

Hypercoagulation and Antithrombotic Treatment in Coronavirus 2019: A New Challenge

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Abstract

The novel coronavirus 2019 (COVID-19) is clinically characterized by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for a high number of patients needing mechanical ventilation or intensive care units treatment and for the elevated mortality risk. A link between COVID-19 and multiorgan failure may be dependent on the fact that most COVID-19 patients are complicated by pneumonia, which is known to be associated with early changes of clotting and platelet activation and artery dysfunction; these changes may implicate in thrombotic-related events such as myocardial infarction and ischemic stroke. Recent data showed that myocardial injury compatible with coronary ischemia may be detectable in SARS-CoV-2 patients and laboratory data exploring clotting system suggest the presence of a hypercoagulation state. Thus, we performed a systematic review of COVID-19 literature reporting measures of clotting activation to assess if changes are detectable in this setting and their relationship with clinical severity. Furthermore, we discussed the biologic plausibility of the thrombotic risk in SARS-CoV-2 and the potential use of an antithrombotic treatment.

Keywords

- ▶ thrombosis
- ▶ hypercoagulability
- ▶ infectious diseases

Introduction

The novel coronavirus 2019 (COVID-19) is being rapidly diffused worldwide from China to Europe and now in United States, so creating serious medical and social issue to contain its potentially dangerous complications. COVID-19 is, in fact, complicated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for a high number of patients needing mechanical ventilation or intensive care units (ICU) treatment and for the elevated mortality risk. However, lung damage is not the only reason for the high death risk as other organs such as heart and kidney may be seriously damaged and favor poor survival. This entails that SARS-CoV-2 is a multiorgan disease with mechanisms such as, for example, systemic inflammation which may precipitate organ failure. A link between COVID-19 and multiorgan failure may be

dependent on the fact that almost all patients hospitalized for COVID-19 disease are complicated by pneumonia, which is known to be associated with systemic inflammation and thrombotic-related events such as myocardial infarction (MI) and ischemic stroke.^{1,2} Accordingly, previous studies reported that patients with pneumonia display changes of clotting and platelet activation,^{3,4} which occur during the early phase of disease and may precipitate systemic or local thrombosis. It is arguable, therefore, that SARS-CoV-2 patients may experience thrombotic events in coronary and cerebral trees or in other circulatory districts including lung and kidney. Clinical data so far reported are suggestive of vascular complications occurring in the coronary circulation while the involvement of other districts is still unclear.^{5–7} Conversely, there are many studies reporting that the behavior of clotting variables and platelet count in COVID-19 patients is suggestive of a hypercoagulation

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state. As clinical presentation and complications of COVID-19 is wide, in this review we sought to determine if changes of clotting variables are dependent on the severity of the disease. To this purpose, we performed a systematic review of the SARS-CoV-2 literature reporting measures of clotting activation to assess if changes are detectable in this setting and their relationship with clinical severity. Thus, clotting variables have been examined in patients divided according to the severity of SARS-CoV-2. Furthermore, we discussed the biologic plausibility of the thrombotic risk in SARS-CoV-2 and the potential use of an antithrombotic treatment.

Eligibility Criteria

Types of studies: clinical studies in patients with COVID-19 infection in humans that assessed the following laboratory parameters: d-dimer, platelet counts, prothrombin time, activated partial thromboplastin time, alanine aminotransferase, and aspartate aminotransferase. The studies included in this systematic review had to show COVID-19 infection with severe disease and control group.

No publication date or publication status restrictions were imposed. Only publications written in English language were included in this systematic review.

Information Sources

The studies were identified by searching electronic databases. This search was applied to PubMed, ISI Web of Science, SCOPUS, and Cochrane database. The last search was run on March 28, 2020. Reference lists of all studies included in the present systematic review were screened for potential additional eligible studies.

Search

Two investigators (D.P. and L.L.) independently searched in the electronic databases combining the following text terms and MeSH terms: (("coronavirus" [MeSH Terms] OR "coronavirus" [All Fields]) AND ("COVID-19" [All Fields] OR "COVID-2019" [All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR ("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020 [PDAT]))) AND "humans"[MeSH Terms].

Study Selection

Two authors (L.L. and D.P.) independently reviewed titles and abstracts generated by search. Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our systematic review. For potentially eligible studies or if the relevance of an article could not be excluded with certitude, we procured the full text. Disagreements were resolved by discussion between L.L. and D.P.; if no agreement reached, a third author (F.V.) decided.

Studies not including a control group and animal studies were excluded. Case reports, editorials, commentaries, letters, review articles, and guidelines were also excluded from the analysis. ►Fig. 1 reports the PRISMA diagram.

