


Case Report

A case series of patients with bleeding in COVID-19: A multicenter experience in Sri Lanka.P. Herath¹, Y. J. Costa², I. S. Somaratne³, A. Sivashangar^{4*}¹Apeksha hospital, Maharagama, Sri Lanka²North Colombo Teaching Hospital, Ragama³General Sir John Kotelawala Defence University, Sri Lanka⁴Faculty of Medicine, University of Colombo, Sri Lanka**Abstract**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with coagulopathy, which leads to severe life-threatening complications apart from lung pathology. The occurrence of thrombotic phenomena is well reported, but few cases with major bleeding have been documented. The underlying mechanism for bleeding in coronavirus disease 2019 (COVID-19) has not been clearly understood. We describe 5 cases of COVID-19 infection with significant bleeding, managed at different hospitals in Sri Lanka. By sharing this experience, we hope to enlighten clinicians to look out for rare but potentially fatal bleeding manifestations related to COVID-19 infection.

Keywords: COVID-19, SARS-CoV-2, coagulopathy, bleeding, hypofibrinogenemia, anticoagulation**Copyright:** © 2022 Herath P *et al.*  This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Funding:** None**Competing interest:** None**Received:** 02.10.2022**Accepted revised version:** 25.11.2022**Published:** 24.12.2022*✉ **Correspondence:** nallathambisivashankar@yahoo.com <https://orcid.org/0000-0002-2590-8272>

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Introduction

Coronavirus disease 2019 (COVID -19) is a pandemic viral disease. The clinical manifestations vary from mild symptoms of upper respiratory tract infection to severe lethal pneumonia. Later on, many cases were reported with extrapulmonary manifestations and multi-organ involvement [1]. There are many published data on hypercoagulability (thrombosis) with COVID-19 infection and its pathogenesis. On the other hand, there are few published case reports and case series on bleeding manifestations such as intracerebral, retroperitoneal, gastrointestinal, deep muscle and vascular catheter-related [2–5]. The understanding of

bleeding with severe COVID-19 is limited. Interestingly, in most patients, the occurrence of bleeding manifestations was noticed after exposure to supratherapeutic levels of anticoagulation. This was observed during the latter part of the stay in the ICU when the inflammation was reducing [4]. A study conducted in China demonstrated that bleeding in COVID-19 was due to imbalances in platelet production and disruption [6]. Meanwhile, there are few published data on mortality due to bleeding manifestations. Hitherto, there are no published data on bleeding associated with COVID-19 infection in Sri Lanka.

patients. Here we describe 5 cases of bleeding in patients with COVID-19.

Case descriptions

Case 1

A 41-year-old, previously healthy, obese (BMI-31 kg/m²) male patient was admitted to Colombo North Teaching Hospital, Ragama, with SARS-CoV-2 pneumonia following a history of 10 days of fever and respiratory symptoms. He was initially managed with non-invasive ventilation (high flow nasal oxygen and then changed to continuous positive airway pressure (CPAP), intravenous antibiotics, intravenous dexamethasone, two doses of tocilizumab and thromboprophylaxis with subcutaneous (SC) enoxaparin 80 mg daily. The D-dimer level was normal on admission (114 ng/ml) with haemoglobin (Hb) 14.7 g/dL, platelets 240 x10⁹/L and normal basic coagulation tests.

Despite all of the above treatments, he continued to require high-flow oxygen. On the seventh day of admission, his D-dimer test was repeated, and a CT pulmonary angiogram (CTPA) was performed with the suspicion of pulmonary embolism. His D-dimer level was very high (2984 ng/mL), and CTPA showed pulmonary embolism in the segmental branch of the right posterior basal pulmonary artery. Therefore, his SC enoxaparin was adjusted to a therapeutic dose (80 mg bd). Following five days of therapeutic anticoagulation, he experienced intense abdominal pain with hypotension, tachycardia, and hemodynamic instability. An emergency ultrasound scan (USS) of the abdomen showed a 10 cm x 6 cm hypoechoic area in the left iliac fossa suggestive of a left psoas haematoma. His Hb dropped by 3 g/dL with normal coagulation studies and platelets count (344 x10⁹/L). Interestingly, his D-dimer level dropped to 517 ng/mL and he was found to have hypofibrinogenaemia. His SC enoxaparin was discontinued immediately. Since he was hemodynamically unstable, the team could not proceed with any surgical intervention. Meanwhile, he was supported with blood transfusions and inotropes. Unfortunately, he succumbed following extensive resuscitation. A pathological postmortem performed showed a massive retroperitoneal haematoma, bilateral lung haemorrhages, left psoas haematoma and the presence of a left pulmonary artery thrombus.

