Prevalence and clinical implication of thrombocytopenia and heparin-induced thrombocytopenia in patients who are critically ill with COVID-19

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ABSTRACT

As the COVID-19 pandemic continues to evolve, different clinical manifestations are better understood and studied. These include various haematologic disorders that have been shown to be associated with increased morbidity and mortality. We studied the prevalence of one unusual manifestation, heparin-induced thrombocytopenia (HIT) and its clinical implications in patients who are severely ill with COVID-19 in a single tertiary centre in Israel. The presence of thrombocytopenia, disseminated intravascular coagulation (DIC) and HIT, and their association with clinical course and outcomes were studied. One-hundred and seven patients with COVID-19 were included. Fifty-seven (53.2%) patients developed thrombocytopenia, which was associated with the worst outcomes (ventilation, DIC and increased mortality). Sixteen (28.0%) patients with thrombocytopenia were positive for HIT, all of which were supported by extracorporeal devices. HIT was independently associated with ventilation days, blood product transfusions, longer hospitalisation and mortality.

Platelet abnormalities and HIT are common in patients who are critically ill with COVID-19 and are associated with the worst clinical outcomes. The mechanisms underlying HIT in COVID-19 are yet to be studied; HIT may contribute to the dysregulated immunologic response associated with COVID-19 critical illness and may play a significant part in the coagulopathy seen in these patients. As many patients with COVID-19 require aggressive thromboprophylaxis, further understanding of HIT and the implementation of appropriate protocols are important.

KEYWORDS: thrombocytopenia, HIT, ECMO, COVID-19

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Introduction

COVID-19 caused by SARS-CoV-2 has developed into a global pandemic. Disease burden is estimated at 500 million confirmed infections and nearly 6,200,000 deaths (as of April 2022).[1] Some reports demonstrate that survival rates in those who are critically ill do not exceed 50%.[2]

In symptomatic hospitalised cases, COVID-19 primarily manifests as a respiratory tract infection that may progress to acute respiratory distress syndrome and, eventually, multi-organ failure. This sequela is suggested to be the result of hyper-inflammation syndrome.[3]

COVID-19 has prominent haematological manifestations; one of which is thrombocytopenia (platelet count $<150 \times 10^9$/L), which is associated with an increased risk of severe illness and mortality. The mechanisms underlying thrombocytopenia are likely multifactorial. However, thrombocytopenia, in itself, has been reported to be associated with disease severity and mortality.[4] During the SARS epidemic, it was suggested that the dual effect of the viral infection and mechanical ventilation lead to endothelial damage triggering platelet activation, aggregation and lung thrombosis, causing vast platelet consumption.[4] Coronaviruses may also directly infect bone marrow elements resulting in abnormal haematopoiesis or trigger an auto-immune response against blood cells. Hence, auto-antibodies and other antibodies produced during viral infection may deposit on the surfaces of

platelets leading to their elimination by reticuloendothelial cells, resulting in increased platelet destruction.[4,5]

Coagulation disorders that may ultimately result in intravascular coagulopathy are frequent among patients with COVID-19 and especially those with severe disease.[3] Furthermore, patients infected with SARS-CoV-2 are at increased risk for thromboembolism. Early and prolonged pharmacological thromboprophylaxis with low-molecular-weight heparin (LMWH) is currently highly recommended by many.[3,6] Important markers for hypercoagulability include an increase in D-dimer levels, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), and a rise in fibrin degradation products.

Heparin-induced thrombocytopenia (HIT) is a significant complication associated with heparin therapy, with a reported prevalence of 0.5%–5% among adult patients. The diagnosis of HIT is complex and is based on both clinical suspicion and heparin antibodies in the setting of active heparin use. It is further supported by the timing of thrombocytopenia and presence of thrombosis in the absence of other causes of thrombocytopenia.[7] Only a few previous case reports have been published regarding HIT in patients with COVID-19, so this phenomenon may still be under-recognised.[8–10]

The aims of this study were to understand the differences in severity of COVID-19 in those with thrombocytopenia compared with those without thrombocytopenia, and to determine the incidence and impact of HIT. We assessed haematological derangements and compared between groups evaluating clinical course and outcomes.

