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Review article

# Fresh frozen plasma for neutralizing SARS-CoV-2: "An exploratory cross-sectional study and review of the state of the art"

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ABSTRACT

Restitution of humoral immunodeficiency is essential to clear SARS-CoV-2. Intravenous unspecific immunoglobulins are expensive and restricted. So recently donated fresh frozen plasma (FFP) could be useful in this scenario but, are all units neutralizing against SARS-CoV-2?

We explored this on 52 donations obtained from "Centro de Transfusión, Tejidos y Células de Málaga, Spain", from April to June 2022. Donors status about SARS-CoV-2 previous infection or vaccination was unknown. Neutralizing activity (at dilutions ≥ 1/160) against real Delta (not circulating), BA.2 (dominant circulating variant), BA.5 (irrupting variant), and BQ.1.1 and XBB.1.5 (not circulating yet) was determined.

Higher anti-Spike IgG antibodies cut-offs predicted efficacy of FFP. Different cut-offs have been reported in the literature, but all papers have in common that levels over the higher range of quantification can predict neutralizing activity of recently donated FFP against circulating variants of concern, if used early after donation, not requiring clinical data from donors.



## Capacidad neutralizante del plasma fresco congelado frente al SARS-CoV-2: un estudio piloto transversal y revisión de las evidencias en la literatura

*Palabras clave:*
COVID-19
Pacientes inmunodeprimidos
Plasma fresco congelado
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Anticuerpos IgG frente a la espiga del SARS-CoV-2
Actividad neutralizante

RESUMEN

Restituir la inmunodeficiencia humoral es esencial para aclarar el SARS-CoV-2. Las inmunoglobulinas humanas inespecíficas intravenosas son caras y de uso restringido. El plasma fresco congelado donado recientemente podría ser útil en este escenario, pero ¿son todas las unidades donadas neutralizantes?

En 52 donaciones (abril-junio 2022) al Centro de Transfusión, Tejidos y Células de Málaga, España, determinamos la actividad neutralizante (a diluciones ≥ 1/160) contra cepas reales Delta (no circulante ya), BA.2 (circulante dominante), BA.5 (irrumpiendo), y BQ.1.1-XBB.1.5 (no circulantes aún). Se desconocían los aspectos relativos al SARS-CoV-2 de los donantes.

Los puntos de corte más elevados de anticuerpos IgG frente a la espiga predijeron la eficacia del plasma fresco congelado. En la literatura, todos aquellos valores por encima del rango más elevado de cuantificación predicen una buena actividad neutralizante del plasma fresco congelado recientemente donado contra las variantes de SARS-CoV-2 circulantes, si se usa pronto tras la donación, sin requerirse datos clínicos de los donantes.



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## Introduction

Soon after the irruption of SARS-CoV-2 pandemic, it was clear that immunocompromised patients had a protracted, and sometimes deadly, course of the disease. This was observed in patients with innate immune deficiencies, hematological cancers, anti-CD20 based treatments and transplantation.[1] Though COVID-19 convalescent plasma (CCP) has not shown clear benefits in general population with mild, moderate or severe COVID-19,[2] from the beginning many clinicians reported a favorable evolution of persistent COVID-19 after administering CCP to their patients.[3] In Spain, CCP was elaborated following specific recommendations of the Spanish Ministry of Health[4] and was supplied by the "Red Andaluza de Medicina Transfusional, Tejidos y Células" belonging to the "Sistema Sanitario Público de Andalucía". However, since end of year 2021 no more CCP was elaborated so we had to use CCP made from convalescent patients of pre-Omicron variants of concern (VOCs) for Omicron infected immunocompromised patients. As shown by others,[5,6] pre-Omicron CCP was not as effective as before against Omicron VOCs, as we needed higher amounts of plasma and repeated doses, and negativization of SARS-CoV-2 PCR was not always obtained. Even CCP collected during circulation of Omicron BA.1 had a low neutralization capacity against SARS-CoV-2 Omicron BQ.1.1.[7]

Another early approach treating COVID-19 in immunocompromised patients was the development of monoclonal antibodies targeting the SARS-CoV-2 spike protein. However, they were highly specific for every variant/subvariant, so every new one required a new monoclonal antibody. Bamlanivimab plus etesevimab neutralized alpha variant, casirivimab plus indevimab neutralized alpha-delta variant, sotrovimab neutralized Omicron BA.1, tixagevimab plus cilgavimab neutralized Omicron BA.2 and bebtelovimab neutralized Omicron BA.4.[8] Today they are not recommended against SARS-CoV-2.[9] Even new monoclonal antibodies as pemivibart[10,11] or sipavibart,[11,12] useful neutralizing Omicron JN.1, have low or no activity against KP.1, LB.1 and KP.3.3. So in this race we arrive always late. In Spain there was access to casirivimab plus indevimab and sotrovimab as treatment against SARS-CoV-2, and to tixagevimab plus cilgavimab as prophylaxis against SARS-CoV-2.

Antivirals against SARS-CoV-2 as remdesivir or nirmatrelvir/ritonavir have shown efficacy in immunocompromised patients, even in monotherapy, when they are used soon after the infection.[13,14] Efficacy was enhanced using CCP or sotrovimab.[13] However, in immunocompromised patients with persistent COVID-19, antiviral monotherapy failed frequently, and dual antiviral therapy was needed for eradicating SARS-CoV-2. Most cases required monoclonal antibodies like sotrovimab or tixagevimab plus cilgavimab, too.[15–21]

A recent systematic review and meta-analysis suggests that transfusion of CCP is associated with mortality benefit for patients who are immunocompromised and have COVID-19,[22] and specific guidelines support the use of CCP for immunocompromised patients with COVID-19.

