COVID-19, Antiphospholipid Antibodies, and Catastrophic Antiphospholipid Syndrome: A Possible Association?

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ABSTRACT: Since the 2019 novel coronavirus (COVID-19) was first detected in December 2019, research on the complications and fatality of this virus has hastened. Initially, case reports drew an association between COVID-19 and abnormal coagulation parameters. Subsequently, cross-sectional studies found a high prevalence of thrombosis among ICU and non-ICU COVID-19 patients. For that reason, certain studies tried to explain the pathogenic mechanisms of thrombosis, one of which was the emergence of anti-phospholipid antibodies (aPL). Although aPL have been found positive in very few patients, their association with thrombotic events stays debatable. Given the thrombotic manifestations of COVID-19 and the potential role of aPL, the catastrophic form of APS (CAPS) might be a major fatal phenomenon. However, to date, there has been no clear association of CAPS to COVID-19. Moreover, since infections, including viral respiratory similar to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are considered main etiologies for CAPS, it could be possible that SARS-CoV-2 can induce CAPS although no evidence is currently found. High quality studies are needed to develop a clear idea on the pathogenic role of aPL in the progression of thrombosis in COVID-19 patients, and how such patients could be fit into a thromboprophylaxis plan.

KEYWORDS: Antiphospholipid antibodies, coronavirus, thrombosis, catastrophic antiphospholipid syndrome, screening, management

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Background

The most recent 2019 novel coronavirus (COVID-19) is believed to have originated in Wuhan, Hubei Province, China. As the confirmed infected cases spanned the globe, the World Health Organization (WHO) declared COVID-19 a global health emergency.[1] Initial emerging reports associated COVID-19 infection with altered coagulation parameters.[2-4] Similarly, multiple reports documented increased D-dimer levels,[3,5-7]which has been associated with severe infection.[8] D-dimer levels seem a prognostic indicator as they were found to be 4-fold higher in patients who did not survive the hospitalization compared with survivors.[3]

The incidence of venous thromboembolism (VTE) among patients with severe COVID-19 infection not on routine thromboprophylaxis has been reported to be 25%.[9] Despite routine thrombosis prophylaxis, 20% of patients were diagnosed with VTE, of whom 13% were symptomatic.[10] Additionally, a high incidence (14.7%) of asymptomatic deep venous thrombosis (DVT) has been recorded in a cohort of COVID-19 patients admitted to non-intensive care units (ICU).[11] Elevated levels of D-dimer were significantly associated with asymptomatic DVT.[11] However, all these studies were single-center studies.

Among ICU patients in Dutch hospitals, where standard and intermediate low-molecular-weight heparin (LMWH) prophylaxis was applied, the cumulative incidence of VTE was 27% and of arterial thrombotic events was 3.7%.[12] Out of 184 ICU patients on thrombophylactic regimens, 75 underwent thrombotic events, the majority of which were pulmonary embolism (PE) events (65/75).[13] These patients were at a significantly higher risk of all-cause death, in spite of therapeutic anticoagulation.[13] Similar observations have been reported in ICU patients in France and Italy.[14,15] Interestingly, Tang et al suggested that thrombosis was associated with a poorer prognosis.[3] Autopsies performed on 12 COVID-19 patients showed that PE was the direct cause of death in 4 patients.[16] Furthermore, histologic analysis of pulmonary vessels of 7 COVID-19 patients showed widespread thrombosis with microangiopathy.[17] The high prevalence of PE among COVID-19 patients has been explained by the inflammatory nature of the disease rather than by an embolic mechanism of DVT in critically ill patients.[18]

The placentas of COVID-19 pregnant patients seem to be susceptible to thrombosis as well, which might predispose to recurrent miscarriages, a hallmark of antiphospholipid syndrome. For instance, Mulvey et al studied the placental pathology of 5-full term births to COVID-19 patients. All 5 placentas exhibited thrombosis with no complement deposition.[19] Similarly, Shanes et al assessed 16 placentas from patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[20] Compared to controls, COVID-19 placentas show increased prevalence of placental injury patterns reflecting abnormalities in oxygenation which may reflect a systemic inflammatory or hypercoagulable state.[20]

Although emerging evidence hints on the association of COVID-19 with thrombosis in ICU and non-ICU patients, the real incidence is still unknown. The primary aim of this review is to shed light on the thrombotic role of antiphospholipid antibodies in the setting of COVID-19, possibly leading to catastrophic antiphospholipid syndrome. As a second aim, we try to discuss the thrombophylactic plans that COVID-19 positive patients with presence of antiphospholipid antibodies can undergo.

The Pathogenic Mechanisms

COVID-19 infection may predispose to thrombophilia in several ways. Endothelial dysfunction, characterized by increased levels of von Willebrand factor (vWF), systemic inflammation, by activation of Toll-like receptors, and a pro-coagulatory state, by tissue factor pathway activation, are among the suggested pathogenic mechanisms.[21] Given that in a subgroup of patients with severe COVID-19 infection, high plasma levels of proinflammatory cytokines were found, a state of pro-coagulation is possible.[22] For example, elevated levels of factor VIII, fibrinogen, vWF, and D-dimer were found among COVID-19 patients with acute ischemic stroke.[23] In addition, complement activation may contribute to hemostatic activation leading to pathological features such as microvascular injury and coagulopathy.[24] Angiotensin-converting enzyme (ACE)-2 acts as a viral receptor on the surface of several pulmonary and extra-pulmonary cell types including endothelial cells, which allows viral binding and entry.[25] As such, SARS-CoV-2 can infect endothelial cells contributing to systemic vasculitis, thromboembolism, and disseminated intravascular coagulation (DIC).[26] Because Neutrophil Extracellular Traps (NETs) have the potential to propagate inflammation and microvascular thrombosis, Zuo et al assessed the sera of COVID-19 patients versus controls for NETs proteins. Cell-free DNA, myeloperoxidase (MPO)-DNA, and citrullinated histone H3 (Cit-H3) were elevated in patients which might contribute to cytokine release and respiratory failure.[27] Furthermore, because severe hypoxia develops in some COVID-19 patients, hypoxia-inducible transcription factors might alter genes that regulate thrombus formation in these patients.[27] Of note, immune-mediated damage by antiphospholipid antibodies (aPL) might be of a contributing role.

