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Antiphospholipid antibodies and COVID19- mortality and thrombotic events; A systematic review and meta-analysis

Reza Jafarzade Esfehani (Ph.D)[1], Mohammad Ali Khalilifar (Ph.D)[2], Hadi Esmaeili Gouvarchinghaleh (Ph.D)[3], Golamhossein Alishirid (MD)[4], Alireza Shahriary (Ph.D)[4*]

[1] *Student Research Committee Baqiyatallah University of Medical Sciences, Tehran, Iran.*
[2] *Blood born Disease research center, Academic Center for Education, Culture, and Research (ACECR)-Khorasan Razavi, Mashhad, Iran.*
[3] *Applied Virology Research Centre, Baqiyatallah University Medical Sciences, Tehran, Iran.*
[4] *Chemical Injuries Research Center, Systems Biology and poisoning Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran.*

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ABSTRACT

Introduction: Among various proposed pathologic mechanisms during the coronavirus disease 2019 (COVID-19) pandemic, overproduction of autoantibodies is not widely studied. Antiphospholipid antibodies (aPLs) are target proteins that have affinity toward charged phospholipids. APLs are thought to have pro-thrombotic potentials that increase during thromboembolism. The present systematic review and meta-analysis aimed to evaluate the relationship between serum aPLs level and COVID-19 mortality, severity, and thrombotic events**.**

Methods: This systematic review and meta-analysis was conducted on all open access published articles in Medline, Scopus and Google Scholar. Studies evaluating individuals over the age of 18 years who were diagnosed with COVID-19 and had positive aPLs; and provided data on mortality or thrombotic events were included.

Results: Of the initially identified 512 articles, 22 studies (overall 1462 patients) were finally included in the analysis. The prevalence of positive aPLs was 48.1%. Among the 372 patients with positive aPLs, 156 patients (41.9%) had severe COVID-19 that indicated a significant relationship between COVID-19 severity and aPLs positivity ($p<0.05$). The prevalence of thrombotic events in aPLs positive patients was 26.3% that indicated a significant relationship between aPLs positivity and the development of thrombotic events ($p=0.03$). APLs positivity was related to anytime mortality in COVID-19 patients ($p=0.01$).

Conclusion: The present review demonstrated that aPLs are linked to COVID-19 severity and thrombotic events but not short-term mortality. Further studies with longer follow up periods are warranted.

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Introduction

In late 2019, a novel viral infection was reported in Wuhan city, China and soon spread worldwide. This novel coronavirus disease caused by severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2) had considerable similarity with the bat-derived (SARS)-like coronaviruses (1). Similar to the recent coronavirus pandemics including the Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-1, the SARS-CoV-2 infection has less severity in most of the populations but some individuals may develop severe disease requiring intensive care unit (ICU) admission (2). A recent meta-analysis reported that the infection fatality rate of COVID-19 was 0.68% (3). Although COVID-19 has a lower fatality rate compared to SARS and MERS, it spreads faster than previous

***Corresponding author:** Alireza Shahriary,
Chemical Injuries Research Center, Systems Biology and poisoning institute, Baqiyatall University of Medical Sciences, Tehran, Iran
***E-mail:** Shariary961@gmail.com
***Tel:** 009391357042*

coronavirus outbreaks (4).

Early reports demonstrated that most COVID-19 patients suffer from respiratory insufficiency and develop acute respiratory distress syndrome. Later on, many studies highlighted that cardiovascular complications were high among COVID-19 patients. Such findings suggested that although the main infection site is the respiratory system, COVID-19 is accompanied with other systemic pathophysiologic processes in other organs. Therefore, pathologic mechanisms other than inflammatory responses became the focus of many clinical and experimental studies.

Alongside various pathologic mechanisms proposed for COVID-19, autoimmune reactions and the overproduction of autoantibodies have not been widely addressed in the literature. Autoimmunity is a complex phenomenon resulting from different mechanisms. Interactions and molecular mechanisms behind the development of autoimmune reactions are still unclear. Similar to other human diseases, the development of autoimmune diseases has specific predisposing factors, among which, infectious agents are considered as well-known risk factors that serve as triggers for autoimmune reactions (5).

