ORIGINAL ARTICLE

Thromboprophylaxis in hospitalized COVID-19 patients: the efficacy and safety of the approved hospital protocol

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KEY WORDS

bleeding, COVID-19, mortality, thromboprophylaxis, thrombotic events

ABSTRACT

INTRODUCTION Prothrombotic coagulopathy in COVID-19 has led to a strong recommendation for thromboprophylaxis in all hospitalized patients, although there are large differences in the dosage regimens among hospitals and their outcomes remain uncertain.

OBJECTIVES We aimed to determine the incidence of thrombotic events and bleeding in patients with COVID-19 using the approved local thromboprophylaxis protocol.

PATIENTS AND METHODS We adapted a self-developed pharmacological thromboprophylaxis protocol based on clinical and laboratory risk assessment of thrombosis in 350 consecutive patients (median age, 67 years) with confirmed COVID-19, treated in designated wards at a single center in Kraków, Poland from October 10, 2020, to April 30, 2021. We recorded in-hospital venous and arterial thromboembolic events, major or clinically relevant bleeding, and deaths along with other complications related to heparin administration.

RESULTS Thromboprophylaxis with low-molecular-weight heparin was administered in 99.7% of patients, 57 (16%) were treated in the intensive care unit. As many as 92% of patients followed the protocol for more than 85% of hospitalization time. Thromboembolic events occurred in 16 patients (4.4%): venous thromboembolism (n = 4; 1.1%), ischemic stroke (n = 4; 1.1%), and myocardial infarction (n = 8; 2.2%). Hemorrhagic complications were observed in 31 patients (9%), including fatal bleeds (n = 3; 0.9%). The overall mortality was 13.4%. The prophylactic, intermediate, and therapeutic anticoagulation preventive strategies with heparin were not related to any of the outcomes.

CONCLUSIONS The thromboprophylaxis protocol approved in our institution was associated with a relatively low risk of thromboembolism and bleeding, which provides additional evidence supporting the adoption of institutional strategies to improve outcomes in hospitalized patients with COVID-19.

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INTRODUCTION In 2021, the COVID-19 pandemic with a high risk of thromboembolic events remains a major public health challenge in most countries.[1] Despite widely introduced prophylaxis and vaccination programs, there are concerns regarding the next spike in cases, caused by the new variants of the virus.[2] Although in 2020 we learnt a great deal about SARS-CoV-2 infection,[3,4] there are still therapeutic dilemmas to be solved, including the optimal prevention of thromboembolic episodes.

There is compelling evidence that massive activation of blood coagulation and platelets related to inflammation and endothelial injury

WHAT'S NEW?

This study aimed to assess the efficacy and safety of the thromboprophylaxis algorithm approved in our hospital. Thrombotic events, with higher than usual occurrence, are commonly reported in patients with COVID-19. Until now, limited data exist to guide the intensity of antithrombotic prophylaxis. We concluded that the risk of arterial and venous thromboembolic events in COVID-19, according to our protocol, can be reduced by optimizing low-molecular-weight heparin administration with a good safety profile.

with the subsequent venous and arterial microthrombosis and macrothrombosis are observed in a large proportion of hospitalized patients with COVID-19.[5] Initial reports suggested a high rate of venous thromboembolism (VTE), ranging from 13% to 69%.[6,7] Most experts recommended that thromboprophylaxis with heparins should be initiated in all hospitalized COVID-19 patients unless there are absolute contraindications.[8] Several experts suggested, despite the absence of high-quality evidence, that heparin doses exceeding those used in standard prophylaxis should be used in severe cases.[9] However, it has been shown that the heparin dose escalation could result in a higher rate of clinically relevant hemorrhagic episodes without lower rates of thromboembolism or mortality among in-hospital COVID-19 patients.[5]

It is recommended by the American College of Chest Physicians and other societies to develop local clinical practice recommendations in order to optimize patient-important health outcomes and care for patients who have experienced or are at risk for thrombotic events.[10] That is why it is crucial to establish a local protocol for thromboprophylaxis that would be efficient and safe.[8] In COVID-19, the published protocols differ substantially from each other, including the types and intensity of antithrombotic regimens.[10-12] Of note, it has been reported that heparin-based regimens are not beneficial in critically ill patients with COVID-19, especially those receiving mechanical ventilation, but they might be effective in hospitalized patients not admitted to the intensive care unit (ICU).[13]

Due to the paucity of data on real-life results of standardized antithrombotic regimens in COVID-19, we investigated the effects of the thromboprophylaxis model adopted in patients with COVID-19 treated in a tertiary Polish hospital in the second and third wave of the pandemic.

