Supplementary appendix to High-titre methylene-blue treated Convalescent Plasma as an early treatment for COVID-19 outpatients: A randomized clinical trial

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COnV-ert GROUP OF AUTHORS

- **Fight AIDS and Infectious Diseases Foundation**

Susana Ferrer, Mireia Gallardo, Maria Ubals, Camila González-Beiras, Martí Vall-Mayans, Clara Suñer, Claudia Laporte, Aroa Nieto, Xavier Comas-Leon, Zahida Jiménez, Ferran Ramírez-Viaplana

- **Hospital Universitari Germans Trias i Pujol (HUGTiP)**

Maria Delgado Capel, Beatriz Díez Sánchez, Maria Pons Barber, Cristian Gonzalez Ruiz, Laura Navarrete Gonzalez, David González García, Ainhoa Vivero Larraza, Victor Carceles Peiró, Clàudia Roquer López, Neus Robert, Carles Palet

- **Hospital Universitari de Bellvitge**

Carlota Gudiol, Pablo Casares Gonzalez, Gemma Arcos Vila, Begoña Flores Aguilera, Graciela Rodríguez-Sevilla, Macarena Dastis Arias

- **CUAP Manresa**

Judit Roca Font, Katherine M. Carrasco Matos, Glòria Saüch Valmaña, Carla Vidal Obradors

- **Hospital Comarcal de Sant Bernabé**

Silvia Tarres García, Margarida Curriu Sabatès, Raquel Nieto Rodríguez

- **Blood Bank Department - Banc de Sang i Teixits (BST)**

Rosa Línio, Miriam Fornos, Natàlia Casamitjana, Eva Alonso, Núria Martinez, Laura Analía Maglio, Laura Comellas Fernandez, Nadia Garcia, Luis Hernández, María Isabel González, Anna Bravo, Yolanda García, Silvia Sauleda Oliveras

- **Gerència Territorial Metropolitana Nord**

Tatiana Vertiz, Sergio Benavent, Andrea Sofia Bianco, Joaquim Verdaguer, Ney Nicanor Briones Zambrano, Maria Viozquez Meya

- **Metropolitana Nord Laboratory**

Águeda Hernández

- **Microbiology Service, Metropolitana Nord Laboratory**

Cristina Casaña Lopez, Antoni E. Bordoy, Victoria González Soler, Montserrat Giménez, Alexa París

- **IrsiCaixa AIDS Research Institute**

Silvia Marfil, Benjamin Trinité, Eulàlia Grau

ADDITIONAL METHODS

Methods S1. Study sites and catchment population

Study sites	Principal Investigator(s)	Health region
Hospital Universitari Germans Trias i Pujol	Oriol Mitjà	Àmbit Metropolità Nord
Hospital Universitari de Bellvitge	Pierre Malchair	Àmbit Metropolità Sud
CUAP Manresa	Anna Ruiz-Comellas Anna Ramírez-Morros	Catalunya Central
Hospital Comarcal de Sant Bernabé	Rosa Amado Simon Joana Rodríguez Codina	Catalunya Central

Methods S2. Convalescent plasma collection, testing, processing, storage, and distribution

Plasma collection and distribution

The study convalescent plasma was supplied by the regional blood and tissue bank (*Banc de Sang i Teixits de Catalunya* – BST). The BST is a public agency of the Catalan Department of Health whose mission is to guarantee the supply and proper use of human blood and tissue in Catalonia. The BST has a network of blood donation centres located at Catalonia's leading hospitals, and implements a system of whole blood process control, from the initial moment of donation to the final step, transfusion.

Convalescent plasma donors were recruited and screened, according to the standard donor selection guidelines in Spain, mostly by 5 out of 12 donation centres located in leading hospitals in Barcelona health region. Convalescent plasma was obtained via plasmapheresis from donors with a prior diagnosis of Covid-19 confirmed by a positive RT-PCR or a positive test for SARS-CoV-2 antigen. Plasma units had a volume between 235 and 315 ml (gross weight between 275 and 350 g), and from apheresis between 470 and 630 ml (gross weight between 535 and 695 g). All convalescent plasma units were inactivated with methylene blue and labelled following standard procedures.

Convalescent plasma was centralized and stored at regional blood and tissue bank facilities (*Banc de Sang i Teixits de Catalunya* – BST), and after being screened for high anti-SARS-CoV-2 IgG titres and selected for the COnV-ert study, was distributed to the four different study centres.

Characteristic of donors:

- Basic criteria:
    - Man or woman with no pregnancy history (or who have been tested and found negative for anti-HLA antibodies using a validated assay).
    - Age ≥ 18 years and <65 years (<70 years for regular donors)
    - Weight ≥ 50 kg
    - No history of previous transfusions
- Donor Informed Consent and Plasmapheresis Informed Consent
- Prior diagnosis of Covid-19 documented by a positive RT-PCR or a positive test for SARS-CoV-2 antigen, whether the individual had symptoms or not.
- A deferral period of at least 14 days after symptom resolution and at least 7 days after resolution of fever.
- Evaluation of laboratory tests:
    - ABO/Rh(D) test; Irregular Antibody
    - Test serologies: HBV, HCV, HIV, Syphilis, HTLV I and II, T. cruzy, T. pallidum, WestNile virus
    - IgG, IgM, IgA antibodies anti-SARS-CoV-2

    - Antibodies anti-HLA, anti-HNA, anti-HPA (for women without pregnancy or transfusion history)
- Maximum volume 616 g (600 ml)
- If donor >1 donation of convalescent plasma, cut-off ≥ 3 (Euroimmun techniques to measure anti-SARS-CoV-2 IgG), regardless of how long it has been since donor had the disease

Testing of donated plasma

The convalescent plasma was screened for high anti-SARS-CoV-2 IgG titres with a commercial CE-marked **ELISA** microplate coated with recombinant Spike S1 domain protein (Euroimmun Medizinische Labordiagnostika, Lübeck, Germany) by the regional blood bank (*Banc de Sang i Teixits de Catalunya* – BST) in a sample obtained from donated plasma after donation. The US FDA determined that convalescent plasma with a EUROIMMUN sample ≥3.5 qualifies as high titre [1].Only plasmapheresis with a sample to cut-off ratio ≥6 on the EUROIMMUN IgG enzyme-linked immunosorbent assay (ELISA) targeting the spike glycoprotein were supplied for the COnV-ert study. EUROIMMUN IgG has been shown to correlate well with neutralization assays, and a sample to cut-off ratio ≥6 was associated with neutralizing titres of ≥1:100 in convalescent plasma [2,3].

