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Convalescent plasma therapy and long-term SARS-COV-2 antiviral immune response in a prospective cohort of patients with COVID-19

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ABSTRACT

During the SARS-CoV-2 pandemic, the use of convalescent plasma (CP) in high-risk patients was proposed and widely implemented in several countries as a potential COVID-19 therapy. Nonetheless, CP therapy's impact on immune response is nowadays poorly understood, including the correlation between IgG levels, neutralization capacity, and cellular immune response against SARS-CoV-2. Here we evaluated, in a cohort of patients with COVID-19 requiring hospitalization and having received or not CP, as well as in CP donors (recovered from mild disease), the humoral and cellular immune response assessed by titers of SARS-CoV-2 IgG, neutralizing antibodies, and IFN-γ^+/IL-2^+ ELISpot during the first month (early) and up to nine months (long-term) after symptom onset. Results showed higher seropositivity and seroconversion rates between 7–12 days after plasma infusion in CP-recipients. However, similar IgG and neutralizing immune response kinetics between CP-recipients and non-recipients was observed during the first and until the ninth month of analysis. A positive correlation between IgG and neutralizing levels was detected. Compared to outpatient donors, hospitalized individuals showed a higher response at 3 and 6 months after symptoms onset. A sustained SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cell response was observed in outpatients and hospitalized patients, regardless of the CP treatment. We concluded that the CP infusion did not affect the long-term SARS-CoV-2 specific humoral and cellular immune responses. Nonetheless, CP may provide a therapeutic window by promoting a higher humoral response during the acute phase of COVID-19.

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1. Introduction

The COVID-19 pandemic, declared in march 2020, led to over 775 million confirmed cases and 7 million deaths globally (WHO, 2024). In response to the health crisis, scientific and medical communities rapidly focused on developing new treatments, particularly for high-risk individuals (Shaffer, 2020). Among the strategies explored, convalescent plasma (CP) therapy based on passive antibody transfer, was proposed as an early intervention. This approach had shown promise in previous infectious disease outbreaks (Vial et al., 2015; Garraud et al., 2016; Wong and Lee, 2020), including the 2002–2004 SARS and, with mixed results, the 2012 MERS (Cheng et al., 2005; Yeh et al., 2005; Arabi et al., 2016; Ko et al., 2018).

The immune response to SARS-CoV-2 infection has been widely described across diverse cohorts (Dan et al., 2021; Kundu et al., 2022; Rodda et al., 2022). A strong and sustained IgG response has been observed in adults with mild to moderate symptoms, remaining stable for up to five months after infection and correlating with virus neutralization capacity (Wajnberg et al., 2020). In a study of 188 COVID-19 cases ranging asymptomatic to severe, distinct kinetics among antibodies, memory B cells, and $CD4^{+}/CD8^{+}$ *T* cells were described (Dan et al., 2021). Remarkably, the anti-SARS-CoV-2 spike IgG response persisted after 6–8 months, memory B cells peaked at 4 months, and memory T cells declined over time but remained detectable up to 5 months after infection.

In August 2020, the U.S. FDA approved the emergency use of CP for severe SARS-CoV-2 infection cases (Tanne, 2020). Several clinical trials were conducted worldwide to assess its safety and efficacy (Agarwal et al., 2020; Axfors et al., 2021; Begin et al., 2021; Group, 2021; Simonovich et al., 2021, Writing Committee for the REMAP-CAP Investigators; Estcourt et al., 2021). In Chile, a 2020 randomized controlled trial evaluated the CP treatment in hospitalized patients, administering plasma either early (within the first week of symptoms) or later upon respiratory deterioration, but found no significant benefit for early use (Balcells et al., 2021). Although the overall clinical efficacy of CP remains uncertain (Iannizzi et al., 2023), current guidelines still recommend high-titer CP for outpatients at high risk of severe COVID-19 who lack alternative treatments (Bhimraj et al., 2022; Senefeld et al., 2023), and for immunocompromised subjects with prolonged symptomatic infection (Health, Cesaro et al., 2023).

Few studies have examined the immune response following CP therapy, reporting increased antibody titers but lacking long-term follow-up data (Mira et al., 2020; Acosta-Ampudia et al., 2021; Lindemann et al., 2021). Only three studies observed increased IFN-γ production observed in select patient subgroups and limited to 28 days post-infusion. In a large outpatient cohort, a discrete increase in neutralizing antibodies shortly after CP administration was found (McDyer et al., 2023). A significant gaps in understanding CP's long-term immunological effects has been highlighted (Esmaeili et al., 2021). Overall, current evidence on CP's lasting impact in severe and mild COVID-19 remains limited, underscoring the need for further research.

Here we describe the humoral and cellular immune response kinetics in severe COVID-19 patients, receiving or not CP, as well as in plasma donors, during the first month and up to the ninth month after symptoms onset. This study is based on the follow-up of a sub-cohort of hospitalized patients and donors enrolled in a previous study, which was conducted during the early wave of the COVID-19 pandemic. (Balcells et al., 2021)

2. Materials and methods

2.1. Inclusion criteria

This study included three groups of patients from the clinical trial previously described (Balcells et al., 2021). First and second groups were patients ≥18 years old, hospitalized with a COVID-19 qRT-PCR positive test (LightMix SARS-CoV-2 RdRP plus EAV control kit 40–0777–10, TIB MIOLBIOL), with seven days or less from symptoms onset and who were randomized to receive plasma infusion (CP), or no infusion (No-CP). A third group of outpatients with mild COVID-19 clinical presentation who donated CP were also included in the follow-up as Donor group. At the time of plasma donation, volunteers were asymptomatic for at least 28 days, qRT-PCR negative against SARS-CoV-2 in the nasal swab, and anti-SARS-CoV-2 IgG titers ≥ 1:400. Donors were males, females who had never been pregnant, or females who had been tested for anti-HLA antibodies. Plasma collection occurred between 33 and 73 days after symptoms resolved (mean of 44 days). No age-related exclusion criteria was applied. This study was approved by the Institutional Scientific Ethical Committee of Health Sciences at the Pontificia Universidad Católica de Chile (ID 200513023).

