

COVID-19-ASSOCIATED IMMUNE THROMBOCYTOPENIA

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ABSTRACT

The corona virus disease 2019 (COVID-19) is a contagious respiratory tract infection caused by the beta-coronavirus SARS-CoV-2. The World Health Organization declared the COVID-19 outbreak a pandemic on March 11, 2020. Since the COVID-19 pandemic started, more than 166 million patients have been tested positive worldwide with more than 3.4 million related death recorded. COVID-19 has a wide range of signs and symptoms. Hematological changes such as lymphopenia, thrombocytopenia, and coagulation disturbances are not unusual in patients with COVID-19. However, the mechanisms causing these changes are partially comprehended. Immune thrombocytopenia was identified to be among the hematologic autoimmune diseases seen in patients infected with SARS-CoV-2. This review summarizes the evidence on COVID-19-associated immune thrombocytopenia and the underlying mechanisms involved in its development.

Keywords: thrombocytopenia, immune thrombocytopenic purpura, COVID-19, SARS-CoV-2, coronavirus

INTRODUCTION

The Corona Virus Disease 2019 (COVID-19) is a contagious respiratory tract infection caused by the beta-coronavirus SARS-CoV-2. It was first identified in Wuhan, the largest metropolitan area in China's Hubei Province, in late 2019, when a series of pneumonia cases of unknown cause emerged (1). The World Health Organization declared the COVID-19 outbreak a pandemic on March 11, 2020 (2). Since the COVID-19 pandemic started, more than 166 million patients have been tested positive worldwide with more than 3.4 million related death recorded (3).

SARS-CoV-2 infection tends to affect people of all ages, but the clinical manifestations vary depending on their age. Many infections, primarily in children and young adults, are asymptomatic or mild, but severe illness, respiratory failure, and death are more

frequent in the elderly and/or people with comorbidities (4).

COVID-19 has a wide range of signs and symptoms. The most common symptoms at onset of illness are fever, fatigue and cough, but also myalgia, anorexia and in severe cases dyspnea. Headache, dizziness, sore throat, and chest pain are less common symptoms, as are gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and vomiting (4-6). Also, a significant number of patients complained of olfactory and taste disturbances. Anosmia and ageusia are nonspecific symptoms that may be the first or only sign of the condition (7,8).

Most patients reported symptoms of disease, after an incubation period of 1-14 days (typically about 5 days); dyspnea and pneumonia occurred within a median of 8 days from disease onset (8).

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Hematological changes such as lymphopenia, thrombocytopenia, and coagulation disturbances are not unusual in patients with COVID-19. However, the mechanisms causing these changes are partially comprehended (9).

Changes in immune system functions have recently been attributed to the SARS-CoV-2 infection. These changes could range from an abnormal immune response and excessive cytokine production to immune system hyperactivation and a significant increase in immune-inflammatory variables. Autoimmunity and cytokine storm may result from these excessive immune responses (10,11).

Furthermore, studies have identified many cases of COVID-19 patients who developed autoimmune events such as antiphospholipid syndrome, autoimmune cytopenia, Guillain-Barré syndrome and Kawasaki disease. These results suggest that SARS-CoV-2 infection is linked to the development of autoimmune diseases (11,12).

Several hematologic autoimmune conditions have also been identified and shown to complicate COVID-19 management. Immune thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), thrombotic thrombocytopenic purpura (TTP), antiphospholipid syndrome (APLS), autoimmune neutropenia, and Evans syndrome were identified to be among the hematologic autoimmune diseases seen in patients infected with SARS-CoV-2 (11,13).

This review summarizes the evidence on COVID-19-associated immune thrombocytopenia and the underlying mechanisms involved in its development, based on the PubMed database.

MECHANISMS OF THROMBOCYTOPENIA IN COVID-19

The novel coronavirus disease has been linked to thrombocytopenia, which may have various mechanisms of occurrence and it may appear at any time during the disease course (14).

Coronaviruses can infect bone marrow cells, triggering abnormal hematopoiesis. Using various receptors, SARS-CoV-2 inhibits hematopoiesis in the bone marrow, resulting in reduced primary platelet formation and thrombocytopenia. Hemophagocytic lymphohistiocytosis is one of the secondary pathways that lead to the destruction of bone marrow progenitor cells. This is caused by excessive proliferation and activation of the mononuclear macrophage system, which results in a cytokine storm (14,15).