The Role of Antiphospholipid Antibodies (aPL)

In 2003, Chow and Chiu cross-sectional study found incidentally a weak positivity of lupus anticoagulant (LAC) in pediatric patients who were admitted for severe acute respiratory syndrome coronavirus (SARS-CoV).[28] For severe acute SARS-CoV-2 infection, an initial case series found elevated anticardiolipin (aCL) IgA antibodies and anti-β2-glycoprotein I (anti-β2-GPI) IgA and IgG antibodies among 3 patients with multiple cerebral infarctions.[29] This case series was criticized for reporting only IgA antibodies for aCL, as only high titer IgM and IgG isotypes, which are the isotypes included in antiphospholipid syndrome (APS) laboratory criteria, can be evaluated for thrombotic sequelae,[30] although Ali et al later found that severe COVID-19 illness is significantly associated with serum total IgA as well as anti-β2-GPI IgA and aCL IgA.[31] In addition, 2 of the 3 patients in the case series reported had a history of thrombotic events, and all of them had pre-existing cardiovascular disease which further increased the thrombotic risk.

Subsequently, multiple case reports, case series, cohort studies, and cross-sectional studies assessed aPL in COVID-19 patients and some of these studies tried to associate thrombotic manifestations to aPL status. The assessment of LAC in these studies were challenged by the use of low molecular weight heparin (LWMH) and unfractioned heparin that can lead to false positive results.[32,33] Moreover, LAC has a significant association with inflammatory conditions which might explain its intermittent nature[34] and high prevalence among thrombotic COVID-19 patients. Thus, the results are difficult to interpret. In addition, a majority of these studies assessed aPL at one time point and did not perform a repeat test at least 12 weeks apart. In one study,[35] a repeat testing was done after 4 weeks for some aPL positive patients. Interestingly, a major proportion of patients who tested positive for LAC, IgG aCL, and aβ2GP1 on the first occasion turned out negative on the second subsequent test, with around half of LAC negative patients undergoing thrombotic complications, which suggests that thrombosis in COVID-19 patients are secondary to other coagulative processes. However, a significant difference in the prevalence of aPL between critically ill and non-critically ill patients was noted,[36] which justifies the need of studies that can assess the difference of the association between aPL and thrombosis among ICU patients compared to non-ICU patients. A summary of the studies that discussed aPL in the setting of COVID-19 is listed in Table 1. All antiphospholipid assays were performed by ELISA. In addition, the LAC assays were performed according to the International Society on Thrombosis and Haemostasis (ISTH) guidelines.[37] To date, the real prevalence of aPL among COVID-19 patients is still unknown.

Catastrophic Antiphospholipid Syndrome (CAPS)

Definitions and criteria

Antiphospholipid syndrome (APS), characterized by recurrent thrombotic episodes and/or obstetric complications with persistently elevated titers of aPL confirmed at least 12 weeks apart,[55] is recognized as one of the most common causes of acquired thrombophilia.[56] Several clinical complications can arise as a result of APS manifestations, one of which is catastrophic APS (CAPS) (Asherson's syndrome), which is life-threatening. The earliest description of CAPS was in 1984[57] before Ronald Asherson formally defined CAPS in 1992.[58]

Table 1. Literature studies which discussed antiphopholipid antibodies tests in COVID-19 patients.