2.2. Sample collection

Samples were collected following the scheme shown in Fig. 1A. Individuals from each group were followed up before any SARS-CoV-2 vaccine was indicated. Six blood samples for hospitalized patients were taken during the first month from symptoms onset (grouped in the approximate range of days expressed in Fig. 1A) and afterwards at 3, 6, and 9 months since symptoms onset (median time of 3.2, 6.2, and 9.2 months respectively). From donor group, blood samples were collected at four different time points, namely 2, 3, 6, and 9 months after the onset of symptoms (median time of 2.1, 3.2, 6, and 8.8 months, respectively). Samples of infused convalescent plasma (ICP) with a mean IgG titer ≥ 400 were also collected. Serum and plasma samples were separated and stored at −80 °C. Peripheral blood mononuclear cell (PBMC) isolation from whole blood samples was performed by a Ficoll density-gradient centrifugation procedure using SepMate-50 (#86450, Stem Cell Technologies) following the manufacturer's protocol.

2.3. Anti-SARS-CoV-2 IgG determination

The titers of specific anti-SARS-CoV-2 IgG were determined using a commercial enzyme-linked immunoassay (ELISA) semiquantitative kit (#278h-9601–2 G, Euroimmun) pre-coated with an S1 domain antigen of the spike (S) protein of SARS-CoV-2 (Wuhan-like lineage). Briefly, serum samples were initially diluted at 1:100 in sample buffer, followed by a 4-fold dilution (1:400) and several 2-fold serial dilutions ranging between 1:800 and 1:6.400. The assay procedure was performed according to the manufacturer's protocol, and the immunoreactivity was measured at an OD of 450 nm. The IgG titer in each sample was determined as the reciprocal of the end-point dilution or the dilution where the OD ratio (sample/calibrator) was ≥ 1.1 (positive result). Seropositive samples were defined as an OD ratio ≥ 1.1 at dilution 1:100. Seroconversion was defined as a seronegative sample at baseline (OD ratio of the first sample, between 1–6 days after symptoms onset) but seropositive in the following samples or a 4-fold increase in end-point dilution titer from a seropositive baseline.

2.4. Neutralization assays

Pseudotyped viruses were prepared as previously described (Beltran-Pavez et al., 2021). Briefly, SARS-CoV-2 pseudotyped HIV-1-based lentiviruses were produced in HEK293T cells (#CRL-11, 268, ATCC) by transfecting the pNL4.3-ΔEnv-Luc along with the pCMV14–3X-Flag–SARS-CoV-2 SΔ19CT. Cells were incubated at 37 °C and 5 % CO_2, and the supernatants containing the pseudovirus were collected at 48 h post transfection. For neutralizing antibodies (NAb) assays, serum samples were serially diluted from 1:20 to 1:43,740 in supplemented DMEM (#SH30022, HyClone). Each serum dilution was incubated with pseudovirus at 37 °C for 1 hour. Later, HEK293T cells stably expressing the SARS-CoV-2 receptor ACE2 were added to each

