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ORIGINAL ARTICLE

# Lupus anticoagulant associates with thrombosis in patients with COVID-19 admitted to intensive care units: A retrospective cohort study

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## Abstract

**Background:** Thrombosis is a frequent and severe complication in patients with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU). Lupus anticoagulant (LA) is a strong acquired risk factor for thrombosis in various diseases and is frequently observed in patients with COVID-19. Whether LA is associated with thrombosis in patients with severe COVID-19 is currently unclear.

**Objective:** To investigate if LA is associated with thrombosis in critically ill patients with COVID-19.

**Patients/Methods:** The presence of LA and other antiphospholipid antibodies was assessed in patients with COVID-19 admitted to the ICU. LA was determined with dilute Russell's viper venom time (dRVVT) and LA-sensitive activated partial thromboplastin time (aPTT) reagents.

**Results:** Of 169 patients with COVID-19, 116 (69%) tested positive for at least one antiphospholipid antibody upon admission to the ICU. Forty (24%) patients tested positive for LA; of whom 29 (17%) tested positive with a dRVVT, 19 (11%) tested positive

with an LA-sensitive aPTT, and 8 (5%) tested positive on both tests. Fifty-eight (34%) patients developed thrombosis after ICU admission. The odds ratio (OR) for thrombosis in patients with LA based on a dRVVT was 2.5 (95% confidence interval [CI], 1.1–5.7), which increased to 4.5 (95% CI, 1.4–14.3) in patients at or below the median age in this study (64 years). LA positivity based on a dRVVT or LA-sensitive aPTT was only associated with thrombosis in patients aged less than 65 years (OR, 3.8; 95% CI, 1.3–11.4) and disappeared after adjustment for C-reactive protein.

**Conclusion:** Lupus anticoagulant on admission is strongly associated with thrombosis in critically ill patients with COVID-19, especially in patients aged less than 65 years.

**KEYWORDS**
COVID-19, critically ill, lupus anticoagulant, risk factor, thrombosis

**Essentials**

- Lupus anticoagulant (LA) is frequently observed in critically ill patients with coronavirus disease 2019 (COVID-19).
- It is not known whether the presence of LA is associated with thrombosis in patients with COVID-19.
- LA and other antiphospholipid antibodies were determined in critically ill patients with COVID-19.
- We found a strong association between LA and thrombosis that disappeared after adjusting for C-reactive protein.

## 1 | INTRODUCTION

In the first years of the coronavirus disease 2019 (COVID-19) pandemic, many patients with severe COVID-19 developed arterial or venous thrombosis. The incidence of thrombosis is highest in patients with COVID-19 admitted to the intensive care unit (ICU).[1] The profound coagulopathy observed in patients with COVID-19 coincides with a prolonged activated partial thromboplastin time (aPTT) in 20% of cases.[2] In general, a prolonged aPTT is linked to a clotting factor deficiency or the presence of an inhibitor of coagulation such as antibodies against factor VIII (FVIII), heparin use, or, depending on the aPTT reagent, lupus anticoagulant (LA). The latter seems to occur frequently in the context of COVID-19; a recent study shows that 91% of these prolonged aPTTs is related to LA.[2] LA is defined as a phospholipid-dependent prolongation of the clotting time caused by (auto)antibodies directed to protein-phospholipid complexes.[3] These so-called antiphospholipid antibodies are known to interfere with both procoagulant and anticoagulant processes. LA has mainly been attributed to autoantibodies against the phospholipid-binding plasma proteins β2GPI or prothrombin, which form the central antigens in the rare autoimmune disease antiphospholipid syndrome (APS).[4–6] However, other antibodies directed toward phospholipid-binding proteins can cause LA as well. The presence of LA is a strong acquired risk factor for thrombosis.[7,8] In severe cases, LA causes thrombotic microangiopathy (TMA), known as catastrophic APS. This life-threatening form of APS is characterized by rapidly progressive and widespread vascular occlusions leading to multiple organ failure.[9] Severe COVID-19 infections are complicated by TMA-like pathology, which might be related to the presence of antiphospholipid antibodies and thus the LA phenomenon.

