Journal of Blood Disorders

Open Access

Austin Publishing Group

Review Article

Bleeding and Bleeding Risk in COVID-19 (Delta Variant) Patients

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Received: April 15, 2022; **Accepted:** May 11, 2022; **Published:** May 18, 2022

Abstract

Background: COVID-19 pneumonia is often responsible for severe acute respiratory syndrome (SARS), complicated by coagulative tendency. But, even if less frequently respect to thrombosis, bleeding and hemorrhages at various sites can also happen. Here, we described the main causes of bleeding and hematomas in Delta variant-COVID-19 patients and their principal locations.

Methods: Endothelial dysfunction, happening for the inflammatory reaction, induces an impaired hemostatic balance that can manifestin two phases: the first phase is characterized by a prevalence of thrombosis and may be followed by a prevalence of fibrinolysis, with bleeding at various sites. The employment of anticoagulant therapy (heparin) can also worsen the profibrinolytic conditions. For that,Delta variant of COVID-19, especially in unvaccinated patients, can induce bleeding and hematomas, even if with a lesser incidence (ranging from 4.8% to 8%) respect to thromboses.

Results: Bleeding complications can affect intracerebral or gastrointestinal parenchyma. Iliopsoas hematoma, with or without hemorrhage, is another common manifestation in COVID-19. Most common causes of these are: thrombocytopenia, hyperfibrinolysis and the use of anticoagulant drugs employed for antagonize the thrombotic complications.Contrarily to thrombotic events, often happening during first two weeks, bleeding manifestations and hemorrhages can tardily occur (up to fourth week). Concordantly, the values of platelet's count and fibrinogen serum levels decrease in the second two weeks, while PT and aPTT increase.

Conclusion: Even if thrombosis complications are frequent in unvaccinated COVID-19 (Delta variant) patients, bleeding and hematomas less frequently occur. But, further observations needed for define the causes and the preferential sites of hemorrhages in these.

Keywords: COVID-19; Delta variant; Hemostatic balance; Bleeding; Hemorrhages; Hyperfibrinolysis; Anticoagulant drugs

Introduction

The Severe Acute Respiratory Syndrome (SARS) was firstly evidenced in Whuan-China in December 2019 [1].Omicron variant of COVID-19 was isolated in South Africa in November 2021 [2]. The most common symptoms include fever, cough, dyspnea, myalgia, gastro-intestinal and neurological symptoms [3,4]. Patients can also suffer of respiratory insufficiency, often evolving in acute respiratory failure [5] complicated by the interstitial pneumonia showing "ground glass" opacities detected on chest CT scan (Figure 1), and multi-organ failure (MOF) [6].

Coagulopathies likely due to the inflammatory state (cytokine storm), are frequent complications of Delta variant of COVID-19, These are induced by the activation of coagulation system [7,8] and are especially frequent in the lungs' parenchyma and in other organs. Contrarily, bleeding complications are rather rare events during COVID-19 infection. In fact, the percentage of COVID-19 patients with bleeding complications range from 4.8% to 8%. Among these subsets of patients, 3.5% had major bleeding [9].

Some factors that could explain the bleeding are reported in these patients, such as thrombocytopenia, hyper-fibrinolytic state, pro-inflammatory response, over-administration of anticoagulant drugs [10,11].

Thrombocytopenia

Usually, the antiplatelet drugs contribute to decrease thrombotic events in COVID-19 patients. But this therapy can also lead to the reduction in platelet's count, with consequent increased risk for hemorrhages [12]. Concerning this, we underlined that Acetyl-Salicylic Acid (ASA), already employed for primary and secondary prevention of cardiovascular events [13], could be able to protect against thrombotic complications in COVID-19. Therefore, this drug, supplied in the long run, could be responsible for hemorrhages in these patients [14].

The possible mechanisms of COVID-19 related thrombocytopenia are the following[15]:

- Platelet antibodies formation;

Citation: Cacciapuoti F, Tirelli P, Guida A, De Sena A, Sarti G and Cacciapuoti F. Bleeding and Bleeding Risk in COVID-19 (Delta Variant) Patients. J Blood Disord. 2022; 9(1): 1067.

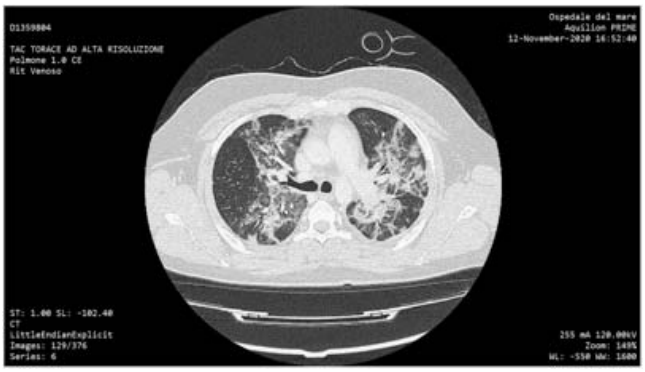

Figure 1: CT scan showing severe bilateral interstitial pneumonia ("ground glass" opacities) found in a patient with COVID-19.