SARS-CoV-2 also induces thrombocytopenia by increasing levels of autoantibodies and immune complexes, which causes the immune system to specifically destroy thrombocytes. Platelets with specific antigens can be coated by anti-platelet antibodies and immune complexes, resulting in immune-mediated destruction in the peripheral blood (ie. immune thrombocytopenia – ITP) (14).

Lung injury occurs as a consequence of viral infection and inflammation. Damaged lung tissues and pulmonary endothelial cells can stimulate platelets in the lungs, inducing aggregation and the formation of microthrombi, which enhances platelet consumption (14,16).

COVID-19-ASSOCIATED IMMUNE THROMBOCYTOPENIA

Immune thrombocytopenic purpura (ITP) is an uncommon autoimmune condition marked by platelet counts below 100,000 platelets per microliter and increased bleeding risk (17). Patients who exhibit thrombocytopenia without a known underlying cause are diagnosed with primary ITP. ITP caused by other disorders (autoimmune diseases, lymphoproliferative disorders), infectious agents or medications is known as secondary ITP (18). Environmental and genetic predisposition have been identified as risk factors for ITP. Among the environmental factors involved in the occurrence of autoimmune thrombocytopenia, several infectious agents are associated with the appearance of this condition, especially in children (eg *Helicobacter pylori*, hepatitis C virus, human immunodeficiency virus, cytomegalovirus, Epstein Barr virus, and other viruses) (19).

Molecular mimicry is one of the proposed mechanisms by which infections contribute to autoimmunity. To evade the immune response, viral proteins mimic platelet receptors. Cross reactivity against platelet receptors can arise as a result of an immune reaction to these viral proteins, resulting in autoantibodies specific for both the viral protein and platelet receptors (19,20).

Thrombocytopenia is among the most challenging disease entities for physicians to deal with on a daily basis. Mild thrombocytopenia has been reported in approximately 5–10% of patients with symptomatic SARS-CoV-2 infection (21). Other studies showed that nearly 36% of COVID-19 patients were found to have moderate thrombocytopenia (22). Deep throm-

bocytopenia, on the other hand, is uncommon and is linked to disease severity (23). Huang et al. noted that COVID-19 non-survivors (20%) were more thrombocytopenic than COVID-19 survivors (1%) (24), while Tang et al. showed that thrombocytopenia is a negative prognostic factor during SARS-CoV-2 infection (25).

Several case reports of isolated thrombocytopenia linked to COVID-19 have recently been described (Table 1). Zulfiqar et al. published the first single case report indicating that COVID-19 infection could be linked to immune thrombocytopenia. He described a case of “de novo” ITP in a 65-year-old woman with COVID-19 who underwent a multi-drug treatment, including intravenous immunoglobulin (IVIG), prednisolone, and eltrombopag, to recover completely (26).

Similar to this case (Patient #1), additional eleven patients (Patients #2, #3, #4, #5, #6, #10, #11, #13, #14, #15, #16) had previous fever or respiratory symptoms that started 4 days to 4 weeks before admission (26-36). Only two patients (Patients #7, #8) were diagnosed with ITP and had no COVID-19 signs or symptoms. In these patients, Ahmed et al. pointed to thrombocytopenia as an early manifestation of the disease, without any other COVID-19 specific symptoms. Both patients presented with haemorrhagic manifestations and severe thrombocytopenia, which responded immediately to intravenous immunoglobulin with a persistent response over time (16).

The preponderance of the cases described (Patients #2, #3, #4, #7, #8, #9, #12, #13, #16) had thrombocytopenia with evident signs of bleeding upon admission (16,27,28, 32-33,36). In some other eight cases, thrombocytopenia was identified significantly later (Patients #1, #5, #6, #9, #10, #11, #14 and #15) (16,26,28,29,30,31,34,35). The majority of critically ill patients develop thrombocytopenia later in the course of the disease, and was associated with a longer hospital stay and a higher mortality (Patients #5, #6, #9, #11 and #14) (16,28,29,31,34). In a retrospective analysis, Chen et al. reported that COVID-19-associated delayed-phase thrombocytopenia developed in 11.8 percent of enrolling patients and that it is more likely to develop in elderly patients or patients with a low lymphocyte count on admission (37).

The reported nadir platelet counts among the patients diagnosed with COVID-19-associated immune thrombocytopenia were extremely variable, ranging

from 23 000 cells/L (Patient #11) to 0 cells/l (Patient #7) (29,31).

