ORIGINAL PAPER

Anti-A and SARS-CoV-2: an intriguing association

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Vox Sanguinis

Background Blood groups and anti-A isohemagglutinin may be involved in susceptibility to SARS-CoV-2 infection.

Materials and Methods We retrospectively studied 268 COVID-19 convalescent plasma donors and 162 COVID-19 inpatients (total 430 subjects, confirmed by RT-PCR) and 2,212 healthy volunteer first-time blood donors as a control group. These were further divided into two groups: those with anti-A (blood types O and B) and those without it (types A and AB). Titres of nucleoproteins, and neutralizing SARS-CoV-2 antibody were measured in the convalescent plasma donors and inpatients. Multivariate logistic regression and non-parametric tests were applied.

Results Persons having types O or B showed less infection prevalence than those of types A or AB (OR = 0·62, 95% CI 0·50–0·78; $P < 0·001$), but there was no difference when COVID-19 inpatients were analysed. Immunoglobulins M, G and A were lower in COVID-19 subjects of types O or B group than those of A or AB (0·16 vs. 0·19; $P = 0·03$, 2·11 vs. 2·55; $P = 0·02$, 0·23 vs. 0·32; $P = 0·03$, respectively).

Conclusion In this retrospective cohort, COVID-19 individuals were less likely to belong to blood types O and B, and also had lower SARS-CoV-2 antibody titres than A and AB individuals. COVID-19 severity did not associate with the blood groups.

Key words: ABO groups, anti-A, SARS-CoV-2.

Background

Since December 2019, when the first outbreak of novel coronavirus disease (COVID-19) occurred in Wuhan, China, over 33 million people have been diagnosed, and over one million people have died worldwide [1]. It is unclear which individual characteristics determine susceptibility and intensity of symptoms. However, age, sex, ethnicity, hypertension, body mass index and haematological biomarkers, such as D-dimer, thrombocytopenia and lymphopenia [2,3], have already been associated with a worse outcome.

Recently blood types and anti-A isohemagglutinin have been associated with susceptibility to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [4,5]. Considering that the first studies reported type A as a risk factor and O as protection, some authors have suggested that anti-A and not the blood type itself could be responsible for the findings [6].

The human ABO histo-blood group system has a single gene located on the terminal portion of the long arm of chromosome 9 (9q34.2), with three main alleles; one recessive *O* and two co-dominant *A* and *B* [7]. Differences

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in blood group antigen expressions and presence or absence of anti-A or -B provide strong defensive lines against infection [8]. In persons with O blood type, characterized by the absence of A or B antigens, stimulation by microbiota having glycan motifs similar to A or B antigens, leads to a natural production of anti-A and anti-B [9]. Type B individuals also produce anti-A but in lower titres [10]. Interestingly, in 2003, during the SARS-CoV outbreak in China, the O blood group was considered protective against infection—OR = 0·18 (0·04–0·81) [11]. Later, a cell-binding assay showed that either a monoclonal or human natural anti-A could inhibit the SARS-CoV S protein/ACE2 interaction [12]. At a cellular level, this supports the idea that the type O protection against SARS-CoV involves the antibodies rather than the antigens.

Based on these findings, our study aimed to analyse the association of SARS-CoV-2 infection with the presence of anti-A (In types O and B) or its absence (in types A and AB), related to the production of antibodies to SARS-CoV-2 nucleoprotein (NP; IgA, IgM and IgG) and neutralizing antibodies (nAb).

Methods and materials

Ethics statement

The study was approved by both hospitals' Institutional Review Boards (IRB) and the Brazilian Commission on Ethics and Research (CONEP) under requests CAAE 32558220.0.0000.0071 and CAAE 30259220.4.2001.5461. All patients and COVID-19 convalescent plasma donors provided written informed consent.

Subjects

We analysed a retrospective cohort of 430 people with COVID-19 [268 convalescent plasma donors (CCPD) and 162 inpatients (CIP)] from both hospitals. All patients and plasma donors had a previous diagnosis confirmed by RT-PCR.

