


ORIGINAL ARTICLE

Convalescent plasma for COVID-19: Donor demographic factors associated high neutralising antibody titres

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Abstract

Background: Convalescent plasma containing high levels of SARS-CoV-2 antibodies has been studied as a possible treatment for COVID-19. Better understanding of predictors of high antibody levels is needed for improving supply of high-quality therapeutic plasma.

Aims: We have evaluated demographic and clinical factors associated with the probability of a convalescent plasma donor having high SARS-CoV-2 IgG antibody levels.

Methods: A total of 29,585 convalescent plasma donors employed during the first and second waves of the COVID-19 pandemic in England were included in this study. All had been tested for SARS-CoV-2 IgG antibodies by EUROimmun ELISA. A multivariable logistic regression model was used to quantify the association of the demographic and clinical factors with high (EUROimmun S/Co>6.0) SARS-CoV-2 IgG antibody level.

Results: Most of the donors were male (23,024; 78%), with white ethnic background (24,598; 83%) and had not been tested for SARS-CoV-2 (15,266; 52%). Overall, less than 20% of convalescent plasma donors with confirmed or suspected SARS-CoV-2 infection harboured high SARS-CoV-2 antibody levels ($n = 4,978$). We found that older male donors who had been hospitalised with COVID-19 were most likely to harbour high levels of antibodies. White donors were less likely to have high SARS-CoV-2 antibody levels than donors with Asian or black ethnic backgrounds residing in affluent areas likely reflecting ethnic inequality previously associated with SARS-CoV-2 infection.

Discussion: In a time of great uncertainty, and predicted new waves associated with newly emerging SARS-CoV-2 variants, these results will help us to target future convalescent plasma collections.

KEYWORDS

antibody level, convalescent plasma, COVID-19, SARS-CoV-2 infection

1 | INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first recorded in China at the end of 2019 and has since continued to spread throughout the world. While many eagerly await the coronavirus vaccinations as the main pandemic exit

strategy, the search for effective prophylactic and supportive therapies to treat vaccine non-responders continues.¹ Convalescent plasma containing high levels of neutralising antibodies to SARS-CoV-2 is a potential means to reduce morbidity and mortality. Although recent meta-analysis including 33 convalescent plasma trials with 16 477 patients with COVID-19 demonstrated that convalescent plasma

treatment did not decrease all-cause mortality,^{2,3} it may be beneficial if given in early stages of infection^{4–7} or used to treat those unable to mount an effective immune response.^{3,8–10} Although immunisation programmes are advancing very fast, rapid spread of new SARS-CoV-2 variants with several mutations in the spike (S) glycoprotein that may show increased resistance to neutralisation have raised concerns^{11–13} and might support future use for convalescent plasma.

We have previously demonstrated a correlation between virus neutralising antibody titres and antibody reactivity in commercial EUROimmun ELISA IgG tests in convalescent plasma collected from individuals with confirmed or suspected SARS-CoV-2 infection at least 28 days after the resolution of their symptoms.^{14,15} Based on that, we adopted a strategy where all donations with a signal to cut-off (S/CO) ratio of 6.0 or higher in the EUROimmun assay were released for clinical use without further virus neutralisation testing.¹⁴ Replacement of live virus neutralisation testing performed externally with in-house EUROimmun testing has allowed testing of a large number of donations in a very short timeframe. All convalescent plasma donations are tested for SARS-CoV-2 IgG antibodies by EUROimmun assay at NHS Blood and Transplant testing laboratories in Filton and Manchester, and results transferred directly into our donor management database.

A better understanding of the predictors of high antibody levels is important for improving access to high-quality therapeutic plasma. It has been previously demonstrated that high neutralising antibody levels correlated with male sex, older age, and severity of SARS-CoV-2 infection,^{16,17} albeit derived from studies with small sample sizes (<500). To obtain more definitive data on predictive factors for high neutralising antibody levels, we have evaluated donor demographic and clinical factors associated with high antibody levels based on the EUROimmun IgG result in a large cross-sectional study of 29 585 donors in England in 2020.

2 | METHODS

2.1 | Study cohort

This study includes 29 585 convalescent plasma donors with a confirmed or suspected SARS-CoV-2 infection, all at least 28 days post the resolution of their symptoms at the time of donation between 22 April and 16 December 2020. All had been tested for SARS-CoV-2 IgG antibodies by EUROimmun ELISA.^{14,15} Many of these donors donated more than once during the study period but only data from their first donation or sample were included in the analysis. To optimise use of available session time, some donors (including female donor and those without a confirmed SARS-CoV-2 infection) were invited for a medical assessment and sample-only collection before a full donation was collected.

