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Transfusion and Apheresis Science 61 (2022) 103302

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

The demographic and serological characteristics of COVID-19 convalescent plasma donors: Identification of basic criteria for optimal donor selection

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ARTICLE INFO

Keywords:
COVID-19 serotherapy
SARS-CoV-2
Serologic tests
Donor selection

ABSTRACT

Background and Objectives: Convalescent plasma has attracted significant attention as a therapeutic option against infectious agents for more than a century. In March 2020, the use of Convalescent COVID-19 plasma (CCP) as a new research drug for COVID-19 treatment was approved by the FDA. The development of SARS-CoV-2 IgG antibodies following infection or vaccination is likely to be essential to provide adequate immunity for the population to halt the COVID19 pandemic. This study aimed to identify the criteria that would be used to determine the most appropriate CCP donors with the highest effective antiviral antibody titers.

Materials and Methods: In this prospective cohort, univariate analyses and multivariate regression analyses were performed to evaluate the relationship between characteristics of 11949 CCP donors and COVID-19 disease severity prior to donation with antibody titers estimated using ELISA technique and rapid tests.

Results: The antibody titer was measured among 8206 (68.7 %) donors. Elderly male and nulliparous female CCP donors who resided in the areas with high load of virus had positive ELISA and rapid test results as well as high levels of SARS-CoV-2 IgG antibodies titer. Moreover, the long hospital stay and elderly donors were the variables associated with high levels of SARS-CoV-2 IgG antibodies.

Conclusion: This study suggests that nulliparous female and male donors with positive rapid tests who resided in areas with a higher prevalence of SARS-CoV-2, with more than 40 years of age and long hospitalization time can be the preferred donors for CCP donation.

1. Introduction

The most recent formidable threat to the global health is the proceeding outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the responsible virus for coronavirus disease-19 (COVID-19), which became epidemic in mid-December 2019 in Wuhan, China. Three months later than the emergence of COVID-19, the Director General of the World Health Organization, declared the COVID-19 a global pandemic [1]. At the time of writing, COVID-19 pandemic is the gravest current challenge worldwide with approximately 230 million infected patients and over than 4.7 million deaths as of September 26, 2021. By this time, more than 5.4 million people were infected in Iran, and 118,191 people have died. Nowadays, COVID-19 has limited therapeutic options which have mainly been empirical and experimental. There are no specific acknowledged antiviral agents targeting SARS-CoV-2 [2]. Vaccination is the best approach to control rampant epidemic and its destructive effects on global economy and public health [3]. Despite the unprecedented and extensive efforts currently being made to manufacture and distribute enough safe and effective COVID-19 vaccine worldwide, it seems time-consuming to establish active immunity to the SARS-CoV-2 virus in every individual around the world successfully. Therefore, the use of effective therapies to treat severe cases of the disease to reduce mortality rate until equitable global access to the eventual COVID-19 vaccines is achieved, is of

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https://doi.org/10.1016/j.transci.2021.103302
Received 2 June 2021; Received in revised form 23 October 2021; Accepted 26 October 2021
Available online 29 October 2021

Table 1
Interpretation of serologic test.

	IgG	IgM	Donation status
1	Positive	Positive	*Therapeutic use
2	Positive	Negative	* Therapeutic use
3	Negative	Negative	Nontherapeutic use
4	Negative	Positive	28-day deferral (donor can apply for donation 28 days later)

* Related to male and nulliparous female donors.

substantial importance. Equipping the body with passive immunity through the transfusion of convalescent plasma donated by patients who have recovered from an infection would be effective at least in early stages of outbreaks of such emerging viral pathogens as SARS-CoV-2, for which therapeutic options are limited [4]. Based on the promising results obtained from treating other viral diseases such as influenza, Ebola, SARS, and Middle East respiratory syndrome (MERS), it has been approved that convalescent plasma can also treat COVID-19 [5–7]. Humoral immune response by targeting the immunodominant SARS-CoV-2 Spike (S) protein seems to be highly correlated with virus neutralization through hampering the interaction between S protein and the virus receptor, angiotensin converting enzyme 2 (AEC2) [8]. It has been shown that transfusion of COVID-19 convalescent plasma containing these neutralizing antibodies (nAbs) to patients affected with COVID-19 could effectively reduce viral load in the patients' body [9]. Convalescent plasma therapy will be successful if plasma be donated by recovered people from COVID-19 who have high concentrations of neutralizing antibodies, without the risk of virus transmission via transfusion to the recipient [10]. Hence, identifying factors associated with the production of anti-SARS-CoV-2 antibodies affects the success rate of convalescent plasma therapy [11]. In this regard, this study aimed to find out how SARS-CoV-2 IgG antibodies are influenced by demographic and clinical characteristics of donors such as age, sex, ABO/Rh blood group, disease severity, ethnicity and the place of residence in terms of virus load. This study could provide a roadmap for selecting individuals possibly with high levels of anti-SARS-CoV-2 IgG antibodies as preferred donors for CCP donation.

2. Materials and methods

A prospective cohort study incorporating a total of 11,949 COVID-19 Convalescent Plasma (CCP) donors in the cohort.

