



# SARS-CoV-2 IgG Antibody and its Clinical Correlates in Convalescent Plasma Donors: An Indian Experience

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Received: 18 February 2021 / Accepted: 23 September 2021 / Published online: 18 November 2021  
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**Abstract** SARS-CoV-2, a novel coronavirus, emerged a year ago in Wuhan, China causing a new pandemic. Convalescent plasma therapy has been applied previously to many infectious diseases and has shown a successful result. This study was planned to assess the Anti-SARS-CoV-2 IgG antibody levels in convalescent COVID-19 patients. In this study, serum samples from 210 persons infected by SARS-CoV-2, treated and discharged from the hospital were collected. Anti-SARS-CoV-2 IgG antibody levels

were detected using a chemiluminescence assay. A directory of convalescent plasma donors was created. Anti-SARS-CoV-2 IgG antibody levels vary substantially in the study population with a mean of 51.2 AU/ml. On comparing the serum anti-SARS-CoV-2 IgG antibody levels, a significant difference was observed between the subjects who had cough and those who did not ( $p = 0.0004$ ). Similar significant findings were found with total protein and globulin levels on comparing the individuals with different antibody status (positive, negative and equivocal). The middle-aged and old age people had high Ab titres compared to younger individuals and the duration of the hospital stay was found to be positively correlated with the anti-SARS-CoV-2 IgG antibody. Cough, age and duration of the hospital stay was found to play a significant role in the development of Anti-SARS-CoV-2 IgG levels. Further, the data suggests that blood groups have a lesser impact on the severity of disease and the development of antibodies. Patients who present with the cough are more likely to develop antibodies.

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**Keywords** Convalescent plasma Therapy · IgG antibody · COVID-19 · SARS- Co-V-2

## Introduction

SARS-CoV-2, a novel coronavirus belonging to the group of beta coronaviruses, emerged a year ago in Wuhan, China causing a new pandemic. Since then, the world has witnessed, approximately 197,073,011 infected cases with 4,210,030 deaths (as of 31 July 2021) [1]. In India, the 1st case was detected on January 30, 2020. India has the second-largest number of coronavirus cases in the world after the US. From recent studies, it has emerged that the SARS-

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CoV-2 infection may also result in asymptomatic and mild infections, leading to obscuring of the actual number of cases [2]. Although testing for the SARS-CoV-2 in India has been significantly ramped up achieving one million tests in a single day on 21 August, the tests performed are way under the required testing number when compared to the population of 1.4 billion. Due to this under testing, the majority of the cases remain undetected who are either asymptomatic or have a mild disease [3].

For more than a decade, convalescent plasma (CP) therapy has been applied previously to many infectious diseases. It has shown a successful result in past coronavirus diseases like the Middle East respiratory syndrome (MERS) and Severe acute respiratory syndrome (SARS). Therefore, both the United States *Food and Drug Administration* (USFDA) and the Indian Council of Medical Research (ICMR) had approved the use of CP in COVID-19 patients in the early phase of the Pandemic. ICMR sponsored PLACID trial was published recently [4]. This trial recruited 462 patients from 39 tertiary care hospitals across India. This study did not report any benefit in all-cause mortality or progress to a severe course in patients with moderate disease. However, a higher proportion of patients in the intervention arm showed improvement in the resolution of dyspnoea and fatigue. The study also concluded that high-titre plasma *may* be more beneficial than low-titre plasma for COVID-19 patients. Based on this study the CP continued to find a place in the recommended guidelines, in 'off label' use [5]. A UK based double-blinded RECOVERY trial involving 5000 patients was published recently [6]. The results of the trial reported that high titre convalescent plasma transfusion did not reduce mortality or improve patient outcome. After the RECOVERY trial results, the national task force of the ICMR, along with experts from the Health Ministry has dropped the use of convalescent plasma from the recommended treatment guidelines for COVID-19 [7].