IDSA Guidance on the use of convalescent plasma to treat immunocompromised patients with COVID-19 remarks that CCP is a safe and effective treatment for COVID-19 in immune compromised patients. For optimal effect, CCP should be recently and locally collected to match circulating variant. CCP should be considered for the treatment of immune compromised patients with acute and protracted COVID-19. CP containing high-titer SARS-CoV-2 antibodies, retains activity against circulating SARS-CoV-2 variants, which have otherwise rendered monoclonal antibodies ineffective.[23] IDSA guidelines on the treatment and management of patients with COVID-19 conclude that based on limited studies and mechanistic reasoning, CCP may be more effective if given at high titers early in course of hospitalization, in patients with undetectable or low levels of anti-SARS-CoV-2 antibodies, or in those with a humoral immune deficiency. The guideline panel suggests FDA-qualified high-titer CCP in the ambulatory setting for persons with mild-to-moderate COVID-19 at high risk for progression to severe disease, who have no other treatment options. In ambulatory patients, CCP may be more effective if the product used contains high titers of neutralizing antibodies and is used early in clinical presentation or in subpopulations of patients who do not have an adequate humoral immune response even at later stages of disease.[24]

GESITRA-IC (Group for the study of infection in transplantation and other immunocompromised host) of SEIMC (Spanish Society of Infectious Diseases and Clinical Microbiology) recognizes that immunocompromised patients might benefit from CCP given their underlying deficit in B- and T-cell immunity. This group recommendations are: 1. Treatment with one or two units in solid organ transplantation patients with mild or early-stage COVID-19 may reduce the risk of progression to severe disease (recommendation IIID). 2. Treatment with hybrid plasma is preferred, with dosing based on clinical or virological response. 3. The use of early CCP alone or associated with antiviral treatment and immunomodulatory therapy in solid organ transplantation receptors hospitalized for moderate to severe COVID-19 is safe and may improve clinical course and increase survival (recommendation IIB).[25]

Israeli Society of Infectious Diseases consensus statement on diagnosis and management of persistent COVID-19 in immunocompromised patients suggests for patients with persistent COVID-19 antibody-based treatment (monoclonal antibodies if available or CCP; hyperimmune serum or intravenous immunoglobulins can be considered) and short term (5–10 day) combination antiviral treatment with two of the following: remdesivir, nirmatrelvir/ritonavir, molnupiravir. For relapsed or non-responders patients, suggests consider administering monoclonal antibodies, if available and not given earlier, or repeating CCP and combination antiviral treatment for longer duration (>10 days).[26]

ECIL-10 (10th European Conference on Infections in Leukemia) COVID-19 working group recommends in moderately or severely immunocompromised hematological malignant patients with mild-moderate COVID-19 early treatment with antivirals; and in selected very severely immunocompromised patients or in patients with imminent necessary chemotherapy or cellular therapy, a combination of two antivirals or combination of antiviral plus monoclonal antibodies/convalescent plasma or prolonged antiviral treatment. Anti-inflammatory treatment with short-term steroid course is recommended only if COVID-19 related inflammation is present. In hematological malignant patients with COVID-19 requiring oxygen support, is recommended antiviral therapy with remdesivir or combination of two antivirals or an antiviral and monoclonal antibodies/convalescent plasma. Anti-inflammatory treatment with short-term steroid course is recommended only if COVID-19 related inflammation is present, and a second immunosuppressant can be considered if COVID-19 inflammation is present and worsening despite steroids. Finally, in patients with critical COVID-19, is recommended remdesivir, or combination of two antivirals or an antiviral plus monoclonal antibodies. Anti-inflammatory treatment with short-term steroid course is recommended only if COVID-19 related inflammation is present, and a second immunosuppressant can be considered if COVID-19 inflammation is present and worsening despite steroids. High-titer convalescent plasma can be useful in critical ventilated patients (preferably within the first 48 hours after ventilation initiation) in addition to standard of care.[27]

Finally, Clinical Practice Guidelines from the Association for the Advancement of Blood and Biotherapies (AABB) suggest CCP transfusion in addition to the usual standard of care for hospitalized patients with COVID-19 and preexisting immunosuppression.[28]

In the middle of 2022, with monoclonal antibodies ineffective and CCP elaborated before Omicron era, we had no real possibilities for improving humoral immunity against SARS-CoV-2 in our immunocompromised patients.

After Focosi's advice in September 2022 pointing that recently collected fresh frozen plasma (FFP) could qualify as CCP, as it comes from regular donors, most of them vaccinated and convalescent of COVID-19,[29] we tried to explore the activity of recently donated FFP neutralizing Delta (no longer circulating when donations were done), BA.2 (dominant circulating VOC, though disappearing at the end of the period when donations were done), BA.5 (irrupting VOC at the end of the period when donations were done), and BQ.1.1 and XBB.1.5 VOCs of Omicron SARS-CoV-2 (not circulating yet).[30]

## Materials and methods

### *Materials*

FFP samples were supplied by the "Centro de Transfusión, Tejidos y Células de Málaga", integrated in the "Red Andaluza de Medicina Transfusional, Tejidos y Células", belonging to the "Servicio Andaluz de Salud". Donations were done from April to June 2022. Donors status about SARS-CoV-2 previous infection or vaccination was unknown. Approval by an Ethics Committee was not considered necessary. Donors signed written informed consent.