2.1. Donors of convalescent plasma

Iranian Blood Transfusion Organization (IBTO) encouraged Iranian general population via public dissemination channels, including traditional or social media, to donate CCP from May to December 2020. CCP donors were identified as allogeneic and they were considered healthy if a physician examined their clinical history and confirmed so at the time of referral. Inclusion criteria for the CCP donation were considered to be:

- Proven prior COVID-19 infection by real-time PCR,
- Elapse of at least 28 days since being fully recovered

The severity of previous COVID-19 disease in CCP donors was determined in the present study.

Mild illness: donors who had a variety of signs and symptoms at the time of prior COVID-19 (including fever, cough, sore throat, lethargy, headache, muscle aches, nausea, vomiting, diarrhea, loss of taste and smell) but without any shortness of breath, dyspnea or abnormal chest imaging.

Moderate illness: donors who showed lower respiratory disease evidence during clinical evaluation or imaging and had more than 94 % oxygen saturation (SpO2) in room air at sea level.

Severe illness: donors with SpO2 < 94 in room air at sea level, the ratio of partial arterial pressure of oxygen to fraction of oxygen-inspired (PaO2 / FiO2) <300 mm Hg, respiratory rate> 30 breaths per minute, or lung infiltrates > 50 %.

All donors expressed their informed consent to donate CCP via plasmapheresis or whole blood donation. Also, they met the standard criteria for plasma donation, including a negative serological result for hepatitis B, C, HIV, HTLV, and syphilis. CCP donors fully recovered and symptom-free for 28 consecutive days could also return to donate just like allogeneic donors. The study was approved by High Institute for Education and Research in Transfusion Medicine: IR.TMI.REC.1399.018. The maximum plasma volume was 500 cc collected from apheresis (source plasma) or 500 cc whole blood (recovered plasma). Plasma was collected by apheresis equipment using MCS+ (HAEMONETICS, USA) and XJC2000 (NIGALE, China). Therapeutic CCP was collected for injection into patients diagnosed with laboratory-confirmed COVID-19 infection as a therapeutic approach. Therapeutic CCPs included source/recovered COVID-19 FFP from all males and nulliparous females with positive rapid test results. However, nontherapeutic CCP units included source/recovered COVID19- FFP from all primi/multiparous women and men/nulliparous women whose IgG

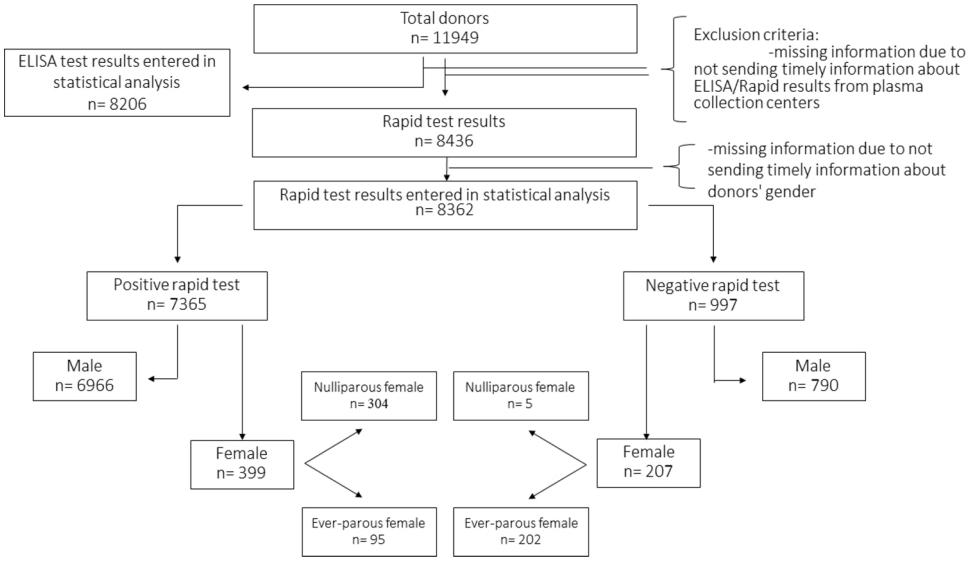


Fig. 1. Flow chart of the study design.

Table 2
Convalescent plasma donor's characteristics.