Clotting Changes in Coronavirus 2019

We analyzed some variables of variable of clotting and fibrinolysis activation along with platelet count in all COVID-19 population (►Table 1) and in patients according to disease severity (►Table 2). The latter was defined as acute respiratory distress syndrome (ARDS), need of mechanical ventilation/ICU treatment, nonsurvivor patients, or severe pneumonia.⁸ Our analysis considered globally nine reports.^{9–17}

D-Dimer

D-dimers values were reported in all (9–12 and 14–17) but one study¹³ and definition of increased values in six out of eight studies.^{9,10,12,15–17} Among the six studies, one¹⁷ reported only the percentage of patients with increased values of D-dimer while the other reported also the absolute values. The percentage of patients with elevated D-dimer was almost wide with high values ranging from 14 to 46%. Analysis of D-dimer according to disease severity was reported in six studies (►Table 2), and all consistently showed increased values of D-dimer in patients with severe versus nonsevere disease; significance was shown in all but two studies.^{14,17} These data are in accordance with a recent meta-analysis showing enhanced D-dimer according to disease severity.¹⁸

Platelet Count

Platelet count data were extrapolated from seven studies,^{9–13,16,17} of which six^{9–12,16,17} reported changes in terms of low platelet count. Reduced platelet count was detected from 5 to 18% of the entire population; platelet count was roughly around 100,000 μL and in some cases below this value. The impact of disease severity on platelet count was reported in five studies^{11–13,16,17} with a significant reduction in nonsurvivors compared with survivors; however, a trend toward a reduction of platelet count in patients with severe disease was reported in all studies, which is in accordance with a previous report showing that thrombocytopenia is more frequent in patients with severe disease.¹⁹

Prothrombin Time

We extrapolated data from 8 (9–16) studies, but only 5^{9,10,12,15,16} reported changes in terms of PT prolongation, which was detected from 2 to 11% of the entire population. The rate of PT prolongation was not reported in all, but one study⁹ where a small prolongation can be appreciated. Conversely, analysis of PT according to disease severity was done in six studies,^{11–16} where PT was reported be longer in patients with severe compared with those without severe disease; prolongation of PT was more evident in nonsurvivors with values exceeding 15 to 16 seconds.

Activated Partial Thromboplastin Time

We extrapolated data from six studies (9–11 and 14–16) but only three^{9,10,16} reported changes in terms of aPTT prolongation, which was detected from 6 to 26% of the entire population. The rate of aPTT prolongation was unclear with only one study showing a modest increase. Five studies reported the behavior

