ORIGINAL ARTICLE

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# Qualifying coronavirus disease 2019 convalescent plasma donors in Israel

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## Abstract

**Background and Objectives:** Passive immunization using investigational COVID-19 convalescent plasma (CCP) is a promising therapeutic strategy and could improve outcome if transfused early and contain high levels of anti-SARS-CoV-2 antibodies. We report the management of a national CCP collection and distribution program in Israel.

**Materials and Methods:** From 1 April 2020 to 15 January 2021, 4020 volunteer donors donated 5221 CCP units and 837 (20.8%) donors donated more than once. Anti-nucleocapsid IgG antibodies were determined using chemiluminescent immuno-assay method (Abbott). A statistical model based on repeated IgG tests in sequential donations was created to predict the time of antibody decline below sample/cut-off (S/CO) level of 4.0.

**Results:** Ninety-six percent of CCP donors suffered a mild disease or were asymptomatic. Older donors had higher antibody levels. Higher antibody levels (S/CO ≥4) were detected in 35.2% of the donors. Low positive (S/CO ≥1.4–3.99) were found in 37%, and 27.8% had undetectable antibodies (S/CO ≤1.4). The model predicted decrease antibody thresholds of 0.55%/day since the first CCP donation, providing guidance for the effective timing of future collections from donors with high antibody levels.

**Conclusions:** An efficient CCP collection and distribution program was achieved, based on performing initial and repeated plasma collections, preferably from donors with higher antibody levels, and only antibody-rich units were supplied for therapeutic use. The inventory met the quantity and quality standards of the authorities, enabled to respond to the growing demand of the medical system and provide a product that may contribute to improve prognosis in patients with COVID-19.

**KEYWORDS**
antibodies, convalescent plasma, donors

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2), is one of the biggest global health threats of the last century.

At the time of this writing, a year into the pandemic, specific treatment remains elusive [1]. Although the available vaccines may become a principal game changer in the prevention of new infection, passive immunization by transfusion of COVID-19 convalescent plasma (CCP) is still used widely. This strategy is based on century-old reports that describe the efficacy of treating patients during the 1918 influenza A pandemic by transfusions of CCP [2–4] and from small reports, showing encouraging clinical benefit of CCP in patients with severe COVID-19 [5–7].

Based on these reports, the Israeli Ministry of Health (MOH) requested Magen David Adom National Blood Services in Israel (MDANBS) to establish an investigational CCP program as a part of a national COVID-19 treatment protocol.

As of today, data accumulated worldwide suggest that transfusion of CCP is safe and effective [8, 9]. Recent data from matched controlled studies [10, 11], from randomized clinical trial [12] and from retrospective analysis [13] showed benefit of CCP in patients treated early with CCP containing high-titre antibodies (Ab), while others did not show decrease in mortality [14, 15]. Based on these data, U.S. Food and Drug Administration (FDA) issued on 4 February 2021 a revision of the Emergency Use Authorization (EUA) for CCP and limited the authorization to the use of high-titre CCP only [16]. Several trials are ongoing, investigating clinical benefit of CCP [17] and standardization of serological and neutralization assays [18].

In Israel, transfusing CCP is currently an integral component of the early treatment of COVID-19, as a part of a national investigational program. All aspects of CCP collection, processing, testing and distribution to hospitals nationwide are centrally performed by Magen David Adom National Blood Services (MDANBS), to assure standardization, quality and impartiality. The treatment protocol was based on transfusion of two CCP units (200 ml each) 24 h apart, to patients approved by the MOH research committee. The results of treating the first group of COVID-19 patients have been previously reported [19], and the correlation of clinical benefit with higher anti-SARS-CoV-2 Ab in transfused CCP was shown.

A key question for every CCP collection and distribution centre is how to select the right plasma donors. In this article, we report our experience accumulated since 1 April 2020, in recruiting CCP donors and in inventory management, as our aim is to qualify and supply for transfusion CCP units with highest anti-SARS-CoV-2 antibody levels.