A sample of each convalescent plasma unit was collected during preparation and masking of interventional product by unblinded BST staff in each participating centre and sent to a centralized laboratory (*IrsiCaixa laboratory*) for prospective characterization of neutralizing antibody titres. More than one participant could receive plasma from the same donor.

Methods S3. Convalescent plasma neutralizing activity

Pseudovirus generation and neutralization assay: HIV reporter pseudoviruses expressing SARS-CoV-2 S protein and Luciferase were generated. pNL4-3.Luc.R-.E- was obtained from the NIH AIDS Reagent Program [4] SARS-CoV-2.SctΔ19 was generated (GeneArt) from the full protein sequence of SARS-CoV-2 spike with a deletion of the last 19 amino acids in C-terminal, human-codon optimized and inserted into pcDNA3.4-TOPO [5]. Expi293F cells were transfected using ExpiFectamine293 Reagent (Thermo Fisher Scientific, USA) with pNL4-3.Luc.R-.E- and SARS-CoV-2.SctΔ19 (Wuhan-Hu-1 or B.1.1.7), at an 8:1 ratio, respectively. Control pseudoviruses were obtained by replacing the S protein expression plasmid with a VSV-G protein expression plasmid as reported [6] Supernatants were harvested 48 hours after transfection, filtered at 0.45 μm, frozen, and titrated on HEK293T cells overexpressing WT human ACE-2 (Integral Molecular, USA). Briefly, neutralization assays were performed in duplicate in Nunc 96-well cell culture plates (Thermo Fisher Scientific), 200 TCID50 of pseudovirus were preincubated with three-fold serial dilutions (1/60–1/14,580) of heat-inactivated plasma samples for 1 hour at 37ºC. Then, $1x10^4$ HEK293T/hACE2 cells treated with DEAE-Dextran (Sigma-Aldrich, USA) were added. Results were read after 48 hours using the EnSight Multimode Plate Reader and BriteLite Plus Luciferase reagent (PerkinElmer, USA). Neutralization capacity of the plasma samples was calculated by comparing the experimental Relative Light Units (RLU) calculated from infected cells treated with each plasma to the max RLUs (maximal infectivity calculated from untreated infected cells) and min RLUs (minimal infectivity calculated from uninfected cells) and expressed as percent neutralization: %Neutralization = (RLUmax–RLUexperimental)/(RLUmax–RLUmin)*100. The ID50 (reciprocal dilution inhibiting 50% of the infection) was calculated by plotting and fitting the log of plasma dilution vs. normalized response to a 4-parameters equation in Prism 9.0.2 (GraphPad Software, USA).

The neutralization assay has been previously validated in a large subset of samples with a replicative viral inhibition assay [7]. Furthermore, to facilitate conversion to International Units (IU), we tested in our assay a panel of plasma samples containing a dilution series of a high titre convalescent plasma calibrated in IU/mL using the standard 20/130 obtained from the National Institute for Biological Standards and Control (NIBSC, United Kingdom)[8]. Experimental neutralization titres can be converted to IU/mL using the following regression formula (IU/ml = 4160/(2^($Log_2^{(experimentalID50-13.962)/-0.9798}$) derived from assay calibration with the pre-quantified control as shown in Figure.

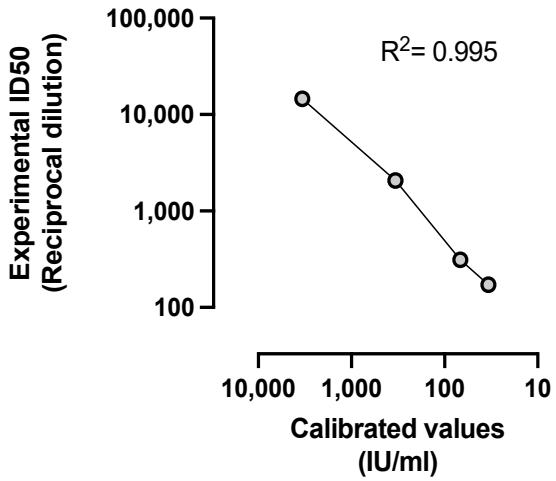


Figure. Correlation between experimental ID50 values and calibrated neutralization titres.

Methods S4. Characterization of serologic status of enrolled participants at baseline

Blood samples from all enrolled participants were collected at baseline and sent for prospective characterization of SARS-CoV-2 antibodies at a central laboratory (Microbiology Service, *Metropolitana Nord Laboratory, Institut Català de la Salut, Badalona, Spain*). Serologic status was defined according to the results of the ELISA for detection of anti-SARS-CoV-2 IgM and IgG, considering seropositivity if the participant was IgG+/IgM-, IgG-/IgM+ or IgG+/IgM+.

We tested samples by Chemiluminescence immunoassay (CLIA) in a fully automated platform (LIASISON® XL). We used recombinant Trimeric Spike glycoprotein as antigen LIAISON® SARS-CoV-2 TrimericS IgG quantitative SARS-CoV-2 IgG (DiaSorin, Vercelli, Italy) and S1-RBD as antigen. LIAISON® SARS-CoV-2 IgM qualitative SARS-CoV-2 IgM (DiaSorin, Vercelli, Italy).

Methods S5. Analysis of SARS-CoV-2 Viral Load by RT-PCR

The detection of the SARS-CoV-2 virus was performed from nasopharyngeal swabs at a centralized laboratory (*Microbiology Department, Clinical Laboratory Metropolitana Nord, Badalona, Barcelona, Spain*). Three nasopharyngeal swabs were collected from each participant, at baseline, D7 and D28. RNA was extracted using the STARMag reagent (Seegene) on the Microlab Starlet IV (Hamilton Life Science Robotics) automatic extractor, according to the manufacturer's protocol. The presence of SARS-CoV-2 was confirmed by retrotranscription and real-time PCR in a single step with the Allplex 2019-nCoV assay (Werfen) on the CFX96 instrument (BIO-RAD).

