Frequency and clinical correlates of antiphospholipid antibodies arising in patients with SARS-CoV-2 infection: findings from a multicentre study on 122 cases

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Abstract

Objective

COVID-19 features include disseminated intravascular coagulation and thrombotic microangiopathy indicating a hypercoagulable state. We aimed to investigate antiphospholipid antibodies (aPL) prevalence and clinical relationships in a large cohort of COVID-19 patients.

Methods

We analysed the prevalence and titres of serum aPL in 122 patients with COVID-19 and 157 with primary antiphospholipid syndrome (PAPS) and 91 with other autoimmune rheumatic diseases (oARD) for comparison. IgG/IgM anticardiolipin (aCL) and IgG/IgM anti-beta2glycoprotein I (β2GPI) were assayed using homemade ELISA, IgA aCL and anti-β2GPI by commercial ELISA kits and lupus anticoagulant (LAC) by multiple coagulation tests following updated international guidelines.

Results

Prevalence of IgG and IgM aCL and of IgG and IgM anti-β2GPI across COVID-19 patients were 13.4%, 2.7%, 6.3% and 7.1%, being significantly lower than in PAPS ($p<0.0001$ for all). Frequency of IgG aCL and IgM anti-β2GPI was comparable to oARD (13.4% vs. 13.2% and 7.1% vs. 11%, respectively), while IgG anti-β2GPI and IgM aCL were lower ($p<0.01$). IgA aCL and IgA anti-β2GPI were retrieved in 1.7% and 3.3% of COVID-19 patients, respectively. Positive LAC was observed in 22.2% COVID-19 vs. 54.1% of PAPS ($p<0.0001$) and 14.6% of oARD ($p=0.21$). Venous or arterial thromboses occurred in 18/46 (39.1%) COVID-19 patients and were not associated with positive aPL ($p=0.09$).

Conclusion

Thrombosis is a frequent manifestation during COVID-19 infection. However, prevalence and titres of aPL antibodies or LAC were neither consistently increased nor associated with thrombosis when measured at a single timepoint, therefore not representing a suitable screening tool in the acute stage of disease.

Key words

COVID-19, SARS-CoV-2, thrombosis, microangiopathy, antiphospholipid, lupus anticoagulant

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Introduction

The recent outbreak of SARS-CoV-2 infection has caused over 400.000 deaths worldwide [https://www.worldometers.info/coronavirus/] and is being intensively studied from the pathogenic point of view. The disease, COVID-19, is driven by a novel type of Coronavirus, whose course may dramatically vary between different individuals, ranging from an asymptomatic or mild form in the majority of cases to a life-threatening systemic disease with pneumonitis complicated by acute respiratory distress syndrome (ARDS) and cytokine release syndrome, which can trigger multiorgan failure and eventually death (1-3). Several reports so far have described an increased rate of thrombosis in COVID-19 patients (4-6), thereby promoting anticoagulation as an advisable part of the therapeutic approach (7). Recently, some authors have reported an increased proportion of anti-phospholipid antibodies (aPL) arising in COVID-19 patients, thereby conjecturing an involvement of aPL in COVID-19-related thrombosis (8-10). Besides the pathogenic aspect, this fact would imply anticoagulation to be long standing. aPL antibodies are known to be associated with systemic infections: in particular, IgA anti-beta2-glycoprotein 1 (β2GPI) and IgA anti-CL seem to be incited by respiratory infections (8, 11). aPL antibodies have been hypothesised to be triggered during SARS-CoV-2 infection by the aberrant exposition of proteins associated to phospholipids, such as β2GPI (12).

The topic has raised interest across the rheumatology community usually handling the aPL patients. SARS-CoV-2 infection was recently shown not to be more prevalent across patients with rheumatic diseases (13), where it mirrors frequencies similar to those of the general population. Growing evidence has been released both in support and against an increased prevalence of aPL antibodies in COVID-19 patients (8-10, 14), suggesting that several interfering factors could blur the results.