The CCPD group comprised convalescent patients who had had mild symptoms (no hospitalization during their COVID-19 evolution). Eligibility criteria required a positive diagnostic test by naso-oropharyngeal swab (NOS) RT-PCR and resolution of symptoms for at least 14 days. The candidates were then tested for SARS-COV-2 by RT-PCR either on peripheral blood or NOS swab. If the RT-PCR was negative, the plasma was collected, and antibodies to SARS-CoV-2 nucleoprotein (anti-NP - IgA, IgM and IgG) and neutralizing antibodies (nAb) were measured.

The CIP group was composed of patients with a positive SARS-CoV-2 RT-PCR, who had moderate to severe symptoms and needed hospitalization. Blood type information was available in the electronic chart. Samples for anti-NP and nAbs were drawn by the time of admission.

In order to avoid blood group bias from repeat donors, given that blood type O ('universal donor') is usually over-represented, our control group (CG) comprised 2212 first-time voluntary healthy blood donors from Hospital Israelita Albert Einstein blood bank database, who donated whole blood from August to October 2019, before the COVID-19 outbreak in Brazil.

Subjects of blood types A and AB were grouped as 'without anti-A' (A/AB group), whereas those with O and B were named 'with anti-A' (O/B group).

Samples tests

Blood typing was done by the automated analyser, gel technique, Erytra Eflexis (Grifols, Barcelona, Spain) and IH-platform (Biorad, Creisser, Switzerland).

RT-PCR: A real-time reverse transcriptase polymerase-chain-reaction technique confirmed SARS-CoV-2 diagnosis from naso-oropharyngeal swab specimens. Molecular tests were based on Corman *et al.* [13], with five copies/reaction of sensitivity.

Neutralizing antibodies (nAbs) and anti-nucleocapsid (anti-NP) antibodies (IgM, IgG and IgA): We used the cytopathic effect-based virus neutralization test (CPE-based VNT), which was carried out with SARS-CoV-2 (GenBank: MT350282.1), as previously described [14,15]. Anti-NP was determined according to *Wendel et al.* [15]. Both methods have been described in more detail elsewhere [15].

Data analysis

Age was compared between control, CCPD and CIP groups using the ANOVA test. For sex and blood type analysis we used the chi-square test. CCPD and CIP groups were classified as COVID-19 individuals' group and compared to the CG.

For further analysis regarding the presence or absence of 'circulating anti-A' and its association with COVID-19, we merged our study population into two groups: one 'with circulating anti-A'; including types O and B (O/B group)" and another 'without circulating anti-A'; including types A and AB (A/AB group)."

For adjusted models, we applied multiple logistic regression. The Mann–Whitney test and Spearman's test were used to compare anti-A presence/absence and anti-NP (IgM, IgG and IgA) among groups.

Data were organized in Microsoft Excel 2010 and were analysed using Statistical Package for Social Sciences (SPSS) (Chicago, IL) or GraphPad Prism version 8.0 for

Windows, GraphPad Software (La Jolla, CA, USA). A *P*-value <0·05 was considered significant.

Results

We had age, sex and blood type of all 430 COVID-19 individuals (268 CCPD and 162 CIP) and 2212 healthy volunteer blood donors (control group: CG) However, as they were from a retrospective cohort, the anti-NP and nAbs were available in only 295 of the COVID-19 persons. Table 1 shows the distribution, mean age, sex and blood type among groups. Although blood type O most frequent among blood donors, type A was more common in the COVID-19 group. There was no statistical difference in blood type distribution between CCPD and CIP.

Age and male sex were positively related to COVID-19 (OR = 1·06, 95% CI: 1·05–1·06; *P* < 0·001 and OR = 1·27, 95%CI: 1·02–1·59; *P* = 0·035 respectively). However, the presence of circulating anti-A (O/B group) showed a protective effect against COVID-19 (OR = 0·62, 95% CI: 0·50–0·78; *P* < 0·001), as shown in Table 2.

In order to evaluate the association of circulating anti-A with COVID-19 severity, we compared CCPD and CIP to the CG. Belonging to the O/B group was protective only for CCPD, as shown in Fig. 1 (OR = 0·60, 95% CI: 0·45–0·75 *P* < 0·001).

As type O persons usually have higher anti-A titre, we also performed a sub-analysis for O vs. B blood, as shown in Table 3.

Age was positively related to COVID-19 (OR = 1·05, 95% CI: 1·04–1·06; *P* < 0·001). Sex did not show any association to COVID-19 between these groups. However, a higher titre of circulating anti-A (O group) was protective against COVID-19 (OR = 0·66, 95% CI: 0·46–0·95; *P* = 0·026).