2.2 | Donor data

SARS-CoV-2 IgG antibody level was defined as high if Euroimmun s/co ratio was 6.0 or higher. Donor demographic factors including sex,

age, ethnic origin, blood group, geographic region based on donor centre details, social deprivation score based on donor's home post-code and using Acorn classification,¹⁶ whether they had previously donated blood and donation date were extracted from the NHS Blood and Transplant donor management database. The date of SARS-CoV-2 molecular detection was available from NHS Digital and hospitalisation information (yes/no) was received from NHS Digital or from a web form completed by donors (including those without SARS-CoV-2 molecular detection) to include a set of relevant information, when indicating their interest in becoming a convalescent plasma donor. For donors with data available from NHS Digital, the time interval between SARS-CoV-2 detection and donation was calculated.

2.3 | Statistical analysis

Sociodemographic and clinical characteristics were summarised using descriptive statistics, stratified by SARS-CoV-2 IgG antibody level. A multivariable logistic regression model was developed on the development dataset based on 70% of randomly selected donors to test and quantify the association of the 10 aforementioned factors with high (EUROimmun S/Co >6.0) SARS-CoV-2 IgG antibody level. A stepwise variable selection method was used; candidate explanatory variables were retained in the model if they reduced the model deviance significantly ($p < 0.1$) according to the likelihood ratio test. Donors with missing data for any of the significant variables were excluded from the model.

The logistic regression model is commonly interpreted through the odds ratio. The probability that a donor will exhibit high SARS-CoV-2 antibody levels is linked to the odds through the following equation:

$$\text{odds} = \frac{p}{1-p}$$

Therefore, the higher the odds, the higher the probability and the smaller p is, the closer the odds and the probability become.

Two-way variable interactions were considered between all the variables that were found to be significant as main effects, with the exception of donor centre region and timing of their donation (calculated as days since project began) as any interactions involving these two variables were not considered clinically meaningful. Two continuous variables (timing of the donation calculated as days since project began and the time between SARS-CoV-2 detection and donation) were tested once as a linear variable and once as a non-linear variable. Natural cubic splines were used to represent non-linearity, enabling cubic expressions between 'knots' at the 5%, 35%, 65% and 95% percentiles. A model containing the spline terms would be considered more appropriate than a model containing just the linear term if it reduced the model deviance significantly ($p < 0.1$) according to the likelihood ratio test. Because the time between SARS-CoV-2 detection and donation could not be calculated for donors without a SARS-CoV-2 test, this variable was tested at the end of the modelling

TABLE 1 Demographic factors of 29 585 convalescent plasma donors, England, 22 April to 16 December 2020

Demographic factors	Categorisation	Total	No. High antibody levels	%
Sex	Female	6561	1216	19
	Male	23 024	3762	16
Age group (years)	17–24	2346	239	10
	25–34	6433	626	10
	35–44	6779	858	13
	45–54	7756	1621	21
	55–64	5760	1525	26
	over 65	511	109	21
Ethnic group	Asian	1658	548	39
	Black	312	94	30
	Mixed	625	108	17
	Other	271	55	20
	Unknown	2121	411	19
	White	24 598	3762	15
Blood group (data missing for 194)	A	12 259	2158	18
	B	3138	584	19
	O	12 471	2000	16
	AB	1253	204	16
Region	East Midlands	1587	282	18
	East of England	1835	342	19
	London	9759	1519	16
	North East	2176	383	18
	North West	4493	794	18
	South East	3021	509	17
	South West	1969	274	14
	West Midlands	2548	483	19
	Yorkshire	2197	392	18
Social deprivation (data missing for 810)	Affluent achievers	9709	1702	18
	Rising prosperity	5338	706	13
	Comfortable communities	7003	1270	18
	Financially stretched	3956	666	17
	Urban adversity	2771	511	18
Previous blood donor	Yes	6375	802	13
	No	23 210	4176	18
Test group	Not tested	15 266	1878	12
	Tested positive but not hospitalised	13 280	2436	18
	Tested positive and hospitalised	1039	664	64
Total		29 585	4978	17

process on a subset of donors with an available SARS-CoV-2 positive result.

The Hosmer and Lemeshow C statistic (equivalent to the area under the ROC curve) was calculated to assess predictive ability. A value of 0.5 indicates that the model predicts no better than adopting a 50/50 guess and a value of 1 indicates perfect prediction, whereas values between 0.7 and 0.8 show acceptable predictive

ability. Deviance residuals were assessed to identify any outlying observations. Cooks D statistic was plotted for each observation to identify any values that were highly influential in the calculation of the set of parameter estimates (referred to as influential observations). The Delta-betas were also plotted against each observation for each parameter in the model to identify any observations that highly influenced particular parameter estimates.

