Received: 12 August 2023 | Revised: 15 October 2023 | Accepted: 24 October 2023

DOI: 10.1111/vox.13561

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Factors related to the development of high antibody titres against SARS-CoV-2 in convalescent plasma donors from the ConPlas-19 trial

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Funding information
European Regional Development Fund (FEDER); Government of Spain, Ministry of Science and Innovation, Instituto de Salud Carlos III, Grant/Award Number: COV20/00072; SCReN (Spanish Clinical Research Network), Instituto de Salud Carlos III, Grant/Award Number: PT17/0017/0009

Abstract

Background and Objectives: The efficacy of COVID-19 convalescent plasma (CP) associates with high titres of antibodies. ConPlas-19 clinical trial showed that CP reduces the risk of progression to severe COVID-19 at 28 days. Here, we aim to study ConPlas-19 donors and characteristics that associate with high anti-SARS-CoV-2 antibody levels.

Materials and Methods: Four-hundred donors were enrolled in ConPlas-19. The presence and titres of anti-SARS-CoV-2 antibodies were evaluated by EUROIMMUN anti-SARS-CoV-2 S1 IgG ELISA.

Results: A majority of 80.3% of ConPlas-19 donor candidates had positive EUROIMMUN test results (ratio ≥1.1), and of these, 51.4% had high antibody titres (ratio ≥3.5). Antibody levels decline over time, but nevertheless, out of 37 donors tested for an intended second CP donation, over 90% were still EUROIMMUN positive, and nearly 75% of those with high titres maintained high titres in the second sample. Donors with a greater probability of developing high titres of anti-SARS-CoV-2 antibodies include those older than 40 years of age (RR 2.06; 95% CI 1.24–3.42), with more than 7 days of COVID-19 symptoms (RR 1.89; 95% CI 1.05–3.43) and collected within 4 months from infection (RR 2.61; 95% CI 1.16–5.90). Male donors had a trend towards higher titres compared with women (RR 1.67; 95% CI 0.91–3.06).

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Conclusion: SARS-CoV-2 CP candidate donors' age, duration of COVID-19 symptoms and time from infection to donation associate with the collection of CP with high antibody levels. Beyond COVID-19, these data are relevant to inform decisions to optimize the CP donor selection process in potential future outbreaks.

Keywords

anti-SARS-CoV-2, convalescent plasma, COVID-19, donors, passive immunotherapy

Highlights

- More than 80% of convalescent plasma (CP) donors in the ConPlas-19 trial had positive EUROIMMUN antibody results, and of these, >50% had high antibody titres. Those older than 40 years of age, with over 7 days of COVID-19 symptoms and collected within 4 months from infection have a greater probability of developing high titres of anti-SARS-CoV-2 antibodies.
- Antibody levels decline over time, but most donors who were tested for a potential second CP donation remained positive and maintained high antibody titres.
- Beyond COVID-19, these data are relevant to inform decisions to optimize the CP donor selection process in potential future outbreaks.

INTRODUCTION

The safety and efficacy of convalescent plasma (CP) as a therapeutic option for patients with COVID-19 has been thoroughly examined in multiple studies, clinical trials and meta-analyses [1–6]. Emerging from this evidence, current recommendations are for CP to be used in early stages of the disease, in high-risk patients and in those who have not developed an appropriate immunological response, and for CP units to be chosen based on high antibody titres to improve efficacy [7–9]. However, very few studies have focused on CP donors and investigated their characteristics that may associate with the development of antibody titres and efficacy. ConPlas-19 (NCT04345523), a multi-centre randomized open-label clinical trial of CP in hospitalized patients with COVID-19 pneumonia showed a treatment benefit in preventing disease progression or death at 28 days after CP treatment [6]. Here, we now aim to analyse the characteristics of the CP donors enrolled in ConPlas-19 and their potential association with the collection of higher quality CP with high antibody titres.

