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Prevalence of antiphospholipid antibodies in post-COVID and vaccinated individuals

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ABSTRACT:

— ***Objective:*** The outbreak of COVID-19 resulted mainly in respiratory disease; however, apart from that, the infection was presented with random systemic thromboembolic events. This study aimed to measure the serum concentration of antiphospholipid antibodies (IgM/IgG) in post-COVID and vaccinated individuals. Previous research resulted in the absence of IgG antibodies in COVID-19 patients.

— ***Patients and Methods:*** This quantitative study involved 132 participants (93 female cases - 70.5%, and 39 male cases - 29.5%). The age distribution of the participants was between 17 and 55 years. Serum antiphospholipid concentrations were measured by enzyme-linked immunoassay (ELISA) SARS-CoV-2 nucleocapsid protein.

— ***Results:*** There was no significant elevation of IgG antibodies either in post-COVID or in vaccinated individuals. However, the elevation of IgM was more significant.

— ***Conclusions:*** Low serum concentrations of IgM and IgG antiphospholipid antibodies in COVID-19 patients support the existing literature that antiphospholipid antibody elevation is only transient, depending on the severity of the infection.

— ***Keywords:*** Coronavirus, COVID-19, SARS-CoV-2, Autoimmunity, Antiphospholipid.

INTRODUCTION

In December of 2019, the city of Wuhan, China, had seen its first case of a new respiratory virus that presented as a case of pneumonia with unidentified pathogen, just to be identified in January of 2020 as a novel Coronavirus causing the Coronavirus Disease of 2019 (COVID-19)[1].

COVID-19 is a respiratory disease that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the genus Betacoronavirus of the *Coronaviridae* family[2], a single stranded RNA virus, and the culprit of the worldwide pandemic that took the lives of more than 6.6 million people by January of 2023[3]. SARS-CoV-2 is transmitted from one person to another dominantly through aerosols and respiratory droplets[4], with the symptoms of fever and cough being the most prevalent among the patients[5,6]; furthermore, the clinical picture of COVID-19 varies widely within patients, with an array of neurological, dermatological[6], gastrointestinal, and cardiovascular manifestations[7], with the thromboembolism being a relevant complication among patients hospitalized with COVID-19. According to the meta-analysis performed by Xiong et al[8], the prevalence of thrombotic events in COVID-19 patients was 22% and almost doubled (43%) for patients who were admitted to the ICU.

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The discovery of thrombotic events in COVID-19 patients, especially the severe cases where admission to the ICU is required, which is the key problem in this domain, has led scientists to initiate research to find possible causes behind the thrombotic events in the population. The etiology of coagulopathy and thrombosis in severe COVID-19 patients has been proposed[9] as multifactorial etiology with the importance of endothelial damage and release of tissue factor caused by inflammatory response after the binding of SARS-CoV-2 virus to Angiotensin Converting Enzyme (ACE1) receptor and thus activation of the complement system, which is an event shared by COVID-19, and antiphospholipid Syndrome (APS)[10].

APS is an autoimmune disease that is characterized by thrombosis and inflammation, with clinical manifestations that range from venous and arterial thrombosis to fetal loss in pregnant women[11]. These effects are mediated by the presence of the main antiphospholipid antibodies, anti-β2 glycoprotein I antibodies (anti-B2GPI), lupus anticoagulant (LA), and anticardiolipin (aCL) antibodies[12]. The evidence[13] suggests that antiphospholipids, especially anti-β2-glycoprotein I, along with the activation of the complement system, are responsible for the induction of thromboembolic events and thrombosis, which again increases the suspicion of involvement of COVID-19 in triggering thrombotic events related to APS.

The ability of SARS-CoV-2 to induce autoimmunity has been established in recent studies[14,15]. In a recent meta-analysis by Taha and Samavati[16], patients with COVID-19 were found to have a prevalence rate of 46.8% of one or more antiphospholipid antibodies (IgG or IgM). Moreover, with the development of multiple SARS-CoV-2 vaccines[17], the interest in how the vaccination status affects the generation of antiphospholipid antibodies has increased[18,19]; nevertheless, limited research has been done on the follow-up of the serological picture and lingering autoantibodies, specifically antiphospholipid antibodies, in COVID-19 patients and post-vaccine individuals.