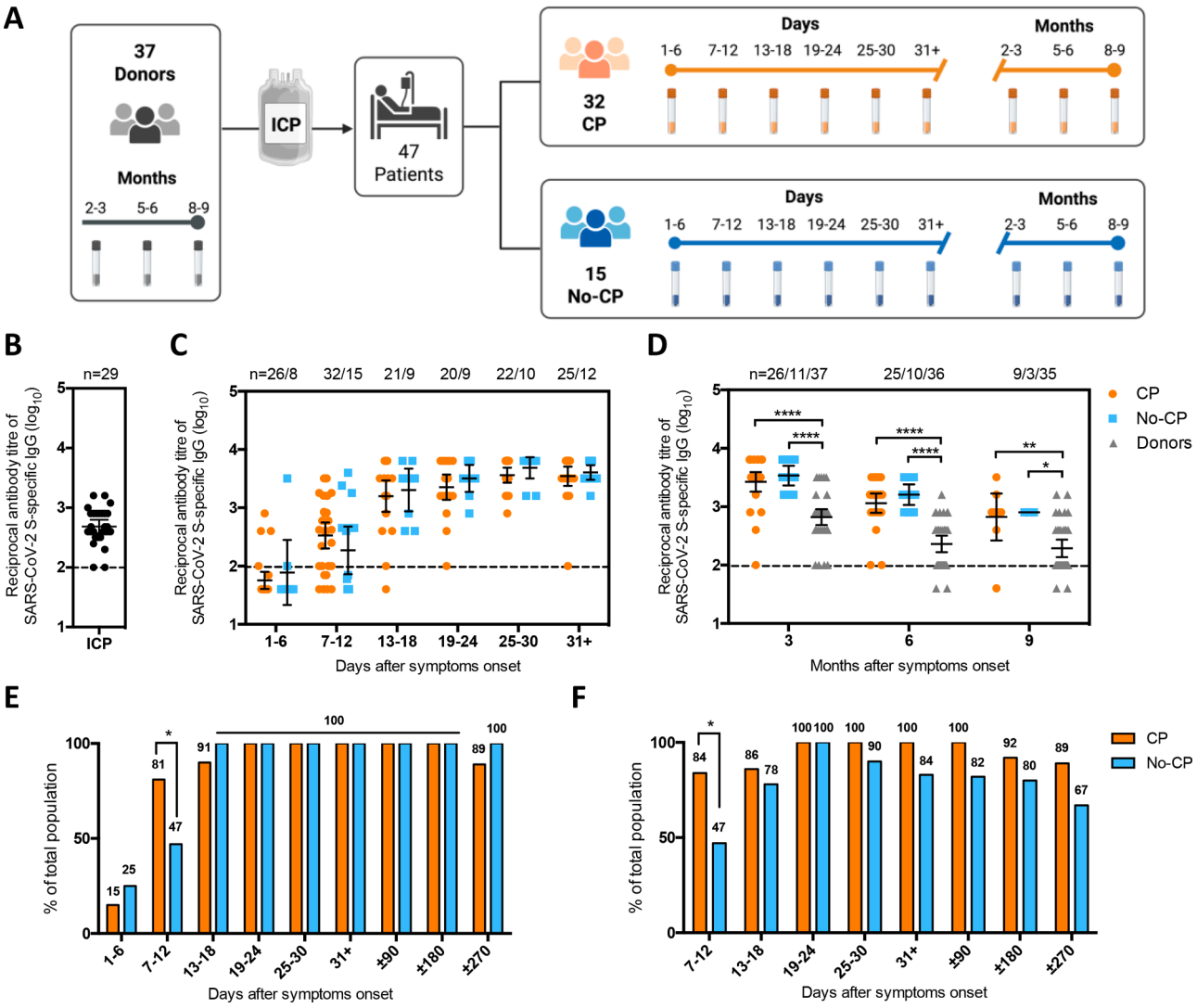

Fig. 1. Kinetics of the humoral anti-SARS-CoV-2-S1 response in sera of patients treated with convalescent plasma (CP), untreated patients (No-CP), and CP donors. **(A)** Of 47 COVID-19 hospitalized patients, 32 received CP within 72 h post-hospitalization (CP, orange), and 15 patients did not receive CP (No-CP, light blue). Also, 37 outpatients CP donors (grey) were included. Hospitalized patients were followed-up, collecting six samples between the first month and months 3, 6, and 9 post symptoms onset approximately. Samples of infused convalescent plasma (ICP) and samples from CP donors at months 2, 3, 6, and 9 post symptoms onset approximately were also included. **(B-D)**. The IgG titers are presented as the Log10 of the reciprocal end-point positive dilution of sera samples from ICPs (B), between the first month post symptoms onset of hospitalized patients CP-treated or not (C), and at 3, 6, and 9 months post symptoms onset of hospitalized and donor individuals (D). The sample size (n) in each time point for each group is presented in the upper part of the panels. The dotted line represents the limit of positivity. The solid lines represent the geometric mean ± 95 % CI. **(E, F)** The humoral response of CP and no-CP groups is also presented in terms of seropositivity (E) and seroconversion (F), which are defined in the materials and methods section, and are expressed as the % of the total population. *$p < 0.05$ with Fisher's exact test.

well. Plates were incubated for 48 h at 37 °C, and firefly luciferase activity was measured. Relative luminescence units (RLUs) of non-transduced HEK293T cells were averaged and considered 100 % neutralization, while RLUs of transduced HEK-ACE2 cells were established as 0 % neutralization. The relative Inhibitory Dose 50 (ID50) was calculated in GraphPad Prism v9.0.1.

2.5. ELISpot for T cell response determination

PBMC samples were thawed, washed with RPMI medium with 20 % FBS (#72,400–047, #10,437–028, Gibco), and incubated in RPMI medium with 10 % FBS overnight. The determination of specific anti-SARS-CoV-2 $CD4^+$ and $CD8^+$ *T* cell response was assessed by a commercial IFN-γ/IL-2 double-color enzymatic ELISPOT assay (#hIFNgIL2, Cellular Technology Limited). Briefly, 2×10^5 PBMCs were added to an ELISpot plate previously activated with 70 % ethanol and containing 2 μg/mL of *mega pools* (MPs) of peptides derived from SARS-CoV-2 proteins described previously (Grifoni et al., 2020). Four MPs were used, constituted by peptides from the S protein (MP-S) and peptides from the rest of the viral proteins (MP-R) designed *in silico* to stimulate $CD4^+$ *T* cells and a mixture of peptides designed to stimulate $CD8^+$ *T* cells (MP-A and MP-B). Phytohemagglutinin (#10576–015, Gibco) was used as a positive control of T cell activation, and a negative control without stimulation was included. Cells were incubated for 48 h at 37 °C and 5 % CO_2. Afterwards, the IFN-γ^+ and IL-2^+ Spot Forming Cells (SFCs) were developed following the manufacturer's instructions. Spots were counted with an ImmunoSpot S6 Micro Analyzer (CTL), and the background value was subtracted from the measured results. ELISPOT results were expressed as the sum of SFC stimulated with MP S-R or MP CD8.

