DR. NICOLAS GENDRON (Orcid ID : 0000-0003-4852-4738)

PROF. BENJAMIN TERRIER (Orcid ID : 0000-0001-6612-7336)

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Lupus anticoagulant single positivity at acute phase is not associated with venous thromboembolism or in-hospital mortality in COVID-19

Brief title: Lupus anticoagulant in COVID-19 patients

Nicolas GENDRON, PharmD PhD[1], Marie-Agnès DRAGON-DUREY, PharmD PhD [2], Richard CHOCRON, MD PhD[3], Luc DARNIGE, MD[1], Georges JOURDI, PharmD PhD [4], Aurélien PHILIPPE[1], Camille CHENEVIER-GOBEAUX, PharmD[5], Jérôme HADJADJ, MD[6], Jérôme DUCHEMIN, MD[4], Lina KHIDER, MD[7], Nader YATIM, MD[8] Guillaume GOUDOT, MD PhD[7], Daphné KRZISCH, MD[9], Benjamin DEBUC, MD[10], Laetitia MAUGE, PharmD PhD[11], Françoise LEVASSEUR[12], Frédéric PENE, MD[13], Jeremy BOUSSIER, MD[5], Elise SOURDEAU[4], Julie BRICHET[9], Nadège OCHAT[9], Claire GOULVESTRE, MD[14] Christophe PERONINO[1], Tali-Anne SZWEBEL, MD[8], Franck PAGES, MD PhD[2], Pascale GAUSSEM, PharmD PhD[15], Charles-Marc SAMAMA, MD PhD[16], Cherifa CHEURFA, MD[17], Benjamin PLANQUETTE, MD PhD[18,19], Olivier SANCHEZ, MD PhD[18,19], Jean-Luc DIEHL, MD PhD[20], Tristan MIRAULT, MD PhD[7], Michaela FONTENAY, MD PhD[12], Benjamin TERRIER, MD PhD[5] and David M. SMADJA, PharmD PhD [1,19]

[1] Université de Paris, Innovative Therapies in Haemostasis, INSERM, F-75006 Paris, France, Hematology department and Biosurgical research lab (Carpentier Foundation), Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75015 Paris, France.

[2]Centre de Recherche des Cordeliers, Sorbonne Université, Inserm, Université de Paris, Team Inflammation, complement and cancer, F-75006, Paris, France, Immunology department, Georges Pompidou European Hospital, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75015 Paris, France.

[3]Université de Paris, PARCC, INSERM, F-75015 Paris, France, Emergency department, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75015 Paris, France.

[4]Université de Paris, Innovative Therapies in Haemostasis, INSERM, F-75006 Paris, France, Hematology department, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75014 Paris, France.

[5]Department of Automated Diagnostic Biology, Hôpital Cochin, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75014 Paris, France.

[6]Université de Paris Imagine institute, laboratory of Immunogenetics of Pediatric Autoimmune Diseases, INSERM UMR 1163, F-75015, Paris Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Assistance Publique Hôpitaux de Paris-Centre (APHP-CUP), F-75014 Paris, France.

[7]Université de Paris, Vascular Medicine department and Biosurgical research lab (Carpentier Foundation), Assistance Publique Hôpitaux de Paris-Centre (APHP-CUP), F-75015 Paris, France.

[8]Translational Immunology lab, Department of Immunology, Institut Pasteur, and Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Assistance Publique Hôpitaux de Paris-Centre (APHP-CUP) F-75015, Paris, France.

[9] Université de Paris, Hematology department, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75015 Paris, France.

[10] Université de Paris, Innovative Therapies in Haemostasis, INSERM, F-75006 Paris, France, Plastic surgery department, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75015 Paris, France.

[11]Université de Paris, PARCC, INSERM, F-75015 Paris, France, Hematology department, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75015 Paris, France.

[12]Université de Paris, Institut Cochin, INSERM, F-75014 Paris, France, Hematology department Assistance Publique Hôpitaux de Paris-Centre (APHP-CUP), F-75014 Paris, France.

[13]Intensive care medicine, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75014 Paris, France.

[14]Immunology department, Assistance Publique Hôpitaux de Paris. Centre-Université de Paris (APHP-CUP), F-75014 Paris, France.

[15]Université de Paris, Innovative Therapies in Haemostasis, INSERM, F-75006 Paris, France, Hematology department, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75015 Paris, France.

[16] Université de Paris, Innovative Therapies in Haemostasis, INSERM, F-75006 Paris, France, Anaesthesia, Intensive Care and Perioperative Medicine Department, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75014 Paris, France.

[17]Anaesthesia, Intensive Care and Perioperative Medicine Department, Assistance Publique Hôpitaux de Paris.Centre-Université de Paris (APHP-CUP), F-75014 Paris, France.

[15]Université de Paris, Innovative Therapies in Haemostasis, INSERM, F-75006 Paris, France, Respiratory Medicine Department and Biosurgical Research Lab (Carpentier Foundation), Assistance Publique - Hôpitaux de Paris-Centre (APHP-CUP), F-75015 Paris, France.

[19]F-CRIN INNOVTE, Saint-Étienne, France

[20]Université de Paris, Innovative Therapies in Haemostasis, INSERM, F-75006 Paris, France, Intensive care unit and Biosurgical research lab (Carpentier Foundation), Assistance Publique - Hôpitaux de Paris-Centre (APHP-CUP), F-75015 Paris, France.

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Address for correspondence:

Prof. David M Smadja, Hematology department and Biosurgical Research Lab (Carpentier Foundation), AH-HP, Georges Pompidou European Hospital, 20 rue Leblanc, 75015 Paris, France, e-mail: david.smadja@aphp.fr

Abstract

Introduction: Antiphospholipid antibodies (APA) clinical relevance in COVID-19 is controversial. We aimed to investigate the prevalence and prognostic value of conventional and non-conventional APA in COVID-19 patients

Methods: This study was a multi-centric, prospective observational French cohort of patients hospitalized for COVID-19 suspicion.

Results: 249 patients were hospitalized for suspected COVID-19, including 154 with confirmed COVID-19 and 95 not confirmed. We found a significant increase in lupus anticoagulant (LA) positivity among COVID-19 positive patients (60.9% versus 23.7% in non-COVID19 patients, $p<0.001$), while prevalence of conventional (anti-cardiolipin and anti-beta-2-GP1, IgG and IgM isotypes) and non-conventional APA (IgA, anti-phosphatidylserine/prothrombin and anti-prothrombin IgG and IgM) were low in both groups. COVID-19 patients with LA positivity had higher levels of fibrinogen (6.0 IQR 5.0–7.0 versus 5.3 g/L IQR 4.3–6.4, p=0.028) and C-reactive protein (CRP, 115.5 IQR 66.0–204.8 versus 91.8 mg/L IQR 27.0–155.1, p=0.019). Univariate analysis did not show any association between LA positivity and higher risk of venous thromboembolism (VTE, OR 1.02, 95% CI 0.44-2.43, p=0.95) or in-hospital mortality (OR 1.80, 95% CI 0.70–5.05, p=0.24). Unadjusted and adjusted (to CRP, age and sex) Kaplan-Meier survival curves according to LA positivity confirmed the absence of association with VTE or in-hospital mortality (unadjusted: p=0.64 and p=0.26, respectively; adjusted: hazard ratio = 1.13 95% CI 0.48–2.60 and 1.80 95% CI 0.67–5.01).