Independent variable	ELISA IgG positive result (ratio ≥1.1)	ELISA IgG negative result (ratio<0.8)	Total donors	Missing data	P Value
age (years) - median (IQR)	40(14)	39(16)	40(13)	1711 (20.8 %)	P<0.0001
Gender – no. (%)				2030 (24.7 %)	P<0.05
male	5113 (92.7 %)	599 (90.6 %)	5712 (92.5 %)		
female	402 (86.6 %)	62 (13.4 %)	464 (7.5 %)		
The location of donors in terms of the prevalence of SARS-CoV-2- no. (%)				1466 (17.9 %)	P > 0.05
Red	3648 (60.8 %)	429 (58.1 %)	4077 (60.5 %)		
Orange	1497 (24.9 %)	213 (28.9 %)	1710 (25.4 %)		
Yellow	857 (14.3 %)	96 (13.0 %)	953 (14.1 %)		
Donation history- no. (%)				2121 (25.8 %)	P > 0.05
First donation	5062 (93.2 %)	598 (91.9 %)	5660 (93.0 %)		
Return	372 (6.8 %)	53 (8.1 %)	425 (7.0 %)		
Ethnicity- no. (%)				1731 (21.1 %)	P<0.0001
Persians	3521 (61.2 %)	404 (55.7 %)	3925 (60.6 %)		
Azeris	1189 (20.7 %)	182 (25.1 %)	1371 (21.2 %)		
Turkmens	251 (4.4 %)	5 (0.7 %)	256 (4.0 %)		
Gilaks	42 (0.7 %)	15 (2.1 %)	57 (0.9 %)		
Arabs	523 (9.1 %)	101 (13.9 %)	624 (9.6 %)		
Baluchs	224 (3.9 %)	18 (2.5 %)	242 (3.7 %)		
Length of hospitalization (days) - median (IQR)	2.74 – 0 (5)	3.01 – 0(6)	2.47 – 0(5)	7206 (87.8 %)	P > 0.05
Chest CT, positive result- no. (%)	60(11.8 %)	5(9.1 %)	65 (11.5 %)	7633 (93.0 %)	P > 0.05
Blood types – no. (%)				2149 (26.2 %)	P<0.01
A	1837 (33.9 %)	203(31.6 %)	2040 (33.7 %)		
B	1338 (24.7 %)	147(22.9 %)	1485 (24.5 %)		
AB	487(9.0 %)	38(5.9 %)	57(8.7 %)		
O	1753 (32.4 %)	254(39.6 %)	2007 (33.1 %)		
Rh- no. (%)				2149 (26.2 %)	P > 0.05
Positive	4930 (91.0 %)	575(89.6 %)	5505 (90.9 %)		
Negative	485(87.9 %)	67(12.1 %)	552 (9.1 %)		
Donation type- no. (%)				2127 (25.9 %)	NA
Recovered	352(6.5 %)	63(9.6 %)	415 (6.8 %)		
Source	5071 (93.5 %)	593(90.4 %)	5664 (93.2 %)		
Type of CCP- no. (%)				2339 (28.5 %)	P<0.0001
Therapeutic			5140 (87.66 %)		
Nulliparous female with positive rapid test	187 (4.03 %)	28 (5.6 %)	215 (4.18 %)		
Men with positive rapid test	4453 (95.97 %)	472 (94.4 %)	4925 (95.82 %)		
Nontherapeutic			723 (12.34 %)		
ever-parous women/ Nulliparous female with negative rapid test	135 (22.88 %)	24 (18.04 %)	159 (22.0 %)		
Men with negative rapid test	455 (77.12 %)	109 (81.96 %)	564 (78.0 %)		

NA: Not applicable.

rapid test was negative.

The prepared plasma was frozen in less than one hour after donation at a temperature of ≤-30 °C by blast freezer during 8 h. Three tubes were taken from each donor for the screening tests, blood grouping, and antibody titration. Titration tubes were centrifuged; consequently, the prepared serums were stored in the freezer at −20 °C.

2.2. Serological test

Meeting the inclusion criteria for CCP donation by each donor was followed by performing a rapid antibody test. The COVID-19 IgG / IgM rapid test strip is a qualitative immunoassay for the detection of anti-SARS-CoV-2 IgG and IgM antibodies in blood or plasma samples (Table 1). This test was performed based on the test catalog of companies; COVID-19 IgG/IgM Rapid Test Dipstick (Whole blood/serum/plasma) Package insert (China, Hangzhou All Test Biotech Co.), Wondfo (China, Hangzhou Wondfo Biotech Co.), and COVID-19 IgG/IgM Antibody Test Kit (Colloidal Gold) Package insert (China, Biosino Bio-Technology and Science Inc).

Table 3
Characteristics of non-parous females / males convalescent plasma donors.