Table 1 Demographic data from subjects included in the study

Variable	Blood donors (CG) (N = 2212)	CCPD (N = 268)	CIP (N = 162)	P
Age[a] (years; Mean ± SD)	37·5 ± 12·0	36·8 ± 8·1	69·3 ± 15·7	<0·001
Gender, *n* (%)[b]				
Female	1004 (45·4)	103 (38·4)	59 (36·4)	0·012
Male	1208 (54·6)	165 (61·6)	103 (63·6)	
Blood group, *n* (%)[b]				
A	785 (35·5)	128 (47·8)	70 (43·2)	<0·001
AB	84 (3·8)	11 (4·1)	7 (4·3)	
O	1117 (50·5)	103 (38·4)	59 (36·4)	
B	226 (10·2)	26 (9·7)	26 (16·1)	

CCPD, COVID-19 convalescent plasma donors; CG, control group; CIP, COVID-19 inpatients; N, number of participants.
[a]ANOVA.
[b]Chi-Square.

Table 2 Multivariate logistic regression for COVID-19 individuals (*n* = 430) and blood donors (CG) (*n* = 2212)

Variable	OR	95% CI Lower	95% CI Upper	P
Age (years)	1·06	1·05	1·06	<0·001
Gender (male)	1·27	1·02	1·59	0·035
Anti-A (O/B)	0·62	0·50	0·78	<0·001

CG, control group; CI, confidence interval, OR, odds ratio.
Age and male gender were positively related to COVID-19 (OR = 1·06, 95% CI: 1·05–1·06; *P* < 0·001 and OR = 1·27, 95%CI: 1·02–1·59; *P* = 0·035 respectively). The presence of circulating anti-A (O/B group) showed a protective factor to COVID-19 (OR = 0·62, 95% CI; 0·50–0·78; *P* < 0·001).

Additionally, we analysed whether anti-NP was associated with the presence of anti-A. We included 295 subjects from the COVID-19 group (148 from O/B group and 147 in the A/AB group). Figure 2 shows the distribution of anti-NP between the groups. The O/B group showed lower median IgM, IgG and IgA levels than for A/AB (0·16 vs. 0·19; *P* = 0·03, 2·11 vs. 2·55; *P* = 0·02, 0·23 vs. 0·32; *P* = 0·03, respectively).

Figure 3 shows the nAb distribution analysis. As the samples' value varies from <1:20 to >1:5120, we divided the nAb titres into two groups: <320 and ≥320 (320 as the middle cut-off point for the reaction range). Patients of types O or B showed a lower trend of neutralizing antibody value and lower frequencies when the titres were higher than 320 (chi-square test = 6·99, *P* = 0·008). The results are shown in Table 4.

There was an evident linear correlation between anti-NP (IgA, IgG and IgM) and nAbs according to the Spearman's correlation test (all *P* < 0·0001), as shown in Fig. 4. We identified a better correlation between IgG and nAbs for both O/B and A/AB groups (*r* = 0·687 in O/B and *r* = 0·640 in A/AB). IgM and IgA did not show such good correlations (O/B group IgA *r* = 0·593; IgM *r* = 0·430 and A/AB group IgA *r* = 0·555; IgM *r* = 0·457).

Discussion

The ABO system can be associated with the inflammatory response and has a varied geographical frequency, with growing evidence that it can affect the predisposition to certain diseases, such as thrombosis or *H. pylori* infection [7]. A meta-analysis recently determined the odds of SARS-CoV-2 positive individuals of having a specific blood type compared with controls. The association of SARS-CoV-2 with blood type A was significant with a pooled OR of 1·23 (95%CI: 1·09–1·40), although the
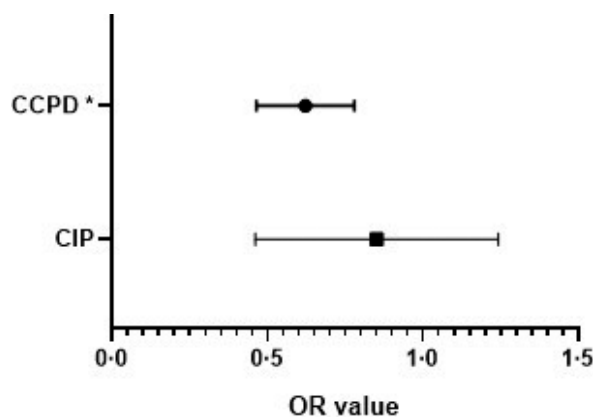
Fig. 1 Odds ratio (OR) for CIP and CCPD compared to blood donors (CG), considering O/B vs. A/AB groups. Legend: O/B group was identified as a protective factor only for CCPD (OR = 0·60, 95% CI: 0·45–0·75), whereas for CIP this effect was not identified (OR = 0·85, 95% CI: 0·45–1·25). Multivariate logistic regression; CCPD, COVID-19 convalescent plasma donors; CIP, COVID-19 inpatients; *$P < 0.001$.