2.6. Statistical analysis

Dichotomous variables were compared with the Fisher exact test and continuous variables with the Mann-Whitney and Kruskal-Wallis tests.

For correlations, a non-parametric Spearman test was performed. The geometric mean titer (GMT) of anti-SARS-Cov2 IgG antibodies was calculated and expressed as the reciprocal of the antibody titer relative to the end-point dilution of sera. The GMT of neutralizing antibody (NAb) titers was calculated, and expressed as the reciprocal value of the sera dilution that determined the relative ID50 calculated. The 95 % confidence interval (95 % CI) of the GMT was calculated for every data group. A p-value <0.05 was considered significant. Analyses and graphs were performed using GraphPad Prism 9.0.1.

3. Results

3.1. Long-term anti-SARS-CoV-2 IgG response

Forty-seven patients hospitalized with COVID-19 pneumonia were enrolled, including 32 receiving early CP treatment, and 15 not receiving CP. At month 6, the follow-up of 15 and 8 individuals from groups CP and no-CP, respectively, was discontinued due to vaccination, while 2, 4, and 2 individuals from groups CP, no-CP, and Donors, respectively, withdrawn before the ninth month. The median days between the symptom onset and the enrollment of donors, CP and No-CP groups were 61.5, 5, and 6 days, respectively. The CP group showed a median age of 62 years (ranging between 32 and 92 years), and the No-CP group showed a median of 60 years (26 and 83 years). Both groups' clinical characteristics were similar, as shown in Table 1. We also enrolled 37 CP donors, and 11 of them provided plasma to patients in the treated group. CP donors presented a median age of 33 years (ranging between 18 and 61 years), being significantly younger than hospitalized individuals.

As shown in Fig. 1A, we first assessed the levels of anti-SARS-CoV-2-S1 IgG in 29/37 ICP samples collected on the day of donation, obtaining a GMT of 484.9 [95 % CI: 374–628], (Fig. 1B). We also analyzed the IgG titers during the first month from symptoms onset for both CP and No-CP hospitalized patients (Fig. 1C). Both groups reached similar plateau IgG titer after 25–30 days from symptoms onset (GMT: 3630 [95 % CI: 2704–4873] and 4850 [95 % CI: 3193–7368], respectively). No significant differences between groups were observed at any of the analyzed time points. We compared the long-term humoral response between hospitalized patients and donors, finding that both hospitalized CP and No-CP groups underwent a similar decay rate of antibody titers (Fig. 1D). When compared with donors, the antibody titers of both groups of hospitalized patients were higher in the long-term.

Analyzing the humoral response regarding seropositivity, we observed that the CP group showed a higher early response between the first two weeks post symptom onset compared to the No-CP group (81 % vs. 47 % respectively, $p = 0{,}0131$). However, from the third week the seropositivity was similar between both groups (Fig. 1E). Interestingly, seroconversion rates were also higher in the CP group compared to No-CP group evaluated at the 7–12 days since symptoms onset (85 % vs. 50 % respectively, $p = 0.025$), while in the following days the seroconversion rate between both groups was similar (Fig. 1F). Noteworthy, a positive correlation ($p = 0{,}0026$) was found between IgG titers in ICP and the serum titers in the respective recipients, at days 7–12 from symptoms onset (Suppl. Fig. 1A).

We performed an age stratification analysis of both groups, only observing that CP-recipients younger than 50 years old show higher IgG titers than donors (Suppl. Fig. 2). A linear model comparing CP, No-CP, and Donor groups during the long-term immune response, adjusted for age, showed that individuals in the CP group had significantly higher levels of anti–SARS-CoV-2-S1 IgG compared to the No-CP group ($p = 0.016$). The Donor group also exhibited higher antibody levels than the No-CP group, after adjustment for age. Additionally, each additional year of age was associated with an increase of 39.43 units in IgG levels ($p < 0.001$) (Suppl Fig 3).

3.2. Long-term neutralization ability against SARS-CoV-2

Next, we sought to evaluate the kinetics of the neutralizing capacity of antibodies in each group. The NAb titers in ICP samples had a GMT of 724 [95 % CI: 502–1045] (Fig. 2A). No difference was found in the NAb kinetics in both treated and untreated groups until days 19–24. However, from day 25 and over one month post symptom onset, patients receiving CP displayed lower ID50 titers than No-CP patients (GMT: 6267 [95 % CI: 4239–9264] vs. 17,582 [95 % CI: 8442–36,619] at days 25–30; and 5465 [95 % CI: 3770–7924] vs. 14,916 [95 % CI: 7353–30,259] at days +31, respectively) (Fig. 2B). The neutralization response after 3 months since symptoms onset showed similar titers for both treated and untreated groups. Still, the CP group reached higher titers at 6 months since symptoms onset compared to the no-CP group (Fig. 2C). Both hospitalized groups showed higher ID50 titers at month 3 compared with donors, but the difference was no longer significant at month 6.

Contrasting with the IgG titers, no correlation was found between NAb titers in ICP and those in CP-treated patients at 7–12 days from symptoms onset (Suppl. Fig. 1B). Grouping the data of CP, no-CP, and donor groups as a general SARS-CoV-2 infected population, we found a significant correlation ($p < 0.005$) between anti-SARS-CoV-2 IgG and NAb titers at months 1–2, 3, 6, and 9 since symptoms onset (Fig. 2d-G).