Conclusions: COVID-19 patients have an increased prevalence of LA positivity associated with biological inflammation markers. However, positive LA at admission is not associated with VTE risk and/or in-hospital mortality.

Key Words: COVID-19, coagulopathy, antiphospholipid antibodies, lupus anticoagulant, thrombosis, inflammation

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and associated with non-specific respiratory syndromes, ranging from mild upper airway symptoms to hypoxemia requiring mechanical ventilation support (1–3). An important feature of COVID-19 is the associated-coagulopathy that correlates to disease severity and in-hospital mortality (4,5), without any sign of disseminated induced coagulopathy in contrast to previous reports (6). There is increasing reports of venous thromboembolism (VTE) and arterial thrombosis irrespective of the use of pharmacological thromboprophylaxis (7–14). Both macrothrombosis, in particular pulmonary embolism (PE)(15) and microthrombosis into the lungs, have been largely described (16). Microthrombosis could be consequence of vascular injury and the link between coagulopathy and severity and/or mortality in COVID-19 (17).

Antiphospholipid syndrome (APS) is an acquired thrombophilia leading to use of long term anticoagulation therapy (18). Classification of APS requires the presence of one clinical event (thrombosis or pregnancy morbidity) and at least one persistently positive laboratory test for antiphospholipid antibodies (APA), the latter including lupus anticoagulant (LA), anti-cardiolipin (aCL) and anti-beta-2-GP1 (aβ2GP1) IgG and/or IgM (19,20). Autoantibodies to phospholipids and phospholipid-binding proteins like anti-prothrombin (aPT), aCL or aβ2GP1 participate to leukocyte and endothelial activation and induce both arterial and VTE. Combination of positive tests in APA profile and particularly triple positivity (LA, aCL, aβ2GP1, same isotype) identifies patients at high risk for thrombosis and allows a more confident diagnosis of APS. Furthermore, very often, triple positive patients are also positive for anti-phosphatidylserine/prothrombin antibodies (aPS/PT), giving additional risk for thromboembolic events to the usual APA profile (tetra-positive patients) (21). Moreover, APA are not specific to APS but can be detected in healthy individuals and in different clinical setting, including autoimmune conditions, drugs or infectious disease (18). APA have been largely described during other viral infections (22) and their pathogenicity in these contexts remains controversial. During COVID-19 outbreak, several reports described potential association between APA and thrombotic events (32). Previous studies exploring LA described between 45% and 88% of positivity in different cohorts in the medical ward and/or intensive care unit (ICU) settings (10,23–25). Only one study suggested in vitro that APA positivity in sera of COVID-19 patients could be prothrombotic but LA testing was not assessed (26). To the best of our knowledge, there is no large cohort describing complete screening for LA and associated APA.

Moreover, association of APA with VTE or in-hospital mortality in COVID-19 is still a matter of debate.

In the present study, we aimed to investigate the prevalence of conventional and non-conventional APA and explore their relevance according to VTE and mortality outcomes in a large cohort of 249 patients with suspected COVID-19.

Patients and methods

Study design and population

This study was a multicenter, prospective and observational cohort study conducted in a two university hospitals in Paris (France): Hôpital Européen Georges Pompidou and Hôpital Cochin. From March 14, 2020 to April 20, 2020, patients with suspected SARS-CoV-2 infection were prospectively included. Inclusion criteria were: patients aged over 18 years, presenting with an infectious syndrome and suspected COVID-19, who presented to the emergency department of both hospitals with hospitalization criteria or directly addressed for hospitalization. Suspected COVID-19 had at least one or more symptoms among the following: fever, headache, myalgia, cough, dyspnea, rhinorrhea and digestive symptoms. All suspected COVID-19 patients were tested for SARS-CoV-2 infection by nasopharyngeal swabs and screened for hospitalization criteria based on local guidelines (27) and defined as described in **Supplemental Table 1**. Suspected COVID-19 patients fulfilling hospitalization criteria were admitted in dedicated departments (medical ward or ICU), while awaiting laboratory confirmation of SARS-CoV-2 infection. Diagnosis of SARS-CoV-2 infection was confirmed by a positive result of a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay and/or typical computerized tomography (CT) scan findings of COVID-19 pneumonia.

The study was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before they were enrolled (SARCODO 2020-A01048-31, NCT04624997). For all patients included, baseline characteristics (demographic, treatment, cardiovascular risk factors and body mass index, BMI), clinical, biological data and CT-scan evaluations were collected from the medical records using a standardized data collection.

Laboratory confirmation of SARS-CoV-2 infection

Nasopharyngeal swabs were collected in universal transport medium (Xpert® nasopharyngeal sample collection kit) at hospital admission as previously described (28). SARS-CoV-2 was detected using Allplex™ 2019-nCoV Assay (Seegene), a multiplex RT-PCR assay that detects in real time three target genes (E gene, RdRP gene and N gene) in a single tube. Data were automatically analyzed using Seegene viewer software. Only qualitative data were considered.

Routine blood examinations

All samples were collected at admission on EDTA, sodium heparin or 0.129 M trisodium citrate tubes (9NC BD Vacutainer, Plymouth, UK). Routine lab tests were complete blood count, creatinine, C-reactive protein (CRP), interleukin-6 and ferritin levels. Global coagulation tests were activated partial thromboplastin time (K-APTT, CK Prest APPT, Diagnostica Stago, Asnières, France), prothrombine time (PT) ratio, fibrinogen, soluble fibrin monomer, (STA®-Liatest FM; Diagnostica Stago) explored on a STA-R® Max (Diagnostica Stago) coagulometer as previously described (26). D-dimer levels were determined using the Vidas® D-Dimer assay (Biomérieux, Marcy-Etoile, France) according to the manufacturer's instructions.

Lupus anticoagulant (LA) testing

LA assays were performed by the local center, according to the International Society of Thrombosis and Haemostasis (ISTH) Scientific Standardization Committee (SSC) guideline (29). Briefly, citrated blood was double centrifuged for 15 minutes (min) at 2000 g (room temperature). The obtained platelet-poor plasma was tested for a prolonged clotting time with two tests based on different principles (i.e, aPTT and dilute Russell viper venom time, dRVVT). LA testing was performed by a three-step procedure including screening, mixing, and confirmation. dRVVT using LA1 and LA2 reagents (Siemens, Germany) and aPTT using Automated APTT (Trinity Biotech, Ireland) and a reagent with a weak sensitivity to LA, CK Prest (Diagnostica Stago). The dRVVT assay contains heparin-neutralizer able to quench unfractionated or low molecular weight heparin (up to 1.0 UI/mL) that might lead to false positive detection of LA. In case of LA testing during unfractionated heparin/low molecular weight heparin, anti-FXa activity was quantified and verified to be below the heparin-neutralizer cut-off of 1.0 UI/mL (**Supplemental Table 2).**

Solid phase antiphospholipid antibodies testing

aCL and aβ2GP1of IgG, IgM and IgA isotype antibodies were measured in the plasma by BIO-FLASH Chemiluminescent Immuno Assay technology (QUANTA Flash® β_2 GP1 INOVA Diagnostics, Werfen, Les Lilas, France) with a cut-off value (99th percentile) at 20 AU as previously described (30). aPS/PT antibodies of IgM and IgG isotype were measured in the serum by ELISAs

(Quanta Lite, INOVA Diagnostics, Werfen) with a cut-off value (99th percentile) at 30 AU as previously described (30). aPT antibodies of IgG and IgM isotype were measured by ELISAs (Orgentec Diagnostika, Mainz, Germany) with a cut-off value (99th percentile) at 10 AU.

