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Review

Coronavirus Disease 2019: Hematological Anomalies and Antithrombotic Therapy

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After the first cases of COVID-19 appeared in Wuhan, China at the end of 2019, the disease quickly become a pandemic that has seriously affected the economic and health systems in more than 200 countries and territories around the world. Although most patients have mild symptoms or are even asymptomatic, there are patients who can develop serious complications such as acute respiratory distress syndrome or venous thromboembolism requiring mechanical ventilation and intensive care. Hence, it is important to identify patients with a higher risk of complications in a timely manner. Thus, the objective of this paper is to review the hematological laboratory parameters that consistently are altered in COVID-19 and to identify their relationship with the severity of the disease. According to 11 selected reports, the frequency of patients aged > 65 years is higher among subjects severely affected or deceased; likewise, males predominantly suffer from comorbidities such as hypertension, diabetes or obesity. Retrospective studies have identified alterations in various hematological and inflammatory parameters as part of the host's response to infection and a secondary increased risk of different thrombotic events. Among these altered parameters, D-dimer, C-reactive protein, and interleukin-6 have been tested as prognostic biomarkers due to their close relationship with the severity of the disease. Actually, they can reliably indicate the use of antithrombotic therapy at prophylactic or therapeutic doses (mainly D-dimer), as has already been established in those patients who, after an individualized assessment, appear to be at high risk for thrombotic events.

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Introduction

In December 2019, some patients affected from pneumonia of unknown etiology and who had visited the local seafood market were detected in Wuhan city, Hubei province, China (Rothan and Byrareddy 2020). Shortly afterwards, a novel coronavirus was identified as the causative pathogen and denominated Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2); consequently, the ensuing disease was named coronavirus disease of 2019 (COVID-19) by the World Health Organization (WHO) on February 11, 2020 (Lai et al. 2020). Further critical clinical manifestations are coagulopathy and thromboinflammation secondary to infection that lead to sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulopathy (DIC) in severe cases and non-survivors (Connors and Levy 2020).

Coronaviruses are a subfamily of positive single-stranded RNA viruses belonging to the Coronaviridae family. Coronaviruses generally cause mild respiratory illness, but two highly pathogenic coronaviruses have caused worldwide epidemics and a sizeable number of deaths: in 2003, the severe acute respiratory syndrome coronavirus (SARS-CoV) and in 2012, the Middle East respiratory syndrome coronavirus (MERS-COV) (Singhal 2020). Thus, SARS CoV-2 is the third coronavirus that causes a human

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disease whose prognosis is usually unfavorable in elderly people and/or in patients with underlying disorders that lead to severe and even fatal respiratory complications. Indeed, the current pandemic entails a large number of human losses and serious repercussions on the economic and health systems (Shanmugaraj et al. 2020; Wu and McGoogan 2020; Zhang et al. 2020a).

Recent investigations have identified different hemostatic alterations related to COVID-19, including a noticeable increase in D-dimer levels and mild thrombocytopenia, which may confer a higher risk of complications or death. In contrast, there are not enough results to establish a reliable relationship for other parameters. Taken together, these hemostatic disorders increase the risk of suffering different thrombotic complications, although the underlying mechanisms remain unknown; moreover, it has been proven that anticoagulant therapy can reduce the mortality ratio in patients with a high risk of thrombotic events such as venous thromboembolism (VTE) (Bikdeli et al. 2020; Tang et al. 2020a). Hence, a consensus guideline specialized in the management and prevention of different thrombotic complications in patients with COVID-19 is clearly needed.

This paper provides a traditional review according to conventional criteria (Grant and Booth 2009) about the hematological laboratory parameters that are consistently altered in COVID-19 and their relationship with the severity of the disease. Hence, our review focuses on the link between hematological findings and severity of COVID-19 in order to identify prognostic biomarkers and to provide a useful guideline for the antithrombotic management of patients infected with SARS-CoV-2.

Search in PubMed

Both authors searched independently relevant articles in the PubMed database using alone or combined the following text terms and MeSH terms: ("COVID-19" [Supplementary Concept]) AND "Hematologic Tests"[Mesh], (covid-19) AND (clinical features), ((SARS-CoV-2) AND (clinical characteristics)) AND (clinical parameters) (COVID-19) AND (coagulation). The last search was performed on May 5, 2020.