Until now, it was unclear whether the presence of LA is associated with thrombosis in critically ill patients with COVID-19. Recent literature describes the presence of antiphospholipid antibodies in patients with COVID-19.[2,10–16] However, these studies failed to show an association between the presence of antiphospholipid antibodies and thrombosis in patients with COVID-19. Several studies were limited to the detection of anti-β2GPI or anticardiolipin IgM and IgG as citrated plasma samples were not available.[12,14,15] Moreover, the number of patients included in these studies is often limited.[10,14] Further investigation into the risk factors for thrombosis in COVID-19, and the possible role that LA plays in this process, can provide valuable insights for clinical practice of patients with COVID-19. Obtaining this knowledge is essential for decision making concerning the intensity of thromboprophylaxis or treatment of thrombosis, especially in critically ill patients admitted to the ICU who are at highest thrombotic risk.

In this study, we investigated whether the presence of LA is associated with thrombosis in a cohort of patients with COVID-19 who were admitted to the ICU. Furthermore, we focused on the identification of the causal antibody population using solid-phase binding assays with phospholipids and phospholipid-binding proteins, including β2-glycoprotein I and prothrombin, the known antigens for LA-inducing autoantibodies.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient population

Patients aged 18 years and older with confirmed COVID-19 virus infection who were admitted to the ICU of the University Medical Center (UMC) Utrecht or Erasmus Medical Center (Erasmus MC) Rotterdam for respiratory support (mechanical ventilation or Optiflow Nasal High Flow therapy) between March 2020 and March

2021 with a hospital length of stay greater than 7 days (including their stay at ward afterwards) were eligible for inclusion in this retrospective multicenter cohort study. The COVID-19 diagnosis was confirmed with a reverse-transcriptase polymerase chain reaction real-time assay of nasal and pharyngeal swabs. Patients were excluded if (i) they had a thrombotic event within 3 months before ICU admission, (ii) they were on direct oral anticoagulants (DOACs), or (iii) died within 7 days after ICU uptake. All patients received either prophylactic, high prophylactic, or therapeutic dose low-molecular-weight heparin (LMWH) (dalteparin or nadroparin) or unfractionated heparin. Thrombotic complications, including pulmonary embolism (PE), deep vein thrombosis (DVT), jugular vein thrombosis, myocardial infarction, stroke, and arterial thrombosis, were confirmed with computed tomography pulmonary angiography or duplex ultrasound. Diagnosis of myocardial infarction was based on (i) a typical rise and fall of troponin or creatine kinase-MB, and (ii) at least one of: chest pain or other clinical correlates of myocardial ischemia, ST depression or elevation on electrocardiogram (ECG), new left bundle-branch block or new pathological Q-waves on ECG, or findings of significant coronary artery disease or new culprit lesion on percutaneous transluminal coronary angioplasty. Importantly, in the Erasmus MC, routine computed tomography pulmonary angiography was performed in all patients before admission to the ICU, whereas in the UMC Utrecht, diagnostic tests were applied only if thrombotic complications were clinically suspected. The indication and timing of computed tomography pulmonary angiography in the UMC Utrecht was determined by alterations in clinical markers of PE including unexplained hemodynamic deterioration, right ventricular strain, worsening P/F-ratio or increasing $CO_2$ gap. Patients were followed until they died, until transfer to another hospital, or until discharge from the ward with a maximum of 2 weeks after ICU discharge. Baseline data on coagulation (prothrombin time (PT), aPTT, fibrinogen, platelet count, D-dimer) and inflammation (C-reactive protein (CRP)) and preexisting comorbidities were extracted from the electronic patient file. Informed consent was obtained by an opt-out approach. The study was approved by the local medical ethical committees of the UMC Utrecht and Erasmus MC and was performed on behalf of the Dutch COVID & Thrombosis Coalition.[17]

## 2.2 | Plasma samples

The first available citrated blood sample (3.2% sodium citrate) that was drawn after ICU admission was used. Plasma was frozen at −80°C at the local biobank. Plasma samples were thawed before analyses, which were completed within 4 h of sample thawing.

