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Thrombocytopenia and coronavirus: A prognosis and progression of the Coronavirus disease

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Abstract
Coronavirus pneumonia has been detected in Wuhan City since December 2019. Today, coronavirus 2019 (COVID-19) has become an epidemic worldwide. Although this disease is not fully understood, it can show different symptoms over time. One of the components involved in the body by this virus is platelets that communicate directly with several different types of viruses, including the SARS-CoV virus family, via integrins, P-selectins, and pseudo-receptors. Mechanism of action includes the virus's direct effect on bleeding and maturation of megakaryocytes, increased adhesion and activation of platelets, and platelet consumption in abscesses of damaged lung tissue. Therefore, Covid-19 disease can affect platelet function, which in itself can directly or indirectly affect thrombocytopenia. Pathology of bone marrow aspiration from three patients with Covid-19 thrombocytopenia indicates abnormal megakaryocyte maturation. In addition, it can be associated with the severity and mortality of the disease. In other words, thrombocytopenia can be used as a prognostic factor in patients with progressive Covid- 19, which has been reported in 5 to 40% of COVID-19 patients. This study attempts to gather information and recent reports on thrombocytopenia in patients with Covid-19.
Key words: Covid-19, Platelets, Thrombocytopenia

Introduction

Since December 2019, coronavirus pneumonia has been detected in Wuhan City, China, in Hubei Province, China. Over time, the virus has spread worldwide. COVID-19 is a new respiratory disease with various clinical symptoms such as fever, fatigue, dry cough, and shortness of breath. The mechanism of this disease is not fully understood to date, so the symptoms vary from person to person. Some patients have mild symptoms at the onset of the disease. Unusual symptoms include abdominal pain, headache, palpitations, and chest pain. However, changes in blood cells in patients with COVID-19 are common symptoms, including decreased lymphocyte count and platelet count. Thrombocytopenia has been reported in 5 to 40% of COVID-19 patients. Patients with thrombocytopenia appear to be more severe by Covid-19 disease (1). Studies have shown a significant association between thrombocytopenia and the severity of Covid-19(2). Platelet counts are significantly lower in these patients. Lower platelet counts in patients with COVID-19 were reported in a study of 85 patients with no clinical or radiological improvement after ten days (3).

In another study by Wang et al., Lower platelet counts were reported in severe disease than disease recovery. However, most patients with COVID-19 show only mild thrombocytopenia, even with severe disease. A study conducted in Singapore on Covid-19 patients had only 5% of admitted patients with higher than normal platelets (4). In a study on platelet count in patients with COVID-19, the mean platelet counts in studies reported on platelet count

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in COVID-19. According to studies, the mean platelet counts in patients with COVID-19 from ~ 160 to 215 × 109 / L in COVID-19 patients in general to 120 to 200 200 109 / L in high-intensity patients(5). Tang et al. Reported a link between blood clotting and mortality in 183 patients with COVID-19, and out of a total of 21 patients rescued from Covid-19, 12 who did not survive had lower than normal platelet counts(6). As a result, mild thrombocytopenia is a common finding in COVID-19 patients. Platelet counts <109/100 L are rare, and there is also a link between high platelet counts and a poor prognosis (7). We tried to summarize the causes and reports of thrombocytopenia in patients with Covid-19.

Mechanism of thrombocytopenia COVID-19

Platelets interact directly with several different types of viruses, including the SARS-CoV virus family, through integrins, P-selectins, and pseudo-receptors, and platelets may be involved in SARS-CoV and MERS-CoV outbreaks (8, 9). In 30 to 50% of patients, thrombocytopenia has been described in patients with SARS and Covid-19(10). The mechanisms of thrombocytopenia in SARS-CoV infection were investigated in 2003 by Young et al. (11). According to their studies, their mechanism of action includes the direct effect of the virus on bleeding and maturation of megakaryocytes and increased adhesion and activation of platelets and platelet consumption in abscesses of damaged lung tissue (11). Activation of platelets in the pulmonary bloodstream can affect the activity of the bloodstream and aggravate damage to the lung parenchyma, causing respiratory failure and frequent need for mechanical ventilation (12, 13), which is described as one of the major conflicts in covid-19 virus (14).

