



REVIEW PAPER

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Coagulation markers in diagnostic and monitoring of thromboembolic complication in COVID-19

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ABSTRACT

Introduction. Coronavirus disease 2019 (COVID-19) was first observed in China in Wuhan city, Hubei province in December, 2019, and specified as a pandemic by the World Health Organization (WHO). COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2).

Aim. The aim of this article is to discuss epidemiology of thromboembolic complication in COVID-19.

Material and methods. This article is a review done in regards to discuss clinical features of the anticoagulation treatment in COVID-19.

Analysis of the literature. A review is discussed an anticoagulation treatment in 41 manuscripts.

Conclusion. Most commonly coagulation abnormalities in patient with COVID-19 is mild thrombocytopenia. Apart from their typical role in thrombosis and hemostasis, platelets mediate key aspects of immune and inflammatory.

Keywords. anticoagulation, coagulation abnormalities, COVID-19

Introduction

To date has been reported 193 097 950 cases, 4 146 985 deaths and 175 532 906 recovered. The symptomatic phase manifests generally with fever, cough and myalgia to severe respiratory failure. The diagnosis is con-

firmed using reverse transcriptase PCR. Laboratory abnormalities usually include: leukocytosis, leukopenia (reported in 63% of patients), neutrophilia, hypoalbuminemia, hyperglycemia and elevated liver enzymes, lactic dehydrogenase (LDH), C-reactive protein (CRP),

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ferritin, creatinine kinase, troponin and myoglobin levels. One of leading clinical features of the severe infection is a coagulopathy.^{1,2} Therefore, coagulation tests may be considered useful to discriminate severe cases of COVID-19. The clinical presentation of COVID-19-associated coagulopathy is organ dysfunction primarily with high risk of venous thromboembolism, while hemorrhagic events are rarely seen.³ Excessive inflammation, platelet activation, endothelial dysfunction, and stasis are at the root of thromboembolic complications in COVID-19.⁴ COVID-19 associated alterations of hemostasis is multifactorial. Endothelial dysfunction is triggered by increased levels of von Willebrand Factor; systemic inflammation, by Toll-like receptor activation; a procoagulatory state, by tissue factor pathway activation.⁵ Moreover, increased secretion of interleukins (IL-1, IL-2, IL-6, IL-7, interferon- γ inducible protein 10, MCP-1, MIP1-a), tumor necrosis factor (TNF)-alpha and, granulocyte colony stimulating factor (G-CSF) may promote lymphocyte apoptosis by cytokine storm.^{6,7} Complement activation is also thought to be heavily involved in thrombosis by complex C5b-9, C3a and C5a.

Aim

We investigated the feasibility of an increase in research towards the better understanding of COVID-19.

Material and methods

All materials are based on data base such as PubMed, Science Direct and Medline.

Analysis of the literature

Epidemiology of thromboembolic complication in COVID-19

In Middeldorp et al. analysis demonstrated high risk for venous thromboembolism (VTE) in hospitalized patient with COVID-19 including intensive care units patient (ICU) on days to 2 March from 12 April 2020. Identified 199 patients because of COVID-19. One patient was excluded because he was transferred to another. Of the remaining 198 patients, 148 (75%) were hospitalized after an emergency department visit, whereas 50 (25%) were transferred from another hospital. Seventy-five patients (38%) were admitted to the ICU after being transferred from the ICU of another hospital (n=44), our general ward (n=20), or directly from the emergency department (n=11). After 7 days 39 patients (20%) were diagnosed with VTE.⁸ Lodigiani et al. examined 388 patient who were admitted to a university hospital in Milan between 13.02–10.04.2020. Thromboembolic events recognized in 7.7% (28 patient) half of them were diagnosed within 24 h of hospital admission [9]. In Cui et al study 81 patients with COVID-19 in ICU. VTE proved in 20 patient 25% (25%), 8 of patients with VTE died.¹⁰ Klok et al. confirmed VTE in 27% analyzed

COVID-19 patient.¹¹ In a Klok's cohort of 184 ICU patient with COVID-19 the cumulative incidence of large-vessel thrombotic events was dizzying 49%.¹² On the basis of numerous studies it has been proven that the incidence of thromboembolic complication in patients with COVID-19 may be related to poor prognosis. In this article, we present the known and used markers in the diagnosis and monitoring of thromboembolic complications in patients with COVID-19, whose knowledge of the evolution in will allow to improve diagnosis, treatment, and thus the chances of health and survival of patients with the severe form of COVID-19.