## 2.3 | Lupus anticoagulant assay

Lupus anticoagulant testing was performed according to ISTH guidelines[18] with STA-Staclot screen and confirm dilute Russell's viper venom time (dRVVT) reagents (Stago), and HemosIL Silica Clotting Time (Werfen/Instrumentation Laboratories) LA-sensitive aPTT reagents. All assays were performed on a MC10-plus coagulometer (Merlin Medical) at 37°C. Patient plasma was mixed 1:1 with pooled normal plasma (PNP) to exclude coagulation factor deficiencies and dilute heparins present in the sample. Normalized LA (nLA) ratios were expressed as (screen clotting time of patient/screen clotting time of PNP)/(confirm clotting time of patient/confirm clotting time of PNP). Samples were considered LA positive when clotting times were prolonged (LA screen time greater than the 99th percentile of time recorded for 40 healthy volunteers) and the nLA ratio exceeded 1.11 for dRVVT or 1.18 for aPTT. All reagents contained heparin neutralizing agents, allowing reliable outcomes at heparin levels up to 1 IU/ml for dRVVT and 0.4 IU/ml for LA-sensitive aPTT as determined with an anti–activated factor X assay.

## 2.4 | Antiphospholipid IgM and IgG determination

Quantitative values of anticardiolipin and anti-β2GPI IgG and IgM were measured with Cardiolipin IgM/IgG ELISA (IBL International GmbH) or IMTEC β2GPI antibodies IgG/IgM ELISA (Clindia Benelux BV) with a cutoff value for positivity on 12.0 GPL/ml for anticardiolipin IgG, 7.0 MPL/ml for anticardiolipin IgM, 7.0 GPL/ml for anti-β2GPI IgG, and 7.0 MPL/ml for β2GPI IgM, based on a nonparametric 99th percentile of 120 reference individuals. Quantitative values of antiphosphatidylserine/prothrombin (aPS/PT) IgG and IgM were measured with QUANTA Lite ELISA (Inova Diagnostics) with a cutoff value for positivity on 30 units/ml based on the manufacturer's recommendations.

## 2.5 | Statistical analysis

A statistical power analysis was performed for sample size estimation. Based on a 3.6-fold increased risk for venous thromboembolism (VTE) in LA carriers in the general population,[7] an incidence of thrombosis of 30% in patients with COVID-19 admitted to the ICU[1] and a prevalence of LA of 20% in patients with COVID-19,[2] a sample size of at least 165 patients was required to estimate the risk of thrombosis in LA carriers with 80% power and two-tailed significance level of 0.05. Continuous variables are presented as medians and range, and categorical variables are presented as counts (*n*) and frequencies (%). A Mann–Whitney test was used to compare two groups of continuous variables, and $\chi^2$ test was used to determine differences between categorical variables. Statistical analysis to study the association of LA and other antiphospholipid antibodies with thrombosis occurrence was performed using logistic regression. Risk for thrombosis associated with LA are reported as odds ratio (OR) with 95% confidence interval (CI). We checked for potential confounders including sex, body mass index (BMI), length of stay at the ICU, (duration of) mechanical ventilation, and comorbidities as listed in Table 1. In addition, we checked for potential effect modifiers including age, BMI, sex, comorbidities as listed in Table 1,

length of stay at the ICU, intensity of anticoagulation, D-dimer, CRP, fibrinogen, platelet count, and mechanical ventilation. All analyses were performed with SPSS Statistics version 27.0 (IBM).

## 3 | RESULTS

### 3.1 | Patient characteristics

Between March 2020 and March 2021, 311 patients with suspected COVID-19 were admitted to the ICU of the UMC Utrecht. Of these patients, 48 patients were not eligible for inclusion because COVID-19 infection could not be confirmed, 34 patients because of thrombosis before admission to the ICU, 46 patients because their hospital length of stay was too short, and 9 patients because of use of DOACs. A total of 174 of 311 patients from the UMC Utrecht met the inclusion criteria, of whom only 119 patients (68%) could be analyzed due to missing blood samples. Age, sex, and thrombotic complications were similar for patients with or without available blood samples. An additional random sample of 50 of 113 critically ill patients with COVID-19 from the Erasmus MC who met the inclusion criteria and for whom a citrated plasma sample was available were included to achieve a total of 169 patients. Baseline characteristics of these 169 patients are presented in Table 1. The median age was 64 years (range, 18–81) and 136 (80%) patients were men. The median stay at the ICU was 17 days (range, 2–181) and 156 (92%) patients received mechanical ventilation. Although all patients received at least standard-dose thromboprophylaxis, 58 (34%) patients developed thrombotic complications during their stay at the ICU (median of 10 days after ICU admission; range, 1–74). PE was the most common thrombotic complication ($n = 47$) followed by VTE, which includes DVT ($n = 5$) and jugular vein thrombosis ($n = 4$). Arterial thrombosis ($n = 3$), stroke ($n = 2$), and myocardial infarction ($n = 1$) were less frequently observed. Hypertension ($n = 53$) was the most frequent comorbidity in this cohort of patients with COVID-19, followed by cardiovascular disease ($n = 37$), diabetes ($n = 37$), and previous thrombosis ($n = 23$). None of the patients with a history of thrombosis had been diagnosed with APS.