Methods

Patients and data collection

All patients who were critically ill with COVID-19 that were admitted to a single tertiary corona critical care unit (CCCU) between March 2020 and November 2020 were included. Viral RNA was confirmed in all patients by reverse transcriptase – polymerase chain reaction (RT-PCR) assay. Data were collected retrospectively from hospital admission until discharge from the CCCU or death. Time to outcome was calculated from hospital admission. The study was conducted in accordance with the tenets of the Declaration of Helsinki, and with approval of the institutional review board (IRB).

Patients' vital signs (including heart rate, respiratory rate, invasive blood pressure, oxygen, medications, laboratory results and ventilator settings) were extracted from electronic medical records. Complete blood count, serum chemical screen panel, clotting functions and blood gas analysis were performed routinely on all patients who were critically ill, 2–4 times a day, according to severity. As the threshold for the definition of thrombocytopenia varies, for the purpose of this study, a threshold of a platelet count lower than 150×10^9/L was chosen for the definition of thrombocytopenia based on previous studies on SARS-CoV-2.[3,4] Patients who developed thrombocytopenia following the initiation of heparin treatment were suspected to have HIT. The criteria for HIT were defined according to the American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia, ie ≥4 in the 4Ts score as well as positive latex enhanced immunoassay (ELISA; the assay that was used throughout the study for heparins/PF4 antibodies in serum ≥1 U/mL).[11]

Confirmatory function platelet assay was not routinely performed due to lab restrictions on COVID-19-positive samples. Disseminated intravascular coagulopathy (DIC) was defined according to the International Society on Thrombosis and Haemostasis (ISTH) score.[12]

Statistics

We described variables according to their properties. Categorical variables were reported in frequencies and percentages. Significance was assessed using the chi-squared test or Fischer's exact test. Normally distributed continuous variables were reported as mean and standard deviation values, and significance was assessed using Student's t-test. Continuous variables that were not normally distributed were reported as median and interquartile range (IQR) values, and significance was assessed using the Mann–Whitney *U* test. All statistical tests were two sided, and a $p<0.05$ was considered significant. We also constructed a boxplot showing the days to platelet nadir in patients receiving LMWH, unfractionated heparin (UFH) and device support (continuous venous–venous hemofiltration (CVVH) or extracorporeal membrane oxygenation (ECMO)). The statistical analysis was carried out using R version 4.0.0 software (The R Foundation) and PyCharm community edition, v 2020.1.1 (JetBrains).

Results

A total of 107 patients were included in the cohort. The median age was 64 years (54.00–71.50) with a majority of men (81.1%). Interestingly, most patients presented with characteristics of a metabolic syndrome: 38.3% had diabetes, median body mass index (BMI) was 28.5 kg/m^2, 45.8% had hypertension and 44.9% had a background of dyslipidaemia. Eighty-five out of 107 (79.4%) patients required mechanical ventilation early during their CCCU stay (Table 1).

To assess the association of thrombocytopenia with outcome, we compared two groups of patients: the first group consisted of 50 (46.7%) patients with platelet counts that remained higher than 150×10^9/L throughout their CCCU stay (non-thrombocytopenic group) and the second group consisted of 57 (53.2%) patients who had thrombocytopenia (platelet count $<150 \times 10^9$/L) at least once during their stay in the CCCU. Women were more prominent in the non-thrombocytopenic group than the thrombocytopenic group (14 (28.6%) vs six (10.5%), respectively; $p=0.03$). Otherwise, both groups had similar demographic and clinical background characteristics (Table 1).

Patients with thrombocytopenia had a more severe course and a poorer prognosis then those who maintained normal platelet counts (Table 2): the need for mechanical ventilation was significantly more frequent among the patients who developed thrombocytopenia ($p<0.05$) as well as a significantly higher need for supplemental blood products ($p<0.001$). This trend was also seen when looking at specific types of blood products (ie platelets, fresh frozen plasma and packed red blood cell transfusions). Hospital length of stay (LOS) was significantly longer for the patients who were discharged alive from the thrombocytopenic group compared with the survivors without thrombocytopenia ($p=0.05$), as was mortality (more than half of the patients within the thrombocytopenic group died versus less than a third of the non-thrombocytopenic group; $p=0.02$). A multivariate analysis was negative for an association of these findings with age and sex (data not shown).