MATERIALS AND METHODS

Study design

This is an ad hoc retrospective sub-study of the multi-centre open-label randomized ConPlas-19 clinical trial (NCT04345523) [6, 10]. The clinical trial was approved by the Research Ethics Committee of the Hospital Universitario Puerta de Hierro Majadahonda in Madrid, Spain (PI57-20 from 23 March 2020). This ad hoc study was approved by the Research Ethics Committee of the Hospital Universitario Puerta de Hierro Majadahonda in Madrid, Spain (PI 92/22 from 26 April 2022) and by the Research Ethics Committee of the Universidad Autónoma de Madrid, Spain (CEI-125-2561 from 15 July 2022). Informed consent was obtained from all donors.

CP donors

ConPlas-19 enrolled CP donors from 30 centres in Spain, including hospitals and regional transfusion centres, between April and November 2020. Potential donors were identified using local registries of convalescent COVID-19 patients. In the context of the pandemic, an initial assessment of their eligibility was made by telephone. Donors eligible for screening were assessed according to EU requirements and the Spanish regulations for plasma donation (RD 1088/2005) [11, 12]. EUROIMMUN anti-SARS-CoV-2S1 ELISA IgG assays (EUROIMMUN, Luebeck, Germany) were performed in all screened donors prior to donation to confirm the presence of anti-SARS-CoV-2 antibodies. Donors selected had a laboratory-confirmed SARS-CoV-2 infection, had been asymptomatic for at least 14 days prior to CP collection and were positive for anti-SARS-CoV-2 IgG (EUROIMMUN ratio ≥1.1). In keeping with FDA recommendations, high antibody titres were defined by EUROIMMUN ratios ≥3.5 [13]. Donors could undergo more than one CP apheresis process as long as they continued to fulfil criteria and had confirmed SARS-CoV-2 antibodies in a new sample. Donors' characteristics included in this sub-study were age, gender, ABO blood group, symptom duration and time to donation between symptom onset and antibody testing. Further details of ConPlas-19 have been reported [6, 10].

Data management and monitoring

The screened CP donors were registered using a web-based electronic Case Report Form performed with ORACLE clinical. Remote data

monitoring was performed by dedicated staff, independent of the site investigators, with source data verification performed for donors recruited for critical data points that were previously established in the monitoring plan.

Statistical analysis

A detailed statistical analysis plan for ConPlas-19 has been already reported [6]. The current statistical analysis to describe and analyse retrospectively donors' characteristics and their association with CP titres in the different analyses has used Student's *t*-test, Fisher's exact test, analysis of variance, and simple linear and multinomial logistic regression analyses. *p*-values <0.05 were considered statistically significant. The statistical analysis was conducted with STATA/IC 16.1 version (StataCorp, College Station, TX, USA).

RESULTS

Donors' characteristics

ConPlas-19 enrolled 400 CP donors between April and November 2020 (Figure 1 and Table 1). Three additional donor candidates were initially screened and selected, but did not sign the informed consent. They were mostly men (78.8%), with a median age of 40.5 years (IQR 30.5–50.5). Male donors were a median of 4 years older than female donors (42.0 vs. 37.9; $p = 0.003$). The distribution of donors' ABO blood type matched that of the Spanish population [14]: 44.6% group A, 39.4% group O, 8.8% group B and 7.2% group AB, with the commonest types being A positive (36.8%) and O positive (33.2%). Donors' COVID-19 diagnosis was confirmed by RT-PCR in 292 cases (73%). Nearly 30% of donors, during the early phase of the pandemic, when there was not a wide availability of serological tests, had a high clinical suspicion of infection despite a confirmatory SARS-CoV-2 RT-PCR being either not performed or negative. All these donors had a confirmed serological diagnosis of SARS-CoV-2 infection prior to collection. Donors' COVID-19 severity was not recorded in the study protocol. Their median duration of symptoms of SARS-CoV-2 infection was 13 days (IQR 7–19), and it increased with donor age at a rate of 0.17 days for each year increase in donor age (95% CI, 0.09–0.25; $p < 0.001$). We did not find an association between symptom duration and donor sex or ABO blood type.