Statistical analysis

Continuous data were expressed as median (interquartile range, IQR) and categorical data as proportion. Patients were compared according to COVID-19 viral status and to the positivity of LA**.** Continuous and categorical variables were compared using respectively Mann-Whitney test and Fisher exact test. In the multivariate analysis, we used logistic regression model to identify risk factor of VTE and in-hospital mortality. The model was adjusted on age, gender and CRP (as binary variable dichotomized according to the median). For the survival analysis, the start of the study was triggered by the diagnosis of SARS-CoV-2 infection and hospitalization. The end of the study was defined either by the death of the patient during the hospitalization or by discharge alive from the hospital. Survival time was calculated as the difference between the date of the diagnosis of SARS-CoV-2 infection and the date of event occurrence (VTE and in-hospital mortality) or the date of hospital discharge. We used Cox proportional Hazard (PH) model adjusted for age, gender and CRP to investigate the relationships between LA positivity and outcomes (VTE or in-hospital mortality). Kaplan-Meier method was used to represent Cox PH model results according to the positivity of LA. In the unadjusted survival analysis, survival curves were compared using log rank test.

All analyses were 2-sided and a p-value <0.05 was considered statistically significant. Statistical analysis was performed using R studio software including R version 3.6.3 (R Development Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Overall, 249 patients admitted to hospital for suspected COVID-19 were included. Among them, 154 (61.8%) had confirmed COVID-19 whereas 95 (38.2%) did not have COVID-19 and were ultimately found to have other diagnoses (**Supplemental Table 3**). These two groups were not strictly comparable in terms of gender, age, BMI, cardiovascular risk factors, medical history, clinical features and symptoms (**Table 1**). Hence, COVID-19 patients were more often male with increased BMI and with more fever and respiratory symptoms as previously described in COVID-19 (1–3). At admission, when compared to non-COVID-19 patients, COVID-19 patients were more likely to have dyspnea, decreased SpO2, pneumonia on the CT-scan, increased respiratory rate-breath per minute and more subsequently referred to ICU in particular for acute respiratory distress syndrome. In terms of biological features, regarding coagulation disorders, COVID-19 patients had higher median D-dimer levels, longer K-aPTT and lower PT ratio. In COVID-19 patients, fibrin monomers were negative and associated with hyperfibrinogenemia without thrombocytopenia.

Higher prevalence of LA positivity but not other APA is found in COVID-19 patients

LA positivity was assessed at admission of confirmed COVID-19 and non-COVID-19 patients. When compared to non-COVID-19 patients (**Figure 1A**), we found higher prevalence of LA positivity among confirmed COVID-19 patients (60.9% versus 23.7%, $p<0.001$). Interestingly, among all COVID-19 patients tested for LA, 9 (7.8 %) received hydroxychloroquine at admission and among them, 6 (75.0%) had LA positivity and 3 (25.0%) LA negativity.

The prevalence of solid phase immunoassays for conventional and non-conventional makers of APS in COVID-19 patients and non-COVID-19 patients is described in **Table 2**. Regarding aCL positivity, IgG, IgM and IgA were low in both groups, respectively, 3.2%, 7.4% and 2.1% in non-COVID-19 patients versus 5.8%, 1.3% and 1.9% in COVID-19 patients. aCL IgM were significantly more frequent in non-COVID-19 patients ($p=0.008$). aβ2GP1 positivity, IgG, IgM and IgA were low in both groups, respectively found in 0.0%, 4.2% and 2.1% in non-COVID-19 patients versus 3.2%, 1.9% and 1.3% in COVID-19 patients. aβ2GP1 IgA were significantly more frequent in non-COVID-19 patients ($p<0.001$). aPS/PT positivity, IgG and IgM were 0.0% and 10.5% in non-COVID-19 patients, respectively, compared to 0.0% and 4.5% in COVID-19 patients, without any significant difference between groups. Finally, IgG and IgM aPT positivity was 7.4.0% and 5.3% in

non-COVID-19 patients, respectively, compared to 7.1% and 6.5% in COVID-19 patients, aPT IgM were significantly more frequent in COVID-19 patients (p=0.003). Among COVID-19 patients with LA positivity (n=70), 62 (88.6%) were isolated and 8 (11.4%) were associated with ≥1 other APA (aCL and/or aβ2GP1 and/or aPS/PT, IgG or IgM, **Figure 1B**).

LA positivity in COVID-19 is associated with inflammation markers and not with VTE or in-hospital mortality

In COVID-19 patients, those with LA positivity or not were comparable in terms of gender, age, BMI, cardiovascular risk factors, medical history and time from illness onset to hospitalization (**Table 3**). Furthermore, risk factors for VTE (age, BMI, cancer, previous DVT/PE) did not differ between both groups (p >0.05 for each).

However, when compared to patients negative for LA, COVID-19 patients with LA positivity had higher levels of fibrinogen (6.0 g/L, IQR 5.0–7.0 versus 5.3 IQR 4.3–6.4, p=0.028) and C-reactive protein (CRP, 115.5 mg/L IQR 66.0–204.8 versus 91.8 mg/L, IQR 27.0–155.1, p=0.019). Strikingly, COVID-19 patients with LA positivity did not have significantly different levels of interleukin-6 and ferritin than COVID-19 patients negative for LA.

The percentages of patients referred to ICU (55.6% versus 61.4%), who developed VTE (26.8% versus 27.1%) and in-hospital mortality (15.6% versus 24.3%) were not significantly different for COVID-19 patients with negative or positive LA testing respectively (p >0.05 for each).

As shown in **Table 4,** in both univariate and multivariate analyses (adjusted on CRP, sex and age), LA positivity was not associated with higher risk of VTE (OR 1.02, 95% CI 0.44–2.43, p=0.95 in the logistic regression and OR 1.01, 0.42–2.48, p=0.98 in multivariate analysis). Furthermore, LA positivity was not associated with higher in-hospital mortality in both univariate (OR 1.80, 95% CI 0.70–5.05, p=0.24) and multivariate analyses (OR 1.69, 0.58–5.35, p=0.35), in contrast to age (OR 1.04, 1.01–1.09, p=0.030) and CRP (OR 3.30, 1.12–11.32, p=0.039). Finally, Kaplan-Meier survival curves according to LA positivity showed that in COVID-19 patients LA positivity at admission did not predict the risk of VTE (p=0.64, **Figure 2A**) even after adjustment to CRP, age and sex (**Figure 2B**), or the risk of in-hospital mortality (p=0.26, **Figure 2C**) even after adjustment to CRP, age and sex (**Figure 2D**).