REFERENCE	SCENARIO	APL TESTED	RESULTS	NUMBER OF PATIENTS WITH THROMBOSIS
Chow and Chiu[28]	21 pediatric patients	LAC	3 LAC	0 A or V
Zhang et al[29]	3 patients with multiple cerebral infarctions	aCL (IgA) aβ2GPI (IgA and IgG)	3 aCL (IgA) and aβ2GPI (IgA and IgG) 0 LAC	3V 3A
Beyrouti et al[38]	6 patients with large-vessel occlusive stroke	LAC aCL (IgM and IgG) aβ2GPI (IgM and IgG)	5 LAC 1 triple positive: aCL (IgM), aβ2GPI (IgM and IgG), and LAC.	6 A 1 V
Bowles et al[39]	216 patients	LAC	44 Prolonged aPTT. 31 of 34 patients with prolonged aPTT: LAC positive	0 A 1V
Harzallah et al[40]	56 patients	LAC, aCL, and aβ2GPI	25 LAC 5 aCL or aβ2GPI 3 double positive	NA
Helms et al[14]	57 ICU patients	LAC	50 LAC	NA
Galeano-Valle et al[41]	24 non-ICU patients who had DVT or PE.	aCL (IgM and IgG) aβ2GPI (IgM and IgG)	2 aCL (IgM) 2 aβ2GPI (IgM)	11 A 9 V 4 PE* and V
Previtalli et al[42]	35 deceased patients with autoptic proven thrombotic microangiopathy	aCL (IgA, IgG, and IgM) aβ2GP1 (IgA, IgG, and IgM)	1 aCL (IgG) 2 aCL (IgM) Low titers (< 3X the cut off).	All Unspecified thrombotic events
Zhang et al[43]	19 ICU patients	aCL (IgA, IgM, and IgG) aβ2GP1 (IgA, IgM, and IgG) LAC	10 aCL or aβ2GP1 7 multiple isotypes of aPL.	4 A (aPL positive) 0 A or V (aPL negative)
Xiao et al[36]	66 ICU 13 Non-ICU patients	aCL (IgA, IgM, and IgG) aβ2GP1 (IgA, IgM, and IgG) LAC	31 ICU aPL 19 ICU aβ2GP1 (IgA) 15 aβ2GP1 (IgA) and aCL (IgA) 2 ICU LAC	5 ICU (aPL positive)
Pineton de Chambrun et al[44]	25 ICU patients	aCL (IgA, IgM, and IgG) aβ2GP1 (IgA, IgM, and IgG) LAC	13 aCL 3 aβ2GP1 23 LAC 13 Double positivity 3 Triple positivity	6 A (aPL positive)
Hossri et al[45]	2 patients with thrombotic events	aCL (IgA, IgM, and IgG) aβ2GP1 (IgA, IgM, and IgG)	Case 1: Significantly positive aCL (IgM and IgG) Case 2: Positive aCL (IgM and IgG)	Case 1: A Case 2: A
Devreese et al[35]	31 patients	aCL (IgA, IgM, and IgG) aβ2GP1(IgA, IgM, and IgG) LAC	teen patients were single LAC positive, 2 triple positive, 1 double positive, 1 single aCL and 3 aCL IgG and LAC positive. 16 LAC 2 triple positive 1 double positive 3 aCL IgG and LAC positive 9 of 10 re-tested LAC positive turned negative. Double positive patient became negative.	7 A and V. (At least 1 aPL positive) 4 of LAC positive patients who became negative had thrombosis.
Popovic et al[46]	11 patients	aCL and aβ2GP1	3 aCL 1 aβ2GP1	11 A
Siguret et al[47]	74 ICU	aCL (IgM and IgG) aβ2GP1 (IgM and IgG) LAC	65 with any single positive isotype	1 A (Triple positive)
Bertin et al[48]	56 patients	aCL (IgM and IgG) aβ2GP1 (IgM and IgG)	aCL IgG significantly associated with the severe form of the disease	1 A (aCL IgG)

(Continued)

Table 1. (Continued)

REFERENCE	SCENARIO	APL TESTED	RESULTS	NUMBER OF PATIENTS WITH THROMBOSIS
Escher et al[49]	72 patients	aCL (IgM and IgG) aβ2-GPI (IgM and IgG)	, IgG anti-cardiolipin antibodies (ACA) and anti-beta2-glycoprotein I (anti-β2-GPI) were negative, but IgM ACA elevated at 121.9 CU (normal <20 CU) and IgM anti-β2-GPI elevated at 275.3 CU (normal <20 CU) Positive aCL (IgM) and aβ2-GPI (IgM).	0A 0V
Fan et al[50]	86 patients	aCL (IgM, IgG, and IgA) aβ2-GPI (IgM, IgG, and IgA)	Significantly higher prevalence among patients with ischemic stroke than no stroke.	4 A
Amezcua-Guerra[51]	21 patients	aCL (IgM and IgG) aβ2-GPI (IgM and IgG) Antiprothrombin (IgM and IgG) Antiphosphatidylserine (IgM and IgG) Antiphosphatidylinositol (IgM and IgG) Antiannexin V (IgM and IgG)	12 aPL positive 3 aCL (IgM) 2 aCL (IgG) 0 aβ2-GPI (IgM) 1 aβ2-GPI (IgG) 1 Antiprothrombin (IgM) 0 Antiprothrombin (IgG) 3Antiphosphatidylinositol (IgM) 2Antiphosphatidylinositol (IgG) 0Antiphosphatidylinositol (IgM and IgG) 4 Antiannexin V (IgM) 1 Antiannexin V (IgG)	2 A
Gatto et al[52]	122 patients	aCL (IgM and IgG) aβ2-GPI (IgM and IgG) LAC	13.4% aCL (IgG) 2.7% aCL (IgM) 6.3 % aβ2-GPI (IgG) 7.1% aβ2-GPI (IgM) 22.2% LAC	NA
Gil et al[53]	30 LAC positive COVID-19 patients	aCL (IgM and IgG) aβ2-GPI (IgM and IgG)	0% aCL (IgG) 3.7% aCL (IgM) 0 % aβ2-GPI (IgG) 3.7% aβ2-GPI (IgM)	8 V 9A
Gutierrez et al[54]	27 patients	aCL aβ2-GPI LAC	0% aCL 3.7% aβ2-GPI 22.2% LAC	3V 1A

Abbreviations: A, Arterial event; aCL, Anti-cardiolipin antibodies; anti-β2-GPI, anti-β2-glycoprotein I; aPL, Antiphospholipid antibodies; LAC, Lupus Anticoagulant; PE, Pulmonary embolism; V, Venous event.
*Pulmonary embolism (PE) considered as an arterial event.