A growing number of reports indicate development of autoimmune diseases, including Guillain Barre Syndrome, Miller Fisher syndrome, and Kawasaki-like disease following SARS-CoV-2 infection (6-9). Antiphospholipid antibodies (aPLs) are among the primary autoantibodies involved in many clinical diseases, including systemic lupus erythematosus and other autoimmune disorders.

Among autoantibodies, aPLs are target proteins with an affinity toward charged phospholipids. Anticardiolipin antibodies (aCL), anti-β2-glycoprotein I antibodies (aβ2GP), and lupus anticoagulant (LA) are among the primary aPLs that are thought to have pro-thrombotic potentials and are mainly elevated during venous or arterial thromboembolism. Experimental studies demonstrated that passive transfer of aPLs or removing aPLs by plasmapheresis could affect the development of thrombotic events (10,11).

The production of aPLS is triggered in various clinical settings, including viral infections and COVID-19 (12). Although many clinical studies and review studies demonstrated a considerable increase in aPL production during COVID-19; however, the consequences of such overproduction are not clearly understood and there are controversial results regarding the relationship between SARS-CoV-2 induced aPLs and disease outcomes (13-26).

Some studies reported an association between increased incidence of thrombosis in SARS-CoV-2 infected patients and specific aPLs, including LA, and suggested therapeutic anticoagulation regimens in patients with elevated level of aPLs (15). On the other hand, some studies demonstrated that, similar to other acute viral infectious diseases, SARS-CoV-2 infection induces a considerable level of aPL positivity which is associated with neither increased risk of thrombosis nor in-hospital mortality (17).

Therefore, despite an increasing number of reports regarding the elevated level of aPLs following SARS CoV-2 infection, there is a growing number of controversial results regarding the relationship between aPLs in COVID-19 patients and their outcome highlighting the lack of a quantitative analysis on this issue.

Objectives

As aPLs evaluation can be performed in many clinical settings, identification of the relationship between aPLs positivity and adverse COVID-19 outcomes can make these autoantibodies possible screening markers of high-risk COVID-19 patients. Therefore, these autoantibodies can be further used in clinical decision making to prevent mortality and thrombotic events.

Considering the growing body of evidence regarding the prevalence of aPLs positivity in COVID-19 patients, systematic review and meta-analysis can be a fast and reliable method to evaluate the relationship between aPLs positivity and COVID-19 outcomes. Therefore, the present systematic review and meta-analysis evaluated the relationship between serum aPLs and COVID-19 mortality, severity, and thrombotic events in adults.

Material and methods

The present study was conducted according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement (supplementary table 1).

Search methods for identification of studies

We designed our search strategy to cover all open access international English articles indexed in Medline and Scopus according to the following combination of keywords: "COVID-19" OR "Coronavirous disease 2019" OR "SARS-COV-2" OR "severe acute respiratory syndrome coronavirus-2" AND "Antiphospholipid", "Anticardiolipin" OR "Anti-B2 glycoprotein" OR "Lupus anticoagulant". Manual search was also performed in the reference list of the included studies and the Google Scholar. The online search was carried out with no time limit and all published studies until August 2022 were screened.

Table 1: Summary of clinical studies addressing the mortality rate among COVID-19 patients who had tested for aPLs