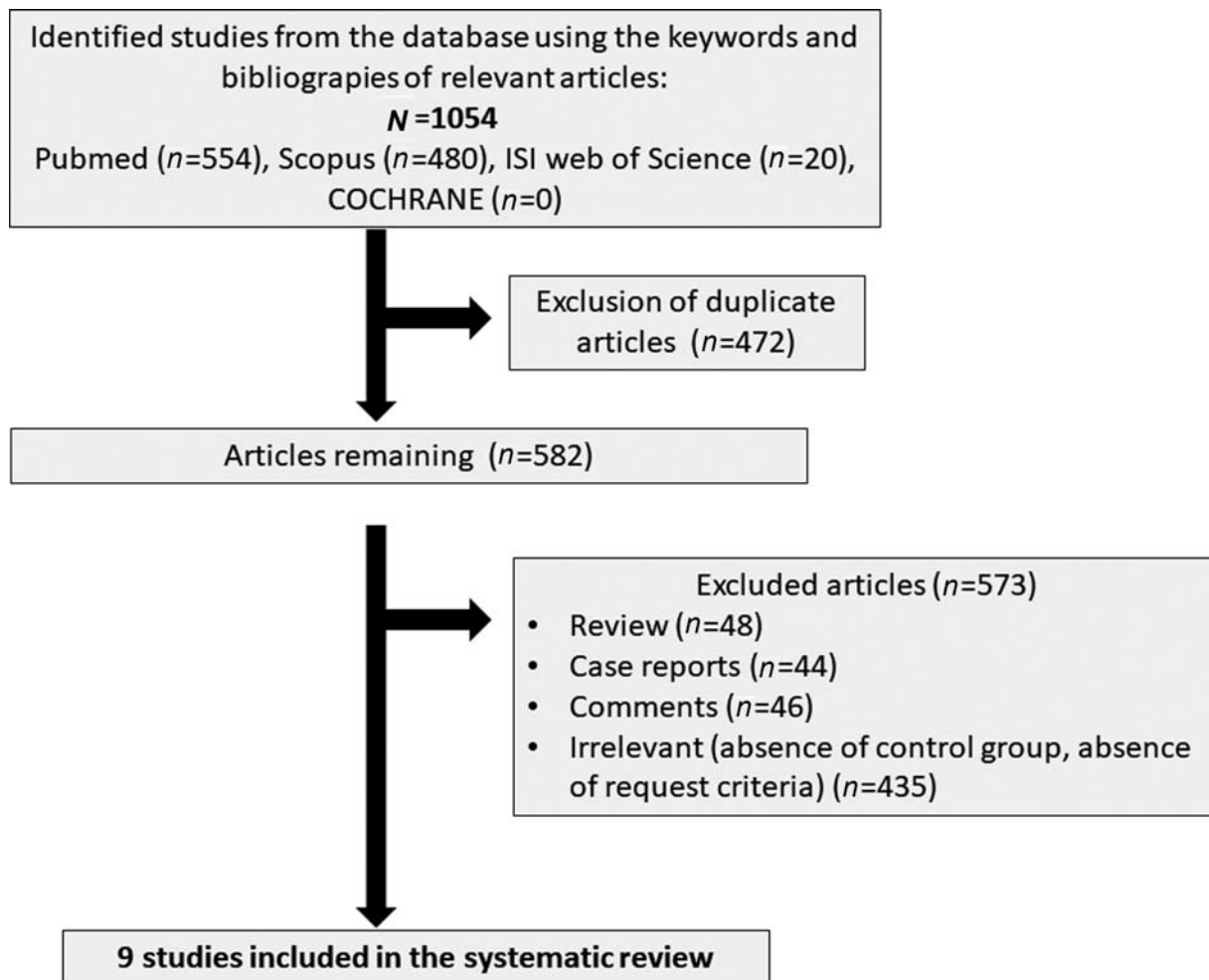


Fig. 1 Flow chart of the studies included in the systematic review.

of aPTT according to the disease severity.^{11,12,14–16} Data are difficult to interpret as prolongation as well as shortening aPTT were reported in patients with severe versus nonsevere disease; prolongation of aPTT seemed to occur in nonsurvivors, but data need to be confirmed.

Liver Failure in Coronavirus 2019

As the prolongation of PT and aPTT could be dependent upon impaired liver biosynthesis and/or coagulopathy,²⁰ we analyzed if COVID-19 patients showed changes in transaminases.

We found six studies^{9–12,16,17} reporting alanine transaminase (ALT) serum values: changes in terms of values exceeding normal range was reported in four,^{9,10,12,17} which showed ALT increase in 12 to 31% of patients. The rate of ALT increase was unclear as only one study showed absolute values, which were approximately twofold the normal range. Four studies^{11,12,16,17} reported ALT values according to the disease severity, and only two showed a modest increase in case of ARDS or poor survival.^{12,16}

We found five studies^{9–11,16,17} reporting aspartate aminotransferase (AST) serum values; changes in terms of values exceeding normal range were reported in four,^{9–11,17} which showed AST increase in 18 to 62% of the entire population and in one study reporting absolute values, the AST increase was

modest. Three studies^{11,16,17} reported AST values according to the disease severity and only two^{11,16} showed a modest but significant increase (► **Table 2**). Together, these data show that in COVID-19 liver failure is almost modest and, thereby, does not seem to have an impact on clotting changes.

Biological Plausibility of Hypercoagulation in Coronavirus 2019

Hospitalized patients affected by COVID-19 are frequently complicated by serious pneumonia, which may occur, from roughly 80 to 100% of cases.^{11,21,22} Considering that respiratory tract infections are associated with an increased risk of vascular disease, including artery and venous thrombosis, it is not surprising that SARS-CoV-2 may be complicated by clotting changes that ultimately lead to thrombosis. Among artery thrombosis complications patients with pneumonia may experience MI in approximately 10% of cases, and less frequently, ischemic stroke.³ In SARS-CoV-2 patients, detailed description of cardiovascular complications is still lacking even if in some reports it is possible to appreciate data indicating the occurrence of myocardial damage as depicted by enhanced levels of troponin associated or less with EKG changes compatible with MI.^{6,7} Conversely, no data have been so far reported regarding

Table 1 Coagulation and liver parameters in patients with coronavirus 2019 infection

