Covid-19 and Thromboembolic events

Ioannis Ntouvas[1], Chrysanthi Papageorgopoulou[2], Konstantinos Nikolakopoulos[2]

The coronavirus pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reportedly associated with a high risk of thrombotic complications. It is well established that viral infections are linked to coagualation alterations as part of an interaction between the immune system and blood coagulation. Both systems are closely intertwined for an effective immune response that limits the infection. The key point is the recruitment of leukocytes simultaneously with the activation of coagulation where clot components, such as fibrin, serve as a scaffold for cell adherence and migrations [1]. On the other hand, pathogens such as viruses may induce tissue factor (TF) expression, a major activator of coagulation, on monocytes and endothelial cell surfaces. Therefore, there is an activation of coagulation that could lead to both Venous Thromboembolic Events (VTE) as well as hemorrhagic complications [2]. It is not well established why some viruses cause hemorrhages (e.g Ebola), others thrombose (e.g. cytomegalovirus, SARS-CoV-2) and others both complications (e.g. varicella zoster virus).

Many studies suggest that there is a substantial increase of thromboembolic events in Covid-19 patients. Hence, in a large study from Milan, including 388 patients, 61 of whom were admitted to the Intensive Care Unit (ICU), the reported VTE rate was 7.7%. VTE incidence was higher in ICU patients (16.7% versus 6.4%). It is worth mentioning that half of the thromboembolic events were diagnosed within 24 h of hospital admission, raising the question whether thrombosis is an early complication of Covid-19 or a determinant of further deterioration [3]. In a retrospective study at the Amsterdam University Medical Center, including 198 patients (74 in ICU and 124 on medical ward), 33 (17%) were identified with VTE. The proportion was dramatically higher in ICU patients (39% vs 3.2%), although they had received thromboprophylaxis at standard or double doses [4]. Likewise, Klok et al. [5], found a 31% incidence of VTE in ICU patients with Covid-19, despite thromboprophylaxis. Similarly, Cui et al. [6] in 81 ICU patients with Covid-19 pneumonia, found an 25% incidence of VTE.

The increased VTE rate in Covid-19 patients, combined with an extensive alteration in biological markers (e.g. D-Dimers), suggest an abnormal hypercoagulability. In a retrospective cohort study from Wuhan-China, among hospitalized SARS-CoV-2 patients, 68% had D-dimer levels above the upper limit. Although, D-Dimer levels do not constitute a specific marker for VTE, increased levels reveal the impact of SARS-CoV-2 to coagulation. More importantly, the D-dimer increase was dynamic. It continues to rise as the disease progresses, reflecting a prognostic indicator of mortality [7]. Furthermore, in an another study, it is reported that prothrombin, a natural anticoagulant, was lower in Covid-19 patients [3]..Additionally, in a case series in France, the lupus anticoagulant was identified in 25 of 56 patients (45%) admitted with Covid-19 [8].

Covid-19, compared with other bacterial or viral infections, seems to have a stronger correlation with VTE. The first 107 consecutive Covid-19 patients admitted to ICU in a single center in France, were compared to patients admitted to the same ICU one-year prior with influenza and other diseases. At the time of analysis, 22 (20.6%) of the Covid-19 patients had Pulmonary Embolism (PE). In contrast, one year prior, the general and influenza ICU population, had PE rates of 6.1% and 7.5%, respectively [9]. In another, multicenter study from the Netherlands, the incidence of thrombotic complications in hospitalized Covid-19 patients were

[1]General Hospital of Patras, Patras, Greece
[2]Department of Vascular Surgery, University Hospital of Patras, Patras, Greece

Received: 14 Sep 2020; Accepted: 23 Dec 2020

Key words: *Covid-19; thromboembolic events; ICU*

considerably higher compared to that of hospitalized influenza patients, suggesting a possible SARS-COV-2 specific effect [10]. Furthermore, a prospective cohort study from France, which included 150 Covid-19 patients, with Acute Respiratory Distress Syndrome (ARDS) and 233 ARDS patients due to bacterial and other viral infections, in 4 ICUs, revealed that Covid-19 patients had statistically significant higher rates of PE (11.7% versus 2.1%) [11].

Another point of view, regarding the VTE and Covid-19 correlation is that according to several studies, there is a disproportionate high number of PE not related to deep vein thrombosis [12]. This emerges a hypothesis that the pathophysiology of the pulmonary thrombotic events in Covid-19 may not be embolic at all, which in turn could have major implications for treatment. A review of 10 autopsies of Covid-19 patients (5 men, 5 women) found evidence of microthrombi in lung tissue, thus raising the suspicion that in-situ pulmonary thrombosis may be the main pathophysiological mechanism [13].

In conclusion, Covid-19 is a very contagious virus, with a high proportion of thromboembolic events. Patients admitted to ICU are in a higher risk for VTE, despite thromboprophylaxis. Therefore, it is of vital importance to be alert for VTE, when treating Covid-19 patient admitted to hospital, especially in the ICU.

Conflict of interest disclosure: *None to declare*

Declaration of funding sources: *None to declare*

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Corresponding author:

Ioannis Ntouvas
D. Gounari 187, Patra, 26331
Tel.: +30 6936 188344,
E-mail: ntouvas@gmail.com