No	Author (reference number)	COVID-19 population	Mean (range) of age (years)	COVID-19 Detection method	Population characteristics	Specific clinical conditions included (number of patients)	Exclusion criteria	aPLs	Outcome measures	Prevalence of aPLs (%)	Most common aPL (%)
1	Najim et al. (27)	60	52.8	RT-PCR	ICU patients	Stroke (3) and VTE (1)	Thrombophilia (including APS), autoimmune and auto inflammatory rheumatic disease	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Arterial and venous thrombotic events and mortality during ICU admission	22/60 (37%)	LA (35%)
2	Gendron et al. (17)	154	67 (51-87)	RT-PCR and CT scan	Hospitalized	Cancer (18) and stroke (7)	NA	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Venous thrombotic events and mortality during admission	70/115 (60.9%)	LA (60.9%)
3	Amezcua-Guerra et al. (18)	21	(54-67)	NA	Hospitalized	Stroke (1) and cancer (1)	NA	aCL IgG/IgM, aβ2GP IgG/IgM, And anti-PS/PT antiphosphatidylinositol and antiannexin V antibodies	Venous thrombotic Events, bleeding and mortality up to 30 days	12/21 (57.1%)	Antiannexin V (19%)
4	Ferrari et al. (28)	89	(63-71)	RT-PCR	Severe and non-severe	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Deep vein thrombosis or pulmonary embolism, and mortality during admission	64/89 (71.9%)	LA (66.3%)
5	Hollerbach et al. (35)	53	64	RT-PCR	Severe	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM, And anti-PS/PT	In hospital mortality	29/53 (54.7%)	NA
6	Hollerbach et al. (21)	121	68	RT-PCR	Severe	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM, And anti-PS/PT	In hospital mortality	51/121 (42.1%)	NA
7	Pascolini et al. (14)	33	70 (22-90)	RT-PCR and CT scan	NA	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM, ANA*	In hospital mortality	8/33 (24.2%)	aCL IgM (62.5%)
8	Zhang et al. (22)	19	(60-70)	RT-PCR	Severe	Stroke and cancer	NA	aCL IgG/IgM/IgA, aβ2GP IgG/IgM/IgA, LA*	28 days mortality	10/19 (52.6%)	aβ2GP IgA (70%)
9	Gil Reyes et al. (15)	68	56	RT-PCR	NA	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Arterial and venous thrombotic events and mortality	30/68 (44%)	LA (44%)
10	Vlachoyiannopoulos et al. (23)	29	64.2 (43+85)	RT-PCR	Severe	Cancer (1) and autoimmune disease (1)	NA	aCL IgG/IgM, aβ2GP IgG/IgM*	In hospital mortality	16/29 (55.1%)	aβ2GP (37.9%)

11	Karahan et al. (24)	31	56.7	RT-PCR	Severe	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM/IgA, LA*	Arterial and venous thrombotic events and mortality	9/31 (29.03%)	LA (23.08%)
12	Joncour et al. (29)	104	71 (52-81)	RT-PCR	Non-severe	VTE (16), Cancer (27) and stroke (11)	NA	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Thrombotic events	49/104 (47.1%)	LA (39.6%)
13	de Chambrun et al. (25)	25	47 (35-64)	NA	Severe	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Thrombotic events	24/25 (98%)	LA (92%)
14	Tvito et al. (16)	43	63 (30-94)	NA	NA	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Thrombotic events	16/43 (37%)	LA (37%)
15	Volmer et al. (26)	79	64	RT-PCR	Severe	VTE (3) and cancer (4)	LA negative COVID-19 patients	aCL IgG/IgM, aβ2GP IgG/IgM, LA	Thrombotic events	10/42 (23%)	aCL IgM (23.2%)
16	Xiao et al. (30)	66	64.5	RT-PCR	Severe and none-severe	Cancer (4), autoimmune disease (2) and VTE (11)	NA	aCL IgG/IgM, aβ2GP IgG/IgM/IgA, LA*	Thrombotic events	31/66 (47%)	NA
17	Gutiérrez López de Ocáriz et al. (19)	27	58 (20-90)	RT-PCR	Hospitalized	Autoimmune disease (3) and cancer (2)	Patients receiving warfarin or direct oral anticoagulants were excluded	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Thrombotic events	7/27 (26%)	LA (23%)
18	Gatto et al. (20)	122	57	NA	Hospitalized	-	NA**	aCL IgG/IgM, aβ2GP IgG/IgM, LA*	Thrombotic events	56/122 (45.9%)	LA (22%)
19	Devreese et al. (31)	31	63 (38-82)	NA	ICU patients	Stroke (1), cancer (6) and autoimmune diseases (3)	NA	aCL IgG/IgM, aβ2GP IgG/IgM/IgA, APS/PT, LA*	Thrombotic events	23/31 (74.1%)	LA (67.7%)
20	Espinosa et al. (32)	158	61.4	RT_PCR	Hospitalized	Thrombosis (28), respiratory failure (47), mortality (1)	NA	aCL IgG/IgM, aβ2GP IgG/IgM, LA	Thrombotic events	37/158 (23.4%) in first sample, 17/58 (29.3%) in second sample	LA (21.4%) in first sample, aCL (17.2%) in second sample
21	Atalar et al. (33)	73	52.5	RT-PCR	Hospitalized	Thrombosis (3), mortality (2)	malignancy, renal transplantation, hemodialysis, chronic hepatitis, autoimmune disease, taking quinidine, procainamide, hydralazine	aCL IgG/IgM, aβ2GP IgG/IgM, LA	Thrombotic events	22/73 (22%)	LA (80%)
22	Constans et al. (34)	128	65 (18-99)	RT-PCR	Hospitalized	Thrombosis (6), mortality (27)	Receiving anti-thrombotic	LA	Thrombotic events, mortality	128/211 (60%)	LA(60%)