3.3. SARS-CoV-2 specific T-cell memory immune response

We analyzed the T cell-specific immune responses in hospitalized patients as a single group –independent of CP treatment status– and compared them with the outpatients group of donors. Results are presented as SFC of IFN-γ^+ (Fig. 3A and B) or IL-2^+ (Fig. 3C and D) secreting cells. The data indicates the presence of both types of response in both groups, hospitalized and outpatients, from month 1–2 to month 9. In the case of the IFN-γ^+ response, hospitalized patients showed a sustained response when stimulated with MP S-R (median SFC: 23 at the first month, 31 at month 3, and 47 at month 9 since symptoms onset) with a non-significant tendency to increase in time, and similar when stimulated with MP CD8 (median SFC: 10 at the first month, 6 at month 3, and 12 at month 9 since symptoms onset). The IL-2^+ response was also sustained in time, showing higher stimulation against MP S-R than against MP-CD8 (median SFC MP S-R: 22 at month 1, 57 at month 3, and

Table 1
Clinical characteristics of SARS-CoV-2 infected patients included.

Characteristic	CP $n = 32$	No CP $n = 15$	Donors $n = 37$	p-value
Age years, median (range)	62 (32–92)	60 (26–83)	33 (18–61)	<0.0001*
Sex men, N (%)	18 (56)	7 (47)	27 (73)	
Days from onset symptoms to enrolment, median (range)	5 (1–7)	6 (4–14)	61.5 (35–107)	<0.0001*
Days of hospitalization, median (range)	11.5 (4–37)	9.5 (2–25)	NA	
CALL Score, median (range)	10 (9–14)	10 (9–12)	NA	
SOFA score, median (range)	2 (0–7)	2 (0–4)	NA	
Mechanical ventilation, N (%)	5 (16)	1 (7)	NA	
Death, N (%)	5 (16)	0 (0)	NA	
Comorbidities (%)	29 (91)	15 (100)	NA	
Obesity, N (%)	3 (9)	2 (13)		
Diabetes, N (%)	8 (25)	5 (33)		
Hypertension, N (%)	27 (84)	12 (80)		
Cancer, N (%)	1 (3)	0 (0)		
Corticosteroids, N (%)	27 (84)	9 (60)	NA	
Immunosuppressants, N (%)	6 (19)	2 (13)	NA	

CALL Score: Likelihood of severe COVID-19 progression according to Comorbidities, Age, Lymphocyte count, and LDH. SOFA score: Sequential Organ Failure Assessment.

* $p < 0.05$ significant. Chi-squared test (categoric). Kruskal-Wallis and Mann-Whitney tests (continuous).