Patients with CAPS share certain clinical and laboratory criteria including: involvement of 3 or more organs, systems, and/or tissues, acuity of manifestations, small-vessel occlusion in at least 1 organ, and presence of elevated titers of aPL.[59] When all 4 criteria are present, a "definite CAPS" diagnosis is confirmed.[60] If a patient meets 3 of the 4 criteria, "possible CAPS" is diagnosed.[60] CAPS is frequently associated with thrombocytopenia and hemolytic anemia.[61] LAC, which best predicts thrombotic events in APS patients,[62] is highly prevalent among CAPS patients.[61] The IgG isotype of aCL antibodies is more frequent than the IgM isotype.[61]

To date, few data exist on the association of COVID-19 thrombosis and CAPS. Since Robba et al hinted on multiple organ dysfunction including lungs, brain, heart, and kidneys with hematological complications,[63] Suri and Bening suggested that COVID-19 thrombosis could be a form of presentation of CAPS.[64] On the other hand, the single center study performed by Previtali et al studied the sera of 35 deceased patients for the presence of IgA, IgG, and IgM aCL and anti-β2GP1 antibodies, as well as IgG and IgM anti phosphatidylserine/prothrombin (PS/PT) antibodies.[42] Only 3 patients had slightly positive aCL and another 3 patients were positive for PS/PT antibodies.[42] Although the patients in this cohort fulfilled the main clinical diagnostic criteria of CAPS, almost all patients were negative for aPL. Even the aPL positive patients were not considered CAPS positive because aPL levels in CAPS are very high.[65] In addition, the major difference between CAPS and COVID-19 associated thrombosis is the normal fibrinogen levels in CAPS which comes in contrast to COVID-19 thrombosis[66] (Figure 1).

Etiologies

The pathogenesis of CAPS is not well understood due to the limitation of current studies. However, it is well known that a precipitating factor usually plays an inciting role. Infections

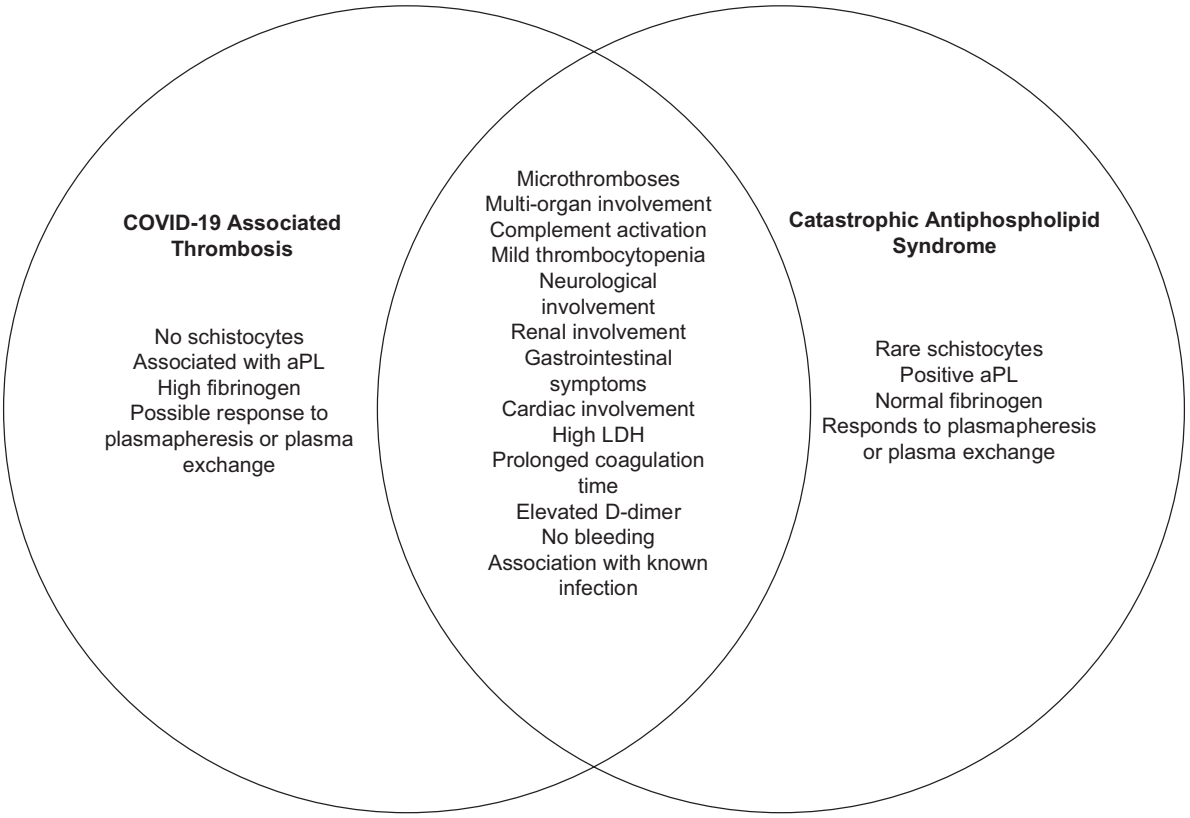

Figure 1. The shared and unshared clinical and laboratory manifestations between COVID-19 associated thrombosis and catastrophic antiphospholipid syndrome as reproduced from Merrill et al.[66]
Abbreviations: aPL, antiphospholipid antibodies; LDH, lactate dehydrogenase;

are the risk factors in around half of the patients, followed by surgical procedures (17%), malignancies (16%), anticoagulation withdrawal or low international normalized ratio (INR) (8%), obstetric complications (8%), drugs (5%), and systemic lupus erythematosus (SLE) flares (3%).[61] With regards to infections, the most commonly involved system is respiratory (33%) followed by urinary tract (19%), followed by the dermatologic (13%) and the gastrointestinal (8%).[67] It seems that by molecular mimicry, some of the infectious agents might induce nonpathogenic aPL and pathogenic anti-β2-GPI.[68] In addition, vascular endothelial injury might induce the event of thrombosis.[69] Since complement activation, which is a phenomenon that has been linked to COVID-19, is contributory to APS pathogenesis, at least in murine models, the association between thrombosis in APS and COVID-19 could be valid but necessitates further functional studies.[70,71]