- Splenic/hepatic platelets' sequestration;
- Viral infection or inflammation causing marrow/megakaryocyte suppression;
- Platelet clearance due to the increased endothelial damage.

Hyper-fibrinolysis

Fibrinolysis is the physiologic process that counterbalances the coagulation. The equilibrium between fibrinolysis and coagulation produces a homeostasis of the hemostatic balance [16]. On the contrary, hyper-fibrinolysis is the pathologic process through the hemorrhage prevails in this balance (mismatch) [17].The chief component of the balance between fibrinolysis and coagulation is the plasmin, a serine protease, derived by its precursor, plasminogen, and responsible for the fibrin degradation (Figure 2). Under physiological conditions, homeostasis of the system is regulated by the activators (pro-fibrinolytic) and inhibitors (anti-fibrinolytic) factors of plasminogen. Often, COVID-19 patients have some pre-existing co-morbidities, such as systemic hypertension, diabetes mellitus, coronary and/or cerebro-vascular disease, chronic obstructive pulmonary disease, or kidney dysfunction. These co-morbidities can induce an elevated plasmin concentration, with hyperfibrinolytic response [18]. It must be remembered that proteolytic breakdown of the fibrin results in the generation of D-dimer.

Inflammatory Response

COVID-19 enters the cells by attaching a spike protein to Angiotensin-Converting Enzyme 2 (ACE-2) receptor. This entrance requires the proteolysis of the S1/S2 domains of the spike protein by some proteases, such as plasmin. After binding to the ACE-2 receptor (through S1 domain), the S2 protein is activated to enter the host cell.In this, tissue Plasminogen Activator (tPA), urokinase type Plasminogen Activator (uPA) and Plasminogen Activator Inhibitor (PAI-1) are involved. Specifically, tPA and uPA contribute to the development of the lung injury, while PAI-1 has a protective function. The resultant coagulation abnormalities depend on the effect of the virus on the balance between the pro-coagulant and anti-coagulant pathway. Usually a virus, by activating both the coagulative and fibrinolytic components, could induce a *severe* inflammatory response that can be responsible for hemorrhages. Contrarily, a virus activating the anticoagulant pathway could induce a mild

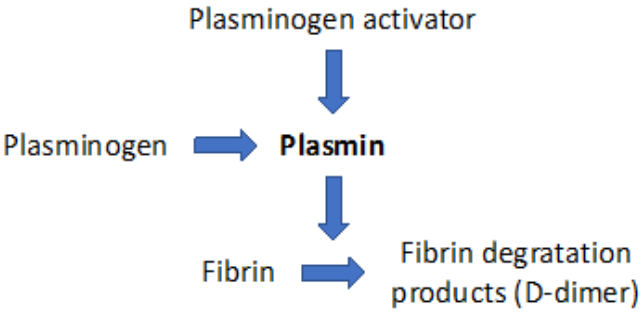

Figure 2: The central role of Plasmin in the fibrin degradation.

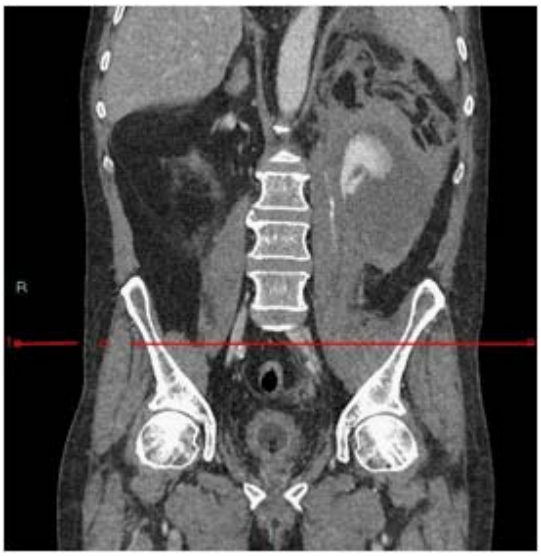

Figure 3: CT-scan Extensive retro-peritoneal hematoma and hemorrhage (red arrow).

inflammatory response that can generally induce bleeding [19]. For example, patients with dengue produce antibodies against the virus activating plasminogen and fibrinolysis, contributing to the bleeding. In contrast, SARS-CoV-2 can cause hyperfibrinolysis without any significant bleeding [20].

