



COVID-19 Convalescent Plasma Donor Characteristics: Correlation with Blood Group, Age, Gender, Symptoms and their Association with SARS CoV-2 Antibody Levels: A Bi-centric Study from India

Mitu Dogra ^{a*#}, Rasika Setia ^{a#}, Sangeeta Pathak ^{b#},
Gokhula Prasath Thangavel ^{a#}, Tamojit Chakraborty ^{b#}, Surjit Singh ^{b#}
and Anil Handoo ^{c#}

^a Department of Transfusion Medicine, BLK Superspecialty Hospital, New Delhi, India.

^b Department of Transfusion Medicine, Max Super Speciality Hospital, Saket, New Delhi, India.

^c Department of Hematology, BLK Superspecialty Hospital, New Delhi, India.

Authors' contributions

This work was carried out in collaboration among all authors. Authors RS, MD made conceptualization. Authors SP, TC, RS, MD, RY and GPT collected CP. Authors RS and MD wrote the methodology. Authors GPT, RS and MD statistical analyses and interpretation. Authors RY and GPT collected resources. Authors RS and MD writing the original draft of the manuscript. Author RS and AH writing review and editing of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2021/v42i2230556

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/79315>

Original Research Article

Received 21 November 2021
Accepted 25 December 2021
Published 26 December 2021

ABSTRACT

Background: Understanding demographics and collection characteristics of Convalescent Plasma (CP) donors is the corner stone for maintaining a viable inventory of high titre CP products in an acute-crisis setting. The Specific objectives of this study were to find a correlation between SARS-CoV-2 antibody level with age, gender and blood group in CP donors.

Materials and Methods: An observational, retrospective study was conducted at blood centres of two multispecialty hospitals in Delhi from 1st November 2020 to 31st January 2021. 936 consenting

Dr.;

*Corresponding author: Email: drmithu25@yahoo.in;

COVID-19 recovered individuals were screened and underwent a medical interview for eligibility for CP donation from both blood centres, of which 750 qualified for CP collection. 400/ 750 (53.3%) CP donations were from centre A and 350/750 (46.7%) were from centre B. Donor characteristics data for both centres was retrieved from the blood bank donor management database and records from both the centres.

Results: The results of this study revealed that majority were males 727 (96.93%) and 23 (3.07%) were females with mean age was 35.09±8.7 years. 41-50 years showed higher median SARS-CoV-2 antibodies. Of the 936 donors screened for CP collection, 186 donors got deferred due to various reasons, resulting in a mean deferral rate of 19.87%. The commonest reason (15.05%) was absence of detectable/low SARS CoV-2 antibodies. Group-wise median antibody levels were AB>B>A>O at both centres. Moderate correlation (correlation coefficient =0.721) between number of symptoms and SARS CoV-2 antibody levels was observed; high symptom scores showed high SARS CoV-2 antibodies values (correlation coefficient=0.721; $p < 0.00001$). The individual symptom-wise predictors like fever ($p = 0.002$) and acute gastroenteritis (GE) or (GE-like syndrome) ($p < 0.001$) were positive predictors for high SARS CoV-2 antibodies. Cold ($p = 0.006$) and absence of symptoms ($p = 0.060$) were negative predictors. To summarize a collective significant effect exists between the symptoms and SARS CoV-2 antibody levels. Donors with symptoms like fever and GE or GE like syndrome showed significantly higher SARS Cov-2 antibodies. Female donors as compared to male donor, donors in age group of 41-50 years and donors with blood group AB compared with other groups had higher median levels of SARS CoV-2 antibodies.

Conclusion: Awareness of CP donor characteristics, post-screening deferrals, and correlates of antibody values with age, symptoms and blood group will help improve collection outcomes and give better preparedness for future recurrent waves due to evolution of more virulent SARS-CoV-2 strains and fill treatment gap till availability of more specific treatment.

Keywords: Convalescent plasma; SARS-CoV-2; plasma therapy.

1. INTRODUCTION

The world was introduced to this century's worst pandemic-THE COVID-19 Pandemic in December, 2019. Caused by the novel coronavirus - SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), healthcare systems across the globe have crippled under this huge challenge and with no definitive standard or approved treatments options till date. Passive immunisation using Convalescent plasma (CP) has long been used as a therapeutic tool in blood transfusion for achieving immediate short-term immunisation and have shown therapeutic potential against infectious agents [1]. CP products can be obtained by collecting whole blood or plasma from patients who have survived previous infection and developed humoral immunity against the pathogen responsible for the disease in question [2]. The plasma thus extracted containing pathogen-specific antibodies (in this case-SARS CoV-2 antibodies) and has become a well-recognized emergency or empirical therapy, [3] which has been successfully applied in the field of cell therapy and immunotherapy [4].

US-FDA on April 13, 2020 authorized the use of convalescent plasma as a potentially effective

treatment of the patients, as an investigational drug [5]. The Ministry of Health and Family Welfare, Govt. of India on 13th June 2020, in their "Clinical Management Guidelines: COVID 19, Version 3", endorsed off-label use of convalescent plasma for COVID 19 patients with moderate disease who are not improving (oxygen requirement is progressively increasing) despite use of steroids [6]. As the COVID-19 pandemic continues to rage, so does its devastation and case counts continue to escalate steeply worldwide, CP currently remains the most accessible viral-specific therapy for hospitalized patients [7-12]. Measurements of antibody response among patients with COVID-19 show that the majority patients develop IgM and IgG within 2 weeks of symptom onset, with specificity towards receptor-binding domain (RBD) and spike protein viral epitopes correlating with virus neutralization [13,14].

Identifying, recruiting, selecting, collecting, and preparing plasma from convalescent patients with adequate SARS-CoV-2-neutralizing Ab titres in catastrophic situation like that faced in recent times has become the biggest challenge well within the remit of most blood transfusion services across the globe. Thus understanding demographics and other collection

characteristics of donors who qualify for CP donation is the corner stone for maintaining a viable inventory of high titre CP products in an acute crisis setting. Recent interim recommendations issued by the Association for the Advancement of Blood & Biotherapies (AABB), have endorsed not only safety of CP, but have also recommended use of high-titer CP as close to symptom onset as possible as the main predictors of its effectiveness [15].

