CORRESPONDENCE

Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19

TO THE EDITOR: Patients with coronavirus disease 2019 (Covid-19) have a profound hypercoagulable state, and complicating venous thrombotic events are common.[1-3] Abnormalities in coagulation screening measures, including a prolonged activated partial-thromboplastin time (aPTT), have been reported in patients with Covid-19.[4] This finding could be seen as a reason to avoid the use of anticoagulation at both therapeutic and prophylactic doses.

A prolonged aPTT may indicate a clotting-factor deficiency or the presence of an inhibitor of coagulation that is either specific (e.g., antibody to factor VIII) or nonspecific (e.g., lupus anticoagulant). Lupus anticoagulant can affect in vitro tests of blood coagulation but typically is not associated with bleeding. As part of the antiphospholipid syndrome, lupus anticoagulant is associated with a thrombotic risk. We investigated the cause of prolonged aPTT in patients with Covid-19.

Blood specimens obtained from 216 patients who were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were received for coagulation screening, and 44 (20%) were found to have a prolonged aPTT. The specimens from 9 patients were excluded, and those from 35 patients were investigated further. (Details of the methods are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

A summary of the results is provided in Table 1. The median age was 57 years, and 24 patients were male. Pulmonary embolism was confirmed in 1 patient, and clinically suspected thrombosis was present in 1 patient. No clinically significant bleeding or arterial thromboses were reported.

No patients were found to have deficiencies in factor VIII or factor IX. In 5 patients, marginal reductions in factor XI were found that were unlikely to be of clinical significance. The factor XII level was 50 IU per deciliter or lower in 16 patients. Lupus anticoagulant assays were performed in 34 patients, and 31 (91%) were positive. The presence of lupus anticoagulant was indicated by two assays (dilute Russell's viper-venom time [DRVVT] and lupus anticoagulant–sensitive aPTT) in 18 of 34 patients (53%), by DRVVT alone in 7 (21%), and by lupus anticoagulant–sensitive aPTT alone in 6 (18%). All lupus anticoagulant–positive specimens had a prolonged aPTT with a 50:50 mix (i.e., in a sample made up of 50% patient plasma and 50% normal plasma).

In a historical control cohort of 540 specimens received for lupus anticoagulant testing, 43 (8%) had an aPTT of 30 seconds or longer, and 11 of the 43 (26%) were positive for lupus anticoagulant. The percentage of specimens that were positive for lupus anticoagulant was significantly higher among the patients with Covid-19 than in the control cohort ($P<0.001$) (see the Supplementary Appendix).

In our study, most patients with Covid-19 who were admitted to the hospital with a prolonged aPTT were positive for lupus anticoagulant (91%) and often had an associated factor XII deficiency. It is important to note that neither observation is associated with a bleeding tendency; factor XII is not required for hemostasis, and the presence of lupus anticoagulant, if persistent, can be associated with a thrombotic tendency within the antiphospholipid syndrome. Further study is required to determine the role, if any, of lupus anticoagulant in the pathogenesis of Covid-19 thrombosis.

Although we detected heparin in 28 of the 35 specimens, the DRVVT assay contains heparinase, which neutralizes any heparin effect that might lead to false positive detection of lupus anticoagulant. An association between lupus anticoagulants and acquired factor XII deficiency secondary to

Table 1. Demographic and Clinical Characteristics and Laboratory Findings in 35 Patients with Covid-19 and a Prolonged aPTT.*

Characteristic or Finding	Value in Patients (N=35)	Reference Range
Mean age (95% CI) — yr	56.6 (18.6–83.4)	—
Male sex — no. (%)	24 (69)	—
Taking oral anticoagulant at admission — no.	0	—
Thrombosis status — no. (%)		
Arterial	0	—
Venous, confirmed	1 (3)	—
Venous, suspected	1 (3)	—
Mean (95% CI) values on coagulation assay		
aPTT — sec	35.5 (30.0–54.6)	21–29
PT — sec	11.8 (10.2–14.1)	8.8–11.7
aPTT 50:50 — sec	32.6 (29.0–38.0)	21–29
Factor VIII level — IU/dl	199 (100–369)	52–153
Factor IX level — IU/dl	125 (62–205)	58–138
Factor XI level — IU/dl	81 (37–144)	58–148
Factor XII level — IU/dl	55 (26–100)	52–164
Anti–factor Xa heparin activity on heparin assay — no. (%)		
<0.05 IU/ml	7 (20)	—
0.05–0.19 IU/ml	7 (20)	—
0.20–0.40 IU/ml	14 (40)	—
0.41–0.50 IU/ml	5 (14)	—
>0.50 IU/ml	2 (6)	—
LA test result†		
Positive — no./total no. (%)	31/34 (91)	—
DRVVT — no.	7	—
LA-sensitive aPTT — no.	6	—
Both tests positive — no.	18	—
Negative — no./total no. (%)	3/34 (9)‡	—

* The abbreviation aPTT denotes activated partial-thromboplastin time, CI confidence interval, DRVVT dilute Russell's viper-venom time, LA lupus anticoagulant, and PT prothrombin time.
† Assays for lupus anticoagulant were performed with 34 of the specimens.
‡ The 3 specimens that were negative for lupus anticoagulant had levels of factor XII that were deemed sufficient to prolong the aPTT.

factor XII antibodies has been described previously. It is notable that the aPTT prolongation in the patients in our study was present despite substantial elevations in factor VIII, which shortens the aPTT.

We suggest that a prolonged aPTT should not be a barrier to the use of anticoagulation therapies in the prevention and treatment of venous thrombosis in patients with Covid-19. In our opinion, clinicians should not withhold use of anticoagulants for thrombosis while awaiting further investigation of a prolonged aPTT, nor should they withhold thrombolytic therapy in the face of a high-risk pulmonary embolism on the basis of a prolonged aPTT alone.

Louise Bowles, M.B., B.S.
Sean Platton, M.Sc.
Nada Yartey, M.Sc.
Minal Dave, M.Sc.
Kurtis Lee, M.Sc.
Daniel P. Hart, M.B., Ch.B., Ph.D.
Vickie MacDonald, M.B., B.Chir., Ph.D.
Laura Green, M.D.
Suthesh Sivapalaratnam, M.D., Ph.D.
K. John Pasi, M.B., Ch.B., Ph.D.
Peter MacCallum, M.D.

Royal London Hospital
London, United Kingdom
k.j.pasi@qmul.ac.uk

Drs. Bowles and Platton contributed equally to this letter.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on May 5, 2020, at NEJM.org.

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DOI: 10.1056/NEJMc2013656