### *Outcomes*

Main outcomes were determining Spike IgG antibody (anti-S) levels against SARS-CoV-2, Nucleocapsid protein antibody (anti-N) positivity, and neutralizing activity of plasma against VOCs Delta and Omicron BA.2, BA.5, BQ.1.1 and XBB.1.5 of donated samples. It would be of interest if a threshold of both antibodies could predict higher neutralizing activity of donated plasma. As most authors suggest, those FFPs who neutralized SARS-CoV-2 at dilutions $\geq$ 1/160 were considered high neutralizing activity ones.[31,32]

### *Laboratory procedures*

IgG anti-S level was determined by indirect chemiluminescent immunoassay (CLIA) in plasma, following the instructions of the insert of COVID-19 spike quantitative VIRCLIA® IgG Monotest, by Vircell®. This is a qualitative/quantitative and automated assay. Values over 30 binding antibody units per ml (BAU/ml) were considered positive. Total anti-N level (including IgG) was determined by electro-chemiluminescence immunoassay (ECLIA) in plasma, following the instructions of the insert of Elecsys® Anti-SARS-CoV-2, by Roche®. This is a qualitative and automated assay. A cut-off index (COI) over 1 was considered positive. Neutralization (NT) assay: Viruses: B.1.617.2 (Delta) strain hCoV-19/Spain/GA-CHUM-33984566/2021; hCoV-19/Spain/GR-PTS-62028048/2022 lineage BA.2; hCoV-19/Spain/GR-PTS-50555187/2022 lineage BA.5; hCoV-19/Spain/GA-CHUVI-19548166 lineage BQ.1.1 and hCoV-19/Spain/GR-PTS-51107845 lineage XBB.1.5 were used in this study. Cell line: Vero C1008 [Vero 76, clone E6, Vero E6](ECACC 85020206) cells were obtained from the European Collection of Authenticated Cell Cultures (ECACC) and cultured in MEM Eagle with Earle's BSS, with 25 mM HEPES, 2 mM L-glutamine (LONZA, Verviers, Belgium), and 1× antibiotic-antimycotic mixture (GIGCO, NY, USA), supplemented with 10% fetal bovine serum (FBS)(BioWest, Nuaillé, France). Vero E6 cells were seeded 72 h before the infection in 96-well plates (Corning, Maine, USA). Assay: Briefly, 70 μL of each serum was two-fold serially diluted in culture medium with 2% FBS, from 1:20 to 1:2560 dilution. A total of 70 μL of cell culture medium containing 100 media tissue culture infectious dose ($TCDI_{50}$) of the virus was added to every well containing diluted serum. Plates were incubated at room temperature for 1 h and 100 μL of each mixture of serum dilution and virus were added to a Vero E6 plate well from which the culture medium had been previously removed. After 5-day incubation at 37 °C in 5% $CO_2$, full cytopathic effect (CPE) was evaluated by microscopic examination. The highest serum dilution that completely inhibited the CPE was considered as the NT titer. Every serum sample was assayed in NT with the five strains: Delta, BA.2, BA.5, BQ.1.1 and XBB.1.5. Neutralization Assays were done in a Biosafety Level-3 (BSL-3) facility belonging to Vircell, S.L. in Granada (Spain).

### *Statistical analysis*

A descriptive analysis of quantitative variables was done. Levels of anti-S by anti-N positivity or negativity were calculated using Student's *t*-test. Correlation between neutralizing titers against VOCs and Anti-S levels were expressed using Box-and-Whisker plots. ROC curves were developed for determining accuracy and Youden's Index. This let us determine positive predictive value (PPV), negative predictive value (NPV), sensitivity (Se) and specificity (Sp) of obtained cut-off values. SPSS v21 was used.

## Results

From April to June 2022, 52 plasma samples were collected from 52 anonymous blood donors. Data about vaccination against SARS-CoV-2 or previous infection with SARS-CoV-2 were not available for those donors. All but one (98%) had SARS-CoV-2 anti-S IgG positive levels. Between positive sera, mean value was 5140 BAU/ml, median 3441 BAU/ml and range run from 599 to >10000 BAU/ml. Fifteen of those 51 donors (29%) had levels > 10,000 BAU/ml, but as sera were not diluted for quantification, 10,000 BAU/ml was considered as the value for those donors in the statistical analysis. Thirty-two donors (61%) had SARS-CoV-2 anti-N positive levels. Between positive sera, mean COI was 38.1, median was 8.64 and range run from 1.08 to 209.

The only donor who had no anti-S antibodies, had anti-N determination positive (COI 3) suggesting a previous SARS-CoV-2 infection with no lasting anti-S antibodies. Neutralizing activity of serum from this donor against all tested VOCs was < 1/20.

Donors with anti-S and anti-N positive antibodies (31/51 = 61%) should represent people with previous SARS-CoV-2 infection, vaccinated or unvaccinated against SARS-CoV-2. Donors with anti-S positive but anti-N negative antibodies (39%) should correspond to vaccinated ones.

Anti-N positive donors had recent infections, leading to higher anti-S levels, as anti-N antibodies decay faster than anti-S antibodies. Anti-N negative donors might have been vaccinated or infected months prior to sample collection, which could explain the observed differences. In fact, mean and median anti-S of anti-N positive donors was 6434 and 8190 BAU/ml, while mean and median anti-S of anti-N negative donors was 2813 and 1463 BAU/ml (Fig. 1, A).

There was no correlation between anti-N COI values and anti-S antibody levels. This finding was not unexpected as anti-N determination is a qualitative and not a quantitative one (Fig. 1, B).

Ten donations were obtained in April, twenty-nine in May and thirteen in June. During that period of time, VOC mainly circulating in Spain was BA.2 from week 13 to 20, and from week 20 to 26 shifted to BA.5 (Fig. 2, A).[30]

Having in mind that donor patients could have been exposed to delta, BA.2 and BA.5 VOCs, neutralizing activity of sera was determined (Fig. 2, B).

