Convalescent or standard plasma versus standard of care in the treatment of COVID-19 patients with respiratory impairment: short and long-term effects. A three-arm randomized controlled clinical trial

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Abstract

Background: The efficacy of early treatment with convalescent plasma in patients with COVID-19 is debated. Nothing is known about the potential effect of other plasma components other than anti-SARS-CoV-2 antibodies.

Methods: To determine whether convalescent or standard plasma would improve outcomes for adults in early phase of Covid19 respiratory impairment we designed this randomized, three-arms, clinical trial (PLACO COVID) blinded on interventional arms that was conducted from June 2020 to August 2021. It was a multicentric trial at 19 Italian hospitals. We enrolled 180 hospitalized adult patients with COVID-19 pneumonia within 5 days from the onset of respiratory distress. Patients were randomly assigned in a 1:1:1 ratio to standard of care (n = 60) or standard of care + three units of standard plasma (n = 60) or standard of care + three units of high-titre convalescent plasma (n = 60) administered on days 1, 3, 5 after randomization. Primary outcome was 30-days mortality. Secondary outcomes were: incidence of mechanical ventilation or death at day 30, 6-month mortality, proportion of days with mechanical ventilation on total length of hospital stay, IgG anti-SARS-CoV-2 seroconversion, viral clearance from plasma and respiratory
Background

Given the lack of evidence for effective treatment of COVID-19 during the first wave of pandemic, empirical and historical interventions have re-emerged as options for the control of the disease. That is the case of convalescent plasma, which has been considered an emergency intervention in several pandemics [1–5]. Initially available observational or control matched studies on COVID-19 patients were encouraging, suggesting that COVID-19 Convalescent Plasma (CCP) could reduce mortality, improve clinical outcomes, and confirming its safety [6–13]. The majority of those studies suggested that treatment in early phases of infection and high titer antibodies could represent the keys for its efficacy. However, at the time the current trial was designed, it had not been investigated whether the potential efficacy of CCP could be attributable only to its specific antibody content or if other substances in plasma, as anti-inflammatory cytokines and natural or acquired antibodies, could exert positive immunomodulation effects. Thus, due to tolerability and potential benefits at that time, we designed a 3-arm randomized trial to explore the effectiveness of high titer CCP or Standard Plasma (SP) in early phases of infection as therapeutic options to add to Standard of Care (SC) to control short and long-term progression of the disease.

Results: 180 patients (133/180 [73.9%] males, mean age 66.6 years [IQR 57–73]) were enrolled a median of 8 days from onset of symptoms. At enrollment, 88.9% of patients showed moderate/severe respiratory failure. 30-days mortality was 20% in Control arm, 23% in Convalescent (risk ratio [RR] 1.13; 95% confidence interval [CI], 0.61–2.13, \( P = 0.694 \)) and 25% in Standard plasma (RR 1.23; 95%CI, 0.63–2.37, \( P = 0.544 \)). Time to viral clearance from respiratory tract was 21 days for Convalescent, 28 for Standard plasma and 23 in Control arm but differences were not statistically significant. No differences for other secondary endpoints were seen in the three arms. Serious adverse events were reported in 1.7%, 3.3% and 5% of patients in Control, Standard and Convalescent plasma arms respectively.

Conclusions: Neither high-titer Convalescent nor Standard plasma improve outcomes of COVID-19 patients with acute respiratory failure.

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Keywords: COVID-19 therapy, COVID-19 convalescent plasma, COVID-19 outcomes, Randomized clinical trial
and then randomized in a 1:1:1 ratio according to a computerized generated sequence (for details on randomization see the Study Protocol available in the online version—see Supplementary Information). Study flow is presented in Fig. 1.

The trial used a blinded interventional arm design. The web-based random procedure was unpredictable by all those involved in the study, who received only the assignment either to the standard arm or to the experimental arms with plasma. Only the transfusion Centers knew the type of plasma (SP or CCP) assigned to patients in the experimental arms. They were responsible for blinding the three plasma bags (SP or CCP) and accompanying certificates, with black tags reporting “TRIAL PLASMA.”

Participants were randomized to receive either Standard of care or SC + three units of Standard Plasma (SP) collected in the pre-COVID-19 era (before September 2019), or SC + three units of high-titre CCP. The SC was not strictly defined, but the trial protocol recommended to follow national or international updated guidelines for COVID-19. CCP was collected in May and June 2020 from donors recovered from first-wave COVID-19 infection, when the predominant variant in our area was the 20A S614G lineage (https://clades.nextstrain.org/). The plasma units were administered on days 1, 3, and 5 after randomization. Plasma infusion was discontinued whether a severe life-threatening reaction to transfusion happened or in case of withdrawal of written consent for any reason.