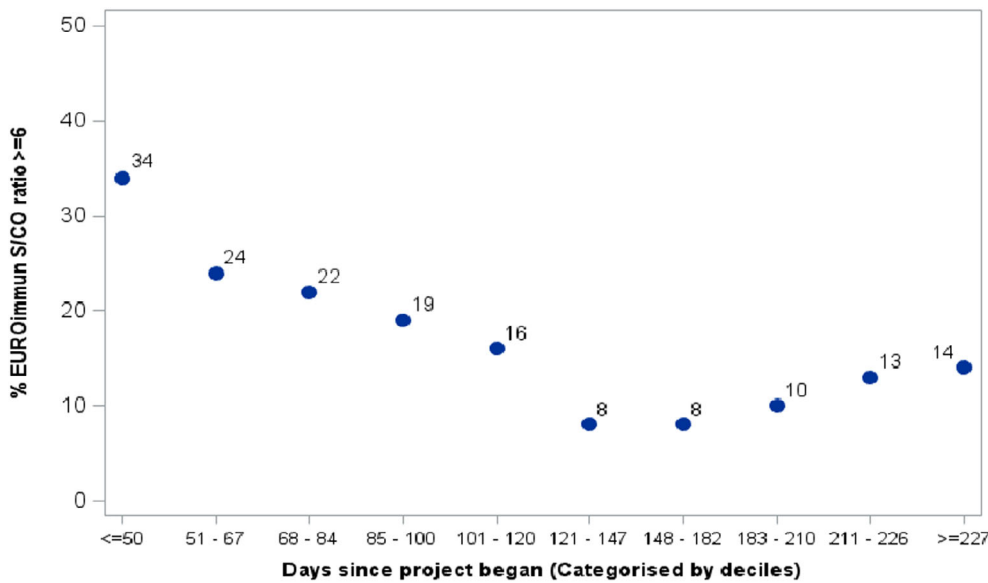


FIGURE 1 Proportion of donors with ‘high antibody levels’ by timing of donation (defined as ‘days since project began’ categorised by deciles)

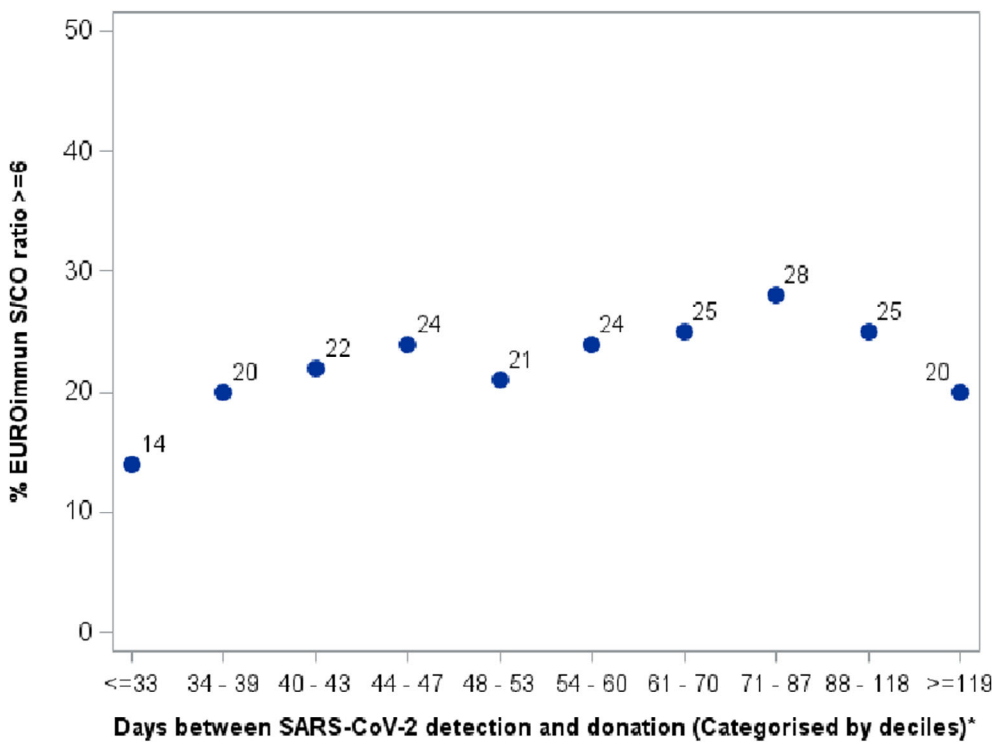


FIGURE 2 Proportion of donors with high antibody levels by duration between SARS-CoV-2 detection and donation (categorised by deciles). Data shown for the 12 637 donors who had a SARS-CoV-2 positive test date available

2.4 | Model validation

The parameter estimates from the developed model were used to calculate the estimated probability of high SARS-CoV-2 antibody level for all donors with complete data in the validation dataset based on the remaining 30% of donors. These donors were divided into four groups defined by the quartile values of the equivalent estimated probabilities calculated from the development dataset. A logistic regression model for the probability of high SARS-CoV-2 antibody level (defined as S/CO ratio of 6.0 or higher in the EUROimmun assay) was fitted to the validation dataset in order to assess odds ratio

differences between these four groups of donors. The distribution of estimated probabilities was also compared between the donors with low and high SARS-CoV-2 antibody levels in the validation dataset.