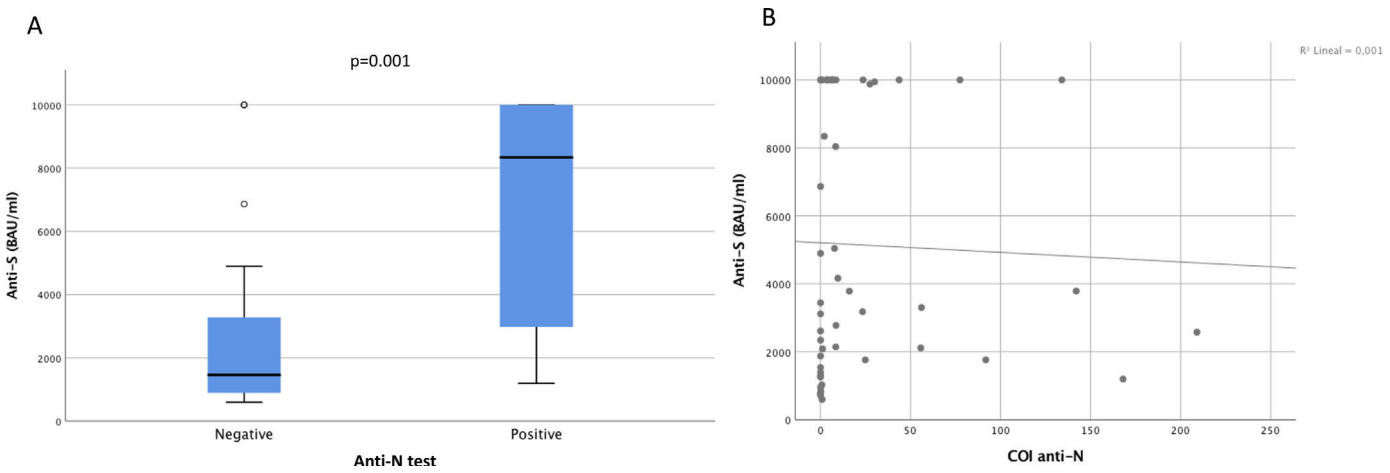


**Fig. 1.** (A) Distribution of Anti-S units, expressed as BAU/ml, in plasma from anti-N negative (20) and anti-N positive (32) donors. The bloxplots indicate the IQR and the whisker length is limited to 1.5 times the IQR. Medians are indicated as horizontal lines within the boxes. (B) Dispersion diagram and simple linear regression line analyzing Anti-S units, expressed as BAU/ml, as a function of anti-N values in plasma from 52 donors.

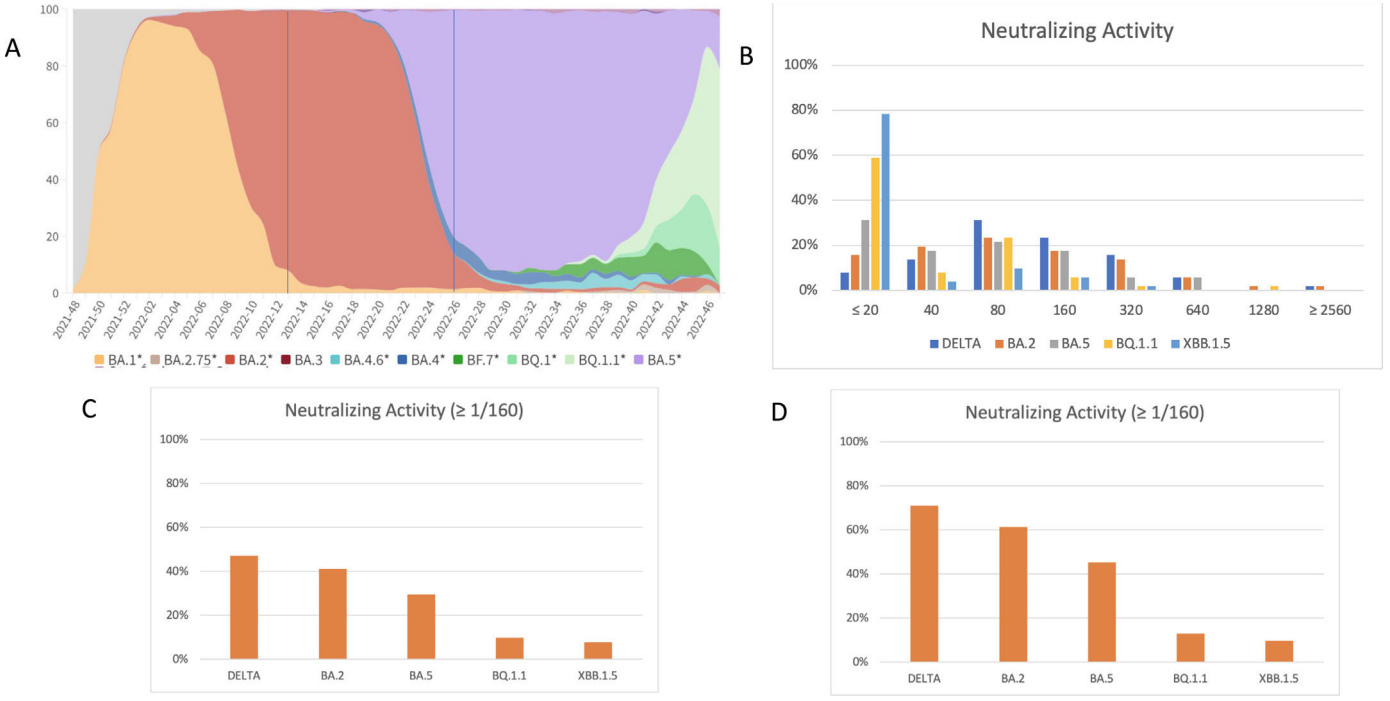


**Fig. 2.** (A) Evolution of Omicron variants of concern (VOCs) in Spain between 2021 week 48 and 2022 week 48. Percentages were obtained from samples sequenced randomly. Vertical lines remark circulating VOCs during the period when plasma donations were done. Data from SiViEs (Spanish surveillance system), 2022 Dec 9th (with permission).[30] (B) Neutralizing activity of donors plasma (1/) against every VOC analyzed (52 samples). (C) Neutralizing activity (≥1/160) of Anti-S positive donors plasma against analyzed VOCs (51 samples). (D) Neutralizing activity (≥1/160) of Anti-S anti Anti-N positive donors plasma against analyzed VOCs (31 samples).