*aPLs defined as detection of any aPL, including anticardiolipin IgG/IgM, anti-β2-glycoprotein IgG/IgM, or lupus anticoagulant if present.
**None of the patients reported having a history of thrombophilia (including APS), autoimmune and autoinflammatory rheumatic disease.
Lupus anticoagulant (LA); Anticardiolipin (aCL); Anti-β2-glycoprotein (aβ2GP); antiprothrombin, antiphosphatidylserine (anti-PS/PT); antineuclear antibody (ANA); Reverse transcriptase polymerase chain reaction (RT-PCR); computed tomography (CT); Venous thromboembolism (VTE); Intensive care unit (ICU)

Criteria for considering studies for this review

Two independent authors accomplished the literature selection steps independently, first by screening titles and abstracts of retrieved articles for eligibility. Then, retrieved articles were selected based on discussion between the two authors.

Disagreement between the researchers was addressed through discussion with a third author. Finally, the full texts of relevant articles were read and data were extracted from the studies that fulfilled the eligibility criteria. The eligibility criteria included: (i) studies including every individual older than 18 years old who was diagnosed with COVID-19 based on RT-PCR or serological testing with any type of clinical disease severity; (ii) reporting data on any of the following aPLs (IgG or IgM or IgA) and positive: aCL or aß2GP or LA or antiphosphatidylserine/prothrombin(aPS/PT); (iii) providing mortality rate (in-hospital or out of hospital mortality), or thrombotic events (any type of arterial or venous thrombosis in any organ).

Case reports and case series with small populations (<10 patients) and articles on specific populations (for example studies on COVID-19 patients with cerebrovascular accidents) were not included.

Data extraction and bias assessment

Two authors independently extracted the following data: general study details, including author names and sample size, aPL test results, COVID-19 severity, and outcomes, including mortality and thrombotic events. The authors evaluated the risk of bias in each study using the "Tool to Assess Risk of Bias in Cohort Studies" developed by the CLARITY Group at McMaster University and "The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional study" (Supplementary table 2). Quantitative assessment was performed using the Review Manager Software version 5.4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

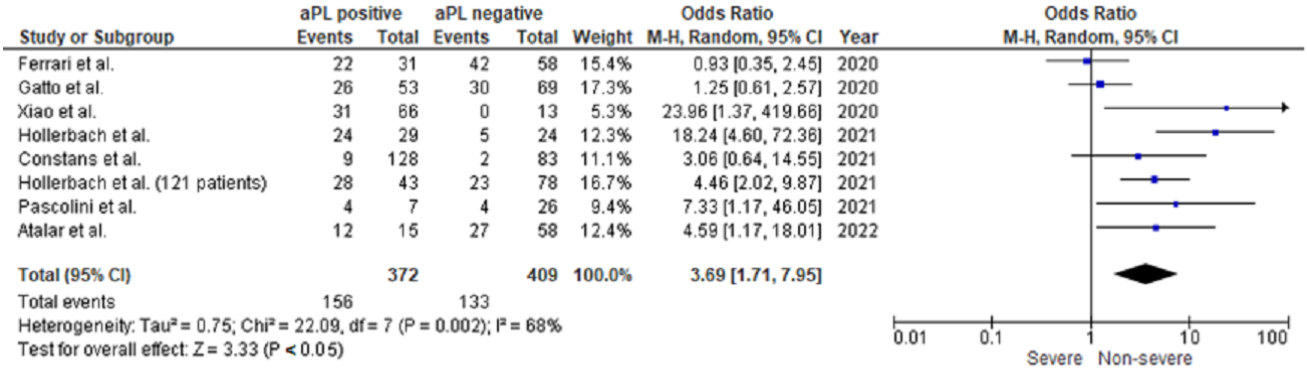

Table 2. Forest plot on the odds of aPL positivity in severe COVID-19 compared with non-severe COVID-19 patients

Statistical analysis

Data from all the retrieved studies were imported to the Review Manager Software version 5.4.1. Odds ratios (OR) and 95% confidence intervals (CI) and/or inverse variance approach were reported.

