Safety and Efficacy of Convalescent Plasma in Elderly COVID-19 Patients: The RESCUE Trial

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Abstract

Objective: To assess the safety and efficacy of convalescent plasma (CP) transfusion in elderly people with moderate to severe coronavirus disease 2019 (COVID-19) living in a long-term care facility (LTCF).

Patients and Methods: Twenty-two consecutive elderly patients with COVID-19 infection living in an LTCF in Lombardy, Italy, who were given CP during May 15 to July 31, 2020, were enrolled in a prospective cohort study. Their clinical, instrumental, and laboratory parameters were assessed following the CP treatment. The overall mortality rate in this group was compared with that recorded in other LTCFs in Lombardy during the 3-month period from March to May 2020.

Results: Of the 22 patients enrolled, 68.2% (n=15) received 1 CP unit, 27.3% (n=6) received 2 units, and 4.5% (n=1) received 3 units. Of the CP units transfused, 76.7% (23/30) had a neutralizing antibody titer of 1:160 or greater. No adverse reactions were recorded during or after CP administration. Improvements in clinical, functional, radiologic, and laboratory parameters during the 14 days after CP transfusion were observed in all 19 patients who survived. Viral clearance was achieved in all patients by the end of follow-up (median, 66 days; interquartile range, 48-80 days). The overall mortality rate was 13.6% (3/22), which compared favorably with that in the control group (38.3% [281/733]; P=.02) and corresponded to a 65% reduction in mortality risk.

Conclusion: Early administration of CP with an adequate anti—severe acute respiratory syndrome coronavirus 2 antibody titer to elderly symptomatic patients with COVID-19 infection in an LTCF was safe and effective in eliminating the virus, restoring patients’ immunity, and blocking the progression of COVID-19 infection, thereby improving patients’ survival.

Trial Registration: ClinicalTrials.gov: NCT04569188.
Lombardy, which has a population (about 11 million people) similar to that of Wuhan, was devastated by a wave of infections, or rather a “tsunami,” at the end of February 2020.1 Thousands of patients with severe COVID-19 respiratory symptoms requiring hospital admission arrived contemporaneously at the emergency departments of many Lombard hospitals, quickly overwhelming the capacity of these facilities to admit patients.4 More than one-third of all cases of COVID-19 infection (101,119/272,912) and nearly half of the total COVID-19-related deaths recorded in Italy (16,876/35,507, data updated on September 16, 2020) occurred in Lombardy, generating an unprecedented health and social emergency in the region.5

Among patients with COVID-19 infection, elderly people are more severely affected.6 The mean age of patients dying of SARS-CoV-2 infection in Italy was 80 (interquartile range [IQR], 74-88) years,5 and a similar pattern was observed in other countries,5-8 especially among hospitalized patients.9,10 A particularly critical situation was observed among elderly patients with COVID-19 infection living in long-term care facilities (LTCFs) in Italian regions hit more heavily by SARS-CoV-2 infection. During the 3-month period from March to May 2020, more than 50% of deaths recorded among the 678 accredited LTCFs in Lombardy were caused by COVID-19.11 Elderly individuals living in LTCFs are at increased risk for morbidity and mortality associated with COVID-19 infection because of their chronic illnesses and the impact of congregate housing on viral spread.12-14 Unfortunately, given the emergency situation, most of these elderly patients died in their LTCF without receiving adequate treatment or supportive care in a hospital setting.

To try to stop this silent hecatomb and considering our positive experience on the early use of convalescent plasma (CP) in patients with moderate to severe COVID-19 infection,15,16 we designed and conducted an interventional trial, the RESCUE (Real-time Evaluation of Safety and Efficacy of Convalescent Plasma Units Transfused to Elderly Patients With COVID-19) study, to assess the safety and potential efficacy of hyperimmune plasma infusions in elderly patients with moderate to severe forms of COVID-19 living in LTCFs.