Most authors consider desirable neutralizing titers for CCP those ≥1/160. So defined, 51 anti-S positive donations were neutralizing against Delta, BA.2 and BA.5 in a 47, 41 and 29%, respectively (Fig. 2, C). Restricting this analysis to the 31 anti-S and anti-N positive samples, donations were neutralizing against Delta, BA.2 and BA.5 in a 71, 61 and 45%, respectively (Fig. 2, D).

Then, we analyzed the relation between neutralizing titers and anti-S levels for VOCs delta, BA.2 and BA.5 separately; including all those 51 patients with anti-S antibodies, and the subgroup of those 31 patients with anti-S and anti-N antibodies. For every analyzed VOC, we obtained a sigmoidal curve, where the higher neutralizing activity of the sera correlated with a higher anti-S value. There was a clear difference in anti-S levels distribution between sera with neutralizing activity ≥ 1/160 and those under 1/160, too. Finally, we made ROC (Receiving Operating Characteristic) curves. Results are depicted for delta, BA.2 and BA.5 VOCs in Figs. 3–5, each.

For every variant of SARS-CoV-2, Area Under Curve (AUC) was better when calculated using anti-S values only, than focusing on anti-S values of anti-N positive donors.

Anti-S levels made an AUC curve excellent (0.901) with a Youden's Index of 3974 BAU/ml for neutralizing Delta SARS-CoV-2, good (0.87) with a Youden's Index of 5952 BAU/ml for neutralizing BA.2 SARS-CoV-2, and good (0.81) with a Youden's Index of 7450 BAU/ml for neutralizing BA.5 SARS-CoV-2. Thus, donations with anti-S values over 3974 BAU/ml have an 87% probability of achieving neutralization at titers ≥ 1/160 against Delta VOC. This probability can be improved to 95% with the same cut-off value selecting only anti-N positive sera, but it requires determin-

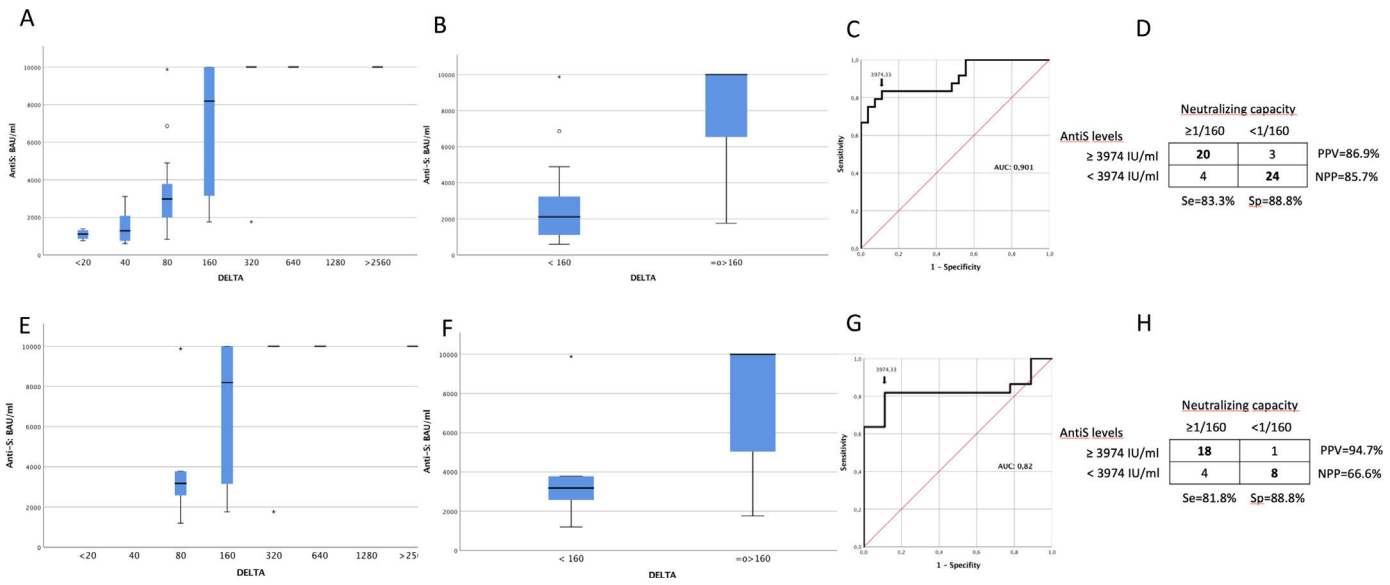


**Fig. 3.** Correlation between neutralizing titers (<1/20 to >1/2560) against Delta SARS-CoV-2 and Anti-S levels (BAU/ml) (A, E); anti-S values from samples with neutralizing activity ≥ 1/160 versus <1/160 (B, F) and ROC curves (C, G) with positive predictive value (PPV), negative predictive value (NPV), sensitivity (Se) and Specificity (Sp) of proposed cut-offs (D, H). A–D graphs analyzed 51 anti-S positive samples; E–H graphs analyzed 31 anti-S and anti-N positive samples. In A, B, E and F, the boxplots indicate the IQR and the whisker length is limited to 1.5 times the IQR. Medians are indicated as horizontal lines within the boxes.