In this original paper we aimed to investigate the prevalence and clinical correlates of aPL antibodies in a wide cohort of COVID-19 patients, compared with patients affected with primary antiphospholipid syndrome (PAPS) and patients with other autoimmune rheumatic diseases (oARD).

Patients and methods

Titres of IgG and IgM anti-β2GPI, of IgG and IgM anti-cardiolipin (CL) antibodies and lupus anticoagulant (LAC) were measured in a cross-sectional fashion on serum samples of patients affected with SARS-CoV-2-associated pneumonia from January 15th, 2020 to April 30th, 2020, and of outpatients with PAPS or oARD for comparison. COVID-19 sera only were also tested for IgA anti-β2GPI and IgA anti-CL.

Diagnosis of COVID-19 was based on the presence of acute interstitial pneumonia and positive nasopharyngeal swab for SARS-CoV-2 polymerase-chain reaction, while patients with PAPS fulfilled the 2006 Sidney criteria (15) and patients with oARD fulfilled specific classification criteria.

Autoantibody detection

IgG/IgM anti-β2GPI and IgG/IgM aCL were assayed using homemade ELISA methods following the European Forum on aPL antibody recommendations (16, 17). Cut-off values for medium–high levels of IgG/IgM anti-β2GPI and IgG/IgM aCL antibodies were calculated as greater than the 99th percentile of sera from 120 healthy blood donors matched for age and sex with the study population (18). Commercial ELISA kits QUANTA Lite® β2 GPI IgA and QUANTA Lite® ACA IgA III (INOVA Diagnostics, A Werfen Group, Milan, Italy) were used for the detection of IgA anti-β2GPI and aCL antibodies, following the manufacturer's instructions. The cut-off values were >20 SAU (Standard β2GPI IgA Unit) for IgA anti-β2GPI antibodies, and >20 APL for IgA aCL antibodies, respectively.

LAC was assessed by multiple coagulation tests following updated international guidelines (19), the dilute Russell Viper Venom Time (dRVVT) and silica clotting time (SCT) tests (HemosIL dRVVT and HemosIL SCT, Werfen Group, Milan, Italy), using platelet-poor plasma samples. Samples with a prolonged screening test not corrected

Table I. Demographics and aPL features in COVID-19 patients and controls. When not available for all patients, data were reported for the higher number of patients with complete records and highlighted in the Table.

	COVID-19 hospitalised	COVID-19 Non hospitalised	COVID-19 Overall	PAPS	oARD
n. of patients	53	69	122	157	91
Gender, n. F (%)	26 (49.1)	36 (52.2)	62 (50.8)	82.8	90.1
Age (years, mean±SD)	64.6 ± 16.6	46.7 ± 17.7	54.3 ± 19.3	43.3 ± 11.6	44.3 ± 13.9
IgG aCL, n. (%)	10/52 (19.2)	5/60 (8.3)	15/112 (13.4)	106 (67.5)	12 (13.2)
IgM aCL, n. (%)	2/52 (3.8)	1/60 (1.7)	3/112 (2.7)	60 (38.2)	13 (14.3)
IgG anti-β2GPI, n. (%	4/52 (7.7)	3/60 (5.0)	7/112 (6.3)	111 (70.7)	19 (20.9)
IgM anti-β2GPI, n. (%)	4/52 (7.7)	4/60 (6.7)	8/112 (7.1)	68 (43.3)	10 (11.0)
LAC, n§. (%)	7/42 (16.7)	9/30 (30.0)	16/72 (22.2)	85 (54.1)	13/89 (14.6)
IgA aCL, n. (%)	2/52 (3.8)	0	2/121 (1.7)	NA	NA
IgA anti-β2GPI, n. (%)	4/52 (7.7)	0	4/121 (3.3)	NA	NA
IgG aCL, mean±SD	13.5 ± 8.7	10.9 ± 7.12	12.12 ± 7.97	53.3 ± 85.4	9.9 ± 11.7
IgM aCL, mean±SD	11.3 ± 12.3	10.01 ± 9.3	10.63 ± 10.78	44.8 ± 71.6	16.1 ± 19.7
IgG anti-β2GPI, mean±SD	1.64 ± 2.33	1.26 ± 1.68	1.44 ± 2.00	54.6 ± 84.1	13.5 ± 10.8
IgM anti-β2GPI, mean±SD	1.71 ± 2.01	2.68 ± 3.25	2.23 ± 2.78	19.9 ± 36.3	4.32 ± 6.12
IgA aCL	7.26 ± 14.5	3.48 ± 3.8	5.11 ± 10.1	NA	NA
IgA anti-β2GPI	8.9 ± 22.6	3.38 ± 3.29	5.77 ± 15.19	NA	NA
Anticoagulation*, n.(%)	43/47 (91.5)	NA	44/49 (89.8)	NA	NA
Thrombosis (any) n.(%)	18/46 (39.1)	0	18/115 (15.7)	79/137 (57.7)	NA