3 | RESULTS

A total of 29 585 convalescent plasma donors were included in our study; they all either donated plasma or were sampled in England between 22nd April and 16th December 2020. Most of them were male (23 024; 78%), with white ethnic background (24 598; 83%), had

TABLE 2 Logistic Regression Model for probability of high SARS-CoV-2 antibody level (model C statistic of 0.758)

Factor	Categorisation	Odds ratio	95% CI	p Value
Test group	Not tested	Effect dependent upon gender and age (Figures 1 and 2)	-	$p < 0.0001^*$
	Tested positive and not hospitalised			
	Tested positive and hospitalised			
Age group	17–24	Effect dependent upon test group and gender (Figures 1 and 2)	-	$p < 0.0001^*$
	25–34			
	35–44			
	45–54			
	55–64			
	65+			
Days from began	Non-linear term	Figure 4	-	$p < 0.0001$
Blood group	A	1.14	1.04, 1.24	0.0007
	B	1.07	0.93, 1.23	
	AB	0.77	0.62, 0.97	
	O	1	-	
Previous blood donor	No	1	-	0.002
	Yes	0.841	0.75, 0.94	
Ethnic group	Asian	Effect of dependent upon Social deprivation Indicator (Figure 3)	-	0.004*
	Black			
	Mixed			
	Other			
	Unknown			
	White			
Social deprivation indicator	Affluent achievers	Effect dependent upon ethnic group (Figure 3)	-	0.04*
	Rising prosperity			
	Comfortable communities			
	Financially stretched			
	Urban adversity			
Donor centre region	East Midlands	1.05	0.85, 1.31	0.06
	East of England	1.17	0.96, 1.44	
	London	0.93	0.80, 1.09	
	North East	1.00	0.82, 1.22	
	North West	1.04	0.88, 1.22	
	South East	0.86	0.71, 1.03	
	South West	0.88	0.71, 1.08	
	West Midlands	1	-	
	Yorkshire and The Humber	1.04	0.85, 1.27	
Sex	Male	Effect dependent on age and test group (Figures 1 and 2)	-	0.06*
	Female			
Sex x test group	Interaction term	Figures 2 and 3		0.002
Age group x test group	Interaction term	Figures 2 and 3		0.02
Age group x sex	Interaction term	Figures 2 and 3		0.04
Ethnic group x social	Interaction term	Figure 4		0.04

Note: *p-Value should not be interpreted alone as this factor is included as part of a significant interaction term.

either blood group A (12,259; 42%) or O (12,741; 43%), donated in the London region (9759; 33%), were new blood donors (23 210; 78%) and had not been tested for SARS-CoV-2 (15 266; 52%;

Table 1). Only a small proportion of our donors had been hospitalised with SARS-CoV-2 infection (1039; 3.5%). Overall, 4978 (17%) convalescent plasma donors exhibited high SARS-CoV-2 antibody levels as

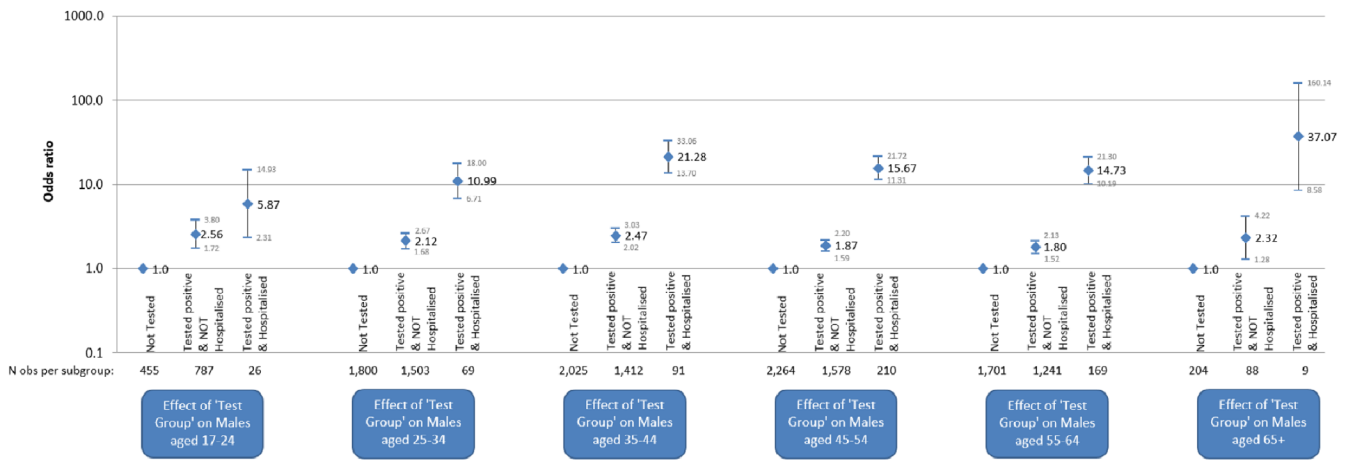


FIGURE 3 The interdependent effect of test group and age group on probability of high SARS-CoV-2 antibody levels for male donors