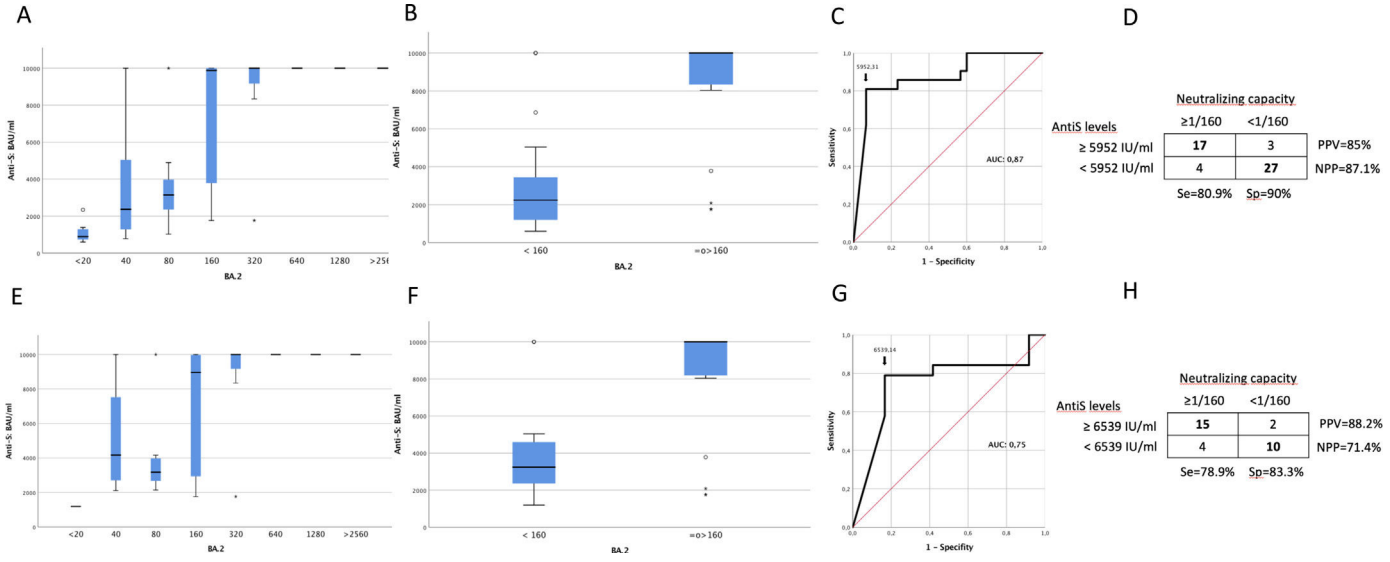


**Fig. 4.** Correlation between neutralizing titers (<1/20 to >1/2560) against BA.2 SARS-CoV-2 and Anti-S levels (BAU/ml) (A, E); anti-S values from samples with neutralizing activity ≥ 1/160 versus <1/160 (B, F) and ROC curves (C, G) with positive predictive value (PPV), negative predictive value (NPV), sensitivity (Se) and Specificity (Sp) of proposed cut-offs (D, H). A–D graphs analyzed 51 anti-S positive samples; E–H graphs analyzed 31 anti-S and anti-N positive samples. In A, B, E and F, the boxplots indicate the IQR and the whisker length is limited to 1.5 times the IQR. Medians are indicated as horizontal lines within the boxes.

ing anti-N to donors samples too. Donations with anti-S values over 5952 BAU/ml have an 85% probability of achieving neutralization at titers ≥ 1/160 against BA.2 VOC. This probability can be improved to 88% increasing the cut-off value to 6539 BAU/ml, selecting only anti-N positive sera, but it requires again determining anti-N to donors samples too. Finally, donations with anti-S values over 7450 BAU/ml have only a 63% probability of achieving neutralization at titers ≥ 1/160 against BA.5 VOC. Unfortunately, selecting only anti-N positive sera did not improve this percentage.

Not unexpectedly, only five samples (10%) had neutralizing activity ≥ 1/160 against BQ.1.1, and four of those five (8%), against XBB.1.5, both not circulating yet. Neutralizing titers against BQ.1.1 were 1/160 (3), 1/320 and 1/1280, and anti-S levels were 8341 and >10,000 (4) BAU/ml, respectively. Four samples were anti-N positive and one, who neutralized at 1/320 titer, anti-N negative. Neutralizing titers against XXB.1.5 were 1/160 (3) and 1/320, and anti-S levels were over 10,000 BAU/ml. Three samples were anti-N positive, and the one who neutralized at 1/320 titer, anti-N negative. Such a low sample size does not let to elaborate a ROC curve. Though most sera neutralizing BQ.1.1 and XBB.1.5 had anti-S titers over 10,000 BAU/ml, it is tempting to assume that those titers guarantee efficacy of those sera donations. However, fifteen samples had anti-S titers over 10,000 BAU/ml and only five (33%) and four (27%) had neutralizing activity against BQ.1.1 and XBB.1.5, respectively.