Independent variable	ELISA IgG positive result (ratio ≥1.1)	ELISA IgG negative result (ratio<0.8)	Total donors
age (years) - median (IQR)	33(39)/40(48)	28(34)/37(43)	33(39)/40 (47)
The location of donors in terms of the prevalence of SARS-CoV-2- no. (%)			
Red	120(71.0 %)/2337(61.1 %)	21(77.8 %)/237 (58.2 %)	141(71.9 %)/2574 (60.8 %)
Orange	31(18.3 %)/963(25.2 %)	6(22.2 %)/119 (29.2 %)	37(18.9 %)/1082 (25.6 %)
Yellow	18(10.7 %)/525(13.7 %)	0(0%)/51(12.5 %)	18(9.2 %)/576 (13.6 %)
Donation history- no. (%)			
First donation	181(97.3 %)/4096(92.9 %)	27(96.4 %)/425 (91.4 %)	208(97.2 %)/4521 (92.7 %)
Return	5(2.7 %)/314 (7.1 %)	1(3.6 %)/40(8.6 %)	6(2.8 %)/354(7.3 %)
Ethnicity- no. (%)			
Persians	97(62.6 %)/2256(62.3 %)	15(55.6 %)/210 (53.3 %)	112(61.5 %)/2466 (61.5 %)
Azeris	33(21.3 %)/819(22.6 %)	6(22.2 %)/138 (35.0 %)	39(21.4 %)/957 (23.8 %)
Turkmens	0(0%)/247 (6.8 %)	0(0%)/5(1.3 %)	0(0%)/252 (6.3 %)
Gilaks	2(1.3 %)/37 (1.0 %)	0(0%)/5(1.3 %)	2(1.1 %)/42 (1.0 %)
Arabs	23(14.8 %)/260(7.2 %)	6(22.2 %)/36 (9.1 %)	29(15.9 %)/296(7.4 %)
Length of hospitalization (days) - median (IQR)	0 (0)	0 (0)	0 (0)
Chest CT- no. (%)			
positive result	1(11.1 %)/60 (14.1 %)	1(100 %)/2(7.7 %)	2(20.0 %)/62(13.7 %)
negative result	8(88.9 %)/367 (85.9 %)	0(0%)/24(92.3 %)	8(80 %)/391 (86.3 %)
Blood types – no. (%)			
A	66(36.5 %)/1509(34.4 %)	10(40.0 %)/143 (31.1 %)	76(36.9 %)/1652 (34.1 %)
B	42(23.2 %)/1087(24.8 %)	7(28.0 %)/99 (21.5 %)	49(23.8 %)/1186 (24.5 %)
AB	19(10.5 %)/391(8.9 %)	0(0%)/30(6.5 %)	19(9.2 %)/421(8.7 %)
O	54(29.8 %)/1403(32.0 %)	8(32.0 %)/188 (40.9 %)	62(30.1 %)/1591 (32.8 %)
Rh- no. (%)			
Positive	165(91.2 %)/3992(90.9 %)	22(88.0 %)/416 (90.4 %)	187(90.8 %)/4408 (90.9 %)
Negative	16(8.8 %)/398 (9.1 %)	3(12.0 %)/44 (9.6 %)	19(9.2 %)/442(9.1 %)
Donation type- no. (%)			
Recovered	3(1.6 %)/238 (7.4 %)	0(0%)/55(11.7 %)	3(1.4 %)/383(7.8 %)
Source	183(98.4 %)/4113(92.6 %)	28(100 %)/415 (88.3 %)	211(98.6 %)/4528 (92.2 %)

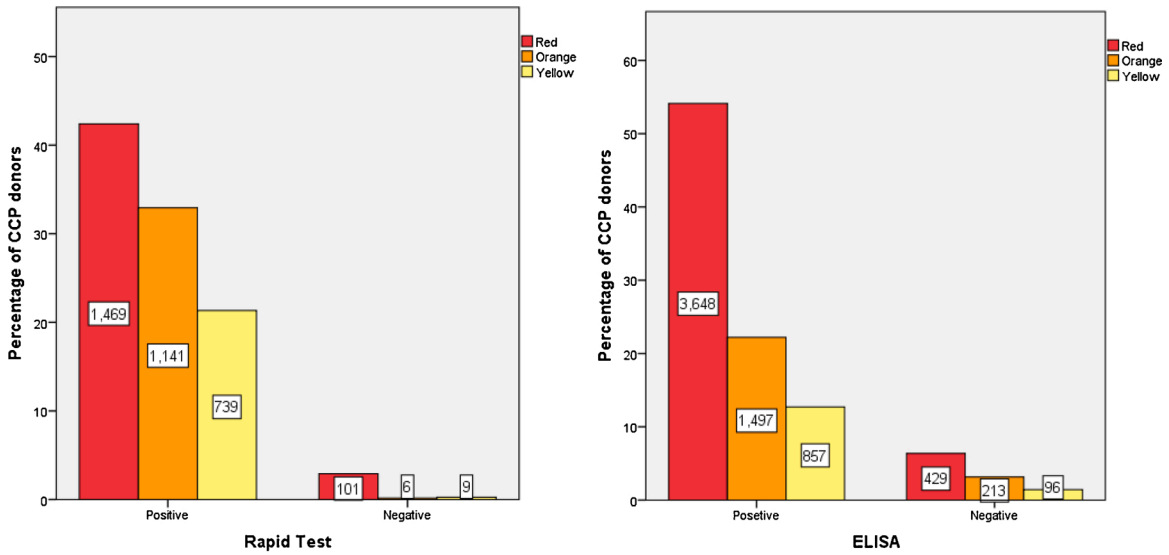
Table 4
Univariate and multivariate logistic or linear regression for factors related to ELISA and Rapid outcome and SARS-CoV-2 IgG antibody titers.