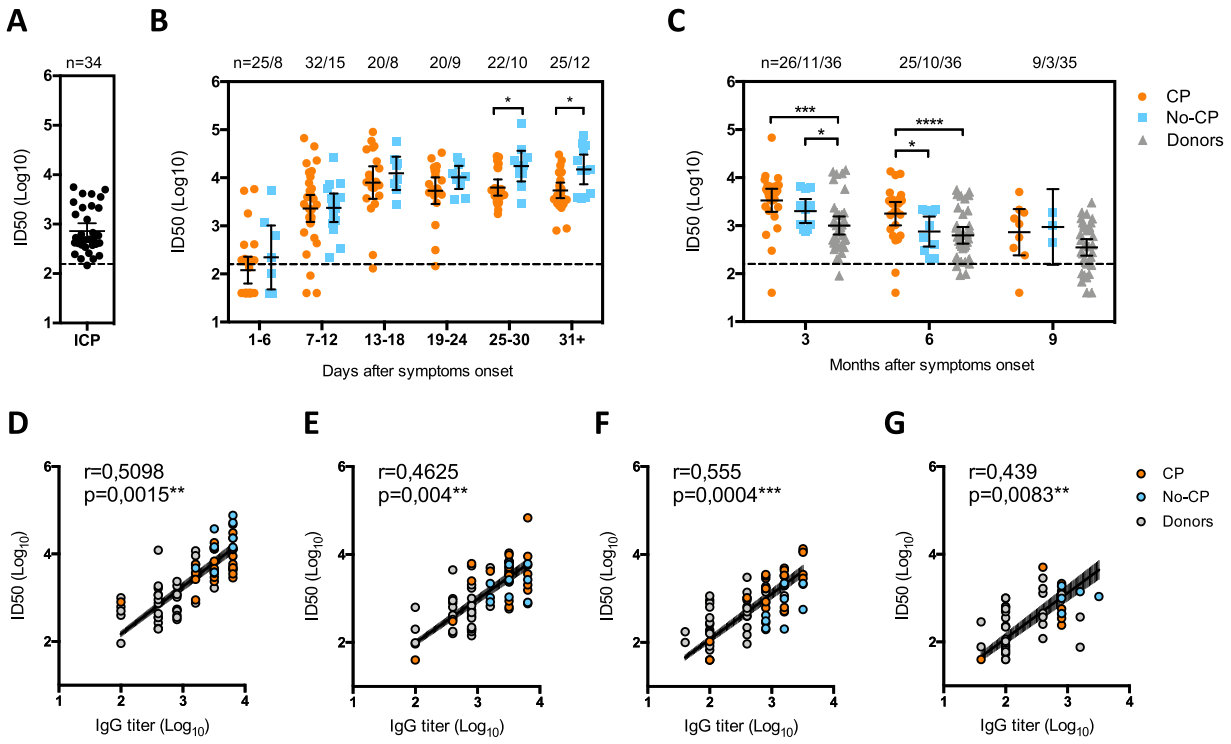

Fig. 2. Kinetics of the humoral response determined by the neutralizing ability against SARS-Cov-2 in sera from CP treated, untreated hospitalized patients, and donors. **(A-C)** The neutralizing antibody titers are expressed as Log_{10} of the 50 % of the inhibitory dose (ID50) in infused convalescent plasma (ICP, A), the first month post symptoms onset of hospitalized patients CP or No-CP treated (B), and at 3, 6, and 9 months post symptoms onset of hospitalized and donor individuals (C). The sample size (n) in each time point for each group is presented in the upper part of the panels. The dotted line represents the detection limit. The solid lines represent the geometric mean ± 95 % CI. *$p < 0.05$ with Mann-Whitney's test. **(D-G)** Correlation between the Log_{10} of the IgG anti-SARS-CoV-2-S1 titers and the Log_{10} of the neutralizing antibody titers at months 1–2 (D), month 3 (E), month 6 (F), and month 9 (G) post symptoms onset of hospitalized patients and donors. A fitted curve from a linear regression with the 95 % CI as a shadowed area around the line are included. $p < 0.05$ was considered significant Spearman's correlation.

29 at month 9; MP-CD8: 1 at month 1, 7.5 at month 3, and 25 at month 9).

The results for the outpatient donor group showed higher SFC dispersion, and both stimulation conditions, MP S-R and MP CD8, resulted in a similar magnitude of IFN-γ^+ and IL-2^+ responses over time. No statistical difference was observed between hospitalized and outpatients responses (Fig. 3A-D).

4. Discussion

In the early months after the SARS-CoV-2 pandemic onset, CP from recovered COVID-19 donors was used as a compassionate strategy for treating severe COVID-19. However, the available evidence regarding the effects of CP infusion on the immune response was limited. Here, we show data concerning the humoral and cellular immune responses after CP infusion in hospitalized patients with severe COVID-19, compared to hospitalized patients' non-CP infused and outpatients, up to 9 months after receiving CP or not. In agreement with previous studies (Agarwal et al., 2020; Dan et al., 2021; Gharbharan et al., 2021), we observed that during first month and up to the ninth month after CP infusion, patients reached similar titers of anti-SARS-CoV-2 IgG and NAbs than untreated patients. Regarding the cellular immune response, both groups of hospitalized patients showed a sustained T-cell response with a slight tendency to increase over the ninth month. Both long-term sustained humoral and cellular responses might be typical of the response to SARS-CoV-2, independently from CP treatment.

Increasing evidence has shown that the humoral immune response against SARS-CoV-2 among severe and mild COVID-19 individuals reaches its maximum around the first-month post symptoms onset, following a progressive decay in both IgG and neutralization titers (Feng et al., 2021; Wang et al., 2021; Xiang et al., 2021; Yan et al., 2021). Patients with severe disease seem to reach higher antibody titers than those with milder diseases, but the former show a faster decline in their titers (Feng et al., 2021; Yan et al., 2021; Zhang et al., 2021). We observed this humoral response kinetics in hospitalized and outpatients, and as expected, a higher seropositivity and seroconversion in subjects early after receiving CP. This observation has been previously related to a protective role of the CP infusion (Shenoy et al., 2021). However, donors titers were lower compared to both hospitalized groups, suggesting that it might be related to an additive effect. Even though the antibody titers of both hospitalized groups and donors decreased after the third month from symptoms onset, the GMT of all groups always remained above the seropositive limit (Fig. 1D, dotted line). This is likely related to a stable specific memory $CD4^+$ *T* cell response as found by us and others, supporting antibody generation (Sekine et al., 2020; Dan et al., 2021).

We observed a time correlation between IgG and neutralization titers among hospitalized and CP donors. During the follow-up, none of the enrolled subjects reported new symptoms and/or positive COVID-19 tests, notwithstanding those asymptomatic re-infections during this period cannot be ruled out. It has been estimated that maintaining the neutralization titers in sera above 20.2 % of the maximum titer reached by the convalescent population protects from detectable SARS-CoV-2 infection, and only a 3 % of this value would be enough to protect from severe COVID-19 (Khoury et al., 2021). According to this, our hospitalized cohort was protected from re-infections until the sixth month of follow-up approximately and protected from severe COVID-19 until at least the ninth month of follow-up, and probably up until the first year post-symptoms onset. However, this estimation depends on the sensitivity of the neutralization assay performed, and the SARS-CoV-2 variant that individuals were exposed to.