### 3.2 | Clinical outcomes

As expected, patients who developed thrombosis showed higher levels of markers of inflammation CRP and coagulopathy (D-dimer) compared to patients without thrombosis (Table 2). Median CRP was 154.5 mg/L in patients with thrombosis and 70 mg/L in patients without thrombosis. Median D-dimer was 5.9 mg/L (UMC Utrecht) or 3.2 mg/L (Erasmus MC) in patients with thrombosis and 1.2 mg/L (UMC Utrecht and Erasmus MC) in patients without thrombosis. In addition, we found a prolonged PT in patients (from UMC Utrecht) who developed thrombosis versus patients who did not develop a thrombotic event. BMI was lower in patients who developed a thrombotic event (median, 27.3) compared to patients who did not develop thrombosis (median, 28.9). No differences in age, aPTT, platelet count, and fibrinogen were observed between patients with and without thrombosis. Heparin levels were below the threshold for sample exclusion in all samples for dRVVT testing, while heparin levels exceeded the threshold in 22 samples for LA-sensitive aPTT testing.

Lupus anticoagulant, anticardiolipin, anti-β2GPI, and anti-PS/PT IgM and IgG were determined in all patients (Table 3). Of the 169 patients, 117 patients (69%) tested positive for at least one type of antiphospholipid antibody. Forty patients (24%) tested positive for LA, of whom 29 (17%) tested positive with a dRVVT, 19 (11%) tested positive with a LA-sensitive aPTT, and 8 (5%) tested positive on both tests. Of all antiphospholipid antibodies, IgG and IgM antibodies directed towards β2GPI were most frequently observed, in 38% and 29% of patients, respectively. Only one patient tested positive for aPS/PT IgG. Two patients had moderate (40–80 GPL/SGU) and one patient had high (>80 GPL/SGU) anti-cardiolipin IgG titers, and one patient had moderate titers of anti-β2GPI IgM antibodies (40–80 MPL/SMU). Thrombosis occurred only in the patient with high titers of anticardiolipin IgG. Eight patients were triple positive (tested positive for LA, anticardiolipin, and anti-β2GPI antibodies, same isotype) and four patients were tetra positive (triple positive including aPS/PT antibodies). D-dimer levels were elevated in patients tested positive for LA (4.3 mg/L) compared to patients tested negative for LA (1.5 mg/L) ($p < 0.001$).

According to guidelines for LA testing, samples are positive for LA when LA is detected with either a dRVVT or an LA-sensitive aPTT. Although LA detected with a dRVVT was associated with thrombosis (OR, 2.4; 95% CI, 1.1–5.4), LA detected with an LA-sensitive aPTT was not (OR, 1.3; 95% CI, 0.5–3.3) (Table 3). Positivity for either test was also not associated with thrombosis (OR, 1.6; 95% CI, 0.8–3.3). Two of eight triple-positive patients and one of four tetra-positive patients had thrombosis. Neither anticardiolipin, anti-β2GPI, or aPS/PT antibodies were associated with thrombosis. The association of antiphospholipid antibodies with thrombosis remained similar after adjusting ORs for the confounding variables sex, length of stay at the ICU, history of arterial or venous thrombosis, hypertension, and hypercholesterolemia (Table 3). Because high CRP levels can influence LA-test results in the aPTT system[19] and CRP-levels were high in the study population, we adjusted for CRP. However, this had no effect on the risk of thrombosis associated with a positive LA-sensitive aPTT outcome (OR, 0.9; 95% CI, 0.3–2.4). After adjustment for CRP in patients with a positive LA based on the dRVVT, the association between LA and thrombosis disappeared (OR, 1.1; 95% CI, 0.4–3.0). Only a few patients tested positive for both tests, precluding analysis of the risk of thrombosis in these patients.