PATIENTS AND METHODS

Study population

Consecutive patients diagnosed with COVID-19 and hospitalized in John Paul II Specialist Hospital in Kraków, Poland from October 10, 2020, to April 30, 2021 were retrospectively analyzed. The exclusion criterion was age younger than 18 years. Medical data, that is, demographics, concomitant diseases, duration of hospitalization, and medications, as well as clinical outcomes related to thrombotic and bleeding episodes during hospitalization, were collected based on hospital records, using a standardized self-developed questionnaire. We enrolled all patients with confirmed COVID-19 who were discharged or died at our institution from the opening of the COVID-19 designated ward.

The bioethical committee approval was not required. The hospital data were analyzed as part of the recommended quality of care control according to the internal regulations.

The diagnosis of COVID-19 was made following the World Health Organization interim guidance and confirmed by the reverse transcriptase–polymerase chain reaction (RT-PCR) for the SARS--CoV-2 test from a nasopharyngeal swab, conducted at the hospital laboratory.

All patients were classified into one of 2 groups based on the severity of COVID-19.[14,15] Group 1 (mild COVID-19) included patients without severe comorbidities, with initial oxygen saturation as measured by pulse oximetry (SpO_2) greater than 94%, and who required 4 l/min of oxygen flow or less during hospitalization. Group 2 (severe COVID-19) included patients with severe comorbidities such as recent stroke, acute myocardial infarction (MI), or other life-threatening conditions requiring therapy in the ICU, or patients in an early postoperative period with initial SpO_2 of 94% or less, or those who required more than 5 l/min of oxygen flow during hospitalization.

Thromboprophylaxis model Pharmacological thromboprophylaxis was administered according to a protocol developed at our hospital. Until the end of October 2020, a simplified model was used. The anticoagulation intensity was classified as: prophylactic, intermediate, or therapeutic, depending on the daily dose of enoxaparin administered subcutaneously, which was adjusted for weight and creatinine clearance.

Standard prophylactic-intensity anticoagulation, enoxaparin of 40 mg or less once daily (in obese patients of >100 kg, the dose was 0.5 mg/kg of weight/day) was administered to patients with COVID-19 without contraindications and additional risk factors for thrombosis, who before the hospitalization had not received any anticoagulants.

Intermediate-intensity anticoagulation, enoxaparin of 1 mg/kg body weight once daily, was administered to patients not receiving anticoagulants prior to admission, but presenting with a high risk of VTE, associated with the following risk factors: prior VTE, known thrombophilia, active cancer, active inflammatory bowel disease, age over 75 years, immobilization (especially during oxygen therapy or mechanical ventilation), rapid increase in D-dimer levels by 1000 ng/ml per day.

Therapeutic-intensity anticoagulation, enoxaparin of 1 mg/kg body weight twice daily, was administered to patients with documented pulmonary embolism (PE), or deep venous thrombosis (DVT), echocardiographic signs of right

ventricular overload, a rapid increase in D-dimer levels, or clinical findings suggestive of VTE (without imaging studies). It was advised to replace oral anticoagulation with heparin at therapeutic doses during hospitalization. It was allowed to continue therapy with vitamin K antagonists in stable patients with a mechanical heart valve or history of intracardiac thrombi, if it was possible to monitor the international normalized ratio daily. Continuation of direct oral anticoagulants (DOACs) was permitted. However, it was recommended to replace DOACs with heparin in patients with severe COVID-19 or with high risk of relevant drug–drug interactions.

It was suggested to monitor anti-Xa activity in patients weighing more than 100 kg or less than 50 kg as well as in those with creatinine clearance of less than 30 ml/min while on enoxaparin. It was also advised to measure platelet count after 5 days since the first dose of a low-molecular-weigh heparin (LMWH) or earlier in patients who had already been treated with LMWH to rule out heparin-induced thrombocytopenia (HIT), diagnosed as described.[16] We recommended measuring D-dimer levels every 24 to 48 hours in all patients. In patients with a platelet count of less than 50 000/μl, with active bleeding or coagulopathy, it was recommended to administer mechanical thromboprophylaxis instead of a pharmacological strategy.

The anticoagulation intensity was changed according to the clinical condition of the patient. Possible causes of enoxaparin dose escalation included a rapid increase of D-dimer levels, blood products transfusion, clinical signs of PE / MI / ischemic stroke, parenteral nutrition, hemodialysis, and significant arrhythmia.

Outcomes All outcomes were recorded from the day of admission to the COVID-19 ward (time 0) until either hospital discharge or in-hospital death.