Our study aimed to investigate the expression of antiphospholipid antibodies (IgM/IgG) in post-COVID, vaccinated, and individuals who were infected prior to vaccination to investigate the potential relationship with thromboembolic events occurring in COVID-19 patients and post-COVID-19 immunization.

PATIENTS AND METHODS

The study is a descriptive, quantitative study that analyzed blood samples of 132 registered participants (93 female cases - 70.5%, and 39 male cases - 29.5%). The age distribution of the participants was between 17 and 55 years.

Subjects

Five different groups (Table 1) were formed by complex consideration of clinical - COVID-19 positive/negative determined serologically by enzyme-linked immunoassay (ELISA), SARS-CoV-2 nucleocapsid protein specific IgG antibody, and vaccination statuses of the cases:

- COVID-19 negative/SARS-CoV-2 nucleocapsid IgG negative/vaccinated - 33 (25.0%; 16, 17.2% - females, 17, 43.6% - males) registered participants;
- COVID-19 negative/SARS-CoV-2 nucleocapsid IgG positive/vaccinated - 17 (12.8%; 14, 15.1% - females, 3, 7.7% - males) registered participants;
- COVID-19 positive/SARS-CoV-2 nucleocapsid IgG positive/vaccinated - 22 (16.7%; 21, 22.6% - females, 1, 2.6% - male) registered participants;
- COVID-19 positive/SARS-CoV-2 nucleocapsid IgG negative/unvaccinated - 26 (19.7%; 13, 14.0% - females, 13, 33.3% - males) registered participants;
- COVID-19 positive/SARS-CoV-2 nucleocapsid IgG positive/unvaccinated - 34 (25.8%; 29, 85.3% - females, 5, 14.7% - males) registered participants.

Inclusion Criteria

COVID-19 positive were patients who recovered from COVID-19 after paucisymptomatic disease and did not require hospitalization nor corticosteroid therapy; in all participants, SARS-CoV-2 infection was documented through clinical symptoms

Table 1. Categories of study subjects according to inclusion criteria.

Group	Female	Male	Total
COVID-19 negative / SARS-CoV-2 anti-nucleocapsid protein IgG negative/vaccinated	16 (17.2%)	17 (43.6%)	33 (25.0%)
COVID-19 negative/SARS-CoV-2 anti-nucleocapsid protein IgG positive/vaccinated	14 (15.1%)	3 (7.7%)	17 (12.8%)
COVID-19 positive/SARS-CoV-2 anti-nucleocapsid protein IgG positive/vaccinated	21 (22.6%)	1 (2.6%)	22 (16.7%)
COVID-19 positive/SARS-CoV-2 anti-nucleocapsid protein IgG negative/vunaccinated	13 (14.0%)	13 (33.3%)	26 (19.7%)
COVID-19 positive/SARS-CoV-2 anti-nucleocapsid protein IgG positive/unvaccinated	29 (85.3%)	5 (14.7%)	34 (25.8%)

and PCR test for SARS-CoV-2 through a nasopharyngeal swab. COVID-19-negative individuals were defined as patients without current or past clinical history of the disease.

Diagnostic Procedures

The NovaLisa SARS-CoV-2 (COVID-19) IgG ELISA diagnostic kit (NovaTec Immunodiagnostics GmbH, Dietzenbach, Germany) was applied for determining IgG directed against SARS-CoV-2 nucleocapsid protein. According to the manufacturer's instructions, the determined positive results correspond to a specificity of 99.53%, and the analytical sensitivity is defined as the probability of the assay scoring positive in the presence of the specific analyte. The study has been performed according to the ELISA kit-specific protocol, and the absorbance was measured at 450 nm wavelength. For the calculation of results, we used the manufacturer's guidelines: sample absorbance value x 10 / cut-off control absorbance value. The results were interpreted as: a) positive > 11, b) equivocal (9 - 11), and c) negative < 9.