## MATERIALS AND METHODS

### Donor population

The Ethics Committee of the MOH approved an Institutional Review Board (IRB) protocol to recruit individuals who recovered from COVID-19 as potential CCP donors and conduct laboratory tests to qualify and supply CCP units for treatment. CCP collections were initiated on 1 April 2020, according to the first FDA protocol [20], with local modification to comply with the MOH regulations and the IRB protocol [21], similar to programs established simultaneously around the world [22].

Potential CCP donors required evidence of COVID-19 by molecular tests and two consecutive negative test results after symptomatic recovery, thereafter 14-day deferral needed before plasma collection.

Recovered COVID-19 patients were referred to the MDANBS by various sources, including MOH's database, the Israeli Defense Forces, cohorts in closed ethnic communities and social media. Donors gave their consent for transfer of personal data to MDANBS.

All CCP donors were non-remunerated volunteers whose health histories complied with MOH and MDANBS criteria for blood donations. Only males or nulliparous females were recruited to mitigate the risk of transfusion-associated acute lung injury (TRALI). A Donor Recruitment Call Center was established and operated by trained MDANBS personnel, who conducted telephone interviews with potential donors to assure compliance with requirements. Pre-donation screening included evaluation of potential donors' records in the MDANBS computer database (Progesa, MAK-system) to identify prior disqualifying deferral.

### Plasma collection

CCP collections were initially performed at the main MDANBS plasmapheresis donation centre that routinely performs apheresis plasma collections and had been involved in similar projects previously [23]. To respond to the rapidly growing demands for CCP, four additional donation sites were opened, additional mobile apheresis equipment (MCS+, Haemonetics, Covina, CA) was purchased and extra apheresis operators were trained.

In addition to the standard MDANBS Donor Health Questionnaire, every donor signed an informed consent for the CCP collection.

Apheresis collections of 600 ml of CCP were obtained, divided into three 200-ml units, frozen at $-30^\circ$C within 22 h and labelled as Apheresis Convalescent Plasma according to ISBT-128 standards (ISBT code E9743). As anti-SARS-CoV-2Ab testing was not available during the first 2 weeks of CCP collections, we saved archive samples for further studies.

### Donors' testing

Blood samples from each donation were tested according to MOH and MDANBS standards and the IRB protocol, including ABO/Rh, *Treponema pallidum* haemagglutinin assay (PK7300 Beckman Coulter, Brea, CA), red blood cells (RBC) antibody screening (Erytra, Grifols, Spain), serological tests for human immunodeficiency virus I/II (HIV-I/II), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus I/II (HTLV-I/II) (Alinity S, Abbott, Green Oaks, IL) and individual donor nucleic acid testing (ID-NAT) for HIV-I/II, HCV, HBV and West Nile virus (WNV) (Panther, Grifols, Spain).
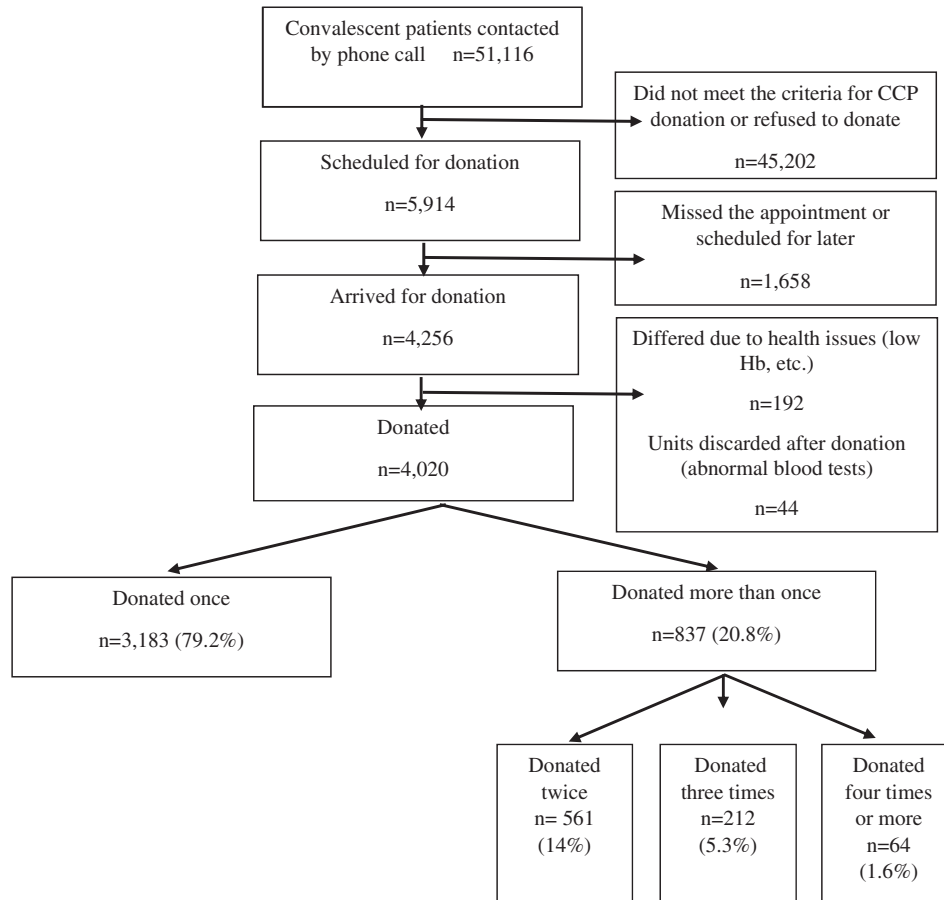
**FIGURE 1** Recruitment of convalescent plasma donors (1 April–15 January, 2021). CCP, COVID-19 convalescent plasma;Hb, haemoglobin