Venous thromboembolism was defined as a symptomatic episode of DVT and / or PE confirmed by ultrasonography and / or computed tomography angiography. Clinical symptoms suggestive of PE were sudden shortness of breath, chest pain, hemoptoe, or tachycardia, while for DVT, it was swelling and / or pain in the affected leg.[17]

Transient ischemic attack was defined as a transient, lasting less than 24 hours, episode of neurological dysfunction due to the focal brain, spinal cord, or retinal ischemia, without persistent tissue injury. Ischemic stroke was defined as an episode of neurological dysfunction lasting more than 24 hours.[18]

Myocardial infarction was defined as acute myocardial injury detected during hospitalization by abnormal cardiac troponin in the setting of evidence for acute myocardial ischemia.[19]

In-hospital mortality was defined as death that occurred during the hospital stay.

Major bleeding was defined by the International Society on Thrombosis and Hemostasis guidance and included fatal bleeding, hemorrhage occurring in a critical area or organ, or bleeding causing a fall in hemoglobin of 2 g/dl or more, or leading to transfusion of 2 or more units of whole blood or packed red blood cells. Nonmajor clinically relevant bleeding was defined as bleeding that leads to a physician-guided medical or surgical treatment for bleeding, or change in antithrombotic therapy.[20]

Statistical analysis Continuous variables are presented as medians and interquartile ranges (IQRs) whereas categorical and ordinal variables are expressed as numbers and percentages. Normal distribution was assessed with the Shapiro–Wilk test. The Mann–Whitney test was used to compare quantitative variables between 2 independent groups as appropriate. The χ^2 test or the Fisher exact test was applied for the comparison of qualitative variables between 2 groups. *P* values of less than 0.05 were considered statistically significant. The R,[21] and Statistica 12.5 software (StatSoft Inc, Tulsa, Oklahoma, United States) were used to compute all statistical analyses.

RESULTS The study included 365 patients with COVID-19. Fifteen participants, including 6 critically ill patients transferred from another hospital to our institution who died within 13 days of hospitalization, were excluded from analysis due to lack of access to complete medical data. Eventually, a total of 350 patients (211 [60%] men and 139 [40%] women) were analyzed. There were 233 patients (66.6%) with mild COVID-19, including 138 men, at a median (IQR) age of 66 (55–76) years, while 117 patients (33.4%), including 69 men and 42 women, at a mean age of 69 years, had severe COVID-19 (TABLE 1).

Oxygen therapy was administered in 242 patients (69%) and mechanical ventilation was used in 47 patients (13%). Sixty-one patients (17.4%) with mild COVID-19 did not require any oxygen supplementation. The other treatments used to treat COVID-19 were as follows: remdesivir (n = 85; 24.7%), convalescent plasma (n = 71; 20.6%), tocilizumab (n = 3; 0.9%), and dexamethasone (n = 216; 62.8%) (TABLE 2).

Thromboprophylaxis On admission to the COVID-19 ward, 347 patients (99.1%) received thromboprophylaxis with a LMWH. Two patients did not receive a LMWH due to contraindications and mechanical thromboprophylaxis was used. One patient, a 20-year-old woman with mild COVID-19 with low risk of thrombosis did not receive any thromboprophylaxis based on a physician's decision against the hospital recommendations. On admission, 145 patients (41.7%) received a prophylactic-dose LMWH, 75 (21.6%) intermediate-dose thromboprophylaxis, and 127 (36.6%) were on therapeutic-dose LMWH.

Thromboembolic events Thromboembolic events occurred in 16 patients (4.5%). There were 8 patients (2.3%) with acute MI, while symptomatic VTE and ischemic stroke were each diagnosed in 4 patients (1.1%). Thromboembolism occurred in 6 patients (10%) out of those treated in the ICU: 5 patients had MI (8.8%) and 1 had stroke (1.7%). All the patients died. Thromboembolism was not associated with age, sex, body mass index, or comorbidities, including hypertension and diabetes (TABLE 1). Severe COVID-19 was associated with higher risk of MI during hospitalization (P = 0.02; TABLE 3). Among patients free of thromboembolic events, there were more patients who received a thienopyridine due to prior invasive cardiology procedures and an angiotensin-converting enzyme inhibitor for the management of hypertension or heart failure (TABLE 1). There was no association of thromboembolic events during hospitalization with any laboratory variables including baseline D-dimer or C-reactive protein concentrations. The same holds true for different anticoagulation regimens used according to our protocol.

