, Sint Blasius General Hospital, Dendermonde (W.S.), the Department of Intensive Care Medicine, Saint-Pierre Medical Clinic, Ottignies (N.D.S.), the Department of Intensive Care Medicine, Onze-Lieve-Vrouw General Hospital, Aalst (N.M.), the Department of Intensive Care Medicine, University Hospitals Leuven, Leuven (G.M.), Blood Services from the Red Cross, Mechelen (V.C.), Blood Services from the Red Cross, Suarlée (T.N.), and the Department of Intensive Care Medicine, Centre Hospitalier Régional Mons-Hainaut, Mons (P.-F.L.) — all in Belgium.

REFERENCES

1. Johns Hopkins Coronavirus Resource Center. COVID-19 dashboard (https://coronavirus.jhu.edu/map.html).
2. Chang R, Elhusseiny KM, Yeh Y-C, Sun W-Z. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes — a systematic review and meta-analysis. PLoS One 2021;16(2):e0246318.
3. Luo L, Shaver CM, Zhao Z, et al. Clinical predictors of hospital mortality differ between direct and indirect ARDS. Chest 2017;151:755-63.
4. ICNARC. Reports: COVID-19 report. July 2021 (https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports).
5. Lim ZJ, Subramaniam A, Ponnapa Reddy M, et al. Case fatality rates for patients with COVID-19 requiring invasive mechanical ventilation. a meta-analysis. Am J Respir Crit Care Med 2021;203:54-66.
6. Lucas C, Klein J, Sundaram ME, et al. Delayed production of neutralizing antibodies correlates with fatal COVID-19. Nat Med 2021;27:1178-86.
7. Buetti N, Wicky P-H, Le Hingrat Q, et al. SARS-CoV-2 detection in the lower respiratory tract of invasively ventilated ARDS patients. Crit Care 2020;24:610.
8. Saud Z, Ponsford M, Bentley K, et al. Mechanically ventilated patients shed high-titer live severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) for extended periods from both the upper and lower respiratory tract. Clin Infect Dis 2022;75(1):e82-e88.
9. Dupont L, Snell LB, Graham C, et al. Neutralizing antibody activity in convalescent sera from infection in humans with SARS-CoV-2 and variants of concern. Nat Microbiol 2021;6:1433-42.
10. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323:1582-9.
11. 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.
12. Axfors C, Janiaud P, Schmitt AM, et al. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. BMC Infect Dis 2021;21:1170.
13. Misset B, Hoste E, Donneau A-F, et al. A multicenter randomized trial to assess the efficacy of CONvalescent plasma therapy in patients with Invasive COVID-19 and acute respiratory failure treated with mechanical ventilation: the CONFIDENT trial protocol. BMC Pulm Med 2020;20:317.
14. Guidet B, de Lange DW, Boumendil A, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. Intensive Care Med 2020;46:57-69.
15. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192-e197.
16. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
17. Wu H-S, Chiu S-C, Tseng T-C, et al. Serologic and molecular biologic methods for SARS-associated coronavirus infection, Taiwan. Emerg Infect Dis 2004;10:304-10.
18. Devos T, Van Thillo Q, Compernolle V, et al. Early high antibody titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma. Eur Respir J 2022;59:2101724.
19. Ulloa AC, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 omicron variant severity in Ontario, Canada. JAMA 2022;327:1286-8.
20. Sciensano. Belgium COVID-19 epidemiological situation: variants (http://datastudio.google.com/reporting/c14a5cfc-cab7-4812-848c-0369173148ab/page/urrUC?feature=opengraph).
21. Focosi D, Franchini M, Pirofski L-A, et al. COVID-19 convalescent plasma and clinical trials: understanding conflicting outcomes. Clin Microbiol Rev 2022;35(3):e0020021.
22. Food and Drug Administration. FDA updates emergency use authorization for COVID-19 convalescent plasma to reflect new data. February 4, 2021 (https://www.fda.gov/news-events/fda-brief/fda-brief-fda-updates-emergency-use-authorization-covid-19-convalescent-plasma-reflect-new-data).
23. 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.
24. O'Donnell MR, Grinsztejn B, Cummings MJ, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest 2021;131(13):e150646.
25. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021;384:1015-27.
26. Lambermont B, Rousseau A-F, Seidel L, et al. Outcome improvement between the first two waves of the coronavirus disease 2019 pandemic in a single tertiary-care hospital in Belgium. Crit Care Explor 2021;3(5):e0438.
27. Nasa P, Azoulay E, Khanna AK, et al. Expert consensus statements for the management of COVID-19-related acute respiratory failure using a Delphi method. Crit Care 2021;25:106.
28. Writing Committee for the REMAP-CAP Investigators. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. JAMA 2021;326:1690-702.
29. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021;397:2049-59.
30. Allahyari A, Seddigh-Shamsi M, Mahmoudi M, et al. Efficacy and safety of convalescent plasma therapy in severe COVID-19 patients with acute respiratory distress syndrome. Int Immunopharmacol 2021;93:107239.
31. Bennett-Guerrero E, Romeiser JL, Talbot LR, et al. Severe acute respiratory syndrome coronavirus 2 convalescent plasma versus standard plasma in coronavirus disease 2019 infected hospitalized patients in New York: a double-blind randomized trial. Crit Care Med 2021;49:1015-25.
32. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
33. Menk M, Estenssoro E, Sahetya SK, et al. Current and evolving standards of care for patients with ARDS. Intensive Care Med 2020;46:2157-67.
34. Desmecht S, Tashkeev A, El Moussaoui M, et al. Kinetics and persistence of the cellular and humoral immune responses to BNT162b2 mRNA vaccine in SARS-CoV-2-naive and -experienced subjects: impact of booster dose and breakthrough infections. Front Immunol 2022;13:863554.
35. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15.