Infectious agents. Escherichia coli has been reported to be the most frequently causative microorganism for CAPS.[67] However, viruses, fungi, and protozoa can also induce catastrophic events. Questioning whether SARS-CoV-2 can induce CAPS, the association of other viral infections with CAPS can give an idea. A few respiratory viral infections have been outlined to cause CAPS. For instance, Durkin et al reported the first case of CAPS presumably induced by the influenza A virus subtype H1N1 virus.[72] A second report of CAPS triggered by swine flu (H1N1) viral infection with adult respiratory distress syndrome (ARDS) has been published in 2019.[73] Similarly, Kallur et al reported a catastrophic hypercoagulable state case induced by influenza B infection.[74] In addition, 7 cases of CMV associated with CAPS that have been reported[67,75-78] although CMV infection itself is a known thrombotic agent.[69] Epstein Barr Virus (EBV) has been reported as a cause of CAPS.[77,79] Despite all these reports, there are still no clear reports of CAPS associated with COVID-19.

Controversial Prophylaxis

The huge burden of thrombotic events, in the presence or absence of aPL, on COVID-19 patients sheds light on the thrombophylactic regimen that such patients must undergo. The American Society of Hematology recommends an escalated dose (One-half) thrombophylaxis for ICU patients compared to the standard dose for ward patients.[80] The options of anticoagulation include low molecular weight heparin (LMWH), unfractionated heparin (UFH), and fondaparinux.[80] Direct oral anticoagulants (DOACs) can also be considered, although the implications on using the intermediate doses are not clear.[80]

The ISTH recommendations relied on expert opinion to determine the thrombophylactic regimens for admitted COVID-19 patients.[81] Because patients could be admitted to ICU and non-ICU settings, ISTH stratified the guidelines