The anti-phospholipid screen ELISA kit (Dia. Metra, Perugia, Italy) for routine analysis was used for quantitative measurement of IgG and IgM class auto-antibodies directed against 2-glycoprotein-mediated anionic phospholipids. The study was again performed according to the ELISA kit-specific protocol, and the absorbance was measured at 450 nm wavelength. For the calculation of results, we used the manufacturer's guidelines: a Lin-Log plot was applied for the determination of standards and sample concentration based on their optical density. The concentration of IgM and IgG < 10 AU/ml was considered as normal; the concentration of autoantibodies >/= 10 AU/ml was considered as elevated.

Statistical Analysis

Descriptive statistical analysis was conducted using IBM SPSS version 26 software (IBM Corp., Armonk, NY, USA) to summarize the key characteristics of the data. The prevalence rate was expressed in percentages according to the COVID-19 infection status, SARS-CoV-2 anti-nucleocapsid protein IgG status, vaccination status, and sex. Measures of central tendency and dispersion were estimated and expressed as mean ± standard deviation, and confidence interval (CI) at the 95% confidence level for the antiphospholipid antibody levels were also estimated for all categories.

Ethics Procedures

The present study has been approved by the Bioethics International Committee of the Petre Shotadze Tbilisi Medical Academy, approval code: IRB20220120, January 20, 2022. All procedures performed in the present study were in accordance with the Helsinki Declaration (as revised in 2013). The participants were informed about the study design and objectives. All participants provided informed consent for inclusion and for anonymous data publication before they participated in the study.

RESULTS

The overall seroprevalence of IgM and IgG is 12.1% in the 5 groups, collectively, with the following breakdown of each group (Table 2):

1. Six positive participants for antiphospholipid antibodies (IgM) out of 33 participants (18.1%) and from the COVID-19 negative/SARS-CoV-2 nucleocapsid IgG negative/vaccinated group, with a mean level of the antibodies of 9.58 ± 6.30 AU/ml (95% CI: 7.34; 11.81).
2. Two positive participants for antiphospholipid antibodies (IgM) out of 17 participants (11.7%) from the COVID-19 negative/SARS-CoV-2 nucleocapsid IgG positive/Vaccinated group, with a mean level of the antibodies of 7.48 ± 3.92 AU/ml (95% CI: 5.47; 9.50).
3. One positive participant for antiphospholipid antibodies (IgM) out of 22 participants (4.5%) from the COVID-19 positive/SARS-CoV-2 nucleocapsid IgG positive/vaccinated group, with a mean level of the antibodies of 7.19 ± 2.10 AU/ml (95% CI: 6.25; 8.12).
4. Five positive participants for antiphospholipid antibodies (IgM) out of 26 participants (19.2%) from the COVID-19 positive/SARS-CoV-2 nucleocapsid IgG negative/unvaccinated group, with a mean level of the antibodies of 11.71 ± 13.65 AU/ml (95% CI: 6.20; 17.23).
5. Two positive participants for antiphospholipid antibodies (IgM) out of 34 participants (5.8%) from the COVID-19 positive/SARS-CoV-2 nucleocapsid IgG positive/unvaccinated group, with a mean level of the antibodies of 7.66 ± 2.05 AU/ml (95% CI: 6.94; 8.38).

The highest expression of IgM antiphospholipid antibodies has been revealed in the COVID-19 positive/SARS-CoV-2 nucleocapsid IgG negative/unvaccinated group with 5 out of 26 cases (19.2%), and the lowest expression was in the COVID-19 positive/SARS-CoV-2 nucleocapsid IgG positive/vaccinated group with 1 out of 22 (4.5%) positive cases.

IgG antiphospholipid antibodies expression was low across all groups with no significant elevation, with one positive case in each of the following groups: COVID-19 negative/SARS-CoV-2 nucleocapsid IgG positive/vaccinated group, COVID-19 positive/SARS-CoV-2 nucleocapsid IgG negative/unvaccinated group, and COVID-19 positive/SARS-CoV-2 nucleocapsid IgG positive/unvaccinated group.

