

## RESEARCH LETTER

# A pilot study on the impact of congenital thrombophilia in COVID-19

## 1 | INTRODUCTION

Complex interactions between various processes underlie the strong propensity for thrombosis in COVID-19 patients, but the individual circumstances that predispose to these complications have to date not been clearly established.<sup>1</sup>

Congenital thrombophilia is associated with early and recurrent thrombosis. Both, severe thrombophilic defects (deficiency of antithrombin, protein C and protein S) and mild prothrombotic polymorphisms (mainly FV Leiden and prothrombin G20210A) significantly increase the risk of thrombosis, particularly if combined with additional factors.<sup>2</sup> Thus, inherited thrombophilia might contribute to the increased risk of thrombosis in COVID-19 patients as suggested in some reviews or editorials.<sup>3</sup> However, in the analysis of bibliographical sources obtained from PubMed (January 2021) with the terms 'COVID-19' and 'thrombosis', no single study contains information concerning congenital thrombophilia apart from the description of a palmar digital vein thrombosis in a patient who was heterozygous for FV Leiden.<sup>4</sup>

The aim of our study was to investigate the association between inherited thrombophilias and COVID-19 manifestations and severity.

## 2 | MATERIAL AND METHODS

### 2.1 | Patients

The study included two cohorts of patients:

*Cohort No. 1: Patients with congenital antithrombin deficiency.* We have established a large registry of 331 unrelated subjects with antithrombin deficiency and molecular characterization (1998-2019).<sup>5</sup> During March-April 2020, physicians in charge of these patients reviewed medical records and performed telephone interviews in search of cases with COVID-19. Two out of 253 revised cases from this cohort had a positive quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) for SARS-CoV-2. We report one additional case (P3), a Belgian patient with

known antithrombin deficiency and confirmed SARS-CoV-2 infection.

*Cohort No. 2: Patients with COVID-19.* A total of 155 consecutive patients with COVID-19 requiring hospital admission at Morales Meseguer and Reina Sofia University Hospitals (Murcia, Spain) during March-April 2020 were included in this cross-sectional study. In all patients, SARS-CoV-2 infection was assessed by qRT-PCR. Final follow-up date was July 14, 2020. None of these patients had a previous diagnosis of congenital thrombophilia. To identify genetic risk factors for thrombosis, we selected patients younger than 75 years old (y.o.) within this cohort (N = 87) for whole exome sequencing (WES).

### 2.2 | Genetic analysis

Genomic DNA was extracted from peripheral blood samples using QIAamp DNA Blood Mini kit (Qiagen-GmbH).

Whole exome sequencing analysis was performed by Beijing Novogene Bioinformatics Technology.

Sanger sequencing was done to validate genetic variants of interest.

Prediction of pathogenicity was done using *Mutation taster*.<sup>6</sup>

The prothrombin G20210A polymorphism was genotyped by commercial hydrolysis probes (C\_8726802\_20-Taqman).

### 2.3 | Data collection and statistical analysis

The clinical information collected included patient's demographics and comorbidities, at-admission pneumonia severity score (CURB-65), development of acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission, radiologically confirmed thrombosis and death.

Routine laboratory parameters during hospitalization comprised lactate-dehydrogenase (LDH), C-reactive protein (CRP), interleukin-6 (IL-6), complete hemogram, basic coagulation tests and D-dimer (DD).

**TABLE 1** Demographic, clinical and biological characteristics of patients with COVID-19 carrying congenital thrombophilias