Main Bleeding Sites and Anticoagulation

In COVID-19 patients, Gastro-Intestinal (GI) bleeding (Figure 3) can be associated with the use of corticosteroids [21]. But active bleeding and/or hematomas are especially dependent by the prophylactic employment of Low Molecular Weight Heparin (LMWH) or UnFractionated Heparin (UFH) in attempt to prevent the thrombosis [22,23]. Patel et al. reported a case of intestinal bleeding in a COVID-19 patient treated with LMWM [24]. Atypical hematomas in the GI district were also described in a COVID-19 patient receiving an anticoagulant drug [25]. In addition, intracerebral hemorrhage, with or without intraventricular hemorrhage (Figure 4), was reported in COVID-19 patients treated with heparin [26]. This is due to the formation of an immune complex, which induces the platelet's activation responsible for thrombocytopenia that favors intracerebral hemorrhage [27]. Florian et al. described two cases of intracranial hemorrhages in healthy COVID-19 patients that did not previously

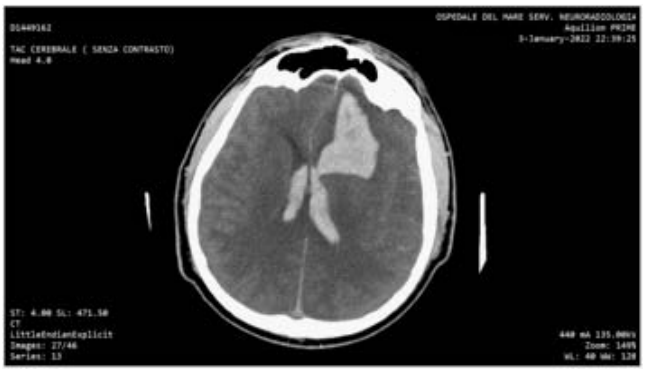

Figure 4: Cerebral CT scan: Large cerebral hemorrhage, with ventricular flooding.

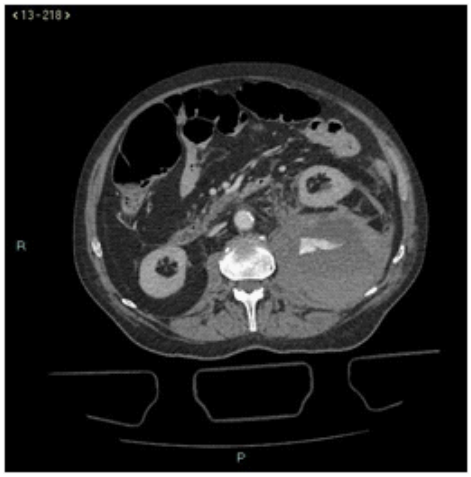

Figure 5: CT scan: Ileo-psoas hematoma and hemorrhage (red arrow) in a COVID-19 patient.

receive prophylactic anticoagulation [28]. In these cases, the possible explanation of devastating cerebral events can be hypoxemia [29]. Another reason can be the development of antiphospholipid antibodies [30]. Severe hypertension and endothelial dysfunction may be another frequent cause of this phenomenon [31]. But, a frequent finding in COVID-19 patients is iliopsoas hematoma. It consists in a retroperitoneal hemorrhage involving the iliopsoas muscle (Figure 5) [32]. Some predisposing factors can be responsible for this event, such as supra-prophylactic doses of anticoagulants, advanced age, and contemporary hemodialysis [33]. Separately may be considered the COVID-19 patients suffering from non-valvular atrial fibrillation and so treated with Direct Oral Anticoagulants (DOACs). But, DOACs resulted superior to Vitamin K Anticoagulants (VKACs) because of lower risk of intracranial hemorrhages [33]. Similarly, these drugs were non-inferior to conventional anticoagulants (VKACs) in term of efficacy, inducing less bleeding in a broad spectrum[34-37].

Conclusion

COVID-19 is a zoonosis due to a Coronaviridae family, able to infect human and non-human mammals and birds [38]. In humans, thrombotic complications of the lungs (interstitial pneumonia) with "ground-glass" opacities are some frequent findings.Manifestations of thrombotic tendency and/or bleeding or hematomas are especially frequent in patients affected by the variant Delta rather than the Omicron and still unvaccinated. Underlying mechanisms of thrombotic events include hyperinflammatory response with "cytokine storm", endothelial dysfunction and hypercoagulability due to the platelets' hyper-aggregation [10,11-39,40]. On the contrary, bleeding and/or hematomas are less common than thrombosis. Thrombotic complications usually happen during the first two weeks, while hemorrhages and/or hematomas can occur later (second two weeks) [41,42]. In the same way, the serum levels of D-dimer and ferritin increase in the first period (day 1-14), while the values of platelets' count and the fibrinogen decrease during the late phase (day 15-30). Concordantly, the values of Prothrombin Time (PT) and of Activated Partial Thromboplastin Time (aPTT) increase in the same period [43]. This evidence requires more attention to the employment of anticoagulation drugs to antagonize thrombotic events, for avoid hemorrhagic complications in unvaccinated patients affected by COVID-19.

It must be also specified that both thrombotic and bleeding complications in COVID-19 more frequently happen in unvaccinated patients suffering from Delta variant. On the contrary, the Omicron variant (prevailing today) seems to be less lethal in multiple vaccinated patients especially, even if it's more contagious. However, this variant doesn't seem to induce major events related to the impaired hemostatic balance [44-46]. Conclusively, more randomized clinical trials are necessary to determine the optimal dose of heparins in unvaccinated patients suffering from Delta variant and to better clarify the pathogenic differences between Delta and Omicron variants of COVID-19.

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