Most patients with bleeding symptoms reported manifestations such as epistaxis, purpuric and petechial rash, ecchymoses, or mucosal bleeding, according to our findings. Only 3 patients out of 16 suffered from intracerebral bleeding (28), intraventricular haemorrhage (31) and subarachnoid haemorrhage (26), one out of which died.

Diagnosing COVID-19-associated immune thrombocytopenia might be challenging because of various other possible causes, such as coagulation activation by COVID-19 infection leading to disseminated intravascular coagulation and subsequent thrombocytopenia. Also, medications used for treating COVID-19, including heparin, azithromycin, and hydroxychloroquine, may trigger thrombocytopenia (38). In the case report published by Zulfiqar et al., the patient had used amoxicillin-clavulanic acid and low-molecular-weight-heparin before the detection of thrombocytopenia, which might also be contributing to the decreasing of the platelet count (26).

The diagnosis of ITP is based on the patient's past medical history, systemic physical examination, and an extensive hematological workup that includes a complete blood count and a peripheral blood smear. To rule out viral-mediated thrombocytopenia, patients should be evaluated for HCV and HIV. In situations of isolated thrombocytopenia, bone marrow analysis is not indicated unless there is a suspicion for aplastic anemia, leukemia, or myelodysplastic syndrome (39).

ITP therapy seeks to minimize severe bleeding by ensuring a balanced platelet count. Treatment for COVID-19-related ITP might be complicated. Intravenous immunoglobulin, glucocorticoids, and thrombopoietin receptor agonists are all commonly used and effective treatments. IVIG is usually designated for individuals with ITP who require a quick rise in platelet levels. IVIG has the liability of not being curative and of being poorly tolerated (40). Because IVIG suppresses macrophage phagocytic functions, it may be effective in treating COVID-19 infection at an incipient phase (19,41).

Concerning the management of the documented cases, medications used were: steroids (prednisone, dexamethasone, and methylprednisone), intravenous immunoglobulin (IVIG), thrombopoietin receptor agonists (TPO-RA e.g. Romiplostim and Eltrombop-