Table 2. Number of antiphospholipid IgM antibodies positive participants per group.

Group of Participants	Number of antiphospholipid IgM antibodies positive males per group	Number of antiphospholipid IgM antibodies positive females per group	Total number of positive participants per group (males+females)	Total number of equivocal participants per group (males+females)	Total number of participants per group (positive + equivocal + negative)
COVID-19 negative/ SARS-CoV-2 nucleocapsid IgG negative/vaccinated group	**5**	**1**	**6**	**12**	**33**
COVID-19 negative/ SARS-CoV-2 nucleocapsid IgG positive/vaccinated group	**0**	**2**	**2**	**3**	**17**
COVID-19 positive/ SARS-CoV-2 nucleocapsid IgG positive/vaccinated group	**0**	**1**	**1**	**5**	**22**
COVID-19 positive/ SARS-CoV-2 nucleocapsid IgG negative/unvaccinated group	**4**	**1**	**5**	**9**	**26**
COVID-19 positive/ SARS-CoV-2 nucleocapsid IgG positive/unvaccinated group	**0**	**2**	**2**	**12**	**34**
Total	**9**	**7**	**16**	**41**	**132**

The expression of IgM antiphospholipid antibodies was higher among males, with 9 cases out of 16 (56.2%) and 7 positive cases among females out of 16 (43.8%).

Another important observation regards individuals who had "high" normal/equivocal levels (IgM ≥ 8 AU/ml and <10 AU/ml) of IgM antiphospholipid antibodies: 41 out of 132 participants (31%), of which 25 out of 41 individuals are females (62.5%) and 16 males (37.5%), which requires further investigation.

DISCUSSION

The effects of COVID-19 infection on the development of antiphospholipid antibodies has been highlighted in a recent meta-analysis[16], especially focused on critically ill patients, where the prevalence of antiphospholipid antibodies was established with a pooled prevalence (IgM or IgG) of 7.10% and 5.8% for aCL and anti-B2GPI, respectively, for participants who were not hospitalized or admitted to the ICU, in comparison to 28.8% and 12.0% for aCL and anti-B2GPI, respectively, among the ICU patients[16]. Our study yielded similar findings, with 16 positive cases detected out of the 132 participants, with a 12.1% overall positivity, especially since all of the participants of our study presented mild symptoms of COVID-19 and did not require hospitalization. In contrast, the pooled prevalence of antiphospholipid antibodies (IgM or IgG) of hospitalized COVID-19 patients by the previous study showed 46.8% positivity, with 13.9% and 6.7% for aCL and anti-β2 GPI (IgM or IgG), respectively16, underlying the significant association between the severity of the COVID-19 infection and the levels of antiphospholipid antibodies.

The highest expression of antiphospholipid antibodies was detected among those who were COVID-19 positive (detected by PCR method) with SARS-CoV-2 nucleocapsid IgG antibodies negative - unvaccinated individuals, which seems paradoxical at first glance, yet can be explained by the data presented in a study by Petersen et al[20], which was performed to determine the seroprevalence of SARS-CoV-2 IgG antibodies in previously infected individuals. 2,547 individuals who tested positive for SARS-CoV-2 by RT-PCR method were tested for SARS-CoV-2 IgG antibodies directed against the viral S1 domain. Of those individuals, 160 (6.3%) were found to lack detectable IgG antibodies, similar to the seemingly contradictory findings in our results.

Similarly, Gudbjartsson et al[21] yielded comparable results: they tested 1,215 individuals, who had previously been positive-tested with qPCR method, for pan-Ig for the nucleoprotein N (Roche, Wantai BioPharm,

Beijing, China) and found 108 individuals (8.9%) with negative results for the SARS-CoV-2 antibodies.