Discussion

COVID-19-associated coagulopathy is associated with microthrombosis, VTE and arterial thrombotic complications (14,15,31). To the best of our knowledge, the present study is the first one testing all APA in a large cohort of suspected COVID-19 patients, including both confirmed and not confirmed COVID-19. This study explored the relevance of conventional and non-conventional APS markers at COVID-19 admission, to assess whether they might play a role for the prognosis of the disease. As previously mentioned (10,23–25), we found a high prevalence of LA in COVID-19 patients contrasting with the low prevalence of aCL antibodies IgG and IgM and aβ2GP1 IgG and IgM detected by solid phase immunoassay. Positivity for LA in COVID-19 patients was significantly associated with inflammatory biomarkers such as higher fibrinogen and CRP levels but not interleukin-6 or ferritin levels. Discrepancy between different inflammatory markers and LA positivity association suggested that those inflammation markers do not have the same relevance in COVID-19. Further studies need to decipher the exact involvement of inflammatory proteins and COVID-19 severity and/or their involvement in COVID-19 associated coagulopathy. Along this line, LA testing in acute phase inflammatory conditions is not recommended because high CRP and fibrinogen levels may induce false positive results (29,32,33).

Early during COVID-19 outbreak, Zhang *et al* described three cases of a critical COVID-19, characterized by the absence of LA and the presence of aCL IgA, aβ2GP1 IgA and IgG antibodies without details on titers (34). The three patients experienced ischemic events associated with multifocal thrombosis. APA can be transitory positive in patients with infectious conditions (22) and these antibodies are rarely associated with thrombotic events, explain why this association cannot be reliable in critically ill patients. One study on 56 COVID-19 patients described the association of aCL IgG levels with COVID-19 severity (35) but without testing LA positivity. Only one study suggested that APA positivity could be prothrombotic *in vitro* and *in vivo* after injection of IgG purified from COVID-19 patient serum positive for APA in mice that accelerated venous thrombosis (26). However, a major flaw of this study is the absence of APA-specificity of the COVID-19 patients purified IgG. In this latter study LA testing was not assessed.

APA can be transitory positive in patients with infectious conditions (22) and these antibodies are rarely associated with thrombotic events, explain why this association cannot be reliable in critically ill patients. Whether COVID-19 APA are similar to the ones found in other infectious diseases such as HCV, HBV and HIV remains to be determined (18,22).

In our study, we demonstrated that LA positivity in COVID-19 patients was not associated with more VTE, in particular PE, or with a poorer prognosis. Our results are in accordance with previous reports on smaller cohorts suggesting the lack of association between APA and COVID-19 severity and/or VTE (24,25,36). The high prevalence of stroke (13) or VTE in severe COVID-19 (15,30), in particular PE, is unusual and has rarely been reported in other viral infections as influenza virus (8). In the study by Devreese et al (37), 10 COVID-19 patients were tested again one month after the first testing and all but one patient initially positive for LA became negative. This latter report reinforces the hypothesis that LA may be transient and/or artefactual due to acute phase of infection and increased CRP and fibrinogen levels. Furthermore, Pengo et al (38) showed that in suspected APS patients, the initial single APA positive phenotype was confirmed in only 40% of subjects. LA are heterogeneous antibodies detected under various clinical circumstances where cellular damage, due to infectious, autoimmune or inflammatory stimuli, leads to plasma membrane remodeling including release of membrane microparticles and exposure of anionic phospholipids. LA activity may be induced by aβ2GP1 and/or aPT antibodies that provoke a dimerization of β2GP1 and/or prothrombin enhancing their affinity for negatively charge phospholipid (39). Strikingly, such high prevalence of LA/APA in of COVID-19 patients have rarely been observed with other pathologies, which probably reveals significant or massive cellular destruction specific to COVID-19.

Medium/low APA titers were consistently found in COVID-19 patients. We acknowledge that in the present study, APA testing were performed during the acute phase what is discouraged in the guidelines because of potential interference and guidelines recommend retesting after 3 months to avoid overdiagnosis by classification of transient positivity of APA (19,20,33). Of note, heparin therapy was not an issue in our study for LA testing because our reagents contain heparin neutralizers and anti-FXa activities in patients anticoagulated with heparin were below the cut-off of the neutralizer.

Limitation of our study is the small sample size of both groups and heterogeneity of our non-COVID-19 control group.

In summary, our study demonstrates that COVID-19, similarly to other acute infectious inflammatory diseases, has high prevalence of LA positivity, but the latter is not associated with more VTE and/or in-hospital mortality. LA and APA testing is not recommended and must be discouraged during the acute phase of COVID-19 as for other viral infections. A biological confirmation should anyway be necessary after recovery.

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Conflict of interest statement

All the authors have nothing to disclose with the present study.

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Figure legends

Figure 1. Prevalence of LA positivity in COVID-19 patients admitted at the hospital and its association with other APA.

A) At admission, LA positivity was assessed in COVID-19 (n=115) and non-COVID-19 (n=93) patients. When compared to non-COVID-19 patients, we found higher prevalence of LA positivity among COVID-19 patients (n=70, 60.9% versus, n=22, 23.7%, p<0.001).

B) Venn diagram of APA profile among COVID-19 patients with LA positivity associated or not to other APA. Using web-based tool for Venn diagrams (40) we showed the low prevalence of aCL (IgG or IgM) and/or aβ2GPI (IgG or IgM), and/or aPS/PT associated positivities (IgM, none of COVID-19 patients were positive for IgG).

LA: lupus anticoagulant; APA: antiphospholipid antibody; aCL: anti-cardiolipin antibodies; IQR: interquartile range; aβ2GPI: anti-beta-2-GPI antibodies; aPS/PT: anti-phosphatidylserine-prothrombin antibodies;

Figure 2. Kaplan–Meier survival curves, illustrating the prognostic impact of lupus anticoagulant at admission during COVID-19.

In COVID-19, LA did not predict VTE (A) even after adjustment on CRP, age and sex (B). In COVID-19, LA did not predicted in-hospital mortality (C) even after adjustment on CRP, age and sex (D).

LA: lupus anticoagulant, VTE: venous thromboembolism, HR: hazard ratio.

Table 1. Demographic, clinical and biological characteristics of patients on admission according to COVID-19 viral status

IQR: interquartile range; BMI: body mass index; CV: cardiovascular; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; SpO2: pulse oximetric saturation; IQR: interquartile range. CRP: C-reactive protein; K-APTT: kaolin activated partial thromboplastin time; PT: thromboplastin time.