97% of the units used in the trial had IgG anti-SARS-CoV-2 > 40 Arbitrary Units (AU)/ml by a quantitative Chemiluminescence-Immunoassay (CLIA) (LIAISON® SARS-CoV-2 S1/S2 IgG) showing to be concordant with Plaque Reduction Neutralization Test (PRNT): 40AU/ml = PRNT titer > 1:80. The three doses (100–300 ml each) of CCP were chosen possibly from different donors to reach a total median administered amount of 70.000 AU of neutralizing antibodies.

A detailed description of COVID-19 convalescent donors and of CCP process methods are presented in Additional file 1.
The primary outcome was 30-days mortality rate. Secondary outcomes were: incidence of mechanical ventilation (MV) or death at day 30, 6-month mortality rate, proportion of days with MV (originally defined as days in ICU) on total length of hospital stay, proportion of patients showing seroconversion to IgG anti-SARS-CoV-2, viral clearance by RT-PCR on plasma and respiratory tract samples, and variations in Sequential Organ Failure Assessment (SOFA) score from randomization, with assessments on day 2, 4, 6, 10, 14, 21, 28 or until discharge or death. Laboratory methods of SARS-CoV-2 RNA extraction and quantitation, and SOFA score are described in Additional file 1.

Complete data were not available for the other endpoint defined in the protocol (proportion of patients with drug treatment modification).

Safety outcome was the proportion of patients developing any Adverse Events (AEs) assessed daily from randomization to day 30 or discharge or death. Definition of AEs is reported in Additional file 1, as well as complete participant timeline for blood tests and clinical parameters to be reported on daily Case Report Forms.

The study design involves comparing each of the two experimental arms with the control without correction for multiplicity [15]. We calculated a sample size of 180 patients (58 per arm, rounded to 60) to assess a reduction from 25 to 10% of 30-days mortality (primary endpoint), with an alpha error (1-tail) of 0.10 and a statistical power of 80%.

The trial was analysed according to the intention-to-treat principle.

The comparisons of the proportion of deaths and of MV or death at 30 days and proportion of deaths at 6 months were stratified (by the severity of respiratory failure) and estimated in terms of RR with a Mantel–Haenszel Chi-square test. A secondary analysis, adjusted for the stratification criterion and few unbalanced critical prognostic factors (age, sex, BMI, CCI, blood group), was conducted with a Poisson regression model to estimate adjusted RRs. Subgroup analyses for the primary endpoint were performed, including in the same model the interaction terms between treatment arms and the following variables: (a) planned: stratification level, age group (<65; 65–74; 75+ years), sex, and (b) exploratory: blood group (A vs others), days from symptom onset to randomization (0–5, 6–10, ≥11) and the viraemic and serologic test results (positive, negative) at baseline. Cumulative incidence of virus clearance from plasma and respiratory tract samples and seroconversion to IgG anti-SARS-CoV-2 were compared in terms of sub-distribution Hazard Ratios (sHR) with Fine and Gray models, considering death or discharge as competing events.

We compared the percentage of MV days using an ordinal logistic model and variations of serum IgG anti-SARS-CoV-2 levels and SOFA scores during hospitalization using generalized linear mixed models for repeated measures. Statistical analyses were performed with SAS v. 9.4 and STATA v.15.

Results

From June 2020 to February 2021, 180 patients (73.9% males) were enrolled in the trial, the majority between October 2020 and January 2021, during the second pandemic wave; follow-up ended in December 2021. Demographic, clinical characteristics and treatment at baseline of the enrolled patients are listed in Table 1. The median age was 66.6 years (IQR 57.0–73.0). Most patients (88.9%) showed moderate to severe respiratory failure at enrollment, with a mean SOFA score of 2.99 (SD 1.66).

The three arms were well balanced for COVID-19 related variables, with some unbalances for age, sex, BMI and blood groups.

The mean amount of IgG anti-SARS-CoV-2 administered to a single patient with three doses of CCP was 93,431 AU, comparable to three 350 ml units with a PRNT >1:160. 56/60 patients (93.3%) in the SP arm and 54/60 (90%) in the CCP arm completed plasma infusion. Eight patients (four in each experimental arm) died within day 5 (2 deaths after the first infusion in CCP arm and 6 deaths after the second infusion: 4 in the SP arm and 2 in CCP arm). Furthermore, in the CCP arm, two patients withdrew consent for infusion, one, the day after enrollment, before the first infusion and one after the second infusion, because of a moderate allergic reaction.

Overall, with 41 deaths out of 180, the overall 30-days mortality rate was 22.8% (95%CI: 17.3–29.4), with increasing risks according to the severity of respiratory failure at enrollment (mild: 10%, intermediate: 13.7% and severe: 40%).

In comparison with patients treated with SC, who experienced a 30-days mortality of 20%, no reductions were seen for patients treated with CCP (23.3%; RR 1.13; 95%CI, 0.61–2.13, P = 0.694) or with SP (25.0%; RR 1.23; 95%CI, 0.63–2.37, P = 0.544) (Fig. 2A and Table 2). These results were confirmed with a multivariable model including age, sex, BMI, CCI, blood group, and the stratification variable (severity of respiratory failure) (Additional file 1: Table 1s) as well as by subgroup analyses (Fig. 3).