ID	Gene	Gene variation	HGMD <sup>®</sup> / rs number	Age (y)	Sex	History of Thrombosis (age 1st event)	CURB-65 <sup>a</sup>	ARDS	ICU
Cohort No. 1: Patients with prior diagnosis of congenital antithrombin deficiency developing COVID-19									
P1	<i>SERPINC1</i>	Complete deletion	New	26	F	VTE (22 y)	Asymptomatic (SARS-CoV-2-positive qRT-PCR)		
P2	<i>SERPINC1</i>	c.391 C > T p.L131F	CM930050	52	M	ICD (50 y)	2	No	No
P3	<i>SERPINC1</i>	c.439A > G p.T147A	New	66	M	VTE (35 y)	3	Yes	Yes
Cohort No. 2: Patients with COVID-19 hospitalization harbouring thrombophilic defects detected by WES									
P4	<i>SERPINC1</i>	c.1246G > T p.A416S	CM910058	67	M	No	0	No	No
P5	<i>SERPINC1</i>	c.872G > A p.R291H	New	24	F	No	0	No	No
	<i>F5</i>	c.1601G > A p.R534Q	rs6025						
P6	<i>SERPINC1</i>	c.439A > G p.T147A	New	35	F	No	0	No	No
P7	<i>PROS1</i>	c.1595C > T p.T532I	New	38	F	ICD (33 y)	0	No	No
P8	<i>PROS1</i> <sup>e</sup>	c.122G > T p.R41L	CM163572	56	M	ICD (40 y)	2	Yes	Yes
P9	<i>PROS1</i>	c.1501T > C p.S501P	CM951058	62	M	No	0	Yes	Yes
P10	<i>PROC</i>	c.118C > T p.R40C	CM941178	70	M	No	2	Yes	Yes
P11	<i>PROC</i>	c.400 + 5G>T	CS910458	46	F	No	0	Yes	Yes
P12	<i>F5</i>	c.1601G > A p.R534Q	rs6025	67	M	No	0	No	No
Patients with COVID-19 hospitalization with prothrombin G20210A polymorphism detected by targeted genotyping									
P13	<i>F2</i>	c.*97G > A	rs1799963	53	M	No	0	No	No
P14	<i>F2</i>	c.*97G > A	rs1799963	66	F	No	1	No	No
Reference values									

Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; DD, D-dimer; F, Female; HGMD<sup>®</sup>, Human Gene Mutation Database; ICD, Ischemic cerebrovascular disease; ICU, intensive care unit; IL-6, interleukin-6; LDH, lactate-dehydrogenase; LMWH Proph, Prophylactic dose LMWH; LMWH Therap, Therapeutic dose LMWH; LMWH, Low molecular weight heparin; M, Male; OAC, oral anticoagulation; PE, pulmonary embolism; VTE, venous thromboembolism.

<sup>a</sup>CURB-65 score at hospital admission.

<sup>b</sup>International Society on Thrombosis and Haemostasis Score of disseminated intravascular coagulation.

<sup>c</sup>Antithrombotic therapy during COVID-19 admission with enoxaparin as LMWH was classified as standard prophylaxis (40 mg QD), high-risk prophylaxis (1 mg/Kg QD), and therapeutic regimens (1 mg/Kg BD).

<sup>d</sup>Venous thrombotic event during hospital admission due to COVID-19.

<sup>e</sup>P8 also had antiphospholipid antibodies.

<sup>f</sup>The patient refused the antithrombotic treatment during hospital stay.

COVID-19-associated coagulopathy was graded according to the disseminated intravascular coagulation (DIC) score of the International Society of Thrombosis and Hemostasis (ISTH).<sup>7</sup>

Comparison of COVID-19 patients with and without thrombophilia pooled from the two cohorts was performed by a matched case-control study (1-N, N = 4), on the values

CRP mg/L Peak	IL-6 ng/L Peak	LDH IU/L Peak	DD, mg/L		ISTH-DIC <sup>b</sup> Peak	Antithrombotic therapy during COVID-19 <sup>c</sup>	VTE COVID-19 (day) <sup>d</sup>	Death
			Basal	Peak				
						LMWH Therapy (previous OAC)	No	No
113.0	—	515	1.13	1.13	1	No <sup>f</sup> (previous OAC)	No	No
372.0	36.0	1714	4.0	19.90	2	LMWH Therapy (previous OAC)	No	No
24.0	4.6	662	1.10	1.78	1	LMWH Proph (standard dose)	No	No
4.0	—	294	0.21	0.69	0	No	No	No
127.0	16.8	548	0.98	1.37	1	No	No	No
6.0	—	343	1.03	1.11	1	LMWH Proph (previous OAC)	No	No
90.0	—	692	1.12	5.50	5	LMWH Therap (previous OAC)	No	No
282.0	105.7	1035	0.58	6.66	2	LMWH Proph (5 d) (high-risk dose)	No	Yes
111.0	90.8	799	1.00	5.34	4	LMWH Proph (high-risk dose)	No	No
285.0	201.0	1355	7.90	8.25	2	LMWH Proph (2 d) LMWH Therap	PE (d2)	No
4.0	—	359	0.67	1.18	1	LMWH Proph (standard dose)	No	No
19.0	13.6	504	0.38	0.42	0	LMWH Proph (standard dose)	No	No
55.3	5.6	368	1.28	2.22	1	No	No	No
0-1.0	0-4.4	208-378	0-500					