It is important not only to focus on the clinical endpoints of a CP therapy, but also to describe the impact of donor characteristics (age, gender, blood group, symptoms of COVID-19, interval between SARS-CoV-2 diagnosis and CP collection) on the antibody content in the CP products. CP collections might become more effective if donor characteristics correlating with higher functional antibody activity are better understood. This study is unique as till date, there is no study from India on COVID-19 convalescent plasma collection analysing major CP donor characteristics and SARS-COV-2 antibody response.

2. AIMS AND OBJECTIVES

To study the clinical and serological characters of the voluntary donors who visited both the blood centers for CP donation. In one of the two centres we also analysed variation of antibody levels according to symptomatology, as we all know that efficacy of convalescent plasma therapy relies on robust antibody response in convalescent plasma donors.

3. MATERIALS AND METHODS

This is an observational, bi-centric, retrospective, study done at blood centres of two multispecialty hospitals in Delhi, with dedicated COVID-19 management units. Donor characteristics data for both centres was retrieved from the blood bank donor management database and records for a period of 3 months, from 1st November 2020 to 31st January 2021. The donor selection was based on standard blood bank donor selection requirements (Drugs and Cosmetics Second Amendment Rules, 2020) [16] and additional inclusion criteria as per the emergency release authorization issued by the Ministry of Health and Family Welfare (MOHFW), Govt. of India", for off-label use of convalescent plasma for COVID-19 in moderate disease [17] with the CP collection donor selection and collection guidelines released by the Indian Council of Medical

Research (ICMR), New Delhi [18]. CP was collected from COVID-19 recovered individuals meeting the above requirement after taking informed consent.

3.1 Study Design and Setting

CP donor data was taken two blood centres with blood collection, component preparation and apheresis facility collecting CP from COVID-19 recovered patients. These blood centres are attached to two large 500+ bedded multispecialty hospitals in New Delhi, India and each hospital having dedicated wards to treat COVID-19 patients. Both hospitals are a part of the chain of Max group of hospitals.

Study population was divided into two groups based on the collection centres where CP was collected:

Centre A- Blood centre (Department of Transfusion Medicine) of BLK-Max Super Speciality Hospital (Dr. B.L. Kapur Memorial Hospital), New Delhi, India.

Centre B –Blood centre (Department of Transfusion Medicine) of Max Super Speciality Hospital, New Delhi, India.

3.2 Ethical Approval

The study was approved by the Institutional Ethics Committee (IEC), (EC/AARCE/Approval Letter/2020/96, dated 08/09/2020). Informed consent for the procedure as per standard operating procedure along with consent for performing any additional tests on blood samples, for study/ research purpose was taken from all CP donors prior to the procedure. In view of retrospective study design, and no risk of disclosure of the donor identity involved in this study, the requirement to obtain the blood donors' consent to review the donor records was waived off by the IECs. Confidentiality of the data was maintained, and the study procedures were performed in compliance with the 1964 Helsinki declaration and its later amendment [19].

3.3 Donor Selection

All CP donors meeting traditional allogeneic blood donor criteria per the standard blood bank donor selection requirements (Drugs and Cosmetics Second Amendment Rules, 2020)

[16] the following additional selection criteria as defined by MOHFW were included:

- Men or nulliparous women who were aged between 18 and 60 years
- Body weight greater than 55 kg.
- Prior diagnosis of COVID-19 documented by a confirmed by rRT-PCR test or a Rapid antigen test (RAT) by an ICMR approved assays. Additionally, the symptoms must have completely resolved for 28 consecutive days before donation or a period of 14 days before donation with rRT-PCR negative test results for SARS-CoV-2 from oropharyngeal and nasopharyngeal swabs. In case of repeat, CP donation and interval of at least 2 weeks of the first plasma donation was ensured.

Donors fulfilling these requirements underwent a medical interview, with routine donor medical examination, and explained about donation of plasma via plasmapheresis.

Data captured by Centre A, additionally included details pertaining to onset of disease, duration and type of symptoms [fever; cough; non-specific symptoms (body ache or headache); runny nose or cold; shortness of breath (SOB); acute gastroenteritis (GE) (GE-like syndrome): nausea, vomiting, or abdominal pain; anosmia or ageusia].

3.4 CP Donor Screening

All routine screening tests, including ABO blood grouping; Rhesus phenotype; complete blood counts (including Hemoglobin (Hb), Platelet count, Total and differential leucocyte count), antibody screening for clinically significant antibodies (Extended Rh, Kell, Duffy, Kidd, MNS) and serum protein estimation was carried out. Donors with Hb >12.5g/dl, platelet count >1.5x 10⁹/L, TLC within normal limits, total serum protein > 6gm/dl and antibody screening negative were accepted. Screening for HIV, hepatitis B or C virus, syphilis, and malaria were conducted as per departmental standard operating procedures (SOPs) in accordance with the Drugs and Cosmetics (Second Amendment) Rules, 2020 therein for plasmapheresis and guidelines prepared by the Director General of Health Services and Central Drugs Standard Control Organization in conjunction with the Indian Council of Medical Research, Government

of India for Convalescent plasma collection [16-18].

3.5 SARS-CoV-2 Antibody Test

Efficacy of CP is hypothesized to be associated with the concentration of neutralizing antibodies (nAb) to SARS-CoV-2. nAb levels have been shown to correlate best with anti-S1 IgG and anti-S1 total Ig levels [20-22].

At center A, donors were tested for Anti-SARS-CoV-2 IgG (S1) antibodies on VITROS-3600 chemiluminescent immunoassay (CLIA) in accordance with manufacturer instructions. Institutional cut-off of 5 S/Co was taken for donor selection and titer of 12 S/Co was considered as high titer CP [23-25].

Centre B Tested the donors on the LIAISON® XL Analyzer (DiaSorin S.p.A., Saluggia, Italy) applying the manufacturer's cut-off >15.0 AU/mL (borderline results 12.0 – 15.0, required a re-test algorithm) [26].

3.6 Plasma Collection

At centre A, CP was obtained by apheresis using Amicus™ (Fresenius Kabi) or Trima Accel® (Terumo BCT, Lakewood, CO) cell separators and at Centre B Apheresis was performed using Haemonetics MCS + LN90 00-220E blood cell separator (Haemonetics, Boston, MA, USA). 400-450 ml plasma was collected from each donor and divided into two 200-225-ml aliquots and stored at less than -30°C. Units were thawed at 37°C for before issuing for transfusion. The mean volume of plasma collected was 405.34±14.09ml. The Average time taken was 30.49±6.49minutes. Only 5 out of 750 donors who underwent CP collection procedure, suffered mild adverse reactions during the procedure. There were 2 small hematomas and 3 experienced minor citrate reactions in the form of mild dysesthesias, resolved by adjustment of the inlet pump flow rate and oral calcium supplements.