Table 3 Multivariate logistic regression analysis for O vs. B blood groups, comparing COVID-19 patients and blood donors (CG)

Variable	OR	95% CI		P
		Lower	**Upper**	
Age (years)	1·05	1·04	1·06	<0·001
Gender (male)	1·34	0·99	1·82	0·062
Anti-A (O/B)	0·66	0·46	0·95	**0·026**

CI, confidence interval; OR, odds ratio.
COVID-19 patients O blood group ($n = 103$), COVID-19 patients B blood group ($n = 26$), Blood donors O group ($n = 1117$), Blood donors B group ($n = 226$). Age was positively related to COVID-19 (OR = 1·05, 95% CI: 1·04–1·06; $P < 0.001$) and the presence of a higher titre of circulating anti-A (O group) showed a protective factor to COVID-19 (OR = 0·66, 95% CI: 0·46–0·95; $P = 0.026$).
Bold indicates statistical significant values ($P < 0.05$).

Fig. 2 COVID-19 individuals ($n = 295$) IgM, IgG, and IgA distribution between A/AB and O/B groups. Legend: O/B group showed an IgM, IgG and IgA median level lower when compared to A/AB (0·16 vs. 0·19; *$P = 0.03$, 2·11 vs. 2·55; #$P = 0.02$, 0·23 vs. 0·32; &$P = 0.03$, respectively).Mann–Whitney test.

and without anti-A (A/AB). Moreover, we showed a greater protective effect of type O compared with B subjects, suggesting that anti-A from the former might be more effective. Our data suggest that higher anti-A titres could improve the host defence. It is a plausible argument, since type B produces lower titres of anti-A [10].

Our findings are similar to previously reported studies that group O was associated with a lower risk of infection than non-O blood types [4]. We did not find any statistically significant difference between CCPD donors and COVID inpatients (CIP), like other studies [18] that did not identify any relationship between blood type and intubation or death rate. In contrast, one study in China found fewer cardiovascular diseases and lesser severity in the O group [17].

Our study's primary limitation is the control group used: voluntary first-time blood donors from a single hospital. In Brazil, data regarding blood type belong to local centres, and data for the Brazilian population as a whole are unsatisfactory. Few papers show the prevalence of type O among Caucasians, mixed race and Afro-descendants (46·5%, 53·2% and 47·9%, respectively) followed by A-type (39·4%, 29·6% and 31·9% respectively) [20]. Our control group was similar to the ABO blood type distribution in Brazil, supporting our findings. Moreover, only voluntary first-time blood donors were included in the control group to avoid possible bias for over-representing any blood type in repeat donors.

The ABO type could be involved in the S protein SARS-CoV and SARS-CoV-2 cell-binding mechanism

random-effect meta-analysis revealed a considerable heterogeneity among studies [16]. Despite our first-time volunteer blood donors being mainly of type O, this was not the most prevalent type among COVID-19 patients. This finding is similar to previous studies that reported ABO blood group association with SARS-CoV in 2003 [11] and with SARS-CoV-2, in 2020 [4,17,18]. One possible mechanism is that blood types A and B have sugars crucial to the O-glycosidic target, functioning as a possible site for binding the virus to the host [19].