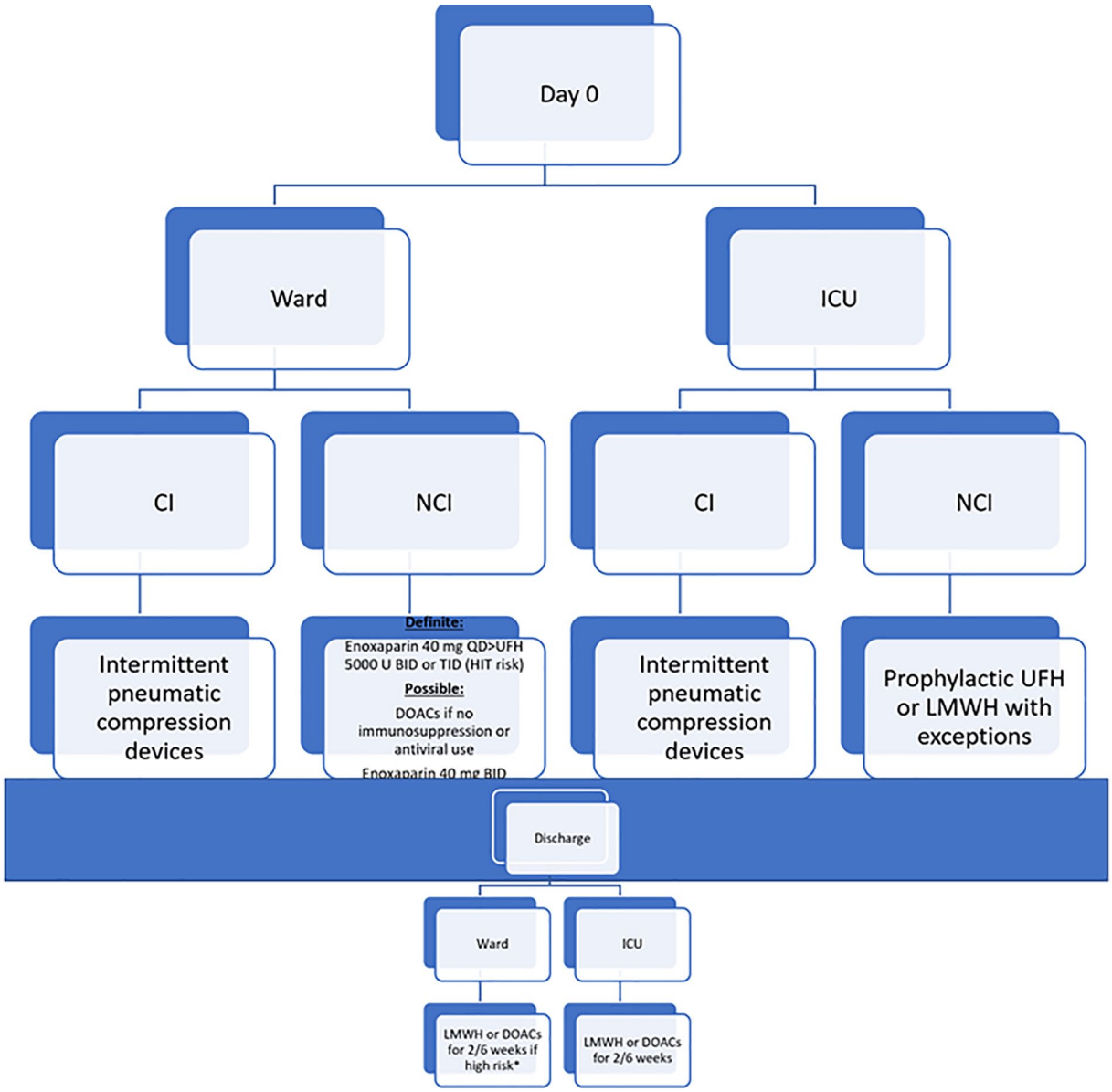

Figure 2. Anticoagulation management of admitted COVID-19 patients, whether to the ward or to the ICU, based on the International Society on Thrombosis and Haemostasis (ISTH) guidelines.
Abbreviations: ICU, intensive care unit; CI, contraindications; NCI, no contraindications; UFH, unfractioned heparin; DOACs, direct oral anticoagulation; LMWH, low molecular weight heparin.
*Advanced age, stay in the ICU, cancer, a prior history of VTE, thrombophilia, severe immobility, an elevated D-dimer (>2 times ULN), and an IMPROVE VTE score of 4 or more.

accordingly (Figure 2). The thromboprophylactic regimens should be modified according to body weight.[81]

The exact thrombophylactic recommendation for aPL positive COVID-19 patients is still unclear. Whether triple or double positive patients should receive the same thrombophylactic regimen as single positive patients is also unclear. Increasing the LMWH dose or introducing aspirin with a direct oral anticoagulant (DOACs) are among the suggestions, taking into consideration the risk of bleeding. There is an urgent need for high quality data, especially from randomized controlled trials, to determine the safest and most effective thrombophylactic regimen for aPL positive COVID-19 patients with or without thrombotic complications.

Conclusion

COVID-19 seems to induce a hypercoagulable state, particularly in severe cases despite thrombophylactic regimens. Although aPL have been present in few patients in single-center studies, the majority of these patients had positive LAC which is associated with infectious and inflammatory conditions. On the contrary, aCL and anti-β2-GPI antibodies were found positive in very few patients with venous thrombotic complications. Since

infectious etiologies, including viral respiratory agents similar to SARS-CoV-2, are the main risk factors for the development of CAPS, the role of SARS-CoV-2 in inducing vascular events seems reasonable, but needs further studies. To date, there are no studies that link COVID-19 to CAPS. Therefore, screening COVID-19 patients for aPL, to assess the possibility of developing fatal thrombotic complications such as CAPS, is currently not supported by evidence. Although standard management with LMWH has been recommended, COVID-19 patients with or without presence of aPL are still suffering thrombotic complications. Thus, different thrombophylactic regimens could be useful taking into consideration the bleeding risk. High quality studies, such as randomized clinical trials, are needed to guide anticoagulation in aPL positive COVID-19 patients who undergo thrombotic events.

Authors' Contributions

Georges El Hasbani reviewed the literature and wrote the first draft of this manuscript.
Ali T Taher critically revised the manuscript and conceptualised the figures.
Ali Jawad critically revised the manuscript.
Imad Uthman proposed the manuscript and critically revised it.