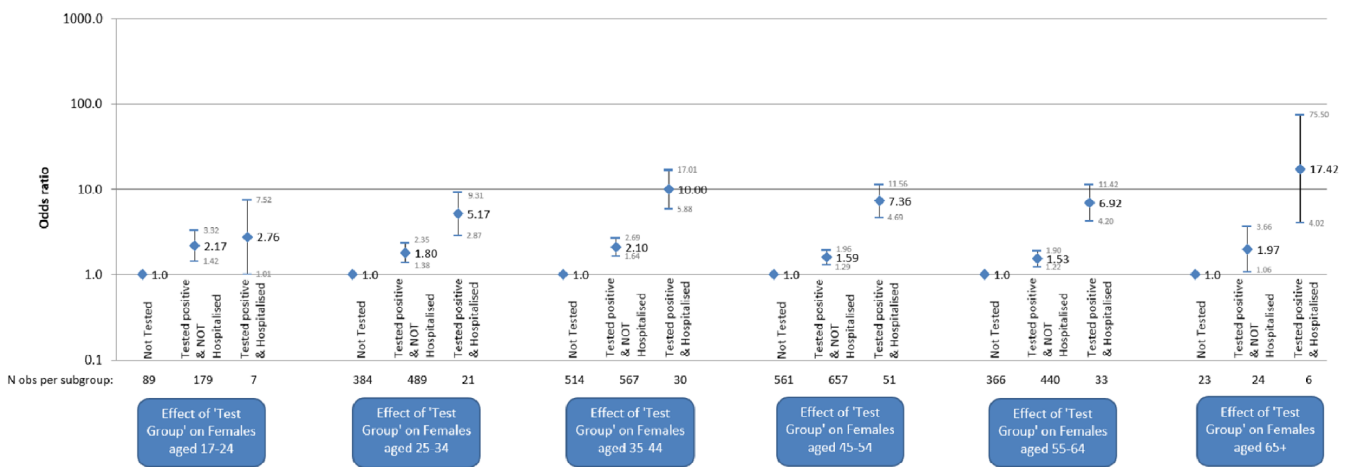


FIGURE 4 The interdependent effect of test group and age group on probability of high SARS-CoV-2 antibody levels for female donors

defined by a EUROimmun S/CO ratio of 6 or higher. A high proportion of Asian and Black ethnicity donors showed high levels of antibodies (39% and 30%, respectively), but the highest proportion of donors with high antibody levels were seen among those who had been hospitalised with SARS-CoV-2 infection (64%). The proportion of donors with EUROimmun S/CO ratio of 6 or higher by ‘time since project began’ and ‘duration between SARS-CoV-2 detection and donation’ are summarised in Figures 1 and 2 respectively.

Multivariable modelling was used to identify variables associated with high antibody levels whilst adjusting for the effect of all the factors we tested found to be influential. Data from 20 795 donors was used for model development, and from 8790 donors for model validation. The final model was based on 20 073 donors when excluding donors with missing blood group and social deprivation data; similarly, 8511 donors were included in validation set. All the factors considered in the analyses were found to significantly influence the probability of high SARS-CoV-2 antibody levels (defined as EUROimmun S/CO ratio 6.0 or higher) at the 10% significance level with the exception of time between SARS-CoV-2 detection and donation (Table 2).

Note that this factor could only be tested for donors that had been tested for SARS-CoV-2 and a test date was reported ($n = 14\ 319$). Four two-way interaction terms were found to be significant and retained in the model: gender and test group ($p = 0.002$), age and test group ($p = 0.02$), age and gender ($p = 0.04$), ethnic group and social deprivation indicator ($p = 0.04$). Two further two-way interaction terms were found to be significant (previous blood donor and gender, previous blood donor and test group) but the clinical interpretation was thought to be questionable and so these terms were excluded from the model. One final interaction term, between social deprivation and age, was found to be significant but was kept out of the model firstly because its inclusion would overcomplicate the interpretability of the model (age was already involved in two other significant interaction terms) and secondly because the p -value for an interaction term was relatively high at 0.09 and hence considered less important than the other interaction terms involving age.

In our multivariable analysis, blood group A donors (OR 1.14, 95% CI 1.04–1.24) were found to have a significantly higher probability of high SARS-CoV-2 antibody levels than blood group O donors,