These data open up interesting perspectives on the role of platelet activation and the potential benefits of antiplatelet agents in COVID-19(15). However, these questions need to be addressed in future research. To the best of our knowledge, no study of platelet activation in patients with COVID-19 has been reported (16).

Platelet gene expression and function in COVID-19 patients

To solve the thrombotic complications in patients with Covid-19, we must understand the pathogenesis of patients with Covid-19(17). Studies in changes in platelet gene expression in patients with SARS and Covid-19 have shown that RNA sequences in patients with Covid-19 show changes in platelet gene expression that changes. The gene expression is usually associated with altered protein expression, antigen presentation, and mitochondrial dysfunction (18). p Selectin was increased after activation. Platelet activation and accumulation can be partly attributed to MAPK signaling pathway activation and thromboxane production (19). These findings suggested that SARS-CoV-2 infection is associated with platelet hyperactivity, which may contribute to the pathophysiology of COVID-19 (20).

Immune Thrombocytopenic Purpura in a Patient with Covid-19

Thrombocytopenic purpura is an immune disease in which the blood doesn't clot normally. This condition is now more commonly known as immune thrombocytopenia (ITP)(21). According to recent reports, deep thrombocytopenia in patients with COVID-19 is caused by immune thrombocytopenic purpura (22). Thrombocytopenia in a patient with COVID-19 includes DIC and sepsis-induced thrombocytopenia. Severe SARS-CoV-2 infection is associated with blood clotting (23).

A case report of a patient with COVID-19 coronavirus showed thrombocytopenic purpura after intravenous immunoglobulin and high-dose dexamethasone (24). The study showed that in the presence of deep

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thrombocytopenia in a patient with COVID-19, it is necessary to eliminate the immune response that causes purpura (25). Four patients have experienced symptoms of Purpuric Lesions. On day nine, they experienced symptoms of a cerebral hemorrhage, which could be prevented with early diagnosis and treatment (26). The time sequence, in this case, indicated Covid-19 as a causative agent of thrombocytopenia in the immune system in this patient (27). Although cerebral hemorrhage did not have significant side effects, reports such as these show signs of awareness of Covid-19-related complications (28). Thrombocytopenia was negative, but these patients showed cutaneous and mucosal purpura symptoms, two of whom received intravenous antibody therapy, while one recovered without any treatment (29).

Thrombocytopenia as an initial manifestation of COVID-19

Thrombocytopenia has been a common manifestation in Covid-19 patients since the coronavirus epidemic in 2019(29). The etiology of thrombocytopenia is likely to be very effective in COVID-19. This could be due to the direct effect of Covid-19 on host cells (30). Hematopoietic and stromal bone marrow cells lead to dysfunction of bleeding and inhibition of bone marrow growth or production of cytokines, which leads to the destruction of bone marrow progenitor cells(31). Another mechanism considered is platelet production, which causes thrombocytopenia in the early stages. Platelet depletion can also be due to increased platelet consumption by infection and inflammation, especially in the lungs, which causes damage to pulmonary endothelial cells(32). It activates platelets in the lungs and causes the accumulation and formation of micro thrombosis, which leads to increased platelet consumption (33). In a meta-analysis of 31 studies involving 7613 patients with COVID-19, the results showed a significant association between thrombocytopenia and patients with severe COVID-19 symptoms admitted to medical facilities(34). However, other clinical, biological, and radiological factors affect the severity and outcome of COVID-19(34).