Overall EUROIMMUN ELISA test results

An initial EUROIMMUN ELISA test was carried out in 392 of the 400 donors recruited for the study (98%). Median time from COVID-19 symptoms onset to the first ELISA to be assessed as CP donors was 50 days (IQR 39–62). A majority of 315 (80.3%) donor candidates had a positive anti-SARS-CoV-2 EUROIMMUN result in the first serological testing, while 63 (16.1%) were negative and 14 (3.6%) had an indeterminate result (Figure 2). There were no differences in donors' serological status depending on having a microbiological confirmation of SARS-CoV-2 infection by RT-PCR: 80.9% of donors with versus 78.8% of those without a confirmed SARS-CoV-2 diagnosis by RT-PCR did have anti-SARS-CoV-2 antibodies ($p = 0.668$). Donors selected based on a high clinical suspicion without RT-PCR had overall a similar profile and characteristics to those with a confirmed diagnosis by RT-PCR. Median antibody level of donors with a positive screening ELISA test result was 3.53 (IQR 2.29–5.39). We did not find any factor (age, sex, ABO blood group, duration of symptoms and time between symptom onset and

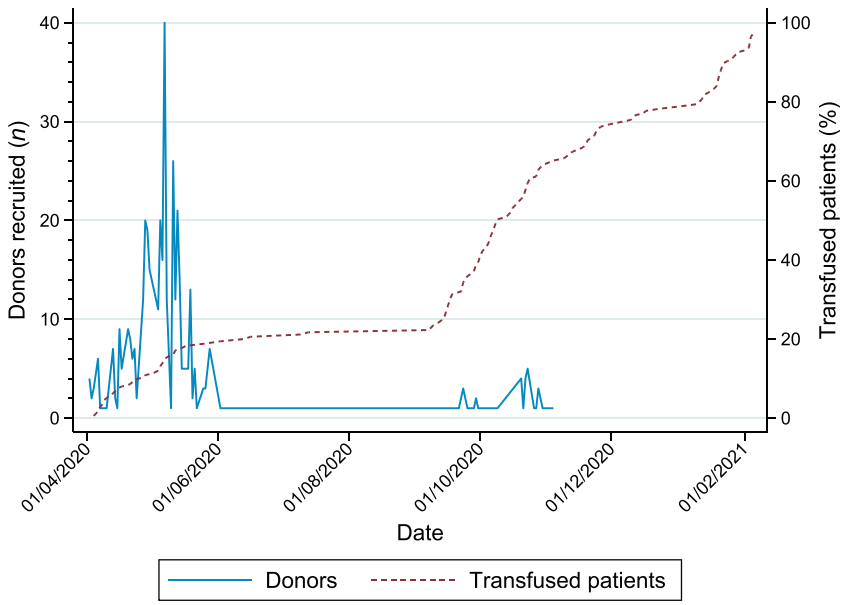

FIGURE 1 Donors' recruitment and convalescent plasma transfusion over time.

TABLE 1 Donors' basal characteristics.

Characteristic	All ($N = 400$)[a]
Sex, *n* (%)	
Male	315 (78.8%)
Female	85 (21.2%)
Age, median (IQR), years	40.5 (30.5–50.5)
ABO blood group, *n* (%)[b]	
Group A	173 (44.6%)
Group O	153 (39.4%)
Group B	34 (8.8%)
Group AB	28 (7.2%)
Period of inclusion, *n* (%)	
First wave	359 (89.8%)
Second wave	41 (10.2%)
SARS-CoV-2 RT-PCR at diagnosis, *n* (%)	
Positive	292 (73%)
Negative	7 (1.8%)
Not performed	74 (18.5%)
Unknown	27 (6.7%)
Duration of COVID-19 symptoms, median (IQR), days	13 (7–19)
Donor's antibodies at screening, *n* (%)[c]	
Positive	315 (80.3%)
Negative	63 (16.1%)
Indeterminate	14 (3.6%)
Time from symptoms onset to first antibody test, median (IQR), days	50 (39–62)

[a]There were three additional donors who were registered in the clinical trial but did not sign informed consent.
[b]There are 12 (3.0%) donors whose ABO blood group is unknown.
[c]There were eight (2%) donors to whom serological tests were not performed.

EUROIMMUN determination) related with not developing IgG anti-SARS-CoV-2 antibodies.