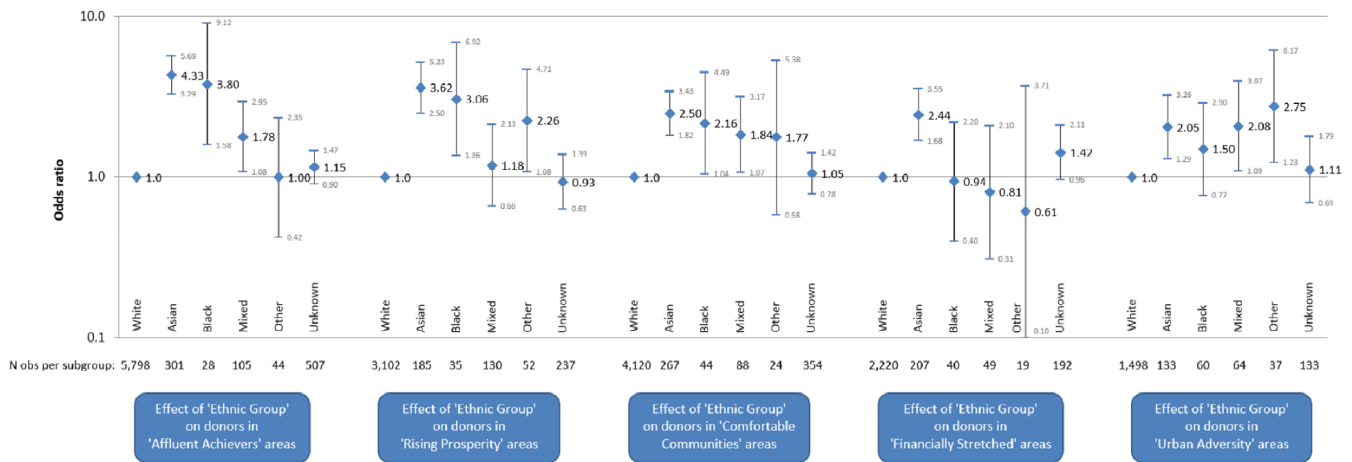


FIGURE 5 The interdependent effect of Ethnic Group and Social Deprivation Indicator on probability of high SARS-CoV-2 antibody levels

whereas donors with AB blood group (OR 0.77, 95% CI 0.62–0.97) were more likely to have lower antibody levels compared to blood group O donors (Table 2).

The influences of age, gender, and test group on the probability that a donor would have high SARS-CoV-2 antibody levels were interpreted collectively due to significant interactions identified between these variables (Table 2). Male donors who had tested positive for SARS-CoV-2 but had not been hospitalised were more likely to have high antibody levels than those without a SARS-CoV-2 positive test across all age groups (Figure 3). Male donors with a laboratory confirmed SARS-CoV-2 diagnosis who were hospitalised were even more likely to have high antibody levels than those who had not been tested or hospitalised, and this impact was pronounced by age: those male donors who were 65 years of age or over, were tested positive for SARS-CoV-2 and hospitalised were most likely to harbour high antibody levels (OR 37.07, 95% CI 8.58–160.14). A similar relationship between age, gender, laboratory diagnosis and hospitalisation status were found for females, but the odds of high SARS-CoV-2 antibody levels were generally lower than for males (Figure 4). However, it is important to note that some of these differences were based on very small numbers of donors. For example, although female donors aged over 65 years who had been hospitalised with COVID-19 were more likely to have high SARS-CoV-2 antibody levels than younger females (OR 17.42, 95% CI 4.02–75.50), that group only included seven members.

Similarly, the effects of donor ethnicity and social deprivation indicator were assessed together due to a significant interaction identified between these two factors (Table 2). White donors were less likely to have high SARS-CoV-2 antibody levels than donors of other ethnic backgrounds (Figure 5). Although it is possible that this could partially reflect differences in ability or willingness to access SARS-CoV-2 testing, a two-way interaction term between test group and ethnicity was not found to be significant ($p = 0.29$) and is not included in the final model. However, the effect of ethnic group differed depending on social deprivation indicator. While donors of Asian origin were found to have the highest odds of high antibody levels

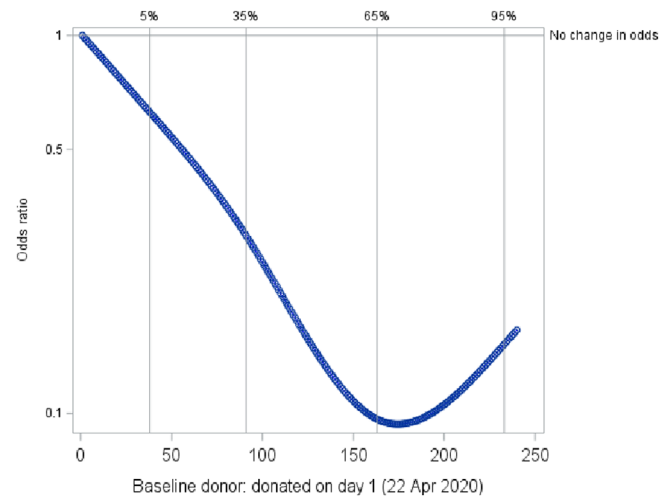


FIGURE 6 Odds ratios illustrating the non-linear effect of days since project began for high SARS-CoV-2 antibody levels

across all social deprivation groups, the odds compared to white donors were highest in the more affluent areas compared to the more deprived areas (OR: 4.33, 95% CI 3.29–5.69 versus OR: 2.05, 95% CI 1.29–3.26). Interestingly, black donors were more likely to have high SARS-CoV-2 antibody levels compared to white donors but only when considering the most affluent areas (OR 3.80, 95% CI 1.58–9.12). This latter result was not due to lack of statistical power.