Bleeding Major bleeding was observed in 9 patients (2.6%) and nonmajor clinically relevant bleeding in 22 (6.3%). We observed massive epistaxis (n = 2; 0.6%), intra-abdominal hemorrhage (n = 2; 0.6%), large subcutaneous hematoma (n = 11; 3.1%), fall in hemoglobin levels of more than 2 g/dl (n = 1; 0.3%), hemoptoe (n = 5; 1.4%), hematuria (n = 6; 1.7%), cardiac tamponade (n = 1; 0.3%), and intracranial hemorrhage (n = 3; 0.9%). Advanced age was associated with higher bleeding risk. There was no difference in bleeding episodes between patients with severe COVID-19 compared with less severe cases. There was an increased prevalence of 2 comorbidities among bleeding COVID-19 patients compared with the nonbleeding ones: peripheral artery disease (32.3% vs 12.2%; P = 0.005) and known malignancy (16.1% vs 5.64%; P = 0.04). The use of 4 classes of drugs on admission was associated with a higher rate of clinically relevant bleeding, that is, DOAC (bleeding patients, 29%; nonbleeding patients, 9.72%; P = 0.004), β-blocker (83.9% vs 49.8%, respectively; P <0.001), angiotensin-converting enzyme inhibitor (71% vs 42%, respectively; P = 0.002), and statins (71% vs 40.8%, respectively; P = 0.001).

As expected, higher risk of bleeding was observed in COVID-19 patients with lower estimated glomerular filtration rate (P <0.001) and hemoglobin (P = 0.01) on admission (TABLE 1). Patients after an invasive cardiac or vascular procedure shortly prior to admission did not present higher bleeding risk.

In 82 patients (23%), the anti-Xa assay was performed to confirm the therapeutic or prophylactic LMWH dose or to achieve a therapeutic dose after a thrombotic event. In this group, hemorrhagic complications occurred in 10 patients (12.2%).

Mortality The overall mortality was 13.4% (n = 47). In the group with thromboembolic events during hospitalization but no hemorrhagic complications, the mortality was significantly higher (P <0.001; TABLE 3). Importantly, 3 COVID-19 patients who experienced bleeding complications died due to hemorrhage. The 3 cases were as follows. A 69-year-old man with chronic heart failure class IV (according to the New York Heart Association) after percutaneous angioplasty of the internal carotid artery a month before admission with mild COVID-19, who received therapeutic LMWH dosage, had fatal intra-abdominal hemorrhage at day 14. The second case was a 85-year-old man with mild COVID-19, with chronic heart failure class IV and third-degree atrioventricular block with DDD pacing implanted at day 3, who was on prophylactic-dose LMWH. One day after DDD implantation fatal cardiac tamponade occurred. The third case was a 57-year-old man with obesity, hypertension, and severe COVID-19 treated in the ICU with the use of extracorporeal membrane oxygenation, who experienced a massive fatal hemorrhage from the site of oxygenation cannula insertion at day 8.

Other complications There were no confirmed incidents of HIT, although 2 patients had a high clinical probability of HIT with more than a 50% fall in the platelet count while on enoxaparin. The 2 patients had immunoglobulin (Ig) G antibodies against heparin-PF4 complexes below the cutoff value (optical density, 0.4).

One patient, a 57-year-old woman, was allergic to LMWH. She had severe respiratory failure requiring mechanical ventilation and developed extensive urticaria following subcutaneous enoxaparin, and consequently subcutaneous fondaparinux, 2.5 mg/d, was administered during hospitalization without complications.

DISCUSSION

The current study assessed the risk of thromboembolism, bleeding, and death among hospitalized COVID-19 patients who followed a local thromboprophylaxis model involving a prophylactic-, intermediate-, and therapeutic-dose LMWH. We found that the model was associated with acceptable risk of arterial thromboembolism and VTE as well as clinically relevant bleeding, along with mortality. Our findings suggest that despite great controversy around the best anticoagulation strategy in COVID-19 patients, the locally approved model of the use of LMWH is of practical value and should be strongly encouraged unless high-quality randomized controlled studies provide robust evidence to support the uniform approach to prevention of thrombosis associated with this disease.

Thromboembolic complications are serious COVID-19 manifestations which often lead to a life-threatening condition.[22-26] A meta-analysis including articles published to June 2020, demonstrated that the overall VTE rate among COVID-19 patients was 9% to 21%, with 5% among non-ICU

and 21% to 31% among ICU patients.[27,28] The risk of VTE was higher than that in hospitalized patients with acute infections. For example, in the 2009 pandemic of H1N1 influenza, the VTE rate was reported at about 6%.[29] A lower risk of VTE in the current study might be explained by the fact that only cases of symptomatic VTE were reported, and that the thromboprophylaxis algorithm was used only after the first wave of COVID-19, in which the rates were the highest. It is worth mentioning that VTE rates observed postmortem were 2-fold higher than those observed in survivors.[30] Therefore, we cannot exclude that some deaths were the consequence of undiagnosed massive PE.

