HANDLING THE COMPLEXITY: THE CASE OF COVID-19 COAGULOPATHY AND THE RISK OF VENOUS THROMBOEMBOLISM

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In December 2019, a cluster of acute respiratory illnesses caused by SARS-CoV-2 virus occurred in Wuhan, Hubei Province, China. The disease has rapidly spread from Wuhan to many other countries worldwide, soon becoming a global health emergency.

Although most patients have mild manifestations and good prognosis after infection, some patients develop severe symptoms and die from multiple organ complications. The pathogenesis of COVID-19, the disease that results from SARS-CoV-2 infection SARS-CoV-2 infection in humans, remains unclear, although it is very likely that the most severe manifestations of COVID-19 may be linked to host-pathogen interaction immune mechanisms. [1]

SARS-CoV-2 infection seems to induce in most critical cases an excessive and aberrant hyper-inflammatory host immune response that is associated with a so-called "cytokine storm", characterized by plasma increase of infection-related biomarkers and of many cytokines and chemokines documented in many observational studies. [1,2]

A pro-thrombotic derangement of the haemostatic system has been reported in most severe forms of COVID-19 infections [3,4].

This finding is consistent with the activation of a coagulative cascade primed by inflammatory stimuli already observed in many other forms of sepsis. Indeed, several studies have demonstrated the close interconnection between thrombosis and inflammation, two processes mutually reinforcing each other [5]. Both coagulation factors and platelets are directly implicated in the modulation of the host immune response, displaying proinflammatory functions independent of their haemostatic effects.

From a clinical perspective, the extent of the derangement in coagulation parameters in patients affected by severe COVID-19 pneumonia was associated to a poor prognosis. [6] In these patients, Low Molecular Weight Heparin (LMWH) at doses registered for prevention of venous thromboembolism (VTE), i.e. Enoxaparin 4000 IU subcutaneously daily, has been proven to be associated with a reduced risk of death [7] and is currently recommended by World Health Organization [8] and by several Scientific Societies, including SISET. [9]

However, some issues about the use of LMWH in COVID-19 pts require further clarification, such as the true incidence of venous thromboembolism in COVID-19 patients.

Data on this issue are puzzling, as they range from 0% to about 8% in general wards [10-13], and from 16% to 35% in the ICU setting, often despite adequate LMWH prophylaxis [12-18]. A strikingly higher rate of VTE, up to 58%, has been reported in consecutive autopsies performed in COVI-19 patients in whom VTE was not suspected before death. [19](Table 1)

This finding prompted some Authors to raise the question whether the pulmonary vessels occlusions observed in COVID-19 patients result from embolization of a deep-venous thrombosis or from a

thrombotic microangiopathy affecting the pulmonary vascular bed [28].

On this regard, it has been suggested that the diffuse bilateral pulmonary inflammation observed in COVID-19 is associated with a novel pulmonary-specific pathophysiological entity termed pulmonary intravascular coagulopathy (PIC), a peculiar form of localized microangiopathy distinct from Disseminated Intravascular Coagulation. [20]

Which lessons can be learned from this quite confusing picture?

The first, and the most important one, is that not always things are as they seems, as highlighted by the complex relationship between the coagulopathy of COVID-19 patients and the risk of VTE.

The acknowledgment of such a complexity involves important practical effects.

Indeed, it is conceivable that higher doses of LMWH might further mitigate cytokines storm and improve the prognosis of COVID-19 patients. However, the paper of Tang and Colleagues showed a non-significant trend towards a negative effect of the treatment with LMW in patients with the less severe degree of coagulopathy, as assessed by a Sepsis-Induced Coagulopathy (SIC) score <4 or d-dimer levels <6-fold the upper limit of normal. This finding could fit with the caveat on the use of high-dose heparin in the setting of microangiopathies, possibly contributing to the described hemorrhagic component of these diseases.

We can conclude that even in the overwhelming scenario of a pandemia the medical knowledge should proceed as usual, step by step, starting from pathophysiology and cautiously moving toward the evidence provided by properly designed randomized controlled trial.

Table I
Reported incidence of venous and arterial thromboembolism in hospitalized COVID-19 patients

Author [ref]	Setting	Reported VTE incidence
Cattaneo [10]	64 general ward pts on LMWH prophylaxis systematic leg compression ultrasonography)	0% DVT
Thomas [11]	63 general ward pts (standard LMWH prophylaxis)	8% PE, 1.5% DVT (including UEDVT)
Lodigiani [12]	314 general ward pts (75% on LMWH prophylaxis) 48 ICU pts (100% on LMWH prophylaxis)	General ward: PE 2.5%, 1% DVT (including UEDVT), **1.9% stroke** ICU: PE 4.2%, 4.1% isolated DVT (including UEDVT), **6.3% stroke**
Middeldorp [13]	123 general ward pts (standard LMWH prophylaxis) 75 ICU pts (doubled LMWH prophylaxis)	General ward: PE 6.6%, 13% DVT (including UEDVT) ICU: PE 15%, 32% DVT (including UEDVT)
Klok, 2020 [14]	184 ICU pts on LMWH prophylaxis	35% PE, 1.6% DVT (including UEDVT) **3.8% ATE**
Poissy [15]	107 ICU pts (100% on VTE prophylaxis)	20.6% PE
Cui [16]	81 ICU pts NOT on LMWH prophylaxis	25% DVT
Llitjos [17]	26 ICU pts (31% LMWH prophylactic, 69% therapeutic) systematic leg compression ultrasonography)	23% PE VTE significantly higher in pts. on prophylactic vs therapeutic anticoagulation (100% vs. 56%)
Helms [18]	150 ICU pts (70% LMWH prophylactic, 30% therapeutic)	16.7% PE 2.6% ATE
Whichmann [19]	***12 consecutive AUTOPSIES on COVID-19-positive pts***	***DVT in 7 of 12 patients (58%) in whom VTE was not suspected before death*** ***PE was the direct cause of death in 4 patients.***

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