We also assessed the significant ($p < 0.0001$) non-linear effect of timing of donation (days since the project began) on the probability of high SARS-CoV-2 antibody levels (Figure 6). The odds of donors having high antibody levels appears to have decreased over time since the beginning of the project. However, the rate of decrease slowed down around mid-October (day 170) co-incident with the increase in reported SARS-CoV-2 cases in the United Kingdom.

As the Hosmer and Lemeshow C statistic was >0.7 , the model was considered to exhibit acceptable predictive ability. Residual analysis highlighted one donor that influenced the age and test group interaction parameter estimate however this donor was kept in the dataset

as it was a genuine observation that led to more conservative results. Some variables with smaller numbers of observations were, by definition, slightly more susceptible to influential values but there were no observations that posed a particular concern.

3.1 | Model validation

The estimated probability of high SARS-CoV-2 antibody level was calculated for 8511 donors in the validation dataset using the parameter estimates from the developed model (Figure S1). The donors were categorised into four groups defined by the quartile values of the equivalent estimated probabilities from the development dataset; and a logistic regression model was used to assess difference in the probability of high antibody levels between these four groups (Table S1). The resulting C statistic of 0.720 indicated good predictive ability of this model. Furthermore, the median estimated probabilities for donors with high SARS-CoV-2 antibody levels was 0.22 compared to 0.10 for donors with low antibody levels (Figure S2). Overall, model validation therefore suggested that our model was able to adequately identify donors with a higher chance of high SARS-CoV-2 antibody levels.

4 | DISCUSSION

This is a large convalescent plasma donor cohort study to date reflecting a commitment of time, resources and generosity from NHS staff and almost 30 000 donors who took part in the convalescent plasma programme in England. To investigate the trends in demographic and clinical factors that influence the probability of individuals with previous SARS-CoV-2 infection to produce a good antibody response in such a large dataset has allowed us to draw robust conclusions from these data.

We showed that older donors, male donors, and donors previously hospitalised with SARS-CoV-2 infection were generally much more likely to have high levels of antibodies. This was consistent with previous findings, based on neutralising antibody testing of a smaller set of donors.¹⁶ It should be noted that during the course of the study, there was a substantial drive to recruit male donors because the preliminary analysis suggested a greater probability of high antibody levels compared to females.¹⁶ Overall, 78% of donors were male. Female donors were generally only recruited if they had confirmed SARS-CoV-2 and thus thought to have increased probability of high antibody levels. Sex differences in COVID-19 severity were first noted in China; hospital admissions and mortality were higher among males than females.^{18–20} Further male bias in COVID-19 mortality has been reported by 37 of the 38 countries providing sex-disaggregated data.²¹ It has been proposed that these differences observed between males and females in response to SARS-CoV-2 infection are likely due to differences in their innate and adaptive immune responses driven by biological sex, including sex chromosomes and sex steroids (reviewed by Scully et al).²¹ Similarly, differences in mortality

between males and females were previously investigated in animal models of SARS-CoV infection, and these were attributed to steroid hormones.²²

With this dataset we were also able to demonstrate that donors from an Asian background had higher likelihood of having high SARS-CoV-2 antibody levels compared to white donors; although this disparity was enhanced in affluent areas, it was also seen in deprived areas. In contrast, the likelihood of having high SARS-CoV-2 antibody levels was increased only among those black donors residing in affluent areas. Data on the disproportionate effect of SARS-CoV-2 infection on black, Asian, and other minority ethnic people and possible reasons underlying that has been recently reviewed.²³ The results suggest that people of black and Asian ethnic groups are more likely to be diagnosed with COVID-19. People from Asian and black ethnic groups have also been shown to be more likely hospitalised with SARS-CoV-2 infection when compared to those with white ethnicity (threefold and twofold, respectively). Furthermore, the evidence emerging from the United Kingdom suggests that those of black or Asian ethnicity are around twice as likely to die from SARS-CoV-2 infection than those of white British ethnicity.²⁴ It has been proposed that black and Asian people are more likely to work in occupations with a higher risk of SARS-CoV-2 exposure or due to overcrowded housing, and might also delay seeking medical care when needed due to their negative past experiences with healthcare.²³ Although these cultural differences may impact the disease risk, it has also been shown recently that poverty is another independent risk factor for COVID-19 related mortality.²⁵ Based on our results, blood donors with Asian background, residing in deprived areas had higher likelihood of high antibody levels than white donors, likely demonstrating increased exposure to SARS-CoV-2 infection. This could reflect the previous findings where the proportion of black household lone parents is higher when compared to other groups, making them possibly more isolated and hence less likely to get infected. Similarly, self-employment rates are highest among Pakistanis and Bangladeshis²⁶ potentially leading to their more frequent exposure to SARS-CoV-2 infection if it has not been possible to isolate due to financial pressure.