Arterial thromboembolism was reported in 8 studies analyzed in the meta-analysis, and the overall rate was 2%, with 1% in non-ICU patients and 5% in ICU patients.[31] We reported similar data, with a higher rate of arterial thromboembolism in ICU cases (10%), and a high rate of MI (8.8% vs 0.5% in previous studies). Since our hospital has 3 large cardiology departments with 24/7 service, it is likely that our group represented a relatively large proportion of high-risk patients with CAD who were prone to recurrent coronary ischemia during COVID-19.

The current mortality rate of 13.4% of combined non-ICU and ICU patients could be considered as a relatively high; however, the reported COVID-19–related deaths depend on local hospital management strategies, national public health structures, and healthcare system organizations, along with ethnic and regional environmental differences.[32,33] Early reports suggested higher COVID-19 death rates in comparison with more recent analyses, which is associated with treatment improvement, especially with the use of remdesivir and glucocorticosteroids, and risk factors reduction.[33,34] The analysis of 86 356 patients with COVID-19 in England, admitted to hospitals from March 2020 to July 2020, showed 26.6% mortality related to COVID-19.[32] In a study of 20 736 patients admitted to 107 acute care hospitals in 31 states in the United States from March 2020 through November 2020 showed 15.8% mortality.[35] Therefore, the mortality rate of 13.4% observed in our study from October 2020 to April 2021 with a large proportion of the patients with cardiovascular disease, including those following high-risk invasive procedures performed at our hospital, reflects the global declining trend in COVID-19 mortality in 2021.

In our thromboprophylaxis model, there were 3 dosage categories. Although our classification model is similar to the guidelines used by other medical centers treating COVID-19, we acknowledge that such a classification is arbitrary.[31] Some authors defined therapeutic-dose enoxaparin as 1.5 mg/kg per day, while we defined therapeutic dosage as 1 mg/kg twice a day.[36] Similar to other studies, our protocol included the possibility of modification of LMWH doses, depending on the clinical state of the patient and possible development of complications.[37] The LMWH dosage was most frequently changed in the ICU. A recent recommendation suggests that LMWH administration should depend on the stage of COVID-19. In stage 1 of the disease, including asymptomatic and mildly symptomatic patients, LMWH administration should be given only in chronically bedridden patients. In stages 2 to 4, including patients with full symptomatic COVID-19, the prophylactic or therapeutic doses depending on the clinical scenario should be administered.[16] It was observed that monitoring D-dimer levels was necessary due to its association with high mortality in COVID-19 patients. Also, it was recommended to check platelet count, prothrombin time, and fibrinogen.[38] In our opinion, additional monitoring of anti-Xa activity in patients on a therapeutic-dose LMWH may be useful in optimizing prophylaxis in high-risk individuals. Nonetheless, we did not provide evidence for the benefits from such a strategy in our real-life cohort. Thus, we need to assess better predictors for higher bleeding risk in COVID-19 patients.

Due to fear of thromboembolic events, some authors have pushed for higher anticoagulation targets, especially in COVID-19 patients treated in the ICU,[39] leading to a routine increase in the dose of anticoagulation beyond prophylactic dosing with hope of reducing the microvascular thrombosis associated with SARS-CoV-2 infection.[40] However, an increased bleeding risk with therapeutic anticoagulation was reported in both critically and noncritically ill COVID-19 patients. It was shown that the rate of major or nonmajor clinically relevant bleeding was 24 per 100 person-months compared with 6.9 per 100 person-months in patients receiving standard prophylactic-intensity anticoagulation.[41] In another study, it was found that two-thirds of major bleeding events occurred in critically ill patients with COVID-19 who were on therapeutic-intensity anticoagulation.[5,42] Recent high-quality evidence supports the use of standard-dose thromboprophylaxis, without dose escalation, in critically ill patients with COVID-19.[43] Nonetheless, we show that there are no significant relationships between doses of LMWH and bleeding occurrence as well as thrombotic events that occurred in patients with both severe and mild courses of COVID-19. Also, we report no statistically significant relationship between LMWH doses and mortality in patients with a mild course of COVID-19. In the group of ICU-treated COVID-19 patients, there is a statistically significant relationship between higher dosages of LMWH and mortality as 70% of those patients received therapeutic anticoagulation for a minimum of 2 days. Of note, we did not observe any association between invasive cardiovascular procedures during COVID-19 and increased bleeding risk, regardless of the prophylaxis used.