Selection Criteria

We considered only articles with two groups, one of mildly affected and asymptomatic patients or control subjects and another of severely affected or deceased patients and in who prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, fibrin degradation products (FDP), D-dimer, C-reactive protein, interleukin 6 (IL-6), and platelet count in diverse combinations were assessed in most or all subjects. Review articles, comments, and letters to the editor were excluded. All the articles retrieved were revised independently by each author and any discrepancy was resolved through a mutual discussion. Finally, 11 articles met the selection criteria.

Clinical Characteristics

Clinical manifestations of COVID-19 appear on average 11.5 days after infection; although most patients (81%) present mild and even imperceptible symptoms, some of them develop severe complications such as acute respiratory disease (ARD) and acute respiratory distress syndrome (ARDS) (Akhmerov and Marban 2020; Muniyappa and Gubbi 2020). The most frequently reported symptoms are fever, cough, chest tightness, and dyspnea (Lake 2020), while the least frequent are sputum, headache, hemoptysis and diarrhea (Jin et al. 2020). However, the clinical spectrum of the disease is wide and even now, some peculiar or new elements are still being identified (Landa et al. 2020).

SARS-CoV-2 Pathogenesis

Despite being a disease of zoonotic transmission, humans are the main infection targets since even recovered patients— unlike to those with other infectious diseases — often continue testing positive for SARS-CoV-2. Therefore, management strategies should focus on developing effective measures to prevent spreading (Jin et al. 2020; Wu and McGoogan 2020).

After entering through the mucous membranes, mainly nasal and pharyngeal, SARS-CoV-2 virions reach the lungs through the respiratory tract and then pass into the blood circulation causing viremia and attacking its target organs, i.e., those that express angiotensin-converting enzyme 2 (ACE2) receptor: heart, kidney, lung, gastrointestinal tract and vascular endothelial cells (Lin et al. 2020).

The coronavirus binds to the ACE2 receptor of the host cell through the spike protein located on its surface and which acts as a mediator in the fusion of the cellular and viral membranes facilitating the infection (Tang et al. 2020c). The spike protein (S) is made up of two regions, namely S1 that joins to the host cell and S2 that participates in the membranous fusion. The S1 region in turn consists of one N-terminal domain and three C-terminal domains. The receptor binding domain is in the C-terminal domain 1 which specifically recognizes its ACE2 receptor. Susceptibility to infection has been related to the affinity between the receptor binding domain and its ACE2 receptor (He et al. 2020; Wan et al. 2020).

Once the spike protein S1 binds to its receptor, it needs to be cleaved by the transmembrane protease serine 2 (TMPRSS2), a crucial step for membrane fusion to take place and the subsequent entry of viral RNA into the cell host (Atri et al. 2020).

The translation of the open reading frame (ORF) generates a unique polypeptide from which 16 non-structural proteins are produced; in turn, these make up the replicase transcriptase complex that participates in genome replication and subgenomic transcription. Subgenomic RNAs encode structural and accessory proteins. After structural protein translation (except Nucleocapsid or N protein), these are directed to the membrane of the endoplasmic

reticulum and then the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), where new replicated RNA, nucleocapsid, and envelope proteins are assembled to generate virions that will be released by exocytosis (Guo et al. 2020; Li et al. 2020) (Fig. 1).

The main findings of the 11 studies here compiled, each with two contrasting groups of subjects (for short, mild/asymptomatic or control vs. severe or deceased), are shown in Tables 1 to 4. Some additional remarks are made here below.

Relationship of Demographic Characteristics with the Severity of COVID-19

Although anyone can be infected, reports from the National Health Commission of the People's Republic of China (May 2020) have shown that eight out of 10 deaths caused by COVID-19 occur in patients older than 60 years and that three quarters of these subjects suffered from comorbidities such as diabetes or cardiovascular diseases; moreover, according to the WHO the proportion of infected men exceeds that of women (Baloch et al. 2020).

From 10 studies that analyzed sex as a variable related to the severity of COVID-19, non-significant differences were reported in seven but three of them identified a higher frequency of men in the group of severely ill or deceased. (Deng et al. 2020; Tang et al. 2020b; Zou et al. 2020). Specifically, Deng et al. (2020) reported a higher frequency of men in the group of deceased patients (67% versus 44% in women, $p < 0.001$); these results are consistent with two other studies conducted in Wuhan and Shanghai (Tang et al. 2020b; Zou et al. 2020) (Table 1). A meta-analysis that included 13 studies determined that critically ill or deceased patients are almost twice more likely to be male (OR = 1.77, IC 95% (1.43, 2.19), $p < 0.00001$) (Zheng et al. 2020).