	Yang et al ⁹	Chen et al ¹⁰	Huang et al ¹¹	Zhou et al ¹²	Yang et al ¹³	Han et al ¹⁴	Tang et al ¹⁵	Wu et al ¹⁶	Guan et al ¹⁷
Number of patients	149	99	41	191	52	94	183	201	1,099
D-dimer	0.22 (0.28)	0.9 (0.5–2.8)	0.5 (0.3–1.3)	0.8 (0.4–3.2)		10.36 ± 25.31	0.66 (0.38–1.50)	0.61 (0.35–1.28)	
Reference range and unit	<0.55 mg/L	0.0–1.5 µg/L	mg/L	≤0.5 µg/L		mg/L	<0.50 µg/mL	0–1.5 µg/mL	mg/L
Increased	21 (14.09%), 0.57 ± 0.01	36 (36%)		>1 µg/L; 72/172 (42%)			21 (11.47%)	44 (23.3%)	260/560 (46.4%) (>0.5 mg/L)
Platelet count	174.5 (78.25)	213.15 (79.1)	164.5 (131.5–263.0)	206.0 (155.0–262.0)	180.62 (mean)			180.00 (137.00–241.50)	168,000 (132,000–207,000)
Reference range and unit	125–350 × 10 ⁹ /L	125–350 × 10 ⁹ /L	× 10 ⁹ /L	× 10 ⁹ /L	× 10 ⁹ /L		× 10 ⁹ /L	125–350 × 10 ⁹ /mL	× 10 ⁹ /L
Decreased	20 (13.42%) 107 ± 12.73	12 (12%)	<100 = 2/40 (5%)	<100 = 13 (7%)			<100 = 12 (6.56%)	37 (18.8%)	315/869 (36.2%)
Prothrombin time	12.20 ± 1.53	11.3 (1.9)	11.1 (10.1–12.4)	11.6 (10.6–13.0)	12.13 (mean)	12.43 ± 1.00	13.7 (13.1–14.6)	11.10 (10.20–11.90)	
Reference range and unit	10–13.5 seconds	10.5–13.5 seconds	sec	<16 seconds	sec	sec	11.5–14.5 seconds	10.5–13.5 seconds	
Prolonged	17 (11.41%), 13.65 ± 0.07	5 (5%)		11/182 (6%) ^a			15 (8.2%)	4 (2.1%)	
Activated partial thromboplastin time	33.29 ± 4.98	27.3 (10.2)	27.0 (24.2–34.1)			29.01 ± 2.93	41.6 (36.9–44.5)	28.70 (23.30–33.70)	
Reference range and unit	22–36 seconds	21.0–37.0 seconds	sec			sec	29.0–42.0 seconds	21–37 seconds	
Prolonged	40 (26.85%), 37 ± 0.99	6 (6%)		37 (19%) ^a				19 (9.7%)	
Alanine aminotransferase (U/L)	20 ± 20.5	39.0 (22.0–53.0)	32.0 (21.0–50.0)	30.0 (17.0–46.0)				31.00 (19.75–47.00)	
Reference range and unit	(U/L); 0–64	(U/L); 9.0–50.0	U/L	U/L				9–50 U/L	U/L
Increased	18 (12.08%), 97.00 ± 42.52	28 (28%)		59/189 (31%) (>40)					158/741 (21.3%)
Aspartate aminotransferase (U/L)	23 ± 15.75	34.0	34.0 (26.0–48.0)					33.00 (26.00–45.00)	
Reference range and unit	(U/L); 8–40	(U/L); 15.0–40.0	U/L					15–40 U/L	U/L
Increased	27 (18.12%), 63.04 ± 25.60	35 (35%) (>40)	8/13 (62%) (>40)						168/757 (22.2%) (>40)

^aRefers to coagulopathy defined as a 3-second extension of prothrombin time or a 5-second extension of activated partial thromboplastin time.

Table 2 Coagulation and liver parameters in patients with coronavirus 2019 infection according to severity of the disease