In past, seroprevalence studies of many diseases have been found to reflect the proportion of people exposed to the infection, which reveals the true burden of the disease in the community. These studies include the detection of specific antibodies to the virus protein. Protection specific Abs, including immunoglobulin G (IgG) Abs and neutralizing Abs (NAbs), are produced by B cells after infection with the virus, which can block the virus from entering the host cells and prevent reinfection. A recent study reported acute antibody responses to SARS-CoV-2 in 285 patients with COVID-19 [8]. Within 19 days of symptom onset, 100% of patients tested positive for antiviral immunoglobulin-G (IgG). Seroconversion for IgG and IgM occurred simultaneously or sequentially. Both IgG and IgM titres plateaued within 6 days of seroconversion [8]. There are many population-based studies on the seroprevalence

of antibodies against SARS-CoV-2 in different countries like France, Italy and Switzerland but none of them have an available database for donors with high antibody titers for convalescent plasma therapy [9]. Similar population-based studies were also started in the United States for the use of convalescent plasma as a treatment modality [10].

Although neutralising antibody titres should be done before administering CP, it is not feasible in all tertiary care centres for the want of biosafety level -3 facility, which are far and few and restricted primarily to research institutes only. The New York Blood Centre & the Con-COVID group from Netherland have both shown a good correlation between commercial serological assays and neutralisation assays [11, 12]. Different commercial platforms being used for the estimation of SARS-CoV-2 IgG antibodies and lack of harmonisation between assays is a hurdle in the estimation of IgG SARS CoV-2 antibodies and adoption of CP as a standard of care in the treatment of COVID-19.

Previous studies have indicated that the blood group antigens found in erythrocytes and other tissues interact with microorganisms such as bacteria, viruses, parasites, and fungi. Differences in blood group antigen expression can increase or decrease host susceptibility to many infections. Infection with Hepatitis C virus, human immunodeficiency virus, and SARS are associated with human blood groups [13–15]. Clinical studies have also been conducted examining the relationship between SARS-CoV-2 and blood groups [16, 17].

The present study was planned to assess the IgG antibody levels for SARS-CoV-2 spike protein S1/S2 in treated and recovered patients from COVID-19 and to prepare a database of potential donors for convalescent plasma therapy in a tertiary health care centre in the North-Western region of India.

## Materials and Methods

This was a cross-sectional study conducted at All India Institute of Medical Sciences (AIIMS), Jodhpur between 11 July and 25 September 2020. A total of 210 COVID-19 patients (tested positive by RT-PCR) were recruited. Patients who had recovered were counselled in person before discharge from wards on the uses of convalescent plasma & encouraged to donate plasma. Patients were counselled on telephone as well. All participants had given their written informed consent before participating in the study and their anonymity was preserved. The study was performed as per the ethical guidelines established in the declaration of Helsinki and was approved by the institutional ethics committee (AIIMS/IEC/2020/3202).

A total of 3.5 ml of blood was drawn, serum was separated and stored at  $-80^{\circ}\text{C}$ , and was defrosted before testing. Blood grouping was done with the standard tube method. CBC was done on a three-part Sysmex XP-100 automated analyser. Anti-SARS-CoV-2 IgG antibody against S1/S2 antigens of SARS-CoV-2 was detected using both FDA and ICMR approved fully automated chemiluminescence analyser Liaison XL (DiaSorin, Italy). As per the kit literature the estimated sensitivity & specificity of this Anti-SARS-CoV-2 IgG antibody test by Liaison XL (DiaSorin, Italy) was 97.4% (95% CI 86.8%–99.5%) & 98.5% (95% CI 97.5%–99.2%) in individuals after 15 or more days of a positive RT PCR test. The positive agreement in comparison to plaque reduction neutralization test (PRNT) is 94.4% (95% CI 88.8%–97.2%) and negative agreement 97.8% (95% CI 94.4%–99.1%). Titers with  $< 12.0$  AU/mL was regarded as negative,  $12.0$ – $15.0$  AU/mL was taken as equivocal and  $> 15.0$  AU/mL was regarded as positive for the antibodies. The average intra-assay imprecision was a 2.8% coefficient of variation (2.8% CV) (range 2.0–3.4% CV), and total-assay imprecision averaged 3.2% CV (range 2.7–3.9% CV) [18].