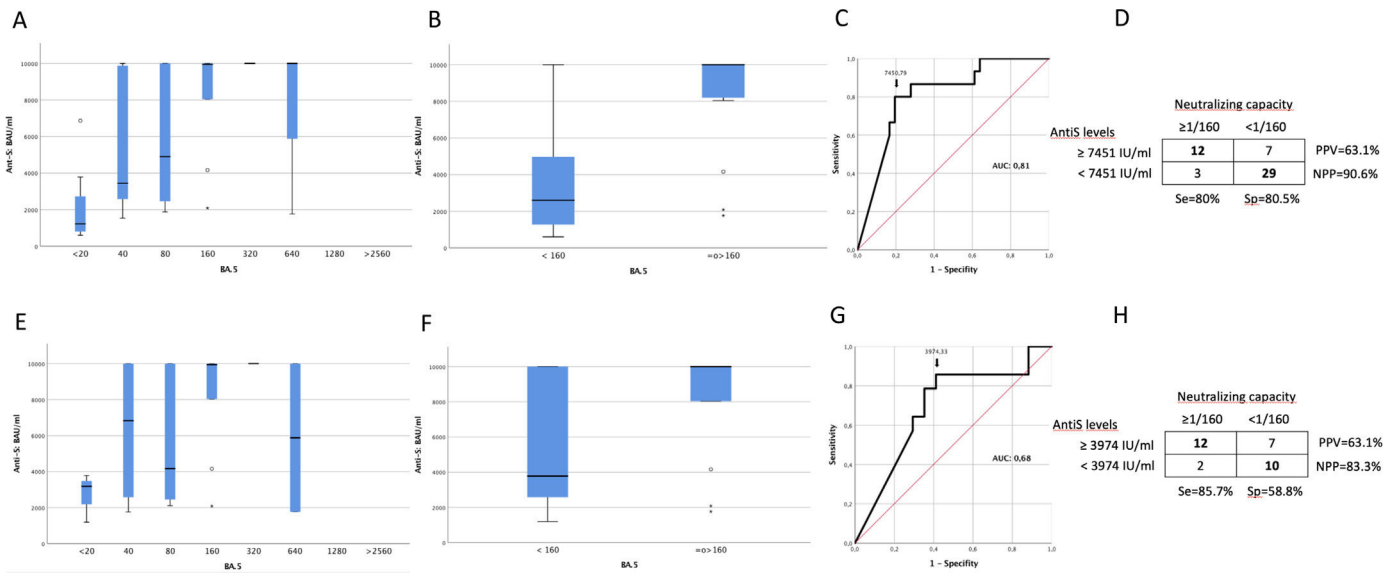


**Fig. 5.** Correlation between neutralizing titers (<1/20 to >1/2560) against BA.5 SARS-CoV-2 and Anti-S levels (BAU/ml) (A, E); anti-S values from samples with neutralizing activity ≥ 1/160 versus <1/160 (B, F) and ROC curves (C, G) with positive predictive value (PPV), negative predictive value (NPV), sensitivity (Se) and Specificity (Sp) of proposed cut-offs (D, H). A–D graphs analyzed 51 anti-S positive samples; E–H graphs analyzed 31 anti-S and anti-N positive samples. In A, B, E and F, the boxplots indicate the IQR and the whisker length is limited to 1.5 times the IQR. Medians are indicated as horizontal lines within the boxes.

## Discussion

COVID-19 continues being an important threat for immunocompromised patients during Omicron era. In fact, in an enormous observational population-based study in UK, immunocompromised individuals accounted for 3.9% of the study population but motivated 22%, 28% and 24% of COVID-19 hospitalizations, ICU admissions and deaths in 2022, respectively.[33] This is quite relevant, as around 3% of U.S. population can be considered immunocompromised.[34] Treatment of COVID-19 in these patients relies on three pillars: double antiviral therapy,[15] reduction of immunosuppressive drugs whenever possible (as transplant patients),[25] and restitution of the humoral immune deficiency when needed.[35] Humoral immune status of the patient can be evaluated determining lymphocyte subpopulations, immunoglobulin levels and anti-S SARS-CoV-2 levels.

Passive immunotherapy containing neutralizing antibodies can be afforded by CCP, monoclonal antibodies or hyperimmune anti-SARS-CoV-2 intravenous immunoglobulins (HIVIG).[35] CCP elaboration requires a donor recently exposed to SARS-CoV-2, better if subsequently vaccinated (vax-plasma), with high neutralizing antibody titers, and not delaying the period between obtention and administration of the plasma to the immunocompromised patient to cover circulating VOCs.[36] It has been shown that Pre-Omicron CCP does not neutralize Omicron VOCs,[6] nor CCP obtained during BA.1 era neutralizes recently circulating VOCs.[7] Although recommended in multiple guidelines in this scenario,[23,37] there are real problems for obtaining recently elaborated CCP in many countries, particularly in Europe.[38,39] We are skeptical about elaboration of new CCP in the future. Regarding monoclonal antibodies, no one are recommended currently by FDA against COVID-19,[9] with the exception of pemivibart for immunocompromised patients, though not approved for treatment.[10] HIVIG are manufactured by fractionation of pooled plasma units and contain IgG at a 10-fold higher concentration than in CCP. The final product is sterile-filtered IgG (>95%) and formulated at 100 mg/ml. HIVIG have notable advantages over CCP, including standardization of dose, pathogen reduction, and measurements of anti-SARS-CoV-2 neutralizing titers prior to release.[40] However, there are logistical challenges to HIVIG production, and several months are required between initiation of CCP collection and distribution of lots.[32] HIVIG manufacturing is expensive,[32] and it is required commitment to elaborate it by the different regulatory Agencies. So HIVIG is not easily accessible.

Today, there is easy access to two products that could reverse humoral immunodeficiency in patients with COVID-19: Commercially available Nonspecific intravenous immunoglobulins (NIVIG) and Fresh frozen plasma (FFP). NIVIG have antibodies against SARS-CoV-2, as more than 96% of U.S. population has been vaccinated or exposed to SARS-CoV-2.[41] NIVIG contain neutralizing anti-SARS-CoV-2 antibodies useful for those patients with failure of humoral immunity.[42] Some commercial products have demonstrated efficacy neutralizing Omicron variants,[43] some others have not.[44,45] More recent Ig products (expiration dates: 2023–2025) contain significantly higher binding and inhibition activities against SARS-CoV-2 proteins, as compared to earlier, or pre-pandemic products.[46] Recently, successful experiences have been published using NIVIG at a median dose of 60 g[47] or 1 g/kg of weight[48] for immunocompromised patients. NIVIG production is expensive and access is restricted because shortage due to a clear imbalance between demand and supply of them.[49] In the future, anti-S levels in NIVIG could diminish, as mild COVID-19 induces less humoral immunity,[50] and less young donors perceive a need to get a seasonal COVID-19 vaccination.