For absolute quantification, a standard curve was built using 1/2 serial dilutions of a SARS-CoV2 RNA (Amplirun® Coronavirus RNA Control, catalogue ref. MBC090, Vircell Microbiologists), run in parallel to a set of samples covering all thermal cycles used in the analysis. Negative samples were assigned to a Ct of 40. The viral load of each sample (in copies/mL) was extrapolated from the standard curve. The viral load was estimated from the corresponding Ct values (RdRP gene).

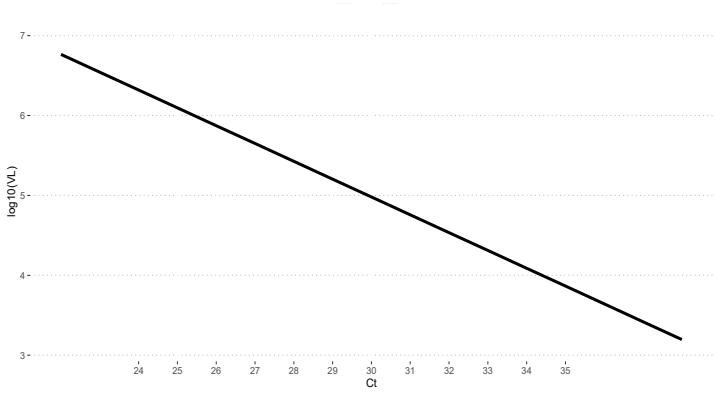


Figure. Standard curve

Methods S6. WHO Clinical progression scale score

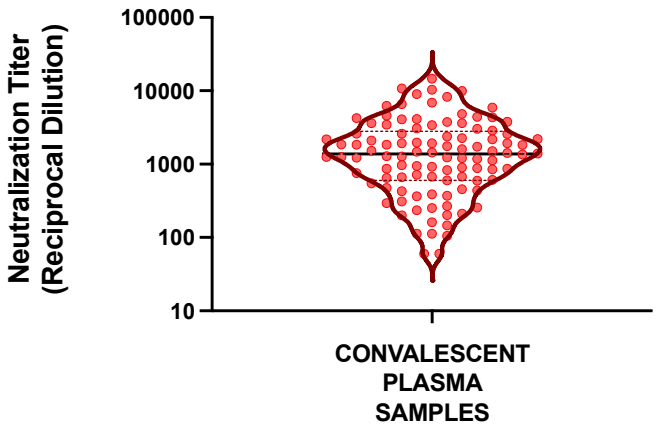
Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe diseases	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FIO_2 \geq 150$ or $SpO_2/FI0_2 \geq 200$	7
	Mechanical ventilation $pO_2/FIO_2 < 150$ ($SpO_2/FI0_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FIO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Death	Death	10

Abbreviations. ECMO: extracorporeal membrane oxygenation; FiO2: fraction of inspired oxygen; NIV: non-invasive ventilation; pO2: partial pressure of oxygen; SpO2: oxygen saturation.

ADDITIONAL RESULTS

Figure S1. Distribution of neutralizing antibody titres (ID50 and IU) against WH1 pseudovirus in plasma donors

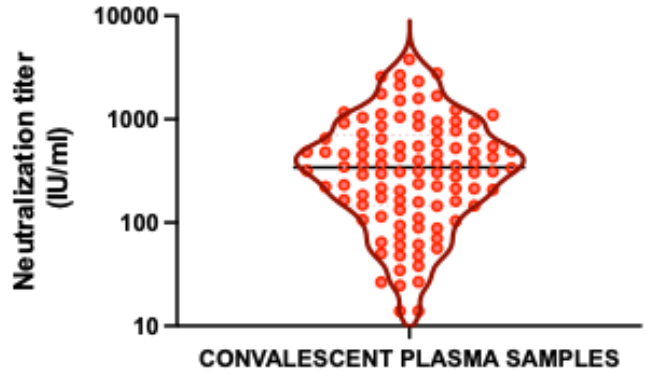
A



C

Donors (n=148)	**ID50** (Reciprocal dilution)
Minimum	60.00
25% Percentile	602.3
Median	**1379**
75% Percentile	2801
Maximum	14580
Range	14520
Mean	2237
Std. Deviation	2602
Std. Error of Mean	255.1

B



D

Donors (n=148)	**ID50** (International units)
Minimum	13.9
25% Percentile	146.8
Median	**341.7**
75% Percentile	704.5
Maximum	3794
Range	3780
Mean	566.1
Std. Deviation	673.0
Std. Error of Mean	68.99

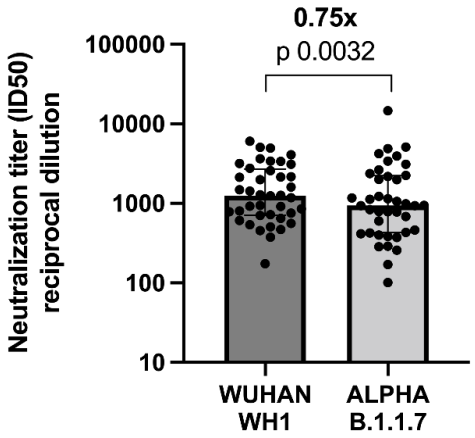
Panel A shows violin plot of titres (as reciprocal dilution) of transfused plasma samples with median (solid lines) and 25 and 75 percentiles (dotted lines).

Panel B shows violin plot of titres (international units) of transfused plasma samples with median (solid lines) and 25 and 75 percentiles (dotted lines).

The full statistical description is shown in panel C (reciprocal dilution) and panel D (international units).