Regarding age as a risk variable, seven of 11 studies found an increased risk of serious illness or death in people older than 60 years, and a lower risk in people of approximately 50 years (Deng et al. 2020; Liu et al. 2020; Tang et al. 2020b; Zhang et al. 2020b; Zhou et al. 2020; Zhu et al. 2020; Zou et al. 2020) (Table 1). These findings are consistent with the results reported by Zheng et al. (2020), who reported that critically ill or deceased patients are six times more likely to be older than 65 years.

Of the eight studies analyzing comorbidities, seven of them determined a higher frequency of pre-existing diseases in patients who died or had severe COVID-19. The most frequent comorbidities among them were hypertension, chronic obstructive lung disease, diabetes, and renal and cardiac diseases (Deng et al. 2020; Huang et al. 2020; Zhang et al. 2020b; Zhou et al. 2020; Zhu et al. 2020; Zou et al. 2020) (Table 2).

Another comorbidity that has been reported with great frequency is obesity, which alone or together with its derived complications of hypertension and diabetes influences the patient's health; however, there are insufficient data to determine the risk of mortality due to obesity (Finer et al. 2020). Reports on the 2009 pandemic of AH1N1 influenza determined that concomitant obesity was a risk factor for hospitalization, mechanical ventilation due to the already known impact of obesity on lung function, and even

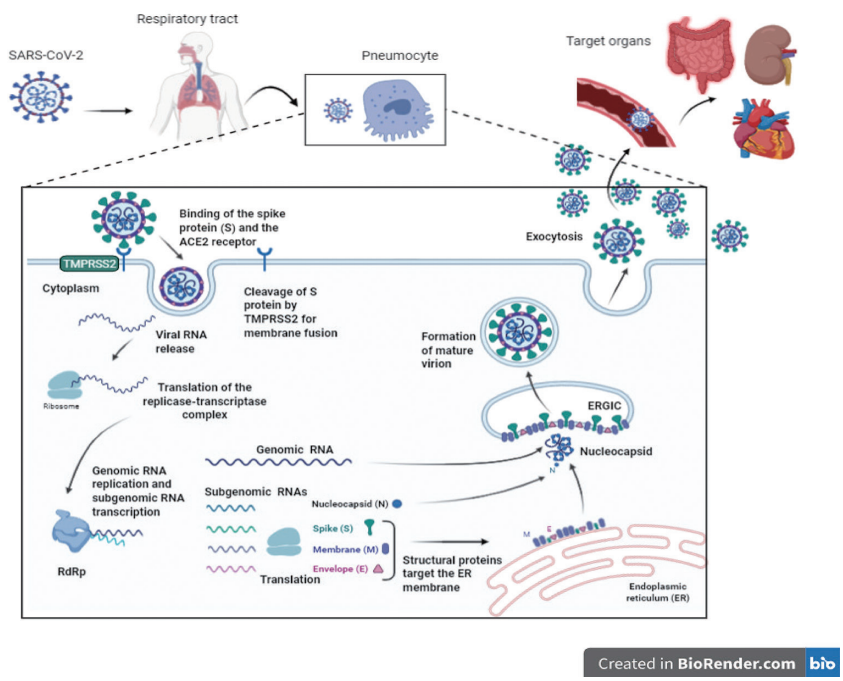

Fig. 1. SARS-CoV-2 pathogenesis.
Summary of the infection process and the replication cycle of SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TMPRSS2, Transmembrane protease serine 2; RdRp, RNA-dependent RNA polymerase; ERGIC, endoplasmic reticulum-Golgi intermediate compartment. Figure was created by the first author with BioRender©.

Table 1. Selected studies and demographic characteristics of the groups.