Table 1. Demographics and clinical features of patients who were critically ill with COVID-19 with and without thrombocytopenia

	Non-thrombocytopenic cohort, n=50	Thrombocytopenic cohort, n=57	p-value
Age, years, median (IQR)	67.50 (53.50–73.00)	61.00 (54.00–68.00)	0.158
Women, n (%)	14 (28.6)	6 (10.5)	0.034
BMI, kg/m^2, median (IQR)	29.40 (26.25–33.62)	27.90 (24.80–30.00)	0.113
Diabetes, n (%)	22 (44.0)	19 (33.3)	0.351
IHD, n (%)	10 (20.0)	8 (14.0)	0.573
Malignancy, n (%)	4 (8.0)	4 (7.0)	1.000
Haematological disorder, n (%)	3 (6.0)	4 (7.0)	1.000
Hypertension, n (%)	22 (44.0)	27 (47.4)	0.877
Dyslipidaemia, n (%)	27 (54.0)	21 (36.8)	0.113
COPD/CLD, n (%)	6 (12.0)	4 (7.0)	0.582
CRF, n (%)	3 (6.0)	9 (15.8)	0.196
Thyroid disease, n (%)	9 (18.0)	3 (5.3)	0.076

BMI = body mass index; COPD = chronic obstructive pulmonary disease; CLD = chronic lung disease; CRF = chronic renal failure; IHD = ischaemic heart disease; IQR = interquartile range.

Further evaluation of the thrombocytopenic group revealed that thrombocytopenia was usually consistent throughout the patients' course and hence the admission, peak and nadir mean platelet counts for the patients within the thrombocytopenic group were all significantly lower when comparing with the non-thrombocytopenic group (Fig 1). Additional differences between the groups include significantly higher peak triglycerides levels, as well as significantly higher serum creatinine peak levels for the thrombocytopenic patients. Table 3 shows a detailed laboratory evaluation of both groups.

Coagulopathies and thrombosis have been shown to play a significant part in the pathophysiology of critical illness and, specifically, COVID-19-associated critical illness. DIC is among the most severe examples of such complication. Fifteen (26.3%) patients within the thrombocytopenic group suffered from DIC compared with only one (2.0%) patient in the non-thrombocytopenic group (p=0.001). The frequency of significant bleeding or thrombotic events was not significantly different between the thrombocytopenic and non-thrombocytopenic group.

Nearly all the patients in our cohort were treated with either LMWH or UFH. Patients were tested for HIT due to clinical suspicion. None of the patients in the non-thrombocytopenic group had heparin/PF4 antibodies level greater than 1 U/mL:

Table 2. Hospitalisation course and outcomes of patients who were critically ill with COVID-19 with and without thrombocytopenia and with and without disseminated intravascular coagulation

	Non-thrombocytopenic cohort, n=50	Thrombocytopenic cohort, n=57	p-value	No DIC, n=91	DIC, n=16	p-value
Mechanical ventilation, n (%)	35 (70.0)	50 (87.7)	0.043	69 (75.8)	16 (100.0)	0.061
Blood products, n (%)	21 (42.0)	41 (71.9)	0.003	47 (51.6)	15 (93.8)	0.004
PLT, n (%)	0 (0.0)	13 (22.8)	0.001	6 (6.6)	7 (43.8)	<0.001
FFP, n (%)	2 (4.0)	13 (22.8)	0.012	8 (8.8)	7 (43.8)	0.001
Cryo, n (%)	0 (0.0)	7 (12.3)	0.030	1 (1.1)	6 (37.5)	<0.001
ECS, n (%)	6 (12.0)	33 (57.9)	<0.001	26 (28.6)	13 (81.2)	<0.001
Bleeding, n (%)	19 (38.0)	29 (50.9)	0.254	36 (39.6)	12 (75.0)	0.018
Thrombosis, n (%)	4 (8.0)	8 (14.0)	0.496	10 (11.0)	2 (12.5)	1.000
LOS, days, median (IQR)	18.00 (7.5–39.5)	33.00 (12.25–40.75)	0.050	22 (12.00–38.00)	34 (18.75–39.50)	0.317
Mortality, n (%)	16 (32.0)	32 (56.1)	0.021	39 (42.9)	9 (56.2)	0.471

Cryo = cryoprecipitates; DIC = disseminated intravascular coagulation; ECS = extracorporeal support; FFP = fresh frozen plasma; IQR = interquartile range; LOS = length of stay (survivors); PLT = platelets.