Figure S2. Distribution of neutralizing antibody titres (ID50) against WH1 and alpha-variant pseudovirus in plasma donors

A



B

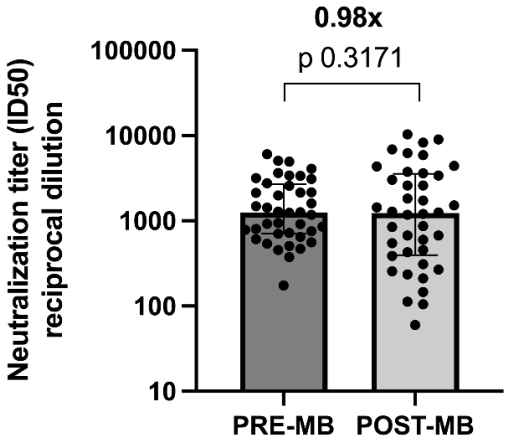
Number of values	**WH1** (n=40)	**ALPHA** (n=40)
Minimum	174	101
25% Percentile	709.3	427.5
Median	**1256**	**943**
75% Percentile	2712	2236
Maximum	6034	14580
Range	5860	14479
Mean	1798	1767
Std. Deviation	1467	2469
Std. Error of Mean	231.9	390.4
Geometric mean	**1305**	**1011**
Geometric SD factor	2.298	2.844

Panel A shows neutralizing antibody titres (as reciprocal dilution) of transfused plasma samples against Wuhan (WH1) and alpha-variant (B.1.1.7) pseudovirus. The full statistical description is shown in panel B.

Statistics: Paired Wilcoxon Test (N=40). Bars in Panel A represent 95% CI and median is represented with a thick horizontal line. Dots in Panel A are neutralization titres (reciprocal dilution) of all samples tested against Wuhan (WH1) and alpha variant (B.1.1.7).

Figure S3. Distribution of neutralizing antibody titres (ID50) pre-MB and post-MB

A



B

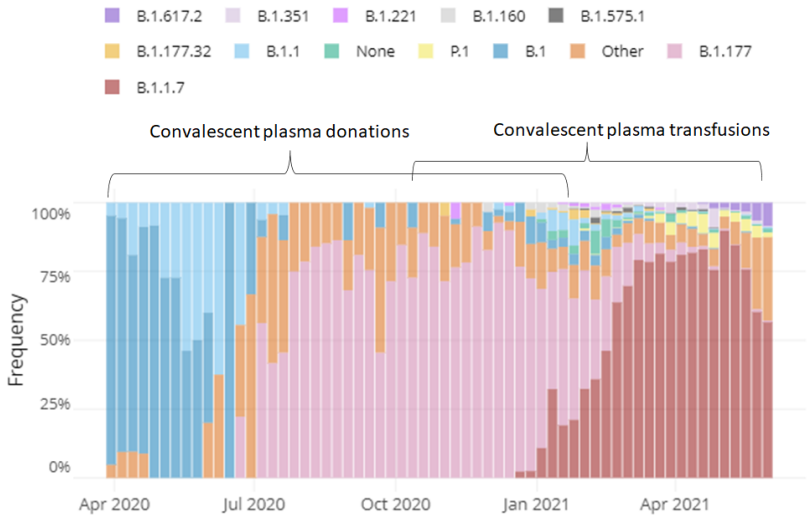
Number of values	**PRE** (n=40)	**POST** (n=40)
Minimum	174	60
25% Percentile	709.3	349
Median	**1256**	**1287**
75% Percentile	2712	3333
Maximum	6034	9038
Range	5860	8978
Mean	1798	2260
Std. Deviation	1467	2588
Std. Error of Mean	231.9	627.7
Geometric mean	**1305**	**1104**
Geometric SD factor	2.298	3.900

Panel A shows neutralizing antibody titres (as reciprocal dilution) of transfused plasma samples pre-methylene blue (MB) treatment and post-methylene blue (MB) treatment. The full statistical description is shown in panel B.

Statistics: Paired Wilcoxon Test (N=40). Bars in Panel A represent 95% CI and median is represented with a thick horizontal line. Dots in Panel A are neutralization titres (reciprocal dilution) of all samples tested pre-MB and post-MB treatment.

Figure S4. Distribution of SARS-CoV-2 variants during donation and recruitment periods

A



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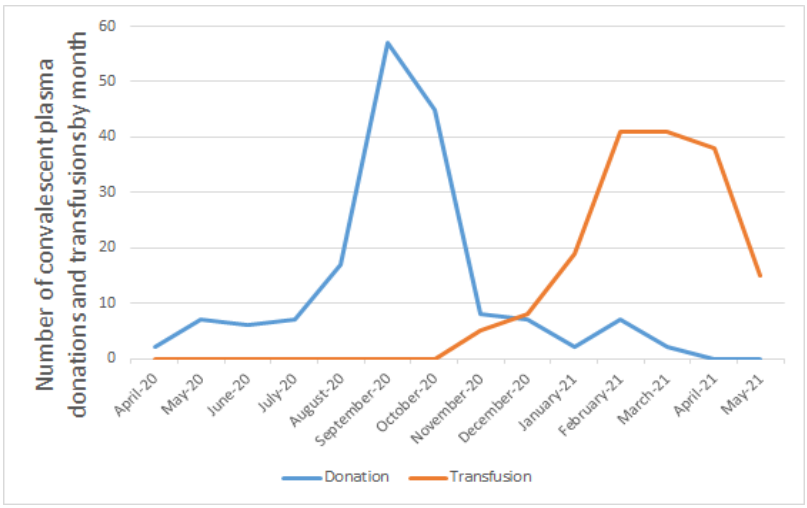


Panel A. Average weekly variants frequency in Catalunya during COnV-ert convalescent plasma donations period (Apr 2020 - Feb 2021) and recruitment period (Nov - Jun 2021); (source http://covidtag.paseq.org/). Panel B. Number of convalescent plasma donations and transfusions by month.

Convalescent plasma donations were collected between April 2020 and February 2021 when the predominant variants in Catalunya were B1 and B1.1 (Mar-May 2020), and B1.177 (Jun-Dec 2020). The Alpha VOC (B.1.1.7) was first reported in Catalunya in January 2021 and didn't become the main circulating strain until February 2021. Approximately 90% of the study participants were included between 1st January and 28th May 2021, during the rapid spread of the B.1.1.7 variant, and when the proportion of Delta VOC (B.1.617.2) cases was negligible (<5%). Gamma VOC (P.1) and Beta VOC (B.1.351) were reported in very low proportions during the whole recruitment period [9].