## Anti-SARS-CoV-2 antibodies

Commercially available assays for anti-SARS-CoV-2 Ab differ by the Ab subclass (IgM, IgA, IgG or total antibody), the targeted antigen (subunit 1[S1] of the spike protein, nucleocapsid protein [N] or the receptor-binding domain [RBD]) and by assay method, that is, lateral flow assay (LFA) [24, 25], neutralizing Ab assay (nAb) [26, 27], enzyme-linked immunosorbent assay (ELISA) [28] and chemiluminescent immunoassay (CLIA) [29, 30]. For this project, we used multiple laboratory methods to test the presence of different anti-SARS-CoV-2 Ab.

1. Anti-S (S1 subunit) SARS-CoV-2 Ab
   Serum samples were tested for anti-S IgG and IgA, using ELISA (EUROIMMUN AG, Germany), performed in the Research Laboratories of the School of Public Health, Tel Aviv University during the first month of the project (April, 2020). A positive result was defined as a sample to calibrator absorbance (S/CO) ratio ≥ 1.1 [28].
2. Anti-N (nucleocapsid protein) SARS-CoV-2 Ab
   Starting 1 May 2020, all CCP collections were tested for anti-N by CLIA, performed on the Architect i2000 SR (Abbott, Green Oaks, IL) automated immunoassay analyser [29]. Testing also included samples retained from the first month's apheresis collections.

Positive result was defined as S/CO≥1.4 [29, 30]. Having accumulated a sufficient CCP inventory (since 1 October 2020), we qualified for transfusion CCP units by S/CO: one unit had an Ab level of S/CO ≥7.0 and another– S/CO ≥4.0, thus an average S/CO≥4.5 was provided, in line with the later decision of FDA, issued on 4 February 2021 [16].