Donors with higher antibody levels

With a median EUROIMMUN test result of 3.53, over half of all positive donors (162 out of 315, 51.4%) met the criteria for antibody high titres, as pre-defined by EUROIMMUN ratios ≥3.5 [13]. These donors with high titres had median levels of 5.33 (IQR 4.26–6.66). Several donor factors are associated with the probability of having high titres (Table 2). Donors with a duration of COVID-19 symptoms >7 days were nearly twice as likely to have high titres (RR 1.89; 95% CI 1.05–3.43; $p = 0.037$), and those who had passed COVID-19 within the previous 4 months from testing for CP collection were 2.6 times more likely to have high titres (RR 2.61; 95% CI 1.16–5.90; $p = 0.021$). In addition, donors older than 40 years of age had a higher probability of developing high titres (RR 2.06; 95% CI 1.24–3.42; $p = 0.005$) than younger donors, and male donors showed a statistical

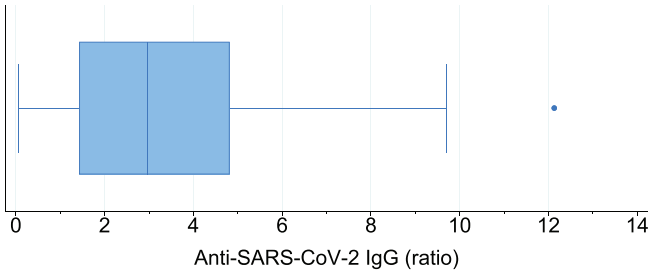

FIGURE 2 Distribution of antibody titres among all recruited donors. Box-and-whiskers diagram showing the distribution of antibody titres in all donors ($n = 392$; minimum: 0.06; p25: 1.43; p50: 2.98; p75: 4.82; maximum: 12.13).

trend towards higher titres of anti-SARS-CoV-2 antibodies than women (RR 1.67; 95% CI 0.91–3.06; $p = 0.098$). ABO blood groups were not associated with antibody levels.

Antibody level testing for subsequent CP donations

Thirty-seven donors with detectable anti-SARS-CoV-2 antibodies (11.7%) were tested at a second time point for a potential second CP donation. These samples were obtained 82 days after the onset of COVID-19 symptoms (IQR 68–195) and 27 days after the first donation (IQR 13–113). A vast majority of 34 of these donors (91.9%) maintained detectable antibodies (EUROIMMUN ratio ≥1.1) in serum in the second analysis. In addition, 17 out of 23 of these donors who had initially high titres (73.9%) maintained high titres in the second sample. Nevertheless, for each month elapsed between donations, antibody levels decreased in 0.17 units (95% CI 0.03–0.35; $p = 0.016$) (Figure 3). Overall, there was median of 1.10 lower EUROIMMUN ratio units in the second sample compared with the first one (95% CI 0.63–1.56; $p < 0.001$), and this reduction was more pronounced in donors with high titres, in whom the decline between first and second donation was of 1.59 units (95% CI 1.04–2.15; $p < 0.001$).

DISCUSSION

This is to our knowledge one of the few studies of CP for COVID-19 focused on the donors enrolled in a clinical trial and on their characteristics that associate with the collection of CP with high anti-SARS-CoV-2 titres. Thus far, research has concentrated primarily on the efficacy of CP in patients, and less information is available about the donors from whom CP is obtained, from which the final efficacy results arise. Available data on anti-SARS-CoV-2 CP donors are mainly descriptive and come from regional centres of blood donation and national CP programmes. This study analyses the CP donors enrolled in the multi-centre, randomized, open-label, clinical trial ConPlas-19 and identifies several donor factors that associate with the collection of higher quality CP with high antibody titres.

TABLE 2 Biological and clinical factors associated with high titres.