*any time during infection. § on reliable LAC tests.
aPL: antiphospholipid; aCL anticardiolipin; B2GPI: beta-2 glycoprotein I; LAC: lupus anticoagulant; COVID-19: coronavirus disease; PAPS: primary antiphospholipid syndrome; oARD: other autoimmune rheumatic diseases; SD: standard deviation; NA: not available.

by mixing with normal pooled plasma, were tested for confirmation by addition of excess of phospholipids. Patients were considered LA positive when the dRVVT and/or SCT screening, mixing and confirm tests were positive. LAC test was considered reliable only in patients who underwent measurement before starting the anticoagulation.

Statistics

Continuous variables were compared by Student t-test or Mann-Whitney or ANOVA according to their distribution. Chi-squared with Fisher's exact test when needed was applied to proportions. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS Software for Windows, v. 25.0, Chicago, IL, and Graph-Pad Prism v. 8.

Ethics

The study was conducted in keeping with Helsinki declaration and approved by the University of Padova.

Results

Patients' characteristics and occurrence of hypercoagulation events

One-hundred and twenty-two patients with COVID-19 were enrolled in the study and were compared with 157 patients with PAPS and 91 patients with oARDs (29 systemic lupus erythematosus; 23 Sjögren's syndrome; 19 systemic sclerosis; 11 rheumatoid arthritis; 9 idiopathic inflammatory myopathies). Fifty-three out of 122 COVID-19 patients (56.6%) were hospitalised due to coronavirus-related pneumonia at the time of evaluation, while the remainder 69 (43.4%) were home-quarantined. Demographics and clinical features of patients are reported in Table I.

Patients with SARS-CoV-2 infection were homogeneously distributed across females and males (50.8% *vs*. 49.2%) and they were older than patients with oARD or PAPS (p<0.0001). Among hospitalised patients in whom full records were retrieved, 18/46 (39.1%) developed a thrombosis during the hospitalisation, namely 17 venous thrombosis and one case of stroke due to occlusion of the *cerebral media* artery which was recorded in a 42-year-old patient with terminal breast cancer and brain metastases. None of the quarantined patients were reported to have developed thrombotic events. Overall, risk factors for thrombosis among COVID-19 patients included hospitalisation (OR [95%CI] 1.64 [1.3–2.07], p<0.001), older age (1.06 [1.02–1.1], p=0.001) and male gender (1.2 [1.04–1.44], p=0.011).

Prevalence of aPL

Across the whole COVID-19 cohort, none but one patient had a former diagnosis of PAPS; this only patient was excluded from aPL analysis. No significant difference in the prevalence of positive aPL or LAC apparent among hospitalised *versus* non-hospitalised COVID-19 patients (50% vs. 43.3% had at least one positive test). No triple positive cases occurred. LAC could be properly tested in 72 patients, with retrieval of 16 positive tests (22.2%). Notably, positive LAC was isolated *i.e.* not accompanied by other aPL specificities in 11/16 positive tests (68.8%), while it was due to a positive SCT test only in 13/16 cases (81.3%).