3. Viral neutralization assay
   As initial reports indicated a positive correlation between anti-S and anti-N IgG values and nAb activity [22, 26], we compared our results of anti-S by ELISA (EUROIMMUN) and anti-S by CLIA (Abbott) with results of neutralization studies for the first 53 CCP units. The Israeli Institute for Biological Research team performed the test, using a modified plaque reduction neutralization test (PRNT) with Vero E6 cells (ATCC® CRL-1586™), as described previously [19].
4. Pre-donation anti-S SARS-CoV-2 rapid point of care (POC) assay
   We evaluated anti-S BELTEST-IT COV-2 Rapid Test (PharmAct AG, Germany) LFA [31], as a part of the pre-donation screening on a capillary blood sample, to avoid collections of plasma from donors with undetectable Ab. Results were obtained within 15 min. Only potential donors with positive IgG by POC results proceeded to the apheresis collection. Venous blood samples were obtained as well for all potential donors (including first and subsequent donations) and tested for anti-N by CLIA.
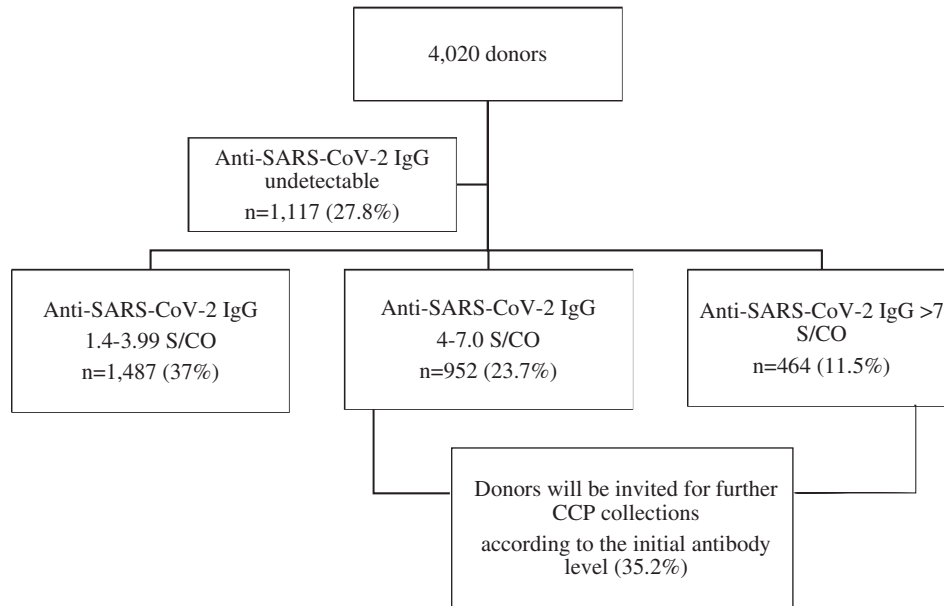
**FIGURE 2** Identification of convalescent plasma donors suitable for further donations, based on anti-nucleocapsid antibody IgG results. CCP, COVID-19 convalescent plasma;S/CO, sample/cutoff
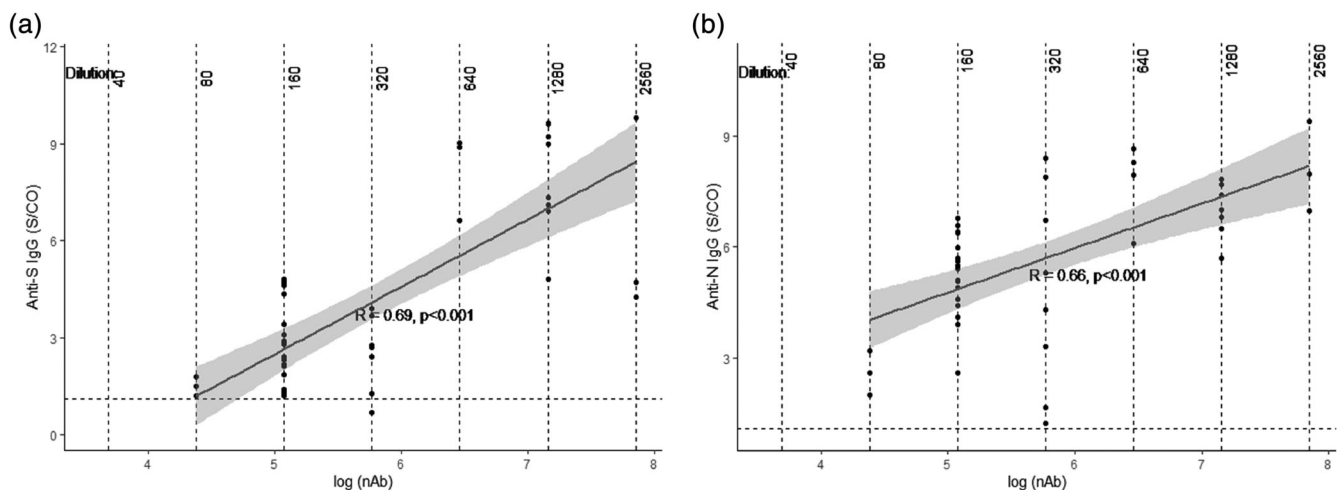