## Statistical Analysis

The data collected were analysed using Microsoft Excel and Stata version 14 for windows. The data are expressed as mean, median and range. Categorical variables were

calculated as frequency and percentage, continuous variables were represented as mean (SD). The normality of the parameters was checked using the Shapiro-Wilks test and found to be non-parametric. Mann Whitney U test and Chi-square test were used to calculate the statistical differences between continuous variables and categorical variables respectively. Multivariable analysis was performed for the clinical measures and symptomatic profiles using logistic regression. The Kruskal–Wallis test was used to compare between 3 or more groups. Spearman correlation test and Bonferroni correction for multiple testing were used to examine the relationship between anti-SARS-CoV-2 IgG antibody levels and other clinical measures. A p-value of  $< 0.05$  was considered statistically significant.

## Results

The demographic profiles, biochemical profile (Anti-SARS-CoV-2 IgG antibody levels, total protein, albumin and globulin), clinical symptom profiles (throat pain, cough, fever, dyspnoea, muscle/ body pain and loss of taste/smell), complete blood count and duration of hospitalisation were observed in all subjects (Tables 1, 2).

The mean (SD) age of the study population was 35.6 (9.3) years while the median and range were 36 and 18–58 years respectively. Among the study subjects, 200 (95%) were males with a mean age of 36.2 years and 10 (5%) were females with a mean age of 28.1 years.

**Table 1** Demographic and clinical laboratory data of the study population

Variables	Study population (n = 210)			
	n (%)	Mean (SD)	Median	Range
<i>Demographic data</i>				
Age (In years)	–	35.64 (9.55)	46.82	18–58
Gender				
Males	204 (97)	–	–	–
Females	6 (3)	–	–	–
<i>Clinical laboratory data</i>				
Anti-SARS-CoV-2 IgG (AU/mL)	–	51.29 (50.41)	31.69	3.8–206
Total protein (gm/dL)	–	7.42 (0.49)	7.60	4.8–8.58
Albumin (gm/dL)	–	4.41 (0.36)	4.53	2.26–5.16
Globulin (gm/dL)	–	3 (0.35)	3.06	2.12–4.31
<i>Haematological profile of plasma donors (n = 97)</i>				
Hb (gm/dL)	–	15.19 (1.5)	15.1	12.1–20.1
Platelets ( $\ast 10^3$ )	–	259 (65)	260	75–451
Monocytes	–	10.8 (4.9)	9.7	4.4–44.3
Neutrophils	–	52 (8)	52.15	38.1–79.5
Lymphocytes	–	36 (7.5)	36.75	14.9–50.5
Neutrophil-to-lymphocyte ratio (NLR)	–	1.57 (0.65)	1.4	0.78–5.35
Total leucocyte count (TLC)	–	7850 (1748)	7650	1300–13,200

**Table 2** The frequency of symptoms & other clinical variables of the study population during the course of infection

Clinical and symptomatic profile Study Population (n = 210)			
Clinical variables	Mean (SD)	Median	Range
Duration of hospital Stay/ home quarantine (days)	11.4 (4.74)	10.72	5–36
Day of antibody test post RT-PCR negative status (days)	41.48 (27.06)	60.24	13–214
Symptomatic profile			Present (%)
Throat Pain			180 (85.7)
Cough			143 (68)
Fever			155 (73.8)
Muscle/Body pain			49 (23.3)
Dyspnoea			32 (15.2)
Diarrhoea			13 (6.1)
Loss of Smell/Taste			73 (34.7)