Incidence of the composite endpoint of MV or death within 30 days was not improved in the experimental arms compared to SC (Fig. 2B and Table 2).

At 6 months, with 46 deaths out of 180, the overall mortality rate was 25.6% (95%CI 19.7–32.4). In comparison with patients treated with SC, no clear differences
|                                | Standard of Care (SC) (N = 60) | SC + Standard Plasma (N = 60) | SC + COVID-19 Convalescent Plasma (N = 60) | Total (N = 180) |
|--------------------------------|-------------------------------|-------------------------------|--------------------------------------------|----------------|
| Sex—no (%)                     |                               |                               |                                            |                |
| Males                          | 40                            | 47                            | 46                                         | 133            |
| Females                        | 20                            | 13                            | 14                                         | 47             |
| Age (years)—no (%)             |                               |                               |                                            |                |
| <55                            | 11                            | 13                            | 11                                         | 35             |
| 55–64                          | 14                            | 12                            | 18                                         | 44             |
| 65–74                          | 24                            | 20                            | 21                                         | 66             |
| 75+                            | 11                            | 15                            | 10                                         | 36             |
| Median—(IQR)                   | 67.5 (58.5–72.0)               | 67.0 (56.5–74.5)               | 65.0 (57.5–73.0)                           | 66.6 (57.0–73.0) |
| Charlson Comorbidity Index—no (%) |                               |                               |                                            |                |
| 0                              | 34                            | 36                            | 31                                         | 101            |
| 1                              | 12                            | 10                            | 19                                         | 41             |
| 2–3                            | 8                             | 9                             | 9                                          | 26             |
| 4+                             | 6                             | 5                             | 1                                          | 12             |
| Comorbidities—no (%)           |                               |                               |                                            |                |
| Cardiovascular diseases        | 9                             | 10                            | 14                                         | 33             |
| Cerebrovascular diseases        | 3                             | 1                             | 1                                          | 5              |
| Chronic pulmonary diseases      | 3                             | 8                             | 3                                          | 14             |
| Diabetes                       | 9                             | 11                            | 9                                          | 29             |
| Chronic kidney diseases         | 1                             | 4                             | 1                                          | 6              |
| Liver diseases                  | 2                             | 1                             | 1                                          | 4              |
| Previous neoplasia             | 7                             | 5                             | 6                                          | 18             |
| Hypertension                   | 25                            | 24                            | 20                                         | 69             |
| Solid organ transplant          | 1                             | 1                             | 2                                          | 4              |
| Body Mass Index—no (%)          |                               |                               |                                            |                |
| <25                            | 19                            | 15                            | 14                                         | 48             |
| 25–29                          | 27                            | 27                            | 29                                         | 83             |
| 30+                            | 10                            | 14                            | 16                                         | 40             |
| n.d                            | 4                             | 4                             | 1                                          | 9              |
| Blood group—no (%)             |                               |                               |                                            |                |
| N/A                            | 4                             |                               | 4                                          | 2              |
| 0                              | 27                            | 28                            | 26                                         | 81             |
| A                              | 23                            | 25                            | 30                                         | 78             |
| AB                             | 1                             | 2                             | 3                                          | 4              |
| B                              | 5                             | 5                             | 3                                          | 13             |
| Onset of symptoms—days         |                               |                               |                                            |                |
| 0–5                            | 16                            | 16                            | 15                                         | 47             |
| 6–10                           | 21                            | 23                            | 25                                         | 69             |
| 11+                            | 22                            | 20                            | 20                                         | 62             |
| Median (IQR)—days              | 9 (5–12)                      | 8 (5–12)                      | 8 (6–11,5)                                 | 8 (5–12)       |
| Symptoms at onset—no (%)        |                               |                               |                                            |                |
| Fever                          | 52                            | 46                            | 48                                         | 146            |
| Cough                          | 35                            | 31                            | 33                                         | 99             |
| Exertional Dyspnea             | 34                            | 29                            | 28                                         | 91             |
| Nausea/Diarrhea                | 9                             | 7                             | 6                                          | 22             |
| Fatigue                        | 9                             | 12                            | 12                                         | 33             |
| Myalgia                        | 7                             | 8                             | 10                                         | 25             |
| Anosmia/Ageusia                | 4                             | 7                             | 7                                          | 18             |
Sixty-eight patients (38%) had undetectable IgG anti SARS-CoV-2 at enrollment, 51 patients (28%) had an antibody titer lower than that of CCP units (< 40 AU/ml), while 61 (34%) had an antibody titer > 40 AU/ml. Time to seroconversion was slightly shorter for CCP (sHR 1.54) and SP (sHR 1.38), but the differences between medians were minor (1 day) and statistically weak (Additional file 1: Figure 1sA). 127 patients (70.6%) showed the presence of SARS-CoV-2-RNA by RT-PCR in plasma samples at baseline and other 17 during follow-up. Viremia became negative in a median time of 5 or 6 days (IQR 4–6), without differences between arms (Additional file 1: Figure 1sB).