	Non-COVID-19 (n=95)	COVID-19 positive (n=154)	*p-value*
Male sex – n (%)	43 (45.3)	111 (72.1)	**<0.001**
Age - years, median [IQR]	76.0 [56.0–87.0]	59.0 [51.0–72.0]	**<0.001**
BMI - Kg/m², median [IQR]	24.2 [21.4–26.6]	27.1 [24.5–31.5]	**<0.001**
Time from illness onset to hospital admission - days, median [IQR]	4.0 [1.0–7.0]	7.0 [4.0–8.0]	**0.001**
CV risk factors			
Hypertension – n (%)	51 (53.7)	66 (42.9)	**0.037**
Dyslipidemia – n (%)	21 (22.1)	29 (18.8)	0.24
Diabetes – n (%)	2 (2.1)	36 (23.4)	**<0.001**
Chronic kidney disease – n (%)	13 (13.7)	15 (9.7)	0.27
Medical history			
Cancer – n (%)	26 (27.4)	18 (11.7)	**0.03**
Coronary heart disease – n (%)	10 (10.5)	7 (4.5)	**0.002**
Stroke – n (%)	10 (10.5)	7 (4.5)	NA
Clinical features			
Fever – n (%)	31 (32.6)	132 (85.7)	**<0.001**
Headache – n (%)	9 (9.5)	42 (27.3)	**<0.001**
Cough – n (%)	40 (42.1)	122 (79.2)	**<0.001**
Productive cough – n (%)	5 (5.3)	15 (9.7)	0.43
Dyspnea – n (%)	59 (62.1)	106 (68.8)	0.42
Myalgia – n (%)	12 (12.6)	62 (40.3)	**<0.001**
Diarrhea – n (%)	12 (12.6)	38 (24.7)	0.064
Pneumonia at CT-Scan – n (%)	26 (27.4)	116 (75.3)	**<0.001**
ARDS – n (%)	2 (2.1)	45 (29.2)	**<0.001**
ICU patients – n (%)	6 (6.3)	88 (57.1)	**<0.001**
Temperature - degrees Celsius, median [IQR]	37.1 [36.6–37.5]	38.3 [37.7–39.0]	**<0.001**
SpO2 - %. median [IQR]	96.0 [92.0–98.0]	93.0 [89.1–96.0]	**<0.001**
Respiratory rate - Breathes per min. median	18.0 [16.0–22.0]	20.5 [18.0–27.8]	**0.001**

[IQR]			
Pulse - Beats per min. median [IQR]	87.0 [78.0–100.0]	92.0 [80.8–105.3]	**0.17**
Biological parameters			
White blood cells - x10^9 per L, median [IQR]	8.20 [6.45–11.1]	6.40 [4.60–9.00]	**<0.001**
Hemoglobin - g/L, median [IQR]	134.0 [115.0–145.0]	128.5 [113.0–143.3]	0.23
Platelet count - x10^9 per L, median [IQR]	223.5 [181.8–265.3]	196.5 [148.3–281.3]	0.074
Polynuclear neutrophils - x10^9 per L, median [IQR]	6.44 [4.32–9.41]	4.83 [3.17–7.51]	0.005
Lymphocytes - x10^9 per L, median [IQR]	1.17 [0.83–1.72]	0.95 [0.66–1.25]	**0.001**
Monocytes - x10^9 per L, median [IQR]	0.60 [0.42–0.83]	0.37 [0.25–0.56]	**<0.001**
CRP - mg/L, median [IQR]	13.6 [2.5–97.6]	104.2 [47.3–173.9]	**<0.001**
Plasma creatinine - µmol/L, median [IQR]	78.0 [62.0–110.0]	75.0 [62.0–102.0]	0.78
K-APTT - sec median [IQR]	29.1 [27.8–32.0]	32.0 [30.0–35.4]	**<0.001**
PT ratio, median [IQR]	97.0 [85.8–107.0]	92.0 [81.0–99.0]	**0.003**
Fibrinogen - g/L, median [IQR]	4.30 [3.35–5.15]	5.70 [4.85–7.00]	**<0.001**
D-dimer – ng/mL, median [IQR]	894.0 [430.0–2266.3]	1170.0 [702.5–2325.5]	**0.039**
Fibrin monomers - µg/mL, median [IQR]	<7.0 [<7.0 – <7.0]	<7.0 [<7.0 – <7.0]	0.15

Table 2. Results of conventional and non-conventional solid phase immunoassays in the study cohort.

aCL: anticardiolipin antibodies; IQR: interquartile range; aβ2GPI: anti-beta-2-GPI antibodies; aPS/PT: anti-phosphatidylserine-prothrombin antibodies; aPT: anti-prothrombin antibodies; LA: lupus anticoagulant.

	Non-COVID-19	COVID-19 positive	*p-value*
aCL IgG			
Titer - median [IQR]	3.0 [2.6–5.5]	3.0 [3.0–9.0]	<0.001
Positive result	3 (3.2)	9 (5.8)	0.088
Missing data	0 (0.0)	6 (3.9)	
aCL IgM			
Titer - median [IQR]	2.8 [1.4–5.5]	2.0 [1.0–3.0]	0.019
Positive result	7 (7.4)	2 (1.3)	0.008
Missing data	0 (0.0)	6 (3.9)	
aCL IgA			
Titer - median [IQR]	2.3 [1.8–4.6]	2.0 [2.0–4.0]	0.22
Positive result	2 (2.1)	3 (1.9)	<0.001
Missing data	2 (2.1)	57 (37.0)	
aβ2GP1 IgG			
Titer - median [IQR]	6.4 [6.4–6.4]	6.0 [6.0–6.0]	<0.001
Positive result	1 (1.1)	5 (3.2)	0.078
Missing data	0 (0.0)	6 (3.9)	
aβ2GP1 IgM			

Titer - median [IQR]	1.1 [1.1–2.1]	1.0 [1.0–2.0]	<0.001
Positive result	4 (4.2)	3 (1.9)	0.091
Missing data	0 (0.0)	6 (3.9)	
aβ2GP1 IgA			
Titer - median [IQR]	4.0 [4.0–4.0]	4.0 [4.0–4.0]	0.55
Positive result	2 (2.1)	2 (1.3)	<0.001
Missing data	2 (2.1)	56 (36.4)	
aPS/PT IgG			
Titer - median [IQR]	6.0 [4.0–9.0]	5.0 [4.0–6.0]	0.007
Positive result	0 (0.0)	0 (0.0)	NA
Missing data	0 (0.0)	0 (0.0)	
aPS/PT IgM			
Titer - median [IQR]	12.0 [6.0–17.0]	8.0 [5.0–13.0]	0.013
Positive result	10 (10.5)	7 (4.5)	0.12
Missing data	0 (0.0)	0 (0.0)	
aPT IgG			
Titer - median [IQR]	4.0 [3.0–6.0]	5.0 [3.0–6.7]	0.12
Positive result	7 (7.4)	11 (7.1)	0.22
Missing data	0 (0.0)	39 (25.3)	
aPT IgM			
Titer - median [IQR]	2.0 [1.0–3. 0]	3.0 [1.9–4.0]	<0.001

Positive result	5 (5.3)	10 (6.5)	0.003
Missing data	0 (0.0)	39 (25.3)	
LA assay			
Positive result among tested patients	22/93 (23.7)	70/115 (60.9)	**<0.001**
Missing data	2 (2.1)	39 (23.2)	

Table 3. Demographic, clinical and biological characteristics of COVID-19 patients on admission according to positivity of lupus anticoagulant.

LA: lupus anticoagulant; IQR: interquartile range; BMI: body mass index; CV: cardiovascular; DVT: Deep venous thrombosis; PE: pulmonary embolism; ARDS: acute respiratory distress syndrome; SpO2: pulse oximetric saturation; K-APTT: kaolin activated partial thromboplastin time; PT: thromboplastin time; CRP: C-reactive protein; ICU: intensive care unit; VTE: venous thromboembolism.