The use of heparins is related to the risk of HIT, a life-threatening complication, that occurs

TABLE 1 Demographic and clinical characteristics of the study population (continued on the next page)

Variable		Overall (n = 350)	Mild COVID-19 (n = 233)	Severe COVID-19 (n = 117)	*P* value	No bleeding complications (n = 319)	Bleeding complications (n = 31)	*P* value	No thrombotic complications (n = 334)	Thrombotic complications (n = 16)	*P* value
Age, y		67 (58–76)	66 (55–76)	69 (62–76)	0.045	67 (57–75)	76 (69–84)	<0.001	67 (58–76)	72.5 (61–79.5)	0.15
Male sex		211 (60.3)	138 (59.5)	73 (62.4)	0.57	188 (58.9)	23 (74.2)	0.12	199 (59.6)	12 (75)	0.22
BMI, kg/m^2		28.3 (24.8–32)	27.6 (24.6–30.8)	29.7 (26.6–34.6)	<0.001	28.1 (24.8–32)	29 (24.8–31.6)	0.83	28.3 (24.8–32)	28.3 (23.1–31.2)	0.81
Current smoker		42 (13.3)	29 (14)	13 (11.9)	0.61	38 (13.2)	4 (13.8)	0.99	40 (13.2)	2 (14.3)	0.99
Duration of hospitalization, d		14 (11–17)	14 (11–15)	16 (12–20)	<0.001	14 (11–17)	15 (11–17)	0.72	14 (12–17)	14.5 (6–20)	0.81
Comorbidities											
CAD	Stable CAD	48 (13.7)	34 (14.6)	14 (12)	0.28	39 (12.7)	9 (20.9)	0.21	48 (14.4)	0	0.02
	Prior STEMI	10 (2.9)	4 (1.7)	6 (5.1)		10 (3.3)	0		10 (3)	0	
	Prior NSTEMI	14 (4)	11 (4.7)	3 (2.6)		11 (3.6)	3 (7)		13 (3.9)	1 (6.2)	
	Recent STEMI	9 (2.6)	6 (2.6)	3 (2.6)		8 (2.6)	1 (2.3)		9 (2.7)	0	
	Recent NSTEMI	23 (6.6)	19 (8.2)	4 (3.4)		19 (6.2)	4 (9.3)		18 (5.4)	5 (31.2)	
Hypertension		257 (73.4)	167 (71.7)	90 (76.9)	0.29	230 (72.1)	27 (87.1)	0.07	244 (73.1)	13 (81.3)	0.57
Diabetes		117 (33.4)	73 (31.3)	44 (37.6)	0.24	105 (32.9)	12 (38.7)	0.51	111 (33.2)	6 (37.5)	0.72
Prior hemorrhagic stroke		9 (2.6)	5 (2.2)	4 (3.4)	0.49	8 (2.51)	1 (3.23)	0.57	9 (2.69)	0	0.99
PAD		49 (14)	37 (15.9)	12 (10.3)	0.15	39 (12.2)	10 (32.3)	0.005	46 (13.8)	3 (18.8)	0.48
Liver cirrhosis		8 (2.3)	6 (2.6)	2 (1.7)	0.72	7 (2.19)	1 (3.23)	0.53	8 (2.4)	0	0.99
Prior major bleed		24 (6.9)	13 (5.6)	11 (9.4)	0.18	21 (6.58)	3 (9.68)	0.46	23 (6.89)	1 (6.25)	0.99
History of malignancy		23 (6.6)	15 (6.4)	8 (6.8)	0.89	18 (5.64)	5 (16.1)	0.04	22 (6.59)	1 (6.25)	0.99
Active malignancy		37 (10.6)	22 (9.4)	15 (12.8)	0.33	31 (9.72)	6 (19.4)	0.12	36 (10.8)	1 (6.25)	0.99
AF		81 (23.1)	52 (22.3)	29 (24.8)	0.61	69 (21.6)	12 (38.7)	0.03	77 (23.1)	4 (25)	0.77
COPD		25 (7.1)	18 (7.7)	7 (6)	0.55	22 (6.90)	3 (9.68)	0.48	22 (6.59)	3 (18.8)	0.12
Asthma		26 (7.4)	18 (7.7)	8 (6.8)	0.77	26 (8.15)	0	0.15	23 (6.89)	3 (18.8)	0.11
Medication											
DOAC		40 (11.4)	27 (11.6)	13 (11.1)	0.89	31 (9.72)	9 (29)	0.004	38 (11.4)	2 (12.5)	0.70
VKA		18 (5.1)	11 (4.7)	7 (6)	0.61	16 (5.02)	2 (6.45)	0.67	18 (5.39)	0	0.99
β-Blocker		185 (52.9)	124 (53.2)	61 (52.1)	0.85	159 (49.8)	26 (83.9)	<0.001	176 (52.7)	9 (56.3)	0.78
ACEI		156 (44.6)	104 (44.6)	52 (44.4)	0.97	134 (42)	22 (71)	0.002	153 (45.8)	3 (18.8)	0.03
ARB		33 (9.4)	23 (9.9)	10 (8.5)	0.70	30 (9.4)	3 (9.68)	0.99	30 (8.98)	3 (18.8)	0.18
Calcium blocker		76 (21.7)	52 (22.3)	24 (20.5)	0.70	67 (21)	9 (29)	0.31	73 (21.9)	3 (18.8)	0.99
Aspirin		124 (35.4)	82 (35.2)	42 (35.9)	0.90	109 (34.2)	15 (48.4)	0.11	116 (34.7)	8 (50)	0.21