3.7 Statistical Analysis

Quantitative variables were calculated as mean ± standard deviation or medians and overall ranges (minimum–maximum). Linear regression between 2 parameters was quantified by goodness of fit. Correlations between 2 data sets were calculated using Pearson's correlation coefficient and the t distribution with n-2 degrees

of freedom. P values < 0.05 were considered to indicate statistical significance while P values < 0.0001 were considered to indicate highly statistical significance. Statistical analysis was done using IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

4. RESULTS

4.1 Donor Characteristics

Donor characteristics data was retrieved from the blood bank donor management database and records from both the centres. 936 consenting COVID-19 recovered individuals were screened for eligibility for Convalescent plasma donation from both blood centres, of which 750 qualified for CP collection. Deferral rate was defined as the total number of donors deferred at time of collection out of total number of presenting donors [27].

In the present study, 400/ 750 (53.3%) CP donations were from centre A and 350/750 (46.7%) were from centre B. Majority of the donors were 727 (96.93%) and 23 (3.07%) were females and the mean age of donors was 35.09±8.7 years with a median age of 34 (20-60) years. Female donors were younger than male donors [mean age of males was 35.09± 8.7 years and females was 27.8± 3.86 years and difference in age was statistically significant ($p = 0.0001$)]. 606/750 (80.8%) of the donors were replacement donors. 19.2% voluntary donors were either hospital staff or walk in regular blood donor who had recovered from COVID-19 infection and volunteered to donate CP.

Most of the donors were into professional service (35.5%), followed by semi-professional /self-employed (27.1%), government service (15.8%), student (11.6 %), and 10% into other activities. Of those involved in professional services and government services, 11.8% of them were healthcare workers and 3.2% were policemen. Among different blood groups, B donors were most common (44.13%). Other blood groups were O -24.8%, A positive-22%, AB 9.07%. Further demographic and clinical characteristics are presented in Table 1.

4.2 Deferral

Of the 936 donors screened, 186 donors got deferred due to various reasons, resulting in a mean deferral rate of 19.87%. The characteristics of deferred donors are shown in Table 2.

On a gender basis, the deferral rate was higher in male donors (79.57% compared to 20.43% female donors, $p < 0.0001$). Commonest deferral reason was absence of detectable/low SARS CoV-2 antibodies (15.05%), inadequate time gap from last plasma donation (9.68%), low Hb (9.14%), low platelet count (8.60%), high blood pressure (7.53%) and poor venous access (5.91%). 5.37 % donors tested reactive for transfusion transmissible infections (HIV 1&2, HBV, HCV or Syphilis). 13.44% donors were rejected during screening as they not have a diagnostic test report (ICMR approved test) for COVID-19 infection (i.e. diagnostic evidence of COVID-19 infection) described in section 1.2 above.

4.3 Median SARS CoV-2 IgG (S1) Levels Comparative by Blood Donor Characteristics: Gender, Age and Blood Group

Among the 750 donors who donated, donors with blood group AB compared with other groups had higher median levels of SARS CoV-2 antibodies at both centres [Fig. 1 (a) & (b)]. Centre A: 48.59 S/Co for group AB, 41.2 S/Co for group B and 39 S/Co for group A and 35.5 S/Co for group O; similar trend was seen at Centre B. Centre B: 76 AU/ml for group AB, 69.1 AU/ml for group B and 58.6 AU/ml for group A and 47.4 AU/ml for group O.

At Centre A, median levels of SARS CoV-2 antibody levels were higher in females compared to males (49.32 S/Co vs 38.09 S/Co) and similar trend was observed in the donors who donated at Centre B (female 63 AU/ml vs males 52.9 AU/ml) [Fig. 2 (a) & (b)].

Age group of 41-50 years showed higher median SARS CoV-2 antibody levels at both the centres (Centre A: 51.36 S/Co for age group 41-50 vs 45.15 S/Co for age group 31-40years, 38.5 S/Co for 51-60 years and 37.1 S/Co for 20-30 years and at Centre B: 82.1 AU/ml in 41-50 years, 59.9 AU/ml in 31-40 years, 54.85 AU/ml in 51-60 years and 44.9 AU/ml in 20-30 years age group) (Fig. 3a & 3c). However, antibody levels showed weak correlation with age of the donors (coefficient of linear regression between donor and SARS CoV-2 antibody level in Centre A $r^2=0.0245$; correlation coefficient =0.49; Centre B $r^2 = 0.004$; correlation coefficient =0.06 Fig. 3b & 3d).

Table 1. Convalescent plasma donor characteristics (Combined Centre A & B)

Total screened n (%)	
Male	875 (93.48)
Female	61 (6.52)
Total deferred n (%)	
Male	P < 0.0001 148 (79.57)
Female	38 (20.43)
Total Donated n (%)	
Female	23 (3.07)
Male	727 (96.93)
Type of Donor	
Voluntary	144(19.2)
Replacement	606(80.8)
First time	390 (52)
Repeat	360(48)
Age, years	
Mean \pm SD (Range)	P = 0.0001
All	35.09 \pm 8.7 (20-60)
Female	27.8 \pm 3.86 (21-36)
Male	34.8 \pm 8.74 (20-60)
Weight, kg	
Mean \pm SD (Range)	p < 0.001
All	73.32 \pm 14.10
Female	60.22 \pm 9.75
Male	74.38 \pm 13.86
Blood group, n (%)	
A	165 (22)
B	331(44.13)
AB	68 (9.07)
O	186 (24.8)
Hemoglobin g/dl(Mean \pmSD)	14.92 \pm 1.42
Platelet Count (x10⁹/l) (Mean \pmSD)	236.9 \pm 63.1
Total leukocyte count (x10⁹/l) (Mean \pmSD)	7.62 \pm 2.62
Serum albumin g/dL	4.1 \pm 0.6
Occupation %	
Professional service	36
Government service	16
Semi-professional /self-employed	27
Students	12
Other	10
Interval between rRT-PCR/RAT positive test and plasma donation (days)-mean \pmSD (min-max)	63.93 (21.52) (15-119)
SARS CoV-2 Antibody	Mean \pm SD(range)
Centre A	
Antibody S/CO	50.21 \pm 41.52 (9.59-207.2)
Centre B	
Antibody AU/ml	84.01 \pm 76.31(16-400)
SARS CoV-2 Antibody from rRT-PCR positive result	n (%) Mean \pmSD
Centre A	
P = 0.2336	
45 days and less	49 45.13 \pm 33.93 S/Co
More than 45 days	351 52.49 \pm 41.27 S/Co
Centre B	
P = 0.1218	
45 days and less	101 73.55 \pm 80.34 AU/ml
More than 45 days	249 88.25 \pm 80.34 AU/ml