**FIGURE 3** Correlation between neutralizing antibody (nAb) activity (*x*-axis) and two serological assays (*y*-axis): (a) anti-S, EUROIMMUN and (b) anti-nucleocapsid (anti-N), CLIA; Abbott. Vertical dotted lines represent the cutoff for nAb positivity at the indicated titre. The dashed horizontal lines represent the cutoff for serological assays positivity. *R* is calculated by Spearman correlation test

## Statistical analysis

Descriptive statistics are presented as mean $\pm$ SD for continuous variables and compared using independent *t*-test or Mann–Whitney test. Categorical variables presented as number of observations and percentage and compared using Pearson $\chi$2 test. To assess correlations between Ab levels measured by EUROIMMUN and CLIA tests, we used Spearman's correlation test.

A statistical prediction model of decline of anti-N Ab in subsequent CCP donations was created by generalized linear mixed models (GLMM) with a random intercept for each participant. GLMM was used to account for clustering with link function fitted to distributions.

The last detectable Ab is the dependent variable, a function of: (1) time between first donation to subsequent donation and (2) initial antibody level. Data were analysed using R software (Version 3.5.1).

## RESULTS

### Donors' demographics and eligibility

From 1 April 2020, until 15 January 2021, the CCP Call Center performed 51,116 telephone interviews (217/day), resulting in 5914 (11.6%) scheduled appointments. Most of the donors referred were
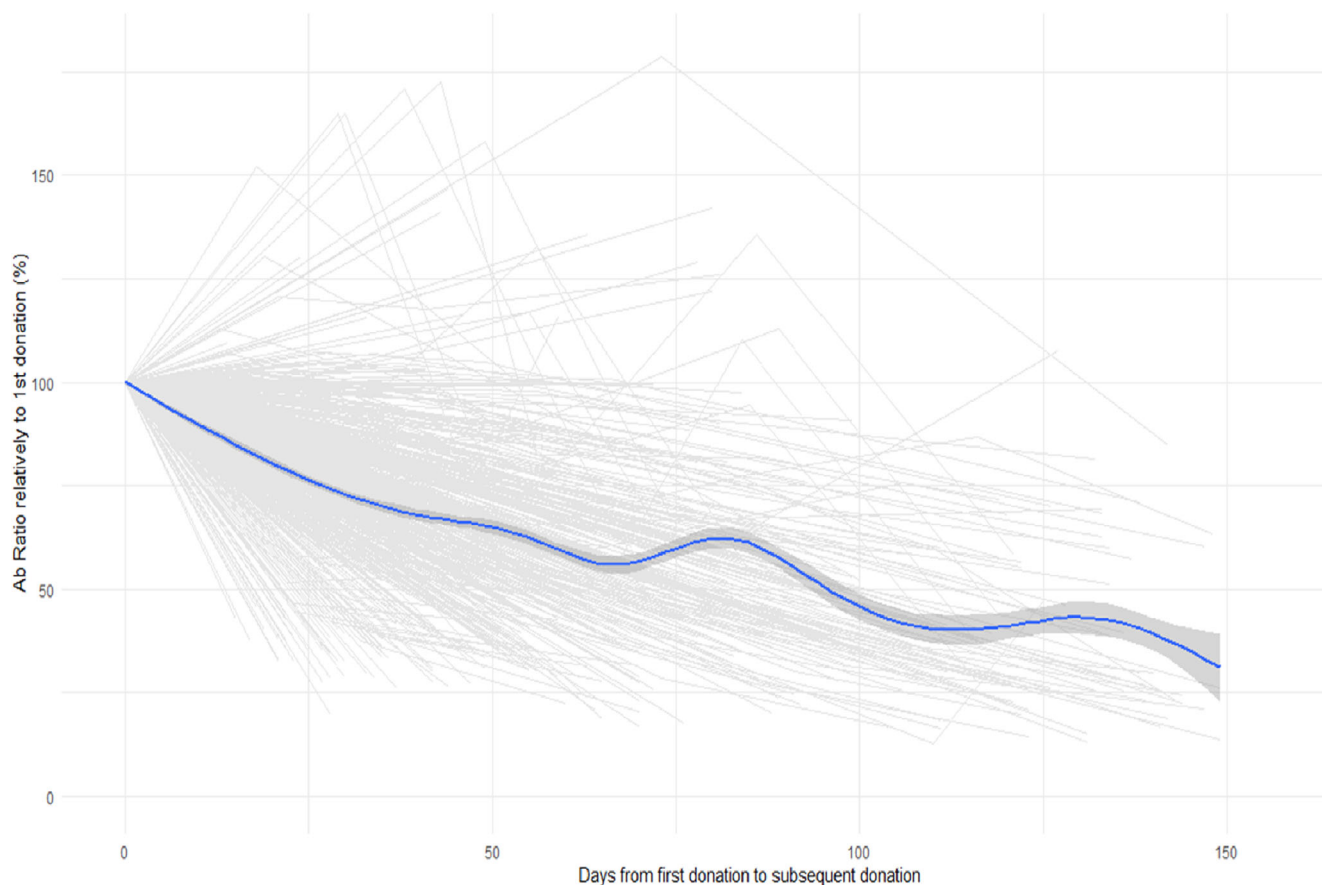
**FIGURE 4** Gradual decrease of anti-nucleocapsid (anti-N) antibody levels (%) in convalescent plasma donors through 150 days since first donation. Anti-N anti-SARS-CoV-2 IgG antibodies detected by chemiluminescent microparticle immunoassay (CLIA; Abbott, Green Oaks, IL). Donors with sample/cut-off ratio (S/CO ≥1.4) were analysed. Ab level in the first donation for each donor was defined as 100% and, in subsequent donations, was calculated (%) relative to his/her first donation. Light grey lines represent donors' anti-N levels (in %) through subsequent donations; trend-line represents the mixed model regression analysis using R software. Ab, antibodies

ineligible for donation due to health reasons or unwilling to donate plasma. Only 72% (4256/5914) of the scheduled donors arrived to the Apheresis collection centres, of whom 4064 donated CCP and 192 (4.5%) were further deferred on site due to health reasons (i.e., low haemoglobin, abnormal blood pressure or other health conditions). The percentage of deferrals on site for CCP donors was lower than for regular blood donors: 11.3% blood donors deferred in 2019 and 10.5% in 2020 due to health reasons. Disqualifying laboratory test results for transfusion-transmitted diseases, abnormal blood count or presence of clinically significant Ab to blood group antigens were found in blood samples of 1.08% CCP donors (44/4064), comparing to 0.53% among blood donors in 2019 and 0.58% in 2020. Final analyses were performed on 4020 CCP donors (Table S1, Figure 1), their mean age was $32.6 \pm 12.9$ years and 736/4020 (18%) were female and 36% were first-time donors. About 96% of the CCP donors (3859/4020) were asymptomatic or had a mild COVID-19; 161/4020 (4%) had moderate disease. Analysis of the first 726 CCP donors' self-reports revealed that the mean time from the onset of symptoms to the first CCP collection was $45.6 \pm 14.5$ days.

## Anti-SARS-CoV-2 antibodies

First 230 CCP collections were tested by EUROIMMUN. Anti-S1 IgG Ab were undetectable in 17% (39/230). As the results of the test were not available at the time of CCP release, 19 of these CCP units were transfused. Two-weeks' follow-up was available for 15 patients that received at least one unit of CCP with undetectable anti-S1 IgGAb levels, and as discussed previously [19], the lower mean antibody level in transfused plasma was a predictor of worse outcome in the group of 49 patients analysed in the study [19].