	Multinomial logistic regression			
Variable	**RR**	***p***	**95% CI**	
Age				
<40 years (reference group)	1			
≥40 years	2.06	0.005	1.24	3.42
Sex				
Women (reference group)	1			
Men	1.67	0.098	0.91	3.06
ABO blood group				
Group O (reference group)	1			
Group A	1.04	0.883	0.61	1.77
Group AB	0.69	0.456	0.26	1.81
Group B	1.24	0.648	0.49	3.11
Symptom duration				
<7 days (reference group)	1			
≥7 days	1.89	0.037	1.05	3.43
Time from onset to EUROIMMUN testing				
≥4 months (reference group)	1			
<4 months	2.61	0.021	1.16	5.90

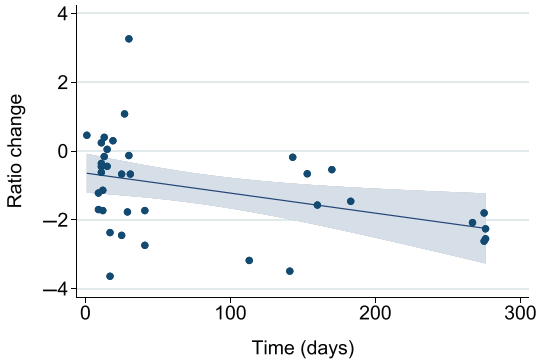

FIGURE 3 Change in antibody titres in donors considered for a second convalescent plasma donation. The horizontal axis represents the time in days between the first and second EUROIMMUN test values in donors considered for a second donation ($n = 37$). Dots represent the individual change of antibody levels in each donor between donations; the dark line represents the fitted values and the grey area represents the 95% CI of the mean.

Donors with a duration of COVID-19 symptoms of more than 7 days had CP with higher anti-SARS-CoV-2 titres than donors with shorter duration of symptoms. Patients with severe forms of COVID-19 are known to develop higher antibody levels [15], although some studies suggest that these patients do not develop effective humoral and cellular immune responses [16]. Unfortunately, beyond duration of symptoms, our clinical trial protocol did not collect the severity of COVID-19 in CP donors. The CAPSID trial has studied its CP donors, and although duration of symptoms was not evaluated, the authors found that the number of symptoms was associated with higher antibody titres [17].

Our study suggests that CP donors collected within 4 months from the beginning of COVID-19 symptoms are more likely to have high anti-SARS-CoV-2 antibody titres. A decline in antibody levels with time from infection was clearly identified in our series, and it appeared more pronounced in donors with high titres. Other studies have shown similar results. Chen et al. reported that most cases show a decrease in anti-SARS-CoV-2 IgG antibodies in the third month since recovery from COVID-19 [18]. Prus et al. also showed that the decrease was more marked after 12 weeks and recommended an earlier CP collection between 4 and 8 weeks from recovery from COVID-19 [19]. Of note, our experience with a subgroup of 37 donors who were tested for an intended second CP donation is nevertheless reassuring, as it shows that a vast majority of 92% of those donors still had anti-SARS-CoV-2 antibodies at a median of 24 days from the first CP donation, and 74% of those with high titres maintained high titres in the second sample.

In our series, donors over 40 years of age were more likely to have CP with high titres. Age has been described as a factor associated with antibody titres in several studies [20–23], including some large multivariate regression analyses that found a positive correlation with age even when adjusting the model by hospitalization history [24], and showed that the rate of antibody decline was significantly slower for donors over 55 years of age [25]. The reasons underlying the impact of age on anti-SARS-CoV-2 immune response are not clear [26], but some authors suggest that it may be linked to immunesenescence and the generation of immunoglobulins with lower antigen specificity in these patients [27]. In addition, our data found a statistical trend towards male donors having higher anti-SARS-CoV-2 antibodies. The literature on this topic is less clear. Some studies have shown that women have higher antibody titres, but also a faster rate of decline with time, compared with men [25]. Others, on the contrary, concur with our findings of higher titres in males, albeit in association with a more severe presentation of COVID-19 in these patients [28]. Finally, our findings do not support an association between antibody levels and ABO blood group. There is a clear association of blood group A with a higher risk and severity of COVID-19 [29–31], but the evidence of an association between ABO blood group and antibody levels are not clear in the literature [20, 21, 23].