The mean levels of anti-SARS-CoV-2 IgG antibody levels of the study population were 51.2 AU/ml, while the median and range were 37.15 and 3.8–206 AU/ml respectively. Similarly, the mean, median and range of the biochemical parameters were represented in Table 1. Out of the total study population, 145 (69%) tested positive, 55 (26%) tested negative and 10 (5%) tested equivocal for Anti-SARS-CoV-2 IgG antibody levels. On analysing the symptoms, the maximum number of study subjects were having throat pain (85.7%), fever (73.8%) and cough (68%). The mean (SD) of the number of days of hospitalisation or home quarantine was 11.4 (4.6) days, while the median and range were 11 days and 5–36 days respectively. Similarly, the mean (SD) of other clinical measures, like the number of days after PCR negativity after which antibody level was estimated as 41.8 (28.4), whereas median and range were 36 days and 13–214 days respectively (Table 2). Out of these 145 positively tested patients, 97 patients donated plasma. On comparing the neutrophil-to-lymphocyte ratio (NLR) of these 97 patients with the Anti-SARS-CoV-2 IgG antibody levels, there was a non-significant positive correlation ( $r = 0.28$ ,  $p = 0.4$ ) (Table 3). A significant weak negative correlation was found between the NLR and the number of days after PCR negativity, after which the antibody level was estimated ( $r_s = -0.2$ ,  $p = 0.01$ ) (Table 4).

On comparing the serum anti-SARS-CoV-2 IgG antibody levels between individuals with and without symptoms, a significant increase in the antibody levels was observed between the subjects having cough ( $p = 0.0004$ ) (Table 5). Further, on comparing the status of the antibodies (positive, negative and equivocal) with the clinical and demographic profiles a significantly higher antibody level was found between the subjects who had cough and those who did not ( $\chi^2 = 11.89$ ,  $p = 0.003$ ) (Table 6). The total protein and globulin levels have significantly differed

between different antibody status ( $\chi^2 = 10.15$ ,  $p = 0.006$  and  $\chi^2 = 7.01$ ,  $p = 0.03$ ) (Fig. 1). Logistic regression was run to understand the effects of the clinical features and symptoms on development of antibodies. The number of days of hospital stay and cough significantly predicted the antibody development ( $p = 0.025$  and  $p = 0.016$  respectively).

On correlation analysis, no significant correlation was found between Anti-SARS-CoV-2 IgG antibody levels and biochemical parameters (after the Bonferroni correction for multiple testing) (Table 3). The serum Anti-SARS-CoV-2 IgG antibody levels showed a nonsignificant positive correlation with both duration of hospital stay/home quarantine ( $p = 0.2$ ) and with the number of days after which the antibody test was done ( $p = 0.3$ ).

In the total study population, 83 (40%) were having O positive blood group, 69 (33%) were having B positive blood group, 45 (21%) were having A positive blood group & 13 (6%) were having AB positive blood group. Out of all the positively tested individuals (145) for antibodies, 57 (39.3%) had O positive blood group. On comparing the blood groups with the antibody status and other clinical parameters, no significant difference was found.

## Discussion

Ever since WHO declared COVID-19 as a global pandemic, the whole world has been looking for the development of an effective treatment or vaccine against SARS-CoV-2 infection. Since then, convalescent plasma therapy has emerged as one of the treatment plans for SARS-CoV-2 infection. Convalescent plasma therapy, classic adaptive immunotherapy, has been applied to the prevention and treatment of many infectious diseases for more than a decade. Over the past decades, convalescent plasma

**Table 3** Comparison of frequency of symptoms & other clinical variables with different antibody status (negative, equivocal and positive) of the study population