of age and Charlson comorbidity index (CCI). Conditional logistic regression analysis was performed to fit the model with multiple controls (Appendix S1).

Statistical analysis, sample size/power estimation, and case-control matching were performed by using Stata/IC16 (StataCorp, USA).

### 3 | RESULTS

#### 3.1 | Patients with congenital antithrombin deficiency

Three patients with known congenital antithrombin deficiency suffered from qRT-PCR confirmed SARS-CoV-2 infection (Table 1).

*P1* was a 26-year-old woman, healthcare worker, with prior history of venous thrombosis (22 y.o.), who had type I (quantitative) antithrombin deficiency caused by the complete deletion of the antithrombin coding gene in one allele. Long-term oral anticoagulation was started since the thrombotic event. In April 2020, institutional screening for SARS-CoV-2 by qRT-PCR revealed a positive result. She remained completely asymptomatic and did not require any medical care.

*P2* was a 52-year-old man with metabolic syndrome, advanced chronic kidney disease and prior history of ischemic stroke (50 y.o.). He had type II (qualitative) antithrombin deficiency caused by the heterozygous p. Leu131Phe (c.391 C > T) variant (CM930050; antithrombin Budapest 3). The patient was on long-term anticoagulation with vitamin K antagonists (VKA). In March 2020, he was admitted to the hospital with moderate COVID-19 pneumonia. Switching oral anticoagulation to filtration-rate-adjusted low molecular weight heparin (LMWH) was proposed, but rejected by the patient, who decided to stop all forms of anticoagulation. As no respiratory aggravation was evidenced, he was discharged after 24 days. Notably, no thrombotic events were recorded neither during admission nor during the first 60 days of ambulatory follow-up.

*P3* was a 66-year-old man from African origin, recipient of a renal transplant, with history of recurrent thrombosis. He was diagnosed with a mild type II antithrombin deficiency caused by p. Thr147Ala (c.439A > G) variant<sup>8</sup> and was on long-term anticoagulation with VKA. In April 2020, the patient was admitted to the ICU with severe COVID-19 requiring intubation. Oral anticoagulation was switched to filtration-rate-adjusted LMWH. On day 21, he was discharged from the ICU, and on day 38, he was transferred to a revalidation facility, where he completed his recovery. No thrombotic events were documented. Remarkably, the anti-FXa activity observed 7 days after COVID-19 diagnosis, at peak DD levels (19.9 mg/L), was very similar to that recorded in 2018 (69 and 56%, respectively).

#### 3.2 | Patients with COVID-19 who were found to have congenital thrombophilia

The search for severe thrombophilia by WES in 87 COVID-19 patients younger than 75 years was restricted to the genes

encoding antithrombin (*SERPINC1*), protein C (*PROC*) and protein S (*PROS1*) (Table 1). Variants were selected because they were described in HGMD<sup>®</sup>, had very low minor allele frequency (MAF) and/or had predictions of pathogenicity.