Overall, positive aPL antibodies (any specificity) and LAC were significantly less frequent among the COVID-19 population compared to PAPS patients (p<0.0001 for all), as shown in Table I. Compared to oARD, significantly lower rates of IgG anti-β2GPI (6.3% *vs*. 20.9%, p=0.002) and IgM aCL (2.7% *vs*. 14.3%, p=0.003) were retrieved, while rates of IgM anti-β2GPI, IgG aCL, and LAC did not significantly

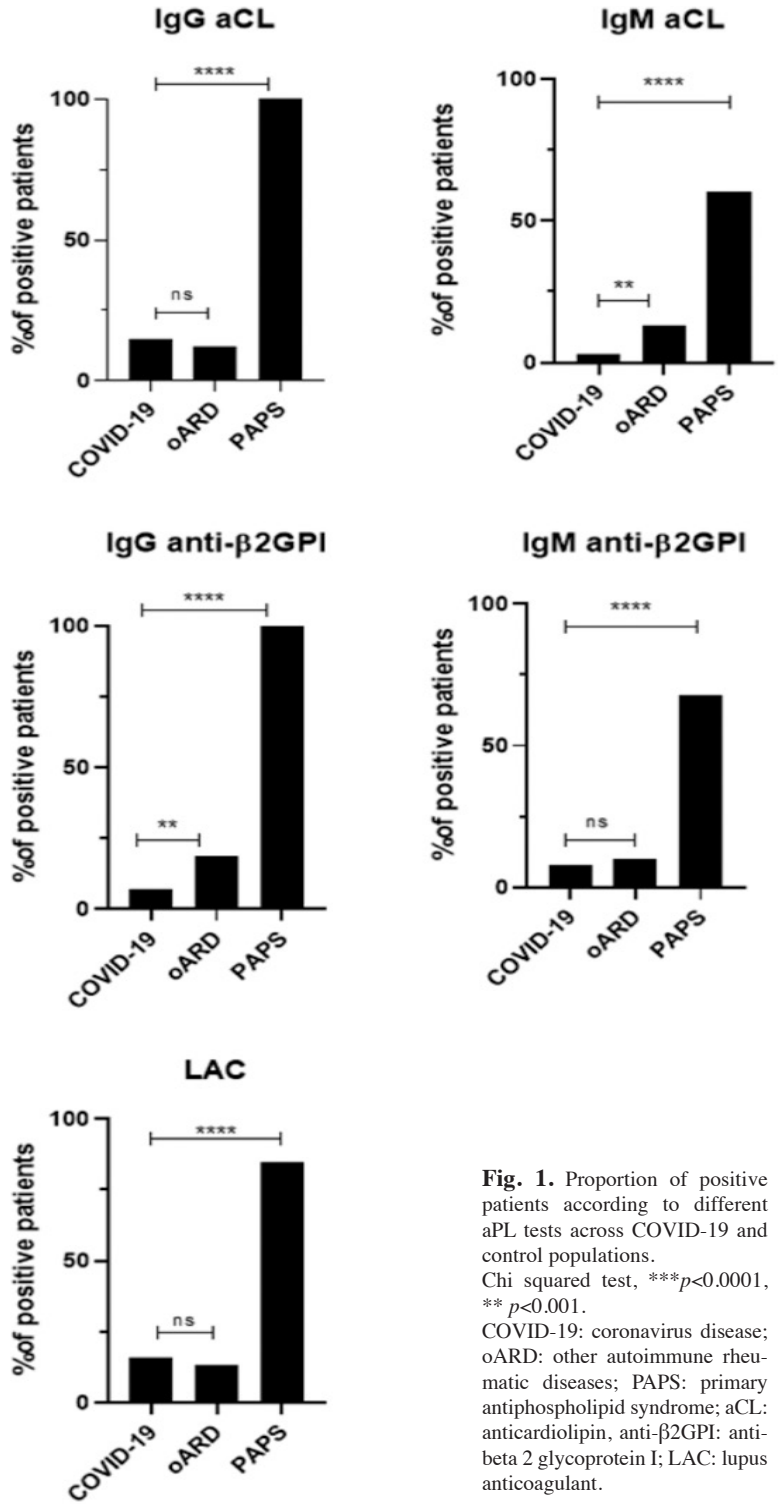

Fig. 1. Proportion of positive patients according to different aPL tests across COVID-19 and control populations.
Chi squared test, ***p<0.0001, ** p<0.001.
COVID-19: coronavirus disease; oARD: other autoimmune rheumatic diseases; PAPS: primary antiphospholipid syndrome; aCL: anticardiolipin, anti-β2GPI: anti-beta 2 glycoprotein I; LAC: lupus anticoagulant.

