Covid 19 and venous thromboembolic disease. Review on a series of patients

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INTRODUCTION

In December 2019, the first cases of an atypical pneumonia named COVID-19 (the acronym in English for "Coronavirus Disease 19") by the World Health Organization, and caused by the SARS-CoV2 virus (severe acute respiratory syndrome coronavirus-2), appeared in Wuham, China [1]. Currently the infection is considered a pandemic which has caused more than 300,000 deaths worldwide in less than 6 months.

Over the weeks and given the magnitude of the problem, several series of cases of patients infected with SARS-CoV2 have been published in different countries, including ours, basically describing clinical characteristics, laboratory data, and radiological findings [1-9].

COVID-19 and coagulopathy

Three of the publications of the Ning Tang group of Huazhong University [10-12], caused the medical community to turn their attention to the existence of inflammatory and coagulation disorders very characteristic of patients with COVID-19, and some of them related to the worst prognosis. Increments on factor VIII, fibrinogen, ferritin, interleukin-6, and especially D-dimer (DD) were described. In the group of patients with D-dimer elevation receiving heparin treatment, the mortality was lower compared to the group that hadn´t been treated [10-11]. Tang et al, conclude that patients with sepsis-associated coagulopathy, or significant elevations in DD levels, could benefit from an anticoagulant treatment [10-11].

After performing a meticulous study of the publication by Tang et al., some authors wonder if the elevation of the D-dimer, in the patients provided, could be due to the existence of pulmonary embolisms in many of them, since only 99 of the 449, had received thromboprophylaxis with heparin [13].

Since then, a large number of publications have appeared showing the importance of the thrombotic phenomena, especially venous, in patients infected with SARS-CoV2. Thus venous thrombosis has been described related to acute coronary events [14], with aortic thrombosis [15], in pregnant women [16], causing hypokinesia of the right ventricle [17], in travellers[18], etc.

However, both the incidence and prevalence of a venous thromboembolic disease (VTE) in COVID-19 infected patients, are unknown. The high risk of contagion associated with the moving of these patients in different hospital areas, as well as the fact that many of them are under an invasive ventilation at the time of the suspicious diagnosis[19], these are some of the situations that prevent us from knowing exactly the VTE in these patients. Some authors even recommend starting an anticoagulant treatment under the suspicion of VTE, and postponing diagnostic tests for pulmonary embolism (PE) and deep vein thrombosis (DVT).

With all the above, it was necessary to publish series of patients, to see if the clinical cases described above were simple anecdotes or on the contrary, if there was a close relationship between COVID-19 and venous thrombotic phenomena.

COVID-19 and VTE: case series

Until the presentation date of this work (June 17), and after an exhaustive bibliographic search, we have been able to find 26 series with three or more patients diagnosed with acute infection by COVID-19 and VTE[20-46], simultaneously. The analysis was performed on a total of 667 patients, 357 with PE and 287 with DVT (Table 1). As a whole, the publications present a very noticeable heterogeneity, so drawing conclusions on aspects such as what may be the best thromboprophylaxis treatment would be inappropriate given that in some series do not provide information in this regard.

Most of them agree in highlighting that a high incidence of VTE exists in admitted patients with COVID-19, both in the conventional ward, but mostly in those who required admission in Intensive Care Unit (ICU) 21-25, reaching a percentage between 13-85% of patients [31,34].

In some centres, the presence of COVID-19 is clearly related to a greater number of VTE cases in connection with the same period of the previous year; and even this year, patients who are COVID-19 negative have a lower incidence of VTE compared to those infected with SARS-CoV-2 [22,29,32].

The performance of diagnostic tests for VTE, CT angiography and venous Doppler echo is not uniform. There is a predominance of a greater number of authors who perform both[21-25,31,36,] the rest perform either only CT angiography [28-30,33], or only venous Doppler echo[26,27,32,34,35]. Despite the practical equality between the performed diagnostic tests, there is a greater number of patients with the diagnosis of PE. The Cattaneo series stands out, which, after performing a venous ultrasound on 64 patients infected with COVID-19, asymptomatic for VTE, did not diagnose any case of DVT [47]. In opposi-

