Mini Review

Incidence, pathogenesis and management of thromboembolic complications in severe COVID-19

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Key words:
- COVID -19
- Thromboembolism
- Coagulopathy

Abbreviations:
APTT: Activated Partial Thromboplastin Time
ACE2: Angiotensin-converting enzyme 2
DVT: Deep Vein Thrombosis
DIC: Disseminated Intravascular Coagulation
IL-6: Interleukin -6
LMWH: Low molecular weight heparin
PE: Pulmonary Embolism
PT: Prothrombin Time
VTE: Venous Thromboembolism

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ABSTRACT

Arterial and venous thromboembolic events are frequent complications of severe COVID 19 with an estimated incidence approximately 30%. High levels of D-dimers and fibrinogen, prothrombin time (PT) prolongation and mild thrombocytopenia compose the hypercoagulable profile of COVID 19 patients, while positive antiphospholipid antibodies have also been reported. The hyperinflammatory state in combination with the endothelial damage by the virus and the diffuse microvascular thrombosis contribute to the pathogenesis. Vigilance should be maintained for the early diagnosis of thrombotic complications. Low molecular weight heparin (LMWH) has been shown to reduce mortality in high risk patients, while the administration of higher dose of anticoagulants (intermediate, therapeutic) in order to prevent thromboembolic disease is further investigated.
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INCIDENCE

COVID 19 is associated with a high incidence of thromboembolic disease, especially in critically ill patients, where ARDS has been shown to increase significantly the odds of thrombotic and cardiovascular events[1]. Specifically, major arterial or venous thromboembolism and symptomatic venous thromboembolism (VTE) complicated COVID 19 in 35.3% and 27.0% of ICU patients and 2.6% and 2.2% of hospitalized non-ICU patients. The majority of them (89.4% and 84.7% respectively) received prophylactic anticoagulation[1]. Additionally, thrombotic complications, both venous and arterial, were reported in 31% of 184 COVID 19 ICU patients, of which 81% were pulmonary embolisms (PE)[2]. When F.A. Klok et al extended the mean period of observation from 7 to 14 days the cumulative incidence was raised to 49%, with PE representing 87% of thrombotic events[3]. In a prospective cohort study in 4 French ICUs, 64 thrombotic complications

were recognized in 150 patients (43%) with COVID 19 ARDS, of which 25 (16.7%) were PE[4]. Significantly more pulmonary embolisms were detected in COVID 19 ARDS compared with non COVID 19 ARDS. In the last two studies all patients were treated with prophylactic or therapeutic anticoagulation[2,4]. In a retrospective study with 81 ICU patients with severe COVID19 pneumonia VTE incidence was 25%[5], while in two studies from France[6,7] where a venous ultrasound of the inferior limbs was performed in all COVID 19 patients admitted to the ICU, including the asymptomatic ones, the incidence of VTE was 65% and 69% respectively[7]. COVID 19 is also an independent risk factor for ischemic stroke, after adjusting for age, sex, and major vascular risk factors[8]. Ischaemic stroke complicated 4.6% of 219 COVID 19 patients, who were significantly older than patients without stroke ($p<0.001$), had more cardiovascular risk factors, such as hypertension, diabetes mellitus and history of cerebrovascular disease (all $p<0.05$) and presented with more severe COVID-19 ($p<0.01$)[9]. Finally, 7.7% of ICU patients suffered a non–ST-segment elevation myocardial infarction (MI)[1].

PATHOGENESIS

Severe COVID 19 is characterized by a hypercoagulable state, leading to increased susceptibility to thrombosis. Pathological coagulation values have been found in 20-55% of hospitalized patients, namely increased d-dimers, prolonged prothrombin time (PT), mild thrombocytopenia and, in late disease, decreased fibrinogen level[10]. A worse prognosis is associated with Disseminated Intravascular Coagulation (DIC) and coagulation abnormalities (elevated D dimers, PT prolongation)[11,12] Yan Zhang et al collected the coagulation parameters for 19 ICU COVID 19 patients: 100% had elevated D dimers and FVIII activity, 74% had high fibrinogen level and prolonged PT, 58% had prolonged Activated Partial Thromboplastin Time (APTT) and 37% developed thrombocytopenia. Decreased levels of protein C, protein S and antithrombin were detected and 53% had positive antiphospholipid antibodies. In terminal stage disease a lower FV, FVII, and higher PT were observed[13]. In another prospective cohort study, lupus anticoagulant was positive in 50/57 (87.7%) tested patients and elevated Von Willebrand factor (vWF) activity and vWF antigen (vWF:Ag) were also reported[4]. Increased thrombogenesis of COVID 19 is related to the activation of coagulation system, the possible development of DIC, while the role of antiphospholipid antibodies must be further investigated.