Table 1 (continued)

|                      | Standard of Care (SC) (N = 60) | SC + Standard Plasma (N = 60) | SC + COVID-19 Convalescent Plasma (N = 60) | Total (N = 180) |
|----------------------|-------------------------------|--------------------------------|---------------------------------------------|-----------------|
| Others               | 7                             | 11.7                           | 5                                           | 8.3             | 2                             | 3.3             | 14                           | 7.8             |
| Onset of respiratory failure—days |
| 0–1                  | 21                            | 35.0                           | 19                                          | 31.7            | 21                            | 35.0            | 61                           | 33.9            |
| 2–3                  | 28                            | 46.7                           | 31                                          | 51.7            | 28                            | 46.7            | 87                           | 48.3            |
| 4–5                  | 11                            | 18.3                           | 10                                          | 16.7            | 11                            | 18.3            | 32                           | 17.8            |
| Median (IQR)—days   | 2 (1–3)                       | 2 (1–3)                        | 2 (1–3)                                     | 2 (1–3)         | 2 (1–3)                       |                  | 2 (1–3)                     |                 |
| Degree of respiratory failure—no (%) |
| Mild                 | 7                             | 11.7                           | 6                                           | 10.0            | 7                             | 11.7            | 20                           | 11.1            |
| Moderate-severe      | 32                            | 53.3                           | 32                                          | 53.3            | 31                            | 51.7            | 95                           | 52.8            |
| Severe               | 21                            | 35.0                           | 22                                          | 36.7            | 22                            | 36.7            | 65                           | 36.1            |
| Oxygen supplementation devices—no (%) |
| Low flow nasal cannula | 2                         | 3.3                            | 6                                           | 10.0            | 9                             | 15.0            | 17                           | 9.4             |
| Venturi Mask±reservoir | 12                     | 20.0                           | 7                                           | 11.7            | 8                             | 13.3            | 27                           | 15.0            |
| High flow nasal cannula | 4                        | 6.7                            | 3                                           | 5.0             | 1                             | 1.7             | 8                            | 4.4             |
| NIV/CPAP             | 38                            | 63.3                           | 44                                          | 73.3            | 41                            | 68.3            | 123                          | 68.3            |
| Mechanical Ventilation | 4                        | 6.7                            |                                             |                 | 1                             | 1.7             | 5                            | 2.8             |
| SOFA score—mean (SD) | 3.1 (1.80)                    | 2.96 (1.43)                    | 2.9                                         | 1.74            | 2.9                           | 1.66            |                  |                 |
| Plasma SARS-CoV-2 RNA—no (%) |
| Negative             | 18                            | 30.0                           | 19                                          | 31.7            | 16                            | 26.7            | 53                           | 29.44           |
| Positive             | 42                            | 70.0                           | 41                                          | 68.3            | 44                            | 73.3            | 127                          | 70.6            |
| Plasma IgG anti SARS-CoV-2—no (%) |
| Negative             | 20                            | 33.3                           | 19                                          | 31.7            | 29                            | 48.3            | 68                           | 37.8            |
| Positive             | 40                            | 66.7                           | 41                                          | 68.3            | 31                            | 51.7            | 112                          | 62.2            |
| Median IgG anti-SARS-CoV-2—median (IQR) | 40.1 (61–89.8) | 20.4 (9.7–40.9) | 15.8 (4.4–53) | 22.6 (60–67.5) |
| Treatments at enrolment—no (%) |
| Heparin              | 57                            | 95.0                           | 56                                          | 93.3            | 54                            | 90              | 167                          | 92.8            |
| Glucocorticoids      | 56                            | 93.3                           | 59                                          | 98.3            | 54                            | 90              | 169                          | 93.9            |
| Antibiotics          | 43                            | 71.7                           | 41                                          | 68.3            | 45                            | 75              | 129                          | 71.7            |
| Remdesivir           | 13                            | 21.7                           | 8                                           | 13.3            | 9                             | 15              | 30                           | 16.7            |
| Tocilizumab          | 1                             | 1.7                            | 2                                           | 3.3             | 3                             | 5               | 6                            | 3.3             |
| Other Immunosuppressants | 2                        | 3.3                            | 1                                           | 1.7             | 3                             | 5               | 6                            | 3.3             |
| Combinations         |
| Heparin+glucocorticoids+antibiotics | 41                | 68.3                           | 39                                          | 65.0            | 38                            | 63.3            | 118                          | 65.6            |
| Heparin+glucocorticoids | 13                        | 21.7                           | 17                                          | 28.3            | 12                            | 20.0            | 42                           | 23.3            |
| Glucocorticoids+antibiotics or other drugs | 1 | 1.6                            | 2                                           | 3.3             | 2                             | 3.3             | 6                            | 3.30            |

IQR denotes Interquartile range. NIV indicates non-invasive ventilation, CPAP Continuous Positive Airway Pressure, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, and SOFA Sequential Organ Failure Assessment

were seen for patients treated with SP (RR 0.98; 95%CI, 0.55–1.76, P = 0.951) or with CCP (RR 0.85; 95%CI, 0.48–1.53, P = 0.600).
Median time to viral clearance in the respiratory tract was reached in a slightly shorter time in the CCP arm (21 days) than in SC (23 days), but the difference was not statistically sound (Additional file 1: Figure 1sC).

