Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Increased prevalence of heparin induced thrombocytopenia in COVID-19 patients

The first cases of severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection were diagnosed in Northern Italy in February 2020. The coronavirus disease 2019 (COVID-19) pandemic is responsible for a marked increase in intensive care unit (ICU) admission rates with high mortality (1). Between February 22nd and April 15th, among more than 900 COVID-19 patients admitted to S. Matteo Hospital Foundation, a tertiary academic hospital in Pavia, 172 required intensive treatment.

Inflammation and thrombosis appear to play a pivotal role in SARS-CoV-2 infection. Due to the high thrombotic risk, prophylactic doses of low molecular weight heparin (LMWH) may be appropriate in hospitalized COVID-19 patients, and anticoagulant therapy may improve their prognosis (2). Heparin-induced thrombocytopenia (HIT) is a rare, potentially life-threatening complication of heparin therapy. HIT is mediated by anti-platelet factor 4 (PF4)/heparin antibodies and is characterized by a hypercoagulable state (3). Moreover, a minority of patients develop clinically relevant complications, including HIT with thrombosis, which is referred as HITT (3). Common risk factors for HIT include surgery, exposure to unfractionated heparin (UFH) or low molecular-weight heparin (LMWH), hemodialysis and extracorporeal membrane oxygenation (ECMO) (4). Thrombocytopenia in critically ill patients is quite common and often leads physicians to consider HIT in the differential diagnosis. However, HIT is not usually the cause, as its incidence is reported between 0.02% and 0.45% (5).

We describe two cases of HIT in COVID-19 patients admitted to our ICU. Table 1 shows the baseline characteristics of the study population.

Case report 1

A 59-year-old male patient referred to our hospital for COVID-19-related pneumonia with respiratory distress. Laboratory exams on admission are shown in Table 1. SARS-CoV-2 infection was confirmed by reverse-transcriptase-polymerase-chain-reaction (RT-PCR) on nasopharyngeal swab. The patient received supplemental oxygen with continuous positive airway pressure (CPAP), empirical antibiotics, hydroxychloroquine and prophylaxis for venous thromboembolism (VTE) with low-molecular-weight heparin (enoxaparin 4000 IU/day). Due to progressive severe respiratory failure, on day 5 the patient was transferred to the ICU, where invasive mechanical ventilation was initiated. Renal function worsened (creatinine serum level up to 359.87 μmol/l) and required continuous renal replacement therapy (CRRT); enoxaparin was replaced by calcium heparin at a dose of 5.000 IU/0.2 ml every 8 h. After 18 days of heparin exposure, laboratory tests showed a decline of platelet count, with a reduction of 50% by day 21 (day 15 of calcium heparin). Calculated 4 T score was 5 and HIT expert probability (HEP) score was 6. Anti-PF4-antibody testing was positive and confirmed by the high-heparin confirmatory step. Heparin was promptly stopped and replaced with fondaparinux at a dose of 1.5 mg/day with normalization of platelet count.

The clinical status was improving, when the patient experienced a cardiac arrest and computed tomographic scan of the chest showed bilateral pulmonary embolism. Fondaparinux was then replaced with argatroban. Deep vein thrombosis was excluded. Therapy with argatroban was well tolerated, without recurrence of thrombosis or adverse effects. A few days later, *Candida parapsilosis* was isolated from blood cultures, and the patient died of septic shock.

Case report 2

An otherwise healthy 50-year-old male patient was admitted to the ICU with SARS-CoV-2 -related bilateral pneumonia and acute respiratory distress syndrome (ARDS). He was intubated and vasopressor support was required for hemodynamic instability. Hydroxychloroquine, azithromycin and enoxaparin (6000 IU every 12 h) were initiated. Given the persistent severe hypoxia and hypercapnia, the patient received veno-venous extra-corporeal membrane oxygenation (VV-ECMO) with intravenous heparin sodium. Thrombocytopenia with a 50% decrease in platelet count was observed after 16 days of heparin exposure (10 days of heparin sodium). Calculated 4 T score was 4 and HEP score was 3. Suspecting HIT, heparin was stopped and replaced by bivalirudin at standard dose with normalization of platelet count. Anti-PF4-antibodies tested positive. The improvement of the patient's medical condition enabled the discontinuation of ECMO (after 21 days) and vasopressors; VTE prophylaxis with fondaparinux (2,5 mg/day) was initiated. Then, the patient developed urinary tract infection and Acinetobacter baumannii was isolated from bronchoalveolar lavage, but he was finally discharged home in good condition after 69 days of hospitalization.

Thrombocytopenia was a common laboratory finding among the 172 COVID-19 patients admitted to the ICU of our hospital. A platelet count below 100,000 cells/uL was found in 43 patients (25%), and a platelet count of 100,000–150,000 cells/uL was found in 42 patients (24,41%). Anti-PF4 antibody test was performed in 14 patients with suspected HIT and one case of HIT, and one of HITT were diagnosed (1.16%) while the test was negative in 11 patients and one patient presented only a weak positivity (0.41 anti PF4 Optical Density units) that suggests a very low probability of HIT (< 5%).