Quantification of neutralizing activity of convalescent plasma was tested at IrsiCaixa laboratory, using a neutralization assay with pseudoviruses expressing the spike of the original SARS-CoV-2 isolate Wuhan-Hu-1 (WH1). The investigators had previously tested the neutralizing activity of sera from infected and vaccinated individuals against WH1, D614G mutant and the Alpha VOC (B.1.1.7 variant). Their results showed that neutralizing activity of plasma obtained from B1 and B1.1 convalescent patients was minimally reduced against the Alpha VOC (B.1.1.7 variant)[5]. The vast majority of lab studies have found no significant change in neutralizing activity of plasma from patients infected in the first wave against Alpha VOC (B.1.1.7), while there was a remarkable reduction in neutralizing activity against Gamma VOC (P.1), Beta VOC (B.1.351), and Delta VOC (B.1.617)[10–16].

Table S1. Cross-neutralization of SARS-CoV-2 variants

No significant change in neutralizing activity
Fold change <3
Fold change 3-10
Fold change 10-100
Fold change >100

		B.1.1.7 (Alpha variant) compared to original virus
Nature [10]	**n 20** Authentic clinical viral isolates	Fold change ID_{50} (mean): 1.4 **(p=0.522)** relative to WA1 (wild-type virus) **Not statistically significant.**
Nat Med [12]	**n 58** Authentic clinical viral isolates	Mean ID_{50}: 1.3 x10^3 and 1 x10^3 (10^2 to 2 x10^4) for B.1.1.7 and D614G, respectively. **Not statistically significant.**
JAMA [13]	**n 20** Focus reduction neutralization tests (FRNTs)	$FRNT_{50}$ (GMTs) 168 for WA1 (95% CI, 113-249); 91 for B1 (95% CI, 60-138); 145 for B.1.1.7 (95% CI, 96-220). **Not statistically significant.**
Cell Rep [11]	**n 2** Pseudovirus neutralization assay	Fold change ID_{50}: -1 to -2.9 **(p=0.15)** relative to 614G. **Not statistically significant.**
Viruses [5]	**n 48** Pseudovirus neutralization assay	Fold change ID_{50} (median): 0.7 WH1/B.1.1.7 **Not statistically significant.**
J Infect [17]	**n 90** Authentic clinical viral isolates	Fold change ID_{50} (mean): -1.6 **(p=0.0002)** relative to 20A.EU1 (lineage B.1)
Cell [15]	**n 34** Focus reduction neutralization test (FRNT)	Fold change $FRNT_{50}$ (GMTs): -2.9 **(p<0.0001)** relative to Victoria (early Wuhan-related strain)

		B.1.1.7 (Alpha variant) compared to D614G
Cell Host Microbe [14]	**n 15** Pseudovirus neutralization assay	Fold change ID_{50} (median): -1.5 (range 0.7 to 5.5; IQR -1.1 to -1.8) relative to D614G. **Not statistically significant.**
Viruses [5]	**n 48** Pseudovirus neutralization assay	Fold change ID_{50} (median): 1.17 **(p<0.0001)** D614G/B.1.1.7
Nature [18]	**n 27** Pseudovirus neutralization assay	Fold change ID_{50} (mean): -4.5 **(p=<0.001)** relative to D614G

		B.1.351 (Beta variant)
Nature [10]	**n 20** A) Authentic clinical viral isolates B) Pseudovirus neutralization assay	A) Fold change ID_{50} (mean): -9.4 **(p<0.0001)** relative to WA1 (wild-type virus) B) Fold change ID_{50} (mean): -22 **(p<0.0001)** relative to D614G
Cell Rep [11]	**n 2** Pseudovirus neutralization assay	Fold change ID_{50}: -3 to -7.3 **(p=0.0001)** relative to D614G
Nat Med [12]	**n 58** Authentic clinical viral isolates	Fold change ID_{50} (mean): -5 to -10 **(p=0.0012)** relative to D614G

		B.1.617.2 (Delta variant)
Cell [19]	**n 50** Pseudovirus neutralization assay	Fold change $FRNT_{50}$ (GMTs): -2.7 **(p<0.0001)** relative to Victoria (early Wuhan-related strain)

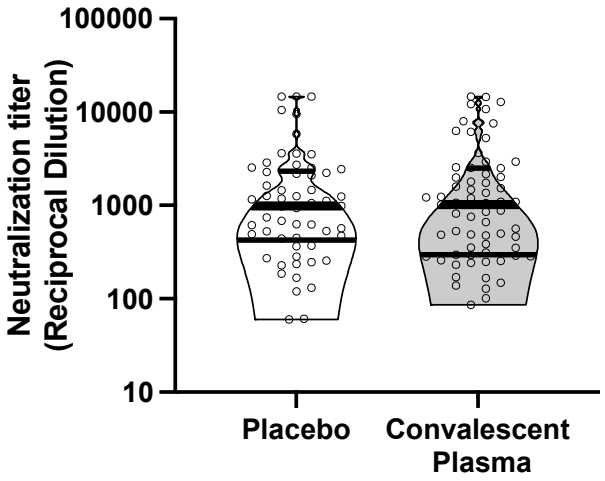
Abbreviations: n: number of convalescent patients; $ID_{50:}$ Reciprocal dilution of serum that neutralized 50% of the virus; $FRNT_{50}$: Focus reduction neutralization test with reciprocal dilution of serum that neutralized 50% of the virus; GMTs: geometric mean titres

Table S2. Subjects per participating site

Study sites	**Total** (n=376)	**Placebo** (n=188)	**Convalescent plasma** (n=188)	**Distance from plasma central blood bank**
Hospital Universitari Germans Trias i Pujol	275 (73.1)	135 (71.8)	140 (74.5)	≈11 km
Hospital Universitari de Bellvitge	73 (19.4)	39 (20.7)	34 (18.1)	≈12 km
CUAP Manresa	16 (4.3)	7 (3.7)	9 (4.8)	≈60 km
Hospital Comarcal de Sant Bernabé	12 (3.2)	7 (3.7)	5 (2.7)	≈90 km