*VTE is composed of DVT alone or PE alone or DVT+PE

COVID-19 patients	**LA negative (n=45)**	**LA positive (n=70)**	***p-value***
Male sex – n (%)	37 (82.2)	48 (68.6)	0.16
Age - years, median [IQR]	59.0 [45.0–74.0]	59.5 [52.0–72.0]	0.83
BMI - Kg/m², median [IQR]	27.3 [24.7–32.1]	27.2 [25.3–30.7]	0.86
Time from illness onset to hospital admission - days, median [IQR]	5.0 [3.0–9.0]	7.0 [4.0–8.0]	0.47
CV risk factors			
Hypertension – n (%)	18 (40.0)	33 (47.1)	0.58
Dyslipidemia – n (%)	9 (20.0)	16 (22.9)	0.44
Diabetes – n (%)	10 (22.2)	20 (28.6)	0.73
Chronic kidney disease – n (%)	5 (11.1)	9 (12.9)	1.00
Medical history			
Cancer – n (%)	6 (13.3)	7 (10.0)	0.80
Coronary heart disease – n (%)	22 (48.9)	42 (60)	0.58
Atrial Fibrillation – n (%)	4 (8.9)	4 (5.7)	0.81
Stroke – n (%)	3 (6.7)	4 (5.7)	1.00

Previous DVT – n (%)	1 (2.2)	1 (1.4)	0.50
Previous PE – n (%)	2 (4.4)	1 (1.4)	0.60
Clinical features			
Fever – n (%)	34 (75.6)	62 (88.6)	0.09
Headache – n (%)	16 (35.6)	24 (34.3)	0.94
Cough – n (%)	33 (73.3)	55 (78.6)	0.53
Productive cough – n (%)	10 (22.2)	5 (7.1)	**0.029**
Dyspnea – n (%)	25 (55.6)	48 (68.6)	0.13
Myalgia – n (%)	17 (37.8)	27 (38.6)	0.61
Diarrhea – n (%)	11 (24.4)	13 (18.6)	0.70
Pneumonia at CT-Scan – n (%)	30 (66.7)	50 (71.4)	0.58
ARDS – n (%)	15 (33.3)	21 (30.0)	0.50
Temperature - degrees Celsius, median [IQR]	38.0 [37.4–38.5]	38.4 [37.7–38.8]	0.09
SpO2 - %. median [IQR]	94.0 [89.3–96.0]	92.8 [89.1–95.0]	0.20
Biological parameters			
K-APTT - sec median [IQR]	31.0 [29.2–33.0]	31.9 [30.0–34.0]	0.52
PT ratio, median [IQR]	87.0 [80.8–99.0]	93.0 [84.8–102.3]	0.15
Fibrinogen - g/L, median [IQR]	5.3 [4.3–6.4]	6.0 [5.0–7.0]	**0.028**
D-dimer – ng/mL, median [IQR]	1503.0 [807.0–2658.0]	981.0 [634.8–1891.8]	0.15
Fibrin monomers - µg/mL, median	<7.0 [<7.0–<7.0]	<7.0 [<7.0–<7.0]	0.68

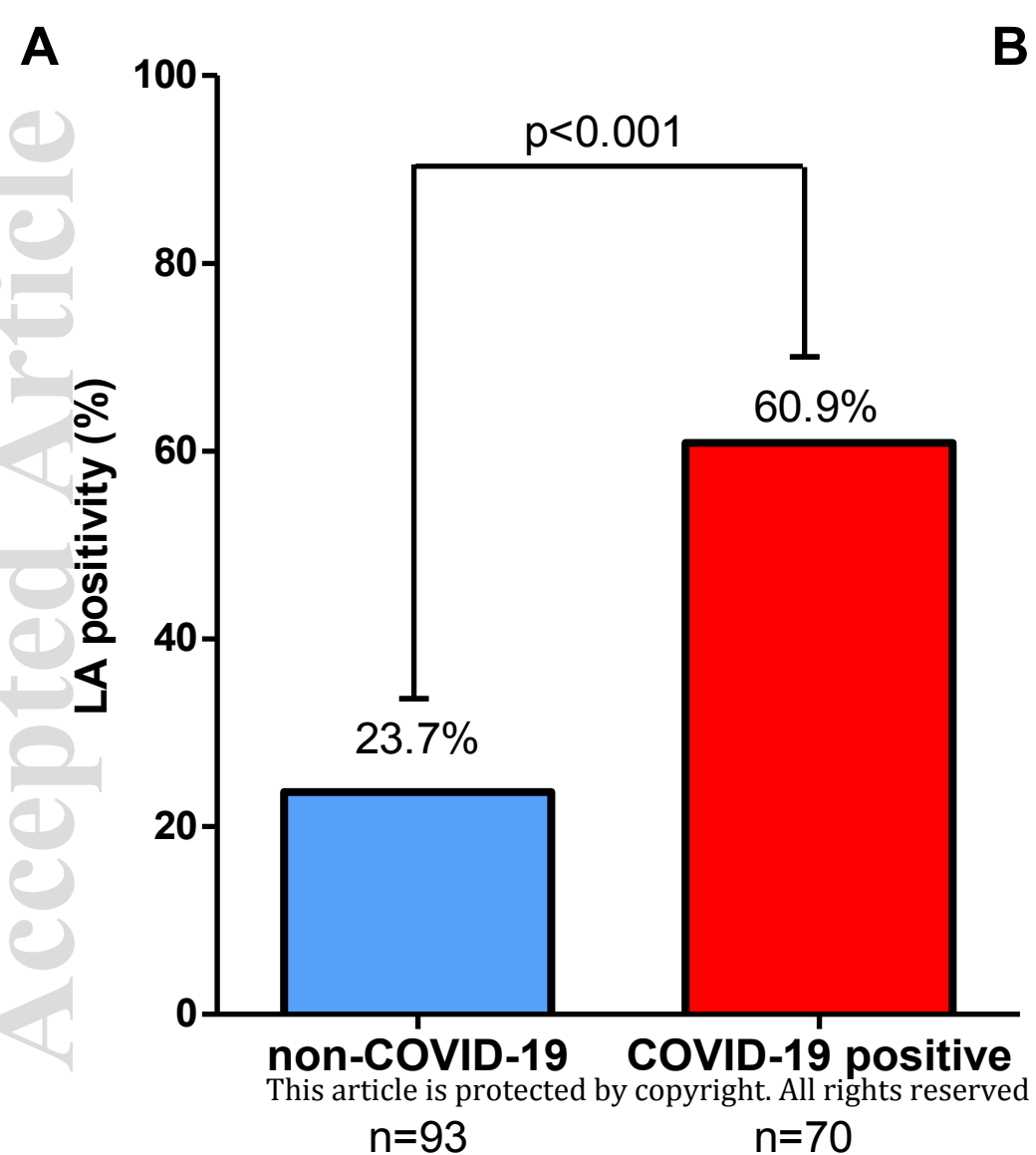
[IQR]			
Plasma creatinine - µmol/L, median [IQR]	80.5 [58.5–101.8]	79.5 [68.0–117.8]	0.34
CRP – mg/L, median [IQR]	91.8 [27.0–155.1]	115.5 [66.0–204.8]	**0.019**
Interleukin-6 – pg/mL, median [IQR]	36.0 [16.3–82.5]	28.70 [12.7–97.8]	0.98
Ferritin - µg/L, median [IQR]	909.0 [336.0–1718.0]	731.0 [270.5–1040.5]	0.27
Peak levels during hospitalization			
Plasma creatinine - µmol/L, median [IQR]	94.5 [74.8–140.5]	101.0 [79. 5–278.5]	0.24
CRP - mg/L, median [IQR]	148.2 [98.5–237.3]	170.95 [106.8–282.5]	0.27
Ferritin - µg/L, median [IQR]	1005.0 [336.0–2797.0]	931.50 [377.5–1578.2]	0.67
Fibrinogen - g/L, median [IQR]	7.12 [4.92–8.60]	7.00 [5.60– 9.11]	0.46
D-dimer – ng/mL, median [IQR]	3767.0 [1430.0–6528.5	3399.0 [832.8–9490.5]	0.86
Outcomes			
ICU patients – n (%)	25 (56.8)	43 (62.3)	0.70
ICU length stay – days median [IQR]	17.0 [5.0–25.0]	18.0 [5.0–30.0]	0.79
VTE* – n (%)	12 (26.8)	19 (27.1)	0.95
Symptomatic PE – n (%)	10 (22.2)	15 (21.4)	1.00
Symptomatic DVT – n (%)	5 (11.1)	6 (8.6)	0.89
Renal replacement therapy – n (%)	7 (15.6)	16 (22.9)	0.47
Discharged – n (%)	31 (68.9)	39 (55.7)	0.37