The systemic hyperinflammatory response, observed in severe COVID 19, enhances coagulopathy[14]. Ranucci et al noticed a significant association between interleukin -6 (IL-6) and fibrinogen levels, supporting the concept of thromboinflammation[15], the interaction between inflammation and coagulopathy[16], while IL-6 has been shown to induce the procoagulant tissue factor (TF)[13]. Similarly D dimers ($p<0.001$) and CRP ($p<0.05$) were significantly elevated in COVID 19 patients with stroke[9] SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors which are expressed in the epithelial cells of lungs, upper respiratory system, intestine, kidneys, heart, vessels and pancreas[17]. In the vascular endothelium it triggers an inflammatory response, as a lymphocytic "endotheliitis", which contributes to the thrombus formation[18]. The disruption of the vascular endothelium losing its antithrombotic protection and the procoagulant effect of the inflammatory mediators lead to *in situ* immunothrombosis[3,15]. Widespread pulmonary microthrombi have been documented in autopsy studies resulting in microvascular thrombosis[18]. Coagulopathy may also be related to hepatic dysfunction which may complicate COVID 19, and is also accompanied by coagulation abnormalities such as PT prolongation and thrombocytopenia[19].

Regarding cerebrovascular events, 65.6% of ischemic strokes were considered as cryptogenic and 34.4% as embolic of undetermined source. Cryptogenic stroke was possibly related to COVID 19 coagulopathy. Compared with stroke patients without COVID 19, patients with COVID 19 and stroke, were significantly younger ($p=0.001$), had higher D-dimer level ($p=0.011$) and erythrocyte sedimentation rate ($p=0.001$), had more frequently an elevated troponin level ($p<0.001$) and less commonly presented with risk factors such as hypertension and history of prior stroke or transient ischemic attack ($p=0.017$ and $p=0.007$ respectively)[20]. Concerning acute coronary syndromes, an obstructive disease was diagnosed in 6/9 (67%) patients who underwent coronary angiography, while non obstructive disease was assumed to have a significant part in the pathogenesis of myocardial injury, with hypoxia, coronary spasm, microthrombi and direct endothelial injury contributing to it[21].

Management of of thromboembolic complications

Anticoagulation mainly with low molecular weight heparin (LMWH) reduced 28 day mortality in COVID 19

patients who had severe coagulation disorders, namely a sepsis-induced coagulopathy (SIC) score ≥4 (p = 0.029), or D-dimer >6-fold of upper limit of normal (p =0.017)[22]. Similarly, among 525 COVID 19 patients, administration of LMWH reduced in hospital all cause mortality, especially for critically ill patients, elderly (age > 65), and patients with high levels of IL-6 (> 10 times upper limit level), and D-dimer (> 5 times upper limit level)[23]. Moreover, M. Ranucci et al noticed that a higher dose of LMWH resulted in a significant decrease of fibrinogen levels and D-dimers[16]. Patients with marked inflammatory response seem to be more benefited[10] as heparin has also shown anti inflammatory and antiviral properties. Surface proteoglycans, that mediate the binding of SARS-CoV-2 to ACE2 receptor, can be displaced by heparin, preventing its entry into host cells[24]. Intravenous tPA (Alteplase) was also administered off-label by J. Wang et al in 3 patients with COVID 19 ARDS and high levels of D dimer with an initial transient improvement in PO2/FiO2 ratio observed[25].