Coagulation markers in VTE in patient with COVID-19 disease

D-dimers as a the most common coagulation abnormality in COVID-19

In VTE there is an increase in the concentration of D – dimers end product of fibrin degradation by plasmin. It is not a VTE specific marker, because its high levels are found in many diseases. The cut-off point is value 500 ng/ml. Keep in mind that over 60 years of age the specificity and clinical utility of the D- dimer has increased.¹³ D-dimer are sensitive (80–100%) for VTE. Therefore, normal levels rule out VTE. High level of D-dimer in COVID-19 patients associated with excess thrombin generation secondary to endothelial activation induced by the infectious, hypoxemia and microthrombosis.¹⁴ An elevated D-dimer found in up to 45% of COVID patients, is recognized as an independent risk factor for death.¹⁵⁻¹⁷ To Tang et al. research were classified 183 patients suffered from COVID-19. The changes in coagulation markers were followed from day 1 to day 14 after admission at three-day intervals. The non-survivors patients (n=21) revealed significantly higher D-dimer compared to survivors (n=162) on admission. The study has shown that existence of DIC is common in deaths. abnormal coagulation results, especially markedly elevated D-dimer and FDP, may have the potential to guide therapy and evaluate prognosis.¹⁸ Al-Samkari based on an analysis of 400 patients stated that D-dimer >2500 ng/mL gives adjusted odds ratio for thrombosis, 6.79.¹⁹ On the basis of tests performed in two French centers researchers concluded that at admission, D-dimer < 1.0 $\mu\text{g/ml}$ has an excellent negative predictive value for VTE whereas the risk of thromboembolic events is strikingly high in patients with D-dimer level $\geq 3.0 \mu\text{g/ml}$, which leads to the conclusion that anti-clotting prophylaxis should be dependent on the level of D-dimers.²⁰

C-reactive protein (CRP)

In humans, CRP is a major acute phase protein whose concentration may increase more than 1,000-fold in severe inflammatory states. Human CRP is a pentameric protein composed of five identical non-covalently

bound subunits of 206 amino acid residues with a molecular weight of ~23 kDa.²¹ The increase in inflammation markers underlying the systemic vasculitic processes and the defects in the coagulation that cause most parenchymal lesions in vital organs. CRP is an early predictor for critically COVID-19.²² Cerebral venous thrombosis (CVT) is a unusually neurovascular emergency that has been encountered in some COVID-19 patients. Ming Tu et al. studies and 14 COVID-19 patients with CVT at the median age 43 years. The time taken from onset of COVID-19 symptoms to CVT diagnosis was a median of 7 days. A significant proportion of patients had raised D-dimer (75.0%) and CRP levels (50.0%) should be suspected in COVID-19 patients presenting with headache or seizures.²³ Wang et al. judged 19 out of the 88 COVID-19 cases who have developed deep vein thrombosis (DVT). In addition, among the 18 patients who died, 5 were diagnosed with DVT. Most of these patients had no complaint of lower limb discomfort. The blood samples for these laboratory assays were collected on the day of admission and were reviewed every 3–5 days. CRP levels on admission had positive correlations with the severity of illness and estimated 52.3–120.8mg/L.²⁴