All 5221 donations from the 4020 donors were tested for anti-N by CLIA; 1117/4020 (27.8%) had an anti-N S/CO <1.4 (negative); 1487/4020 (37.0%) had S/CO of 1.4–3.99 (low positive); 952/4020 (23.7%) had S/CO 4.0–7.0 (positive) and 464/4020 (11.5%) had S/CO >7.0 (high positive) (Figure2). Antibody levels were higher in older donors:96 individuals older than 60 years had a mean $\pm$ SD S/CO of $5.74 \pm 2.65$, while the youngest 506 donors (age 17–20 years) had a mean $\pm$ SD S/CO of $3.74 \pm 1.79$ ($p < 0.001$) (Table S2). In stratification to age strata, there was no difference in antibody levels between genders.

Results of 199 rapid point-of-care test (POC) were compared to the anti-N results: 171/199 (85.9%) showed concordant results, with 143 positive and 28 negative by both assays. Disagreement of POC with anti-N CLIA was observed in 28/199 samples. Of them, 27/199 were positive by the POC assay and negative by the anti-N assay and 1/199 negative by the POC assay and positive by the anti-N assay. The positive predictive value (PPV) for POC was 0.84 and the negative predictive value (NPV) was 0.97, with sensitivity of 99.3% and specificity of 50.9%. Comparison of anti-S by EUROIMMUN and anti-N by CLIA was performed on 139 samples; PPV of EUROIMMUN was 0.96 and NPV was 0.63 (sensitivity of 92.4% and specificity of 79.2%).

NAb activity was determined in 53 CCP units from 29 donors, as described previously [19]. The median nAb titre was 1:160 (interquartile range [IQR] 1:160–1:640, range 1:20–1:2560). NAb titre was <1:160 in eight CCP units (15.1%) and ≥ 1:160 in 84.9%. Taken as a continuous variable, the IgG anti-S by EUROIMMUN yielded positive correlation $r = 0.69$ ($p < 0.001$) with nAb after logarithmic transformation of both variables. IgG anti-N by CLIA showed a positive correlation of $r = 0.66$ ($p < 0.001$) with nAb, both by Spearman's rank correlation (Figure 3).

## Gradual decrease of antibody level over time

Of 4020 apheresis donors, 837 (20.8%) had more than one CCP collection; 561 donated twice, 212 donated three times, 44 donated four times, 16 donated five donations and 4 had six donations (Table S1). As we aimed to deliver only antibody-rich CCP to COVID-19 patients, only donors with initial anti-N IgG level of S/CO ≥ 4.0 were invited for subsequent donations, and two CCP units were delivered to patients: one unit with IgG S/CO ≥ 7.0 and one with S/CO ≥ 4.0, providing an average S/CO ≥ 4.5.

The timeframe of Ab decrease was predicted by statistical model as 0.55%/day (Table S3, Figure 4) and could be calculated relatively to the level at the first collection, for example, if initial S/CO was 10.0, the decrease to S/CO of 4.0 will take 92.65 days (Table S4).

## Blood groups in CCP donors

The prevalence of ABO/Rh blood groups in CCP donors was similar to that of blood donors in the general Israeli population, according to the MDANBS database from 2019. Higher prevalence of blood group A and a lower prevalence of group O among COVID-19 patients reported previously [32, 33] was not seen in CCP donors in Israel; however, higher percentage of AB group in convalescents (9%) comparing to blood donors (8%) was statistically significant ($p = 0.002$).

## DISCUSSION

This report describes the steps taken to rapidly establish a program for the recruitment of volunteer CCP donors, qualifying their plasma by a multi-assay laboratory protocol and supplying it to COVID-19 patients in Israel. Over 2300 COVID-19 patients treated until 15 January 2021, as a part of an investigational, multi-institutional national program.