PATIENTS AND METHODS

Patient Selection

Between May 15, 2020, and July 31, 2020, a total of 22 consecutive elderly residents in LTCFs with COVID-19 infection were enrolled in this prospective cohort study, which was registered at clinicaltrials.gov as NCT04569188 and approved by the local ethical committee on May 15, 2020. Follow-up was closed on September 15, 2020. An LTCF (“Green Park”) was identified for the conduction of this study, fundamentally for the following reasons: proximity to the city hospital of Mantua, a large number of residents (n=240, mostly not self-sufficient with aging-related chronic diseases), and the presence of well-trained experienced medical and nursing staff with the availability of laboratory and imaging equipment. In addition, to avoid cross-infections, during the COVID-19 outbreak the facility was divided into 2 separate areas, one for COVID-19–positive patients with specific personnel, and another for COVID-19–free residents. A medical team from the Respiratory Unit of Mantua City Hospital was responsible for the initial clinical evaluation of SARS-CoV-2–infected patients to identify those potentially eligible for inclusion in the study.

The inclusion criteria were: (1) elderly patients (aged ≥65 years) with a nasopharyngeal swab positive for SARS-CoV-2 by polymerase chain reaction (PCR) assay; (2) new onset or worsening of recent-onset respiratory symptoms (<10 days); (3) evidence of pulmonary infiltrates by chest imaging and respiratory distress defined as moderate (≥24 breaths/min, oxygen saturation ≤95% while breathing room air, PaO2 to fraction of inspired oxygen [PaO2:FIO2 ] ratio <300) or severe (≥30 breaths/min, oxygen saturation ≤93% while breathing room air, PaO2:FIO2 ratio <200); (4) the patient’s signed informed consent; and (5) no participation in other clinical trials. Exclusion criteria were: (1) a diagnosis of moderate to severe COVID-19 infection present for longer than 10 days; (2) proven hypersensitivity or allergic reaction to plasma, blood products, or immunoglobulins; and (3) manifest desire not to be included in the research protocol.
Patients meeting the inclusion criteria were enrolled in the protocol of CP infusion and the following biochemical examinations were performed: blood group typing; blood cell count; nasopharyngeal swabs for SARS-CoV-2 RNA detected by reverse-transcriptase PCR assay; measurements of C-reactive protein (CRP), lactate dehydrogenase, interleukin 6 (IL-6), ferritin, creatinine, D-dimer, alanine aminotransferase, and aspartate aminotransferase levels; and a chemiluminescent immunoassay for anti–SARS-CoV-2 IgG antibodies (LIAISON SARS-CoV-2 IgG; DiaSorin). The laboratory tests were carried out in the Central Laboratory of the city hospital of Mantua. In addition, clinical and instrumental monitoring (ultrasonography or radiography of the chest) was performed. Patients’ concomitant therapies at enrollment and during follow-up were also recorded.

All instrumental and laboratory tests, with the exception of blood group typing, which was performed at baseline and then checked before each CP transfusion, were performed on days +1 (baseline, before CP transfusion), +3, +5, +7, and +14 after CP infusion, and the results, along with clinical evaluation, were entered into a Case Report Form. At the end of follow-up, each patient enrolled in the study underwent final clinical, instrumental (chest ultrasonography), and laboratory (SARS-CoV-2 PCR testing on nasopharyngeal swab) evaluations. All these procedures were carried out directly by the medical and nursing staff of the LTCF, according to the protocol and with the active supervision of chest physicians of the Respiratory Unit of Mantua city hospital.

Outcomes
The primary outcome of this study was to evaluate the efficacy of early administration of CP in elderly patients with moderate to severe COVID-19 infection, measured as the rate of improvement in clinical symptoms and laboratory and imaging tests following CP transfusion and the prevention of progression of patients’ symptoms and need for hospitalization.

A secondary outcome was the safety of CP treatment, measured as the rate of adverse reactions to CP transfusion. The type, degree, and outcome of adverse events occurring during or after (within 72 hours) CP transfusion were recorded, according to the Guideline on Good Pharmacovigilance Practices of the European Medicines Agency [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf).

Another secondary clinical outcome was the overall mortality rate at 28 days and at the end of follow-up in the CP treatment group compared with that of a cohort of SARS-CoV-2–infected individuals not receiving CP (control group), but comparable in terms of demographic characteristics (elderly persons living in an LTCF in Lombardy) and follow-up period (March-May 2020). These data were retrieved from the Italian national survey on the contagion by SARS-CoV-2 in LTCFs conducted by the Italian National Institute of Health (ISS) [11].