TABLE 1. Reported COVID-19 induced immune thrombocytopenia cases

Patient (reference)	Age, Gender	Comorbidities\ Past Medical History	COVID-19 sign & symptoms	ITP signs and symptoms	Chest imaging	Days from admission to thrombocytopenia	Platelet count in evolution, cells/ μ L	Other laboratory tests	Autoimmune profile	ITP treatment	Other treatments	Evolution and outcome
Patient #1 Zulficar et al (26)	65 yo, female	hypertension, autoimmune hypothyroidism	On presentation: 4-day history of fatigue, fever, dry cough, abdominal discomfort; diminished breath sounds bilaterally with bibasilar rales	On day 4: lower-extremity purpura, epistaxis On day 9: right frontal headache, (head CT scan: subarachnoid microhemorrhage in the right frontal lobe)	CT scan: ground-glass opacities in the lower zones	4	On presentation: 183000; On day 4: 66000; On day 5: 16000; On day 7: 8000; Nadir: 1000	Elevated CRP levels (55mg/l), LFTs showed cholestasis; Increased fibrinogen level	Increased thyroid peroxidase antibodies; antiplatelet negative factor 4; antiplatelet antibodies, and antinuclear antibodies	IVIg 1g/kg – 2 doses; platelet transfusion; prednisolone (100mg); eltrombopag (75mg/day)	intravenous amoxicillin–clavulanic acid; LMWH; oxygenation therapy	On day 10: platelet count increased to 139,000 cells/ μ L, the headache had resolved, the purpura had disappeared Discharged
Patient #2 Murt et al (27)	41 yo, male	unremarkable	cough and runny nose 15 days ago	On presentation: nasal petechiae; nasal bleeding; purpuric rash;	CT scan: bilateral ground glass opacities	On presentation	Nadir: 9000	Negative viral hepatitis panel and rheumatological markers	Negative	IVIg 1g/kg – 2 doses	Favipiravir	Pneumonia gradually resolved in 5 days; 2 days after treatment platelet count increased to: 54,000 cells/ μ L; At 4-weeks follow-up 50-100,000 cells/ μ L; discharged
Patient #3 Bomhof et al (28)	59 yo, male	stage IV neuroendocrine tumor (NET) of the small bowel	coughing and fever 10 days before presentation; contact with a positive case	On presentation: oral mucosal petechiae, spontaneous skin hematomas	NR	On presentation	Nadir: 3.000	NR	Positive platelet autoantibodies	platelet transfusion, without increment; IVIG 1g/kg – 2 doses; dexamethasone	NR	Platelet count increased to 47 000 cells/ μ L, then dropped to 19,000 cells/ μ L when dexamethasone was started leading to a platelet count of 51,000 cells/ μ L on day 27; discharged
Patient #4 Bomhof et al (28)	66 yo, female	hypertension	4 weeks before admission: fever, dyspnea and coughing, followed by diarrhea and vomiting for several days	On presentation: petechiae, spontaneous epistaxis and increased blood loss from hemorrhoids since 3 weeks	NR	On presentation	Nadir: 2.000	NR	Negative platelet autoantibodies	platelet transfusion – 1 unit (no response); dexamethasone 40mg/day – 4 days (no response); IVIG – on day 6 (responsive)	NR	Platelet count increased to 32,000 cells/ μ L on day 22; discharged
Patient #5 Bomhof et al (28)	67 yo, male	Hypertension, diabetes mellitus	On presentation: fever, coughing and dyspnea since 9 days; Day 2: respiratory failure, ICU admitted; Day 3: intubated	Intracerebral bleeding	CT scan: bilateral infiltrates; segmental pulmonary embolism (on day 10)	9	Day 10: 112,000; On day 12: 3,000 (nadir)	NR	NR	platelet transfusions	unfractionated heparin	Platelet count did not increase on platelet transfusions; on intracerebral bleeding within 24 hours; exitus
Patient #6 Deruelle et al (29)	41 yo, male	Hypertension, obesity	On presentation: acute respiratory failure; fever, cough, and dyspnea for the previous 13 days	On day 10: mild bleeding in endotracheal tube secretions	CXR: mild ARDS; bilateral opacities	8	On presentation: 261,000; On day 10: 24,000; On day 14: 19,000; On day 19: 56,000	increased CRP, ferritin, fibrinogen, mild liver cytolysis; highly elevated d-Dimers;	Negative anti-PF4 antibodies, antinuclear factors	On day 14: methylprednisolone 1 mg/kg/day; On day 20: IVIG 1g/kg	mechanical ventilation, neuromuscular blocking agents, LMWH, danaparoid sodium, ceftaxime	Two days after the IVIG infusion, the platelet count returned to normal; discharged on day 38
Patient #7 Ahmed et al (16)	50 yo, male	No known prior comorbidities	Asymptomatic, contact with a positive case	On presentation: epistaxis; generalised petechial rash, oral blisters	CXR: normal	On presentation	Nadir: 0 (day 1)	Normal -urea and electrolytes, LFTs, haemolysis screen, coagulation profile, viral serology	Negative	IVIg 1 g/kg – 2 doses;	tranexamic acid; nasal packing	Two days after the IVIG infusion, the platelet count increased to 11,000 cells/ μ L, and then to 25,000 cells/ μ L in the next 24 hours; At 2-weeks follow-up: 103,000 cells/ μ L; discharged