As previously proposed, the presence of anti-A, and not the blood type, could be associated with the susceptibility to SARS-CoV-2 infection [6], although future studies must prove this assumption. Our results are similar, with a statistical difference between groups of patients with anti-A (B/O)
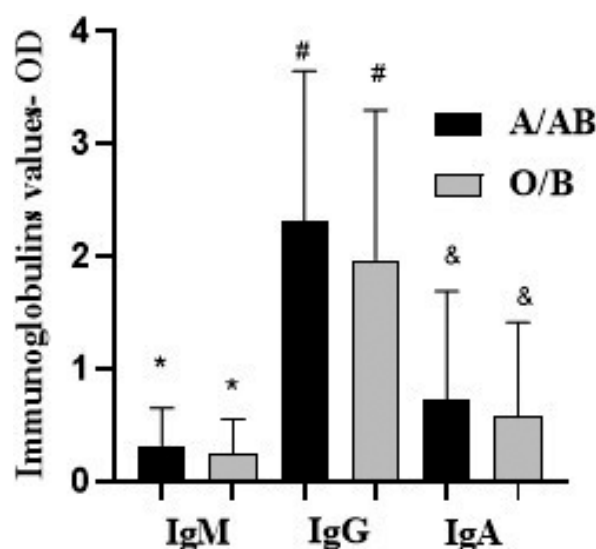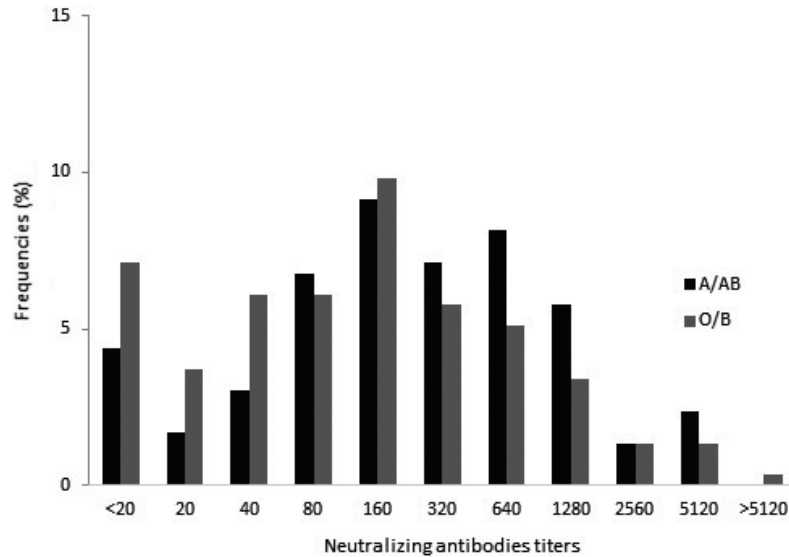
Fig. 3 Distribution of the frequencies of COVID-19 individuals (*n* = 295) neutralizing antibodies between A/AB and O/B groups. Legend: O/B group showed a neutralizing antibody lower value trend and lower frequencies when the titres were higher than 320.

Table 4 Distribution of COVID-19 individuals (*n* = 295) neutralizing antibody (nAb) titres in two groups: <320 and ≥320

ABO Group	nAb titres		χ^2	*P*	OR (95% CI)
	<320	≥320			
O/B	97 (65·5)	51 (34·5)	6·99	0·008	0·53 (0·33– 0·85)*
A/AB	74 (50·3)	73 (49·7)			

O/B COVID-19 individuals had a lower chance of having values ≥320. *0·54 (0·34; 0·87), when adjusted by age and gender.

[12,19]. Genetic research also has increased in this area. Genome-wide association analysis in an Italian-Spanish group showed that A-positive people are at higher risk of respiratory failure in COVID-19, due to the rs657152 A/C single nucleotide polymorphism at 9q34.2. Also, some procoagulant markers are associated with genetic variation at the ABO locus, and this region could have a role in modifying genes [21].

Curiously, when we evaluated specific immunoglobulin production, we found a statistically significant difference for IgM, IgG and IgA results, with median values lower in the O/B group. Similarly, neutralizing antibody titres were lower in the O/B group.

