# Is Lupus Anticoagulant a Significant Feature of COVID-19? A Critical Appraisal of the Literature

Emmanuel J. Favaloro, PhD, FFSc (RCPA)[1,2] Brandon Michael Henry, MD[3] Giuseppe Lippi, MD[4]

[1] Department of Haematology, Sydney Centres for Thrombosis and Haemostasis, Institute of Clinical Pathology and Medical Research (ICPMR), NSW Health Pathology, Westmead Hospital, Westmead, New South Wales, Australia
[2] School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, New South Wales, Australia
[3] Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[4] Section of Clinical Biochemistry, University of Verona, Verona, Italy

**Address for correspondence** Emmanuel J. Favaloro, PhD, FFSc (RCPA), Department of Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, New South Wales, 2145 Australia (e-mail: emmanuel.favaloro@health.nsw.gov.au).

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## Abstract

The term "lupus anticoagulant (LA)" identifies a form of antiphospholipid antibodies (aPLs) causing prolongation of clotting tests in a phospholipid concentration-dependent manner. LA is one of the laboratory criteria identified in patients with antiphospholipid (antibody) syndrome (APS). The presence of LA in patients with APS represents a significant risk factor for both thrombosis and pregnancy morbidity. There have been several reports of similarities between some of the pathophysiological features of COVID-19 and APS, in particular the most severe form, catastrophic APS. There have also been many reports identifying various aPLs, including LA, in COVID-19 patients. Accordingly, a very pertinent question arises: "Is LA a feature of COVID-19 pathology?" In this review, we critically appraise the literature to help answer this question. We conclude that LA positivity is a feature of COVID-19, at least in some patients, and potentially those who are the sickest or have the most severe infection. However, many publications have failed to appropriately consider the many confounders to LA identification, being assessed using clot-based assays such as the dilute Russell viper venom time, the activated partial thromboplastin time (aPTT), and the silica clotting time. First, most patients hospitalized with COVID-19 are placed on anticoagulant therapy, and those with prior histories of thrombosis would possibly present to hospital already on anticoagulant therapy. All anticoagulants, including vitamin K antagonists, heparin (both unfractionated heparin and low-molecular-weight heparin), and direct oral anticoagulants affect these clot-based assays. Second, C-reactive protein (CRP) is highly elevated in COVID-19 patients, and also associated with severity. CRP can also lead to false-positive LA, particularly with the aPTT assay. Third, persistence of aPL positivity (including LA) is required to identify APS. Fourth, those at greatest risk of thrombosis due to aPL are those with highest titers or multiple positivity. Most publications either did not identify anticoagulation and/or CRP in their COVID-19 cohorts or did not seem to account for these as possible confounders for LA detection. Most publications did not assess for aPL persistence, and where persistence was checked, LA appeared to represent transient aPL. Finally, high titer aPL or multiple aPL

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positivity were in the minority of COVID-19 presentations. Thus, at least some of the reported LAs associated with COVID-19 are likely to be false positives, and the relationship between the detected aPL/LA and COVID-19-associated coagulopathy remains to be resolved using larger and better studies.

The term "lupus anticoagulant (LA)" identifies a form of antiphospholipid antibodies (aPLs) causing prolongation of clotting tests in a phospholipid concentration-dependent manner. LA is one of the laboratory criteria identified in patients with antiphospholipid (antibody) syndrome (APS).[1,2] The term "lupus anticoagulant" is actually a double misnomer, as it represents neither a specific feature of systemic lupus erythematosus (SLE) nor an "anticoagulant."[3,4] Indeed, the presence of LA in patients with APS represents a significant risk factor for both thrombosis and pregnancy morbidity.[1,2,5] Thus, patients with LA positivity are considered to carry a theoretical risk of a thrombophilia-like disorder.

COVID-19 (coronavirus disease 2019) has been declared a pandemic, and is caused by infection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Thought to have originated in Wuhan, China, in late 2019, COVID-19 is now well-known to reflect a prothrombotic disorder,[6] and thrombosis in various forms affects a high proportion of severely infected individuals. For example, a recent meta-analysis has suggested a venous thrombosis rate, including deep vein thrombosis (DVT) and pulmonary embolism (PE) of close to 30% in patients with severe COVID-19.[7] Acute myocardial ischemia (infarction) and cerebrovascular accidents may also develop in as many as 8 and 3% of COVID-19 patients needing intensive care,[8] while systemic coagulopathy and disseminated intravascular coagulation may onset in as many as 7% of such patients.[9] There is also evidence of microthrombosis in multiple organs including lungs, kidneys, and liver, only identifiable on autopsy, in patients who have died due to COVID-19.[10–13] Anticoagulant therapy is therefore routinely applied to nearly all patients hospitalized with COVID-19.

There have been several reports of similarities between some of the pathophysiological features of COVID-19 and APS, in particular the most severe form, catastrophic APS (CAPS).[14–16] Indeed patients with COVID-19 appear to fulfill the main clinical diagnostic criteria for CAPS: evidence of involvement in three or more organs, development of manifestations simultaneously or in less than a week, and confirmation by histopathology of small vessel occlusion in at least one organ.[16] There have also been many reports identifying various aPL, including LA, in COVID-19 patients. The search for aPL in COVID-19 may have been sparked by an early publication by Zhang et al 2020[17] in the *New England Journal of Medicine*.

Given the above, some relevant questions would naturally arise. Given (1) LA is associated with thrombosis, (2) patients with COVID-19 suffer thrombosis, (3) some aspects of COVID-19 pathology strongly resemble CAPS, and (4) aPLs, including LA, have been identified in COVID-19 in several studies, perhaps the most pertinent question: "Is LA a feature of COVID-19 pathology?" In this review, we critically appraise the literature to help answer this question.

## Thrombosis-Associated LA versus Laboratory-Detected LA

Before we specifically address this question, some additional pertinent background information is required. First, despite an association of LA and other aPL with thrombosis risk in APS and in other potential autoimmune diseases, the presence of a laboratory-detected LA or/and other aPLs per se do not, in themselves, reflect a prothrombotic risk factor, even if persistent, and do not warrant pharmacological intervention,[18,19] except perhaps for those with high titer aPL and multiple positivity.[20,21] Indeed, laboratory-detected LA is often found in asymptomatic patients, many of who will never develop thrombosis. For example, laboratory-detected LA often arises as a result of a follow-up to an unexpected prolonged activated partial thromboplastin time (aPTT). This may occur, for example, when an aPTT is ordered as a screening assay for preoperative bleeding risk,[22] and should an LA-sensitive APTT reagent be used for the test. This "chance" finding may cause some angst in the requesting clinical team, who may then be tempted to cancel or postpone surgery, and notwithstanding expert recommendations to not use the aPTT for such purpose,[22] or else to preferentially use an LA-insensitive aPTT reagent for general screening purposes, and reserving LA sensitive aPTT regents for formal LA investigations in (for example) APS workups.[23]

There are many other reasons why a laboratory-identified LA may not reflect a prothrombotic marker, in particular due to preanalytical or analytical issues causing false-positive LA test results. The presence of anticoagulants, in particular, can give rise to false LA findings. This may even reflect a circular argument of sorts, as patients with thrombosis, or at risk of thrombosis, including those with APS, may be placed on anticoagulant therapy for thrombosis treatment or prevention. If the LA tests are performed while the patient is undergoing anticoagulant therapy, then there is a great risk of a false-positive LA. The possibility of a false-positive LA is true for most anticoagulants, in part depending on how the LA tests are performed. This is expanded on later.

## Lupus Anticoagulant Testing Guidelines

There are three groups who have recently provided guidelines on LA testing, the International Society on Thrombosis

 

and Haemostasis (ISTH), the Clinical and Laboratory Standards Institute (CLSI), and the British Committee for Standards in Haematology (BCSH). The ISTH has prepared a series of such guidelines, starting in 1991[24] and last updated in 2020,[23] although most laboratories are probably still using and referring to the 2009 guidelines.[25] The BCSH published their guidance in 2012,[26] and the CLSI published their guidance in 2014.[27] All this historical context has some relevance to LA testing in 2021, in particular as related to anticoagulant effects. The 2009 ISTH and 2012 BCSH guidelines were published when the main anticoagulants were vitamin K antagonists (VKAs; such as warfarin) and heparins, including unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). The presence of these anticoagulants in the blood of patients on therapy taken for tests can affect clotting assays, including those for LA. Thus, these guidelines attempted to address strategies for assessment of LA in the presence of these anticoagulants, but did not cover the direct oral anticoagulants (DOACs), as these had not yet been introduced into clinical practice.