Table 2. Deferred donor details (Combined Centre A & B)

Reason for deferral	N=186	%
Overage/underage	5	2.69
Low platelet count	16	8.60
Anaemia/Low haemoglobin	17	9.14
Underweight	5	2.69
Poor venous access	11	5.91
High blood pressure	14	7.53
High blood Sugar	2	1.08
Absence of detectable/Low SARS CoV-2 antibodies	28	15.05
On Medication	5	2.69
Skin allergy	1	0.54
Minor/ Major Surgery	5	2.69
Inadequate time gap	18	9.68
Hepatitis B	3	1.61
Hepatitis C	4	2.15
Syphilis positive	3	1.61
Coronary Artery Disease	4	2.15
H/o parity	18	9.68
No COVID-19 positive diagnostic test result	25	13.44
Anxiety before donation	2	1.08

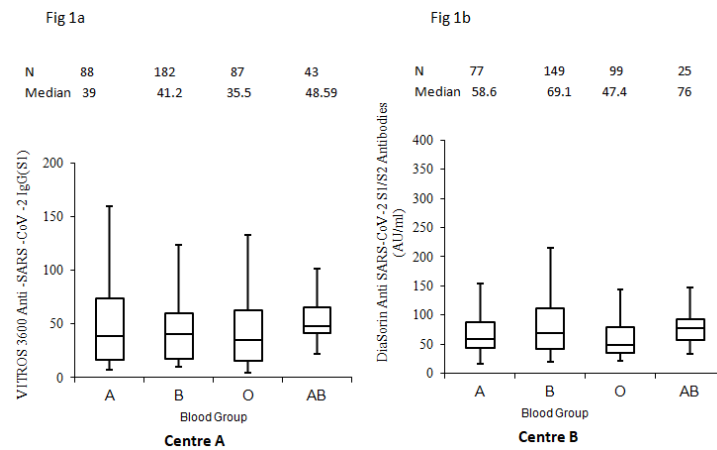


Fig. 1. Median SAR CoV-2 antibody levels, by blood donor blood group

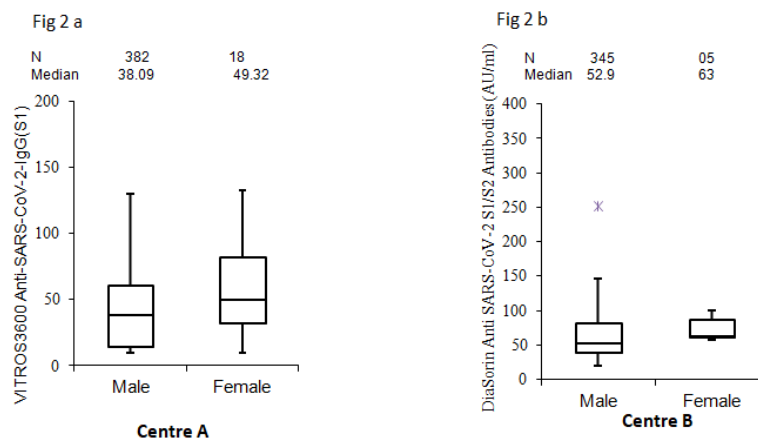


Fig. 2. Median SAR CoV-2 antibody levels, by gender

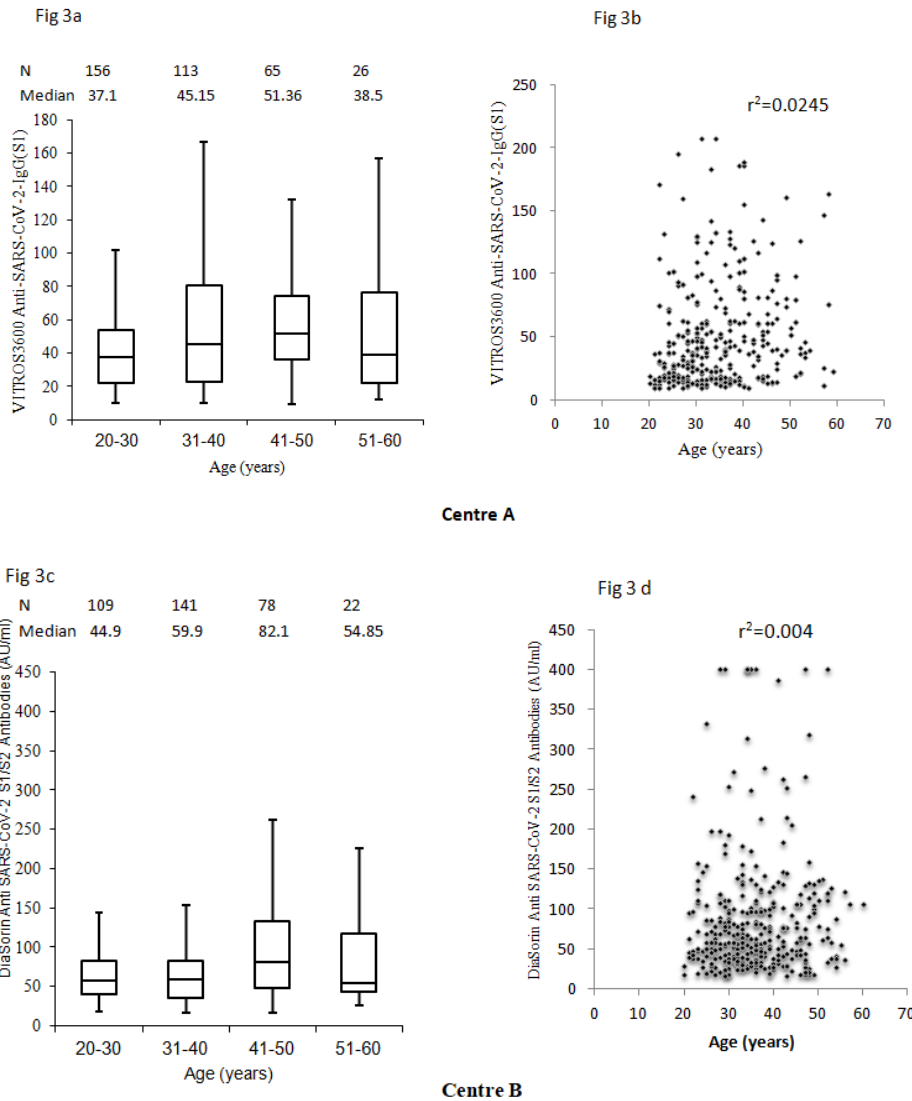


Fig. 3. (a) Median SAR CoV-2 antibody levels, by age, centre A; (b) Linear regression between age and SARS CoV-2 antibody levels, Centre A; (c) Median SAR CoV-2 antibody levels, by age, centre B; (d) Linear regression between age and SARS CoV-2 antibody levels, Centre B

4.4 Additional Characteristics of CP Donors from Centre A

At centre A additional data regarding disease onset and symptoms experienced by the donors at the time of infection were captured. 94% of the donors had been symptomatic and 6 % were asymptomatic at the time when they were rRT-PCR positive.

Donors were categorized as mild, moderate and severe categories on symptomatology as per NIH guidelines [28].

Overall, 73% (292/400) of donors had mild symptoms, 27 % (108/400) had moderate

symptoms and none had severe symptoms. 4 donors were known hypertensives under control on medication, 3 had diabetes mellitus controlled on medication and others did not have any comorbid conditions. During the period of rRT-PCR positivity, most participants (89%) got home management. The rest of them were managed at COVID-19 dedicated hospitals (4% managed in wards and 7% at dedicated quarantine centres). No donors needed ICU management.

Data captured by Centre A, also included details pertaining to onset of disease, duration and type of symptoms [fever; cough; non-specific symptoms (body ache or headache); runny nose or cold; shortness of breath (SOB); acute

gastroenteritis (GE) or (GE-like syndrome): nausea, vomiting, or abdominal pain; anosmia or ageusia). A symptom scoring was done according to number of symptoms. Each symptom was given a score of 1. Fever, cough, sore throat, rhinorrhoea& nasal congestion, GE or GE-like syndrome, non-specific symptoms (body ache or headache) were the most common symptoms. 18% of the donors experienced 4 or more symptoms. The number of COVID-19 symptoms (symptom score) reported by the CP donors showed a moderate linear correlation with the SARS Cov-2 antibody levels ($r^2 = 0.5193$; correlation coefficient =0.721; $p < 0.00001$) [Table 3 & Fig. 4].