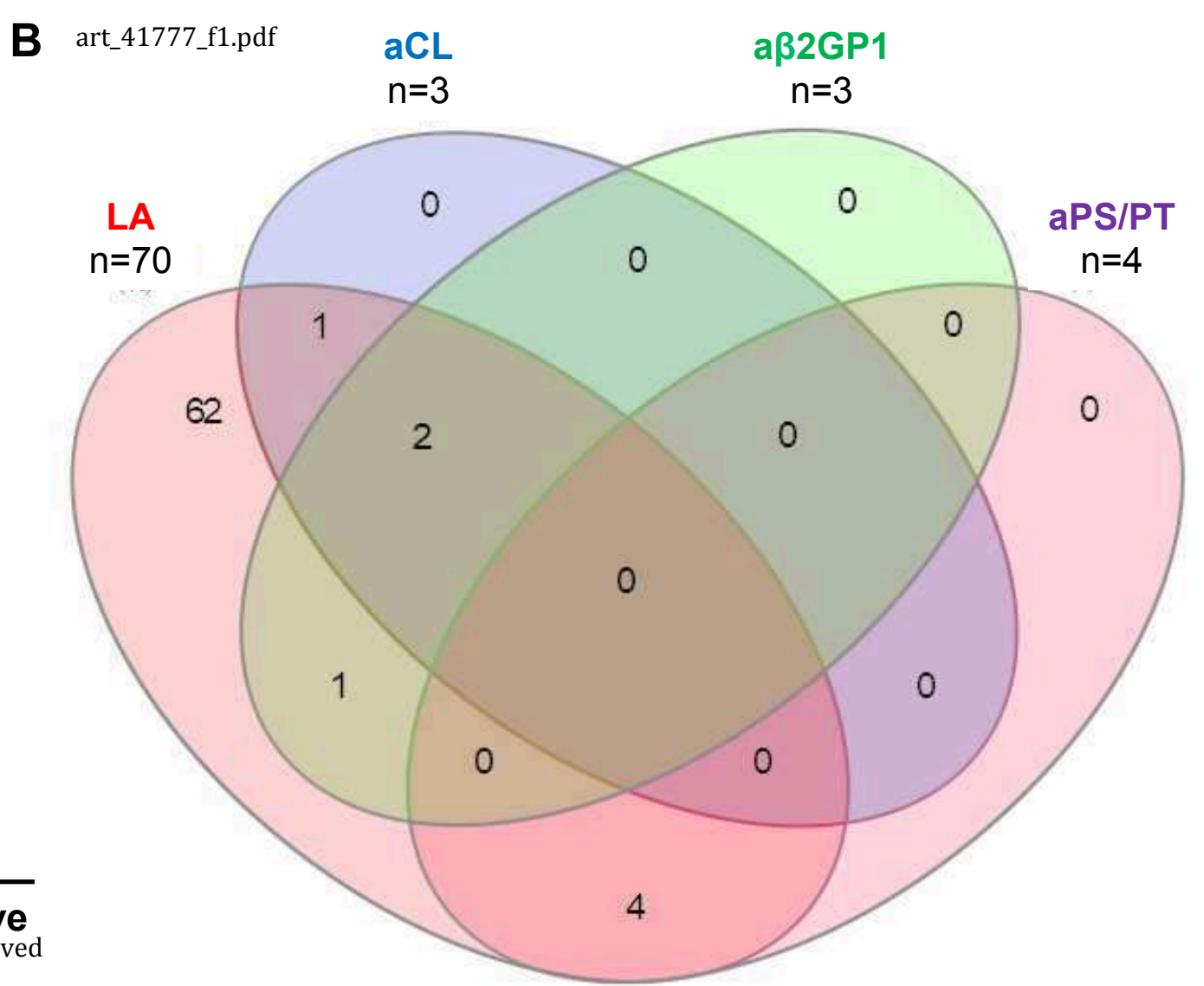
	Deceased – n (%)	7 (15.6)	17 (24.3)	0.42

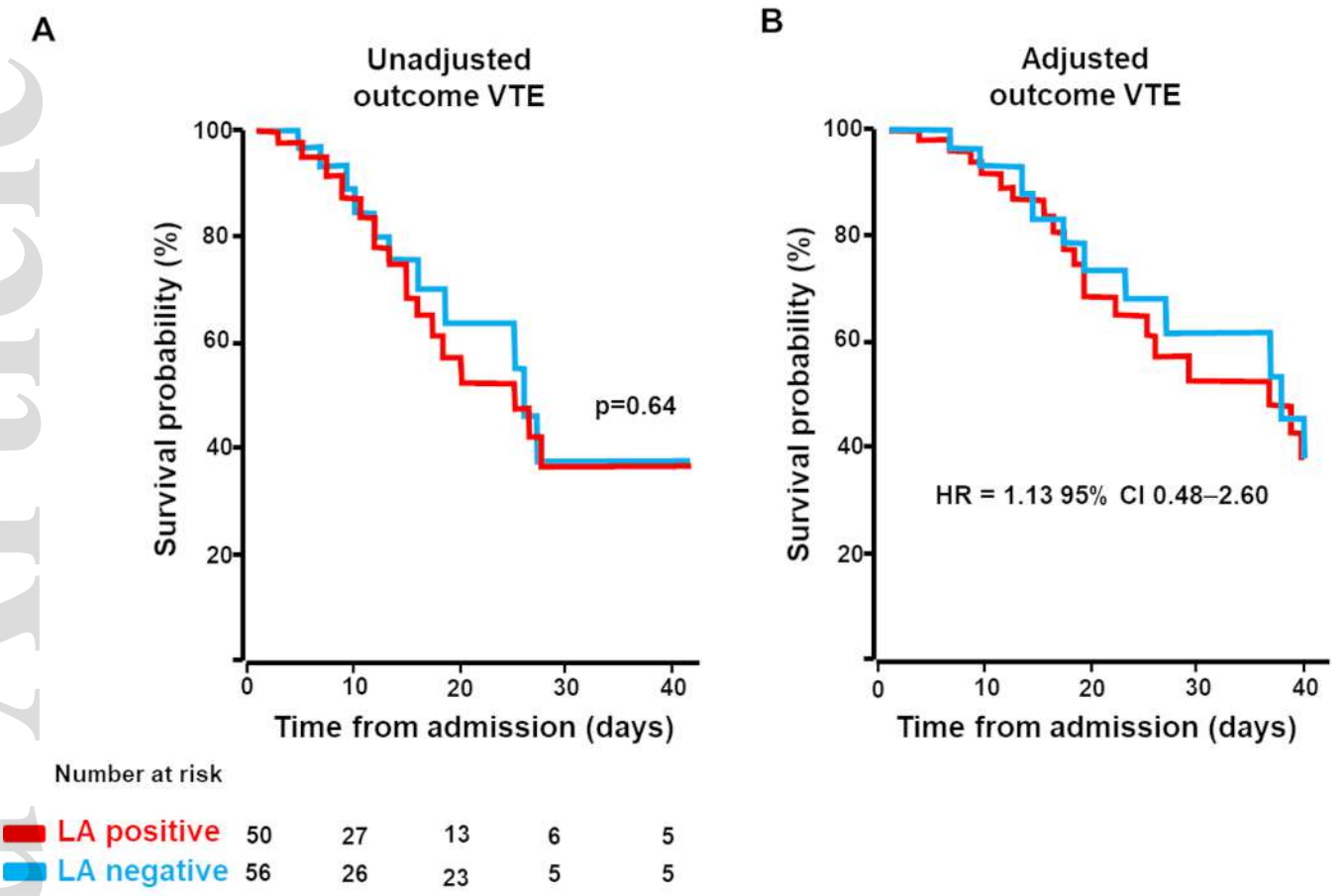
Table 4. Association between lupus anticoagulant positivity, venous thromboembolism and in-hospital mortality outcomes using logistic regression analysis.