## Assays Used for LA Detection/Exclusion and Anticoagulant Interference

The main assays used for LA identification/exclusion are the dilute Russell viper venom time (dRVVT) and the aPTT.[28,29] The silica clotting time (SCT) represents a form of aPTT assay marketed by at least one of the major commercial providers, and is becoming increasingly popular for assessing LA, sometimes instead of the "classical" aPTT.[28] The strategies employed for countering anticoagulant effects in LA investigations, as considered in the earlier LA test guidelines,[25,26] include (1) the addition of a heparin neutralizer in dRVVT reagents, capable of neutralizing therapeutic heparin levels up to approximately 1 U/mL and (2) the use of mixing studies to eliminate or dampen the effects of VKAs, which essentially create "factor deficiencies" of factors II, VII, IX, and X. Thus, therapeutic heparin levels should not affect the dRVVT, but will affect the aPTT, which in essence is used in many laboratories to monitor UFH therapy. Heparin will also affect the SCT (unless the reagent contains a heparin neutralizer). The commercial SCT reagents in most common use do not contain any such heparin neutralizers. There may also be a common misconception that LMWH does not affect the LA tests (dRVVT, aPTT, or the SCT). Like UFH, LMWH should not affect the dRVVT unless the level is supratherapeutic, and exceeds the heparin neutralizing capacity of the reagents in use. Similarly, as LMWH comprises mostly anti-Xa activity, in contrast to UFH which expresses mostly anti-IIa activity, LMWH will have a reduced effect on aPTT and SCT compared with UFH. However, LMWH will prolong both SCT and aPTT in a concentration-dependent manner, especially when therapeutic levels are exceeded. Finally, VKAs will affect dRVVT, aPTT, and SCT, given effects on FII, FVII, FIX, and FXI. Although mixing of patient plasma with normal plasma was identified as an early way of "normalizing" the VKA effect, and making both dRVVT and aPTT test results, when performed as directed by the guidelines, more specific for LA,[25] this is no longer recommended in the most recent ISTH guidelines,[23] since, in theory, false-positive and false-negative LA findings may ensue.

The situation with anticoagulant interference in LA testing magnified considerably with the advent of the new/novel oral anticoagulants or DOACs. These anticoagulant agents affect all the LA clot-based assays (e.g., aPTT, dRVVT, and SCT),[30–33] and since they are "inhibitors" (to either factor IIa or Xa), mixing samples containing DOACs with normal plasma only partially abrogates their effects. Moreover, unlike the case for heparins, DOAC neutralizers[34] have yet to be formally introduced into commercial dRVVT reagents. Although some of these compounds are now otherwise commercially available, they are not often employed in laboratories, nor has their effect been fully assessed in this context. As noted, the 2009 ISTH[25] and 2012 BCSH[26] guidelines were published before the advent of the DOACs, and thus did not provide any guidance for LA testing in their presence. The CLSI guideline[27] was published as the DOACs were emerging, and thus noted that these had an effect on LA tests; here, the "simple" recommendation was to avoid testing of LA in patients being treated by DOACs.

This is, of course, wishful thinking, and clinicians often ignore such guidance. The situation may go like this—a patient has a thrombosis and is quickly placed on an anticoagulant, and subsequently there is a desire to investigate the cause of the thrombosis. Does the patient have a thrombophilia, for example? Will they need to be on extended anticoagulation therapy? Do they have LA? And thus, tests are often requested on patients who have already started on anticoagulant therapy, despite recognition that the presence or absence of one or more thrombophilic conditions will generally have no impact on therapeutic management in the short term (i.e., within 2–3 months).

## COVID-19—A Prothrombotic Condition

Fast forward to 2020, and the world is in the grips of the COVID-19 pandemic. At the time of this writing, COVID-19 has infected over 120 million people worldwide and has reportedly been responsible for over 2.5 million deaths.[35] COVID-19 is now well-known to reflect a prothrombotic disorder,[6] with various forms of thrombosis implicated in the pathogenesis and morbidity/mortality of infected individuals. A high proportion of individuals (close to 30% in patients with severe COVID-19) suffer from venous thromboembolism, including DVT and PE.[7] Acute myocardial ischemia (infarction), cerebrovascular events, and arterial thrombosis may also develop in a smaller proportion of COVID-19 patients, especially those needing intensive care.[8,9] There is also evidence of microthrombosis in multiple organs including lungs, kidneys, and liver.[10–13]

As part of a search to investigate the mechanisms that promote thrombosis in COVID-19, many tests of hemostasis have been investigated in patients suffering from this disease. Indeed, many tests of hemostasis are abnormal in patients with COVID-19.[36,37] Moreover, COVID-19 appears to affect all aspects of hemostasis,

including primary hemostasis (endothelium, platelets, von Willebrand factor), secondary hemostasis/coagulation, and fibrinolysis.[38–43]

## Literature Search

To give some additional background to this narrative review, we searched the PubMed database (*https://pubmed.ncbi.nlm.nih.gov*) using various iterations of COVID-19 together with various iterations of LA and (anti)phospholipid antibodies. An initial search performed on February 22, 2021, was later updated to be current as of March 6, 2021. Of over 200 separate articles identified by this search, we then excluded general reviews, commentaries, and articles otherwise found to be irrelevant to the topic. We also excluded single case reports, but small case series were included.

## Results of the Literature Review—Is LA Present in COVID-19?

A summary of the literature arising from our search is given in ►**Table 1**. There was a large body of publications.[17,44–69] Although additional relevant articles are likely available in the literature, the captured articles are sufficient for us to critically review the literature. We are focusing here on LA. Although several articles reported on aPL other than, or in addition to, LA, these will largely not be assessed in the current review, and instead are the proposed topic of a second forthcoming review. There was a wide variety of methods employed to identify LA (►**Table 1**), but often, the methodology was not even reported. There was a wide variety also in COVID-19 case numbers and type, including in some reports "severe" COVID-19, using a variety of definitions (i.e., needing mechanical ventilation or intensive care; mortality).

Of interest, LA was not always detected in patients with COVID-19, as some studies clearly reported "no LA" or very few cases of LA in their patient cohort (►**Table 1**). However, many publications instead reported LA in a large proportion of their COVID-19 cohorts, in some cases more than 80%. This seems to identify a dichotomy of opinions around the presence of LA in COVID-19. To put a graphical perspective to the data, ►**Fig. 1** plots the findings from the literature identified in ►**Table 1** according to percentage positive for LA versus number of investigated cases. There is no obvious pattern.

One of the earliest reports on the presence of aPL in COVID-19 was by Zhang et al[17] who published their findings in the *New England Journal of Medicine*. This was a case series report of three patients with COVID-19 in ICU who suffered serious sequelae including multiple infarcts. Interestingly, although aPLs were detected in all three patients, LA was not found in any of the patients. Nevertheless, this study no doubt prompted a wider search for aPL, including LA, in subsequent COVID-19 cohorts. This study could be criticized in several ways. First, the methodology used for aPL detection was not identified, nor were the levels of identified aPL (whether high or low). Persistence of aPL was also not

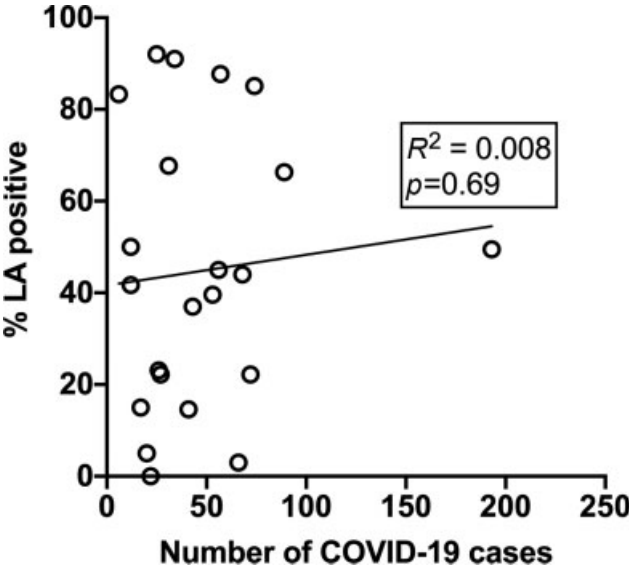


**Fig. 1** The relationship between COVID-19 case numbers reported in the literature and the proportional identification of lupus anticoagulant (LA) positive cases.

evaluated. As the study focused on a particular small group of COVID-19 patients, there was also clear patient selection bias. In other words, the study focused on three patients with serious clinical sequelae who also happened to have aPL. There was no evidence of cause or effect. To take a dichotomous perspective, the first article that we identified as reporting on COVID-19 in this arena was from Yasri and Wiwanitkit.[44] These workers used data collected "according to public official report of CDC of Thailand, the second country in the timeline of this novel coronavirus outbreak" and identified that APS was rare in COVID-19. From the accumulated 2,369 COVID-19 patients (April 8, 2020) with 30 deaths, only 1 patient (0.04%) had been identified with APS.