The median length of hospital stay for the entire population was 15 days, slightly shorter in patients who received CCP or SP than SC (14 and 15.5 vs 17.5, respectively).

The proportion of days of MV on the total length of hospital stay was 10.2%, without meaningful differences between the three arms. A mean reduction from baseline of −0.70 (95% CI, 1.57–0.15, P = 0.107) of the SOFA score during hospitalization was recorded in patients in the CCP arm compared to the SC arm. In contrast, no apparent differences in IgG seroconversions between arms were recorded (Additional file 1: Figure 2sA and B).

A descriptive analysis of the frequency and percentage of patients with altered laboratory values at baseline and during hospitalization (within 30 days since randomization) and 30-day mortality, by treatment arm, is reported in Additional file 1: Table 2s. As expected, for all the variables analysed, especially for D-Dimer and CRP, a strong positive association between altered values and increased mortality was evident.

Details of AEs are described in the Additional file 1: Table 3s. We observed 4 AEs to plasma infusion, 2 in each arm. Severe AEs were: 3 pulmonary thromboembolism, 1 massive cerebral hemorrhage during ECMO,
### Table 2: Study endpoints and comparisons between the experimental arms and control arm in the intention to treat population

|                          | Control arm | Experimental arms | Standard plasma vs control | COVID-19 Convalescent Plasma vs control |
|--------------------------|-------------|-------------------|---------------------------|----------------------------------------|
|                          | Standard of Care (N = 60) | Standard Plasma (N = 60) | COVID-19 Convalescent Plasma (N = 60) | |
|                          | no./total no (%) | no./total no (%) | no./total no (%) | Risk Ratio (95% CI) | p | Risk Ratio (95% CI) | p |
| **Primary endpoint**     |             |                   |                         |                             |   |                         |   |
| 30-days mortality        | 12/60 (20.0) | 15/60 (25.0)      | 14/60 (23.3)            | 1.23 (0.63–2.37)            | 0.544 | 1.13 (0.61–2.13) | 0.694 |
| **Secondary endpoints**  |             |                   |                         |                             |   |                         |   |
| 30-day-incidence of Mechanical Ventilation or death | 14/56 (25.0) | 24/60 (40.0) | 17/59 (28.8) | 1.53 (0.88–2.65) | 0.119 | 1.10 (0.61–1.95) | 0.757 |
| 6-months mortality       | 16/60 (26.7) | 16/60 (26.7)      | 14/60 (23.3)            | 0.98 (0.55–1.76)            | 0.951 | 0.85 (0.48–1.53) | 0.600 |

|                          | Control arm | Experimental arms | Standard plasma vs control | COVID-19 Convalescent Plasma vs control |
|--------------------------|-------------|-------------------|---------------------------|----------------------------------------|
|                          |             |                   | Risk Ratio (95% CI) | p | Risk Ratio (95% CI) | p |
| Time (days) to seroconversion to IgG anti-SARS-CoV-2* | 3 (2–4) | 2 (2–4) | 2 (2–4) | 1.38 (0.79–2.39) | 0.255 | 1.54 (0.89–2.66) | 0.119 |
| Time (days) to RT-PCR viral clearance on plasma median (IQR)** | 5 (4–6) | 6 (4–6) | 6 (4–6) | 1.01 (0.67–1.53) | 0.957 | 0.94 (0.62–1.42) | 0.761 |
| Time (days) to RT-PCR viral clearance on respiratory tract samples: median (IQR) | 23 (21–28) | 28 (20–37) | 21 (15–22) | 0.99 (0.56–1.77) | 0.983 | 1.24 (0.71–2.17) | 0.457 |

|                          | Control arm | Experimental arms | Standard plasma vs control | COVID-19 Convalescent Plasma vs control |
|--------------------------|-------------|-------------------|---------------------------|----------------------------------------|
|                          |             |                   | Mean difference (95% CI) | p | Mean difference (95% CI) | p |
| Percentage of Mechanical Ventilation days: mean (SD) | 11.58 (26.45) | 10.37 (22.23) | 8.81 (22.70) | 1.03 (0.42, 2.53) | 0.950 | 0.79 (0.30, 2.08) | 0.638 |

|                          | Control arm | Experimental arms | Standard plasma vs control | COVID-19 Convalescent Plasma vs control |
|--------------------------|-------------|-------------------|---------------------------|----------------------------------------|
|                          |             |                   | Mean difference (95% CI) | p | Mean difference (95% CI) | p |
| SOFA score variations during hospitalization: mean (SD) **** | 0.89 (3.61) | 0.61 (2.83) | 0.11 (3.38) | – 0.34 (– 1.16, 0.48) | 0.419 | – 0.70 (– 1.57, 0.15) | 0.107 |
| IgG anti-SARS-CoV-2 variations during hospitalization: mean (SD) **** | 88.54 (8.261) | 97.66 (96.59) | 80.19 (84.12) | 2.12 (– 24.99, 20.76) | 0.856 | – 11.47 (– 32.97, 10.03) | 0.296 |