Thrombocytopenia was reported to be prevalent at the time of admission, while thrombocytopenia is rare in the late stages (14 days after the onset of symptoms)(22). A retrospective study in Wuhan, China, found that delayed-stage thrombocytopenia in COVID-19 was more likely to occur in elderly patients or patients with low lymphocyte counts at admission(2). This type of thrombocytopenia, which occurs in the delayed phase of Covid-19 disease, is associated with an increased length of hospital stay and higher mortality(35). Pathology of bone marrow aspiration from three patients with delayed-stage thrombocytopenia also indicates abnormal megakaryocyte maturation(36). A study at 1476 patients at Wuhan Hospital analyzed platelet counts, and in-hospital mortality showed that thrombocytopenia was common in patients with COVID-19 and increased with increased risk of death(37). The lower the platelet count, the higher the mortality rate. At another treatment center in South Korea, the patient was referred to a medical center without respiratory symptoms with symptoms of thrombocytopenia (38).

Delayed-phase thrombocytopenia in patients with coronavirus disease (COVID-19)

Thrombocytopenia was reported to be prevalent at the time of admission, while thrombocytopenia is rare in the late stages (14 days after the onset of symptoms)(2). A retrospective study in Wuhan, China, found that delayed-stage thrombocytopenia in COVID-19 was more likely to occur in elderly patients or patients with low lymphocyte counts at admission. This type of thrombocytopenia,

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which occurs in the delayed phase of Covid-19 disease, is associated with an increased length of hospital stay and higher mortality(2). Pathology of bone marrow aspiration from three patients with delayed-stage thrombocytopenia also indicates abnormal megakaryocyte maturation(36).

Conclusion

Recent reports of coronavirus showed that patients with thrombocytopenia as one of their clinical symptoms develop the disease more severely. It may be necessary because thrombocytopenia has been reported in 5 to 40% of COVID-19 patients. On the other hand, thrombocytopenia is one of the primary complications of patients with Covid-19 hospitalization and is not usually seen in the delayed stage of the disease.

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Conflicts of interest:

The authors declare that they have no competing interests.

References

1. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J.. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res 2020;19(6): 1-13.

2. Lippi G, Plebani M,Henry BM, Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta 2020; 506(1):145-148.

3. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Critical Care 2020; 24(1): 1-9.

4. Iglič VK, Dahmane R, Bulc TG, Trebše P, Battelino S, Kralj MB,etal .From Extracellular Vesicles to Global Environment: A Cosmopolite Sars-Cov-2 Virus. IJCMCR 2020; 4 (1): 4 -16.

5. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W,. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol 2020;146(1):89-100.

6. Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the cardiologist: basic virology, epidemiology, cardiac manifestations, and potential therapeutic strategies. Basic Transl Sci 2020; 5(5):518-536.

7. Qi X, Liu Y, Wang J, Fallowfield JA, Wang J, Li X, et al. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. Gut 2021;70(2):433-436.

8. Amgalan A,Othman M. Exploring possible mechanisms for COVID-19 induced thrombocytopenia: Unanswered questions. J Thromb 2020; **18**(6): 1514-1516.

9. Chao CH, Wu WC, Lai YC, Tsai PJ, Perng GC, Lin YS..Dengue virus nonstructural protein 1 activates platelets via Toll-like receptor 4. leading to thrombocytopenia and hemorrhage. PLoS Pathog 2019;15(4): 1007625-1007633.

10. Khelif A, Saleh MN, Salama A, Portella MD, Duh MS, Ivanova J..Changes in health-related quality of life with long-term eltrombopag treatment in adults with persistent/chronic immune thrombocytopenia: findings from the EXTEND study. Am J Hematol 2019; 94(2):200-2008.

11. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past J Clin Virol 2020;127:104362-104370.

12. Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ,etal, Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol 2020; 251(3):228-248.