Case 2

A 41-year-old female patient with a history of diabetes mellitus and hypertension was admitted to the district general hospital, Hambantota with SARS-CoV-2 pneumonia. She was later transferred to the ICU with acute respiratory failure for intubation and invasive mechanical ventilation. Her Hb was 10.5 g/dL, and her platelet count was normal on admission. Coagulation studies were not performed on admission as she denied any bleeding manifestations. She was managed with intravenous antibiotics and other supportive medications, including thromboprophylaxis with SC enoxaparin 40 mg daily. On the 15th day of admission, she experienced intense pain in her right arm and right thigh. An emergency USS performed showed evidence of a right iliopsoas haematoma, which measured 7 x 9 x 5 cm in size and a right forearm haematoma measuring 2 x 4 x 2 cm. Meantime, her Hb dropped to 4.5 g/dL. Interestingly, her platelet count was 182 x 10⁹/L and the prothrombin time (14 sec) and APTT (24 sec) were normal. D-dimer and fibrinogen levels were not performed due to unavailability. Enoxaparin was discontinued and supported with blood transfusions. The bleeding settled without any surgical or radiological intervention. Later she succumbed on day 22 due to severe SARS-CoV-2 pneumonia.

Case 3

A 38-year-old previously healthy man was admitted to the district general hospital Hambantota with severe SARS-CoV-2 pneumonia. His full blood count was within normal limits. He was managed with intravenous antibiotics, thromboprophylaxis with a therapeutic dose of SC enoxaparin 60 mg twice daily and other supportive medications. The therapeutic dose of anticoagulation was given as per the local protocol for the management of severe COVID -19 pneumonia. On the 21st day of admission, he experienced intense pain on flexion in the right lower limb. An emergency USS performed showed a small rectus sheath haematoma measuring 2 x 2 x 1 cm in size. D-dimer and fibrinogen levels were not done due to unavailability. Enoxaparin was immediately discontinued. His bleeding settled without any specific intervention. Enoxaparin was recommenced with the same dose after two days. Unfortunately, he succumbed on the 26th day of admission due to severe SARS-CoV-2 pneumonia.

Case 4

A 39-year-old male patient with a history of hypertension and dialysis-dependent chronic kidney disease (CKD) awaiting a kidney transplant was admitted to the base hospital, Homagama, with SARS-CoV-2 infection. He was later transferred to the ICU with acute respiratory failure for invasive mechanical ventilation. On admission, his Hb was 8.8 g/dL, and platelets were $288 \times 10^9/L$. Basic coagulation tests were normal with a d-dimer of 218 ng/mL (normal reference <200 ng/mL). He was managed with intravenous antibiotics and other supportive medications, including thromboprophylaxis with SC enoxaparin 30 mg daily. On the seventh day of enoxaparin, he complained of intense left lower abdominal pain. An emergency CT scan of the abdomen was performed, which showed a large retroperitoneal haematoma. His Hb and platelets dropped to 6.4 g/dL and $140 \times 10^9/L$, respectively. His coagulation tests remained normal. His D-dimer level was more than 5000 ng/mL, and fibrinogen was 4.0 g/L. He was given blood and blood component transfusions. Despite this, he continued to bleed, and his Hb further to 4.4 g/dL. An emergency abdominal aortic and mesenteric angiogram was performed, which did not show an active site of bleeding to proceed with embolization. Because he had uncontrollable massive bleeding, an emergency laparotomy was performed with blood and blood components support. The large retroperitoneal haematoma was evacuated with ligation of the right internal iliac artery. Following ligation, he achieved haemostasis. Unfortunately, his SARS-CoV-2 pneumonia was later complicated by super-added bacterial infection and sepsis. On the 31st day of admission, he succumbed due to sepsis and multi-organ failure.