Patients recovered from COVID-19 were referred by the MOH or responded to calls in the social media to become CCP donors. To facilitate recruitment of eligible individuals, personnel of CCP Call Center conducted health-screening interviews. Although only 11.6% of the calls yielded appointments, of which 72% of the donors showed up, remarkable low percentage of donors (4.5%) were deferred on site, compared to a deferral rate of 11% in our regular blood drives. The low percentage of deferrals on site was probably a result of pre-donation telephone interviews with potential donors to assure compliance with requirements, the tactics that were not accepted for regular blood donations. The relatively high percentage of CCP units discarded due to abnormal blood tests (1.08% for CCP vs. 0.42% for blood donations) could be a result of high percentage of first-time donors among CCP donors comparing to regular blood donors (36% vs. 20%, respectively).

Almost all our CCP donors were asymptomatic or had mild COVID-19 disease, as most of potential donors with moderate or severe disease were not qualified for CCP collection, usually due to persistent symptoms. The addition of pre-donation screening method enabled to collect CCP only from donors who showed the presence of antibodies, thus, saving time and resources of both the donors and the blood services.

Based on published data on efficacy of antibody-rich CCP and according to recently approved FDA policy [16], we used a statistical prediction model to optimize our CCP inventory of units with higher IgG antibody levels. Since the model predicted that anti-N Ab decreased at 0.55%/day from the time of the first donation (Tables S3 and S4 and Figure 4), only donors with higher antibody levels were rescheduled for further plasma donations, keeping short periods between collections (2 weeks). All donated units were retested for anti-N antibodies in subsequent donations.

Our study has few limitations. One is the fact that 88.4% of individuals who were referred to the MDANBS were found to be non-eligible due to health issues, parity in women or refused to donate. Consistently low compliance rate of COVID-19 convalescents to donate plasma was recently described by our colleagues [34]. We need to further study this phenomenon. Secondly, we used anti-N Ab as a surrogate marker of anti-viral neutralizing activity; however, follow-up of repeated nAb or anti-S IgG was not available during the study period. Thirdly, no anti-N IgGAb were found in high proportion of our CCP donors, in agreement with published data on lower Ab levels anticipated in cohort of asymptomatic individuals [35] and in patients with mild symptoms [36, 37], with rapid decline of anti-N and nAb [38]. Anti-S antibodies were undetectable in 17% of our donors by EUROIMMUN test and in 14% by the rapid POC lateral flow test. We are awaiting for follow-up results of nAb tests in a larger group of CCP donors that will be performed by the Israeli Institute for Biological Research; they will be helpful to understand better the relationship between anti-N and nAb.

Another limitation was unknown period between recovery and donation in many donors. It is clear that early CCP donation soon after recovery is associated with higher antibody levels, but unfortunately, the donors' information provided from the sites to MDABS was uneven and sometimes incomplete.

Currently, all expectations are concentrated on the results of vaccination programs. Although over 3 million individuals were already vaccinated in Israel by the Pfizer-BioNTech vaccine [39], urgent requests for CCP units for new COVID-19 patients are being added daily. Gaps in knowledge still exist for the timeframe for SARS-CoV-2 antibody formation and decline, the relationship between antibody levels and the severity of COVID-19 disease and the protective effect of antibodies against re-infection with the SARS-CoV-2 wild type or variants [40, 41].

In this ongoing project, we focussed on rapid creation of sufficient CCP inventory, by collection of CCP with higher antibody levels, as we believe that a better outcome for COVID-19 patients can be achieved by providing CCP transfusion early during the course of the disease. This challenging task was achievable and maybe less complicated in Israel, where the country's blood collection processing and supply is concentrated in a centralized Blood Services Establishment. Building a CCP inventory was achieved by being part of an integral, multi-disciplinary program involving community stakeholders (hospitals), governmental regulators (MOH) and research laboratories, all supporting the national program for donor recruitment and laboratory qualification of CCP. We encourage additional programs to share their experiences to support a timely determination of best practices for CCP programs during the current pandemic.

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## CONFLICT OF INTEREST

No conflict of interest to disclose.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.