Study (year)	Number of patients	Severe	Nonsevere	p-Value
D-dimer				
Huang et al ¹¹ (2020)	41 (13 ICU, 28 no ICU)	2.4 (0.6–14.4)	0.5 (0.3–0.8)	p = 0.0042
Zhou et al ¹² (2020)	191 (54 nonsurvivors, 137 survivors)	5.2 (1.5–21.1) ^c	0.6 (0.3–1.0) ^c	p < 0.0001
		>1 µg/L = 44 (81%)	>1 µg/L = 28/118 (24%)	p < 0.0001
Han et al ¹⁴ (2020)	94 (49 ordinary, 35 severe, 10 critical)	Severe: 19.11 ± 35.48 Critical: 20.04 ± 32.39	2.14 ± 2.88	n.r.
Tang et al ¹⁵ (2020)	183 (21 nonsurvivors, 162 survivors)	2.12 (0.77–5.27)	0.61 (0.35–1.29)	p < 0.001
Wu et al ^{16,a} (2020)	117 (no ARDS, 84 ARDS)	1.16 (0.46–5.37)	0.52 (0.33–0.93)	p < 0.001
	40 ARDS alive, 44 ARDS died	3.95 (1.15–10.96)	0.49 (0.31–1.18)	p = 0.001
Guan et al ¹⁷ (2020)	1,099 COVID-19 patients (926 non-severe vs. 173 severe)	65/109 (59.6) > 0.5 mg/L	195/451 (43.2) mg/L	n.r.
Platelet count				
Huang et al ¹¹ (2020)	41 (13 ICU, 28 no ICU)	196 (165–263)	149 (131–263)	p = 0.450
		<100 = 1/13 (8%)	<100 = 1/27 (4%)	p = 0.450
Zhou et al ¹² (2020)	191 (54 nonsurvivors, 137 survivors)	165.5 (107.0–229.0)	220.0 (168.0–271.0)	p < 0.0001
		<100 = 11 (20%)	<100 = 2 (1%)	p < 0.0001
Yang et al ¹³ (2020)	52 (32 nonsurvivors, 20 survivors)	191 (63)	164 (74)	n.r.
Wu et al ¹⁶ (2020)	117 (no ARDS, 84 ARDS)	187.00 (124.50–252.50)	178.00 (140.00–239.50)	0.730
	40 ARDS alive, 44 ARDS died	162.00 (110.50–231.00)	204.00 (137.25–262.75)	0.100
Guan et al ¹⁷ (2020)	1,099 COVID-19 patients (926 non-severe vs. 173 severe)	137,500 (99,000–179,500)	172,000 (139,000–212,000)	n.r.
	<150,000 per mm ³	90/156 (57.7)	225/713 (31.6)	n.r.
Prothrombin time				
Huang et al ¹¹	41 (13 ICU, 28 no ICU)	12.2 (11.2–13.4)	10.7 (9.8–12.1)	p = 0.012
Zhou et al ¹² (2020)	191 (54 nonsurvivors, 137 survivors)	12.1 (11.2–13.7)	11.4 (10.4–12.6)	p = 0.0004
		≥16 seconds = 7 (13%)	≥16 seconds = 4/128 (3%)	p = 0.016
Yang et al ¹³	52 (32 nonsurvivors, 20 survivors)	12.9 (2.9)	10.9 (2.7)	n.r.
Han et al ¹⁴ (2020)	94 (49 ordinary, 35 severe, 10 critical)	Severe: 12.65 ± 1.13 Critical: 12.80 ± 0.87	12.20 ± 0.88	n.r.
Tang et al ¹⁵ (2020)	183 (21 nonsurvivors, 162 survivors)	15.5 (14.4–16.3)	13.6 (13.0–14.3)	p < 0.001
Wu et al ¹⁶ (2020)	117 no ARDS, 84 ARDS	11.70 (11.10–12.45)	10.60 (10.10–11.50)	p < 0.001
	40 ARDS alive, 44 ARDS died	11.60 (11.10–12.45)	11.75 (10.95–12.45)	p = 0.870
Activated partial thromboplastin time				
Huang et al ¹¹	41 (13 ICU, 28 no ICU)	26.2 (22.5–33.9)	27.7 (24.8–34.1)	p = 0.570
Zhou et al ¹² (2020)	191 (54 nonsurvivors, 137 survivors)	27 (50%) ^b	10 (7%) ^b	p < 0.0001
Han et al ¹⁴ (2020)	94 (49 ordinary, 35 severe, 10 critical)	Severe: 29.53 ± 3.48 Critical: 29.41 ± 1.68	28.56 ± 2.66	n.r.
Tang et al ¹⁵ (2020)	183 (21 nonsurvivors, 162 survivors)	44.8 (40.2–51.0)	41.2 (36.9–44.0)	p = 0.096
Wu et al ¹⁶ (2020)	117 (no ARDS, 84 ARDS)	26.00 (22.55–35.00)	29.75 (25.55–32.85)	p = 0.130
	40 ARDS alive, 44 ARDS died	24.10 (22.25–28.35)	29.60 (24.00–35.75)	p = 0.040
ALT				
Huang et al ¹¹ (2020)	41 (13 ICU, 28 no ICU)	49.0 (29.0–115.0)	27.0 (19.5–40.0)	0.038
Zhou et al ¹² (2020)	191 (54 nonsurvivors, 137 survivors)	40.0 (24.0–51.0)	27.0 (15.0–40.0)	0.005
		>40	26 (48%)	33/135 (24%)
Wu et al ¹⁶ (2020) ^a	117 (no ARDS, 84 ARDS)	35.00 (21.50–52.50)	27.00 (18.00–41.50)	0.01
	40 ARDS alive, 44 ARDS died	39.00 (20.50–52.50)	35.00 (23.25–55.25)	0.71
Guan et al ¹⁷ (2020)	1,099 COVID-19 patients (926 nonsevere vs. 173 severe)	38/135 (28.1) > 40 U/L	120/606 (19.8) > 40 U/L	n.r.

(Continued)

Table 2 (Continued)

Study (year)	Number of patients	Severe	Nonsevere	p-Value
AST				
Huang et al ¹¹	41 (13 ICU, 28 no ICU)	44.0 (30.0–70.0)	34.0 (24.0–40.5)	0.10
Wu et al ¹⁶ (2020) ^a	117 (no ARDS, 84 ARDS)	38.00 (30.50–53.00)	30.00 (24.00–38.50)	<0.001
	40 ARDS alive, 44 ARDS died	37.00 (30.00–52.00)	38.50 (32.25–57.25)	0.21
Guan et al ¹⁷ (2020)	1099 COVID-19 patients (926 nonsevere vs. 173 severe)	56/142 (39.4) > 40 U/L	112/615 (18.2) > 40 U/L	n.r.

Abbreviations: ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus 2019; ICU, intensive care unit; n.r., not reported.