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REFERENCES

1. Giwa A, Desai A. Novel coronavirus COVID-19: an overview for emergency clinicians. *Emerg Med Pract*. 2020;22(2 Suppl 2):1-21.
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395(10223):507-513.
3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost JTH*. 2020;18(4):844-847.
4. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943.
5. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet Lond Engl*. 2020;395(10229):1054-1062.
7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497-506.
8. Zhao X, Zhang B, Li P, et al. Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. *medRxiv*. Published online March 20, 2020. doi:10.1101/2020.03.17.20037572
9. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost JTH*. Published online April 9, 2020. doi:10.1111/jth.14830
10. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost JTH*. Published online May 5, 2020. doi:10.1111/jth.14888
11. Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. *Thromb Res*. 2020;192:23-26.
12. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. Published online April 10, 2020. doi:10.1016/j.thromres.2020.04.013
13. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res*. Published online April 30, 2020. doi:10.1016/j.thromres.2020.04.041
14. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. Published online May 4, 2020. doi:10.1007/s00134-020-06062-x
15. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14.
16. Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med*. Published online May 6, 2020. doi:10.7326/M20-2003
17. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med*. Published online May 21, 2020. doi:10.1056/NEJMoa2015432
18. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Heide RSV. Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans. *medRxiv*. Published online April 10, 2020. doi:10.1101/2020.04.06.20050575
19. Mulvey JJ, Magro CM, Ma LX, Nuovo GJ, Baergen RN. Analysis of complement deposition and viral RNA in placentas of COVID-19 patients. *Ann Diagn Pathol*. 2020;46:151530.
20. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental Pathology in COVID-19. *Am J Clin Pathol*. 2020;154(1):23-32.
21. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol*. 2020;127:104362.
22. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *The Lancet*. 2020;395(10235):1517-1520.
23. Tan Y-K, Goh C, Leow AST, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *J Thromb Thrombolysis*. Published online July 13, 2020. doi:10.1007/s11239-020-02228-y
24. Song W-C, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. *J Clin Invest*. Published online May 27, 2020. doi:10.1172/JCI140183
25. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203(2):631-637.
26. Albini A, Di Guardo G, Noonan DM, Lombardo M. The SARS-CoV-2 receptor, ACE-2, is expressed on many different cell types: implications for ACE-inhibitor- and angiotensin II receptor blocker-based cardiovascular therapies. *Intern Emerg Med*. Published online May 19, 2020:1-8. doi:10.1007/s11739-020-02364-6
27. Gupta N, Zhao Y-Y, Evans CE. The stimulation of thrombosis by hypoxia. *Thromb Res*. 2019;181:77-83.
28. Chow EY, Chiu WK. Severe acute respiratory syndrome and lupus anticoagulants in children. *Br J Haematol*. 2003;123(2):367-368.
29. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. 2020;382(17):e38.
30. Connell NT, Battinelli EM, Connors JM. Coagulopathy of COVID-19 and antiphospholipid antibodies. *J Thromb Haemost*. 2020. doi:10.1111/jth.14893
31. Ali OH, Bomze D, Risch L, et al. Severe COVID-19 is associated with elevated serum IgA and antiphospholipid IgA-antibodies. *medRxiv*. Published online July 24, 2020:2020.07.21.20159244. doi:10.1101/2020.07.21.20159244
32. Tang N. Response to "Lupus anticoagulant is frequent in patients with Covid-19." *J Thromb Haemost JTH*. Published online May 7, 2020. doi:10.1111/jth.14890
33. Mehta S, Bhandari S, Mehta S. Cautious interpretation of antiphospholipid antibodies in COVID-19. *Clin Chim Acta*. 2020;509:166.
34. Sidelmann JJ, SjØland JA, Gram J, et al. Lupus anticoagulant is significantly associated with inflammatory reactions in patients with suspected deep vein thrombosis. *Scand J Clin Lab Invest*. 2007;67(3):270-279.
35. Devreese KMJ, Linskens EA, Benoit D, Peperstraete H. Antiphospholipid antibodies in patients with COVID-19: a relevant observation? *J Thromb Haemost*;18:2191-2201.
36. Xiao M, Zhang Y, Zhang S, et al. Brief Report: Anti-phospholipid antibodies in critically ill patients with Coronavirus Disease 2019 (COVID-19). *Arthritis Rheumatol Hoboken NJ*. Published online June 30, 2020. doi:10.1002/art.41425
37. Pengo V. ISTH guidelines on Lupus Anticoagulant testing. *Thromb Res*. 2012;130:S76-S77.
38. Beyrouti R, Adams ME, Benjamin L, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. Published online April 30, 2020. doi:10.1136/jnnp-2020-323586
39. Bowles L, Platton S, Yartey N, et al. Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19. *N Engl J Med*. 2020;383(3):288-290.
40. Harzallah I, Debliquis A, Drénou B. Lupus anticoagulant is frequent in patients with Covid-19. *J Thromb Haemost*. 2020;18(8):2064-2065.
41. Galeano-Valle F, Oblitas CM, Ferreiro-Mazón MM, Alonso-Muñoz J, del Toro-Cervera J, Demelo-Rodríguez P. Antiphospholipid antibodies are not