It can also be noted that some researchers investigating aPL activity in COVID-19 purposely did not look for LA because they recognized the confounders. For example, although they investigate for aPL, Galeano-Valle et al[70] purposely did not assess LA "since testing is not recommended in acutely ill patients and under anticoagulant therapy." As another example, Tang[49] correctly noted that both the ISTH and CLSI urge caution when interpreting LA results in patients receiving anticoagulants. Tang further correctly surmised "Given common use of LMWH and UFH for thromboprophylaxis in COVID-19 inpatients, false-positive results resulting from interference of these anticoagulants may be an important reason for the high positive rate of LA" otherwise found by others, especially when this preanalytical issue is not properly addressed.

## Selection Bias in the Literature

One could hypothesize that the reported incidence of COVID-19-associated LA would be higher in small cases series due to potential selection bias, as identified previously for the

 

**Table 1** Summary of literature related to LA testing in COVID-19[a]

| Reference | Case descriptions and main findings | Number of COVID-19 cases | Method for LA | Number LA positive (%) | Link to COVID-19 severity? | Assessed LA persistence | CRP | Anticoagulants assessed | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Yasri and Wiwanitkit[44] | From accumulated 2,369 COVID-19 patients (8/4/20) with 30 deaths, 1 patient (0.04%) had APS | 2,369 | NR | 1 (0.04%) | NR | NR | NR | NR | |
| Zhang et al[17] | 3 cases with COVID-19 ICU | 3 | NR | 0 ("LA was not detected in any of the patients") | NR | NA | NA | NA | Selection bias |
| Andina et al[45] | 22 COVID-19 children and adolescents with chilblain-like lesions. LA not detected in any | 22 | NR | 0 ("normal in all") | NR | NR | NR | NR | |
| Helms et al[46] | 150 COVID-19 patients in ICU. LA was searched when a coagulation disorder was suspected, based on a prolonged aPTT at ICU admission or on the occurrence of a thrombotic event during ICU stay. Of 57 tested for LA, 50 were positive | 150 (57 tested for LA) | Stago STA-Staclot dRVV and LA-sensitive aPTT STA-PPT LA reagent on STA-R Evolution; positive with either then 1:1 mix Cryocheck PNP, and STA-Staclot dRVV Confirm. LA was considered as positive only if the normalized dRVVT ratio (screen /confirm ratio) was $>1.2$ and all causes of false positive were excluded (i.e. anticoagulation conditions) | 50/57 (87.7%) based on screen/confirm ratio | NR | NR | NR | Identified as present in patients with COVID-19, "all causes of false positive were excluded (i.e., anticoagulation conditions)" | Selection bias; LA searched when a coagulation disorder was suspected |
| Bowles et al[47] | 216 COVID-19. 44 (20%) were found to have a prolonged aPTT. Specimens from 9 patients were excluded, and those from 35 were investigated further. LA assays performed in 34 patients, and 31 (91%) were positive | 216; LA tested in 34, and 31 (91%) were positive | Siemens LA1 reagent dRVVT, Stago PTT-LA reagent for aPTT. Siemens LA2 and Actin FS used as confirmatory reagents for dRVVT and aPTT respectively; mixing studies for aPTT, dRVVT, and LA-sensitive aPTT performed with equal volumes of Technoclone Platelet Poor Plasma. ISTH criteria used to determine LA positivity (normalized ratio in screening test above local RR, normalized ratio of 50/50 mix above local RR, $>10\%$ correction in confirmatory test) | 31/34 (91%) | NR | NR | NR | Heparin detected in 28/35 samples. Siemens dRVVT reagents contain a heparin neutralizing agent (heparin levels up to 1 IU/mL have no effect on results). No other reagents used contain a heparin neutralizer | Selection bias; 35 COVID-19 patients with prolonged aPTT |
| Harzallah et al[48] | 56 COVID-19; 25 (45%) were LA positive | 56 | dRVVT (Hemosil) and sensitive aPTT (Hemosil SCT Screen/Confirm) tests | 25/56 (45%) | NR | NR | NR | NR | |
| Tang[49] | LA performed in dozens of COVID-19 patients and very few positive | "Dozens" | NR | "Very few" | NR | NR | NR | NR | |
| Gatto et al[50] | 122 COVID-19; 53 hospitalized, 69 nonhospitalized | | LA assessed by multiple coagulation tests following updated international guidelines (2009 ISTH), the dRVVT and SCT (HemosIL) platelet poor plasma samples. Samples with a prolonged screening test not corrected by mixing with normal pooled plasma were tested for confirmation by addition of excess of phospholipids. Patients considered LA positive when the dRVVT and/or SCT screening, mixing and confirm tests were positive. | 16/72 (22.2%) overall; 7/42 (16.7%) hospitalized; 9/30 (30.0%) nonhospitalized | No. "No significant association between positive aPL and thrombosis in this relatively large cohort of COVID-19 patients, thereby questioning the true pathogenic value of such finding during acute SARS-CoV-2 infection" | NR | NR | LA test considered reliable only in patients who underwent measurement before starting anticoagulation | |

(*Continued*)



 