Dependent factor	Independent factor	Univariate P	Multivariate OR (95 % CI)	P value
ELISA result	Age	0.000*	0.951 (0.921−0.982)	0.002
	Sex	0.05*		P > 0.05
	Blood group	0.001*		P > 0.05
	Rh	0.2		
	The location in terms of SARS-CoV-2prevalence and red area as a reference	0.06*	2.887 (1.482−5.625)	0.002
	Ethnicity (Persians as references)	0.000*	2.801 (1.015−7.731)	0.047
	CXR/CT scan result	0.3		
	Hospitalization history	0.000*	2.598 (1.300−5.189)	0.007
	Number of hospitalization days	0.9		
	Donation history	0.2		
	Type of CCP	0.000*	18.820 (8.02−44.163)	0.000
Antibody titers	Age	0.000*	0.106 (0.519−4.456)	0.013
	Sex	0.000*		P > 0.05
	Blood group	0.02*		P > 0.05
	Rh	0.9		
	The location in terms of SARS-CoV-2prevalence and red area as a reference	0.000*	0.547 (113.330−157.033)	0.000
	Ethnicity (Persians as references)	0.000*		P > 0.05
	CXR/CT scan result	0.1		
	Hospitalization history	0.000*		P > 0.05
	Number of hospitalization days	0.06*	0.122 (0.459−8.668)	0.029
	Donation history	0.07*		P > 0.05
	Type of CCP	0.000*	0.131 (42.084−192.280)	0.002
Rapid result	Age	0.04*		P > 0.05
	Sex	0.2		
	Blood group	0.2		
	Rh	0.7		
	The location in terms of SARS-CoV-2prevalence and red area as a reference	0.000*	0.321 (0.149−0.690)	0.004
	Ethnicity (Persians as references)	0.000*		P > 0.05
	Donation history	0.02*		
	Type of CCP	0.06*	4.52(2.24−9.123)	0.000

* The variables entered into the logistic regression are multivariate.

2.3. Determination of IgG level against S1 spike protein and its titration in the donated plasma

Measurement of anti-SARS-CoV-2 IgG antibody levels in CCP units was performed by enzyme-linked immunosorbent assay (ELISA) method via commercial kit (Euroimmun AG, Luebeck, Germany) according to the manufacturer's instruction. Patient samples were diluted 1:101 in sample buffer to evaluate antibody titers. The ratios for this dilution are



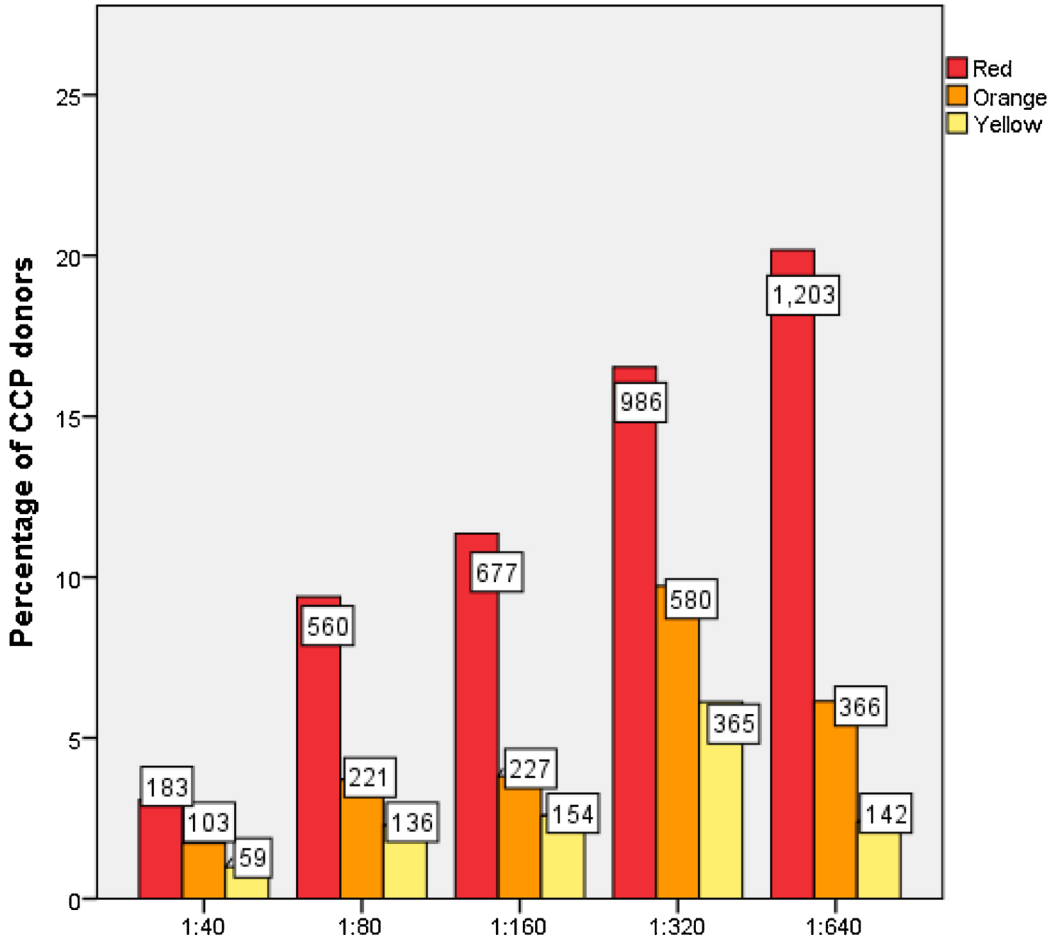


Fig. 2. Correlation between ELISA test and rapid test results and antibody titer in different donation centers across the country in terms of SARS-CoV-2 outbreak. The number of donors has been represented by a box in each test.
Yellow: PCR test is seen in one or more cases, and the risk is as expected. The number of definite new cases per 100,000 people is 1–9.
Orange: The number of definite new cases is 10–24 per 100,000 people.
Red: More than 25 cases per day per 100,000 population.
CCP: Convalescent plasma.

linearly interpolated based on the results obtained for 1:80 and 1:160. This assay applies a specific calibrator to report the ratio of the extinction of the control or patient sample over the extinction of the calibrator. A ratio above the cutoff value ($\geq$ 1.1) defines the final interpretation of positivity. A greater ratio represents higher antibody levels. CCPs containing positive ELISA ratio ($\geq$1.1) and titers above 1:40 are considered antibody-containing plasma.