IQR denotes Interquartile range, LOS length of hospital stay, and RT-PCR reverse-transcriptase–polymerase-chain-reaction
*N = 68 patients without anti-SARS-CoV-2 IgG at baseline (20 Standard of Care, 19 Standard Plasma, 29 COVID-19 Convalescent Plasma). **N = 125 patients with positive RT-PCR viral RNA at baseline (41 Standard of Care, 41 Standard Plasma, 43 COVID-19 Convalescent Plasma). ***OR for an increase of 10% of Percentage of Mechanical Ventilation days ****Reported mean (SD) at day 10
### A. Standard plasma vs control

|                | Standard Plasma | n/total | P Value | RR (95% CI) | Interaction |
|----------------|-----------------|---------|---------|-------------|-------------|
| Sex            | Male            | 8/40    | 1.29    | 0.57, 2.90  | 0.784       |
|                | Female          | 4/20    | 1.04    | 0.27, 4.62  |             |
| Age            | <65             | 4/20    | 0.26    | 0.04, 1.76  | 0.147       |
|                | 65-74           | 4/24    | 1.92    | 0.66, 5.62  |             |
|                | 75+             | 4/21    | 1.31    | 0.43, 3.81  |             |
| Blood group    | A               | 5/23    | 0.92    | 0.30, 2.82  |             |
|                | Others          | 7/37    | 1.46    | 0.61, 3.49  |             |
| Onset of symptoms | 0-5 days       | 4/16    | 1.88    | 0.85, 4.48  | 0.495       |
|                | 6-10 days       | 5/22    | 0.73    | 0.23, 2.39  |             |
|                | 11+ days        | 4/20    | 1.11    | 0.27, 4.61  |             |
| SARS-CoV-2 RNA | Negative        | 1/18    | 1.81    | 0.22, 14.69 | 0.712       |
|                | Positive        | 1/42    | 1.20    | 0.52, 2.42  |             |
| IgG anti-SARS-CoV-2 | Negative    | 6/20    | 0.82    | 0.29, 2.35  | 0.332       |
|                | Positive        | 6/40    | 1.63    | 0.67, 3.96  |             |
| Severity of respiratory failure | Mild | 1/7     | 2.67    | 0.84, 8.50  | 0.110       |
|                | Intermediate    | 3/32    |         |             |             |
|                | Severe          | 8/21    | 0.84    | 0.34, 2.03  |             |

### B. Covid-19 Convalescent plasma vs control

|                | Convalescent Plasma | n/total | P Value | RR (95% CI) | Interaction |
|----------------|---------------------|---------|---------|-------------|-------------|
| Sex            | Male                | 8/40    | 1.27    | 0.56, 2.88  | 0.543       |
|                | Female              | 4/20    | 0.74    | 0.16, 3.52  |             |
| Age            | <65                 | 4/25    | 0.80    | 0.27, 2.93  | 0.677       |
|                | 65-74               | 4/24    | 1.65    | 0.54, 5.19  |             |
|                | 75+                 | 4/11    | 0.79    | 0.20, 3.07  |             |
| Blood group    | A                   | 5/23    | 0.94    | 0.30, 2.92  |             |
|                | Others              | 7/37    | 1.26    | 0.52, 3.18  |             |
| Onset of symptoms | 0-5 days         | 4/16    | 0.69    | 0.14, 2.95  | 0.655       |
|                | 6-10 days           | 5/22    | 1.13    | 0.39, 3.26  |             |
|                | 11+ days            | 3/22    | 1.60    | 0.46, 5.56  |             |
| SARS-CoV-2 RNA | Negative            | 1/18    | 2.72    | 0.38, 19.69 | 0.329       |
|                | Positive            | 1/42    | 1.00    | 0.48, 2.07  |             |
| IgG anti-SARS-CoV-2 | Negative    | 6/20    | 0.85    | 0.32, 2.24  | 0.470       |
|                | Positive            | 6/40    | 1.41    | 0.54, 3.72  |             |
| Severity of respiratory failure | Mild    | 1/7     | 1.00    | 0.09, 12.30 | 0.778       |
|                | Intermediate        | 3/32    | 0.69    | 0.14, 3.49  |             |
|                | Severe              | 9/21    | 1.21    | 0.57, 2.69  |             |

Fig. 3 Forest plot with subgroup comparisons of Standard plasma vs Control (A) and COVID-19 Convalescent plasma vs Control (B). *Not estimated because no events were observed in Standard Plasma arm.
1 myocardial infarction, 1 iatrogenic pneumothorax (reported in 1.7%, 3.3% and 5% of patients in Control, SP and CCP arms respectively) and 41 deaths (for respiratory failure in all cases).