Clinical Details	Antibody status			$\chi^2$	p
	Negative (< 12)	Equivocal (12–15)	Positive (> 15)		
Gender					
Males	52	10	142	1.95	0.37
Females	3	0	3		
Throat pain					
Yes	49	8	123	0.87	0.64
No	6	2	22		
Cough					
Yes	32	3	108	11.89	<b>0.003</b>
No	23	7	37		
Fever					
Yes	37	8	110	1.73	0.42
No	18	2	35		
Muscle/Body pain					
Yes	16	0	33	4.08	0.12
No	39	10	112		
Dyspnoea					
Yes	7	0	25	2.51	0.28
No	48	10	120		
Diarrhoea					
Yes	2	2	9	3.90	0.12
No	53	8	136		
Loss of Smell/Taste					
Yes	19	3	51	0.11	0.94
No	36	7	94		
Co-morbidities DM*					
Present	5	1	16	0.14	0.92
Absent	47	8	122		
HTN*					
Present	4	1	13	0.15	0.91
Absent	48	8	125		
Both DM* & HTN*					
HTN	4	1	13	0.88	0.9
DM	5	1	16		
Both	3	1	7		
None	43	7	109		
Smoking/Alcohol					
Smoking	2	0	7	1.6	0.9
Alcohol	13	2	31		
Both	3	1	14		
None	37	7	93		
Blood Group					
A+	7	4	30	9.5	0.4
A–	1	0	3		
B+	23	3	43		
AB+	1	1	11		
O+	22	2	57		
O-	1	0	1		

\*DM Diabetes melitus, HTN hypertension

**Table 4** Comparison of Anti-SARS-CoV-2 IgG levels of the study population (with and without symptoms & treatment with remdesivir) during the course of infection

Variables	n	Anti-SARS-CoV-2 IgG levels Median (range)	p-value
Throat Pain			
Yes	180	31.7 (3.08–187)	0.11
No	30	40.5 (38–206)	
Cough			
Yes	143	45.25 (3.8–206)	<b>0.0004</b>
No	67	23.75 (3.8–182)	
Fever			
Yes	155	37.9 (3.8–206)	0.46
No	55	31.4 (3.8–200)	
Muscle/Body pain			
Yes	49	35.05 (3.8–183)	0.7
No	161	37.15 (3.8–206)	
Dyspnoea			
Yes	32	35.07 (3.8–206)	0.5
No	178	29.1 (3.8–175)	
Diarrhoea			
Yes	13	34.05 (3.8–182)	0.9
No	197	36.15 (3.8–206)	
Loss of Smell / Taste			
Yes	73	36.9 (3.8–206)	0.42
No	137	32.4 (3.8–195)	
Treatment with remdesivir			
Yes	23	56.5 (15.4–206)	0.13
No	187	32.5 (3.8–177)	

therapy was successfully used in the treatment of SARS, MERS, and the 2009 H1N1 pandemic with satisfactory efficacy and safety [19–21]. Positive tests for IgG, IgM, and IgA are generally described as > 1.0 arbitrary unit/mL or AU/mL [14]. Values for IgG antibodies > 6.5 AU/mL correspond to an antibody titer of approximately > 1:320 and IgG values > 20 AU/mL correspond to titers > 1:1000. An IgG antibody titer of > 1:320 has been recommended by the FDA as a threshold for determining if convalescent plasma should be used in a patient [15]. The FDA also recommends an antibody titer of 1:160, but a titer of 1:80 may be acceptable if another matched unit is not available [16]. Currently, there is insufficient data about how titer levels correlate with viral clearance and even the roles of humoral and cellular immune responses during the infection. In this study, we made a database of potential donors for convalescent plasma therapy by assessing the Anti-SARS-CoV-2 IgG levels in treated and recovered patients from COVID-19.