Finally, another secondary outcome measure was the proportion of patients with conversion of nasopharyngeal swab viral PCR testing from positive to negative, assessed on days +3, +7, and +14 and at the end of the follow-up.

Selection of CP Donors and Hyperimmune Plasma
Eligible donors were either men or nulliparous women aged 18 to 65 years, weighing more than 50 kg, with a laboratory-confirmed diagnosis of SARS-CoV-2 infection that had completely resolved at least 14 days before donation with 2 negative SARS-CoV-2 PCR test results from nasopharyngeal swabs collected 24 hours apart. All routine screening tests for blood donors, including ABO blood group typing, Rh phenotype, complete blood cell count, and screening for human immunodeficiency virus; hepatitis B, C, A, and E viruses; parvovirus; and syphilis, were conducted according to Italian regulations and the indications of the Italian National Blood Center [17].

Hyperimmune plasma was collected through a plasmapheresis procedure using a cell separator and processed and stored in agreement with national CP regulations [17,18]. A plasma volume of about 600 mL was collected during each procedure and immediately divided into 2 bags, each corresponding to a therapeutic CP unit of 300 mL. Collected
CP had an anti-SARS-CoV-2 neutralizing titer of 1:80 or higher. The neutralization test for the identification of anti-SARS-CoV-2-neutralizing antibodies was performed at the Molecular Virology Unit of the University Hospital of Pavia and was based on the

| TABLE 1. Demographic and Baseline Clinical Parameters of the 22 Elderly Patients Enrolled in the Study |
|---------------------------------------------------|----------------------------------|
| Characteristic                                    | Results                          |
| Age (y), median (IQR)                             | 87 (82-90)                       |
| Male/female sex                                   | 11/11                            |
| Male to female sex ratio                          | 1.0                              |
| Body mass index (kg/m²), median (IQR)             | 21.5 (18.0-24.25)                |
| Follow-up (d), median (IQR)                       | 66 (48-80)                       |
| Coexisting diseases, no. (%)                      |                                 |
| Hypertension                                      | 13/22 (59.1)                     |
| Cardiovascular disease                            | 14/22 (63.6)                     |
| Cerebrovascular disease                           | 7/22 (31.8)                      |
| Diabetes                                          | 5/22 (22.7)                      |
| Cancer                                            | 5/22 (22.7)                      |
| Chronic kidney disease                            | 4/22 (18.2)                      |
| COVID-19 severity, no. (%)                        |                                 |
| Moderate                                          | 7/22 (31.8)                      |
| Severe                                            | 15/22 (68.2)                     |
| Symptoms, no. (%)                                 |                                 |
| Fever (>38 °C)                                    | 16/22 (72.7)                     |
| Shortness of breath                               | 18/22 (81.8)                     |
| Chest pain                                        | 7/22 (31.8)                      |
| Cough                                             | 17/22 (77.3)                     |
| Sore throat                                       | 5/22 (22.7)                      |
| Sputum production                                 | 6/22 (27.3)                      |
| Diarrhea                                          | 3/22 (13.6)                      |
| Nausea and vomiting                               | 3/22 (13.6)                      |
| Oxygen supplementation, no. (%)                  |                                 |
| Room air                                          | 3/22 (13.6)                      |
| Nasal cannula/venti-mask                          |                                 |
| <5 L                                              | 4/22 (18.2)                      |
| ≥5 L                                              | 15/22 (68.2)                     |
| Concomitant therapies                             |                                 |
| Antiviral                                         | 2/22 (9.1)                       |
| Antibacterial                                     | 22/22 (100.0)                    |
| Hydroxychloroquine                                | 15/22 (68.2)                     |
| Steroids                                          | 5/22 (22.7)                      |
| Anticoagulant                                     | 16/22 (72.7)                     |
| Median interval between symptom onset and CP therapy (d), median (IQR) | 7 (4.5-8) |
| Chest imaging, no. (%)                            |                                 |
| Unilateral infiltrates                             | 6/22 (27.3)                      |
| Bilateral infiltrates                              | 16/22 (72.7)                     |
| ABO blood type, no. (%)                           |                                 |
| O                                                  | 11/22 (50.0)                     |
| A                                                  | 9/22 (40.9)                      |
| B                                                  | 1/22 (4.5)                       |
| AB                                                 | 1/22 (4.5)                       |

COVID-19 = coronavirus disease 2019; CP = convalescent plasma; IQR = interquartile range.
determination of cytopathic effect, as previously described. The CP transfusions were performed by medical and nursing staff. The CP recipients were transfused with 1 to 3 units of ABO type-compatible CP, according to the clinical response. All procedures were performed in agreement with the routine procedures of the Transfusion Service of Mantua.