Fibrinogen

Fibrinogen is believed to play one of the key roles in the acute phase response caused by tissue damage. Following injury, exposure of activating cell surfaces or matrices activates coagulation and acute inflammation, which work together and lead to thrombin activation and conversion of fibrinogen to fibrin. Fibrinogen known as factor 1 is a glycoprotein complex made in the liver.²⁵ It has been proven in numerous studies on COVID-19 patients that high levels of fibrinogen positively correlate with VTE and the severe course of the disease.²⁶ The effect of virus has been investigated in an in vitro model panel of genes that reveal a procoagulant effect has been reported to be highly expressed in COVID-19 infected mononuclear cells, including fibrinogen (FGB, FGG).²⁷ As the disease recovers, fibrinogen return to normal range. Zoa et al. comparing the coagulation parameters of two groups of COVID-19 patients severe and mild. Changes in factors of coagulopathy in the severe group was higher than that in the mild group (100% vs. 66.1%). The Fibrinogen amount >7.0 g/L in 5.7% of the group of mild disease as compared to 19.1% with severe disease.²⁸

Thrombocytes

Most commonly coagulation abnormalities in patient with COVID-19 is mild thrombocytopenia. Apart from their typical role in thrombosis and hemostasis, platelets mediate key aspects of immune and inflammatory.²⁹ Express a broad array of receptors, Toll-like receptors (TLRs), C-type lectin receptors, and nucleotide-bind-

ing and oligomerization domain-like receptors.³⁰ In early report from China thrombocytopenia occurred in only 12% cases.³¹ Thrombocytopenia is moderate due to presence of extramedullary megakaryocytes that continuously create platelets.³² The formation of platelets is also increased by pro-inflammatory cytokines.³³ According to the Bertolin et al. analysis there is no basis for the use of antiplatelet drugs in COVID-19 therapy. Demonstrated lower platelet reactivity (PR) was observed in patients with COVID-19 in comparison with healthy individuals. The rates of low PR were 27.5% in the COVID-19 group and 21.7% in the control group.³⁴

IL-6

As already mentioned, one of the VTE factors is a cytokine storm accompanied by, among others, an increase in IL-6 or IL-1 values which cause thrombosis by activating platelets, endothelium, monocytes, and the factor VIIa pathway.³⁵ In Ranucci et al. study IL-6 levels were measured at the admission in the ICU in a 16 patient with COVID-19. All the patients had elevated level of IL-6, and a clear association between IL-6 and fibrinogen was demonstrated.³⁶

Homocysteine

A high level of homocysteine in the makes a person more prone to endothelial cell injury, which leads to inflammation in the blood vessels, which in turn may lead to atherogenesis, which can result in ischemic injury. In the last decade, epidemiological observations have pointed towards a plausible association between hyperhomocysteinemia and nervous system neurodegenerative disorders.³⁷ Yang et al. and Ponti et al. observed positive correlation between its level and pulmonary embolism and VTE.^{38,39} Moreover, in COVID-19 with VTE patients it positively correlates with D-dimers.⁴⁰

Other coagulation factors

Helms et al. have made multicenter prospective cohort study in ICU COVID-19 patient. 150 COVID-19 patients were analyzed. Sixty-four clinically relevant thrombotic complications were diagnosed in 150 patients, mainly pulmonary embolisms (16.7%). 28/29 patients (96.6%) receiving continuous renal replacement therapy experienced circuit clotting. Three thrombotic occlusions (in 2 patients) of centrifugal pump occurred in 12 patients (8%) supported by ECMO. Apart from the indicators mentioned in the article, they also dealt with von Willebrand factor (vWF) activity von Willebrand factor antigen (vWF:Ag) and lupus anticoagulant. vWF activity and vWF: Ag were considerably increased, as well as factor VIII. Also 50 patients out of the 57 tested (87.7%) had positive lupus circulating anticoagulant during their hospitalization.⁴¹

Conclusion

Anticoagulation treatment in COVID-19 patients presents a major challenge due to the various mechanisms that must be overcome, because of considering the multi-pathogenesis of thromboembolic complication in COVID-19 patients. Although we currently know of many anticoagulant treatment regimens in COVID-19, there are still no uniform guidelines for the treatment of patients with thromboembolic complications.

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