4.5 Correlates of SARS CoV-2 Antibody Levels Symptom-wise

Multivariable analysis performed on the subset of donors from Centre A for whom data on details of symptom experienced during COVID-19 infection was available. Table 4 shows the results of multiple linear regression analysis for the outcome of SARS CoV-2 IgG(S1) antibodies in S/CO units (on day of donation) and the following independent variables: No symptoms or symptoms like fever, cough/ sore throat/ shortness of breath, cold, symptoms GE or GE-like syndrome, headache/bodyache, anosmia, ageusia.

Table 3. Correlation between symptom score and SAR CoV-2 antibodies (Centre A)

Score	n*(%)	Median (Range)	p < 0.00001
0	24(6)	16.95(9.31-79.5)	r ² =0.5193
1	115(28.75)	32.09 (9.6-90)	
2	103(25.8)	27.9 (9.59-130)	
3	86(21.5)	44.6(25.73-79.93)	
4	40(10)	71.8 (12.89-99.8)	
5	26(6.5)	101.85(28.9-194.9)	
6	6(1.5)	163.8 (63.8-234.21)	

**The majority of donors had several symptoms*

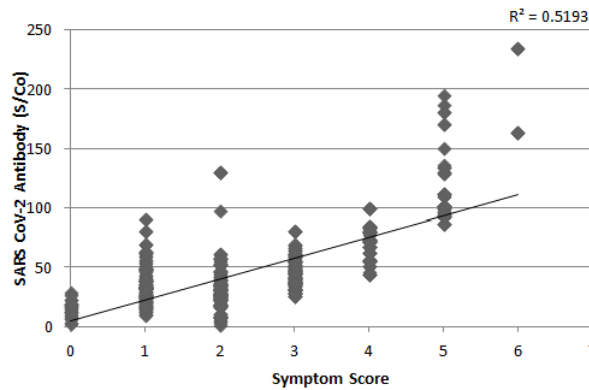


Fig. 4. Correlation between symptom score and SAR CoV-2 antibodies

Table 4. Symptom wise multivariable analyses for correlates SARS CoV-2 antibody levels (Centre A)

Multivariable analysis			
Symptoms	n	β (SE)	p-value
Asymptomatic	24.00	-0.10 (8.78)	0.06
Fever	332.00	0.16 (5.47)	0.000
GE or GE-like syndrome	33	0.46(66.69)	0.000
Anosmia	32.00	0.05 (11.45)	0.49
Ageusia	23.00	-0.10 (13.32)	0.21
Headache/Body ache	28.00	0.00 (6.68)	0.94
Cough/ Sore Throat/ SOB	179.00	0.06 (3.85)	0.23
Cold	49.00	-0.13 (5.73)	0.01

Significant correlates are shown in bold

Results of the multiple linear regression indicated that there was a collective significant effect between the symptoms and antibody levels, ($F(8, 391) = 20.50, p < 0.001, R^2 = 0.295$). The individual predictors were examined further and indicated that fever ($t = 3.085, p = 0.002$), GE or GE-like syndrome ($t = 10.433, p < 0.001$), cold ($t = -2.757, p = 0.006$) and no symptoms ($t = -1.888, p = 0.060$) were significant predictors in the model. Presence of fever as a symptom predicted a mean S/CO increase by 16.87 (6.12 - 27.62), $p = 0.002$. Donors with GE or GE-like syndrome had very high antibody levels and presence of GE or GE-like symptoms predicted a mean S/CO increase by 66.69 (54.13 - 79.26), $p < 0.001$. Absence of symptoms predicted a mean S/CO decrease by 16.58 (0.69 - 33.85), $p = 0.060$. Cold as a symptoms predicted a mean S/CO decrease by 15.80 (5.53 - 27.07), $p = 0.006$.