Statistical Analyses
Continuous variables are reported as mean ± SD or median and IQR as appropriate according to distribution, while categorical data are reported as number and percentage. Comparisons between groups were carried out with an independent t test or Mann-Whitney U test for continuous variables and χ² test or Fisher exact test for categorical variables, as appropriate. All statistical tests were 2 sided, and associations were considered statistically significant when values were below a nominal level of .05 (P < .05). A cohort study with equal follow-up time per participant was designed. A 2 × 2 frequency table was set up, reporting the incidence of death in treated patients and untreated (control) patients. The surviving patients in both groups were enumerated. The inference concerning the null hypothesis of no effect by treatment was obtained using the χ² test or Fisher exact test for categorical variables, as appropriate. All statistical tests were 2 sided, and associations were considered statistically significant when values were below a nominal level of .05 (P < .05). A cohort study with equal follow-up time per participant was designed. A 2 × 2 frequency table was set up, reporting the incidence of death in treated patients and untreated (control) patients. The surviving patients in both groups were enumerated. The inference concerning the null hypothesis of no effect by treatment was obtained using Pearson χ² test and Fisher exact test. Risk was the proportion of individuals who became cases (due to an event, ie, death). Point estimates (means) and CIs were calculated for risk ratio, risk difference, and the number needed to treat to prevent an event. Calculations were done using Stata, version 16.1, software (StataCorp LLC).

RESULTS
Baseline demographic and clinical characteristics of the 22 elderly patients with COVID-19 infection enrolled in the RESCUE study are reported in Table 1. The median age was 87 (IQR, 82-90) years with an equal distribution between sexes (male to female ratio, 1:0). Participants’ median body mass index (calculated as the weight in kilograms divided by the height in meters squared) at enrollment was normal (21.5; IQR, 18.0-24.25 kg/m²). Seventeen of the 22 patients (77.3%) had 2 or more comorbid conditions, classified as follows in order of frequency: cardiovascular disease (63.6%; n=14), hypertension (59.1%; n=13), cerebrovascular disease (31.8%; n=7), diabetes (22.7%; n=5), cancer (22.7%; n=5), and chronic kidney disease (18.2%; n=4). Severe COVID-19 infection was present in most cases (68.2%; n=15). Sixteen of the 22 patients (72.7%) had 3 or more symptoms, which were most frequently shortness of breath (81.8%; n=18), cough (77.3%; n=17), fever (72.7%; n=16), and chest pain (31.8%; n=7; Table 1).

All patients were under antibacterial therapy at the time of CP infusion. A consistent proportion of them were also receiving anticoagulant therapy (16/22; 72.7%) and hydroxychloroquine (15/22; 68.2%). Bilateral pulmonary infiltrates, documented on the chest radiograph or ultrasound, were present in 16 of the 22 elderly patients (72.7%) before CP transfusion. With regard to the number of CP transfused, the 22 patients with COVID-19 infection were transfused with 30 CP units (median 1; IQR, 1-2): 15 patients (68.2%) with 1 CP unit, 6 patients (27.3%) with 2 CP units, and 1 patient (4.5%) with 3 CP units, each unit having a volume of 300 mL. Seven CP units (23.3%) had a neutralizing antibody titer of 1:80, 18 (60.0%) had a titer of 1:160, and 5 (16.7%) had a titer of 1:320. The median interval between symptom onset and the first CP transfusion was 7 (IQR, 4.5-8) days. In cases in which a second unit was administered, the median interval between transfusion of the first and second CP units was 3 (IQR, 3-12) days. The only patient who received a third CP unit was given the third unit 3 days after the second one. No adverse reactions were recorded during or after the CP transfusions.