This is one of the few studies that analyse a possible correlation between humoral response for SARS-CoV-2 and ABO group. In that way, even though we did not observe a statistical difference between the groups
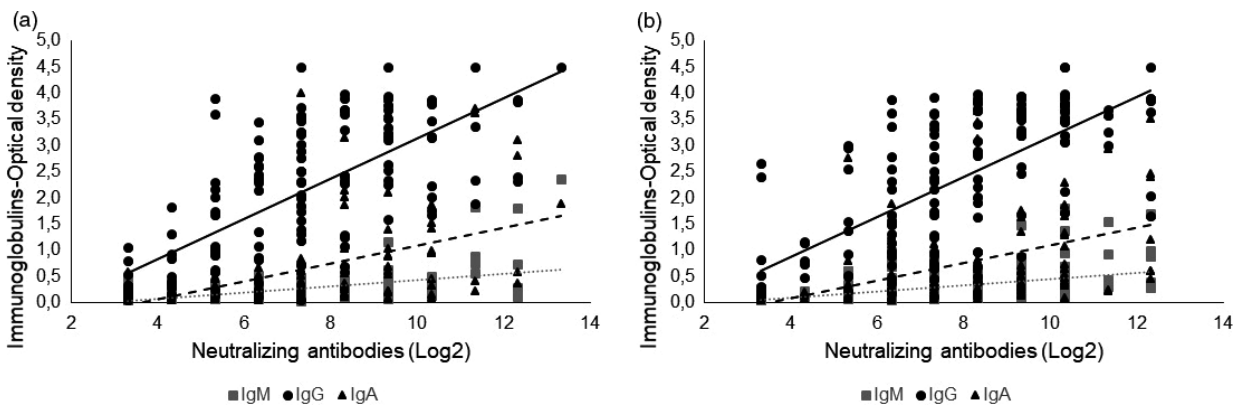

Fig. 4 Linear correlation among COVID-19 individuals (*n* = 295) immunoglobulins and neutralizing antibody titres (Log2), into the group A/AB (a) and O/B (b). Legend: Spearman correlation for A/AB group (left) and for O/B group (right). A better correlation between IgG and neutralizing antibodies was found in both O/B and A/AB (*r* = 0·687 in O/B and *r* = 0·640 in A/AB). IgM and IgA did not show such good correlations (O/B group IgA *r* = 0·593; IgM *r* = 0·430 and A/AB group IgA *r* = 0·555; IgM *r* = 0·457).

CCPD and CIP concerning severity, the profile of increased humoral immune response in A/AB patients is an intriguing question and may be related to other factors, such as the clinical evolution and progression of the disease. Our study did not correlate clinical status and level of IgM, IgG, IgA anti-NP or nAb titres; thus, this parameter correction for ABO status may be biased.

IgA is an immune barrier and can probably neutralize SARS-CoV-2 before the virus reaches and binds to the epithelial cells. This has taken on increased importance recently. IgM and IgG levels have a potential role in the evaluation of severity and prognosis of COVID-19 [22]. In 37 patients, IgA and IgG levels were markedly higher ($P < 0.001$) in patients with severe disease compared with mild disease, while there was no difference in IgM level [23]. Additionally, in a two-year prospective study, IgG antibody and NAb titres were positively correlated in SARS-CoV [24]. However, we did not find any research correlating IgM and IgA, especially in SARS-CoV-2 infections. Future longitudinal studies can show if blood groups interfere with protection antibodies, including the long-term immune response.

The impact of anti-A isohemagglutinin titres in the SARS-CoV-2 infection and its association with neutralizing antibodies is not clear [25]. In our retrospective study, we could not measure the quantitative effect of anti-A. Further studies are required to evaluate both anti-A isohemagglutinin and neutralizing antibody titres, and their role in SARS-CoV-2 infection.

Conclusion

Blood types O and B, which produce anti-A, showed a protective effect against SARS-CoV-2 infection. There was no statistical difference between COVID-19 inpatients and COVID-19 convalescent plasma donors, suggesting that blood types do not associate with COVID-19 severity. Moreover, COVID-19 individuals from types O and B had lower titres of neutralizing antibodies and lower levels of IgM, IgG and IgA anti-nucleocapsid antibodies than did the types A and AB.

Acknowledgements

Conflict of interests

The authors declare no conflict of interests.

Author contributions

Conceptualization – VFD, CBB, APHY, SW, JMK; Investigation – VFD, CBB, APHY, NH, JRRP, RFW, RMF, RRGM, GC, AS, RA, PS, DBA, CPS, ELD, MA, VN, SW, JMK. Formal analysis – VFD, CBB, APHY, SW, JMK; Resources – LFLR, LVR; Writing – VFD, CBB, APHY, SW, JMK. Project administration and funding acquisition – LFR, LVR.

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