Stratifying patients by BMI, sex, history of venous or arterial thrombosis, length of stay at the ICU, intensity of anticoagulation, or the traditional cardiovascular risk factors had no effect on the risk of thrombosis associated with a positive LA test result (results not shown). Age had a strong effect on the risk of thrombosis associated with LA positivity (Table 4). As the median age was

**TABLE 1** Demographic and clinical characteristics of 169 patients with COVID-19

| Characteristic or finding | Thrombosis (*N* = 58) | No thrombosis (*N* = 111) | *p* value |
|---|---|---|---|
| Age, years, median (range) | 64 (25–80) | 65 (18–81) | 0.7 |
| Male sex, *n* (%) | 47 (81) | 89 (80) | 0.9 |
| BMI, median (range) | 27 (20–42) | 29 (19–57) | 0.02 |
| Taking anticoagulants at admission,[a] *n* (%) | 7 (12) | 1 (1) | 0.2 |
| Length of stay in the ICU, days, median (range) | 25 (3–181) | 16 (2–61) | 0.007 |
| Mechanical ventilation, *n* (%) | 54 (93) | 102 (92) | 0.8 |
| Duration, days, median (range) | 21 (0–175) | 11 (0–55) | 0.001 |
| ECMO, *n* (%) | 1 (2) | 2 (2) | 1.0 |
| Medical history/comorbidity – *n* (%) | | | |
| Cardiovascular disease | 11 (19) | 26 (23) | 0.5 |
| Hypertension | 15 (26) | 38 (34) | 0.3 |
| Thrombosis | 8 (14) | 15 (14) | 1.0 |
| Diabetes | 9 (16) | 28 (25) | 0.1 |
| Active cancer | 0 (0) | 0 (0) | – |
| Renal disease | 2 (3) | 10 (9) | 0.2 |
| Hypercholesterolemia | 4 (7) | 9 (8) | 0.8 |
| Cerebrovascular disease | 6 (10) | 3 (3) | 0.04 |
| Anticoagulation therapy upon ICU admission, *n* (%) | | | |
| LMWH prophylactic | 25 (43) | 25 (23) | 0.005 |
| LMWH high-intensity prophylactic | 22 (38) | 70 (63) | 0.002 |
| LMWH therapeutic | 4 (7) | 10 (9) | 0.6 |
| UFH therapeutic | 7 (12) | 6 (5) | 0.1 |
| Thrombosis during ICU stay, *n* (%) | 58 (100) | 0 (0) | – |
| Pulmonary embolism | 47 (81) | – | – |
| Deep vein thrombosis | 5 (9) | – | – |
| Jugular vein thrombosis | 4 (7) | – | – |
| Arterial thrombosis | 3 (5) | – | – |
| Stroke | 2 (3) | – | – |
| Myocardial infarction | 1 (2) | – | – |
| Time between ICU admission and sample availability, days, median (range) | 2 (0–37) | 3 (0–27) | 0.2 |
| Time between ICU admission and thrombotic event, days, median (range) | 10 (1–74) | – | – |

*Note*: Data of BMI are missing for 4 patients.

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

[a]Anticoagulants include vitamin K antagonists and therapeutic LMWH.

64 years, we looked into the effect of LA positivity on thrombosis in patients aged less than 65 years (*N* = 85) and in patients aged 65 years or older (*N* = 84). In LA-positive patients aged less than 65 years, the odds for thrombosis were 3.8-fold higher compared with LA-negative patients of the same age (OR, 3.8; 95% CI, 1.3–11.4). The OR for thrombosis increased to 4.5 (95% CI, 1.4–14.3) in dRVVT-positive patients aged less than 65 years compared with dRVVT-negative patients of the same age. There was no association between LA and thrombosis in patients aged 65 years or older. Age did not change the risk for thrombosis in patients with a positive LA-sensitive aPTT test.