- a. Three heterozygous variants in *SERPINC1* were detected in three patients, all had moderate clinical manifestations associated with COVID-19 but did not require ICU admission nor developed symptomatic thrombosis:
  - The p.Ala416Ser (c.1246G > T) variant (*P4*), which is a relatively frequent variant in Caucasians (rs121909548, MAF:0.00107 ExAC). It causes a type II variant (Antithrombin Cambridge II; CM910058) that moderately increases the risk of thrombosis.<sup>9</sup>
  - The p.Arg291His (c.872G > A) variant (*P5*) (rs377588972, MAF:0.0000157 ExAC). Not described in HGMD<sup>®</sup> (Figure S1A), it might be a neutral polymorphism according to in silico predictions, and therefore, the mutation was not considered to cause thrombophilia. *P5* was also heterozygous for the FV Leiden polymorphism.
  - The p.Thr147Ala (c.439A > G) variant (*P6*), the same type II mutation that was identified in *P3* from the first cohort.
- b. Three heterozygous variants in *PROS1* were detected in three patients, who displayed a quite heterogeneous clinical evolution during hospitalization, but none developed symptomatic thrombotic events:
  - The p.Thr532Ile (c.1595C > T) variant (*P7*), neither found in the genetic databases ExAC nor in 1000 Genomes, was identified. It affects a conserved residue that forms an N-glycosylation sequon (Figure S1B) and was considered a disease-causing variant. *P7* was a 38-year-old woman who had an ischemic stroke when she was 33 y.o. and continued on VKA since then. COVID-19 only caused mild clinical manifestations.
  - The p.Arg41Leu (c.122G > T) variant (*P8*), causing a type II deficiency previously described in other patients with protein S deficiency (CM163572).<sup>10</sup> *P8* was a 56-year-old man with ischemic stroke history (40 y.o.) and antiphospholipid syndrome. Since then, he was under VKA. The clinical evolution of COVID-19 disease was poor, with ARDS requiring prolonged ICU admission.
  - The p.Ser501Pro (c.1501T > C) variant (*P9*). This is a frequent mutation associated with type III deficiency removing an N-glycosylation sequon (Protein S Heerlen, CM951058, MAF:0.00292 ExAC) that significantly increases the risk of venous thrombosis.<sup>11</sup> *P9* was a 62-year-old man who was admitted due to bilateral COVID-19 pneumonia. He had an unfavourable evolution and finally deceased from ARDS.

**TABLE 2** Case-control analysis of clinical and biological features of hospitalized COVID-19 patients with and without thrombophilia