Recent studies indicate that the effectiveness of stored CP in treating

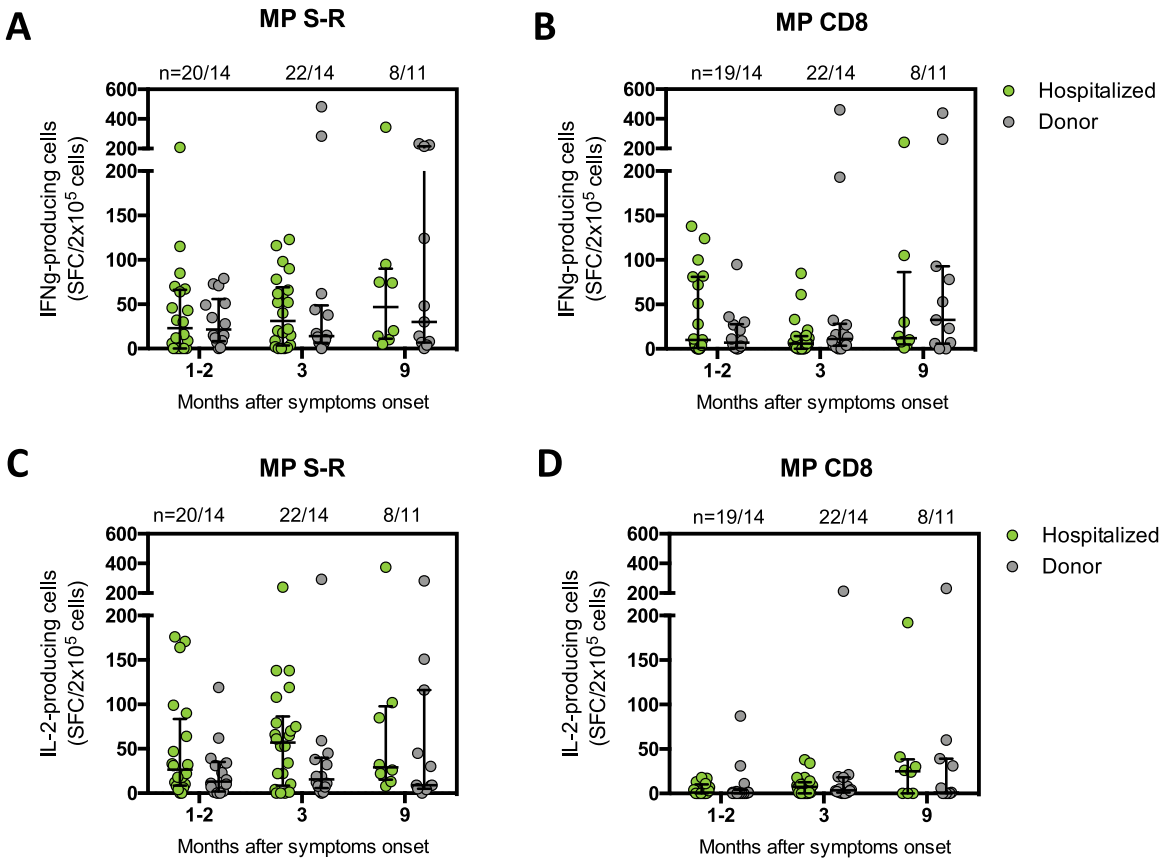

Fig. 3. Cellular immune response against SARS-CoV-2 in COVID-19 hospitalized patients and CP donors. Peripheral blood mononuclear cell (PBMC) samples from hospitalized patients (independent of CP treatment) and outpatients donors collected at months 1–2, month 3, and month 9 since symptoms onset, were incubated with SARS-CoV-2 peptides designed to stimulate a $CD4^+$-related (MP S.R) or $CD8^+$-related (MP CD8) response. The plots show the absolute count of cells secreting IFN-γ (**A, B**) or IL-2 (**C, D**) measured after 48 h of stimulation and expressed as Spot Forming Cell (SFC) per 2×10^5 stimulated cells with the background subtraction included. The sample size (n) in each time point for each group is presented in the upper part of the panels. Data are shown as the median and interquartile range. Mann-Whitney tests were used to evaluate statistical significance, although none was found.

new severe COVID-19 patients may be inconsistent due to the emergence of variants, especially for the Omicron sub-lineages, bearing several spike-mutations that reduce the viral neutralization susceptibility against sera from previous naturally infected and/or vaccinated individuals (Hachmann et al., 2022; Davis-Gardner et al., 2023; Kurhade et al., 2023). We observed that the neutralization ability of pandemic ICP is reduced to almost undetectable levels against the recently circulating Omicron lineage JN.1, supporting this assumption (Suppl. Fig. 4). Concordantly, our study group previously evaluated the humoral immune response of serum from patients who received CP, observing a progressive reduction in the neutralization capacity against emerging Omicron sub-lineages compared to ancestral wild type virus (Barrera et al., 2024). Thus, the recommendation for current CP collection and treatment suggests that it should be performed with plasma from patients infected with the most recently circulating Omicron variants (Bloch et al., 2023). A report showed that hospitalized patients having received CP infusion and recovered from COVID-19, displayed an enhanced viral Nucleocapsid-related antibody response, as it is known that the humoral response against SARS-CoV-2 can also target less variable viral proteins (Hachim et al., 2020; Herman et al., 2022). Nevertheless, using CP from donors who have received heterologous booster vaccination or have recently recovered from COVID-19 may provide a versatile tool for treating prospective severe COVID-19 cases in susceptible populations (Treatment Guidelines Panel, 2024).