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Table 1. Series of patients

	References	Total VTE	PE	DVT	PE-group1	PE-group2	Proximal-DVT	Distal-DVT	Thromboprophylaxis
Klok et al.	21	68	65	3	0	25	1	0	Yes
Poissy et al.	22	27	22	5	2	11	ND	ND	Yes
Helms et al.	23	28	25	3	17	8	ND	ND	Yes
Middeldorp et al	24	33	11	22	0	11	12	9	Yes
Llitjos et al.	25	24	6	18	ND	ND	ND	ND	Yes
Spiezia et al.	26	5	0	5	0	0	ND	ND	Yes
Cui et al.	27	20	0	20	0	0	ND	ND	No
Franco-López et al.	28	8	8	0	3	4	0	0	ND
Leonard-Lorant et al.	29	32	32	0	18	14	0	0	ND
Grillet et al.	30	23	23	0	ND	ND	0	0	ND
Lodigiani et al.	31	16	10	6	3	4	4	1	Yes
Marone et al.	32	16	0	16	0	0	7	4	Yes
Griffin et al	33	3	3	0	1	ND	0	0	Yes
Ren et al.	34	41	0	41	0	0	5	36	Yes
Demelo-Rodríguez et al.	35	23	0	23	0	0	1	22	Yes
Beun et al.	36	23	20	3	4	16	ND	ND	Yes
Bompard et al.	37	32	32	ND	10	22	ND	ND	Yes
Poyiadji et al.	38	72	72	ND	41	31	ND	ND	Yes
Nahum et al.	39	27	ND	27	ND	ND	9	23	Yes
Tveita et al.	40	3	3	ND	ND	ND	ND	ND	Yes/ Not all
Zhang et al.	41	66	1	66	ND	ND	23	43	Yes/Not all
Voicu et al.	42	26	ND	ND	ND	ND	13	13	Yes
Thomas et al.	43	5	5	ND	1	4	ND	ND	Yes
Tavazzi et al.	44	10	2	8	0	2	ND	ND	Yes
Gervaise et al.	45	13	13	ND	6	7	ND	ND	No
Grandmaison et al.	46	23	4	21	ND	ND	7	21	Yes
		667	**357**	**287**	**106**	**159**	**82**	**172**	

Abbreviations: ND, Not documented; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.

tion, we find the results of Ren et al., who diagnosed 85% patients admitted in ICU with COVID-19 as DVT[34].

We have divided the anatomical distribution of PE into two groups: group 1-proximal, which includes PE with central-trunk-lobar location; and 2-distal group, which are segmental and sub-segmental PE. Some series, such as that of Llitjos et al., and Grillet et al., do not specify the distribution [25,30]. In the rest, we found almost twice as many cases in the group 2-distal (159 cases) as in the 1-proximal group (106 cases). The anatomical location of DVTs is wide (proximal, distal, superficial, upper limb, thrombosis of the inferior cava, associated with a catheter, etc.), with a clear predominance of distal DVT over the others.

The timing of the VTE diagnosis is also variable. Generally, in patients admitted to the ICU, it is diagnosed up to the 5th day on average [23]; in the series by Grillet et al., the diagnosis of PE is 12 days after the onset of COVID-19 symptoms [30]. Lodigiani et al., describe that half of thromboembolic events in their 36 patients occur within 24 hours of hospital admission[31].

The anticoagulant treatment prior to the diagnosis of SARS-CoV2 infection, prevented the appearance of VTE in all 19 patients who received it in Middeldorp et al., series [24]. Something different ocurred to a total of 11 anticoagulated patients in the Poissy et al., Llitjos et al., and Leonard-Lorent et al [22,25,29]. In most series, patients were receiving treatment for ETV thromboprophylaxis with the correct doses, even at higher doses, and a small group were anticoagulated, as previously stated. To be highlighted in the series described by Cui et al., of 81 patients admitted to the ICU, the absence of thromboprophylaxis in all is described, including the 20 patients who developed DVT [27].

Anatomo-pathological findings

The first descriptions of the biopsies obtained from cadavers deceased from COVID-19, at a pulmonary level predominated diffuse alveolar damage (DAD) to different degrees, with hyaline membranes and interstitial thickening[48,49]. In Carsana et al., and Dholnikoff et al., minimally invasive autopsies in 48 deaths from COVID-19, in addition to the diffuse alveolar damage, the existence of fibrin thrombi in small pulmonary arterioles is evident in most patients [50,51]. The complete autopsies of 35 deceased patients with COVID-19 have been published, in which the existence of thrombi in the small pulmonary arterial vessels, with small haemorrhages, is revealed again, all of which is compatible with microangiopathy associated to SARS-Cov-19[52-55]. In addition to prostate and pulmonary micro vascular thrombosis, Wichman et al., and Menter et al., confirm the existence of bilateral DVT and fresh pulmonary embolisms, which are identified as the cause of death in a high percentage of patients[54,55].

It should be noted that a third of those who died in the series from Wichmann et al., were receiving anticoagulant treatment before their death. In short, there is data on hypercoagulability, mainly with pulmonary microangiopathic involvement and macrovascular thromboembolic disease, both in the lung and in the lower extremities.