	Case group ( $C_1$ )		Control group ( $C_0$ )	Conditional logistic regression <sup>b</sup>	
	Thrombophilia		No thrombophilia,	OR <sub>10</sub> (95% CI)	P value
	(N = 13) <sup>a</sup>		Matched (N = 52)		
<b>Demographics</b>					
Sex (females), %		38.5% (N = 5)	42.3% (N = 22)	0.85 (0.24-3.01)	.80
Age (y.o.), median (IQR)		56 (42-66.5)	55.5 (44.25-64.75)	1.08 (0.79-1.49)	.63
<b>Comorbidities</b>					
Charlson comorbidity index, median (IQR)		2 (0-3)	1 (0.25-2.75)	1.21 (0.81-1.83)	.35
History of thrombosis, %		30.8% (N = 4)	3.8% (N = 2)	<b>13.75 (1.51-125.20)</b>	<b>.02</b>
Chronic OAC, %		30.8% (N = 4)	3.8% (N = 2)	<b>13.75 (1.51-125.20)</b>	<b>.02</b>
<b>Antithrombotic therapy</b>					
None, %		30.8% (N = 4)	15.4% (N = 8)	2.73 (0.62-12.03)	.18
Standard dose LMWH, %		38.5% (N = 5)	75.0% (N = 39)	<b>0.19 (0.05-0.77)</b>	<b>.02</b>
Escalated/Therapeutic LMWH or OAC, %		30.8% (N = 4)	9.6% (N = 6)	4.11 (0.89-19.00)	.07
<b>At-admission severity</b>					
CURB-65 $\geq 2$ , %		30.8% (N = 4)	23.1% (N = 12)	1.55 (0.37-6.45)	.55
<b>Clinical outcomes</b>					
ARDS, %		38.5% (N = 5)	25.0% (N = 23)	2.42 (0.71-8.32)	.16
ICU admission, %		38.5% (N = 5)	23.1% (N = 12)	2.11 (0.57-7.85)	.27
Thrombosis, %		7.7% (N = 1)	1.9% (N = 1)	4.00 (0.25-63.95)	.33
Death, %		7.7% (N = 1)	1.9% (N = 1)	4.00 (0.25-63.95)	.33
<b>Laboratory data,</b>					
<i>median (IQR)</i>	<b>Normal range</b>				
CRP (Peak), mg/L	0-1.0 mg/L	93.1 (21.4-204.5)	76.6 (29.7-161.5)	1.04 (0.96-1.13)	.32
IL-6 (Peak), ng/L	0-4.4 ng/L	16.8 (5.6-105.7)	12.6 (4.4-35.7)	1.000 (0.993-1.004)	.51
LDH (Peak), IU/L	208-378 IU/L	531.6 (383.7-949.3)	539.6 (428.4-693.6)	1.001 (0.999-1.003)	.27
PT (Peak), %	75%-100%	83.0 (81.0-88.0)	86 (76.25-96.5)	0.98 (0.95-1.02)	.32
APTT ratio (Peak)	0.8-1.3	1.06 (0.95-1.19)	1.05 (0.97-1.14)	1.19 (0.07-21.18)	.91
Fibrinogen (Peak), mg/dL	150-400 mg/dL	488.5 (419.5-612.8)	484 (370.5-614.0)	1.00 (0.997-1.003)	.84
Platelet count (Peak), $\times 10^9/L$	150-450 $\times 10^9/L$	236.0 (171.8-268.8)	214.5 (153.5-259.3)	1.000 (1.000-1.000)	.68
<b>D-dimer</b>					
Basal, mg/L	0-0.5 mg/L	1.03 (0.62-1.21)	0.56 (0.43-0.79)	<b>2.03 (1.00-4.13)</b>	<b>.05</b>
Peak, mg/L	$\times 10^9/L$	1.78 (1.11-6.08)	1.00 (0.61-1.89)	<b>1.76 (1.03-3.02)</b>	<b>.039</b>
<b>ISTH-DIC score</b>					
Basal	0	1 (0-1.5)	0 (0-1)	1.55 (0.87-2.76)	.14
Peak		1 (1-2)	1 (0-2)	1.40 (0.88-2.23)	.15

Abbreviations: APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; DD, D-dimer; ICU, intensive care unit; IL-6, interleukin-6; ISTH-DIC, International Society of Thrombosis and Hemostasis-Disseminated Intravascular Coagulation Score; LDH, lactate-dehydrogenase; LMWH, Low molecular weight heparin; OAC, oral anticoagulation; PT, prothrombin time.

<sup>a</sup>Patient 1 was excluded for this analysis due to mild SARS-CoV-2 infection not requiring hospitalization.

<sup>b</sup>Results from conditional logistic regression for matched case-control analysis: odds ratios of cases ( $C_1$ ) versus controls ( $C_0$ ) (OR<sub>10</sub>), 95% confidence intervals (95% CI) and P values are shown. OR<sub>10</sub> > 1 favours cases over controls. Significant comparisons ( $P \leq .05$ ) are highlighted in bold.

c. Two heterozygous variants in *PROC* gene were detected in two patients, both with a serious clinical course during

COVID-19, requiring ICU admission, and one of them developing a pulmonary embolism:

- The p.Arg40Cys (c.118C > T) variant (*P10*), which has already been described in protein C deficiency (CM941178).<sup>12</sup>
- The splicing mutation c.400 + 5G>T (*P11*), which has previously been described (CS910458) in other patients with protein C type I deficiency.<sup>13</sup> *P11* was a 46-year-old woman with no previous history of thrombosis. She was admitted due to moderate COVID-19 pneumonia and rapidly progressed to ARDS requiring ICU admission. Early high DD levels suggested a thrombotic complication. Computed tomography-angiogram on day 2 showed acute bilateral pulmonary embolism. At that moment, the prophylactic dose of LMWH received at admission was changed to therapeutic dose LMWH and continued during 18 days of hospitalization, which was then switched to VKA.