As LA is caused by antiphospholipid antibodies, we investigated the association between the classical antiphospholipid antibodies and the occurrence of LA. Of all antiphospholipid antibodies, LA was associated only with IgM antibodies directed toward cardiolipin (OR, 6.0; 95% CI, 2.0–18.0) and β2GPI (OR, 2.2; 95% CI, 1.1–4.7).

**TABLE 2** Laboratory results of 169 patients with COVID-19 on day of sample collection

| Laboratory parameter | Thrombosis (*N* = 58) | No thrombosis (*N* = 111) | Reference range | *p* value |
|---|---|---|---|---|
| Coagulation assays, median (range) | | | | |
| PT (s) | | | | |
| UMC Utrecht | 14.8 (11.9–20.9) | 14.3 (11.7–32.6) | 10.0–13.0 | 0.03 |
| Erasmus MC | 13.2 (10.9–18.2) | 13.2 (11.5–15.8) | 10.9–13.3 | 0.7 |
| aPTT (s)[a] | | | | |
| UMC Utrecht | 39.0 (27.0–60.0) | 35.0 (23.0–105.0) | 24.0–34.0 | 0.2 |
| Erasmus MC | 32.0 (20.0–70.0) | 25.0 (18.0–73.0) | 22.0–32.0 | 0.3 |
| Fibrinogen (g/L), median (range) | 6.7 (1.8–11.9) | 5.8 (2.7–10.0) | 2.0–4.0 | 0.1 |
| D-dimer (mg/L), median (range) | | | | |
| UMC Utrecht | 5.9 (0.4–100.0) | 1.2 (0.2–34.0) | 0.00–0.50 | <0.0001 |
| Erasmus MC | 3.2 (0.2–15.2) | 1.2 (0.3–35.2) | 0.00–0.50 | 0.05 |
| CRP (mg/L), median (range) | 154.5 (1.4–480.0) | 70 (1.4–432.0) | 0–10 | <0.0001 |
| Platelet count ($\times 10^9$/L), median (range) | 259 (51–842) | 283 (96–611) | 150–450 | 0.4 |
| Anti-FXa levels,[b] *n* | | | | |
| <0.50 IU/ml | 39 | 56 | | |
| 0.50–0.99 IU/ml | 19 | 54 | | |
| 1.00–1.39 IU/ml | 0 | 1 | | |

*Note*: Data of PT are missing for 8 patients, aPTT for 46 patients, fibrinogen for 33 patients, D-dimer for 34 patients, CRP for 2 patients, and platelet count for 4 patients.

Abbreviations: aPTT, activated partial thromboplastin time; CRP, C-reactive protein; ICU, intensive care unit; PT, prothrombin time.

[a]LA-insensitive aPTT reagent was used.

[b]Determined before mixing with normal plasma. Different assays were used for PT, aPTT, and D-dimer determination, so data for UMC Utrecht and Erasmus MC were separated.

**TABLE 3** Antiphospholipid antibodies and their association with thrombosis

| Antiphospholipid antibody, *n* | Thrombosis (*N* = 58) | No thrombosis (*N* = 111) | Unadjusted OR (95% CI) | Adjusted OR (95% CI)[b] |
|---|---|---|---|---|
| LA positive, any test | 17 | 23 | 1.6 (0.8–3.3) | 1.6 (0.8–3.4) |
| dRVVT | 15 | 14 | 2.4 (1.1–5.4) | 2.5 (1.1–5.7) |
| LA-sensitive aPTT[a] | 8 | 11 | 1.3 (0.5–3.3) | 1.2 (0.4–3.4) |
| Both tests positive | 6 | 2 | NA | NA |
| aCL IgM | 2 | 13 | 0.3 (0.1–1.2) | 0.2 (0.1–1.1) |
| aCL IgG | 3 | 11 | 0.5 (0.1–1.9) | 0.4 (0.1–1.4) |
| aβ2GPI IgM | 19 | 30 | 1.3 (0.7–2.6) | 1.5 (0.7–3.1) |
| aβ2GPI IgG | 22 | 42 | 1.0 (0.5–1.9) | 1.0 (0.5–1.9) |
| aPS/PT IgM | 11 | 24 | 0.8 (0.4–1.9) | 1.0 (0.4–2.2) |
| aPS/PT IgG | 0 | 1 | NA | NA |

Abbreviations: aCL, anticardiolipin antibody; aPS/PT, antiphosphatidylserine/prothrombin antibody; aPTT, activated partial thromboplastin time; aβ2GPI, anti-β2-glycoprotein I antibody; dRVVT, dilute Russell's viper venom time; LA, lupus anticoagulant; NA, not analyzed; OR, odds ratio.