^aHazard ratio for progression to ARDS 1.03 (95% confidence interval: 1.01–1.04), $p < 0.001$; hazard ratio for progression to death 1.02 (95% CI: 1.01–1.04), $p = 0.002$.

^bNumbers refers to coagulopathy defined as a 3-second extension of prothrombin time or a 5-second extension of activated partial thromboplastin time.

^cMultivariable odds ratio for in-hospital death for D-dimer >1 µg/L = 18.42 (95% CI: 2.64–128.55), $p = 0.0033$.

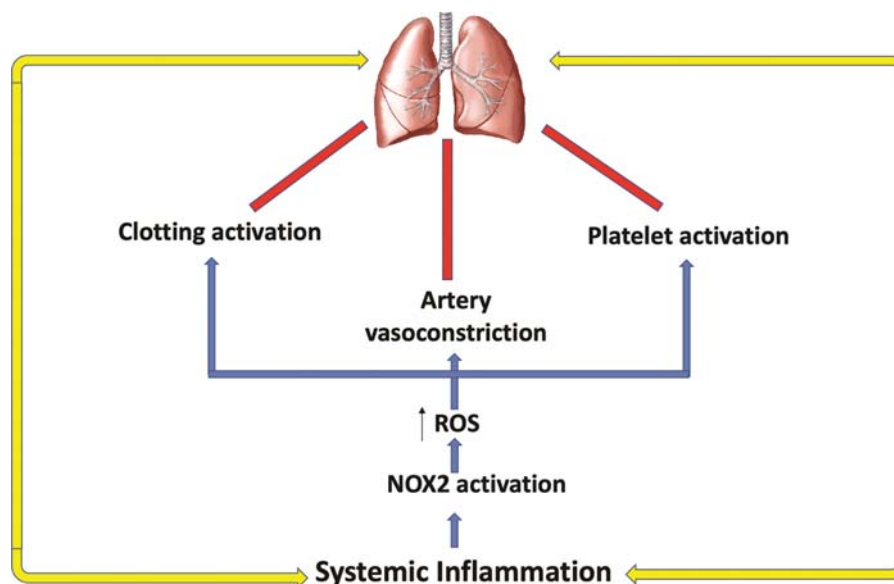
deep venous thrombosis. Systemic coagulation abnormalities, including clotting activation and inhibition of anticoagulant factors, have been observed not only in sepsis but also in pneumonia.

At this last regard, we have previously reported that pneumonia may be associated with clotting activation as well as lowering of natural anticoagulants. Thus, we found enhanced levels of the prothrombin fragment F1 + 2, which is a marker of thrombin generation, along with impaired activation of the anticoagulant Protein C. These changes occurred during the acute phase of the disease and tended to normalize at the discharge.⁴

Platelet activation has been investigated by measuring the soluble levels of CD40L and P-selectin, which were both elevated during the acute phase of pneumonia, along with an overproduction of platelet thromboxane (Tx) B₂²³; of note, platelet TxB₂ was independently associated with the occurrence of MI. Finally, we observed that patients with pneumonia display impaired artery dilatation, which is detectable during the acute phase of the disease and improve at discharge.²⁴

The mechanism accounting for these changes is not clear, but it is intriguing that Nox2, which is the most important enzyme generating reactive oxidant species (ROS), is over-activated in patients with pneumonia.²⁵ Thus, Nox2 is implicated in artery dilatation and platelet activation by inactivating nitric oxide or enhancing platelet eicosanoid production; experimental model of platelet-related thrombosis provided support to the role of Nox2 as in Nox2 animal knockout thrombus growth is prevented.^{26,27}

Thus, there are at least three changes occurring during the acute phase of pneumonia, which may precipitate artery and/or venous thrombosis (→**Fig. 2**). The mechanisms accounting for clotting and vascular changes have not been defined yet by systemic inflammation, including production of reactive oxidant ROS might have a role. In this context, there are growing body of experimental and clinical evidence that Nox2-derived ROS are implicated in both clotting and platelet activation, acting as intrasignaling pathway to promote thrombin generation and platelet aggregation or to impair artery dilatation^{26,27} (→**Fig. 2**). Data regarding Nox2 in SARS-CoV-2 patients are still lacking but should be

**Fig. 2** Hypothetic mechanisms accounting for hypercoagulation in severe acute respiratory syndrome coronavirus 2 patients.

investigated as experimental data provided evidence for a role played by Nox2 upregulation in the systemic inflammation and pathogenicity elicited by several RNA viruses including influenza virus.²⁸

Data regarding clotting changes in SARS-CoV-2 are still sparse and elusive. The only finding which could be consistent with clotting activation is the increase of D-dimer; however, which is not specific for clotting activation as it may also increase as result of systemic proteolysis.²⁹ There is also a trend toward PT prolongation and low platelet count in patients with severe disease, suggesting a role for coagulation in precipitating poor outcomes. Preliminary data regarding the relationship between elevated D-dimer and poor outcome would be in favor of this hypothesis, but limited study methodology precludes definite conclusions.¹²