Analysis was performed using a random effects model. A p-value < 0.05 was considered statistically significant. Statistical heterogeneity was evaluated using the I2 statistics. Heterogeneity across the studies was categorized into low, moderate, substantial, and considerable based on I2 cut-offs of <30%, 31% to 60%, 61% to 74% and > 75%, respectively.

Results

Five hundred and twelve articles were identified according to the study search protocol and 326 articles remained after duplicate removal. Of these, 291 were excluded during the screening phase (title and abstract screening), with 35 records being fully appraised.

Twenty-two studies were finally included in the systematic review and quantitative analyses after removing the studies which did not follow the required study protocol (14-35) (Supplementary Table 1). Although all the included studies considered COVID-19 patients, except for five studies

(16,18, 20, 25, 31), every other article declared using RT-PCR for diagnosis of COVID-19 patients.

Overall, 1462 patients were evaluated for aPLs in retrospective or prospective observational cohorts or control-case studies. Three studies did not consider aPL testing for their entire population. The mean age of the COVID-19 patients was 60.61 years (ranging from 20 to 94 years old).

Among the entire population of included studies, aPLs were positive in 48.1% and LA was the most common aPL (49%). All articles, except three, reported COVID-19 severity among their study populations (14-16). However, four studies indicated that their population was chosen from COVID-19 patients admitted in different hospitals wards with different disease severity (17-20).

While two studies included ICU admitted patients (27, 31), six studies included severely ill patients requiring ventilation support who were admitted either in ICU or other hospitals wards (21-26). We considered these eight studies as studies evaluating severe patients. Only one study considered non-severe patients (29) and two other studies included patients with severe and non-severe diseases (28,30).

Table 1 summarizes the characteristics of included studies. The included studies evaluated at least one of the aPLs, but almost all of the studies did not clearly state their inclusion and exclusion criteria. Only Najim et al. reported that they excluded patients with thrombophilia (including APS), autoimmune and autoinflammatory rheumatic disease as these conditions may interfere with the prediction of aPL testing results (27).

Moreover, Gutiérrez López de Ocáriz et al. excluded patients receiving warfarin or oral anticoagulants, as these drugs may interfere with the interpretation of laboratory data and thrombotic outcomes (19).

Therefore, according to the reported diagnostic challenges in antiphospholipid syndromes by Schreiber et al. (36), we considered specific medical conditions that could affect the interpretation of aPLs results and establishing a hypercoagulable state affecting thrombosis formation, including the history of malignancies, stroke, or previous thrombotic events, and autoimmune diseases.

Disease severity, thrombotic events, and mortality among COVID-19 patients with positive and negative aPLs

Among the included 22 studies, 8 studies evaluated aPLs status in COVID-19 patients with severe disease (14, 20, 21, 28, 30, 33-35). Among 372 patients with positive aPLs, 156 patients (41.9%) had severe disease (Table 2).

Pooling data from these eight studies demonstrated that aPLs positivity was related to severe disease (mean difference of 3.69, 95% CI: 1.71, 7.95; p<0.05; I2=68%). Characteristics of studies that evaluated thrombotic events regardless of specific medical conditions, including previous history of thrombosis, stroke, autoimmune disease, or malignancies are summarized in Table 3 (15-20, 22, 24-31, 33, 34).

Out of the 561 patients, 148 aPLs positive patients (26.3%) had thrombotic events (arterial or venous thrombosis, thromboembolism, and stroke) while 92 out of 560 patients (16.4%) with negative aPLs had thrombotic events (Table 3).