TABLE 1 Demographic and clinical characteristics of the study population (continued from the previous page)

Variable	Overall (n = 350)	Mild COVID-19 (n = 233)	Severe COVID-19 (n = 117)	*P* value	No bleeding complications (n = 319)	Bleeding complications (n = 31)	*P* value	No thrombotic complications (n = 334)	Thrombotic complications (n = 16)	*P* value
Thienopyridine	39 (11.1)	30 (12.9)	9 (7.7)	0.15	31 (9.72)	8 (25.8)	0.01	36 (10.8)	3 (18.8)	0.40
NSAIDs	8 (2.3)	3 (1.3)	5 (4.3)	0.12	8 (2.51)	0	0.99	7 (2.1)	1 (6.25)	0.31
Statin	152 (43.4)	105 (45.1)	47 (40.2)	0.38	130 (40.8)	22 (71)	0.001	146 (43.7)	6 (37.5)	0.62
Insulin	44 (12.6)	21 (9)	23 (19.7)	0.005	40 (12.5)	4 (12.9)	0.99	42 (12.6)	2 (12.5)	0.99
Oral antidiabetic drugs	61 (17.4)	42 (18)	19 (16.2)	0.68	55 (17.2)	6 (19.4)	0.77	61 (18.3)	0	0.09
PPI	129 (36.9)	83 (35.6)	46 (39.3)	0.50	115 (36.1)	14 (45.2)	0.32	124 (37.1)	5 (31.3)	0.63
Laboratory values on admission										
eGFR, ml/min/1.73 m^2	71.5 (55–89)	74 (60–89)	67 (43–87)	0.02	74 (56–89)	57 (39–71)	<0.001	72 (56–89)	65 (28.5–89)	0.33
Hemoglobin, g/dl	13.3 (12.1–14.7)	13.3 (12.2–14.7)	13.2 (12–14.8)	0.88	13.5 (12.2–14.8)	12.4 (9.2–13.3)	0.001	13.3 (12.1–14.7)	14.2 (11.2–15)	0.61
Platelet count, × 10^3/µl	207 (159–264)	207 (163–269)	206 (157–260)	0.44	209 (162–266)	175 (148–228)	0.11	207 (161–264)	200 (148.5–261)	0.84
CRP, mg/l	32.8 (6.4–86.8)	19.3 (5–66.8)	62.4 (20.6–111.6)	<0.001	31.9 (6.5–85.9)	41 (5.4–96.5)	0.91	29.7 (6.3–85.9)	72.6 (23.3–108.7)	0.08
D-dimer, mg/dl	958 (533–2560)	823 (484–1698)	1415 (638–3738)	<0.001	967 (534–2561)	767 (506–2404)	0.63	944 (529–2404)	1532 (647–6671.5)	0.12
SpO_2, %	96 (93–97)	96 (94–97)	95 (91–96)	<0.001	96 (93–97)	95 (92–97)	0.26	96 (93–97)	95 (92–97.5)	0.76

Data are given as number (percentage) or median (interquartile range).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, non–ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PPI, proton pump inhibitor; SpO_2, blood oxygen saturation; STEMI, ST-segment elevation myocardial infarction; VKA, vitamin K antagonist