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13. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev 2020; 54:62-75.
14. Del Rio C, Malani PN. COVID-19—new insights on a rapidly changing epidemic. JAMA 2020; 323(14):1339-40.
15. Watson RA, Johnson DM, Dharia RN, Merli GJ, Doherty JU. Anti-coagulant and anti-platelet therapy in the COVID-19 patient: a best practices quality initiative across a large health system. Hosp Pract 2020;48(4):169-179.
16. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75(23):2950-2973.
17. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323(20):2052-5059.
18. Ouyang Y, Yin J, Wang W, Shi H, Shi Y, Xu B, et al. Downregulated gene expression spectrum and immune responses changed during the disease progression in patients with COVID-19. Arch Clin Infect Dis 2020;71(16): 2052-2060.
19. Manne BK, Denorme F, Middleton EA, Portier I, Rowley JW, Stubben C,et al. Platelet gene expression and function in patients with COVID-19. Blood 2020; 136 (11):1317-1329.
20. Colmenero I, Santonja C, Alonso-Riaño M, Noguera-Morel L, Hernández-Martín A, Andina D, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol 2020; 183(4):729-737.
21. Tumaini Massaro J, Chen Y, Ke Z. Efficacy and safety of thrombopoietin receptor agonists in children with chronic immune thrombocytopenic purpura: meta-analysis. PLT 2019; 30(7):828-835.
22. Pavord S, Thachil J, Hunt BJ, Murphy M, Lowe G, Laffan M and et al. Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic. Br J Haematol 2020;189(6):1038-1043.
23. Amgalan A, Othman M. Hemostatic laboratory derangements in COVID-19 with a focus on platelet count. PLT 2020;31(6):740-745.
24. Deruelle E, Salem OB, Hieng SS, Pichereau C, Outin H, Jamme M. Immune thrombocytopenia in a patient with COVID-19. Int J Hematol 2020;112(6):883-888.
25. Franchini M, Marano G, Cruciani M, Mengoli C, Pati I, Masiello F and et al. COVID-19-associated coagulopathy. Diagnosis 2020;7(4):357-363.
26. Iwasenko JM, Howard J, Arbuckle S, Graf N, Hall B, Craig ME,et al. Human cytomegalovirus infection is detected frequently in stillbirths and is associated with fetal thrombotic vasculopathy. J Infect Dis 2011; 203(11):1526-1533.
27. Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y,et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol 2020; 30 (8):4407-4416.
28. Bandyopadhyay D, Akhtar T, Hajra A, Gupta M, Das A, Chakraborty S and et al, COVID-19 pandemic: cardiovascular complications and future implications. J Cardiovasc Drugs 2020; 20(4):311-324.
29. Lorenzo-Villalba N, Zulfiqar AA, Auburtin M, Schuhmacher MH, Meyer A, Maouche Y , et al, Thrombocytopenia in the course of COVID-19 infection. Eur J Case Rep Intern Med 2020;7(6):111-120.
30. Malik YS, Kumar N, Sircar S, Kaushik R, Bhat S, Dhama K, et al, Coronavirus disease pandemic (COVID-

[DOI: 10.18502/ijpho.v12i2.9078]

19): challenges and a global perspective, Nat Immunol 2020 ; 9(7): 519-522.
31. Chavakis T, Mitroulis I, Hajishengallis G. Hematopoietic progenitor cells as integrative hubs for adaptation to and fine-tuning of inflammation. Nat Immunol 2019; **20** (7): 802-811.
32. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al, Nervous system involvement after infection with COVID-19 and other coronaviruses. Immun. Brain Behav Immun 2020;87(1):18-22.
33. Salamanna F, Maglio M, Landini MP, Fini M. Platelet functions and activities as potential hematologic parameters related to Coronavirus Disease 2019 (Covid-19). PLT 2020; 31(5):627-632.
34. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, Shang Y. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost 2020;18(6):1469-1472.
35. Bösmüller H, Traxler S, Bitzer M, Häberle H, Raiser W, Nann D, Frauenfeld L, et al., The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. Virchows Arch 2020: 1-9.
36. Flower L, Laundy N, Khosravi M, Buckley J, Gale A, Kumar ID,et al, Haemophagocytic lymphohistiocytosis secondary to COVID-19: a case series. Lancet Rheumatol 2021; 3(11): 744-747.
37. Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb 2020; **18**(6): 1469-1472.
38. Wang L, Wan G, Shen Y, Zhao Z, Lin L, Zhang W,et al. A nomogram to predict mortality in patients with severe fever with thrombocytopenia syndrome at the early stage—A multicenter study in China. Plos Negl Trop Dis 2019; **13**(11): 7829-7833.

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