The course of clinical, functional, radiologic, and laboratory parameters during the 14 days following CP transfusion is presented in Table 2 for the 19 survivors. Oxygen saturation and PaO₂/FiO₂ ratio improved significantly following the CP transfusion and this effect was evident already by postinfusion day +3 for oxygen saturation and by day +7 for PaO₂/FiO₂ ratio. In parallel, the number of patients being given oxygen supplementation decreased progressively over time, with a reduction of 73.7% (from 17/19 to 3/19) by day +14 after CP infusion. Accordingly,
pulmonary infiltrates had disappeared in all but 2 patients by day +14.

The amelioration of parameters of oxygenation and of chest images was accompanied by an improvement in symptoms: the proportion of patients with at least 3 symptoms decreased by 63.1% (from 13/19 to 1/19) during the 14 days following CP transfusion. At the end of the follow-up period (median, 66; IQR, 48-80) days, all 19 patients alive were asymptomatic, without evidence of pulmonary infiltrates on chest ultrasound and not requiring oxygen support.

With regard to changes in laboratory parameters after CP transfusion, there were decreases of varying degrees in all tests performed (white blood cell count, lymphocyte count, platelet count, aspartate aminotransferase, alanine aminotransferase, ferritin, IL-6, CRP, lactate dehydrogenase, and D-dimer) during the follow-up period. In particular, ferritin levels decreased by 24% and 44% at days +3 and +14, respectively, following CP infusion. Similarly, IL-6 concentrations decreased by 29% and 56% at days +3 and +14, respectively, following CP infusion. There was also a statistically significant decrease in CRP values at all the time points analyzed (from a median baseline level of 7.40 mg/L to a median level of 0.73 mg/L at day +14 after CP infusion). Plasma D-dimer levels decreased progressively, with the difference reaching statistical significance at day +14 after CP infusion, when D-dimer levels had halved compared with their baseline values (from 1479.0 μg/mL to 774.5 μg/mL [to convert to nmol/L, multiply by 5.476]; P=.01). Notably, the concentration of anti-SARS-CoV-2 IgG antibodies increased following CP infusion (from a median baseline level of 127.0 U/mL to a median level of 157.0 U/mL at day +3 after CP infusion), reaching a plateau at day +7 (158.0 U/mL) and then increasing again by day +14 (194 U/mL).

The overall mortality rate was 13.6% (3/22; Table 3). Of the 3 patients who did not survive, one, a 94-year-old man with moderate COVID-19 infection, died 3 days after CP infusion due to massive hemorrhage related to a sudden rupture of the abdominal aorta (this death was judged unrelated to COVID-19 infection). The other 2 elderly men, aged 79 and 83 years, both with severe COVID-19 infection (bilateral lung infiltrates, >3 comorbid conditions, and PaO₂:FIO₂ ratios of 130 and 140, respectively) were admitted to the hospital because of worsening of respiratory failure and died of progression of the disease 7 and 9 days after the CP transfusion, respectively. The search for SARS-CoV-2 viral nucleic acid performed on day +7 resulted negative. A statistically significant difference was found between the overall mortality in our study and that observed in a similar population of elderly patients with COVID-19 infection living in LTCFs in Lombardy13 (13.6% [3/22] vs 38.3% [281/733]; P=.02; Table 3). The number needed to treat to prevent an event (in this analysis, death) was 4.05 (95% CI, 2.53 to 10.07).

Regarding viral clearance following the CP infusions, 85.7% (18/21) of patients became negative for SARS-CoV-2 RNA assayed by reverse transcriptase PCR within 3 days of the CP infusion, a proportion that increased progressively up to 95.2% (20/21) by 14 days. At the end of the follow-up period (median, 66 days), all 19 elderly patients who were alive were negative for SARS-CoV-2 viral nucleic acid. They were transferred to the COVID-19–free unit of the LTCF. Because no new COVID-19 cases were recorded among LTCF residents, the COVID-19–dedicated area was definitively closed on September 1, 2020.