Study	Subjects studied	Groups	Subjects per group	Sex	p	Age (years)	p
Tang et al. (2020b)	183	Survivors	162	Increased risk of death in men	**0.035**	52.4	**< 0.001**
		Non survivors	21			64	
Zhang et al. (2020a)	95	Non severe	63	Non-significant differences	0.195	Non-significant differences	0.376
		Severe	32				
Zhou et al. (2020)	191	Survivors	137	Non-significant differences	0.15	52	**< 0.0001**
		Non survivors	54			69	
Zhu et al. (2020)	127	Non severe	111	Non-significant differences	0.457	49.95	**0.03**
		severe	16			57.5	
Gao et al. (2020)	43	Mild	28	Non-significant differences	0.194	Non-significant differences	0.503
		Severe	15				
Huang et al. (2020)	41	ICU	13	Non-significant differences	0.24	Non-significant differences	0.60
		No ICU	28				
Liu et al. (2020)	140	Mild	107	Non-significant differences	0.138	62	**< 0.0001**
		Severe	33			77	
Han et al. (2020)	94	Healthy Control	40	-	-	Non-significant differences	> 0.05
		Patients	94				
Zou et al. (2020)	303	Mild	277	Higher severity in men	**0.008**	50	**< 0.001**
		Severe	26			65	
Zhang et al. (2020b)	140	Non severe	82	Non-significant differences	0.219	51.5	**< 0.001**
		Severe	58			64	
Deng et al. (2020)	225	Recovered	116	Increased risk of death in men	**< 0.001**	40	**< 0.001**
		Deceased	109			69	

Selected studies for the analysis of the altered parameters in COVID-19. The number of subjects included and the study groups as well as their demographic characteristics are presented. The age of the subjects is presented in means, a value of $p < 0.05$ was considered as statistically significant.
ICU, intensive care unit.

death. If we add the increase of inflammatory cytokines associated with obesity, it can be inferred that obesity also favors increased mortality in patients with COVID-19 (Dietz and Santos-Burgoa 2020; Ryan et al. 2020). Because the proportion of obesity in each population is different, the health services of countries with a high percentage of obese patients, such as the United States and Mexico, must develop effective plans for the treatment of these patients (Dietz and Santos-Burgoa 2020).

Hemostatic and Inflammatory Parameters Related to COVID-19 Severity

Inflammatory reactions and cytokines storms caused by severe infections have pleiotropic repercussions such as activation of the coagulation system through different pro-coagulant routes; sometimes, it can be imperceptible, but when this activation is very strong, it is reflected in pro-longed PT and APTT and thrombocytopenia due to increased requirements for clotting factors and platelets or to development of disseminated intravascular coagulation (DIC) (Connors and Levy 2020; Levi 2018).

Tang et al. (2020b) reported prolonged PT in patients who died from COVID-19 (of which more than 70% met the ISTH criteria for DIC), compared to surviving patients (15.5 versus 13.6 respectively $p < 0.001$) (Tang et al. 2020b). Similar data were seen in three other descriptive studies conducted simultaneously in deceased or critically ill patients vs. mildly affected patients (Huang et al. 2020; Zhou et al. 2020; Zou et al. 2020) (Table 3).

Whereas Zou et al. (2020) reported that subjects with severe COVID-19 had a longer APTT compared to subjects with mild COVID-19, no differences between these groups

Table 2. Comorbidities in studied subjects with COVID-19.

Study	Groups	Frequency of comorbidities	p	Frequency of specific comorbidities	p
Zhou et al. (2020)	Survivors / Non survivors	Higher frequency of comorbidities in non-surviving subjects	**0.001**	Hypertension	**0.0008**
				Diabetes	**0.0051**
				Coronary heart disease	**< 0.0001**
				COPD	**0.047**
				Chronic kidney disease	**0.024**
Zhu et al. (2020)	Non severe / Severe	Higher frequency of comorbidities in subjects with severe COVID-19	**0.003**	Hypertension	**0.025**
Gao et al. (2020)	Mild / Severe	Higher frequency of comorbidities in subjects with severe COVID-19	-	Diabetes	**0.005**
				COPD	**0.037**
Huang et al. (2020)	No ICU / ICU	Non-significant differences	0.53	-	-
Liu et al. (2020)	Mild / Severe	Higher frequency of comorbidities in subjects with severe COVID-19	-	Cardiopathy	**0.029**
				Hypertension	**0.004**
Zou et al. (2020)	Mild / Severe	Higher frequency of comorbidities in subjects with severe COVID-19	**< 0.001**	Not specified	**-**
Zhang et al. (2020b)	Non severe / Severe	Higher frequency of comorbidities in subjects with severe COVID-19	**0.002**	Electrolyte imbalance	**0.028**
Deng et al. (2020)	Recovered / Deceased	Higher frequency of comorbidities in deceased subjects	**< 0.001**	Hypertension	**< 0.001**
				Lung disease	**< 0.001**
				Heart disease	**0.031**

Studies where significant differences were observed by the presence of the most frequent comorbidities in COVID-19. A value of $p < 0.05$ was considered as statistically significant.
ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.

were found in four different studies, (Gao et al. 2020; Han et al. 2020; Huang et al. 2020; Tang et al. 2020b) (Table 3).