Figure S5. Distribution of neutralizing antibody titres (ID50 and IU) in participants at day 7, according to trial group

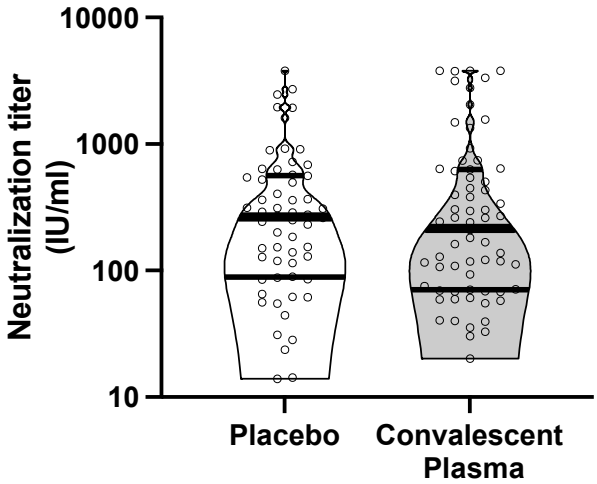
A



C

n 125	**Placebo** n 58	**CP** n 67
Minimum	60	86
25% Percentile	424	296
Median	**989**	**1017**
75% Percentile	2321	2501
Maximum	14580	14580
Range	14520	14494
Mean	2219	2387
Std. Deviation	3516	3583
Std. Error of Mean	461.6	437.7

B



D

n 125	**Placebo** n 58	**CP** n 67
Minimum	13.94	20.07
25% Percentile	88.91	70.72
Median	**265.3**	**215.7**
75% Percentile	562.6	630.9
Maximum	3794	3794
Range	3780	3774
Mean	506.2	658.5
Std. Deviation	731.5	1056
Std. Error of Mean	96.05	129

Panel A shows violin plot of neutralizing antibody titres (as reciprocal dilution) in the placebo and convalescent plasma groups at day 7 after infusion with median (thick line) and 25 and 75 percentiles (thin lines).

Panel B shows violin plot of neutralizing antibody titres (international units) in the placebo and convalescent plasma groups at day 7 after infusion with median (thick line) and 25 and 75 percentiles (thin lines).

The full statistical description is shown in panel C (reciprocal dilution) and panel D (international units).