Early diagnosis and treatment of thromboembolic complications is crucial. D-dimer had a sensitivity of 85.0% and a specificity of 88.5% for diagnosing VTE, with a cut-off value of 1.5 μg/mL[5]. However routine screening of critically ill patients for the detection of asymptomatic VTE with bedside venous ultrasonography is not currently recommended[26]. Acute respiratory deterioration, a significant increase in D dimer levels or unexplained right ventricular dysfunction should prompt the performance of further diagnostic tests such as a CT pulmonary angiogram (CTPA) and venous ultrasound[4]. Taken into account the risk of virus transmission and of transportation of unstable patients, a cardiac echocardiogram with signs of right ventricular dysfunction can be a valuable diagnostic tool. Given the increased incidence and mortality of thrombotic complications, the optimal dose regimen of LMWH needs to be determined especially in critically ill patients and results from studies concerning the administration of either prophylactic, intermediate or full therapeutic anticoagulant dose are pending. The rate of VTE and PE was significantly higher for patients receiving prophylactic anticoagulation compared with those receiving a therapeutic dose (100% versus 56%, respectively, p = 0.03)[7], while in another study 15% of patients that were diagnosed with deep vein thrombosis (DVT) 48 hrs post admission had been treated with prophylactic anticoagulation[6]. Renal function, body mass index, values of coagulation parameters, risk stratification scales and anti-Xa measurement can be employed to determine the thromboprophylaxis strategy[15,27]. According to International Society on Thrombosis and Haemostasis clinical guidance[26] and American College of Chest Physicians (ACCP) guidelines[28], standard dose thromboprophylaxis is currently recommended in all hospitalized patients, while intermediate dose can be considered in critically ill patients who are obese or at high thromboembolic risk[26]. LMWH is recommended over unfractionated Heparin (UFH) in order to minimize staff exposure, while the use of other parenteral anticoagulants, such as danaparoid, bivalirudin, argatroban and fondaparinux in COVID 19 requires further investigation[24]. In case of pharmaceutical anticoagulation contraindication, mechanical VTE prophylaxis (intermittent pneumatic compression) should be applied in critically ill patients. Extended thromboprophylaxis after discharge (14-30 days) should also be considered for high risk patients with LMWH or Direct Oral Anticoagulants (DOACs)[26].

In conclusion, thromboembolic events frequently complicate severe COVID 19, as the interplay between hypercoagulability and excessive inflammation favors thrombogenesis. All hospitalized patients should receive standard dose anticoagulation unless it is contraindicated, while further investigation on the optimal thromboprophylaxis strategy, especially in critically ill and high risk patients, is required.

CONFLICTS OF INTEREST

None.

ΠΕΡΙΛΗΨΗ

Επίπτωση, παθογένεση και αντιμετώπιση των θρομβοεμβολικών επιπλοκών της σοβαρής COVID -19

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Τα θρομβοεμβολικά επεισόδια αποτελούν συχνές επιπλοκές της COVID 19, με υπολογιζόμενη επίπτωση 30%. Τα υψηλά επίπεδα D- dimers και ινωδογόνου, η παράταση του χρόνου προθρομβίνης (PT) και η ήπια θρομβοπενία χαρακτηρίζουν το προφίλ υπερπηκτικότητας των ασθενών με COVID 19, ενώ έχουν επίσης αναφερθεί θετικά αντιφωσφολιπιδικά αντισώματα. Η υπερφλεγμονώδης απάντηση σε συνδυασμό με την ενδοθηλιακή βλάβη που προκαλεί ο ιός και τη διάχυτη μικροαγγειακή θρόμβωση εμπλέκονται στην παθογένεση. Ο διαγνωστικός έλεγχος θα πρέπει να διενεργείται έστω και με χαμηλό δείκτη υποψίας. Η θεραπεία με ηπαρίνη χαμηλού μοριακού βάρους (LMWH) φάνηκε να μειώνει τη θνητότητα σε ασθενείς υψηλού κινδύνου, ενώ μελετάται η χορήγηση υψηλότερης δόσης αντιπηκτικών (ενδιάμεση, θεραπευτική) για την πρόληψη των θρομβοεμβολικών επεισοδίων.

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Λέξεις - Κλειδιά: *COVID 19, θρομβοεμβολική νόσος, διαταραχές πηκτικότητας*

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