Quantification of Anti-SARS-CoV-2 IgG antibody levels in recovered or treated patients is a key tool for the determination of immunity of the population to SARS-CoV-2 infection. Results of our study suggest that majority of the subjects who have recovered from SARS-CoV-2 infection had positive antibody levels. These findings were

similar to many other seroprevalence studies [17]. Although most of the study subjects have a similar duration of hospital stay, the serum antibody titres showed significant variation. Around 40% of the study population failed to develop a significant antibody titre against the SARS-CoV-2. This may be due to different immune response in individuals against COVID-19 around the globe. Similarly, few individuals had developed very high titres of Anti-SARS-CoV-2 IgG levels within 20 days with the same course of infection as of individuals who failed to develop antibodies. These findings were similar to the study done by Wu et al., where 30% of the study population who had recovered from SARS-CoV-2 infection failed to develop the antibodies against the virus [18]. These results may suggest that some other immune factors may play role in the development of the Anti-SARS-CoV-2 IgG in recovered patients. Whether these individuals with low antibody titres are at risk of reinfection has to be explored in future studies. Logistic regression has shown that the duration of the hospital stay has correlated with the antibody status and patients having cough as a symptom had developed positive antibody status. The results of the regression were contradictory to the results of previous studies where the duration of hospital stay negatively correlated with the antibody status [19]. A negative correlation in our study

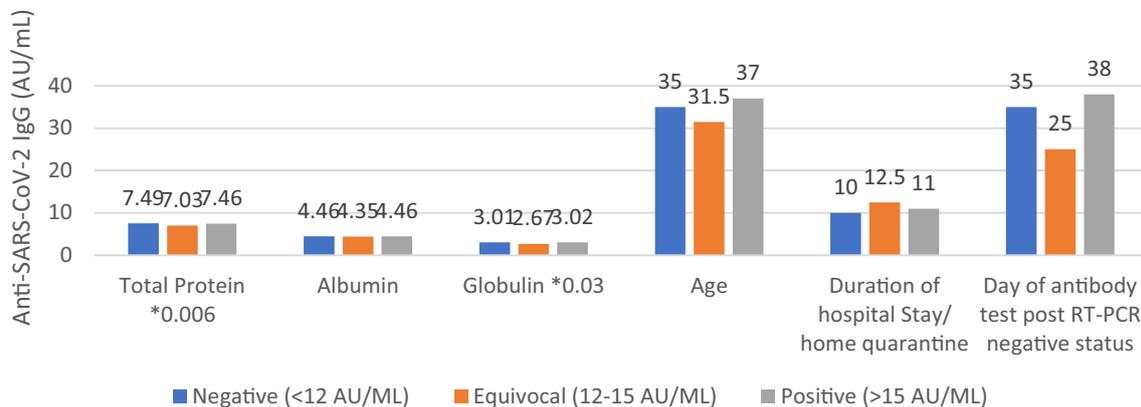
**Table 5** Correlation of Anti-SARS-CoV-2 IgG levels with clinical variables

Variables study population (n = 210)	Anti-SARS-CoV-2 IgG levels	
	$r_s$	p-value
Age	0.0185	0.7
Duration of hospital Stay/ home quarantine	0.084	0.2
Day of antibody test post RT-PCR negative status	– 0.06	0.3
Total Protein	– 0.012	0.8
Albumin	– 0.015	0.8
Globulin	0.005	0.9

**Table 6** Correlation of NLR with the clinical variables of convalescent plasma donors (n = 97)

Variables study population (n = 97)	NLR	
	$r_s$	p-value
Age	0.13	0.2
Duration of hospital Stay/ home quarantine	– 0.05	0.6
Day of antibody test post RT-PCR negative status	– 0.25	<b>0.01</b>
IgG	0.08	0.4
TLC vs IgG antibodies	– 0.15	0.2

\*NLR Neutrophil–Lymphocyte Ratio, TLC Total lymphocyte count



**Fig. 1** Comparison of different clinical variables against the negative, equivocal and positive antibody levels (n = 210)

between duration of hospital stay and antibody status could be attributed to the fact that lower antibody levels meant more severe infection hence the hospital stay was prolonged.