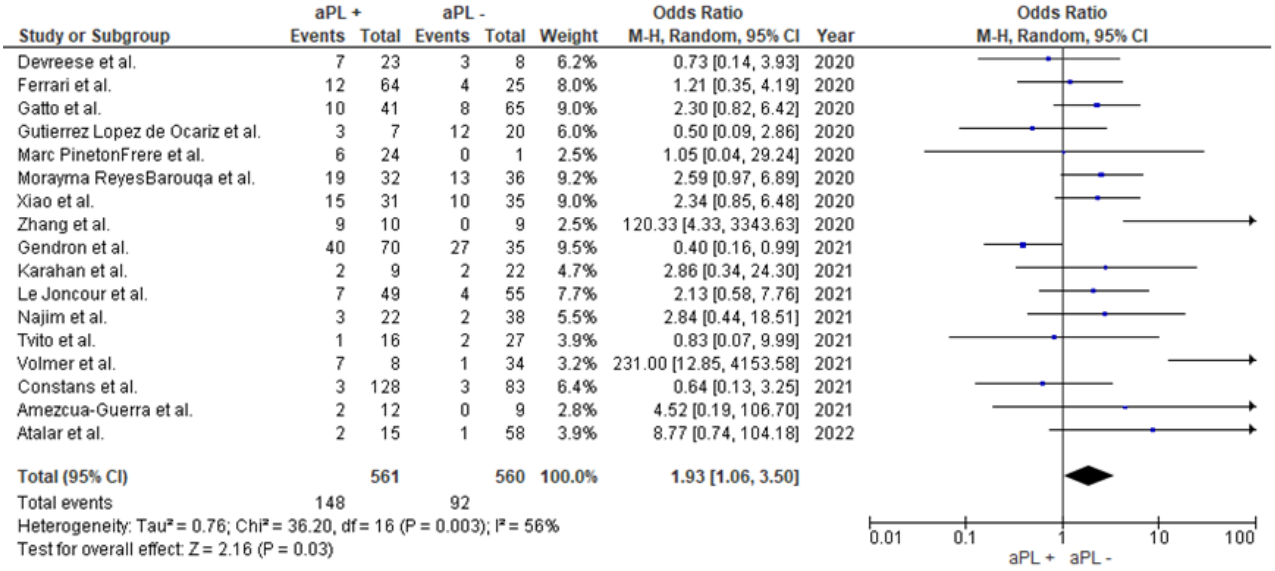

Table 3. Forest plot on the odds of thrombotic events in aPL positive and aPL negative COVID-19 patients.

Pooling data from these studies demonstrated that aPLs positivity was related to the development of thrombotic events (mean difference of 1.93, 95% CI: 1.06, 3.50; p=0.03; I2=56%). Studies evaluating the mortality rate among patients with positive or negative aPLs are presented in Table 4 (14, 15, 17, 18, 21-24, 27, 28, 33, 34). Out of the 478 aPLs positive patients 111 had in-hospital or out-of-hospital mortality, while 62 out of 474 aPLs negative patients died in or out of the hospital. The aPLs positivity was related to mortality (mean difference of 1.98, 95% CI: 1.18, 3.32; p=0.01; I2=35%). (Table 4).

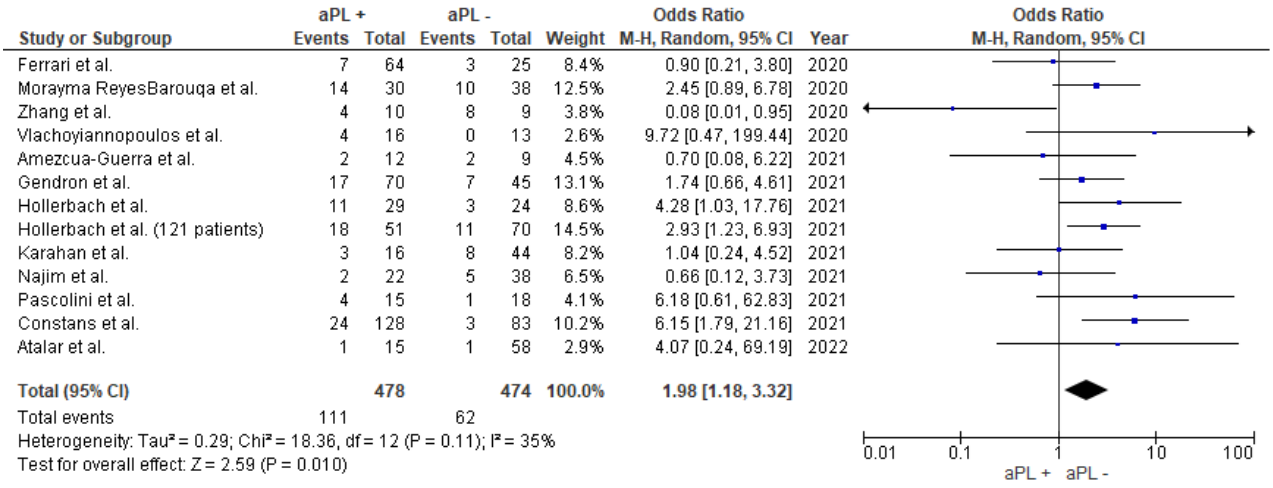

Table 4. Forest plot on the odds of Mortality events in aPL positive and aPL negative COVID-19 patients.