differ between COVID-19 and oARD patients (Fig. 1). Overall, mean titres of aPL were lower in COVID-19 *vs*. oARD patients, with the exception of IgG aCL (Fig. 2).

When referring to the subgroup of COVID-19 patients who developed a thrombotic event over their disease course (18/46), no statistical association between aPL or LAC and thrombosis was found. Nonetheless, 10 out 41 patients with at least one aPL positive test developed a thrombosis *versus* 8 out of 65 patients who were aPL negative (24.4% *vs*. 12.3%, p=0.09). Of note, the only COVID-19 with a former diagnosis of PAPS did not develop thrombosis during COVID-19 infection.

IgA anti-β2GPI and IgA aCL were measured only among COVID-19 patients and were infrequent, with 4/121 (3.3%) patients displaying positive IgA anti-β2GPI and 2/121 (1.7%) IgA aCL. No association with thrombosis could be established.

Discussion

In this study we aimed at investigating prevalence and serum levels of aPL antibodies in a large population of COVID-19 patients analysed for this purpose. The reasons underlying our interest in the topic reside in several reports describing a significant rate of positive aPL in these patients (8-10) which may worsen the prothrombotic state associated with the infection. We observed that hospitalisation, older age and male gender may represent risk factors for thrombosis in COVID-19. It was already described that severely ill patients are more likely to develop thrombosis, while demographic risk factors have not been unequivocally found associated with this complication in patients with SARS-CoV-2 infection (20, 21). However, it should be noted that older and male patients appear to display a more aggressive disease with coagulation disorders (22, 23).

Notably, this is the first study comparing COVID-19 patients with other populations with a well-characterised pro-thrombotic profile and an acknowledged role for aPL, *i.e*. PAPS and patients with immune rheumatic diseases including systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, rheumatoid arthritis and idiopathic inflammatory myopathies. In respect to those groups we could not document an increased aPL frequency. Most importantly, we could not demonstrate a significant association between positive aPL and thrombosis in this relatively large cohort of COVID-19 patients. In this regard, it is worth noting that other studies reporting a high rate of aPL across COVID-19 patients could neither show a parallel increase in thrombosis (9, 10), thereby questioning the true pathogenic value of such finding during acute SARS-CoV-2 infection. Furthermore, it should be mentioned that in most cases describing an