According to a recent study by the American Society of Haematology, individuals with blood type O may have the lowest risk of infection whereas individuals with A and AB may have an increased risk of severe clinical outcomes [20]. In this study, almost all the blood groups have a similar duration of hospital stay and the Rh-positive blood groups were associated with higher antibody levels. The Rh + association with disease positivity appears to be a novel finding and warrants further investigation. Given the relative rarity of Rh-negative blood types, these could not

be ruled out by our patient numbers in this study. Our data suggest that blood groups may have a lesser impact on the severity and the development of the antibodies against the SARS-CoV-2. Similarly, comorbidities like diabetes mellitus (DM) and hypertension (HTN) did not have any significant effect on the development of antibodies, which is in line with a recent seroprevalence study on a Spanish population. [28].

Recent studies indicate neutrophil/lymphocyte ratio (NLR) as a powerful prognostic factor for COVID-19 [29]. NLR was calculated by dividing the absolute neutrophil count by the lymphocyte count. In this study, we have compared both the NLR, an indicator of innate immunity, and IgG, an indicator of acquired immunity. A significant

negative correlation of NLR with the number of days post RT-PCR negative status suggests that inflammation decreases with time. A high NLR connotes more severe disease which led to an enhanced acquired immunological response hence higher antibody levels. Our findings are similar to the other studies indicating that IgG response is also associated with the development of other innate immunity-related markers such as NLR [30].

Like other coronavirus infections, in SARS-CoV-2 infection, age played a major role in severity [31, 32]. In a recent study by Yang et al., patients aged 19–30 years exhibited lower levels of SARS-CoV-2 IgG antibodies than children and older adults [33]. However, in this study, the middle-aged and old people had high Ab titres compared to younger individuals. The exact mechanisms underlying the different SARS-CoV-2 immune responses based on age remain unclear. Age-related quantitative and qualitative changes in the immune system affect cells and soluble mediators of both the innate and adaptive immune responses within lymphoid and non-lymphoid peripheral tissues. These changes determine not only the susceptibility to infections but also disease progression and clinical outcomes thereafter [34]. In this study, the symptom cough was found to play a significant role in the anti-SARS-CoV-2 IgG levels. Similar results were seen with the throat pain, cough and fever in other studies on recovered patients [35]. The role of treatment with remdesivir on anti-SARS-CoV-2 IgG levels is still not fully explored. In our study, there was no significant difference between patients who received remdesivir and who did not. Further studies on immunological aspects of antiviral drugs may give a clear insight into the development of protective antibodies.

There are several operational challenges for the implementation of CP on a mass scale apart from the controversial evidence of its benefit in treating COVID-19. Centralised antibody estimation titre and harmonisation of seroassays should be undertaken to build registries of CP donors.

Multiple barriers exist amongst convalescent COVID-19 patients regarding the donation of plasma. A lurking fear of visiting the hospital amid an epidemic, scare of the procedure of apheresis, fear of waning immunity on donating plasma and reinfection are a few of them. This problem is further compounded by lockdowns & restriction on mobility during pandemics [36].

## Conclusion

Among the patients who recovered from SARS-CoV-2 infection, Anti-SARS-CoV-2 IgG antibody levels appeared to vary substantially. The development of the antibodies positively correlated with the age and duration of the

hospital stay. Further, the data suggests that blood groups may have a lesser impact on the severity and the development of the antibodies. The potential clinical implications of these findings for convalescent plasma therapy, vaccine development and future protection from infection are still needed to be explored.

To the best of our knowledge, this is the first study in the western Indian population that has assessed Anti-SARS-CoV-2 IgG antibody levels in SARS-CoV-2 recovered patients. This study is preliminary and has several limitations. First, the viral loads during the disease course have not been taken into consideration. Second, we did not measure the neutralising antibodies hence we were unable to evaluate the effect of viral clearance on antibodies.

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