Patient (reference)	Age, Gender	Comorbidities\ Past Medical History	COVID-19 sign & symptoms	ITP signs and symptoms	Chest imaging	Days from admission to thrombocytopenia	Platelet count in evolution, cells/ μ L	Other laboratory tests	Autoimmune profile	ITP treatment	Other treatments	Evolution and outcome
Patient #8 Ahmed et al (16)	49 yo, female	No known prior comorbidities	No chest symptoms	On presentation: generalised bruises, gum bleeding for the past 3 days	CXR: normal	On presentation	Nadir: 4,000	Normal -urea and electrolytes, LFTs, coagulation profile; negative viral serology	Negative	IVIg 1 g/kg - 1 dose;	NR	Two days after the IVIG infusion, the platelet count increased to 18,000 cells/ μ L, then to 52,000 cells/ μ L over the next 48 h; discharged
Patient #9 Ahmed et al (16)	96 yo, female	atrial fibrillation, ischaemic heart disease, chronic kidney disease	On presentation: shortness of breath, bilateral coarse crepitations	NR	CXR: bilateral patchy consolidation	5	On presentation: 109,000; Day 5: 3,000	Normal LFTs, coagulation profile & bone profile; negative viral serology	NR	IVIg 0.4 mg/kg - 5 days	oxygenation therapy	Platelet count started improving after the IVIG treatment: 16,000 cells/ μ L; Clinical deterioration, with increasing oxygen requirements;
Patient #10 Humbert et al (30)	84 yo, male	polymyalgia rheumatica, essential tremor	On presentation: 10-day history of cough and progressively worsening dyspnea; bilateral crackles on auscultation	On day 6: sudden onset of spontaneous macroscopic hematuria and bilateral epistaxis	CT scan: diffuse ground-glass opacities and condensations involving more than 50% of pulmonary parenchyma; sub-segmental pulmonary embolism	6	On presentation: 330,000; On day 6: 4,000 (nadir)	Increased fibrinogen	Negative ENA, ANCA, and platelet antibodies; positive lupus anticoagulant antibody	prednisone 1 mg/kg/day; IVIG 1 g/kg - 1 dose	oxygenation therapy; rivaroxaban; hydrocortisone	Two days after the IVIG infusion, the platelet count increased to 57,000 cells/ μ L, and at one week it was at 155,000 cells/ μ L;
Patient #11 Levesque et al (31)	53 yo, male	hypertension, dyslipidemia, type 2 diabetes	On presentation: 3-day history of dyspnea, dry cough and fever;	On day 20: abnormal bleeding from the tracheotomy site; On day 39: small spontaneous intraventricular hemorrhage	NR	20	On presentation: 224,000; On day 20: 23,000	Decreased hemoglobin concentration, lymphopenia; increased creatinine, mildly elevated liver enzymes; negative viral serology	anti-PF4 antibodies weakly positive	IVIg 1 g/kg - 2 doses; intravenous dexamethasone 40 mg/day - 4 doses; platelet and red blood cell transfusions; intravenous tranexamic acid; romiplostim; vincristine	mechanical ventilation; ceftriaxone, azithromycin; unfractionated heparin; renal replacement therapy; piperacillin-tazobactam and ceftazolin	Complications: ARDS, AKI, methicillin-sensitive staphylococcus aureus ventilator-associated pneumonia and ICU-acquired neuromyopathy. The platelet count started to increase on ITP day 11 and reached 178,000 cells/ μ L, 14 days after first dose of IVIG
Patient #12 Tang et al (32)	41 weeks pregnant female	No significant past medical history	On presentation: sore throat, but no other flu-like symptoms	NR	CT scan: infiltrates in the left lower lobe with ground-glass opacities	On presentation	On presentation: 16,000; 2 weeks earlier: 98,000; Day 8: 1,000	NR	Positive platelet auto-antibodies against glycoprotein V	IVIg - 2 days; 2 units of donor thrombocytes	Epidural anesthesia was complicated by hypotension; an urgent caesarian section was performed	Discharged without flu-like symptoms and with stable platelet counts of 82,000 cells/ μ L that normalized 3 weeks later (315,000 cells/ μ L)
Patient #13 Tsao et al (33)	10 yo, female	No significant past medical history	3 weeks prior to presentation: 2 days of fatigue, non-productive cough and fever, in the setting of a known SARS-Cov-2 exposure	On presentation: one day of rash; mouth oral examination notable for wet purpura; petechiae concentrated on her lower extremities, chest and neck; ecchymoses in the popliteal regions and shins	NR	On presentation	On presentation: 5,000	Respiratory pathogen panel: positive for rhinovirus/enterovirus	antinuclear antibodies (ANA) reactive, borderline positive	IVIg 30g (1 g/kg)	400 mg acetaminophen; 30mg (1 mg/kg) diphenhydramine as pretreatment	Discharged; rash and oral lesions improved within 48 hours after IVIG administration; 2 weeks after hospital discharge, her symptoms had completely resolved