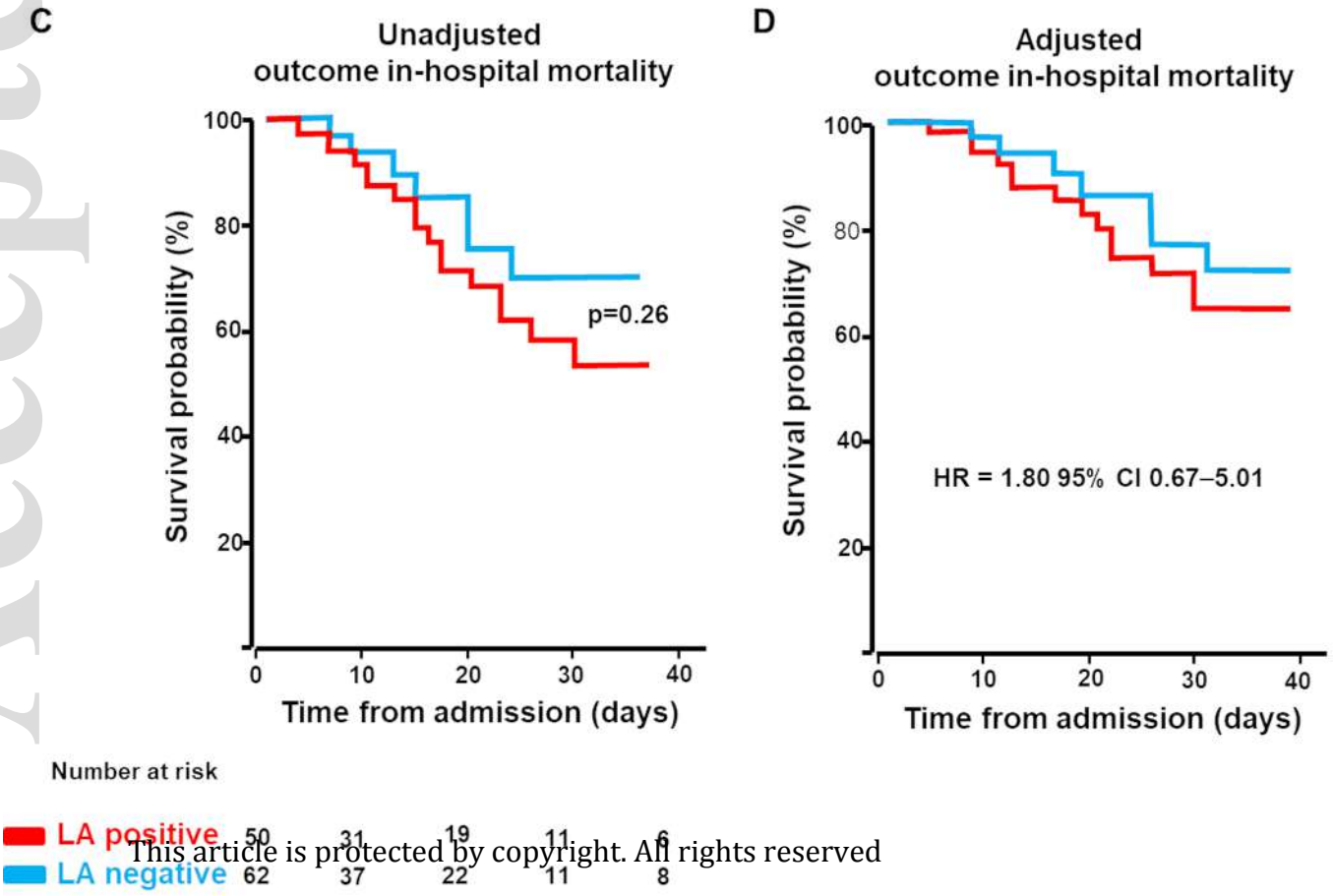
VTE: venous thromboembolism; OR: odd ratio; CI: confidence interval; LA: lupus anticoagulant, CRP: C-reactive protein.* dichotomized according to the median.

Univariate and multivariate logistic regression analysis to assess the risk of VTE			
		OR (univariate) 95% CI	**OR (multivariate) 95% CI**
LA	negative	-	-
	positive	1.02 (0.44–2.43, p=0.95)	1.01 (0.42–2.48, p=0.98)
CRP*	<104.2 mg/L	-	-
	>104.2 mg/L	1.70 (0.79–3.75, p=0.18)	1.67 (0.70–4.15, p=0.26)
Sex	female	-	-
	male	1.16 (0.50–2.84, p=0.74)	0.96 (0.35–2.84, p=0.93)
Age		1.01 (0.98–1.03, p=0.67)	1.00 (0.97–1.03, p=0.94)
Univariate and multivariate logistic regression analysis to assess the risk of in-hospit mortality			
		OR (univariate) 95% CI	**OR (multivariate) 95% CI**
LA	negative	-	-
	positive	1.80 (0.70–5.05, p=0.24)	1.69 (0.58–5.35, p=0.35)
CRP*	<104.2 mg/L	-	-
	>104.2 mg/L	**5.72 (2.17–18.03, p=0.001)**	**3.30 (1.12–11.32, p=0.039**)
Sex	female	-	-
	male	1.56 (0.62–4.51, p=0.37)	2.35 (0.61–11.95, p=0.25)
Age		**1.04 (1.01–1.08, p=0.004)**	**1.04 (1.01–1.09, p=0.030)**









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