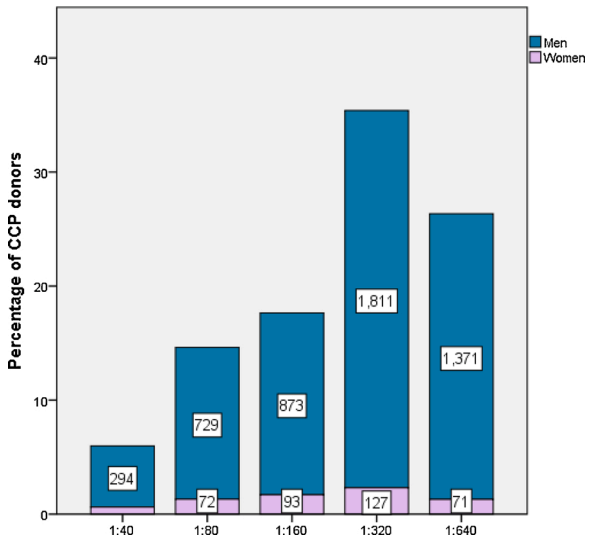


Fig. 3. Correlation between antibody titer results and gender. The number of donors has been represented by a box in each test. CCP: Convalescent plasma.

2.4. Data collection tools

Data were collected prospectively using a predetermined case report forms and Negareh organizational dataset from all Iran's blood centers. Preliminary information about donors such as age, gender, blood type, type of donation, place of residence that determines the particular ethnicity, donation history according to the specific code on each bag for each donor was collected from IBTO software (Negareh dataset).

2.5. Statistical analysis

The analysis was done using SPSS software version 25. Descriptive statistics [mean, median, standard deviation (SD) and interquartile range (IQR)] were used appropriately. We assessed the independent factors using logistic and linear regression with antibody titration results by ELISA method and rapid test results. Independent variables that were significantly associated with a dependent variable in univariate analysis ($p < 0.1$) were included in multivariate binary logistic regression analysis (backward conditional, P for omission <0.1). The results presented as OR with 95 % confidence interval (CI). We used the Chi-Square test to evaluate the relationship between antibody titer and rapid test results. The Mann-Whitney *U* test was used to execute analyses of continuous variables. The categorized data were appropriately compared using the Chi-Square test or Fisher's test. Significance was set at $p < 0.05$.

Role of finding source: The study received no funding and relied on IBTO's internal resources.

3. Results

3.1. Donors of convalescent plasma

CCP was obtained from 11,949 donors with molecular confirmation of previous COVID-19 infection (Fig. 1, Supplement 1). This population included men (92.5 %) more than women (7.5 %) with a mean age of 39.6: 5113 men out of 5712 (92.7 %) and 402 women out of 464(86.6 %) had positive ELISA test results (≥1.1) (Tables 2 and 3). Moreover, comparing males and females regarding positive rapid test results shows the former having 6966 out of 7756 (89.8 %) and the latter 399 out of 606 (65.8 %) (Fig. 1).

Most donors had mild to moderate disease severity at the time of infection, 34.8 % had a history of hospitalization, and 17.5 % had a positive CXR/CT scan result.

3.2. Antibody levels in CCP units

ELISA technique had been performed for 8206 donors (68.7 %), of whom 7275 (88.7 %) had positive results. The median SARS-CoV-2 IgG antibody titer was 1:320 (range <1:40 to ≥1:640) among ELISA IgG positive donors. IgG antibody titers were below the threshold of 1:160 in 1508 CCP units (20.8 %) and between 1:160 and 1:640 in 3676 CCP units (50.8 %).

3.3. Correlation between ELISA results, antibody titers, and rapid tests among CCP donors

A significant difference was observed between antibody titration results and rapid results ($P < 0.0001$). ELISA results were not significantly different from Rapid test ($P = 0.14$ [95 % CI: 0.87–2.52]) (Supplement 2).

3.4. Logistic regression for variables related to ELISA and Rapid results

We assessed and identified eight variables related to ELISA results (Table 4) using univariate analysis:

location in terms of SARS-CoV-2 prevalence (Fig. 2), gender (Fig. 3), blood type (Fig. 4), type of CCP (Fig. 5), history of hospitalization (Fig. 4), CXR/CT scan results, ethnicity and age.

Moreover, five variables were related to Rapid test results, such as age, location in terms of SARS-CoV-2 prevalence, donation history, ethnicity and type of CCP.

In a multivariate logistic regression analysis of these variables, age, location in red areas in terms of SARS-CoV-2 prevalence, therapeutic CCP, ethnicity, and hospitalization history were associated with ELISA results. Also, we identified two variables, including therapeutic CCP and red areas in terms of SARS-CoV-2 prevalence, associated with Rapid results, using multivariate logistic regression analysis (Table 4).