DISCUSSION

Several studies have reported that old age is a significant risk factor for COVID-19–related mortality, with frailty and virus-related decompensation of comorbid conditions being among the most important causes contributing to the poorer outcome in elderly patients with this disease.7-10 On this background, it is not surprising that a particularly critical situation has been observed among elderly residents of LTCFs in which the virus was able to circulate relatively undisturbed, infecting many other hosts and causing high COVID-19–related morbidity and mortality rates.19 For instance, in the Italian national survey by the ISS, in the period from March to May 2020, the COVID-19 mortality rate in LTCFs in Lombardy was more than double the national rate (6.5% vs 3.1%, respectively).11 Furthermore, the lack of special surveillance...
| Variable                                | Basal (A) | Day +3 Post—CP Infusion (B) | Day +7 Post—CP Infusion (C) | Day +14 Post—CP Infusion (D) | P               |
|-----------------------------------------|-----------|-----------------------------|-----------------------------|-----------------------------|-----------------|
| Oxygen saturation (%), median (IQR)     | 93 (91-95)| 96 (95-97)                  | 97 (95-97)                  | 98 (97-98)                  | A vs B, <.01    |
|                                          |           |                             |                             |                             | A vs C, <.001   |
|                                          |           |                             |                             |                             | A vs D, <.001   |
| PacO2:FIO2 ratio, median (IQR)           | 160 (140-260)| 210 (170-265)               | 250 (222.5-307.5)           | 325 (300-345)              | A vs B, NS      |
|                                          |           |                             |                             |                             | A vs C, <.01    |
|                                          |           |                             |                             |                             | A vs D, <.001   |
| ≥3 symptoms, no. (%)                    | 13/19 (68.4)| 6/19 (31.6)                 | 3/19 (15.8)                 | 1/19 (5.3)                 | A vs B, .02     |
|                                          |           |                             |                             |                             | A vs C, <.001   |
|                                          |           |                             |                             |                             | A vs D, <.001   |
| Oxygen supplementation need, no. (%)    | 17/19 (89.5)| 12/19 (63.2)                | 9/19 (47.4)                 | 3/19 (15.8)                | A vs B, NS      |
|                                          |           |                             |                             |                             | A vs C, <.01    |
|                                          |           |                             |                             |                             | A vs D, <.001   |
| Chest imaging, no. (%)                  |           |                             |                             |                             | A vs B, .02     |
|                                          |           |                             |                             |                             | A vs C, <.001   |
|                                          |           |                             |                             |                             | A vs D, <.001   |
| Unilateral infiltrates                  | 5/19 (26.3)| 4/19 (21.0)                 | 2/19 (10.5)                 | 0/19 (0.0)                 | A vs B, NS      |
| Bilateral infiltrates                   | 14/19 (73.7)| 10/19 (52.6)                | 6/19 (31.6)                 | 2/19 (10.5)                | A vs C, <.01    |
|                                          |           |                             |                             |                             | A vs D, <.001   |
| White blood cell count (10^3/µL), median (IQR) | 8.40 (5.37-10.47)| 7.01 (5.37-8.30)          | 6.42 (5.47-9.94)           | 5.78 (4.53-7.87)       | NS              |
| Lymphocyte count (10^3/µL), median (IQR) | 1.20 (0.69-1.50)| 1.35 (1.07-1.57)          | 1.40 (1.09-1.67)           | 1.70 (1.35-2.15)         | NS              |
| Platelet count (10^3/µL), median (IQR)  | 293 (216-350)| 290 (211-363)               | 290 (256-355)              | 281 (218-311)             | NS              |
| C-Reactive protein (mg/L), median (IQR) | 7.40 (1.68-18.26)| 2.54 (1.16-8.32)          | 1.85 (0.67-11.3)           | 0.73 (0.30-2.67)         | A vs B, .037    |
|                                          |           |                             |                             |                             | A vs C, .035    |
|                                          |           |                             |                             |                             | A vs D, .033    |
| Alanine aminotransferase (U/L), median (IQR) | 19.0 (16.0-27.7)| 16.5 (15.0-21.0)          | 18.0 (15.2-21.5)           | 17.0 (15.0-21.2)         | NS              |
| Aspartate aminotransferase (U/L), median (IQR) | 18.0 (16.0-24.5)| 16.5 (15.7-21.2)          | 18.0 (15.2-21.5)           | 17.0 (15.0-21.2)         | NS              |
| Interleukin 6 (pg/mL), median (IQR)     | 522 (29.05-141.7)| 37.0 (23.8-73.6)          | 30.8 (21.5-49.7)           | 22.8 (12.0-52.6)         | NS              |
| Ferritin (ng/mL), median (IQR)          | 401.7 (194.4-786.9)| 305.0 (172.1-470.8)    | 289.7 (98.4-410.5)         | 224.3 (78.0-323.0)        | NS              |
| Lactate dehydrogenase (U/L), median (IQR) | 224.0 (198.5-356.5)| 207.0 (187.5-230.0)     | 193.0 (189.0-255.5)        | 193.0 (181.75-199.0)      | NS              |
| D-Dimer (µg/mL), median (IQR)           | 1479.0 (705.7-1973.7)| 994.5 (675.0-1762.0)    | 791.0 (624.0-1561.2)       | 774.5 (522.5-1106.5)      | A vs B, NS      |
|                                          |           |                             |                             |                             | A vs C, NS      |
|                                          |           |                             |                             |                             | A vs D, D.O1    |
| Anti—SARS-CoV-2 IgG (U/mL), median (IQR) | 127.0 (64.4-205.7)| 157.0 (85.1-230.5)       | 158.0 (84.1-234.0)         | 194.0 (79.2-211.5)       | NS              |
| Viral nucleic acid negative rate, no./total (%) | 0/21 (0.0)| 18/21 (85.7)               | 19/21 (90.5)               | 20/21 (95.2)              | —               |