Case 5

A 44-year-old, previously healthy male patient was transferred to base hospital Homagama with an acute abdomen on the 14th day of SARS-CoV-2 pneumonia. He was already on SC enoxaparin 40 mg twice daily for thromboprophylaxis. He was transfused with two red cell units before being transferred from the local hospital. He did not have any external bleeding manifestations. On arrival at base hospital Homagama, an emergency computed tomography (CT) of abdomen was performed, which revealed a large left psoas haematoma. His Hb was maintained within the normal range following red cell transfusions along with normal platelets and normal basic coagulation tests. Enoxaparin

was discontinued immediately. Since he was hemodynamically stable, he was transferred to the vascular surgery unit at the National Hospital of Sri Lanka for further specialized management of his haematoma.

Discussion

Our cases showed that bleeding is a significant complication of COVID-19 infection, especially when treated with anticoagulation. Further, we observed that bleeding is a late complication compared to thrombosis, and clinicians need to be extra cautious about anticoagulation doses during this period.

Bleeding in SARS-CoV-2 infection is not common as it is mainly a hypercoagulable state. There are several published articles that describe the pathophysiology of thrombotic complications in COVID-19 infection. However, the underlying mechanisms for bleeding needs to be evaluated. There are several mechanisms hypothesized. When looking at the sites of bleeding, findings are not consistent among studies, and few case series have reported bleeding in unusual sites [5].

There have been several studies that have shown an association between anticoagulation and bleeding manifestations. Since SARS-CoV-2 infection is associated with a hypercoagulable state, there is a proven benefit of using thromboprophylaxis during the early phase of the disease. A large retrospective study where 4389 hospitalized patients were observed showed reduced mortality and intubation with anticoagulation with therapeutic dose compared to prophylaxis dose. Meanwhile, it highlighted the rate of bleeding too. Bleeding events were higher among patients on therapeutic anticoagulation compared to those on prophylactic dose and not on anticoagulation. Further, they observed that higher bleeding rates were associated with unfractionated heparin than low molecular weight heparin [7]. In our case series, except case 2, which was on prophylactic anticoagulation, all the other patients were on therapeutic anticoagulation with enoxaparin at the time of bleeding. This finding warrants the review of anticoagulation dose for thromboprophylaxis.

In addition to the above, the occurrence of bleeding was observed between the second and third week of admission. Therefore, it may be hypothesized that the hyperinflammatory phase is over after a week, and the anticoagulant effect is enhanced. This may lead to an overdose of anticoagulation. This was evidenced by a study which observed major bleeding among patients who were admitted with SARS-CoV-2 pneumonia to the

ICU. They observed a reduction in fibrinogen level three to five days before bleeding [4]. Therefore, it was suggested that fibrinogen could be a useful marker for optimizing the anticoagulation dose during the latter stages of SARS-CoV-2 pneumonia [4]. Interestingly, in all our cases, the bleeding manifestations occurred after a week (during the second and third week) following admission. A low and normal fibrinogen level was observed in cases 1 and 4, respectively. Fibrinogen levels in cases 2,3 and 5 were not tested due to the unavailability of the test at respective hospitals. In the cases presented here, bleeding events were observed during the period after the first week of admission with low or normal levels of fibrinogen while on therapeutic doses of anticoagulation. Hence, it is worth investigating this in the future with a larger study population to identify the optimal doses of anticoagulation towards the later stages of the disease.

The other mechanism highlighted was thrombocytopenia associated with COVID-19 infection and bleeding. In a study, which observed 400 patients, it was suggested that a baseline platelet count less than $150 \times 10^9/L$ was an independent predictor of a threefold increase in the risk of major bleeding [8]. Interestingly, among our cases, except case 4, all the other patients had a platelet count of more than $150 \times 10^9/L$. Our findings contradict with results from previous studies. We believe that there are other factors contributing to bleeding in patients with COVID-19 infection other than the platelet count.