Furthermore, using linear regression analysis, the variables related to antibody titration were age, location in red areas in terms of SARS-CoV-2 prevalence, number of hospitalization days, donation history, and plasma type (therapeutic CCP).

4. Discussion

This study suggests several factors associated with high antibody titers to understand characteristics for ideal convalescent plasma donation.

There was a correlation between demographic characteristics including age, gender, location with high virus frequency, and antibody levels in CCP units measured both by ELISA and rapid tests and antibody titers assessed in a subset of CCP donors.

Moreover, high antibody titers were also observed in CCP donors with hospitalization history. IgG-antibody titers equal to or above 1: 640 in CCP units of donors with hospitalization history rather than without hospitalization history were more than two-fold. Like our finding, donors recovered from moderate or severe COVID-19 included in another study [12] had high antibody titers. Previous studies demonstrated that many CCP plasma samples have moderate antibody levels, and commercial experiments have varying degrees of accuracy in predicting nAb activity. A central biological question is: What factors cause a large change in the antibody titer (neutralizing or binding) in CCP donors? Some variables, including the dose of SARS-CoV-2 exposure, can cause variation in the extent and spread of SARS-CoV-2. We reported that in areas where the prevalence of COVID-19 virus was high, antibody titer in donors accordingly increased [13].

Donation history is one of the other variables investigated in this study. The antibody titer in the return donors was estimated lower than that in the first donors; though, the difference not being statistically significant. The lack of significance pertains to the fact that the antibody titer did not decrease given the 28-day interval for CCP donation

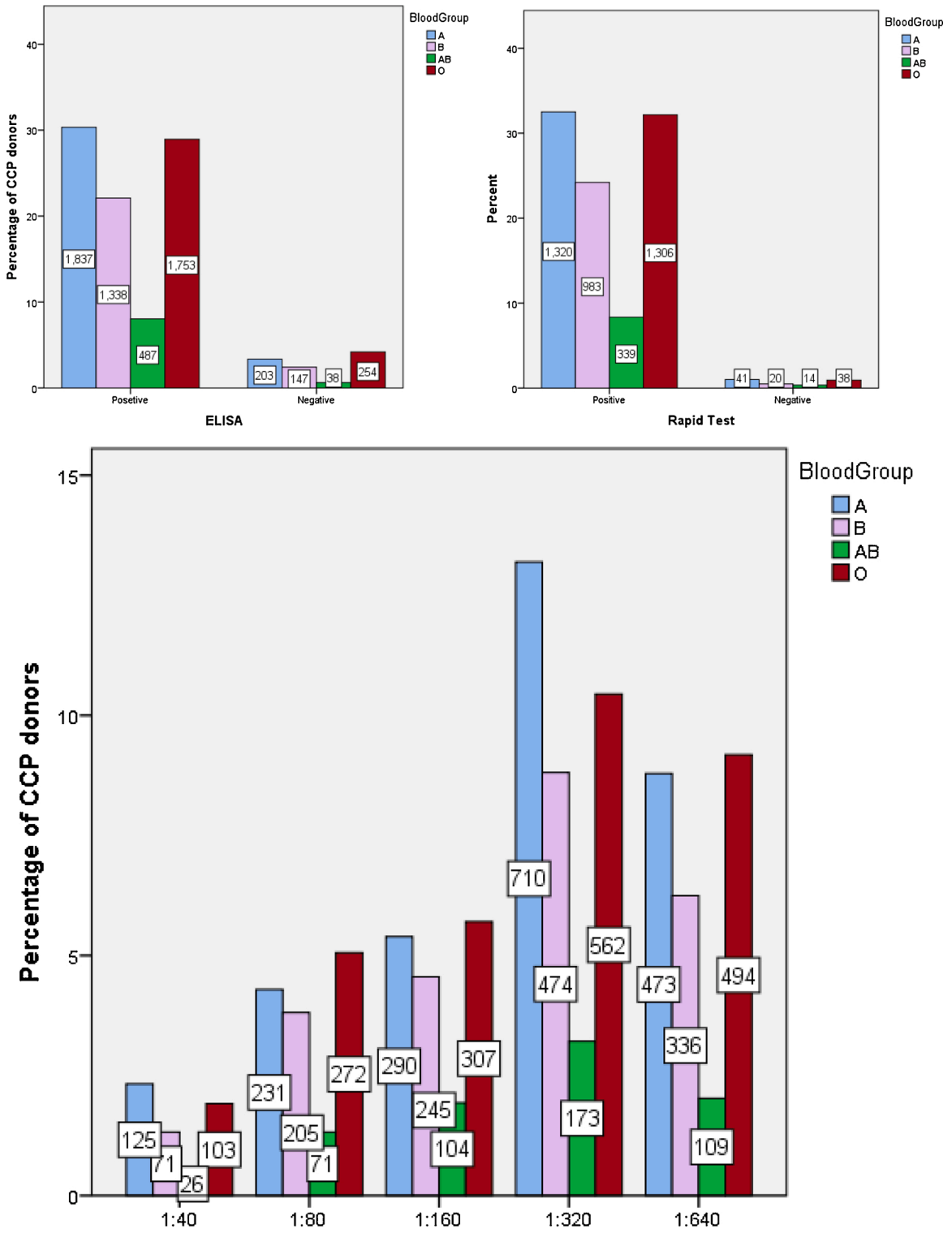


Fig. 4. Correlation between ELISA and Rapid test results and antibody titer in positive ELISAs with blood group. The number of donors has been represented by a box in each test. CCP: Convalescent plasma.

attempts.