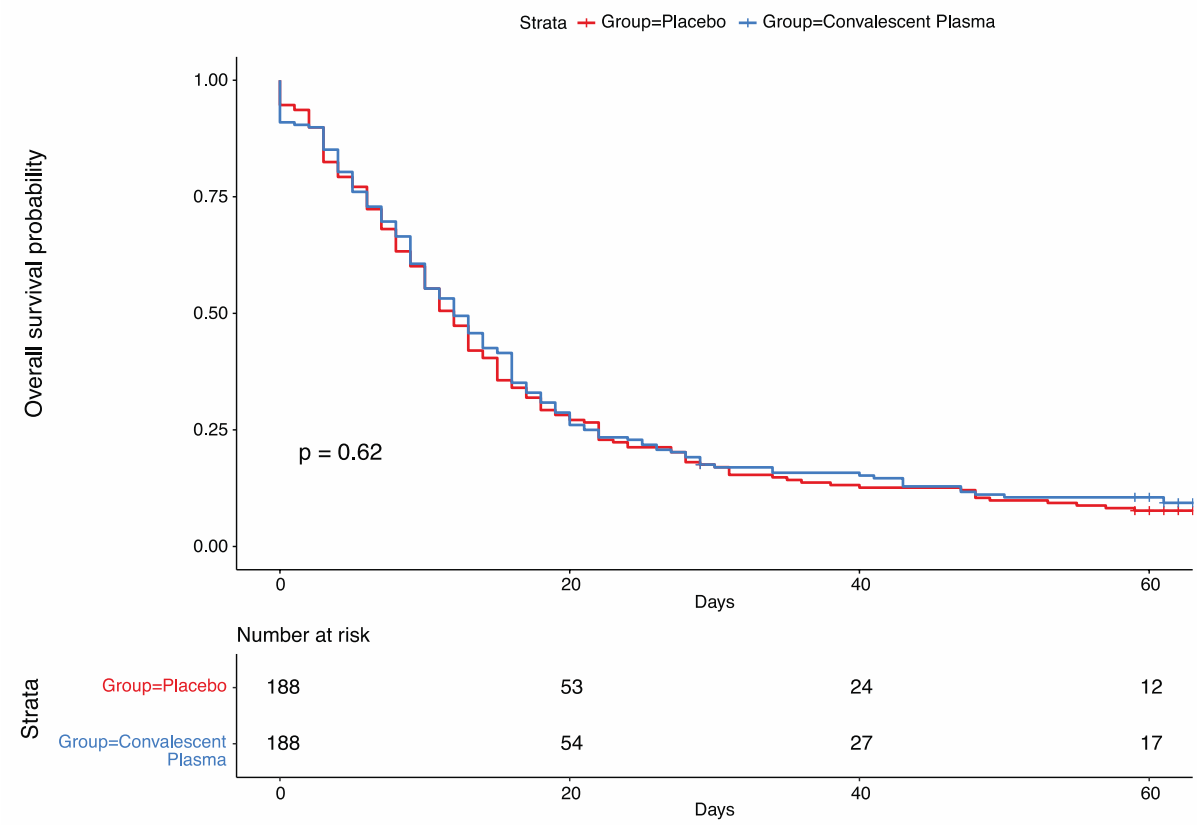
Table S3. Log-binomial regression model

	Hospitalized			
Variables	**No**	**Yes**	**RR (CI 95%)**	**p-value**
Placebo	167 (50.2%)	21 (48.8%)	1.048 (0.597 to 1.839)	0.87
Convalescent Plasma	166 (49.9%)	22 (51.2%)		
Age	57.95 (7.9)	61.47 (8.0)	1.037 (1.009 to 1.065)	0.0103
Male	181 (54.4%)	22 (51.2%)	1.12 (0.638 to 1.966)	0.69
Female	152 (45.7%)	21 (48.8%)		
BMI (mean, SD)	27.49 (4.4)	29.84 (4.9)	1.092 (1.037 to 1.15)	0.0009
Comorbidities				
Smoker	172 (51.7%)	19 (45.2%)	1.257 (0.709 to 2.228)	0.43
Obesity	256 (76.9%)	24 (55.8%)	2.309 (1.325 to 4.024)	0.0031
Cardiac disease	314 (94.3%)	39 (90.7%)	1.574 (0.616 to 4.024)	0.34
Lung disease	305 (91.6%)	38 (88.4%)	1.368 (0.578 to 3.236)	0.48
Neurological disease	322 (96.7%)	41 (95.4%)	1.362 (0.369 to 5.033)	0.64
Diabetes	298 (89.5%)	39 (90.7%)	0.886 (0.335 to 2.348)	0.81
Chronic Renal Failure	327 (98.2%)	43 (100%)	0 (0 to Inf)	0.99
Liver Disease	330 (99.1%)	43 (100%)	0 (0 to Inf)	0.99
Past history of cancer	319 (95.8%)	39 (92.9%)	1.62 (0.556 to 4.717)	0.38
Current episode				
Mild Covid-19	329 (98.8%)	37 (86.1%)	5.935 (3.286 to 10.719)	0.0001
WHO scale (mean, SD)	2.01 (0.11)	2 (0)	0 (0 to Inf)	0.99
Antibody serum status at baseline				
Negative	287 (88.1%)	39 (90.7%)	0.778 (0.292 to 2.069)	0.61
Positive	39 (11.96%)	4 (9.3%)		
Laboratory results				
Lymphocytes (median, IQR)	1.26 (1-1.6)	0.90 (0.8-1.18)	0.204 (0.096 to 0.435)	0.0001
Ferritin (median, IQR)	215.9 (100.2-388.6)	284.5 (184-431.7)	1.001 (1 to 1.002)	0.0107
Prealbumin (median, IQR)	28.1 (22.1-40.1)	23.4 (16.1-58.5)	1 (0.996 to 1.003)	0.83
D-dimer (median, IQR)	334.5 (250-505.8)	422 (255-669.5)	1 (1 to 1)	0.85

Table S4. Clinical trial end points in the per protocol population

	N	Convalescent plasma	Placebo		
Clinical primary end point: hospitalization through day 28		n (%)	n (%)	Relative Risk (95%CI)	P-values
Overall population	Nc=182; Np=185	21 (11.5)	21 (11.3)	1.02 (0.72 to 1.44)	0.93
Virologic primary endpoint: change in viral load from baseline		Mean (SD)	Mean (SD)	Crude difference (95% CI)	P-values
Overall population					
Day 7	Nc=174; Np=172	-2.40 (1.33)	-2.32 (1.43)	-0.09 (-0.34 to 0.16)	0.48
Day 28	Nc=179; Np=172	-3.86 (1.56)	-4.00 (1.45)	0.12 (-0.17 to 0.40)	0.42

Figure S6. Time to resolution of COVID-19 symptoms



		Placebo (n=188)	Convalescent Plasma (n=188)	p-value
Days to symptoms resolution (median [IQR])		12.00 [6.00, 22.00]	12.00 [6.00, 21.25]	0.76
status (%)	*Censored data*	15 (8.0)	20 (10.6)	0.48
	Not Censored data	173 (92.0)	168 (89.4)	

Figure S7. Schoenfeld Test of the proportional hazard assumption and scatterplots of the risk over time