*CP, convalescent plasma; IQR, interquartile range; NS, not significant; FIO2, fraction of inspired oxygen; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**SI conversion factors:** blood cell values are equivalent to 10^9/L; to convert D-dimer values to nmol/L, multiply by 5.476; ferritin values are equivalent to µg/L.

* Nasal cannula or Venturi mask.
systems and testing strategies may have led to significant under-ascertainment and under-reporting of cases, contributing to a general underestimation of the disease burden and mortality in LTCFs. As a consequence, during the COVID-19 pandemic, in some metropolitan areas of Lombardy, we seriously risked losing an entire generation, that of elderly people. With the aim of rescuing these people, we conducted this cohort study, the first exploring the safety and efficacy of CP in a population composed exclusively of extremely old (median age, 87 years) patients with COVID-19 infection.

The results of our study conducted on a cohort of 22 patients were somewhat surprising: CP reduced the mortality risk by 65% compared with that in a control population, enabling the saving of 1 life for every 4 patients treated. Although the overall crude mortality rate was 13.6% (3/22), the COVID-19–related mortality rate was 9.1% (2/22), very similar to the mortality rate observed in the US Food and Drug Administration expanded access program.20 The ability of CP to block the progression of COVID-19 infection observed in our study was also found in a recently published randomized placebo-controlled trial,17 which showed that early (within 72 hours) administration of high-titer CP to mildly ill older adults with COVID-19 infection reduced the progression of the disease. The median time of CP administration after symptom onset was significantly longer in our study (7 days). However, it was not possible to stratify our cohort according to the time of CP infusion because of the small number of patients enrolled and events (ie, deaths) recorded.

The clinically beneficial effects of CP were also clearly evident from the functional respiratory and laboratory indexes immediately after its infusion, already at 72 hours. In particular, the rapid and consistent decreases in all the main laboratory parameters, including CRP, IL-6, and ferritin levels, document the anti-inflammatory properties of CP, in agreement with data available from previously published studies.16-19,22 The improvement in D-dimer levels is also of relevance, considering the frequency of thromboembolic complications during COVID-19 infection.23 This phenomenon is probably secondary to the anti-inflammatory activity of the CP and documents the close links between inflammation and hypercoagulability.

However, the most intriguing laboratory finding of our study is probably the increase in anti–SARS-CoV-2 IgG antibodies over time, which after a first peak phase linked to the passively CP-infused antibodies, reached a steady state and then increased again later by day +14 after infusion. This second wave was probably due to the active production of antibodies by the patient’s own lymphocytes, documented by the progressive increase in lymphocyte count following CP infusion. This finding may shed new light on the potential mechanisms of action of CP.