Additionally, four patients carried mild prothrombotic polymorphisms, all heterozygous (Table 1): two FV Leiden (rs6025, c.1601A > G) (*P5* and *P12*, the first one also carrying a *SERPINC1* variant), and two prothrombin G20210A (rs1799963, c.\*97G > A) (*P13* and *P14*). The frequency of these polymorphisms in our cohort was 4.6% (95% CI: 1.3–11.4%), similar to that expected in Spanish general population (5.7%).<sup>14</sup> The clinical evolution of all these cases was quite mild. No symptomatic thrombotic events were registered in these cases either, despite two of them did not receive any form of thromboprophylaxis.

### 3.3 | Matched case-control analysis of patients with congenital thrombophilia

Cases with COVID-19 and thrombophilia requiring hospitalization pooled from the two cohorts ( $N = 13$ , *P1* was excluded due to mild infection not requiring admission) were individually matched with 4 controls without thrombophilia from cohort No. 2 ( $N = 52$ ) on the values of age and CCI index.

Table 2 summarizes the case-control analysis of clinical and laboratory data. No significant differences in markers of inflammation or cell lysis (CRP, IL-6, LDH) nor in clinical outcomes were observed between both groups. Nevertheless, despite low sample size, patients with thrombophilia had significantly higher baseline and peak levels of DD than those without an identifiable inherited prothrombotic state.

## 4 | DISCUSSION

Thrombosis is a complex disease. There are many examples of the synergistic action of genetic and environmental factors affecting the hemostatic system.<sup>2</sup> The explanation for the strong propensity for thrombosis in COVID-19 patients

is certainly not single-factored. In this context, it seemed interesting to investigate the contribution of congenital thrombophilia to COVID-19 course. This is the first study on the role of congenital thrombophilia in SARS-CoV-2 infection.

The pooled analysis revealed higher DD levels in the presence than in the absence of inherited thrombophilia. The plausibility of this finding might be supported by the well-known fact that subjects with congenital thrombophilia have an impaired control of thrombin generation that may be exacerbated in stress situations.<sup>15</sup>

By using two different strategies, we identified a relatively high number of patients with both mild and severe thrombophilia who suffered from COVID-19. Nevertheless, the small sample size and the reduced number of events preclude additional strong conclusions. Indeed, in our cohort, with a significance level ( $\alpha$ ) of .05, the estimated statistical power to identify a relevant difference on the rate of vascular events ( $\pm 5\%$ ) among both groups is low (20.8%). Notwithstanding, it is remarkable that one of the two patients who developed a thrombotic event was identified as a carrier of protein C deficiency by WES. This finding suggests that severe thrombophilia might increase the risk of thrombosis in COVID-19 patients, but further studies on the search of thrombophilic defects in larger cohorts (ie,  $N \geq 300$ ) would relevantly increase the statistical power ( $\geq 60\%$ ) to clarify this premise.

Finally, it is also notable that most patients with severe thrombophilia did not develop symptomatic thrombotic events during COVID-19, including five subjects who had previous thromboses. Although stronger evidence is required, the reason why the hypercoagulable state that caused the aforementioned vascular events did not facilitate the development of new thrombotic episodes during SARS-CoV-2 infection might be related to the fact that these patients were already treated with anticoagulant drugs before the infection or at the very early stages of the disease. In line with this, previous findings support that long-term anticoagulation at admission appears to protect COVID-19 patients from developing thrombosis.<sup>1</sup>

In conclusion, the results of this pivotal study, which is the first addressing the role of congenital thrombophilia in COVID-19, encourage further research to clarify the biological and clinical consequences of inherited thrombophilic states in SARS-CoV-2 infection, as well as to guide the optimal approach to manage anticoagulation in these cases.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

ME M-B, C B-P, B M-B, R C, A M and J P recruited the samples and performed experimental analysis. ME M-B and C B-P statistically analyzed all data. C O, S H, S M, N R, E B, JM G-V, MT H and K J recruited patients and clinical outcomes and designed the research. V V, J C and ML L designed the research and wrote the paper. All authors read and approved the final manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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