Discussion

The present systematic review aimed to evaluate the possible relationship between aPL positivity and COVID-19 severity, thrombosis, and mortality. According to our findings, 48.1% of COVID-19 patients had aPL positivity and LA was the most common aPL reported in these patients. Positive aPL was related to disease severity, development of thrombotic events, as well as in-hospital or out of hospital mortality among COVID-19 patients.

The main mechanisms behind the induction of autoimmunity following viral infections could be explained differently, but molecular mimicry seems to be one of the most probable autoimmunity mechanisms following SARS-CoV2- infection. Angileri et al. demonstrated the immunologic relevance between SARS-CoV2- virus and human proteins and suggested that many clinical complications following SARS-CoV2- infection, including anosmia, leukopenia, and vascular damage, could be explained by the molecular mimicry of OR7D4, PARP9, and SLC12A6 proteins localized in olfactory receptors, B cells, macrophages, and endothelial cells, respectively (37).

During viral infections, disruption of the immune system tolerance and production of neoepitopes might increase the production of aPLs in the absence of an antigen. On the other hand, viral antigens mimicking human proteins and especially aPLs, develop an antigen-dependent response. However, coronaviruses were not previously linked to aPLs induction. Gkrouzman et al. evaluated the studies about the prevalence of aPL positivity in COVID19-patients till mid2020- and reported that %58 of these patients were positive for aPL (38).

Our study with more restricted inclusion criteria demonstrated that %48.7 of COVID19- patients had abnormal aPL profile (38). Moreover, it was reported that LA, aCL, and aB2GI were positive in %9 ,%64, and %13 of the patients, respectively (38). These aPLs levels were reported to be much higher in a recent study conducted by Egiziano et al. in the United States reporting that LA, aCL, and aB2G1- were positive in up to 15 ,7, and 11 percent of the general population (39).

Schreiber et al. compared the prevalence of aPLs in different medical conditions and reported that during thrombotic events, the level of LA, aCL, and aB2GP1- increased to %24 ,%18, and %18 for arterial and %24 ,%16, and %10 for venous thrombosis, respectively (36). Moreover, in some chronic autoimmune disorders, including systemic lupus erythematosus, the prevalence of LA, aCL, and aB2GP1- was %44-12 ,%34-15, and %19-10 respectively (36).

Whether SARS-CoV2- infection induces thrombosis via increasing aPLs or from alteration of other hemostasis pathways is not clearly understood. Post mortem studies showed that acute respiratory distress syndrome (ARDS) and small peripheral vessels thrombosis are common complications in severe COVID19- patients (40 ,41).

The main possible mechanism behind the coagulopathy in COVID19- patients is the induction of immune system reactions starting from the respiratory tissue. The SARS-CoV2- spike protein binds the virus to the ACE2 surface receptors, and the generation cytokine storm begins from the activated macrophages in the lungs (42).

Tumor necrosis factor (TNF), macrophages inflammatory protein (MIP), monocyte chemotactic protein (MCP), and tumor necrosis-related apoptosis-inducing ligand (TRAIL) are important cytokines that are released by macrophages (42). Besides the secretion of these inflammatory cytokines, activation of membrane attack complex predisposes thrombosis formation and increases vascular permeability (42).

Activation of platelets in such an inflammatory and pro-thrombotic environment induces clot formation and tissue damage (42). Therefore, both ARDS and diffuse intravenous coagulation are the consequences of these processes (42).

On the other hand, the spike protein of SARS-CoV-2 can activate the alternative pathway complement. Activation of the alternative pathway complement leads to endothelial injury and coagulopathy that could be seen in other diseases, including catastrophic APS (43). However, the inflammatory and hypercoagulable state alone may not explain the thromboembolism in COVID-19 patients while prolonged aPTT and absence of bleeding episodes highlight the possible role of other underlying etiologies, including aPLs (44).