Patient (reference)	Age, Gender	Comorbidities\ Past Medical History	COVID-19 sign & symptoms	ITP signs and symptoms	Chest imaging	Days from admission to thrombocytopenia	Platelet count in evolution, cells/ μ L	Other laboratory tests	Autoimmune profile	ITP treatment	Other treatments	Evolution and outcome
Patient #14 Martincic et al (34)	48 yo, male	type 2 diabetes, obesity, obstructive sleep apnea	On presentation: 3-day history of progressive dyspnea, cough, fever, headache, muscle soreness; respiratory rate: 42 breaths/minute; oxygen saturation: 60%; transferred to the ICU	On day 9: macroscopic hematuria after a non-traumatic re-insertion of a urinary catheter; minor bleeding from oral mucosa and blood clots in gastric residual volume	CXR: diffuse bilateral consolidations	Day 9	Day 9: 96,000; Day 12: 2,000 (nadir)	Increased WBC count; increased levels of CRP, fibrinogen, D-dimers; negative viral serology	Direct Coombs test: positive for IgG, indirect Coombs test: negative. Heparin-induced thrombocytopenia (HIT) antibodies: negative	Transfusion of 1 unit (325 ml) of pooled platelet concentrate; IVIG 1 g/kg – 2 doses concomitantly with intravenous dexamethasone 40 mg/day	mechanical ventilation; lopinavir/ritonavir; hydroxychloroquine sulphate; piperacillin/tazobactam; low-dose noradrenalin, nadroparin	One-hour post transfusion platelet count increased from 4,000 cells/ μ L to 9,000 cells/ μ L. The platelet count increased to 185,000 cells/ μ L on the third day of treatment. The platelet count remained normal during the rest of the hospitalization.
Patient #15 Levrant et al (35)	63 yo, female	autoimmune hypothyroidism, stroke	On presentation: 7-day history of asthenia, fever, dry cough, and headaches; bilateral crackles of lung bases; contact with a positive case	On day 26: lower limb purpura; bruises of both arms and legs	CT scan: bilateral and subpleural frosted glass beaches;	Day 26	Day 26: 3,000	Persistent lymphocytopenia; tested negative for the nasal SARS-CoV-2 RT-PCR	Antinuclear antibodies with a nucleolar coloration; direct antiglobulin test and antiphospholipid antibodies negative	IVIG 1 g/kg – 2 doses	Azithromycin 500 mg/day – 6 days; hydroxychloroquine 600 mg/day – 12 days	Platelet levels progressively increased to 38,000 cells/ μ L, 95,000 cells/ μ L, and 145,000 cells/ μ L on days 29, 31, and 33. Purpura of lower limbs and bruises totally disappeared. Discharged on day 33.
Patient #16 Molinaro et al (36)	19 yo, female	No significant past medical history	On presentation: fatigue, ageusia; known SARS-CoV-2 exposure; fever for a few days 2 weeks earlier	On presentation: diffuse petechial rash	CXR: normal	On presentation	On presentation: 2,000 (nadir)	Leukocytosis, lymphocytosis; elevated AST, ALT and serum LDH levels	Positive anti-nuclear antibodies (ANA), positive Connective Tissue Disease (CTD) screen	IVIG 400 MG/KGBW; methylprednisolone 1 MG/KGBW for 5 days	Hydroxychloroquine and antiretroviral agents were also administered	Platelet count increased to 7,000 cells/ μ L (day 3), to 40,000 cells/ μ L (day 4), and to 98,000 cells/ μ L (day 5). Patient discharged

ag), and platelet transfusions. In several of the cases documented, intravenous immunoglobulin administration resulted in a favorable response relatively fast (Patient #2, #7, #8, #13, #15) (16,27,33,35). IVIG was administered for Patient #3 due to active bleeding and the relative contraindication of glucocorticoid medication, which may interact with his prior treatment (somatostatin analog therapy for the neuroendocrine tumor), and for Patient #4 due to dexamethasone treatment failure (28).

Glucocorticoids comprise the main therapy of ITP (40). However, glucocorticoids are considered unsafe for patients with COVID-19 infection as they inhibit immune responses and clearance of the novel coronavirus (9,42).

Thrombopoietin receptor agonists have made a significant contribution to the treatment in patients with immune thrombocytopenia, which are refractory to first-line agents. About 30% of patients have shown a steady rise in platelet counts after treatment (43). Because TPO-RA therapy has demonstrated that the risk of venous thromboembolism has in-

creased in selected patients, it should be used judiciously in COVID-19 infection (44).

CONCLUSIONS

Several hematological abnormalities that might lead to life-threatening bleeding complications were identified in COVID-19. Such manifestations must be included in the clinical evaluation of patients infected by SARS-CoV-2. Since the outbreak of the pandemic, there were several case reports of immune-mediated thrombocytopenia linked to COVID-19. Thrombocytopenia may be attributed to different reasons and promptly diagnosis of the immunological cause is essential, so that proper immunosuppression may be initiated on time. Failure of timely recognition may eventually result in serious complications. The management of ITP should be decided upon the balance of the bleeding risk due to immune thrombocytopenia versus the prospective complication of COVID-19-infection due to immunosuppressive treatment.

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