**Discussion**

At variance with most previous non randomized studies, but in accordance with nearly all randomized controlled trials, we failed to demonstrate any significant improvement of relevant clinical outcomes adding COVID-19 convalescent plasma to the standard of care even though we tried to anticipate as much as possible the treatment and to use high doses of antibodies [10, 16–28]. A trend to a shorter length of hospital stays and a reduction in MV incidence and duration through the hospital stay was seen for CCP treatment, but differences were small and statistically weak. Moreover, no improvement was seen in outcomes by adding SP to SC, thus proving that anti-inflammatory cytokines and natural or acquired antibodies contained in standard plasma did not help in this phase of COVID-19 disease.

Our inclusion criteria permitted enrollment within 5 days since onset of respiratory impairment that was the shortest possible interval considering standards for inpatients in our hospitals (patients were advised to come to the hospital only if respiratory impairment was present). This led to a median interval of 8 days (range 5–12) since the onset of symptoms. Clinical results of our trial are in accordance with those of most randomized controlled studies published to date [14, 17–19, 24, 26, 27, 29, 30], that showed no efficacy of CCP for patients with comparable time since onset of symptoms. Different results, with a reduced risk of evolution of the disease, have only been shown in a single randomized trial [25] that used CCP within 3 days since onset of symptoms, before pneumonia and its complications became clinically evident at variance with other two more recent papers that failed to confirm the efficacy of early use [22, 31]. Our subgroup analyses only suggest a decreasing effect of CCP with increasing time from symptom onset, but the evidence is weak.

In contrast to a randomized trial that was interrupted because 79% of patients at enrollment were showing comparable antibodies titers than CCP [18], in our study only 34% of patients had antibodies titers higher than the lower CCP antibody titers (40 AU/ml) so most patients being in a very early phase of infection before an immune response was appreciable. Nevertheless, even in this early phase, when antibodies titers are not yet raised, passive immunotherapy didn’t seem to play a crucial role in shortening disease history, preventing complication or ameliorating clinical outcomes.

It has also been suggested that the titer of neutralizing antibodies plays a crucial role in the effectiveness of CCP treatment [28]. Our trial neutralizing antibodies total dose, even though no precise comparison amongst trials can be made to date, can be considered one of the highest administered in a randomized trial so far. We enlarged the total volume of CCP administered to patients compared to other studies (3 units). All our plasma units were tested with an ELISA assay that correlates with PRNT, and we estimated a mean infusion of three 350 ml units with a PRNT > 1:160. All participants received plasma from at least two donors (15 patients from 3 donors) trying to increase antibodies heterogeneity. Furthermore, what differs from other treatments is the attempt to standardize the total amount of antibodies administered per patient. A mean total dose of 93,000 AU of antibodies was administered to patients in CCP arm. Nevertheless, no advantage in outcomes was seen with this high dose strategy compared to SC in this phase of the disease. In light of suggestions from a recent paper [29] showing that patients treated with high levels of anti-Spike protein CCP showed worse outcomes, the ELISA test we used, detecting anti-Spike-protein antibodies, despite the excellent correlation with PRNT, could have selected CCP with unfavorable antibody profile for COVID-19 patients’ treatment.

In our study, most enrolled patients (88.9%) were affected by moderate to severe respiratory failure. This selection reflects the greater propensity of physicians to propose study participation to most severe than to mild cases that could be considered a limit of our study. The high prevalence of patients (80%) with detectable SARS-CoV-2 viremia, one of the highest described in the literature, confirms the severity of the disease in our cohort of patients. Our results confirm previous studies showing worse outcomes and increased mortality in plasma RNA+ patients, irrespective of treatment [32–36]. Furthermore, CCP did not increase the clearance of SARS-CoV-2 viremia from plasma, indicating that passive immunization does not play a key role for infection in this phase of the disease.

A slightly faster clearance of virus from respiratory tract samples was seen in CCP patients in accordance with other data [6, 7, 16, 18]. Still, this difference was not statistically sound and is of questionable clinical relevance.

On the other side, no meaningful difference was seen in our trial in number or types of AEs between three arms of treatment confirming the safety of SP and CCP in this subset of patients [37, 38]. The three cases of thromboembolism observed in our trial, one in each treatment arm, were not related to plasma infusion. With strict
daily monitoring of possible AEs, our trial confirms that this amount of plasma (mean = 230 ml, equivalent to 3 ml per Kg) is neutral in terms of coagulation processes in vivo, probably providing a balanced amount of procoagulants and anticoagulant factors.