When controlling for other variables, such as the use of different Rapid and ELISA kits for donors with various sensitivity and specificity, only age, ethnicity, location with high virus frequency, hospitalization history, male and nulliparous female donors who had a positive rapid test were significantly associated with high antibody titers.

The convalescent plasma therapy in treatment of various infectious diseases is not a novel concept. It has recently been used to treat patients with Ebola. It has subsequently contributed to discovering particular antibodies with high virus-neutralizing activity and the development of synthetic monoclonal antibodies to treat Ebola [14]. Currently, the FDA recommends concentrations of nAb $>$ 160, but a lower titer (1:80) is allowed if no alternative is available. The FDA, however, has not provided a methodology used to obtain these levels, despite potential variables. As already described by others, [15], not all CCP units contain measurable antibodies, and 20 % of donors did not have IgG against S1

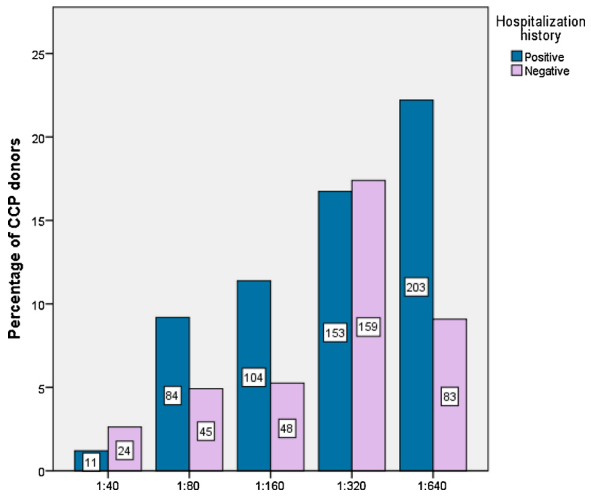


Fig. 5. Antibody titer based on hospitalization history. The number of donors has been represented by a box in each group. CCP: Convalescent plasma.

above the cutoff of the test employed, while in the current study, this rate was 11.3 % of donors. The median antibody titer in our study was 1:320 for CCP units.

Consistent with our finding, antibody titers in CCP units during the 2009 H1N1 pandemic were correlated with donor age, gender, or location with high virus frequency. Similar to our results, donors included in this study [16] had elevated nAb in younger convalescent donors and those who were older than 55 years. Some small case series suggested that male gender, older age, and hospitalization of patients with COVID-19 were consistently associated with increased antibody responses and worse COVID-19 outcome. They appeared to be factored in identifying individuals most likely to have potent antiviral antibodies [15,17,18]. This study reported a more extensive series of CCP donors with a range of variables that might affect antibody titers' quantity.

Our data indicate that despite the vast epidemiological pattern of blood group O among donors in Iran, [19] it was blood group A in our CCP donors, as being more frequent than the others. This is compatible with two other studies [20,21]. The latter described that anti-A antibody inhibits the binding of SARS-CoV-2 protein-expressing cells explicitly to ACE2-expressing cell lines. Therefore, a lower infection chance of blood type O and a higher in blood type A may exist. In a case-control study on blood types of COVID-19 patients [21], the proportion of blood group A was higher than blood group O among SARS-CoV-2+ patients compared to SARS-CoV-2- cases; although in both cases, the result was significant only in Rh-positive blood groups. Blood types were associated with neither the considered factors (age, sex, hypertension, diabetes, overweight, and chronic cardiovascular and lung disorders) nor intubation or death in COVID-19 patients. Similarly, in the present study, no relationship was observed between blood groups and disease severity in terms of lung involvement ($p = 0.5$) or hospitalization history ($p = 0.1$).

This study had some limitations. For example, since CXR/CT scan information and the history and duration of hospitalization were added to this study from October 2020; thus, the amount of data collected is less than other data types, which may be reflected on the results. At the same time, the data such as the duration of previous SARS-CoV-2 infection in donors have not been identified, which may be one factor involved in selecting donors with high antibody titers. The other limitation pertains to antibody titration being performed only by commercial ELISA kits with no cell culture methods or tests to detect neutralizing antibody titer in this study.

Overall, the results of the present study provide a roadmap for selecting individuals possibly with high levels of anti-SARS-CoV-2 IgG antibodies as preferred donors for CCP donation.

CRediT authorship contribution statement

Alieh Fazeli: Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Shahin Sharifi:** Resources, Supervision. **Saeed Mohammadi:** Resources, Writing - review & editing. **Mehran Bahraini:** Methodology, Investigation, Writing - original draft, Writing - review & editing. **Ali Arabkhazaeli:** Data curation, Writing - review & editing. **Nooshin Jelveh:** Formal analysis, Investigation. **Peyman Eshghi:** Conceptualization, Project administration, Funding acquisition.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.transci.2021.103302.

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