Donors with blood group A were more likely to have high SARS-CoV-2 antibody levels than those with blood group O, and those with blood group AB were significantly less likely to harbour high antibody levels compared with blood group O donors. Based on a previous meta-analysis covering over 50 000 patients, individuals with blood group A have a substantially higher risk of SARS-CoV-2 infection and blood group A has also been associated with an increased risk of COVID-19 mortality.²⁷ Furthermore, blood group O has shown to be a protective factor reducing the risk of SARS-CoV-2 infection. It has been speculated previously whether this association might relate to the presence of anti-A antibodies via their ability to block the interaction of SARS-CoV-2 with the ACE receptor, making those with blood group A without these antibodies more vulnerable to SARS-CoV-2 infection than those with blood group O.^{28–30} This protective effect of anti-A antibodies was not seen among those with blood group AB in our study, indicating that this is likely a multifactorial issue, perhaps



also involving other ABO-associated factors such as A and B antigens, coagulation factors and interleukin levels.³¹

It is difficult to explain why the odds of blood donors having high antibody levels decreased during the study period; the odds of high antibody levels on 16 December were 83% lower than on 22 April 2020. Although it is currently unknown whether individuals' low antibody titres will boost their immune responses upon re-exposure or because of SARS-CoV-2 immunisation, this has been suggested based on experimental infection of ferrets.³² As a smaller number of SARS-CoV-2 infections were diagnosed in the UK during the first outbreak between March and May than during the second peak in the Autumn, it might have been anticipated that the number of donors with high SARS-CoV-2 antibody levels would have increased during the study period. However, in the beginning of the pandemic SARS-CoV-2 testing was limited to those with severe symptoms, whereas during the subsequent months, testing increased to include those with milder symptoms and hence our convalescent plasma population likely contained more donors with a previous SARS-CoV-2 diagnosis but with mild symptoms only. It might also be that the decrease in proportion of donors with high antibody levels over the study period was reflected by a general rapid increase in convalescent plasma collections, likely containing more donors from lower-priority groups expected to have lower likelihood to have high antibody levels (i.e. women, younger individuals and those untested). Interestingly, most convalescent plasma donors had not donated previously and were hence newly recruited (78%). This is in contrast to our usual (blood) donor demographics where only 10% of donations are given by new donors (accounting for 17% of all donors).³³ Our results also show that donors who had previously donated blood had 16% lower odds of high SARS-CoV-2 antibody levels compared to those who had not previously given blood, which is likely explained by the targeted recruitment of new convalescent plasma donors, focusing on males with previous laboratory confirmed SARS-CoV-2 infection and calling on existing blood donors to 'sign up' as a donor if they felt they had suffered from COVID-19.

Reassuringly for the convalescent plasma programmes and those having been infected with SARS-CoV-2, the interval between a laboratory confirmed SARS-CoV-2 diagnosis and plasma donation was not found to be significantly associated with the likelihood of them having high antibody levels for the range of durations in our cohort (up to 327 days), indicating that in some donors high SARS-CoV-2 antibody levels remain over time. Decreases in SARS-CoV-2 neutralising antibody levels have been demonstrated in some³⁴⁻³⁷ but not all previous studies.³⁸ One of these studies demonstrated a trend towards lower antibody levels with increased time between symptoms and blood sampling, and a decline of neutralising antibody titres over time based on repeat testing of the same donors.³⁷ The difference between our results and their findings cannot be explained by methodology as Euroimmun IgG assay was utilised in both studies. Furthermore, although both studies focused on convalescent plasma donors, it is important to note that the donor populations were very different. Our study included a higher proportion of males than the study by Boonyaratanakornkit et al³⁷ (78% vs. 48%), a smaller proportion of

donors had been hospitalised (3% vs. 10.8%) and a smaller proportion of them had high antibody levels (17% vs. 60%). Whether these highlighted differences in our donor populations could be associated with different levels of immune memory needs further investigation.

Although our study is based on a large dataset, it also has some limitations. It is important to note that when we consider the effect of age in the model, all donors over 65 years of age must have been previous blood donors and might explain why there are fewer high titre donors in that age group than among those aged between 55 and 64 years. Furthermore, our cohort is composed of eligible blood donors only and all of them had to pass the medical assessment. Approximately 60-70% of female and 30-40% of male first-time donors attending a donation session were actually deferred without testing. For these reasons, our cohort is selective and relates to healthy people eligible to donate convalescent plasma only.

Due to the extensive size of our dataset, we have been able to perform detailed model checking and validation exercises leading us to conclude that our model provides a satisfactory fit to the data and has acceptable predictive ability. With this large dataset we have shown that not only older male donors who were hospitalised with SARS-CoV-2 infection but also donors with an Asian background and donors with a black background residing in affluent areas demonstrate higher likelihood of having high SARS-CoV-2 antibody levels. In a time of great uncertainty, these results take us one step closer to understanding the antibody response to COVID-19 and help us to target convalescent plasma collections further.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors discussed and planned the study, Jennifer Mehew performed the multivariable analysis and drafted the first version of manuscript together with Heli Harvala. All authors critically reviewed the manuscript and accepted the last version of it.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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