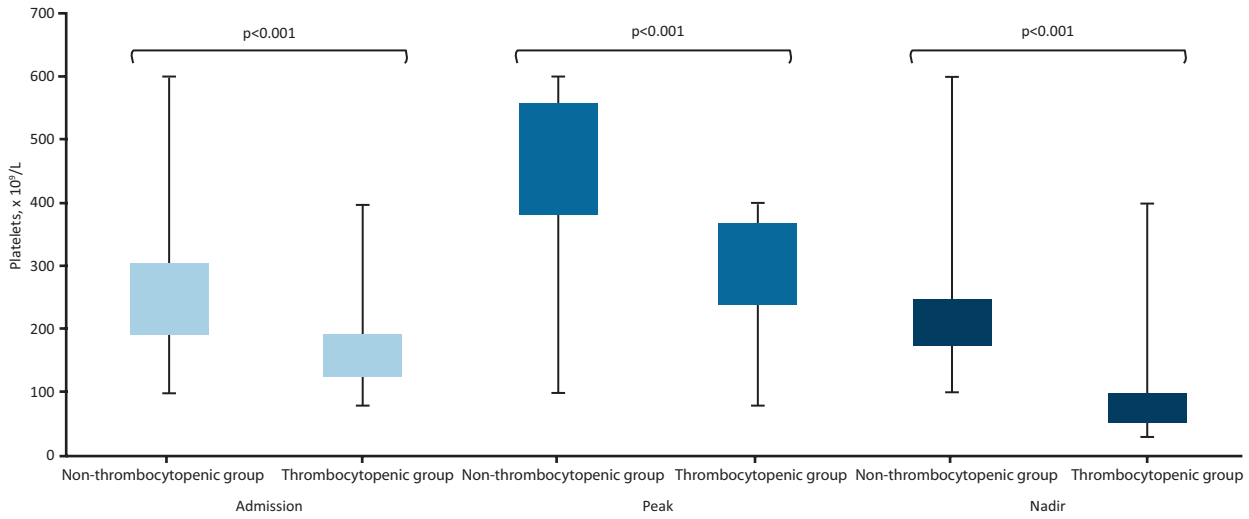

Fig 1. Admission, peak and nadir platelet counts in non-thrombocytopenic and thrombocytopenic groups.

the accepted cut off for a positive result for HIT. However, 16 (28.0%) patients in the thrombocytopenic group had significantly increased heparin/PF4 antibodies level ($p< 0.05$). Fifteen (93.75%) of them also fulfilled the 4Ts criteria for HIT. HIT did not occur unrelated to heparin use. The group of 16 patients positive for heparin/PF4 antibodies was more severely ill when compared with the rest of the cohort. All were mechanically ventilated ($p=0.06$), required more blood product transfusions ($p=0.001$), had more bleeding episodes ($p=0.018$) and had longer hospitalisation ($p=0.026$; Table 4). The hazard ratio (HR) of mortality in patients with HIT was 2.7 (95% confidence interval (CI) 1.0087–7.2493; $p=0.048$).

Interestingly, all patients who required ECMO had thrombocytopenia (22/57 (38.6%) in the thrombocytopenic group vs none in the non-thrombocytopenic group; $p< 0.001$). Out of 31 patients supported by CVVH, 25 had thrombocytopenia (representing 43.9% of the thrombocytopenic group) vs six (12%) in the non-thrombocytopenic group ($p<0.001$). Interestingly, all 16 HIT positive patients were supported by extracorporeal devices (either ECMO or CVVH). The use of ECMO was also more frequent in patients with DIC where 10/16 (62.5%) were supported by ECMO vs only 12/91 (13.2%) patients with no DIC ($p< 0.001$).

Discussion

In this retrospective study of 107 patients who were critically ill with COVID-19, we described total survival rates of more than half (55.1%). There were more men than women, which is concordant with previous reports of significantly more severe COVID-19-associated illness in men.[13]

The mechanism underlying thrombocytopenia is likely multifactorial and might be secondary to physiological decompensation, involve impaired haematopoietic microenvironment and cross reaction of antiviral antibodies.[4,14–16] Thrombocytopenia was found to be associated with the need for ventilation and mortality. Previous studies have shown an association between thrombocytopenia and increased risk for severe clinical course of COVID-19, including multi-organ failure.[4] Notably, a significant percentage (26.3%) of the patients who had thrombocytopenia suffered from DIC (as per ISTH criteria).[17] This is a relatively high prevalence compared with previous studies that showed that DIC may occur in about 10% of patients who were critically ill.[18] Similar to what we have seen in our cohort, the reported 28-day mortality rate of patients with DIC in the intensive care unit ranges from 20% to 50%, which is significantly higher than the mortality rate for patients who do not fulfil the