There is reported evidence that overt disseminated intravascular coagulation (DIC) with SARS-CoV-2

infection is also associated with bleeding [9]. DIC may occur with disseminated COVID-19 infection and systemic disease [10]. Although we did not perform all fibrin markers in our cases, basic coagulation and platelet counts were normal except in case 4, where the patient had marginal thrombocytopenia. Applying a DIC score to each of these cases was not supportive or suggestive of an overt DIC contributing to the management of their bleeding manifestations.

There are other rare pathogenetic mechanisms that were hypothesized. Haemophagocytic lymphohistiocytosis (HLH) could lead to coagulation disorders associated with haemorrhage [11]. There is some evidence that hyper-inflammatory states could induce HLH in COVID-19 patients [12]. However, our patients did not meet the criteria for the diagnosis of HLH due to their normal basic coagulation tests and platelet counts, except for case 4, where he had marginal thrombocytopenia.

Since the SARS-CoV-2 virus binds to angiotensin-converting enzyme-2 receptors and reduces its activity. As a result, the renin-angiotensin-aldosterone axis was activated, leading to an increase in blood pressure. This stimulates endothelial dysfunction and bleeding [2,13]. In our cases, we didn't appreciate elevated blood pressure with the bleeding manifestations. However, we must closely monitor the patients for elevated blood pressure for evidence of bleeding

Consent

Informed written consent was obtained from the patients and their families.

References

1. Tsai PH, Lai WY, Lin YY, Luo YH, Lin YT, Chen HK, et al. Clinical manifestation and disease progression in COVID-19 infection. *J Chin Med Assoc.* 2021;84(1):3–8. DOI: 10.1097/JCMA.0000000000000463.
2. Pavlov V, Beylerli O, Gareev I, Torres Solis LF, Solís Herrera A, Aliev G. COVID-19-Related Intracerebral Hemorrhage. *Front Aging Neurosci.* 2020;12:352. DOI: 10.3389/fnagi.2020.600172.
3. Reisi-Vanani V, Lorigooini Z, Dayani MA, Mardani M, Rahmani F. Massive intraperitoneal hemorrhage in patients with COVID-19: a case series. *J Thromb Thrombolysis.* 2021;52(1):338–44. DOI: 10.1007/s11239-021-02447-x.
4. Godier A, Clause D, Meslin S, Bazine M, Lang E, Huche F, et al. Major bleeding complications in critically ill patients with COVID-19 pneumonia. *J Thromb Thrombolysis.* 2021 Jul 1;52(1):18–21. DOI: 10.1007/s11239-021-02403-9.
5. Singh B, Mechineni A, Kaur P, Reid RJ, Maroules M. COVID-19 and bleeding at unusual locations: Report of four cases. *Hematol Transfus Cell Ther.* 2021; 43(2):214. DOI: 10.1016/j.htct.2021.01.007.

6. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb. Haemost.* 2020; 18(4):844-847. DOI: 10.1111/jth.14768.
7. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. *J Am Coll Cardiol.* 2020;76(16):1815–26. DOI: 10.1016/j.jacc.2020.08.041
8. Chan NC, Weitz JI. COVID-19 coagulopathy, thrombosis, and bleeding. *Blood.* 2020 Jul 7 [cited 2022 Oct 1];136(4):381. doi: 10.1182/blood.2020007335.
9. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood.* 2020;136(4):489–500. DOI: 10.1182/blood.2020006520.
10. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. *Crit Care* 2020; 24: 360. DOI: 10.1186/s13054-020-03077-0
11. Valade S, Mariotte E, Azoulay E. Coagulation disorders in hemophagocytic lymphohistiocytosis/macrophage activation syndrome. *Crit Care Clin.* 2020;36(2):415–26. DOI: 10.1016/j.ccc.2019.12.004.
12. Prilutskiy A, Kritselis M, Shevtsov A, Yambayev I, Vadlamudi C, Zhao Q, et al. SARS-CoV-2 infection associated hemophagocytic lymphohistiocytosis: An autopsy series with clinical and laboratory correlation. *Am J Clin Pathol.* 2020;154(4):466–74. DOI: 10.1093/ajcp/aqaa124.
13. Boira I, Esteban V, Vañes S, Castelló C, Celis C, Chiner E. Major bleeding complications in COVID-19 patients. *Cureus* 2021;13(8). e16816. DOI: 10.7759/cureus.16816.



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