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Table 1
Demographic and clinical characteristics and laboratory findings.

	Patient 1	Patient 2
Demographic characteristics		
Age (years)	59	50
Sex	Male	Male
Initial findings		
Medical history	Hypertension	None
Symptoms at disease onset	Fever, Dyspnea	Fever, Dyspnea
Treatment before admission to ICU	Antibiotic, hydroxychloroquine, LMWH	Antibiotic, hydroxychloroquine, LMWH
Laboratory findings on admission		
Hemoglobin (g/dl) (normal value 13.2–17.3)	13.5	12.3
White cells (cells/uL) (normal value 4000–11,000)	8400	11,600
Total neutrophils (cells/uL) (normal value 1500–8000)	8000	9900
Total lymphocytes (cells/uL) (normal value 1000–4800)	200	600
Platelet count (cells/uL) (normal value 150,000–450,000)	243,000	324,000
Nadir platelet count (cells/uL)	107,000	28,000
AntiPF4 antibodies OD units (normal value <0.4)	0.81	2.13
% inhibition of OD reactivity by high heparin (normal value <50)	88	87
Creatinine (umol/L) (normal value 60–110)	84	76.04
EGFR (ml/min/1.73 m^2) (normal value >90)	88	101
Total bilirubin (umol/L) (normal value 1.71–20.5)	22.57	26.68
Alanine aminotransferase (ukat/L) (normal value 0–0.58)	0.52	1.17
Aspartate aminotransferase (ukat/L) (normal value 0–0.58)	0.68	1.03
Hs-Troponin I (ng/ml) (normal value <0.034)	0.033	0.027
Lactate dehydrogenase (ukat/L) (normal value 2.34–4.68)	10.49	7.58
INR (normal value <1.1)	1.36	1.16
aPTT (s) (normal value 30–40)	28.3	22
Fibrinogen (mg/dl) (normal value 170–410)	580	462
D-Dimer (mg/l) (normal value <500)	4114	3991
Antithrombin (%) (normal value 80–120%)	72.1	89.2
C-reactive protein (ug/l) (normal value 68–8200)	290,900	72,600
Procalcitonin (ng/ml) (normal value <0,5)	7.21	3.77
Platelet count 1 week after heparin interruption (cells/uL)	258,000	210,000
Scores		
4T score	5	4
HEP score	6	3
Thrombotic complications		
Site of thrombosis	Bilateral pulmonary embolism	None

CAD denotes coronary artery disease, ICU intensive care unit, LMWH low molecular weight heparin, PF4 platelet factor 4, EGFR estimated glomerular filtration rate, INR international normalized ratio, aPTT activated partial thromboplastin time, ND not determined, and HEP heparin-induced thrombocytopenia expert probability, OD optical density.

The diagnosis of HIT relies on clinical suspicion, first assessed by probability scores, and then confirmed by laboratory tests. The 4 T score and the more recent HEP score are the most widely used pretest clinical scoring systems (6,7). When an intermediate/high pretest probability is found, it is recommended to perform laboratory tests, including the immunoassay as screening test and the functional assay as confirmatory step.

In our laboratory, we use the PF4 Enhanced® assay (Immunoglobulin G/A/M) (IMMUCOR GTI Diagnostics, Waukesha, Wisconsin, USA) as first-line test for HIT. Optical density (OD) levels reported in this study were derived from PF4 Enhanced® test only and tests were considered positive if OD $>$ 0.40 at 410 nm. A confirmatory step using high heparin concentrations was performed.

Our patients presented an intermediate/high clinical suspicion and a positive laboratory test and both of them had high risk factors for HIT, such as sepsis and extracorporeal circulation (4).

In our past experience, from January 1st 2018 to February 20th 2020, among 2148 consecutive patients admitted to the ICU, anti-PF4 antibody test was performed in 62 patients with thrombocytopenia and only three HITT and one HIT (0.18%) were diagnosed (data obtained from ICU's medical records). This prevalence is comparable to that in previous reports (8).

An association between high risk for pulmonary embolism and COVID-19 is hypothesized by many authors (9). HITT patient's personal and familiar history was negative for thromboembolism, and although the infection may have contributed to a pro-thrombotic state, the temporal sequence of the events suggests a direct correlation of the thrombotic event with HIT.

The limitation of our data is the unavailability of the confirmatory functional assay in our laboratory. In spite of this, it is reasonable to diagnose our patients with HIT based on clinical presentation, pre-test probability, the anti PF4 antibodies OD units, and a rapid increase of platelet counts following discontinuation of heparin.

In conclusion COVID-19 is characterized by marked hypercoagulability, and heparin administration, particularly in patients with severe impairment of respiratory function, has been employed to prevent VTE. Even if HIT is a rare condition, the incidence observed in our case series is higher than that reported in critically ill patients without COVID 19, as recently observed in the literature (10). We hypothesize that the inflammatory state and the activation of the coagulation cascade could play a role in the development of anti-PF4 antibodies. Other mechanisms may also be involved, and further studies are needed.

Declaration of competing interest

None.

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