Some viruses, including human immunodeficiency virus (HIV), Hepatitis-B and C, and Epstein–Barr virus (EBV), are known to cause a pro-thrombotic state by increasing antiphospholipid antibodies (45). These specific viral infections can trigger the production of autoreactive B-cells and subsequently the production of transient non-pathogenic aPLs of IgM isotype. These aPLs isotypes are less likely to be related to the development of a thrombotic process (26). However, as COVID-19 is associated with an increased likelihood of thrombotic events, the production of potentially thrombogenic aPLs in these patients should also be considered as a possible cause of thrombosis formation. It has been demonstrated that SARS-CoV-2 infection is associated with abnormal coagulation and cytokine storm (26). During the cytokine storm phase of the disease, various inflammatory mediators including interleukin-6 induce auto inflammatory reactions (23). The presence of systemic autoimmune reactivities in almost half of the infected patients regardless of their disease severity suggests a post-infectious or para-infectious autoimmune activation in COVID-19 (23).

Therefore, aPLs may be generated in such immune and coagulation dysregulation context (26). Therefore, alongside the induced endothelial damage during COVID-19 and the second hit as the increase of pathogenic aPLs, thrombus formation will occur similar to the process which is seen in APS (26). As stated by Xiao et al., although aPLs positivity may be a transient phenomenon in some COVID-19 patients; however, it may trigger"COVID-19–induced APS-like–syndrome" in some patients (30). Therefore long term follow up of patients with abnormal aPLs could be beneficial (30).

Hollerbach et al. evaluated the possible link between aPLs induced by SARS-CoV-2 infection and thrombosis in more detail. They suggested that delayed onset of clinical manifestations in COVID-19 occurs following the pro-inflammatory and pro-thrombotic exacerbation induced by signaling of lipid-binding aPL. The aPLs are capable of perpetuating the autoimmune signaling loop by targeting EPCR-LBPA as a possible cause for the slow recovery in certain patients with prolong COVID syndrome. Therefore, they suggest that lipid-reactive aPL is capable of inducing thrombo-inflammatory syndrome with a more severe clinical course (21).

Such findings are in line with the result of our meta-analysis indicating that aPL positivity was related to the development of thrombotic events in COVID-19 patients.

However, recommending routine evaluation of aPLs in COVID19- patients can still be debated. A previous study demonstrated that the risk of both arterial and venous thrombosis was high among LA-positive COVID19- patients. Therefore, they suggested the initiation of therapeutic anticoagulation regimens in such patients (15).

LA is an aPLs frequently found in COVID19-patients especially in the acute phase of the disease and is a transient finding. LA and aCLs are associated with the development of thrombotic events during the acute phase of COVID19- infection. Similarly, anticoagulant prescription in the early phase of the infection in patients with abnormal aPLs was recommended by the authors (26).

In contrast to such recommendations, some authors including Gendron et al. believed that although COVID19- patients face an increased level of LA, aPL testing should not be recommended in the acute phase of the disease as for other viral infections (17).

Furthermore, Najim et al. concluded that aPLs are not related to the clinical outcomes of ICU admitted COVID19- patients and suggested that routine screening of aPLs should not be considered in SARS-CoV2- infected patients unless there is reasonable evidence of APS (27).

We believe that such controversial results highlight the need for further studies with long-term clinical follow-up. Therefore, it is more reasonable to perform aPLs tests in a case-by-case decision making and mainly based on the clinical judgment of the physicians until more robust long-term results become available.

Study limitation

Most of the studies included in the present meta-analysis had a small sample size that did not allow the procurement of meaningful clinicolaboratory associations.

Furthermore, pre-infection serological data was not available in almost all the evaluated studies. Moreover, some studies did not provide enough information about previous medical illnesses, including rheumatologic or autoimmune diseases affecting the level of aPLs.

Other shortcomings of the included studies were lack of data on the time lapse between LA testing from admission to thrombotic events or mortality. Additionally, it is not yet clear how long aPLs persist in serum; therefore, long-term studies addressing this issue are strongly recommended.

Conclusion

The present systematic review and meta-analysis demonstrated that %48.1 of COVID19-patients had aPL positivity and positive LA was the most common aPL reported in these patients.

Moreover, aPL positivity was related to disease severity and the development of thrombotic events. Positive aPL was related to mortality in COVID19- patients. However, there is still no long-term follow-up studies, and studies on the duration of aPLs positivity, as well as studies on long-term outcome of COVID19- patients with abnormal aPLs. Therefore, these issues are not clearly understood and need further investigation.

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