**Table 1** (*Continued*)

| Reference | Case descriptions and main findings | Number of COVID-19 cases | Method for LA | Number LA positive (%) | Link to COVID-19 severity? | Assessed LA persistence | CRP | Anticoagulants assessed | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Siguret et al[51] | 74 consecutive mechanically ventilated patients with COVID-19. Received prophylactic (73%) or therapeutic (27%) LMWH or UFH on admission. Thrombotic events reported in 28 patients (38%), including 26 DVT, 4 PE, 1 stroke, and 1 extensive venous catheter thrombosis | 74 | LA diagnosis made using integrated dRVVT screen/confirm (Siemens) LA-sensitive aPTT for screen, then Staclot-LA (Stago), including mixing studies for both dRVVT and aPTT-based tests using PNP (Stago) if needed. Patient dRVVT screen and confirm results were expressed as ratios vs. reference plasma results. Cutoff value was 1.20 for both screen ratio and, if positive, screen ratio/confirm ratio | Positive dRVVT: 63/74 (85.1%)<br>(i) Patients with thrombotic complication: 23/28 (82%)<br>(ii) Patients without thrombotic complications (40/46) (87%)<br>($p = 0.7$) | No. LA highly prevalent but not associated with thrombosis occurrence reported in COVID-19 patients | NR | Elevated CRP levels did not interfere with the integrated dRVVT test system. By contrast, aPTT-based LA results could not be interpreted as (i) PTT-LA assay is affected by both UFH/enoxaparin anti-Xa activity despite sampling preferably performed just before injection; (ii) both PTT-LA and Staclot- LA are affected by elevated CRP levels so that false-positive results could not be excluded in these COVID-19 patients | | |
| Fan et al[52] | 86 patients with confirmed COVID-19. 7/86 exhibited new stroke and 6 (7%) cases were ischemic (i.e., patients with AIS | 86 | "APS panels, including LA (unspecified methods) | NR (12/86 (37.5%) were positive with APS panel; 7/80 (26.9%) patients without AIS; 5/6 (83.3%) patients with AIS | Yes. A significantly higher prevalence of aPL observed in patients with AIS than in those without stroke (83.3 vs. 26.9%, $p < 0.05$). | NR | NR | 48/86 (55.8%) patients received anticoagulation therapy because of underlying coagulopathy or thromboembolic events. All patients with AIS received anticoagulant therapy | |
| Devreese et al[53] | 31 consecutive confirmed COVID-19 patients admitted to ICU | 31 | Three-step LA testing; dRVVT, aPTT-based test systems according to ISTH guidelines (2009 version). All tests done on a STAR Evolution (Stago) using Stago STA-Staclot dRVV screen and confirm, PTT-LA, and Staclot LA reagents. When dRVVT confirm exceeded local cutoff values, screen mix/confirm mix ratios were applied in the confirmation step | 21/31 (67.7%) | 7/9 (77.8%) thrombotic patients had at least one aPL. 16/22 (72.7%) patients without thrombosis were aPL positive, among them two triple positives | 9/10 retested LA-positive patients were negative on a second occasion | "It is important to check CRP levels to avoid false-positive conclusions if only the aPTT system is positive because the aPTT-based test system is prone to interferences by CRP" | "Applying the three-step procedure, UFH does not result in false-positive LA, whereas enoxaparin causes false-positive aPTT-based LAC at supratherapeutic anti-Xa activity levels that exceed the heparin neutralizing capabilities of the reagents. In each sample, we checked the anti-Xa level to avoid false conclusions" | "Our observations support the frequent single LA positivity during (acute phase) observed in COVID-19 infection; however, not clearly related to thrombotic complications" |
| Pineton de Chambrun et al[54] | Assessed aPL profile in 25 patients with prolonged aPTT and confirmed SARS-CoV-2 admitted to ICU. LA positive in 23 (92%) patients | 25 | dRVVT (Siemens, on CS5100 analyzer) | 23/25 (92%) | NR | ND, but mentioned important for future studies to confirm APS | NR | NR | Selection bias; assessed patients with COVID-19 and aPL identified by prolonged aPTT |
| Reyes et al[55] | 187 LA tests requested in 2-mo period of 2020; 119 non-COVID vs. 68 with COVID | 68 | STA-R Max using STAGO reagents as per manufacturer recommendations. dRVVT results reported and interpreted using ISTH guidelines. All samples were screened with the DRVVT assay and a LA-sensitive aPTT. Mix studies performed on all dRVVT tests. Most samples also tested with (hexagonal phospholipid neutralization) STACLOT-LA assay. Cutoff for LA positive (dRVVT and STACLOT-LA) setup at the 99th percentile of normal population. Interpretation of LA positivity was based on a normalized ratio > 1.2 after eliminating potential drug interferences and taking into consideration the mix result to exclude factor deficiency as the main cause of prolonged dRVVT | LA-positive rate by dRVVT in patients who tested negative for COVID-19 was 22% (27/ 119) vs. 44% (30/68) in patients who tested positive for COVID-19 ($p = 0.002$). Of the 30 COVID-19–positive patients positive LA by dRVVT, 17 (59%) were also positive by STACLOT-LA test | Yes. Of 30 patients LA positive, 19 had documented thrombosis (arterial and venous), an event rate of 63%, as compared with a rate for LA-negative patients of 34% ($p = 0.03$) | NR, except in introduction as important for APS diagnosis | Although mean CRP level was higher in patients testing positive for LA by dRVVT (14.4 vs. 7.5 mg/dL; $p < 0.01$), patients with thromboses did not have significantly higher CRP levels than those with no thromboses. After adjusting for CRP, LA was found to be independently associated with thrombosis (odds ratio, 4.39; 95% CI, 1.45–14.57; $p = 0.01$). | Many patients were on DOACs; these were removed using DOAC Remove (Aniara, Ohio) on all plasma samples prior to testing. "dRVVT reagents contain heparin neutralizers eliminating possible interference from heparin" | Selection bias; assessed COVID-19 patients in whom LAs were requested |

**Table 1** (*Continued*)

| Reference | Case descriptions and main findings | Number of COVID-19 cases | Method for LA | Number LA positive (%) | Link to COVID-19 severity? | Assessed LA persistence | CRP | Anticoagulants assessed | Comments |
|---|---|---|---|---|---|---|---|---|---|
| de Ocáriz et al[56] | 27 COVID-19 cases that had been tested for LA during their hospital stay | 27 | dRVVT (HemosIL) and SCT (both screen/confirm, HemosIL) | 6/27 (22.2%) | No. A total of 15 patients (55.5%) had a thrombotic event, from which only 2 had positive LA. 13/15 patients had thrombotic risk factors such as hypertension, dyslipidemia, diabetes, obesity, smoking habit, or cancer. A total of 6 patients (22.2%) required admission to ICU due to respiratory failure following ARDS, 5 of who experienced a thrombotic event, PE being most frequent (56%). In 3/6 (50%), LA was positive. A total of three patients died of respiratory failure, all suffered at least 1 thrombotic event, only 1 had a confirmed LA | NR | Values reported for the 27 COVID-19 patients (7.32 [0.04-36.6]) mg/dL [RR: 0.10-0.50] but not identified as a possible confounder for SCT | All patients were on prophylactic heparin, and the determinations were made 24 h after the last dose. Patients receiving warfarin or DOACs were excluded | Selection bias; COVID-19 that had been tested for LA during their hospital stay |
| Cuenca Saez et al[57] | 11 patients with chilblain-like lesions, some of who had had clinical manifestations associated with SARS-CoV-2 infection up to 2 wk prior onset of the skin lesions. 5 later identified with COVID-19 | 5 | NR | NR | NR | NR | NR | NR | |
| Tvito et al[58] | 43 consecutive COVID-19 | 43 | dRVVT and SCT (HemosIL) screen and confirm assays | 16/43 (37%) LA positive | No. LA positive: 6/11 (54%) with mild disease, 2/13 (15%) with moderate disease, and 8/19 (42%) with severe disease | NR | No significant difference in CRP levels between LA positive vs. negative COVID-19 patients CRP (mean ± SD): LA-positive ($n = 16$) 8.2 ± 8 LA-negative ($n = 27$) 8.2 ± 7 .7 ($p = 0.7$) | All LA-positive patients were on LMWH. 8 patients received prophylactic dose (enoxaparin 40 mg once daily), and 8 received full anticoagulation (7 patients enoxaparin 1 mg/kg twice daily and one enoxaparin 1 mg/kg once daily due to renal failure) | |
| Ferrari et al[59] | 89 consecutive patients hospitalized for COVID-19 | 89 | LA assays performed according to the ISTH recommendations, using screening, mixing, and confirmation tests by means of dRVVT and SCT (HemosIL) screen and confirm. Results expressed as the screen/confirm ratios, normal ranges were <1.20 and <1.16, respectively | LA positive, % ($n$) All patients 59/89 (66.3%) Severe 19/31 (61.3%) Nonsevere 40/58 (69%) $p = 0.85$ | No difference in LA positivity between severe and nonsevere COVID-19. For patients whose anticoagulant treatment had not been modified according to the presence of aPL, no correlation between aPL positivity and the occurrence of DVT or PE, nor with mortality during hospitalization | NR | CRP = 105 (85–103) mg/L (median (IQR in the 89 COVID-19 cohort. CRP concentration was not higher in patients with aPL positivity (aPL negative 184 (122–258) vs. aPL positive 181 (146–218) ($p = 0.85$) | "Patients presenting a severe form of COVID-19 infection received a high prophylactic dose of LMWH (enoxaparin, 40 mg subcutaneously twice a day) in accordance with recent guidelines in COVID-19 management, whereas those hospitalized for a nonsevere form received enoxaparin, 40 mg once a day" | |

(*Continued*)