As for platelet counts, Zhu et al. (2020) and Zhou et al. (2020) observed a significant thrombocytopenia in severely ill and deceased patients as compared to mild patients (Zhou et al. 2020; Zhu et al. 2020); however, two other studies reported non-significant differences in platelet count between the groups (Huang et al. 2020; Zhang et al. 2020a) (Table 3).

Fibrinogen values have been widely related to the severity of the disease, but not consistently. Gao et al. (2020) reported fibrinogen values that agree with those obtained in other studies (Zhu et al. 2020; Zou et al. 2020). An even larger difference was identified by Han et al. (2020), with significant differences of fibrinogen levels in patients with COVID-19 and healthy control subjects, while Tang et al. (2020b) observed no differences between the groups (Tang et al. 2020b) (Table 4).

Regarding FDP, their values have been reported to be associated with COVID-19 severity in different studies. Tang et al. (2020b) identified a higher level of FDP in deceased patients than in survivors (Tang et al. 2020b); this finding in agreement with two other studies, one carried out in healthy control subjects and patients with COVID-19 (Han et al. 2020) and another in mild and severe patients (Zou et al. 2020) (Table 4). Despite of the significant association of FDP in the progression and severity of COVID-19, there are scarce studies on this parameter in part due to the complexity and cost of the test. Instead, numerous studies point out D-dimer as an important prognostic parameter of thrombotic complications, and even though it is not as precise as FDP, it provides a confident thrombosis indicator that is widely available in clinical laboratories (Tang et al. 2020b).

The increased concentration of C-reactive protein in the group of deceased or severe patients found in 100% of the studies assessing this item highlights its strong relationship with the severity of the disease (Deng et al. 2020; Gao

Table 3. Hemostatic parameters in studied subjects with COVID-19 and controls.

Study	Group	PT (s)	p	APTT (s)	p	Platelet count × 10^9/L	p
Tang et al. (2020b)	Survivors	13.6	**< 0.001**	41.2	0.096	-	-
	Non survivors	15.5		44.8		-	-
Zhou et al. (2020)	Survivors	11.4	**0.0004**	-	-	220	**< 0.0001**
	Non survivors	12.1		-		165.5	
Gao et al. (2020)	Mild	12.08	0.068	27.29	0.089	-	-
	Severe	11.26		30.41		-	-
Huang et al. (2020)	No ICU	10.7	**0.012**	27.7	0.57	149	0.45
	ICU	12.2		26.2		196	
Han et al. (2020)	Healthy control	12.08	0.419	28.65	0.518	-	-
	Patients	12.43		29.01		-	-
Zou et al. (2020)	Mild	13.4	**0.003**	39.2	**< 0.001**	-	-
	Severe	13.8		43.2		-	-
Zhang et al. (2020a)	Non severe	-	-	-	-	No difference	> 0.05
	Severe	-	-	-	-		
Zhu et al. (2020)	Non severe	-	-	-	-	205	**0.01**
	Severe	-	-	-	-	155	

The main results of the analyzed hemostatic parameters are summarized. A value of $p < 0.05$ was considered as statistically significant.
PT, prothrombin time; APTT, activated partial thromboplastin time.

et al. 2020; Liu et al. 2020; Zhang et al. 2020a; Zhang et al. 2020b; Zhu et al. 2020) (Table 4).