[a]Data were missing in 22 patients (3 patients with thrombosis, 19 patients without thrombosis) due to activated FX levels that exceeded the threshold for reliable LA-sensitive aPTT test outcome.

[b]Adjusted for the confounding variables sex, length of stay at the ICU, history of arterial or venous thrombosis, hypertension, and hypercholesterolemia.

## 4 | DISCUSSION

In our cohort of critically ill patients with COVID-19, the presence of LA was associated with thrombosis in patients aged less than 65 years. LA was not associated with thrombosis in older patients.

We investigated the association of LA and thrombosis in patients with COVID-19 in a large and well-documented group, allowing proper statistical analysis. Bowles et al.[2] were the first who

**TABLE 4** Lupus anticoagulant and the association with thrombosis in relation to age

| | LA positive | Thrombosis | No thrombosis | Adjusted OR[a] (95% CI) |
|---|---|---|---|---|
| Patients <65 years (*N* = 85) | Any test | 13 | 8 | 3.8 (1.3–11.4) |
| | dRVVT | 12 | 6 | 4.5 (1.4–14.3) |
| Patients ≥65 years (*N* = 84) | Any test | 4 | 15 | 0.6 (0.2–2.3) |
| | dRVVT | 3 | 8 | 1.0 (0.2–4.7) |

Abbreviations: dRVVT, dilute Russell's viper venom time; LA, lupus anticoagulant; OR, odds ratio.
[a]Adjusted for the confounding variables sex, length of stay at the ICU, history of arterial or venous thrombosis, hypertension, and hypercholesterolemia.

mentioned LA in patients with COVID-19 with a prolonged aPTT. They tested 35 patients with COVID-19 with a prolonged aPTT and found 91% LA positive. Harzallah et al.[20] measured antiphospholipid antibodies in 56 patients with COVID-19 and found 25 patients LA positive, and 5 patients anticardiolipin antibody or anti-β2GPI antibody positive. Devreese et al.[10] described the incidence of LA, anticardiolipin, anti-β2GPI, and aPS/PT antibodies and their association with thrombosis in 31 patients with COVID-19 admitted to the ICU. In contrast with our results, they did not find a clear relationship between LA and thrombosis, probably due to their small sample size. As we did not only include LA-positive patients or patients with a suspected positive LA,[11] our results are more generalizable to other patients with COVID-19 admitted to the ICU.

Classically, LA is detected with at least two different tests based on a different clotting test principle because no single test is 100% sensitive for all types of LA.[18] Our results indicate that LA detected with a dRVVT was associated with thrombosis in critically ill patients with COVID-19, while LA detected with an LA-sensitive aPTT reagent was not. The aPTT, which measures the intrinsic pathway of coagulation, is inherently more sensitive to interference than the dRVVT, which measures the common pathway of coagulation. For instance, increased FVIII levels, which are frequently observed in patients with COVID-19, can cause false-negative results within an LA-sensitive aPTT.[18,21] Unfortunately, we were unable to measure FVIII activity in our samples. Moreover, high levels of CRP are known to cause false-positive LA test results in an aPTT-based system, not in a dRVVT.[19] However, the difference in association with thrombosis between dRVVT and aPTT test results in our study could not be explained by the lower sensitivity of the dRVVT test for CRP than the LA-sensitive aPTT test, as correction for CRP did not change the OR for thrombosis in aPTT-positive patients. The reason behind the difference in risk associated with dRVVT and aPTT positivity remains to be determined. Our results show that the association of a positive LA with thrombosis is stronger in younger patients. Although data in the literature is limited, it has been suggested that the prevalence of nonpathogenic antiphospholipid antibodies increases with age.[22] Interestingly, the association between LA and thrombosis disappeared after adjustment for CRP. CRP is a marker of acute inflammation and is increased in patients with COVID-19. Moreover, CRP levels are positively correlated with disease severity and mortality in patients with COVID-19 and have been shown to be predictive of the risk of thrombosis.[23] The presence of LA might also reflect an inflammatory status, as transient LA positivity is reported after infections.[24] Moreover, LA was associated with the presence of IgM antiphospholipid antibodies. As IgM antibodies typically appear in the early phase of an immune response, this fits with a status of LA as "infection-related antibody." In general, these infection-associated antiphospholipid antibodies are considered to be nonpathogenic.[25,26] Devreese et al.[10] retested antiphospholipid antibodies in a small cohort of patients with COVID-19 after 3 months and found that all but one patient tested negative, suggesting that the presence of antiphospholipid antibodies in patients with COVID-19 is transient as well. This does not exclude a causal relationship between LA and thrombosis in COVID-19.