**Table 1** (*Continued*)

| Reference | Case descriptions and main findings | Number of COVID-19 cases | Method for LA | Number LA positive (%) | Link to COVID-19 severity? | Assessed LA persistence | CRP | Anticoagulants assessed | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Zhang et al[60] | 20 COVID-19 patients admitted to ICU | 20 | Detection of LA performed by HemosIL dRVVT screen and confirm assays, as recommended by ISTH | Only 1 patient (5%) in terminal-stage group had positive LA accompanied by high levels of multiple aPL | NR | ND, but mentioned important for future studies to confirm APS | NR | "Due to the significant hypercoagulable status, 17 patients received LMWH 4,000–6,000 IU, subcutaneous injection, twice per day" | |
| Tan et al[61] | Review of all studies reporting AIS occurrence in COVID-19 patients. 39 studies comprising 135 patients; pooled incidence of AIS in COVID-19 patients was 1.2% | 135 | Varied/unspecified | LA reported present in 5/12 (41.7%) reported patients | "a notable number of (AIS) cases tested positive for aPL and a high mortality rate (38%) was reported (in COVID-19 AIS)" | NR | CRP, $n = 80$ mean (SD) 105.6 (91.1) (mg/L) | Anticoagulation identified in 56/77 (72.7%) | |
| Xiao et al[62] | 66 COVID-19 patients who were critically ill and 13 COVID-19 patients who were not critically ill | 79 | dRVVT (HemosIL) screen and confirm, "as recommended by ISTH" | 2/66 (3.0%) critically ill patients were LA positive | Patients with multiple aPLs had a significantly higher incidence of cerebral infarction compared to patients who were negative for aPLs ($p = 0.023$) | NR | CRP mg/L<br>Negative for aPLs ($n = 35$) $88.7 \pm 84.3$<br>Positive for aPLs ($n = 31$): CRP in (a) single/multiple (low) aPL group ($n = 16$) $98.1 \pm 57.6$<br>(b) Multiple (medium/high) ($n = 15$) $99.5 \pm 51.8$ | Anticoagulant therapy:<br>Negative for aPLs (19/35) (54.3%)<br>Positive for aPLs ($n = 31$): (a) single/multiple (low) aPL group (12/16) (75%) (b) Multiple (medium/high) (9/15) (60%) | |
| Fan et al[63] | 12 ICU patients with severe COVID-19 (either mechanical ventilation or on high-flow oxygen) | 12 | dRVVT (STA Staclot) screen and confirm, and PTT-LA on STAR MAX | LA detected in 6/12 (50%) patients | NR (all patients were severe) | NR | NR | The 12 critically ill COVID-19 patients "were not on thromboprophylaxis or anticoagulation at the time of assessment. After risk assessment, all 12 patients were started on pharmacological thromboprophylaxis given their high risk of VTE and evidence for hypercoagulability from hemostatic tests and CWA" | |
| Gazzaruso et al[64] | 192 consecutive patients hospitalized for COVID-19 pneumonia due to SARS-CoV-2 | 192 | LA evaluated "according to recommendations of the ISTH" (2009 version) (but methods not otherwise specified) | LA found in 95/192 patients (49.5%) | No difference in % of patients with LA observed between 130 survivors vs. 62 nonsurvivors (47.7 vs. 53.2%; $p = 0.4745$). Or those requiring mechanical ventilation | NR | CRP (mg/L)<br>RR < 5<br>Total patients ($n = 192$) $142.2 \pm 118.0$<br>Patients with positive LA ($n = 95$) $151.6 \pm 101.5$<br>Patients with negative LA ($n = 97$) $123.0 \pm 101.7$<br>$p = 0.0072$ | "In our study, LA was evaluated on admission and before anticoagulation and therefore the interference due to anticoagulation was not present" | |

 

**Table 1** (*Continued*)

| Reference | Case descriptions and main findings | Number of COVID-19 cases | Method for LA | Number LA positive (%) | Link to COVID-19 severity? | Assessed LA persistence | CRP | Anticoagulants assessed | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Le Joncour et al[65] | 104 COVID-19 patients; 53 assessed for LA. LA found in 21/53 (39.6%) patients | 104, with 53 assessed for LA | LA testing performed on a CS5100 analyzer "according to ISTH guidelines" but methods not specified | 21/53 (39.6%) patients | No. LA was found to be positive in 60% (3/5) of patients with thrombotic event vs. 37.5% (18/48) of those without ($p = 0.374$) | ND, but recognized as study limitation | CRP levels increased with median value of 69 mg/L [30–107] Patients with a thrombotic event had more frequently a past medical history of VTE (36.4 vs. 13.9%) and higher level of CRP (124 vs. 64.2 mg/L, $p = 0.021$) | Oral anticoagulant: Total 15/104 patients (14.4%) Patients without thrombotic event 14/93 (15.1%) Patients with thrombotic event 1/11 (9.1%) ($p = 0.506$) Heparin not mentioned | |
| Bauer et al[66] | 58 patients with clinically suspected COVID-19 in the ED. 17 subsequently tested positive for SARS-CoV-2, while in 41 COVID-19 was ruled out | 17 | dRVVT, normalized ratio, STAR MAX analyzer | All: 7/47 (15%) Non-COVID all: 4/33 (12%) Non-COVID non-ICU 3/27 (11%) Non-COVID ICU 1/6 (17%) COVID all: 3/14 (21%) non-ICU COVID 2/10 (20%) ICU COVID 1/4 (25%) | "We detected a rather moderate frequency of positive LA with no significant difference between the COVID-19 compared with the non-COVID-19 patient group" | NR | CRP mg/L All: 46.5 (12.7, 105.1) Non-COVID all: 56.8 (12.2, 105.2) Non-COVID non-ICU 55.4 (10.1, 105.0) Non-COVID ICU 65.4 (16.4, 100.3) COVID all: 36.6 (18.7, 77.9) non-ICU COVID 36.0 (21.1, 56.7) ICU COVID 77.9 (19.2, 206.7) ($p$ = NS for any comparison) | All hospitalized patients had anticoagulation treatment on admission. Classic prophylactic anticoagulation therapy defined by administration of standard doses of LMWH (4,000 IU Enoxaparin every 24 h for patients $< 100$ kg or 6,000 IU every 24 h for patients $> 100$ kg. Patients with a history of VTE treated with curative anticoagulation using subcutaneous LMWH (100 UI/12 h) | |
| Hamadé et al[67] | 41 COVID-19 patients | 41 | LA testing performed as recommended by ISTH by dRVVT and SCT (Hemosil) (NB: mentioned "dRVVT-based assay") | 6/41 (14.6%); data also reported as composite of "aPL antibodies" (7/41 (17%) were positive for aPL) | 9/41 (22%) developed VTE and 7/41 (17%) were positive for aPL of which 5 had isolated positive LA and 1 had LA with other aPL. Among 7 patients with aPL, 2 (28.6%) had VTE. However, the incidence of VTE in patients negative for aPL was also significant as 20.6% (7/34). aPLs were significantly associated with the transfer to ICUs, $p = 0.018$. Not only the incidence of aPL was quite significant within our cohort, but also we observed 28.6% of VTE in aPL-positive patients | ND, but mentioned important for future studies to confirm APS | CRP elevated in 88% patients. ($106 \pm 72.2$ mg/L) | "All patients had antithrombotic prophylaxis upon admission using LMWH with enoxaparin" | |

(*Continued*)

**Table 1** (*Continued*)

| Reference | Case descriptions and main findings | Number of COVID-19 cases | Method for LA | Number LA positive (%) | Link to COVID-19 severity? | Assessed LA persistence | CRP | Anticoagulants assessed | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Karahan et al[68] | 31 COVID-19 patients in ICU (COVID group) and 28 non-COVID-19 critically ill patients (non-COVID group) | 31 | Stago dRVVT and aPTT with hexagonal phase phospholipids (Staclot LA) on STAR MAX; screen and confirm steps. Local cutoff value for LA set as >99th percentile of distribution | aPLs were positive in 25.8% of the COVID group (8/31) and 25% of the non-COVID group (7/28). LA was the most common aPL present in 23.1% of the COVID-19 group, who underwent measurement (6/26) (others on heparin treatment excluded), while 3.6% of the non-COVID group was LA positive (1/28) ($p = 0.047$) | aPLs were equally positive in critically ill patients among COVID-19 or non-COVID-19 patients. Only LA was observed more in COVID-19 patients | After recovery of COVID-19 and other diseases requiring ICU follow-up, aPL tests were repeated. However, several patients in each group died. LA could not be confirmed in any patient | ND. "Another limitation of our study is that, although it is tried to be prevented by using mixing test and dRVVT reagent, tests may be interfered due to elevated CRP and other inflammatory markers and clotting factor inhibitors" | "...of the patients, who underwent LA testing, those who used UFH or LMWH or vitamin K antagonists were excluded in this study" | |
| Beyrouti et al[69] | 6 consecutive patients assessed over 2-wk period in 2020 with acute ischemic stroke and COVID-19 | 6 | Not specified | 5/6 (83.3%) LA positive | NR | NR | NR | Therapeutic anticoagulation with LMWH noted in 3 cases; apixaban in 1 case; not mentioned in other 2 cases | |