There is evidence that monitoring the levels of different inflammatory parameters such as D-dimer or IL-6 during the course of the disease is of vital importance for the timely identification of patients prone to developing serious complications (Gao et al. 2020). Regarding D-dimer, 87.5% of studies (7/8) found it increased in severely ill or deceased patients (Gao et al. 2020; Huang et al. 2020; Tang et al. 2020b; Zhang et al. 2020a; Zhang et al. 2020b; Zhou et al. 2020; Zou et al. 2020). Likewise, levels of IL-6 were higher in severe or deceased patients than in survivors or mildly affected subjects in 4/5 studies (Gao et al. 2020; Liu et al. 2020; Zhou et al. 2020; Zhu et al. 2020); for instance, Liu et al. (2020) documented that 97% of critically ill patients had values > 7 pg/mL. Noticeably, even the single study reporting non-significant differences between severe and mild patients actually documented significant differences between severe patients and control subjects ($p = 0.003$) (Huang et al. 2020) (Table 4).

Recent investigations have attempted to determine which parameters associated with the severity of COVID-19 can be used as prognostic biomarkers. Gao et al. (2020) proposed that higher levels of IL-6 and D-dimer are early predictors of disease's severity (Gao et al. 2020). They determined that the optimal cut-off point for non-severe pneumonia was 24.3 pg/ml for IL-6 and for D-dimer 0.28 ng/L. The sensitivity and specificity of severe COVID-19 prediction were 73.3% and 89.3% for IL-6 > 24.3 pg/ml; and 86.7% and 82.1% for D-dimer > 0.28 ng/L. Analogously, Liu et al. (2020) determined a cut-off point of 32.1 pg/ml for IL-6 for the development of severe complications with a sensitivity and specificity of 85.19% and 66.67% respectively. They also determined that the cut-off point for C-reactive protein is 41.8 mg/L with a sensitivity and specificity of 88.89% and 72.73% (Liu et al. 2020).

The relationship of each of these biomarkers with the severity and prognosis of COVID-19 has also been individually evaluated in independent studies. For D-dimer, a cut-off of > 1.0 μg / ml as indicator of thrombotic events and complications that lead to severe COVID-19 has been included in recent guidelines for antithrombotic treatment in COVID-19 (Zhai et al. 2020). Although the cut-off point for predicting mortality has not been well established, one study that analyzed D-dimer levels to predict mortality in hospitalized patients determined that D-dimer levels > 2.0 μg/ml were valuable predictors with a sensitivity of 92.3% and a specificity of 83.3% (Zhang et al. 2020c). Likewise, the positive correlation of C-reactive protein levels with the severity of disease and lung lesions highlights the useful-

Table 4. Thrombo-Inflammatory parameters in studied subjects with COVID-19 and controls.

Study	Groups	Fibrinogen g/L	p	FDP μg/mL	p	C-reactive protein mg/L	p	D-dimer μg/mL	p	IL-6 pg/mL	p
Tang et al. (2020b)	Survivors	4.51	0.149	4	**< 0.001**	-	-	0.61	**< 0.001**	-	-
	Non survivors	5.16		7.6		-		2.12		-	
Zhang et al. (2020a)	Non severe	-	-	-	-	Severe patients > 150	**< 0.001**	Severe patients > 1	**< 0.001**	-	-
	Severe	-		-						-	
Zhou et al. (2020)	Survivors	-	-	-	-	-	-	0.6	**< 0.0001**	6.3	**< 0.0001**
	Non survivors	-		-		-		5.2		11	
Zhu et al. (2020)	Non severe	4.23	**0.018**	-	-	8.47	**< 0.001**	0.1	0.195	3.82	**< 0.001**
	Severe	5.74		-		36.64		0.16		24.11	
Gao et al. (2020)	Mild	3.11	**0.014**	-	-	18.76	**0.011**	0.21	**0.007**	10.6	**0.002**
	Severe	3.84		-		39.37		0.49		36.1	
Huang et al. (2020)	No ICU	-	-	-	-	-	-	0.5	**0.004**	No differences	0.13
	ICU	-		-		-		2.4			
Liu et al. (2020)	Mild	-	-	-	-	Severe patients > 8	**< 0.0001**	-	-	Severe patients > 7	**< 0.0001**
	Severe	-		-				-			
Han et al. (2020)	Healthy control	2.9	**< 0.001**	1.55	**< 0.001**	-	-	0.26	**< 0.001**	-	-
	Patients	5.02		33.83		-		10.36		-	
Zou et al. (2020)	Mild	4.33	**0.038**	0.99	**< 0.001**	-	-	0.43	**< 0.001**	-	-
	Severe	4.74		2.61		-		1.04		-	
Zhang et al. (2020b)	Non severe	-	-	-	-	28.7	**< 0.001**	0.2	**< 0.001**	-	-
	Severe	-		-		47.6		0.4		-	
Deng et al. (2020)	Recovered	-	-	-	-	3.22	**< 0.001**	-	-	-	-
	Deceased	-		-		109.25		-		-	

The main results of the analyzed thrombo-inflammatory markers are summarized. A value of $p < 0.05$ was considered as statistically significant.