The prevalence of LA in this study is 24%, which is much higher than the prevalence of LA in the healthy population (<1%). A high incidence of LA positivity has previously been reported in critically ill patients without COVID-19 (52.9%).[27] In that study, LA developed after a prolonged stay at the ICU, with a median time to LA positivity after admission to ICU of 13 days.[27] In contrast, the critically ill patients with COVID-19 enrolled in our study were LA positive within a median of 1.5 days after ICU admission, suggesting that patients were LA positive before ICU admission. This is in line with the high incidence of LA in hospitalized patients with COVID-19 reported by others.[2] Our results apply only to patients with COVID-19 variants that were encountered early in the pandemic; it remains to be determined if LA positivity is observed with similar rates in patients with other COVID-19 variants. Moreover, we have no information regarding ethnicity or race in our study population. This might be an implication, as race and ethnicity are associated with risk of VTE in patients with COVID-19.[28] Evidence has shown that patients with more than one positive test, and particularly those patients with triple positivity (LA, anticardiolipin, and anti-β2GPI antibodies, same isotype), show the strongest association with thrombotic and obstetric complications.[25] In our study, eight patients were triple positive, of which four patients also tested positive for aPS/PT, also known as tetra positivity. Unfortunately, these numbers are too low to determine any association with thrombosis.

The switch from prophylactic anticoagulation at the start of the COVID-19 crisis in March/April 2020 toward high-intensity prophylactic or therapeutic anticoagulation later on, is reflected in the number of thrombotic complications: Whereas 50% of patients on prophylactic anticoagulation developed a thrombotic event, only 28% of patients on high-intensity prophylactic or therapeutic

anticoagulation developed thrombosis. However, the intensity of anticoagulation did not change the risk of thrombosis associated with a positive LA result. A limitation of our study is that the incidence of thrombosis in our study might be underestimated, which might have led to an underestimation of the true association between LA and thrombosis. First, VTE is more difficult to recognize in intubated patients with a higher threshold to perform diagnostic imaging tests because of strict isolation protocols. If all patients had been screened for thrombosis during their stay at the ICU, we might have detected more thrombotic events. Second, although we excluded patients with a recognized thrombosis at ICU admission, routine computed tomography with angiography before admission to the ICU was only performed at the Erasmus MC. Therefore, we cannot exclude that some patients already had thrombosis before enrollment. Third, the information on thrombotic events was limited to the information present, and no follow-up data of the patients transferred to other hospitals were available. Moreover, patients who died of thromboembolic events could have been missed, as autopsy was not routinely performed.

To conclude, LA, as measured on admission to the ICU, is associated with thrombotic complications in critically ill patients with COVID-19 in an age-dependent manner, with a strong association in the younger patients.

## AUTHOR CONTRIBUTIONS

T. Noordermeer, C. Visser, and E. Rademaker collected the data. T. Noordermeer performed the experiments. T. Noordermeer, R. E. G. Schutgens, and R. T. Urbanus analyzed the data and wrote the manuscript. R. E. G. Schutgens, M. P. M. de Maat, A. J. G. Jansen, O. L. Cremer, M. Limper, M. J. H. A. Kruip, H. Endeman, C. Maas, B. de Laat, and R. T. Urbanus designed the study. All authors read and approved the manuscript.

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