No significant correlation was seen when anosmia or ageusia as symptoms were analysed.

5. DISCUSSION

Here, we report a series of 750 convalescent plasma collections across two centres in Delhi. Of the 936 donors screened during this period, 13.44% got deferred as they did not have diagnostic laboratory report for confirming COVID-19 infection as per regulatory requirement. Our findings are similar to those reported by Lasky B et. al who in their study reported a high deferral rate of 10.2% in CP donors. They found that CP donors were more likely to be first-time (56.2%) compared to whole blood or standard apheresis donors (3.0% and 30.6% respectively) and CP donations had a higher rate of donor adverse reactions, deferrals, and product loss than SA donations [29].

In the present study the highest deferral rate (15.05%) was due to absence of detectable/low SARSCoV-2 antibodies, followed by parity (9.68%) in potential female donors. Wendel S et. al. have reported absence of neutralizing antibodies at the time of screening in 21 of the 271 (7.75%) donor screened for CP donation in Brazil [30]. Dhiman Y et.al. in their study have cited multiparity (38%) as one of the main reasons for deferral among potential female CP donors [31]. Their deferral rate is much higher than our findings, as their deferral rates were based on only telephonic recruitment calls made to COVID-19 recovered patients in early phase of the pandemic between May to July 2020.

However, as the pandemic progressed the number of eligible donors increased and hence possibly the reason for lower deferral due to multiparity in our study.

Donors with blood group AB had higher median levels of SARS CoV-2 antibodies compared to other blood groups. Group-wise median antibody levels were AB>B>A>O at both centres. (Centre A: 48.59 S/Co group AB vs 41.2 S/Co group B vs 39 S/Co group A vs 35.5 S/Co group O; Centre B: 76 AU/ml group AB vs 69.1 AU/ml group B vs 58.6 AU/ml group A vs 47.4 AU/ml group O). Female donors showed a higher median SARS CoV-2 antibody levels at both the centres. (Centre A: 49.32 S/Co female vs 38.09 S/Co males; centre B 63 AU/ml female vs 52.9 AU/ml male). Though antibody levels were higher in females than males, the number of female donors was very small 23(3.07%) and difference was not statistically significant. Our findings are similar to those reported by Mehew J et.al in their study on association of gender, age and hospitalisation with neutralising antibody levels. They reported higher median levels of neutralising antibodies with blood group AB compared with other groups (1:148 vs 1:104 for group B, 1:70 for group A and 1:47 for group O). However, contrary to our observation on gender association, they observed that median levels of neutralising antibodies to be higher in men compared to women (1:97 vs 1:47) [32]. Singh P et.al. from India, have reported similar observations on blood group association with neutralizing antibodies and have found neutralising antibodies in significantly higher percentage of people with blood group AB (0.36), followed by B (0.31), A (0.22) and lowest in people with blood group O (0.11). Difference between blood group AB versus O was highly statistically significant ($p < 0.001$) [33]. Some studies have reported that non-O blood group individuals are at higher risk of developing COVID-19 in comparison to O blood group and they have postulated that this is either due to natural antibodies against blood group antigens acting as a part of innate immune response to neutralize viral particles or alternatively, blood group antigens maybe acting as additional receptors for the virus and individuals who are capable of expressing these antigens on epithelial cells, would possibly have a high propensity to be affected by SARS-CoV-2 [34-36]. In our study, we found a higher median SARS CoV-2 antibody levels in donors in age group of 41-50 years compared with other age groups in both the centres. However, levels

showed weak correlation with age of the donors (centre A correlation coefficient=0.49; centre B correlation coefficient =0.06). Other studies however suggest that male gender [37], older age [38], have higher SARS CoV-2 antibodies indicating that they may be susceptible to SARS CoV-2 infection.

Many studies have reported that titers of neutralizing antibodies are associated with disease severity [39-41]. We could not analyse this in our CP donors since none of the donors had severe COVID-19. The donors were given scoring according to the number of reported COVID-19 symptoms, we observed a correlation between number of symptoms and SARS Cov-2 antibody levels. The results revealed that a high symptom scores goes with high SARS CoV-2 antibodies values with moderate linear correlation ($r^2 = 0.5193$; correlation coefficient=0.721; $p < 0.00001$). Koper S. et. al. also reported a positive correlation of neutralization titres with the number of reported COVID-19 symptoms and with the time from SARS-CoV-2 diagnosis to plasmapheresis [42]. Our results on multiple linear regression indicated that a collective significant effect exists between the symptoms and antibody levels. The individual predictors examined indicated that donors who had fever ($t = 3.085$, $p = 0.002$) and GE or GE like syndrome ($t = 10.433$, $p < 0.001$) showed significantly higher SARS Cov-2 antibodies and absence of symptoms ($t = -1.888$, $p = 0.060$) or cold as a symptom ($t = -2.757$, $p = 0.006$) and were significant negative predictors in the model. Association of higher SARS Cov-2 antibody levels with fever and GE or GE like syndrome have not been reported in any other study except a recent study by Amjadi MF et. al. who also demonstrated for the first time that COVID-19 symptoms such as fever, abdominal pain, diarrhea and low appetite, correlated consistently with higher anti-SARS-CoV-2 antibody levels and neutralizing antibody(nAb) titre as compared to other symptoms and difference in nAb titres was statistically significant [diarrhea Nab= 30 (10, 80) ($p < 0.05$) and abdominal pain nAb= 80 (20, 80) ($p < 0.001$) and low appetite Nab= 20 (10, 80) ($p < 0.001$)] Our results and those reported by Amjadi MF et. al. provided new insights into anti-SARS-CoV-2 antibodies development based on these symptoms [43].

One of the limitation of our study is that our analysis for correlates of SARS CoV-2 antibody values are retrospective only and single point

evaluation which requires follow-up to evaluate the dynamics of antibody levels and their symptom-wise dynamics and also to re-assess those cases who were deferred due to absence of detectable/low SARS CoV-2 antibodies.