The inclusion of a study arm with SP, the careful selection of CCP units to administer a comparable dose of antibodies to all treated patients, the masking of the plasma bags, the evaluation of SARS-CoV-2 RNA on patients plasma and in the respiratory tract over time, the strict monitoring of clinical data and the 6 months follow-up represent the originality and the strengths of our study. Due to the substantial expected benefits, the relatively small sample size is the major limitation of our study.

Conclusions
Our study supports the findings from almost all randomized controlled trials that CCP does not offer meaningful therapeutic advantages over standard care in fighting against COVID-19 disease and its complications after the onset of respiratory failure and confirms that there is no reason to continue to use CCP in this subset of patients. Furthermore, it underlines that SP and its potential immune-modulatory effect has no impact on this clinical condition.

Abbreviations
CCP: COVID-19 convalescent plasma; SP: Standard plasma; SC: Standard of care; RT-PCR: Reverse-transcriptase–polymerase-chain-reaction; PaO2: Partial pressure of oxygen; AA: Ambient air; NIV: Non-invasive ventilation; CPAP: Continuous Positive Airway Pressure; ARDS: Acute respiratory distress syndrome; MV: Mechanical ventilation; ECMO: Extra Corporeal Membrane Oxygenation; ALI: ARBUs; CLIA: Chemiluminescence-Immunoassay; PRNT: Plaque Reduction Neutralization Test; SOFA score: Sequential Organ Failure Assessment score; AEs: Adverse events; SHR: Sub-distribution Hazard Ratios.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12879-022-07716-5.

Additional file 1. Supplementary appendix.

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Author contributions
PMM is the Chief Investigator; she conceived the study, led the proposal and protocol development and wrote the manuscript. GCI, FGDR, CG, SDA, FS, ACAS, ML, GCAs, GA, AM, AT, LB, LS, CV, MPri, FE, contributed to study design and to development of the protocol. GCI was the lead trial methodologist. FS, ACAS were trial methodologists and they analyzed results. FD, LL, designed protocol development and wrote the manuscript. GCi, FGDR, CG, SDA, FS, PM is the Chief Investigator; she conceived the study, led the proposal and protocol development and wrote the manuscript. GCI, FGDR, CG, SDA, FS, PM, PO, ITS, RG, RF, PB, AN, LMa, FPM, SR, AB, AR, Mwi, GD, FCAs, AV, RR, AP, DO, RA, BLS, IG, ACI, RLG, ADR, LC, TB, OC, KG, FN, MT, PO, OBo, LMaV, VB, MPri, LAI, MG, MCA, LR, DDm, SF, MMa, MMo, GSe, PSp, GGIa organized donorsâ selection and recruitment and plasma and CCP collection in their hospitals. IF, HH, CP, CD, GGu, CF, DMV, FPol, SHe, ChL, DRo, Sz, MeMa, IA, SG, RBA, VN, LA, MCP, ST, MCA, GSt, VIG, organized patients' data collection for their centers. BM, GSc, CP were responsible for coordinating Hospital organization for the trial. VC, VG, FF, LL, FF, MA, CC, MGM, organized and performed all donors and patients serological and RT-PCR tests. GC, Gl, Csc, FF, Cso, MR, CG, organized plasma and CCP fractionation, treatment and stockage. GR, TDA, CC, SN, VAg, LP, FPl0, GGIa, organized CCP and plasma blinding and assignment. AGDM, AM, SBA, FC, MLR, DB, VP, MML, ACH, ACA, MCa, CAL, VL, LB, VB, GAP, ChCh, SM, SS, FVs, MG, EL, LB, CAL, LS, VG, CN, AF, AL, GDP, MNA, PP, OF, PA, SME, PMA, MGV, APx, EMe, FB, FP, SBE, LL, LG, USa, APA, EC, MNo, FPat, LLo, DrA, GC, MS, GA, RBLo, LA, MF, FAr, FbA, Fbs, FPl0, SM, ER, VP, MMe, EN, PT, LMo, GD, FS, DV, RP, GBv, VS, FPa, SL, EMan, GCa, EV, NL, MPAs, PC, FG, BS, LG, EMag, GR, GMS, AD, PV, GCh, MGI, FR, MGIi, VDB, EA, EP were responsible for organization of recruitment and follow-up of patients, preparation and transmission of daily CRFs at their Hospitals. NBI was responsible for collection and analysis of adverse events. GCl, CG, SDA, ACAs, ML were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are not publicly available due to database complexity for structure and amount of collected data, that request a precise and clear definition of dataset requested and precise objectives before sharing. Data are in any case available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The trial protocol was approved by the ethical Committee of the coordinating center: Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino—A.O. Ordine Mauriziano di Torino—A.S.L. Città di Torino and then by all ethical Committee at each participating center and was conducted following the principles stated in the declaration of Helsinki and the Good Clinical Practice Guidelines. A written informed consent was obtained from all subjects (donors and patients) and/or their legal guardian(s) before enrollment. The informed consent is available in the Study Protocol available in the online version—see Supplementary Information.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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