elevated in patients with severe COVID-19 pneumonia and venous thromboembolism. *Thromb Res*. Published online May 15, 2020. doi:10.1016/j.thromres.2020.05.017
42. Previtali G, Seghezzi M, Moioli V, et al. The pathogenesis of thromboembolic disease in covid-19 patients: could be a catastrophic antiphospholipid syndrome? *medRxiv*. Published online May 6, 2020:2020.04.30.20086397. doi:10.1101/2020.04.30.20086397
43. Zhang Y, Cao W, Jiang W, et al. Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients. *J Thromb Thrombolysis*. Published online July 9, 2020:1-7. doi:10.1007/s11239-020-02182-9
44. Chambrun MP de, Frere C, Miyara M, et al. High frequency of antiphospholipid antibodies in critically ill COVID-19 patients: a link with hypercoagulability? *J Intern Med*. doi:10.1111/joim.13126
45. Hossri S, Shadi M, Hamarsha Z, Schneider R, El-Sayegh D. Clinically significant anticardiolipin antibodies associated with COVID-19. *J Crit Care*. Published online May 29, 2020. doi:10.1016/j.jcrc.2020.05.017
46. Popovic B, Varlot J, Metzdorf PA, Jeulin H, Goehringer F, Camenzind E. Changes in characteristics and management among patients with ST-elevation myocardial infarction due to COVID-19 infection. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. Published online July 15, 2020. doi:10.1002/ccd.29114
47. Siguret V, Voicu S, Neuwirth M, et al. Are antiphospholipid antibodies associated with thrombotic complications in critically ill COVID-19 patients? *Thromb Res*. 2020;195:74-76.
48. Bertin D, Brodovitch A, Beziane A, et al. Anti-cardiolipin IgG autoantibodies are an independent risk factor of COVID-19 severity. *Arthritis Rheumatol*. 2020;72(11):1953-1955.
49. Escher R, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. *Thromb Res*. 2020;190:62.
50. Fan S, Xiao M, Han F, et al. Neurological manifestations in critically Ill patients with COVID-19: A Retrospective Study. *Front Neurol*. 2020;11:806.
51. Amezcua-Guerra LM, Rojas-Velasco G, Brianza-Padilla M, et al. Presence of antiphospholipid antibodies in COVID-19: case series study. *Ann Rheum Dis*. Published online August 4, 2020. doi:10.1136/annrheumdis-2020-218100
52. Gatto M, Perricone C, Tonello M, et al. Frequency and clinical correlates of antiphospholipid antibodies arising in patients with SARS-CoV-2 infection: findings from a multicentre study on 122 cases. *Clin Exp Rheumatol*. 2020;38(4):754-759.
53. Gil MR, Barouqa M, Szymanski J, Gonzalez-Lugo JD, Rahman S, Billett HH. Assessment of lupus anticoagulant positivity in patients with coronavirus disease 2019 (COVID-19). *JAMA Netw Open*. 2020;3(8):e2017539.
54. Gutiérrez López de Ocáriz X, Castro Quismondo N, Vera Guerrero E, Rodríguez Rodríguez M, Ayala Díaz R, Martínez López J. Thrombosis and antiphospholipid antibodies in patients with SARS-COV-2 infection (COVID-19). *Int J Lab Hematol*. Published online August 26, 2020. doi:10.1111/ijlh.13320
55. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost JTH*. 2006;4(2):295-306.
56. Mehdi AA, Salti I, Uthman I. Antiphospholipid syndrome: endocrinologic manifestations and organ involvement. *Semin Thromb Hemost*. 2011;37(1):49-57.
57. Dosekun AK, Pollak VE, Glas-Greenwalt P, et al. Ancrod in systemic lupus erythematosus with thrombosis. Clinical and fibrinolysis effects. *Arch Intern Med*. 1984;144(1):37-42.
58. Asherson RA. The catastrophic antiphospholipid syndrome. *J Rheumatol*. 1992;19(4):508-512.
59. Asherson RA, Cervera R, de Groot PG, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus*. 2003;12(7):530-534.
60. Carmi O, Berla M, Shoenfeld Y, Levy Y. Diagnosis and management of catastrophic antiphospholipid syndrome. *Expert Rev Hematol*. 2017;10(4):365-374.
61. Cervera R, Bucciarelli S, Plasín MA, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the "CAPS Registry." *J Autoimmun*. 2009;32(3-4):240-245.
62. Gebhart J, Posch F, Koder S, et al. Increased mortality in patients with the lupus anticoagulant: the Vienna Lupus Anticoagulant and Thrombosis Study (LATS). *Blood*. 2015;125(22):3477-3483.
63. Robba C, Battaglini D, Pelosi P, Rocco PRM. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. *Expert Rev Respir Med*. 2020;14(9):865-868.
64. Suri HC, Bening DJ. Catastrophic antiphospholipid antibody syndrome and multiple organ dysfunctions in critically ill patients with COVID-19. *Expert Rev Respir Med*. 2020;14(11):1071-1072.
65. Rodríguez-Pintó I, Espinosa G, Cervera R. Catastrophic APS in the context of other thrombotic microangiopathies. *Curr Rheumatol Rep*. 2015;17(1):482.
66. Merrill JT, Erkan D, Winakur J, James JA. Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications. *Nat Rev Rheumatol*. 2020;16(10):581-589.
67. Cervera R, Asherson R, Acevedo M, et al. Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. *Ann Rheum Dis*. 2004;63(10):1312-1317.
68. Asherson RA, Shoenfeld Y. The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome–molecular mimicry? *J Rheumatol*. 2000;27(1):12-14.
69. Nakayama T, Akahoshi M, Irino K, et al. Transient antiphospholipid syndrome associated with primary cytomegalovirus infection: a case report and literature review. *Case Rep Rheumatol*. 2014;2014:271548.
70. Fischetti F, Durigutto P, Pellis V, et al. Thrombus formation induced by antibodies to beta2-glycoprotein I is complement dependent and requires a priming factor. *Blood*. 2005;106(7):2340-2346.
71. Seshan SV, Franzke C-W, Redecha P, Monestier M, Mackman N, Girardi G. Role of tissue factor in a mouse model of thrombotic microangiopathy induced by antiphospholipid antibodies. *Blood*. 2009;114(8):1675-1683.
72. Durkin ML, Marchese D, Robinson MD, Ramgopal M. Catastrophic antiphospholipid syndrome (CAPS) induced by influenza A virus subtype H1N1. *BMJ Case Rep*. 2013;2013:bcr2013200474.
73. Madkaiker S. Catastrophic antiphospholid syndrome—an unusual case report. *Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med*. 2019;23(6):276-280.
74. Kallur L, Marco S, Houshmand F, Mazer M. 456: Influenza B-induced catastrophic hypercoagulable response. *Read Online Crit Care Med Soc Crit Care Med*. 2018;46(1):212.
75. Adhikari A, Chisti MM, Bastola S, Kc O. Rare case of catastrophic antiphospholipid syndrome with spontaneous intracranial haemorrhage. *BMJ Case Rep CP*. 2019;12(3):e227171.
76. Soe MH, Agarwal KA, Akough-Weir A. The wolf hidden behind the clots: catastrophic antiphospholipid antibody syndrome. *Case Rep Med*. 2018;2018:4693037.
77. Plummer MP, Young AMH, O'Leary R, Damian MS, Lavinio A. Probable catastrophic antiphospholipid syndrome with intracerebral hemorrhage secondary to epstein-barr viral infection. *Neurocrit Care*. 2018;28(1):127-132.
78. Damian L, Rednic S, Cristea A, et al. [FRI0276] VIRAL- induced catastrophic antiphospholipid syndrome: two cases with favourable outcome. In: 2004.
79. Abdel-Wahab N, Lopez-Olivo MA, Pinto-Patarroyo GP, Suarez-Almazor ME. Systematic review of case reports of antiphospholipid syndrome following infection. *Lupus*. 2016;25(14):1520-1531.
80. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135(23):2033-2040.
81. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18(8):1859-1865.