The efficacy of CP for COVID-19 still remains controversial. Where a large number of randomized controlled trials have shown negative results of CP therapy, an equally large number of uncontrolled studies have suggested that the antibody content could influence patient outcomes [44]. In a study conducted at our institute, we analysed the efficacy of high titre CP based on 7, 14 and 28-day mortality and also compared disease outcomes in different age groups, time of administration, effect of existing co-morbidities and disease severity, and compared the efficacy of CP therapy along with Remdesvir vis-à-vis CP therapy alone. We observed a significant clinical improvement with a decline in oxygen requirement with lesser 7-day mortality in cases who received CP therapy within 3 days of admission (P value = 0.01). No adverse reaction was reported in any patients who received CP [44]. A "definitive study" from Johns Hopkins University researchers and others have shown that high titer CP in outpatients can cut hospital admissions for COVID-19 by 54% if it is given within 8 days of the onset of symptoms [45].

6. CONCLUSION

Collection and usage of CP is currently waning with increasing vaccination rates and availability of alternative early-stage treatments. Nevertheless, our data on CP donor characteristics, post-screening deferrals, and clinical correlates of antibody values and their correlation with disease severity, symptoms especially fever and/or GE or GE like symptoms) and blood group which determine antibody adequacy may be considered while selecting eligible CP donors. This will help blood centres better prepare CP of optimal quality consisting of high SARS CoV-2 antibody titres for future recurrent waves of COVID-19 infection due to evolution of more virulent SARS-CoV-2 strains and fill the gap until a more specific treatment options become available.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely

no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Garraud O, Heshmati F, Pozzetto B, Lefrere F, Girot R, Saillol A. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. *Transfus Clin Biol.* 2016;23:39–44.
2. Burnouf T, Seghatchian J. Ebola virus convalescent blood products: Where we are now and where we may need to go. *Transfus Apher Sci.* 2014;51:120–5.
3. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liunbruno GM, Grazzini G. Convalescent plasma: New evidence for an old therapeutic tool? *Blood Transfus;* 2016
4. Garraud O. Passive immunotherapy with convalescent plasma against COVID-19? What about the evidence base and clinical trials? *Transfus Apher Sci.* 2020;59(4):102858. DOI: 10.1016/j.transci.2020.102858 Epub 2020 Jun 27. PMID: 32631501; PMCID: PMC7320683.
5. US FDA. Investigational COVID-19 convalescent plasma: Guidance for industry [Internet]; 2020 [Accessed on 17th June 2021]. Available: <https://www.fda.gov/media/13678/download>
6. Ministry of Health & Family Welfare. Clinical Management Protocol: COVID-19 version 3, dated 13/6/20 Available: www.mohfw.gov.in/pdf/ClinicalManagementProtocolforNormalCOVID19.pdf.
7. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest.* 2020;130:1545–8.
8. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest.* 2020;130:2757–65.
9. Focosi D, Franchini M. COVID-19 convalescent plasma therapy: Hit fast, hit hard! *VoxSang;* 2021. DOI: 10.1111/vox.13091 Epub ahead of print. PMID: 33794556
10. Shenoy AG, Hettlinger AZ, Fernandez SJ, et al. Early mortality benefit with COVID-19 convalescent plasma: A matched control study. *Br J Haematol.* 2021;192:706–713.
11. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from COVID-19. *N Engl J Med;* 2021. DOI: 10.1056/NEJMoa2031893
12. Salazar E, Christensen PA, Graviss EA, et al. Treatment of COVID-19 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol.* 2020; 190:2290-303
13. Long QX, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat. Med.* 2020;26:845–848.
14. Premkumar L, Segovia-Chumbez B, Jadi R, Martinez DR, Raut R, Markmann A, et al. The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. *Sci Immunol.* 2020;5(48):eabc8413. DOI: 10.1126/sciimmunol.abc8413. PMID: 32527802; PMCID: PMC7292505.
15. Cohn CS, Estcourt L, Grossman BJ, et al. COVID-19 convalescent plasma: Interim recommendations from the AABB. *Transfusion.* 2021;61(4):1313-1323. DOI: 10.1111/trf.16328. Epub 2021 Mar 7. PMID: 33586160; PMCID: PMC8014606.
16. Final GSR. 166(E) Amendment in Part X B & Part XII B pertains to Blood centre & blood components. Available: [Lhttps://cdsco.gov.in/opencms/opencms/en/Notifications/Gazette-Notifications/](https://cdsco.gov.in/opencms/opencms/en/Notifications/Gazette-Notifications/) Accessed January 12, 2020.