Abbreviations: AIS, acute ischemic stroke; aPL, antiphospholipid antibodies; APS, antiphospholipid (antibody) syndrome; aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; CWA, clot waveform analysis; DOACs, direct oral anticoagulants; dRVVT, dilute Russell viper venom time; DVT, deep vein thrombosis; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; LA, lupus anticoagulant; LMWH, low-molecular-weight heparin; ND, not done; NR, not reported; PE, pulmonary embolism; PNP, pool normal plasma; RR, reference range; SCT, silica clotting time; SD, standard deviation; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a]Data exclude single case studies, and listed in order of PubMed listing. Note that wide variety of methods (not always documented) may be used to assess LA. This will have an influence on findings, but this is not always understood by authors who report on findings. Data also show findings from occasional reviews.

Zhang et al's report for aPL.[17] Thus, there is likely to be additional selection bias in the literature where authors investigate LA (and other aPL). This bias can take two forms. First, researchers are more likely to publish positive findings than to publish negative findings. As an example, Tang[49] responding to a comment on one of his earlier articles indicated that "they had assessed LA in dozens of their COVID-19 patients and very few were positive." The second form of selection bias was apparent in several publications. Here, researchers actively looked for LA in select COVID-19 patient cohorts. This may include those who had raised aPTTs, or with clinical or laboratory suspicion of LA. In these studies, a relatively high level of LA was naturally identified in the studied COVID-19 population[46,47]. One can propose that this might be anticipated, and indeed findings of LA in patients investigated for prolonged aPTT or under clinical or laboratory suspicion of LA would be not unexpected, irrespective of the presence of COVID-19.

## C-Reactive Protein

C-reactive protein (CRP) is well recognized by experts in the field to potentially generate false-positive LA findings, in particular using the aPTT.[71,72] Indeed, if LA is identified only with the aPTT method, then CRP should be excluded as a cause of false-positive LA.[53,71,72] It is important to note that CRP is also highly elevated in patients with COVID-19, including those with reported LA.[51,55,56,58,59,61,62,64–67] Interestingly, however, most researchers reporting on LA in COVID-19 did not mention CRP, nor report data on this biomarker. In some cases, these data may have possibly been reported elsewhere, and in other cases may not have been gathered or even considered. Of further interest, even when investigated or reported, CRP was not always contemplated by the researchers as a potential confounder for LA identification. Where reported, levels of CRP did not differ between COVID-19 cohorts found positive versus negative for LA,[58,59,62] or else a statistically significant difference was reported.[55,64] For example, Reyes et al[55] identified higher levels of CRP in patients testing positive for LA by dRVVT (14.4 vs. 7.5 mg/dL; $p < 0.01$). They also reported that patients with thromboses did not have significantly higher CRP levels than those with no thromboses, and after adjusting for CRP, LA was found to be independently associated with thrombosis (odds ratio, 4.39; 95% confidence interval: 1.45–14.57; $p = 0.01$). Gazzaruso et al[64] also identified higher levels of CRP in patients with positive LA ($n = 95$; $151.6 \pm 101.5$ mg/L) versus those with negative LA ($n = 97$; $123.0 \pm 101.7$; $p = 0.0072$). Of course, none of this is the same as saying that the raised CRP in COVID-19 patients did not influence LA positivity, at least in a portion of "LA-positive" COVID-19 patients. However, it probably does suggest that CRP is not in itself a major driver of any false LA positivity in COVID-19 patients.

## Anticoagulants as a Confounder to LA Testing

Similarly, many publications did not identify whether their COVID-19 cohorts were anticoagulated, or where patients were identified as anticoagulated, what anticoagulants were used for treatment. Some publications did identify the anticoagulants used for treatments, but failed to consider that these same anticoagulants could represent a confounder for LA testing. A few publications identified anticoagulants used for treatments and their possible presence as a confounder for LA testing.

In COVID-19, most patients would be under heparin therapy, with most under therapy with LMWH. Alternatively, some patients would be under DOAC therapy, and some under VKA therapy. Here, we need to reflect on treatment applied to prevent or treat thrombosis arising from COVID-19 or its complications once admitted to hospital, which is likely to be LMWH(/UFH), versus patients who were already on an anticoagulant to treat or prevent thrombosis prior to contracting COVID-19, which then would more likely be a DOAC or a VKA. As mentioned previously, all anticoagulants affect LA testing, as summarized in ►**Table 2**. Thus, the aPTT component of the LA test panel (or the SCT component, as used in some laboratories) would be sensitive to all the anticoagulants (VKAs, all heparins, DOACs). Mitigation of any anticoagulant effect on aPTT or SCT, as used for LA testing, is difficult, as also outlined in ►**Table 2**. Note that the aPTT in particular is also used to monitor UFH therapy, and thus may be purposely designed to be particularly sensitive to UFH. Nonetheless, the SCT would also be very sensitive to UFH. Although it is generally considered that the aPTT is not highly sensitive to LMWH, given the predominant anti-Xa activity (as opposed to predominant anti-IIa activity of UFH), both aPTT and SCT would have some sensitivity to LMWH, according to the concentration present. The dRVVT would be sensitive to VKAs and DOACs, and less sensitive to UFH/LMWH because most commercial reagents contain heparin neutralizers, quenching the heparin activity when within the therapeutic range, and generally up to 1 U/mL heparin. Nevertheless, higher concentrations will affect the dRVVT, which, in the absence of heparin neutralization, becomes very sensitive to heparin.

Some researchers had different strategies for mitigating heparin interference. For example, Devreese et al[53] surmised that "applying the three-step procedure, UFH does not result in false-positive LA, whereas enoxaparin (LMWH) causes false-positive LA at supratherapeutic anti-Xa activity levels that exceed the heparin neutralizing capabilities of the reagents.[73,74]"

For VKAs, the only solution is to either avoid testing or perform mixing studies with normal plasma[25] to correct for the VKA-induced factor deficiency (factors II, VII, IX, X), although this is no longer recommended by the ISTH Scientific and Standardization Committee (SSC) on LA.[23] This would apply to all the LA assays (dRVVT, aPTT, SCT). For heparin, mixing would reduce the effect on the aPTT and SCT, and possibly correct any effect on the dRVVT, should the dilution then lead to a heparin level within a therapeutic range (or generally <1 U/mL). For DOACs, one could use DOAC neutralizers such as DOAC Stop or DOAC Remove,[34] although this in itself may have an unexpected effect on LA detection. Irrespective, laboratories would need to apply such

**Table 2** Effects of anticoagulants on main assays used to investigate LA

| Anticoagulant | Affects aPTT | Affects SCT | Affects dRVVT | Strategies for mitigating effects |
|---|---|---|---|---|
| VKAs (e.g., warfarin) | ++ | ++ | +++ | 1. Avoid testing while on therapy<br>2. Use mixing with normal plasma to normalize factor levels (but may still lead to false-positive or -negative LA, and no longer recommended by the ISTH[23,74])|
| UFH | +++ | ++++ | − (therapeutic level) to +++ (supratherapeutic level) | 1. Avoid testing while on therapy<br>2. Use heparin neutralizer (present in dRVVT reagent)—but won't eliminate all heparin if supratherapeutic<br>3. Use "3-step procedure" for LA testing[23,74] |
| LMWH | + to ++ | ++ | − (therapeutic level) to +++ (supratherapeutic level) | 1. Avoid testing while on therapy<br>2. Use heparin neutralizer (present in dRVVT reagent)—but won't eliminate all heparin if supratherapeutic<br>3. Test at trough (prior to next dose) |
| DOACs | + to +++ | + to +++ | + to +++ | 1. Avoid testing while on therapy<br>2. Use DOAC neutralizer (not present in dRVVT reagents; purchased separately) |

Abbreviations: aPTT, activated partial thromboplastin time; dRVVT, dilute Russell viper venom time; DOACs, direct oral anticoagulants; LA, lupus anticoagulant; LMWH, low-molecular-weight heparin; ISTH, International Society on Thrombosis and Haemostasis[23,74]; SCT, silica clotting time (a form of aPTT); UFH, unfractionated heparin; VKA, vitamin K antagonist.

strategies to mitigate the effect of any anticoagulant and ensure appropriate detection of LA. Thus, laboratories would need to be aware of any anticoagulant effect on the potential for false-positive identification of LA, and also then attempt to mitigate for said effect prior to identification of LA, otherwise a false positive can ensue.