This study has some limitations. Although it stems from a prospective randomized clinical trial, this ad hoc study is retrospective and carries intrinsic limitations of such a design. In addition, we have not analysed neutralizing antibodies (NAbs) anti-SARS-CoV-2. While current guidelines specifically recommend CP treatment with high NAb titres [9], the complexity and technical specifications of neutralization assays, in particular during the first wave of the pandemic when most of our donors were recruited, prevented us from including these results in this manuscript. Furthermore, an analysis of total IgG anti-SARS-CoV-2 (EUROIMMUN assay) provides broader information on the role of the CP, including antiviral activities that depend on the integrity of the Fc region, like complement-dependent cytotoxicity, antibody-dependent cell-phagocytosis and antibody-dependent cell cytotoxicity [5]. More recently, the so-called hybrid plasma or Vax-plasma, obtained from convalescent donors who were subsequently

vaccinated seems to present much higher antibody titres (10-fold to 100-fold) than conventional CP and may be preferable for the treatment of immunocompromised patients [32, 33]. Unfortunately, our study conducted during the early phase of the pandemic, before vaccines were developed, cannot address this comparison. Finally, even though the severity of infection was not an exclusion criterion to select candidate CP donors, in the complex medical scenario of the early pandemic, there was a bias towards recruiting as donors COVID-19 convalescent patients who were younger, with a healthier medical background and who had not suffered a severe COVID-19. Now, we know that some of those characteristics had a negative impact on the antibody titres of the CP collected. Nevertheless, even with such potential bias, 92% of our candidate CP donors were positive for anti-SARS-CoV-2 antibodies, and of these, more than half had high antibody titres. Even without a confirmed microbiological diagnosis by RT-PCR, a high clinical suspicion of past clinical infection was enough in our clinical trial to recruit suitable donors. This strategy of recruitment was successful and proved particularly useful in the early phases of a pandemic where diagnostic tests are neither fully developed nor widely available.

In conclusion, our study suggests that basic demographic and clinical information such as duration of SARS-CoV-2 infection over 7 days, donations performed within the first 4 months since the onset of symptoms and donor's age above 40 years associate with the collection of CP with high antibody levels. Beyond its relevance in the context of COVID-19, we hope that these data will be of relevance and inform decisions to be made in the planning to optimize the CP donor selection process in potential future outbreaks.

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ACKNOWLEDGEMENTS

The authors would like to acknowledge the generous contributions of so many patients with COVID-19 who either donated their plasma after recovering from the disease or agreed to participate as subjects in this study, as well as the many healthcare professionals who, undeterred by the difficulties of the pandemic, helped look after these patients and obtain scientific evidence. This research was funded by the Government of Spain, Ministry of Science and Innovation, Instituto de Salud Carlos III, grant number COV20/00072 (Royal Decree-Law 8/2020, of 17 March, on urgent extraordinary measures to deal with the economic and social impact of COVID-19), co-financed by the European Regional Development Fund (FEDER) "A way to make Europe," and supported by SCReN (Spanish Clinical Research Network), Instituto de Salud Carlos III, project PT17/0017/0009.

C.A.-S., J.L.B.C., R.F.D. and A.R.-M. conceived the clinical trial study. I.R.M., J.L.B.C. and R.F.D. contributed to the design of this study. I.R.M., J.L.B.C., C.V.D.R., A.B.L, J.A.G.E., M.I.G.F., L.G.D., I.V.A., J.A.V., V.P.G.R., E.C., S.U.U., A.L.P.H., T.J.-M., A.M.O.P. and J.L.A.R. contributed to CP collection, qualification and release. A.V.-I. coordinated study activities. M.P.-O. performed and interpreted serology assays. I.R.M., J.L.B.C. and R.F.D. designed and supervised statistical analyses. I.R.M. wrote the first version of the manuscript. R.F.D. corrected the final draft version of the manuscript. All authors contributed to critical revision of the manuscript and approved its final version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Romera Martínez I, Avendaño-Solá C, Villegas Da Ros C, Bosch Llobet A, García Erce JA, González Fraile MI, et al. Factors related to the development of high antibody titres against SARS-CoV-2 in convalescent plasma donors from the ConPlas-19 trial. Vox Sang. 2023.