17. Ministry of Health & family Welfare. Clinical management protocol: COVID-19 version 3, dated 13/6/20
Available: www.mohfw.gov.in/pdf/ClinicalManagementProtocolforNormalCOVID19.pdf.
18. Available: <https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadPublicNoticesFiles/MoHFW%20Convalescent%20Plasma%20in%20COVID%20draft.pdf> (Accessed on 18th June 20221)
19. World Medical Association. World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. *JAMA*. 2013 ;310(20):2191-4.
DOI: 10.1001/jama.2013.281053.
PMID: 24141714.
20. McAndrews KM, Dowlatshahi DP, Dai J, Becker LM, Hensel J, Snowden LM, et al. Heterogeneous antibodies against SARS-CoV- 2 spike receptor binding domain and nucleocapsid with implications for COVID-19 immunity. *JCI Insight*. 2020;5.
21. Luchsinger LL, Ransegnola BP, Jin DK, Muecksch F, Weisblum Y, Bao W, et al. Serological assays estimate highly variable SARS-CoV-2 neutralizing antibody activity in recovered COVID-19 patients. *J Clin Microbiol*. 2020;58.
22. FDA. 2021. Revised COVID Convalescent Plasma EUA.
Available: <https://www.fda.gov/media/141477/download>
Accessed March 2021.
23. FDA. 2020. COVID convalescent plasma EUA.
Available: <https://www.fda.gov/media/141477/download>.
Accessed September 2020
24. FDA. 2020. FDA issues emergency use authorization for convalescent plasma as potential promising COVID-19 treatment, another achievement in administration's fight against pandemic.
Available: <https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment>
Accessed December 2020.
25. FDA. Revised COVID Convalescent Plasma EUA; 2021.
Available: <https://www.fda.gov/media/141477/download>.
Accessed March 2021.
26. Shrivastava M, Shah N, Navaid S, Agarwal K, Sharma G. Blood donor selection and deferral pattern as an important tool for blood safety in a tertiary care hospital. *Asian J Transfus Sci*. 2016;10(2):122-6.
DOI: 10.4103/0973-6247.187938
PMID: 27605848; PMCID: PMC4993080.
27. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) treatment guidelines. National Institutes of Health.
Available: <https://www.covid19treatmentguidelines.nih.gov/>.
Accessed [19/6/2021]
28. Lasky B, Goodhue Meyer E, Steele WR, Crowder LA, Young PP. COVID-19 convalescent plasma donor characteristics, product disposition, and comparison with standard apheresis donors. *Transfusion*. 2021;61(5):1471-1478.
DOI: 10.1111/trf.16286.
Epub 2021 Mar 7. PMID: 33458811; PMCID: PMC8013318.
29. Wendel S, Kutner JM, Machado R, Fontao Wendel R, Bub C, Fachini R, et al. Screening for SARS-CoV-2 antibodies in convalescent plasma in Brazil: preliminary lessons from a voluntary convalescent donor program. *Transfusion*. 2020; 60(12): 2938–51.
30. Dhiman Y, Coshic P, Pandey HC, Khatiwada B, Singh J, Mehta V, Gupta S. Deterrents in recruitment of COVID-19 convalescent plasma donors: Experience from a hospital-based blood centre in India. *Transfus Med*. 2021;31(3):149-154.
DOI: 10.1111/tme.12768.
Epub 2021 Mar 21. PMID: 33749020.
31. Mehew J, Johnson R, Roberts D, Harvala H. Convalescent plasma for COVID-19: Male gender, older age and hospitalisation associated with high neutralising antibody levels, England, 22 April to 12 May 2020. *Euro Surveill*. 2020;25(45):2001754.
DOI:10.2807/1560-7917.ES.2020.25.45.2001754.
PMID: 33183404; PMCID: PMC7667632.
32. Singh P, Srivastava A, Upadhyay S, Singh A, Gupta P, Maurya S, Pandey RK, Shrivastava A, Dev P, Singh V, Mishra R, Shukla M, Chaubey G, Kumar P, Rai V, Tripathy YB, Pathak A, Mishra V, Mallick CB, Shrivastava P. The association of

- ABO blood group with the asymptomatic COVID-19 cases in India. medRxiv; 2021.
33. Shokri P, Golmohammadi S, Noori M, Nejadghaderi SA, Carson-Chahhoud K, Safiri S. The relationship between blood groups and risk of infection with SARS-CoV-2 or development of severe outcomes: A review. *Rev Med Virol*; 2021. Available: <https://doi.org/10.1002/rmv.2247>
 34. Aljanobi GA, Alhajaj AH, Alkhabbaz FL, Al-Jishi JM. The relationship between ABO blood group type and the COVID-19 susceptibility in Qatif Central Hospital, eastern Province, Saudi Arabia: A retrospective cohort study. *OJIM*. 2020;10(02):232-238. Available: <https://doi.org/10.4236/ojim.2020.102024>
 35. Samra S, Habeb M, Nafae R. ABO groups can play a role in susceptibility and severity of COVID-19. *Egypt J Bronchol*. 2021;15:9. Available: <https://doi.org/10.1186/s43168-020-00051-w>
 36. Vahidy FS, Pan AP, Ahnstedt H, Munshi Y, Choi HA, Tiruneh Y, et al. Sex differences in susceptibility, severity, and outcomes of coronavirus disease 2019: Cross-sectional analysis from a diverse US metropolitan area. *PLoS One*. 2021;16:e0245556.
 37. Davies NG, Klepac P, Liu Y, Prem K, Jit M, group CC-w, Eggo RM. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med*. 2020;26:1205–11.
 38. Mehew J, Johnson R, Roberts D, Harvala H. Convalescent plasma for COVID-19: Male gender, older age and hospitalisation associated with high neutralising antibody levels, England, 22 April to 12 May 2020. *Euro Surveill*. 2020;25(45):2001754–7917.
 39. Terpos E, Politou M, Sergentanis TN, Mentis A, Rosati M, Stellas D, et al. Anti-SARS-CoV-2 antibody responses in convalescent plasma donors are increased in hospitalized patients; Subanalyses of a Phase 2 Clinical Study. *Microorganisms*. 2020;8(12):1885.
 40. Bošnjak B, Stein SC, Willenzon S, Cordes AK, Puppe W, Bernhardt G, et al. Low serum neutralizing anti-SARS-CoV-2 S antibody levels in mildly affected COVID-19 convalescent patients revealed by two different detection methods. *Cell Mol Immunol*; 2020.
 41. Körper S, Jahrsdörfer B, Corman V, M, Pilch J, et.al. Donors for SARS-CoV-2 Convalescent plasma for a controlled clinical trial: Donor characteristics, content and time course of SARS-CoV-2 neutralizing antibodies. *Transfus Med Hemother*. 2021;48:137-147. DOI: 10.1159/000515610
 42. Amjadi MF, O'Connell SE, Armbrust T, Mergaert AM, Narpala SR, Halfmann PJ, et al. Fever, diarrhea, and severe disease correlate with high persistent antibody levels against SARS-CoV-2. medRxiv [Preprint]. 2021:2021.01.05.21249240. DOI: 10.1101/2021.01.05.21249240. PMID: 33442707; PMCID: PMC7805469.
 43. Bégin P, Callum J, Jamula E., et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med*. 2021;27:2012–2024. Available: <https://doi.org/10.1038/s41591-021-01488-2>
 44. Setia R, Dogra M, Thangavel GP, Yadav R et al. Convalescent plasma for COVID-19- is it time to say goodbye? A Single-Center, Retrospective, Observational Study from Northern India. *International Blood Research & Reviews*. 2021;32-43. Available: [10.9734/ibr/2021/v12i430158](https://doi.org/10.9734/ibr/2021/v12i430158)
 45. David JS, Kelly AG, Shmuel S, Evan MB, et al. Randomized controlled trial of early outpatient COVID-19 treatment with high-titer convalescent plasma; 2021. medRxiv 2021.12.10.21267485; DOI: <https://doi.org/10.1101/2021.12.10.21267485>

© 2021 Dogra et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
<https://www.sdiarticle5.com/review-history/79315>