The paradoxical results observed – individuals who tested positive for COVID-19 by PCR method but lacked SARS-CoV-2 nucleocapsid IgG antibodies exhibited the highest expression of antiphospholipid antibodies – can be explained through several factors. Firstly, despite the previous PCR-confirmed infection, the absence of humoral response does not necessitate the absence of the infection but indicates an association between the severity of the disease and the level of strength of the humoral response, as the participants of our study were individuals with mild symptoms of COVID-19. This explains the weaker humoral response to COVID-19 and the absence of SARS-CoV-2 IgG antibodies, in comparison to severe COVID-19 patients who required hospitalization and had a stronger humoral response[22]. Secondly, the presence of antiphospholipid antibodies can be attributed to different factors, including age, infections other than COVID-19, and underlying autoimmune diseases[23]. Therefore, those individuals who have a high level of antiphospholipid antibodies expression while tested negative for SARS-CoV-2 nucleocapsid IgG antibodies, might have other risk factors that explain such findings.

The lowest antiphospholipid IgM antibodies expression has been detected in the COVID-19 positive/SARS-CoV-2 nucleocapsid IgG positive/vaccinated group with 1 out of 22 (4.5%) positive cases, which can be attributed to the complexity of the pathogenesis of antiphospholipid antibody formation and the underlying risk factors, where the severity of the disease, genetics, age, and environmental factors play an important role in the probability of the development of antiphospholipid antibodies[24]. Furthermore, antiphospholipid antibodies were found to be only transiently elevated during the duration of the infection, especially in the severe form of the disease[25,26], as the participants of our study had different timelines from the diagnosis of COVID-19 till the enrollment in our study, and only having a paucisymptomatic form of the disease, which is reflected by the high number of equivalent results of antiphospholipid IgM antibodies among all groups, with 41 out of 132 participants (31%) in that "gray zone".

Our results, with 9 males (56.2%) and 7 females (43.8%) positive for antiphospholipid IgM antibodies out of all of the 16 positive cases, do not differ significantly in terms of distribution between males and females, as females are generally more likely to develop antiphospholipid syndrome and the antibodies compared to males. In some studies[24], this ratio came close to 1:1 between males and females, although it is worth noting that in all the groups who were IgG positive for SARS-CoV-2 nucleocapsid, females were the only positive cases for antiphospholipid IgM antibodies in the said groups with no positive male cases-Moreover, 62.5% of the individuals who had equivocal (high normal) levels of IgM were females.

The low expression of antiphospholipid IgG antibodies can be attributed to the effect of immediate sampling and the antibody production being in the acute phase, which will require repeated testing.

Limitations

Despite the insights from our study, several limitations must be highlighted. The relatively small sample size does not allow generalization of the findings, and a bigger sample size is needed to achieve statistically significant results. Moreover, the descriptive design of the study inherently prevents establishing a clear association between COVID-19 infection, vaccination status, and the levels of antiphospholipid antibodies, hence the need for further research.

CONCLUSIONS

The accurate determination of the prevalence of antiphospholipid antibodies in post-COVID and COVID-vaccinated individuals is important to understand the pathogenesis of the thromboembolic events documented in COVID-19 patients and to understand the persistence and long-term effect of such antibodies. Our findings suggest that many factors affect the expression of antiphospholipid antibodies among COVID-19 patients and that the low seroprevalence of IgM and IgG antibodies increases the support for the existing literature. This suggests that it is a transient elevation of those antibodies. Antiphospholipid Syndrome and the etiology of antiphospholipid antibody formation is a vast area of research, as is COVID-19, which requires more studies and more attention.

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Ethics Approval:
The present study has been approved by the Bioethics International Committee of the Petre Shotadze Tbilisi Medical Academy, approval Code: IRB20220120, January 20, 2022. All procedures performed in the present study were in accordance with the Helsinki Declaration (as revised in 2013).

Data Availability:
The datasets created and analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions:
All authors contributed equally to this article. Kobulashvili T, Sharma P, Habeebulla S, and Bakhtadze L have all performed literature reviews and data analyses; Al-Rustum SAJ contributed to data interpretation and manuscript preparation. All authors read and approved the final manuscript.

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Conflict of Interest:
The authors declare that they have no conflict of interest to disclose.

Informed Consent:
The participants were informed about the study design and objectives.
All participants provided informed consent for inclusion and for anonymous data publication before they participated in the study.

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