The cellular immune response is also a key component in protecting against severe acute infections and reinfections. Additional to SARS-CoV-2 neutralizing antibodies, COVID-19 CP contains cytokines such as IL-6, IL-10, IP-10, and IL-2; metabolites such as fatty acyls, and glycerophospholipids; autoantibodies, complement factors and clotting/anti-clotting factors, among others (Rojas et al., 2020; Acosta-Ampudia et al., 2021). The CP treatment has been shown to induce changes in lymphocyte T cell profiles compared to untreated patients, such as an increase in the number of $CD4^+$, $CD8^+$, and $CD3^+$ *T* cells, as well as IFN production, but a decrease in activated/effector $CD8^+$ and memory $CD4^+$ *T* cells phenotype (Mira et al., 2020; Acosta-Ampudia et al., 2021; Lindemann et al., 2021). IFN-γ is an effector cytokine secreted primarily to activate macrophages at the site of inflammation, and IL-2 is a regulatory cytokine that acts as a growth factor for IFN-γ-secretory T cells (Jager and Kuchroo, 2010). Both $CD4^+$ and $CD8^+$ *T* cells are associated with producing IFN-γ and IL-2 in response to SARS-CoV-2 in severe and mild COVID-19 cases (Lucas et al., 2020; Sekine et al., 2020; Rha et al., 2021). Therefore, these cytokines play significant roles in the modulation of the severity of COVID-19, and their secretion seems to be conserved in presence of CP.

In principle, CP antibodies have the capacity to neutralize the virus, thereby curtailing viral replication, antigenic exposure, and the magnitude of both the cellular and humoral responses. The comparison of the cellular response between hospitalized and outpatient donor groups did not show differences at any time post symptoms onset analyzed, suggesting that both groups elicit a long-lasting $CD4^+$ and $CD8^+$ effector T cell memory response induced by SARS-CoV-2 peptides. The magnitude and duration of this response might not be related to severity. While the $CD8^+$ induced response was predominantly IFN-γ-related, the $CD4^+$ response expressed both IFN-γ and IL-2 at the same

levels, which agrees with a polyfunctional profile described for SARS-CoV-2 specific $CD4^+$ cells (Sekine et al., 2020; Moss, 2022). The levels of the $CD8^+$ response in convalescent individuals after two months of COVID-19 hospitalization have been shown to be lower than those in active COVID-19 patients (Orologas-Stavrou et al., 2020). This suggests a contraction of the response, while the $CD8^+$ *T* cells might be maintained months after the infection to support the antiviral response in some patients (see out layers in Fig. 3B, months 3–9 post symptoms onset).

As study limitations, we evaluated the immune response of these patients over a long period, but lost track of some patients due to vaccination strategies and withdrawn, restricting the statistical analysis for no-CP recipients and especially for the last time points. While the compared groups differ in median age, it is a known characteristic for mild COVID-19 patients to be younger than severe COVID-19 patients in the pandemic (Nguyen et al., 2022). The observed age effect could likely be attributed to the severity of the clinical presentation. Given the extensive sampling, we only evaluated two cytokines, and a more detailed study using Intracellular Cytokine Staining assays (ICS) is needed to understand the cellular response in both groups fully. Beyond measuring the circulating NAbs after infection, the evaluation of the B cell memory response would also be essential to estimate protection against reinfections. As seen for the humoral response, the T cell response is induced not only by spike protein-associated peptides but also by peptides belonging to other viral proteins (Heffron et al., 2021), being an interesting and additional target to include the T cell response in vaccine design, with less variability across emerging variants.

Several recent studies and reviews agree that the early treatment with high neutralizing titer CP for severe COVID-19 is still an option that should not be discarded in case of an impaired immune response and/or shortage of other treatments (Casadevall et al., 2023; McDyer et al., 2023; Moog, 2023; Senefeld et al., 2023; Tayyar et al., 2023). While the long-term effects of the CP infusion in reinfections still need to be elucidated, the present study offers significant insights regarding the safety of CP use in relation to an optimal immune memory following its infusion. Its clinical use as an immediate intermediary to improve patients' early response is supported, and its value as an emergency tool against possible future coronavirus pandemics or other infectious diseases is recognized.

CRediT authorship contribution statement

Aldo Barrera: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft, Writing – review & editing, Visualization. **Constanza Martínez-Valdebenito:** Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project administration. **Bruno Nervi:** Conceptualization, Writing – Review & Editing, Funding acquisition. **Aracelly Gaete-Argel:** Methodology, Formal analysis, Investigation, Data Curation, Writing – Review & Editing. **Nicolás M.S. Gálvez:** Validation, Investigation, Writing – Review & Editing. **Catalina Osses:** Writing – Review & Editing, Project administration. **Cecilia Vizcaya:** Resources, Writing – Review & Editing. **María E. Ceballos:** Resources, Writing – Review & Editing. **Jaime Pereira:** Conceptualization, Writing – Review & Editing. **Mayling Chang:** Conceptualization, Resources, Writing – Review & Editing. **Luis Rojas:** Conceptualization, Writing – Review & Editing. **Sebastián Mondaca:** Conceptualization, Writing – Review & Editing. **Carolina Henríquez:** Conceptualization, Resources, Data Curation, Writing – Review & Editing. **Alexis M. Kalergis:** Resources, Writing – Review & Editing. **Alessandro Sette:** Resources, Writing – Review & Editing. **Alba Grifoni:** Resources, Writing – Review & Editing. **Ricardo Soto-Rifo:** Methodology, Writing – Review & Editing, Supervision, Funding acquisition. **Fernando Valiente-Echeverría:** Methodology, Writing – Review & Editing, Supervision, Funding acquisition. **Marcela Ferres:** Conceptualization, Resources, Writing – Review & Editing, Funding acquisition. **María E. Balcells:** Conceptualization, Resources, Writing – Review & Editing, Funding acquisition. **Nicole Le Corre:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Pontificia Universidad Católica de Chile, under protocol number 200513023, dated 04–29–2021. Written informed consent was obtained from all participants prior to sample collection and data analysis.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.crmicr.2025.100440.

Data availability

Data will be made available on request.

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