Furthermore, anticoagulants, especially DOACs, but potentially also heparin, may have a different effect on the screen versus confirm assays, and this will affect any resultant ratio value. It is often the ratio value that is used for identification versus exclusion of LA, which for dRVVT screen/confirm is often a cutoff value of around 1.2.[75] Thus, values below would normally exclude LA, whereas values above would infer LA positivity. Complicating this further, the best approach would be a normalized ratio, which to some extent could mitigate the differential effect on screen versus confirm reagents, but it is not clear if this strategy is used in all laboratories reporting LA in COVID-19.

►**Figs. 2** and **3** show some examples of these concepts applied in practice, respectively, for LMWH and one of the DOACs, rivaroxaban. Note the differential effect of LMWH on the aPTT reagents used as the screen and confirm component (►**Fig. 2**). Similarly, note the differential effect of rivaroxaban on the dRVVT reagents used as the screen and confirm component (►**Fig. 3**). For this aPTT example, the greater effect was observed on the confirm component than on the screen, and thus a false-positive LA by aPTT in a patient using LMWH seems less likely. However, other aPTT reagent pairs may show the reverse pattern. For the dRVVT example, the interference effect is greater on the screen than the confirm component, and thus an LA ratio above 1.2 is certainly possible, leading to possible false-positive LA by dRVVT.

In summary, then, it is likely that at least some of the positive LA findings reported in the literature reflect false positives due to anticoagulant effects that have not been appropriately accounted for by some researchers.

## Persistence of LA Positivity versus Transient Positivity

To identify LA or other aPL as a specific feature of an autoimmune disorder such as APS, one has to prove the persistence of that positivity, generally by repeating the test(s) on a second sample some 12 weeks after the first positive test result.[1,2,23] Again, most researchers reporting on LA positivity in COVID-19 either did not mention this or did not undertake repeated testing. Thus, persistence of LA positivity was not evaluated in most studies, and hence not proven. In the few studies that did attempt to look at persistence, most cases initially positive for LA then became negative for LA,[53] or else repeat testing was complicated by the ongoing patient morbidity or their death.[68] Thus, it seems that any LA positivity that may be identified in COVID-19 patients is mostly transient.

## Transient aPLs Are a Common Feature of Severe Viral Infections

It is well known among those looking after sick patients with various viral infections that aPL may transiently appear in a range of conditions.[76,77] It may be possible to separate groups of patients and aPL profiles. For example, in one meta-analysis, Abdel-Wahab et al[77] reported that three different groups of patients could be identified: "group 1

 

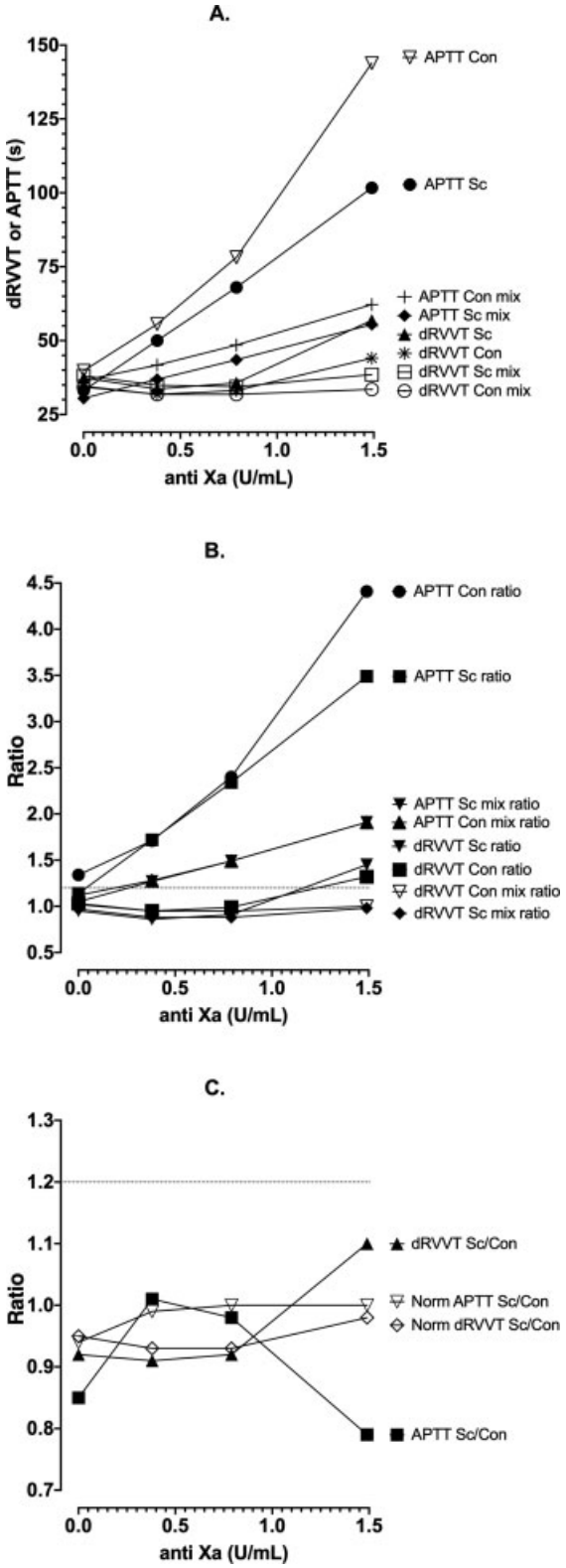


**Fig. 2** The effect of low-molecular-weight heparin (LMWH) on some common lupus anticoagulant (LA) tests. Normal plasma was spiked with increasing concentrations of enoxaparin, ranging from 0 to 1.5 U/mL, and then tests for aPTT (activated partial thromboplastin time) and dRVVT (dilute Russell viper venom time) were performed. While it is recognized that LMWH spiked samples do not behave exactly the same as ex vivo samples, this exercise is useful to show some anomalies in LA test results. (**A**) Effect on aPTT and dRVVT clotting times: (i) note differential effect on aPTT screen (Sc, Siemens Actin FSL reagent; LA sensitive) *vs.* that on aPTT confirm assay (Con, Siemens Actin FS reagent; LA insensitive due to added phospholipid). For this reagent pair, LMWH affects the confirm assay (FS) more than the screen assay (FSL); (ii) a reduced effect is seen on the aPTT assays when performed as mixes with normal plasma; here, the essential consequence is a reduction in LMWH concentration; however, the effect is still greater on the confirm assay (FS) than the screen assay (FSL). Although for the aPTT pair evaluated here, the effect was greater on the confirm assay than on screen, not all aPTT reagent pairs may show this pattern, and the reverse (greater effect on the screen than confirm) is also possible. (iii) A reduced effect is seen with the dRVVT assay, since the reagents contain a heparin neutralizer. Essentially, an effect is seen only for the high LMWH concentration of 1.5 U/mL, and is not seen when the RVVT is performed as a mix test, since the resultant diluted LMWH is able to then be neutralized by the reagent. Nevertheless, the LMWH effect is greater on the screen reagent than the confirm reagent. (**B**) Effect on aPTT and dRVVT ratios. Data from (**A**) plotted as assay ratios (i.e., aPTT and dRVVT clotting times in (**A**) in comparison with normal plasma test times). All aPTT ratios, being the screen and confirm, and also when performed as a mix with normal plasma, are >1.2. Although this in itself cannot be used to identify LA, it may be used to decide on further evaluation for LA by additional testing. Only the dRVVT ratios for the highest LMWH concentration are above 1.2, and only when performed as neat plasma (not when performed as a mix with normal plasma) (due to the presence of heparin neutralizer in the reagents). (**C**) Effect on aPTT and dRVVT final ratios including normalized ratios. Data from (**A** and **B**) plotting screen/confirm ratios including normalized ratios, which essentially normalize the test results by taking into account clotting times obtained with normal plasma. The normalized ratios are similar and close to 1.0 irrespective of the LMWH concentration. Normalized ratios are recommended for use by the LA guidelines. In contrast, the nonnormalized ratios vary according to LMWH concentration. In this example, the highest LMWH concentration has differential effects on screen vs confirm reagents, and also differential effects on aPTT vs. dRVVT. Thus, for aPTT, the non-normalized ratio is <1.0, and for the dRVVT the non-normalized ratio is >1.0. It is possible that for some aPTT and dRVVT reagent pairs, the differential could be so great as to create ratios >1.2, or at least greater than a laboratory determined cut-off value, and thus increase the potential for false-positive LA, should nonnormalized ratios be utilized by a laboratory for assessing the presence of LA.