FDP, fibrin degradation product; IL-6, Interleukin 6.

ness of this biomarker in disease monitoring (Wang 2020). As for IL-6, a meta-analysis that included nine studies with a total of 1,426 patients from China determined a cut-off of 55 pg/ml and 80 pg/ml for predicting severe COVID-19 and a high risk of mortality, respectively. Hence, this biomarker can potentially identify patients at risk at the beginning of the disease (Aziz et al. 2020).

Some of these biomarkers have been considered as prognosis markers by a current guideline, endorsed by the Prevention Treatment of VTE Associated with COVID-19 Infection Consensus Statement Group, composed by ten medical international societies (Zhai et al. 2020).

The thrombotic events and complications that lead to severe COVID-19 have been shown to be correlated mainly with D-dimer (> 1.0 μg/ml) and with the increased values of fibrinogen and FDP. It is therefore recommended to consider therapeutic decisions about the use of thromboprophylaxis or increased doses of therapeutic anticoagulation (Zhai et al. 2020).

At the moment, the interaction among all these biomarkers and their relationship individually or grouped with the prognosis and severity of COVID-19 is unknown. A prospective research under multivariable regression analysis is necessary to approach this issue that will give important data about the mechanisms involved in COVID-19 coagulopathy.

Antithrombotic Therapies

Despite of the evidence that thrombosis is an important cause of severe complications in COVID-19, such as VTE, pulmonary embolism (PE) or acute coronary syndromes (ACS), and the vital assistance that antithrombotic therapy may render, randomized and controlled studies are needed to compare the benefits of prophylactic or therapeutic doses of anticoagulants, and their combination with dual antiplatelet treatment (DAPT) in different sceneries and

individual conditions (Bikdeli et al. 2020). Particularly the recommendation of LMWH at prophylactic doses for severe coagulopathy treatment by COVID-19 (Thachil et al. 2020) has been discussed because, according to medical practice, hypercoagulability related to DIC is treated with early systemic anticoagulation (Barrett et al. 2020).

A retrospective study documented a significant decrease in mortality of approximately 25% ($p = 0.029$) on day 28 in patients at risk of coagulopathy (SIC score > 4) who were treated with heparin (40-60 mg/day enoxaparin or 10,000-150,000 U/day UFH) compared with those who did not, in addition to a decrease in mortality of approximately of 20% patients with D-dimer levels 6 fold upper the normal limit who were treated with heparin ($p = 0.017$), while in patients with lower levels of D- dimer, mortality was similar between heparin users and non-users (Tang et al. 2020a). Therefore, different guidelines have been developed for prevention and management of thrombotic events in patients with COVID-19. In fact, the ISTH has suggested monitoring parameters such as D-dimer, prothrombin time, platelet count and fibrinogen, since they seem to determine the patient's prognosis (Thachil et al. 2020). Furthermore, ISTH endorsed the evidence-based guide published by Bikdeli et al. (2020) for the management of COVID-19 and thrombotic diseases. In Fig. 2, we have summarized the considerations in antithrombotic management of patients with COVID-19 in an algorithm for antithrombotic therapy administration based mainly on such a guideline. Similar resource has been currently proposed by the Cooperative Latin-American Group of Hemostasis (CLAHT), to be discussed by the hematologists and the medical-scientific community in Latin-America, to be applied under proper protocols, to generate an evidence-based guide according to the ethnic and socioeconomic characteristics in our region.

Despite some doubts on whether administering anticoagulants at pharmacological doses improves the patient's prognosis, the American Society of Hematology recommends that patients with severe COVID-19 should receive therapeutic anticoagulation before or as soon as VTE is confirmed. Analogously, Kollias et al. (2020) proposed mandatory prophylactic anticoagulation for all hospitalized patients and pharmacological doses in severe cases.