Perspectives and Conclusion

The data so far reported are suggestive of low-grade intravascular clotting activation, which is evident overall in patients with severe disease. The finding more consistent in support of this hypothesis is the increase of D-dimer, which is almost evident in patients with severe; in a small series of a retrospective study, D-dimer was associated with poor survival.¹⁶ Concerning PT, aPTT and platelet count data are more elusive even if there is a trend for changes suggestive of a hypercoagulation state in patients with severe disease. Thus, future study should employ more sophisticated methodology to screen for hypercoagulation state and, in the same time, clarify if platelet activation occurs also in this setting; in this last context, analysis of systemic markers of platelet activation such as soluble P-selectin or IIb/IIIa could be useful to address this issue. In the meantime, a hot issue is if SARS-CoV-2

patients should be treated or not with antithrombotic drugs and if the clinical presentation may drive this therapeutic decision (►Fig. 3). On the basis of previous reports showing that patients with pneumonia are associated with platelet and clotting activation,^{3,4} interventional trials aimed at assessing the efficacy of antithrombotic treatment, including aspirin or low-molecular-weight heparin (LMWH), should be planned: preliminary data suggested a potential efficacy of aspirin in patients with pneumonia.³⁰ Antithrombotic treatment could be investigated in patients with severe pneumonia or pneumonia complicated by ARDS³¹ or by sepsis³² or needing mechanical ventilation/ICU; the gray area is in case of no pneumonia or pneumonia with low mortality risk according to several risk scores such as PSI,³³ CURB65,³⁴ or SOFA,³² in which antithrombotic treatment may be questionable; the coexistence of elevated D-dimer in patients with mild pneumonia may be another setting to be investigated (►Fig. 3).

In absence of clinical trials and mechanism of disease indicating the prominent role, if any, of platelets or clotting system in favoring SARS-CoV-2 sequelae, treating all SARS-CoV-2 with prophylactic doses of LMWH, independently from clinical presentation and on the basis of laboratory changes suggestive of a hypercoagulation state, may be intriguing but premature until the interplay between hypercoagulation and SARS-CoV-2 is clarified³⁵; previous study in a different clinical setting, that is acutely ill medical patients, demonstrated that without an appropriate definition of hospitalized medical patients at risk of thrombosis, the prophylaxis with LMWH is useless and potentially dangerous.³⁶ Thus, patients with pneumonia, particularly those with severe infections as defined by several scores and suffering from complications as ARDS or sepsis or needing mechanical ventilation/ICU treatment could be candidates to

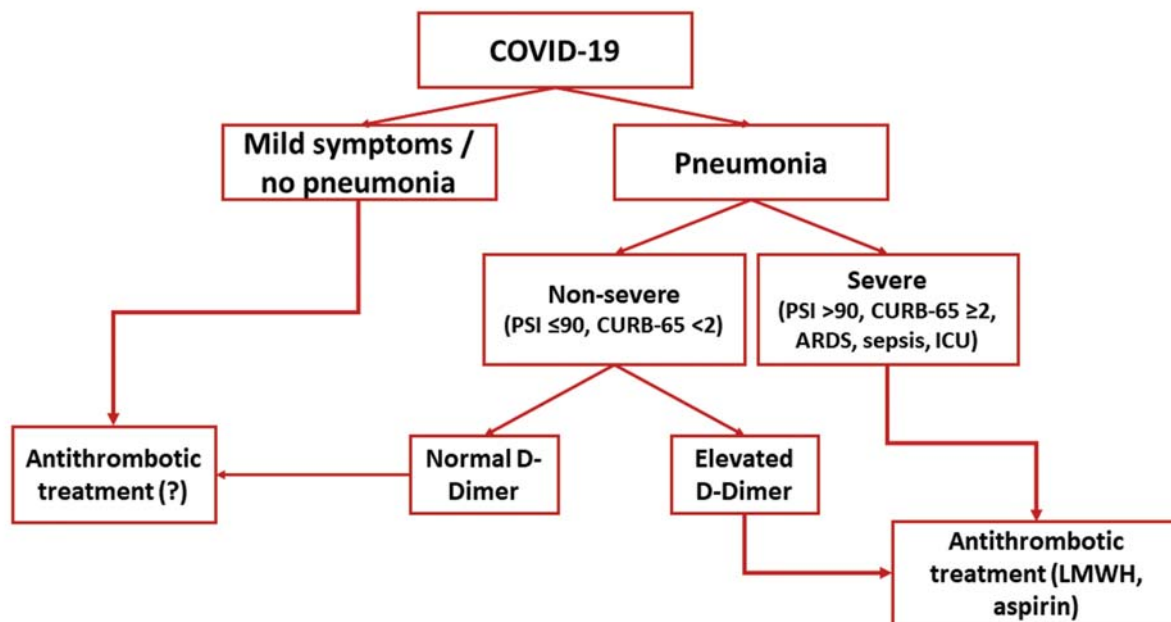


Fig. 3 Suggested algorithm for antithrombotic treatment in severe acute respiratory syndrome coronavirus 2 patients.

randomized clinical trials with antithrombotic treatment (►Fig. 3) to assess if this approach may blunt SARS-CoV-2 sequelae.