Table 3. Peak values during hospitalisation for patients who were critically ill with COVID-19 with and without thrombocytopenia

	Non-thrombocytopenic group, n=50, median (IQR)	Thrombocytopenic group, n=57, median (IQR)	p-value
Triglycerides, mg/dL	180 (113–369)	310 (169–480)	0.042
LDL, mg/dL	99.0 (69.5–144)	129 (78.0–168)	0.154
Creatinine, mg/dL	1.06 (0.90–2.11)	1.81 (1.00–3.45)	0.024
Fibrinogen, mg/dL	824 (723–913)	747 (541–886)	0.021
CRP, mg/L	307 (233–398)	317 (228–357)	0.888
D-dimer, ng/mL	5,880 (2,061–16,004)	20,350 (6,490–32,278)	0.001
INR	1.37 (1.24–1.48)	1.50 (1.35–1.70)	0.007

CRP = C-reactive protein; INR = international normalised ratio; IQR = interquartile range; LDL = low-density lipoprotein; LDH = lactate dehydrogenase.

Table 4. Clinical course and outcomes of patients who were critically ill with COVID-19 with and without heparin-induced thrombocytopenia

	No HIT, n=91	HIT, n=16	p-value
Mechanically ventilated, n (%)	69 (75.8)	16 (100.0)	0.061
Thrombosis, n (%)	9 (9.9)	3 (18.8)	0.544
Bleeding, n (%)	36 (39.6)	12 (75.0)	0.018
Blood products, n (%)	46 (50.5)	16 (100.0)	0.001
PLT, n (%)	4 (4.4)	9 (56.2)	<0.001
FFP, n (%)	10 (11.0)	5 (31.2)	0.078
Cryo, n (%)	4 (4.4)	3 (18.8)	0.111
ECS, n (%)	23 (25.3)	16 (100.0)	<0.001
ECMO, n (%)	8 (8.8)	14 (87.5)	<0.001
CVVH, n (%)	22 (24.2)	9 (56.2)	0.021
Dialysis, n (%)	6 (6.6)	4 (25.0)	0.062
LOS, days, median (IQR)	21.00 (12.00–37.50)	31.50 (21.25–53.25)	0.026
Mortality, n (%)	37 (40.7)	11 (68.8)	0.070

Cryo = cryoprecipitate; CVVH = continuous venous-venous hemofiltration; DIC = disseminated intravascular coagulopathy; ECMO = extracorporeal membrane oxygenation; ECS = extracorporeal support; FFP = fresh frozen plasma; HIT = heparin-induced thrombocytopenia; IQR = interquartile range; LOS = length of stay; PLT = platelets.

DIC criteria. Therefore, to improve patient outcomes, it is crucial to diagnose and treat DIC as soon as possible.[19] Tang *et al* reported on the frequent occurrence of DIC in patients with COVID-19 and serious respiratory failure.[20] DIC was much more frequent in non-survivors (71.4%) than in survivors (0.6%).

Hospitalised patients often suffer from thrombocytopenia that may be related to commencing UFH/LMWH treatment and the development of HIT. The frequency of HIT was previously estimated to be 0.76% in patients receiving therapeutic doses of UFH. In patients receiving antithrombotic prophylaxis with LMWH, the frequency was less than 0.1%. In all heparin-exposed patients, the overall risk of HIT was found to be about 0.2%.[21] Nearly all the patients in our cohort were treated with either LMWH or UFH. Within the thrombocytopenic group, nearly a third of the patients were both positive for heparin/PF4 antibodies and 15 fulfilled the 4Ts criteria for HIT ie other possible explanations for thrombocytopenia were less plausible. Possible manifestation of thrombocytopenia and systemic anticoagulation treatment might be bleeding, which was reported in 40% of non-HIT patients and 75% of HIT patients, though not a typical manifestation. Once HIT was suspected, heparin and its derivatives were withheld and treatment was altered to non-heparin-based anticoagulation, resulting in normalisation of platelet counts in all patients in this group, further supporting the diagnosis. Platelet transfusions were given to a high number of patients, irrespectively of HIT, as bleeding was very common, as described earlier. Possible explanation for the bleeding episodes may be the high doses of anticoagulation as well as COVID-19 pathophysiology. Furthermore, extracorporeal support results in shearing forces that cause coagulopathy.