Nevertheless, there is no evidence of a dose-effect relationship on coagulopathy in COVID-19. Actually, the controversy on whether using thromboprophylaxis or therapeutic anticoagulation for COVID-19 coagulopathy is a "hot topic" approached by different randomized protocols in progress. For instance, one of these trails aims to compare the efficacy and safety of high vs. low doses of LMWH in Italian patients with severe COVID-19 pneumonia and related coagulopathy but who do not require mechanical ventilation (Marietta et al. 2020).

Management of COVID-19 in Patients with Hypocoagulability

Because COVID-19 will likely have a significant impact in patients with different coagulation disorders such

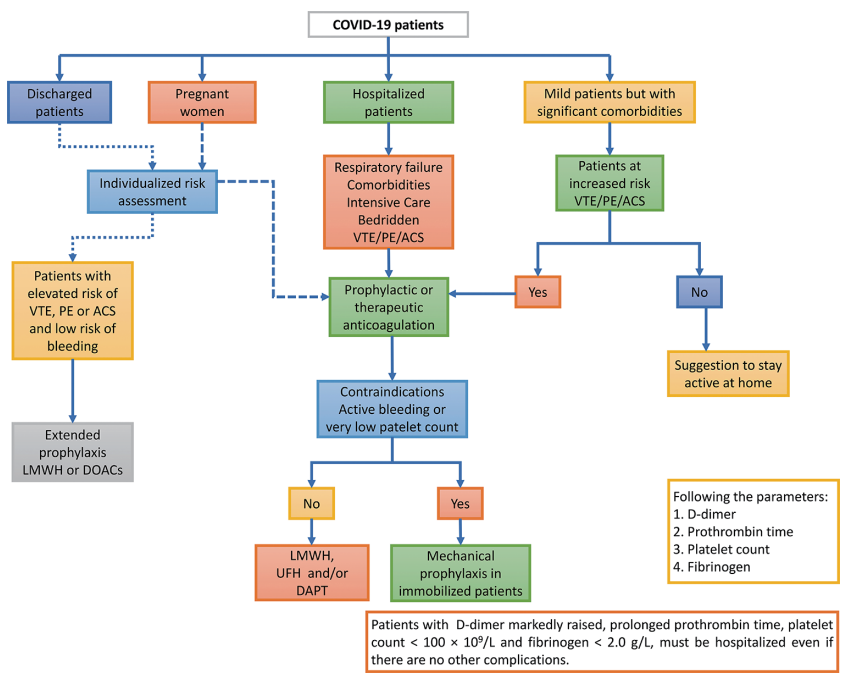

Fig. 2. Anticoagulation recommendations for COVID-19 patients with thrombotic risk.
The recommendations recently endorsed by ISTH are summarized.
LMWH, low molecular weight heparin; UFH, unfractionated heparin; DAPT, dual antiplatelet treatment; DOACs, direct oral anticoagulants. (Bikdeli et al. 2020; Thachil et al. 2020).

as hemophilia, it is necessary to know better the natural history of COVID-19 and its possible repercussions to develop strategies for the early treatment of eventual complications (Hermans et al. 2020).

So far, the concurrence of severe hemophilia A and COVID-19 has only been described in a 35-year-old male patient who presented with myalgia of the extremities and was treated with FVIII; he had mild COVID-19 and a clinical course similar to that in patients without hemophilia, not to mention that no bleeding events occurred (Cui et al. 2020). This indicates that mild SARS-CoV-2 infection does not trigger bleeding events in hemophilia patients and that replacement therapy at the start of COVID-19 may be useful. In addition, hemophilia patients can be treated in an outpatient clinic with antiviral medications such as Oseltamivir or antibiotics such as Cefdinir for which no bleeding side effects have been reported (Cui et al. 2020).

Conclusions

Although D-dimer is confirmed as the most consistent biomarker of VTE in COVID-19-related coagulopathy, C-reactive protein and IL-6 appear to be also reliable prognostic biomarkers. Given the proneness to hypercoagulation, COVID-2019 patients should be monitored closely, and those with a high risk of VTE, treated timely with anticoagulation drugs. More clinical data are needed to investigate specific issues about interactions among biomarkers and their joint relationships with disease progression, as well as about the most effective and safest anticoagulation regimen in COVID-2019 management. Hemophilia patients may not develop bleeding events and be treated conventionally.

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Conflict of Interest

The authors declare no conflict of interest.

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