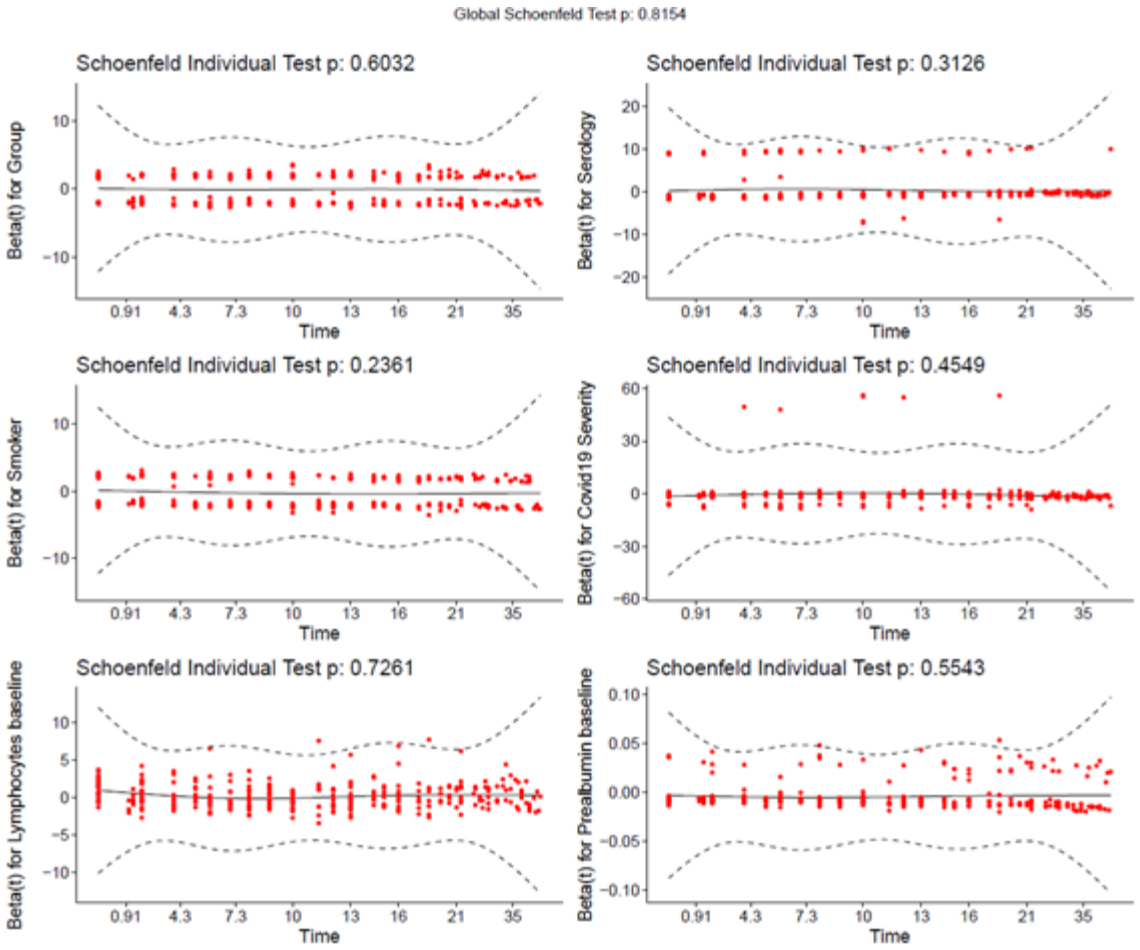


Figure S8. 10-point WHO Clinical progression scale score

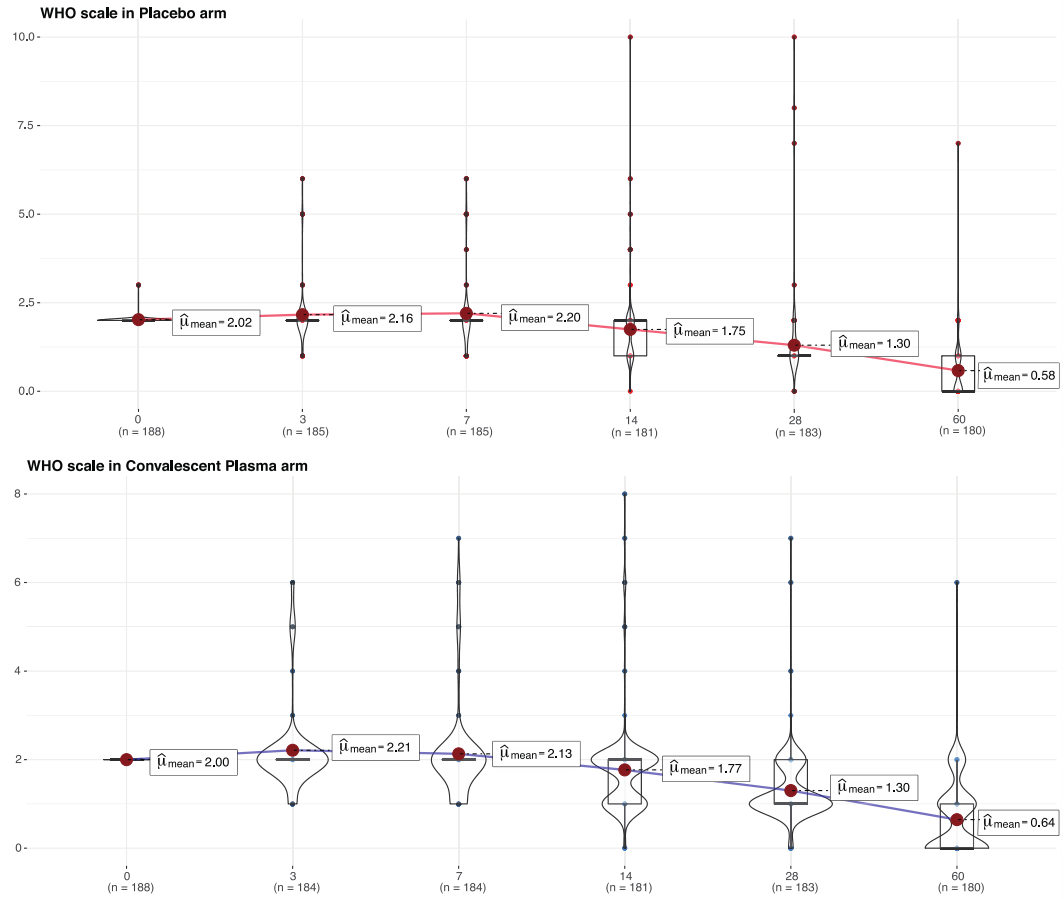


Table S5. Solicited Adverse Events

Treatment Related Adverse Events	**Total** (n=376)	**Placebo** (n=188)	**Convalescent plasma** (n=188)
Total (%)	32 (8.5)	8 (4.2)	24 (12.8)
Local reactions (%)	5 (1.3)	2 (1.1)	3 (1.6)
Vasovagal syndrome (%)	4 (1.1)	3 (1.6)	1 (0.5)
Fever or chills (%)	7 (1.9)	2 (1.1)	5 (2.7)
Gastrointestinal symptoms (%)	2 (0.5)	1 (0.5)	1 (0.5)
Mild allergic reactions (%)	12 (3.1)	0 (0)	12 (6.4)
Severe allergic reactions or anaphylaxis (%)	0 (0)	0 (0)	0 (0)
Thromboembolic events (%)	1 (0.3)	0 (0)	1 (0.5) *
Volume overload (%)	0 (0%)	0 (0)	0 (0)
Acute haemolytic transfusion reaction (%)	0 (0%)	0 (0)	0 (0)
Transfusion-related acute lung injury (TRALI) (%)	0 (0%)	0 (0)	0 (0)
Other (%)	1 (0.3)	0 (0)	1 (0.5)

*Severe Adverse Event

Severe Adverse Events (grade 3-4)	**Total** (n=376)	**Placebo** (n=188)	**Convalescent plasma** (n=188)
Total (%)	48 (12.8)	21 (11.2)	27 (14.4)
Covid19 Related (%)	46 (12.23)	21 (11.2)	25 (12.7)
Related to IP infusion (%)	1* (0.3)	0 (0)	1 (0.5)

*1 thromboembolic event in a participant without pneumonia, was considered as Severe Adverse Event (SAE) possibly related to investigational product and to COVID-19.

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