The risk of thrombosis and associated complications (such as massive pulmonary embolus, limb amputation or death) were reported to be increased among patients who are HIT positive and, therefore, early diagnosis and non-heparin-based anticoagulant treatment are important. On the other hand, misdiagnosis resulting in the initiation of alternative anticoagulants in the presence of thrombocytopenia may result in major haemorrhage. Furthermore, if anticoagulation is suspended unnecessarily, there is a greater risk for thrombosis.[22] As the diagnosis of HIT is challenging and complex, especially in patients supported by extracorporeal measures, a high index of clinical suspicion and awareness are the key to preventing the associated complications.[7,23] We demonstrated that, in our cohort of patients who were critically ill with COVID-19, patients who were HIT positive were more severely ill with a tendency towards increased mortality. Due to the nature of this study, we could not investigate whether HIT was in itself a part of the pathophysiology leading to the complicated course or if it was only a marker for a more severe disease: possibly a 'HIT mimicking' disorder.[23] However, our observation warrants increased awareness to this unusual diagnosis that, if untreated, may contribute to further complications in this fragile population.

Platelet activation and consumption, and ongoing release of PF4 are mechanisms associated with HIT. This mechanism is specifically important in patients requiring extracorporeal support (such as ECMO or continuous haemofiltration) due to the platelet damage resulting from the extracorporeal circuit.[7] Indeed, in our cohort, most of the patients (84.6%) that required extracorporeal support suffered from thrombocytopenia and all patients who were HIT positive were supported extracorporeally (and were, therefore, treated with UFH). Interestingly, even though all HIT positive cases were patients who were supported by extracorporeal support in this cohort, a quarter of the 'no HIT' group were also supported by extracorporeal support.

The main limitations of this study are its small sample size and further larger cohorts are required to understand the association and causality of HIT and severe COVID-19. A further challenge is the difficulty in diagnosing HIT in patients on ECMO, as laboratory diagnosis and clinical scoring are yet to be validated. More advanced thrombocyte functional tests (such as serotonin

release assay or heparin-induced platelet activation (HIPA)) that may be used were not available at our institution for patients who were COVID-19 positive during the COVID-19 pandemic due to technical laboratory hazards. Finally, the HR of mortality of patients ultimately diagnosed as having HIT compared wth patients without a diagnosis of HIT is subject to immortal time bias. Patients can only be diagnosed with HIT if they survive long enough to undergo testing. This would most likely result in an underestimation of the risk of death in patients with HIT.

Conclusion

Coagulation disorders and platelet abnormalities play an important role in the pathophysiology of COVID-19-associated critical illness. In this COVID-19 cohort, thrombocytopenia and DIC were found to correlate with morbidity, mortality and disease severity. The prevalence of HIT and DIC was found to be higher than has previously been reported, and might be a part of the dysregulated immunologic response associated with COVID-19 critical illness. Nevertheless, the impact of HIT in the context of COVID-19 is not yet fully understood. Patients with COVID-19 require aggressive thrombo-prophylaxis. The role of ECMO in the treatment of severely ill patients with COVID-19 has increased dramatically with the increase of COVID-19 critical patients suffering from refractory hypoxaemia. Given the potentially high incidence of HIT in this group of patients, a high index of suspicion should be maintained and screening for HIT, by applying the 4Ts clinical score and performing antibody testing (ELISA), should be considered. Furthermore, a prompt alteration of a non-heparin-based therapy regimen should be considered.

Key points

- COVID-19 may present with different clinical manifestations.
- Coagulation disorders, platelet abnormalities and HIT are common among patients who are critically ill with COVID-19, and are associated with worst clinical outcomes.
- All patients who are HIT positive in this cohort were supported with extracorporeal circuits.
- The mechanisms underlying HIT in COVID-19 are yet to be studied.
- HIT may contribute to the dysregulated immunologic response associated with COVID-19 critical illness as well as playing a part in the coagulopathy frequently seen in these patents.
- Further understanding of HIT and the implementation of appropriate treatment protocols are important. ■

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