Conflict of Interest

None declared.

References

- Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. *Lancet* 2013;381(9865):496–505
- Violi F, Cangemi R, Falcone M, et al; SIXTUS (Thrombosis-Related Extrapulmonary Outcomes in Pneumonia) Study Group. Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. *Clin Infect Dis* 2017;64(11):1486–1493
- Cangemi R, Casciaro M, Rossi E, et al; SIXTUS Study Group; SIXTUS Study Group. Platelet activation is associated with myocardial infarction in patients with pneumonia. *J Am Coll Cardiol* 2014;64(18):1917–1925
- Cangemi R, Della Valle P, Calvieri C, et al; SIXTUS Study Group. Low-grade endotoxemia and clotting activation in the early phase of pneumonia. *Respirology* 2016;21(08):1465–1471
- Clerkin KJ, Fried JA, Raikhelkar J, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. *Circulation* 2020. Doi: 10.1161/CIRCULATIONAHA.120.046941
- Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020. Doi: 10.1001/jamacardio.2020.0950
- Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020. Doi: 10.1001/jamacardio.2020.1017
- Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200(07):e45–e67
- Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020;80(04):388–393
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507–513
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–1062
- Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020(S2213–2600(20)30079–5):
- Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 2020. Doi: 10.1515/cclm-2020-0188/1
- Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18(04):844–847
- Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020. Doi: 10.1001/jamainternmed.2020.0994
- Guan WJ, Liang WH, Zhao Y, et al. China Medical Treatment Expert Group for Covid-19. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. *Eur Respir J* 2020;2000547
- Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost* 2020. Doi: 10.1055/s-0040-1709650
- Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020;506:145–148
- Violi F, Ferro D. Clotting activation and hyperfibrinolysis in cirrhosis: implication for bleeding and thrombosis. *Semin Thromb Hemost* 2013;39(04):426–433
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020. Doi: 10.1001/jamainternmed.2020.0994
- Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020
- Cangemi R, Pignatelli P, Carnevale R, et al. SIXTUS Study Group. Low-grade endotoxemia, gut permeability and platelet activation in community-acquired pneumonia. *J Infect* 2016;73(02):107–114
- Loffredo L, Cangemi R, Perri L, et al; SIXTUS study group; SIXTUS (thromboSis-related eXtra-pulmonary oUtcomeS in pneumonia) study group. Impaired flow-mediated dilation in hospitalized patients with community-acquired pneumonia. *Eur J Intern Med* 2016;36:74–80
- Violi F, Carnevale R, Calvieri C, et al; SIXTUS study group. Nox2 up-regulation is associated with an enhanced risk of atrial fibrillation in patients with pneumonia. *Thorax* 2015;70(10):961–966
- Violi F, Pignatelli P. Platelet NOX, a novel target for anti-thrombotic treatment. *Thromb Haemost* 2014;111(05):817–823
- Violi F, Carnevale R, Loffredo L, Pignatelli P, Gallin JI. NADPH Oxidase-2 and Atherothrombosis: Insight From Chronic Granulomatous Disease. *Arterioscler Thromb Vasc Biol* 2017;37(02):218–225
- To EE, Vlahos R, Luong R, et al. Endosomal NOX2 oxidase exacerbates virus pathogenicity and is a target for antiviral therapy. *Nat Commun* 2017;8(01):69
- Dempfle CE. Use of D-dimer assays in the diagnosis of venous thrombosis. *Semin Thromb Hemost* 2000;26(06):631–641
- Falcone M, Russo A, Cangemi R, et al. Lower mortality rate in elderly patients with community-onset pneumonia on treatment with aspirin. *J Am Heart Assoc* 2015;4(01):e001595
- Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. *JAMA* 2018;319(07):698–710
- Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315(08):801–810
- Aujesky D, Fine MJ. The pneumonia severity index: a decade after the initial derivation and validation. *Clin Infect Dis* 2008;47(Suppl 3):S133–S139
- Myint PK, Kamath AV, Vowler SL, Maisey DN, Harrison BD. The CURB (confusion, urea, respiratory rate and blood pressure) criteria in community-acquired pneumonia (CAP) in hospitalised elderly patients aged 65 years and over: a prospective observational cohort study. *Age Ageing* 2005;34(01):75–77
- Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020. Doi: 10.1111/jth.14817
- Loffredo L, Arienti V, Vidili G, et al. AURELIO Study Group. Low rate of intrahospital deep venous thrombosis in acutely ill medical patients: results from the AURELIO study. *Mayo Clin Proc* 2019;94(01):37–43