In addition to the efficacy data, our study showed the absolute safety of CP transfusion, already evidenced by robust data from the US

| Status | Group 1a (CP treatment) | Group 2b (controls) | Total | Pearson χ² Test | Risk Difference (95% CI) | Risk Ratio (95% CI) | No. Needed to Treat (95% CI) |
|--------|------------------------|---------------------|-------|----------------|--------------------------|---------------------|-----------------------------|
| Dead   | 3                      | 281                 | 284   | 5.55           | −0.2469924 (−0.3946 to −0.099) | 0.3557 (0.1238 to 1.0222) | 4.05 (2.53 to 10.07)       |
| Alive  | 19                     | 452                 | 471   |                |                          |                     |                             |
| Total  | 22                     | 733                 | 755   |                |                          |                     |                             |
| Deaths (%) | 13.6                  | 38.3                | 37.6  |                |                          |                     |                             |

aCP, convalescent plasma.
bGroup 1 comprises the 22 elderly patients with coronavirus disease 2019 living in long-term care facilities who were treated with CP and enrolled in the study. Group 2 is derived from the Italian National Health Service report and includes the 733 control patients with coronavirus disease 19, living in long-term care facilities who did not receive CP therapy.11
Food and Drug Administration expanded access program. The most probable explanation of these positive results lies, in our opinion, in the timing and dosing of CP: the early administration (median, 7 days after symptom onset) of an adequate dose (76.7% [23/30] of units had a neutralizing titer of at least 1:160) of CP was able to eradicate the virus in all patients, halting the progression of COVID-19 and thus avoiding the need for hospital admission (a particularly poor prognostic factor) in all but 2 patients. In addition, the clearance of the virus in these patients blocked circulation of the pathogen within the LTCF, preventing the infection of other elderly residents.

The main limitation of our study is the small number of patients enrolled and the nonrandomized design. Nevertheless, the population of patients enrolled in this single-center study was highly homogeneous and well-studied, with rigorous application of selection criteria and close and careful clinical and laboratory follow-up. Another potential limitation of our study could be the control group selected for the survival analysis. We chose to extract data from the ISS report to have a control population that corresponded as closely as possible to the CP treatment group in terms of demographic characteristics, health status (elderly individuals living in similar LTCFs in the same geographical area), and period of observation. In addition, the high number (nearly 90%) of not self-sufficient residents in our LTCF certainly did not confer any survival advantage to the treatment group over controls. Notably, the mortality rate observed in the present study conducted in elderly patients with moderate to severe COVID-19 infection was comparable to that observed in other trials conducted on younger patients. These results therefore further confirm recently published evidence that biological age and frailty, which are interdependently connected, rather than chronological age, are important predictors of disease severity and survival in patients with COVID-19 infection.

CONCLUSION
The results of our study document for the first time the feasibility, safety, and efficacy of a CP transfusion program for patients with COVID-19 infection in an LTCF setting. The rapid COVID-19 diagnosis and early administration of adequately anti–SARS-CoV-2 antibody-titrated CP was, in our opinion, the winning card because it neutralized the virus and restored patients' immunity, blocking the progression of the viral respiratory disease. As a consequence of this beneficial effect, hospitalization was avoided in a consistent number of patients, who were not therefore exposed to risk factors for shortened survival (eg, prolonged immobilization, nosocomial co-infections, and comorbid conditions).

Nevertheless, our study further confirms that chronological aging and frailty do not necessarily coexist and that even very old people with severe COVID-19 infection deserve to be treated for this dreaded infectious disease because they have the same chance of responding to CP as younger patients with COVID-19 infection. The CP treatment could be preferred to antiviral synthetic drugs in elderly patients with COVID-19 infection because of its independence from renal function and its lack of adverse effects and interactions with other concomitantly administered drugs.

In conclusion, we are proud to share the results of our study with the international scientific community. Although further trials on larger numbers of elderly patients are needed to confirm our extremely positive preliminary results, we hope our findings will help clinicians in Italy and other countries, in which the pandemic is still taking a dramatic toll, to rescue our grandparents, our collective memory, from severe COVID-19.

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Abbreviations and Acronyms: COVID-19 = coronavirus disease 2019; CP = convalescent plasma; CRP = C-reactive protein; FiO₂ = fraction of inspired oxygen; IL-6 = interleukin 6; IQR = interquartile range; ISS = Italian National Institute of Health; LTCF = long-term care facility; NNT = number needed to treat; NS = not significant; PCR = polymerase chain reaction; RESCUE = Real-time Evaluation of Safety and Efficacy of Convalescent Plasma Units Transfused to Elderly Patients With COVID-19; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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