SUMMARY

1. Based on the data provided in the series of clinical and autopsy cases, VTE is a frequent pathological process in patients with COVID-19. It affects two possible non-exclusive forms, a "microvascular" with micro thrombi in lung areas affected by DAD, in relation to microangiopathy, which can progress into the form of local pulmonary thrombosis[56,57]. This form would be consistent with a greater number of cases of segmental-

sub segmental involvement, and even in those cases in the absence of DVT and presence of PE demonstrated by CT angiography. The second is a "macrovascular" form of venous thrombosis, demonstrated both in radiological studies, and especially in necropsies, which causes PE with significant repercussions in right heart chambers, causing death. Prospective series will be published shortly, such as that of the RIETE group with data from 592 patients with VTE and COVID19 infection (Fernández-Capitán et al., pending publication) that will increase our knowledge about these pathologies.

2. The decision to increase thromboprophylaxis doses, or to directly initiate a full-dose anticoagulant treatment to prevent coagulopathy associated with COVID-19, as well as the VTE that may develop, are not based on the results of any clinical trial. However, some guidelines recommend increasing thromboprophylaxis doses based on the results of Ning Tang publications, clinical data from patient series, and information obtained from autopsies. The posture of starting anticoagulant treatment at the time of hospital admission is proposed by some authors based on the significant increase in the number of cases of VTE related to COVID-19 detected in their hospital centres[32]. The guidelines of different scientific societies recommend continuing thromboprophylaxis with the usual doses, justifying its increase based on weight or added risk factors (such as previous VTE or cancer)[58-61]. Vivas et al, recommend increasing the dose or even anticoagulation in those patients with a high thromboembolic risk established by clinical and analytical parameters [62]. Several clinical trials are ongoing, evaluating the suitability of increasing the thromboprophylaxis dose [63].

3. There are discrepancies in regard to the drugs to be used in the treatment of coagulopathy associated with COVID-19 with a clear tendency to thrombotic phenomena. The controversy is established by some authors, considering patients with elevated fibrinogen, factor VIII, and DD, together with anti-thrombin III in the normal range, as components of a pro-coagulant state, which would cause a therapeutic resistance to LMWH [36,64]. Therefore, they recommend a treatment with unfractionated Heparin (HNF) adjusted to anti-Xa levels, and even if there is a clinical worsening, with systemic fibrinolysis [36,64]. The group by Barrett et al., established as the main measure, to anticoagulate with HNF those infected with COVID with severe forms of coagulopathy and clinical deterioration from their admission [64].

4. With the data observed in the autopsies of patients with COVID-19, it becomes evident that there is both a macrovascular and microvascular involvement, preferably venous. Underlying microvascular injury there is a notable impact on the endothelium caused by a tremendously complex inflammatory process and variable in intensity, with mechanisms in which platelets, neutrophils, mast cells, NETs, cytokines, interleukins, haemostasis factors, and complement are involved, among others[65-69]. After seeing the complexity in the pathophysiology of thrombosis caused by COVID-19, it is appropriate to call the process "immunothrombosis" since both processes are linked. We therefore believe that, in addition to trials that would evaluate different anticoagulation modalities and doses for the prevention of coagulopathy and VTE, trials should be launched to study different therapeutic targets [68], as to avoid the inflammatory cascade, in which the thrombotic phenomena are a fundamental part, but not the only one, and probably the final stage of the entire inflammatory process triggered by SARS-CoV2.

CONCLUSIONS

The association between SARS-CoV2 infection and VTE is frequent, as evidenced in the clinical case series, and also in the necropsies of those who died from COVID-19. The incidence and prevalence of COVID-19 associated with VTE are highly variable, due to the difficulty in diagnosing VTE in these patients, caused by their high contagiousness and their clinic situation, mainly in intubated patients. There is a venous microvascular and a macrovascular involvement, with peripheral and central lung embolisms, as well as proximal and distal deep vein thrombosis. The relevance of thromboembolic disease within COVID-19 is due to the fact that its responsibility has been proven in the deaths of a significant number of people infected with SARS-CoV2. The multiple pathological analysis show damage to the vascular endothelium with thrombosis at the pulmonary level, which was initiated by viral infection and with pathophysiological mechanisms involving a large number of elements, therefore the process has been called "immuno-thrombosis". The clinical trials publication on thromboprophylaxis in these patients is essential, given the great controversy that exists on the subject. We believe that venous thrombosis is multifactorial and the final consequence of the entire process which begins with SARS-Cov2 infection. It is necessary to achieve the neutralization of the virus, and also to study possible targets in the immunological process, which would prevent reaching the end in the form of thrombosis.

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