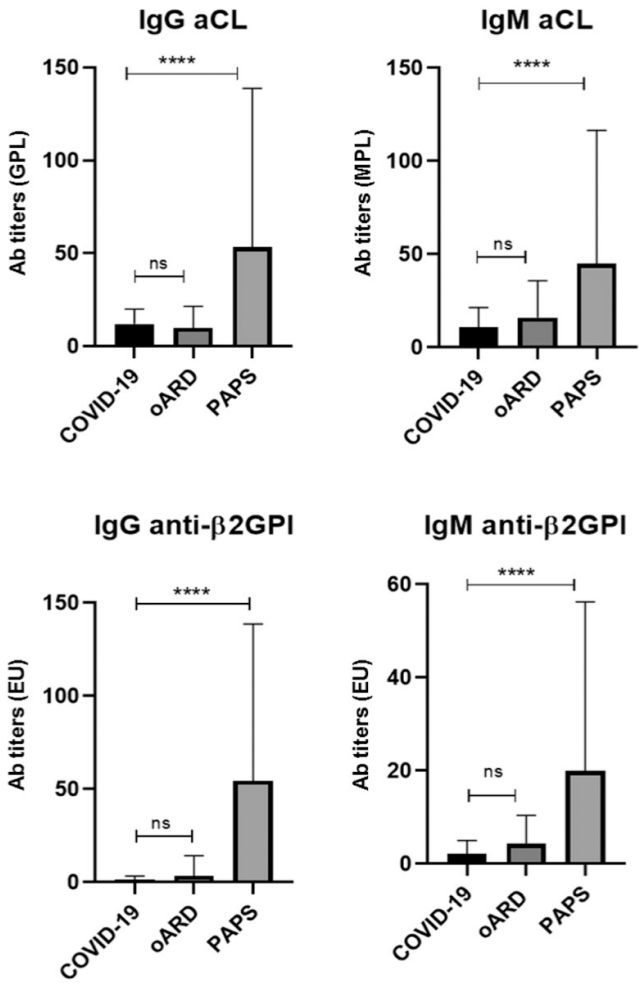

Fig. 2. Titres of different aPL specificities across COVID-19 *vs*. control populations. ANOVA with multiple comparisons, *** $p<0.0001$
COVID-19: coronavirus disease; oARD: other autoimmune rheumatic diseases; PAPS: primary antiphospholipid syndrome; aCL: anticardiolipin, anti-β2GPI: anti-beta 2 glycoprotein I.

increased prevalence of positive aPL, only isolated positive LAC was reported (9,10), which is tricky as a positive LAC test may arise from infections, systemic inflammation or methodological approach (24, 25). In our cohort we have retrieved a relevant proportion of LAC positive tests among COVID-19 patients (22.2%), although in the majority of cases LAC was isolated or only proved positive at SCT test, which entails a lower specificity of the test itself (26). This may suggest either a transient positivity due to the intervening infection or the presence of other specificities which were not analysed and could account for a true positive LAC (27), or the contribution of both these phenomena together.

Besides PAPS in which medium/high levels of aPL represent the pathognomonic aspect, we included the group of patients with autoimmune rheumatic diseases where aPL can be frequently found and can be associated with a clinically evident APS. We noticed that the prevalence of LAC and specific isotypes more convincingly associated with thrombosis (11, 28) were unevenly distributed between COVID-19 and oARD patients in our cohort, with IgG anti-β2GPI rarely found across COVID-19 patients, while LAC, IgG aCL and IgM anti-β2GPI being comparable, the latter being usually considered a risk factor for obstetric APS rather than for thrombosis (11, 29). As the mean rate of positive aPL across healthy donors was reported around at least 1–5% (30), one could speculate that rates of aPL across COVID-19 do increase in respect to the general population, which is further supported by IgG aCL titres being slightly higher among COVID-19 patients, yet the clinical relevance of such fluctuations remains to be determined. Moreover, it should be noted that mean titres of all aPL isotypes but IgG aCL were lower across COVID-19 patients (Fig. 2), thereby suggesting that some aPL specificities may transiently increase during COVID-19 infection, albeit entailing modest titres whose durability and effect need to be further elucidated. In this regard, the crystallised structure of IgG anti-β2GPI antibodies suggests that those arising during COVID-19 could bind a different domain on β2GPI in respect to those found during PAPS (31), therefore adding uncertainty to their actual mechanism *in vivo*.

The main limitation of our study lies in its cross-sectional nature which does not allow further insight on the disease course and would require retesting at 12 weeks. However, these findings are of interest because aPL measurement was conducted with a consistent methodology in a large COVID-19 population compared with a balanced control group, therefore aiding in overcoming single case-related observations.

Overall, it appears that aPL may occasionally arise in COVID-19 as well as during other infections, yet their prevalence and titres are not significantly nor consistently increased among COVID-19 patients and are unlikely to be the primary cause of thrombosis in the acute stage of the disease. However, as the frequency of some isotypes seems higher than their random finding in the general population, longitudinal data could be useful to discriminate patients who maintain positive aPL in the long term and may be at higher risk of thrombosis and consequent need for prophylaxis from those in whom aPL antibodies fade with the resolution of the infection.

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