included patients who fulfilled the criteria for definitive APS (24.6%), group 2 included patients who developed transient aPL with thromboembolic phenomena (43.7%), and group 3 included patients who developed transient aPL without thromboembolic events (31.7%). Thus, secondary cases of APS due to viral infections have been reported.[78] Secondary cases of APS due to infectious agents potentially evolving into CAPS have also been reported and include infections from hepatitis C virus, herpes zoster, as well as bacteria, fungi, parasites, and acute Q fever.[79] The induction of molecular mimicry that leads to production of anti-beta2 glycoprotein I (aβ2GPI) autoantibodies has been proposed as putative cause of secondary APS and CAPS.[80,81]

Thus, the finding of LA positivity in COVID-19 is not unique to COVID-19. To our knowledge, there is no evidence available on comparative infections with other viral agents to identify if the situation in COVID-19 in regard to aPL and LA positivity is worse or greater than that of other severe viral infections. In part, it is also likely that other viral diseases have not been as extensively studied as COVID-19.

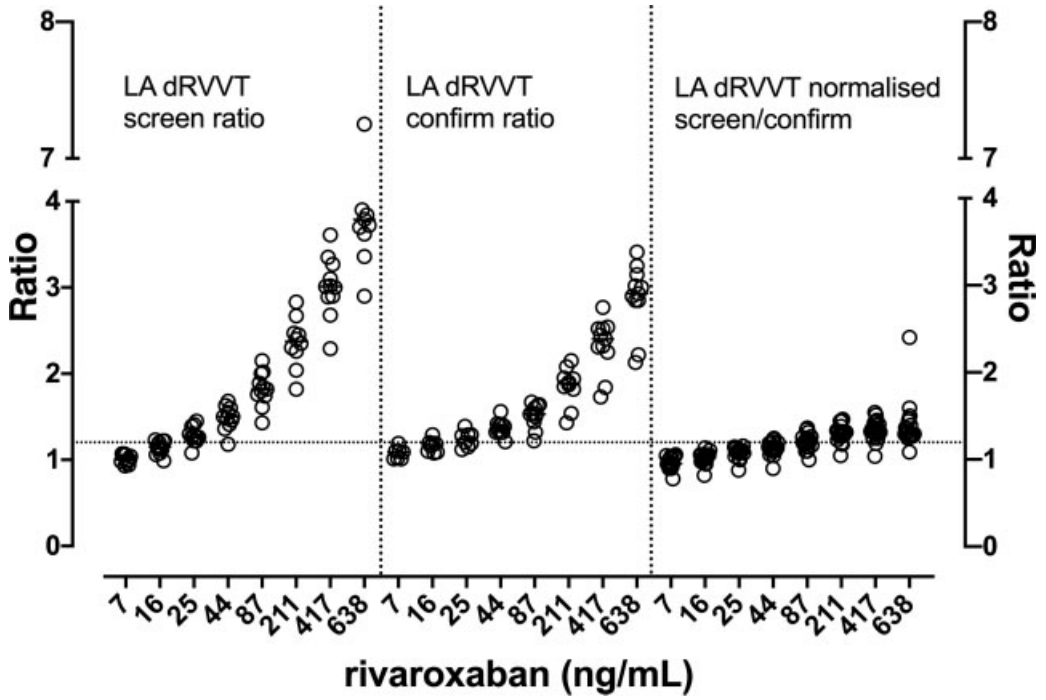


**Fig. 3** The effect of rivaroxaban on lupus anticoagulant (LA) testing by dilute Russell viper venom time (dRVVT). Increasing concentrations of rivaroxaban (*x*-axis) have a corresponding effect on both dRVVT screen (left portion of figure) and dRVVT confirm (middle portion of figure). However, the effect is greater on dRVVT screen than on dRVVT confirm. Thus, dRVVT screen/confirm ratios (even if normalization) can exceed 1.2, or the cutoff used in laboratories to determine LA, and therefore lead to a false conclusion of LA. This occurs at concentrations of rivaroxaban seen in patients on rivaroxaban therapy.

## Does LA Positivity in COVID-19 Reflect a Risk Factor for Thrombosis?

Only a few studies investigated whether LA positivity inferred additional thrombotic risk. Few studies identified a statistical difference in thrombotic risk for LA-positive versus LA-negative patients,[52,55] whereas most did not.[50,51,56,58,59,64–67] There are many potential confounders in this evaluation, and it is unclear if these confounders were considered in all published comparisons. Thus, transient aPL (or LA) positivity may develop in the sickest patients, who will then be most at risk of thrombosis, and therefore LA may just reflect an association with, rather than be responsible for, the pathophysiological events. Irrespective, whether LA positivity in COVID-19 truly reflects an additional risk factor for thrombosis remains currently unresolved.

## General Discussion

Taking all this information into consideration, we would propose that LA positivity *is* a feature of COVID-19, at least in some patients, and potentially those who are the sickest or have the most severe infection. However, we also believe that a proportion of cases identified in the literature as being LA positive reflect false positives, and potentially due to confounding by preanalytical issues, such as patients being on anticoagulants at the time of blood sampling, as well as analytical issues, which are not always easy to identify from the published studies. All anticoagulants affect LA testing, and it is unlikely that all studies took these anticoagulants into account in regard when performing tests and reporting findings, or else perhaps assumed no effect because patients were on therapeutic LMWH therapy. Such assumptions may not be valid, as shown in ►**Fig. 2**, depending on which assays are performed, and how they are performed and reported. Mitigation of DOAC effects would be difficult, and although achievable using DOAC neutralizers,[34,74,82] may again not have been recognized by researchers reporting their results.

Repeat testing for persistence of LA was rarely performed or reported, and where reported suggested a transient nature of the identified "LA." Such transient LA does not identify an autoimmune disease in the classic sense of APS.[1,2] Such transient aPLs are also commonly observed in other viral infections,[76,77] and thus do not seem to be unique to COVID-19. There are also questions remaining over the "additional" thrombotic risk imposed by the LA identified in COVID-19 in these studies, as transient aPLs developed from viral infections are often not associated with thrombosis.

## Conclusion

Larger and better studies are needed to address the residual question regarding the true frequency of LA in COVID-19, and whether these laboratory-detected LA would actually contribute to enhance the thrombotic risk in COVID-19. Nevertheless, we believe that some good-quality studies have already been published, and these should likely guide

 

opinion. These studies are those that reported on LA cognizant of the potential confounders, including CRP and anticoagulant therapy, and which also looked at persistence of antibodies. However, they were in the minority of published studies. All this is not to say that APS cannot develop in patients with COVID-19. As already mentioned, there are certainly similarities between the worst presentation of APS, namely CAPS, and what occurs in the sickest patients with COVID-19. But there are also some notable differences, including general lack of high titer aPL, lack of persistence for LA and other aPL, and unclear relationship between the detected aPL/LA and COVID-19-associated coagulopathy.

Conflict of Interest
None declared.

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