FFP has been suggested as a possible equivalent to CCP, as most population has been exposed to and is vaccinated for SARS-CoV-2. In a report from Italy, more than 80% of random donors qualified according to the FDA criteria for high-titer CCP (>4350 AU/ml).[51]

This moved us to analyze the real neutralizing activity of 52 consecutive plasma donations, being unaware of COVID-19 immune status of donors. Though near all donors had antibodies against SARS-CoV-2 Spike, those exposed naturally to SARS-CoV-2 (i.e., anti-N positive), vaccinated or not, had higher titers of anti-S than vaccinees. And the probability of neutralizing the different VOCs of SARS-CoV-2 at dilutions ≥ 1/160 was higher for plasma from anti-N positive donors too. This points to a better immune response after natural infection ± vaccination than after vaccination against SARS-CoV-2 alone. ROC curves offered anti-S level thresholds with a very good PPV selecting plasma with a neutralizing activity ≥ 1/160 against recently circulating VOCs. While focusing on anti-N posi-

tive plasma improved slightly PPV for neutralizing Delta and BA.2 SARS-CoV-2 (8 and 3%, respectively), this benefit was small and did not happen with BA.5, the irrupting VOC then. Moreover, it implies testing donors plasma for anti-N too, increasing the cost of characterization of FFP as immune. In fact, the AUC in the ROC curve was lower for the given thresholds using anti-S values from anti-N positive samples than using anti-S values alone. So we think there is no need for determining anti-N in donors plasma. For every VOC of SARS-CoV-2 analyzed, a high anti-S value was the main predictor of neutralizing activity of plasma. Not surprisingly, the older the VOC, the lower the threshold of anti-S predictive of neutralizing activity. This can be explained by a higher probability for donors, during period when samples were collected, of having been exposed to Delta VOC previously and/or to an mRNA vaccine developed from Wuhan virus, closely related to Delta VOC. From our data, plasma from donors with anti-S levels over 5952 BAU/ml have a high probability for neutralizing efficiently Delta and BA.2 VOCs, prevalent at that moment. In respect to irrupting BA.5 SARS-CoV-2, a threshold of 7451 BAU/ml had a PPV of 63% for selecting plasma with a neutralizing activity ≥ 1/160. We think that this PPV can be improved selecting a threshold over the upper range (>10,000 BAU/ml in our laboratory) and inactivating the donated plasma. If FFP is not used briefly after the date of donation and is subjected to quarantine, being used 6 months later with other different circulating VOCs, efficacy can be lower.

These results are in line with those obtained by others, and differences can rely on the ELISA used for determining anti-S levels, with different ranges and top values; and the use of neutralizing, pseudoneutralizing o surrogate neutralizing viral tests. Most consider neutralizing titers those ≥1/160, others higher ones. Percentage of neutralization obtained by plasma, i.e. 30,% 70% or 100%, varies too. Diverse series in the literature report high neutralizing activity for anti-S values over 454,[52] 850,[53] 1357,[54] 2300,[55] 4000,[56] 5547,[57] 6278,[58] 6749[59] and 7000[6] BAU/ml. Samples were tested using Architect SARS-CoV-2 IgG II Quant (Abbott, IL, USA),[52,53,58] SARS-CoV-2 Ig G Euroimmun Quantivac (Germany),[6,54,57,59] SARS-CoV-2 IgG Elecsys Roche (Basel, Switzerland),[55] or VITROS SARS-CoV-2 quantitative S IgG and total N Ig assays (QuidelOrtho, San Diego, CA, USA).[56] All thresholds indicated were under the upper limit of quantification of every provider.

Some clinical issues can help to predict FFP with the highest anti-S values, as male sex,[53] older age,[53,60,61] higher body mass index,[53,60] previous COVID-19 and number of vaccinations,[62,63] severity of symptoms after vaccination,[64] shorter interval from disease to donation,[60,61] high-grade fever and more severe symptoms.[53,60,61,63,65] However, addition of these clinical aspects to anti-S levels measurement did not improve the accuracy predicting neutralizing activity for SARS-CoV-2 in comparison with determination of anti-S alone.[53]

We propose that SARS-CoV-2 anti-S IgG be determined in each plasma unit obtained from every blood donation, simultaneously to hepatitis B, hepatitis C, syphilis and HIV testing. As not all FFP is neutralizing against circulating SARS-CoV-2, reporting those units with anti-S levels above the upper limit of quantification as immune plasma against SARS-CoV-2 would be a gigantic step for immunocompromised patients with COVID-19. It could be done with the ELISA test chosen by every center. It is simple. Immune plasma units could be qualified as such and served as required. Minimizing the interval between donation and use of immune plasma would improve neutralizing capacity against the VOC circulating at every moment. This strategy is easy and the cost is SARS-CoV-2 anti-S IgG testing alone. It is more efficacious and cheaper than NIVIG, and it lets using NIVIG for other indications. We only require the approval from national regulatory agencies and Blood Banks with instructions for systematic SARS-CoV-2 IgG testing and reporting those units with levels above the upper limit of quantification as immune plasma. Immunocompromised patients with COVID-19 cannot be again left behind!.[66]

## Conflict of interest

The authors declare that they have no conflict of interest.

## Acknowledgement

To the nurses, permanently implied with the patients.

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