TABLE 2 Treatment of the COVID-19 patients during hospitalization

Variable		Overall (n = 350)	Mild COVID-19 (n = 233)	Severe COVID-19 (n = 117)	*P* value	No bleeding complications (n = 319)	Bleeding complications (n = 31)	*P* value	No thrombotic complications (n = 334)	Thrombotic complications (n = 16)	*P* value
Oxygen therapy	None	108 (31.7)	82 (35.1)	24 (20.5)	<0.001	100 (31.3)	6 (19.4)	0.15	100 (29.9)	6 (37.5)	0.44
	Nasal cannula	171 (48.9)	137 (58.8)	34 (29.1)		157 (49.2)	14 (45.2)		161 (48.2)	10 (62.5)	
	Oxygen mask	12 (3.4)	10 (4.3)	2 (1.7)		10 (3.13)	2 (6.45)		12 (3.59)	0	
	Oxygen mask with reservoir	11 (3.1)	–	11 (6.8)		9 (2.82)	2 (6.45)		11 (3.29)	0	
	High-flow oxygen therapy	48 (14.3)	–	48 (41)		43 (13.5)	7 (22.6)		50 (15)	0	
Duration of oxygen therapy, d		7 (0–13)	5 (0–11)	12 (3–15)	<0.001	6 (0–12)	12 (2–17)	0.003	7 (0–12)	4 (0–17)	0.77
Mechanical ventilation	Absent	303 (86.6)	232 (99.6)	71 (60.7)	<0.001	29 (93.5)	303 (86.6)	0.70	295 (88.3)	8 (50)	<0.001
	Intubation	39 (11.1)	0	39 (33.3)		2 (6.45)	39 (11.1)		31 (9.28)	8 (50)	
	NIV	8 (2.3)	1 (0.4)	7 (6)		0	8 (2.3)		8 (2.4)	0	
ECMO		1 (0.3)	0	1 (0.8)	0.33	1 (0.3)	0	0.99	1 (0.3)	0	0.99
Remdesivir		85 (24.7)	52 (22.3)	33 (29.7)	0.14	78 (24.9)	7 (22.6)	0.77	84 (25.5)	1 (7.14)	0.20
Convalescent plasma		71 (20.6)	38 (16.3)	33 (29.7)	0.004	65 (20.8)	6 (19.4)	0.85	68 (20.6)	3 (21.4)	0.99
Tocilizumab		3 (0.9)	0	3 (2.7)	0.03	3 (0.95)	0	0.99	2 (0.61)	1 (7.14)	0.12
Dexamethasone		216 (62.8)	120 (51.5)	96 (86.5)	<0.001	194 (62)	22 (71)	0.32	205 (62.1)	11 (78.6)	0.21

Data are given as number (percentage) or median (interquartile range).

Abbreviations: ECMO, extracorporeal membrane oxygenation; NIV, noninvasive ventilation

TABLE 3 Outcomes during hospitalization for COVID-19

Variable		Overall (n = 350)	Mild COVID-19 (n = 233)	Severe COVID-19 (n = 117)	*P* value	No bleeding complications (n = 319)	Bleeding complications (n = 31)	*P* value	No thrombotic complications (n = 334)	Thrombotic complications (n = 16)	*P* value
Mortality		47 (13.4)	4 (1.7)	43 (36.8)	<0.001	42 (13.2)	5 (16.1)	0.59	38 (11.4)	9 (56.3)	<0.001
Hemorrhagic complications	Clinically relevant bleeding	22 (6.3)	13 (5.6)	9 (7.7)	0.74	–	–	–	21 (6.29)	1 (6.25)	0.99
	Major bleeding	9 (2.6)	5 (2.1)	4 (3.4)		–	–	–	9 (2.69)	0	
Thrombotic complications	VTE	4 (1.1)	2 (0.9)	2 (1.7)	0.60	4 (1.25)	0	0.99	–	–	–
	Stroke	4 (1.1)	2 (0.9)	2 (1.7)	0.60	4 (1.25)	0	0.99	–	–	–
	Infarction	8 (2.3)	2 (0.9)	6 (5.1)	0.02	7 (2.19)	1 (3.23)	0.53	–	–	–

Data are shown as number (percentage).

Abbreviations: VTE, venous thromboembolism

relatively rarely among LMWH-treated patients.[44] In our study, we did not observe any confirmed incidents of HIT, which indicates that the risk of HIT in patients with COVID-19 on enoxaparin is low. Some authors have published a few cases of HIT during COVID-19; however, most of patients that developed HIT were treated with unfractionated heparin.[45,46] It is well known that patients with COVID-19 often exhibit mild thrombocytopenia, which is associated with an increased risk of inpatient mortality.[47] This abnormality enhanced by the effect of other medications, for example, antibiotics, should be differentiated from HIT even if the latter is quite uncommon in COVID-19.

Several limitations of the current retrospective observational study should be acknowledged. The sample size is relatively small, but the study shows real-life data from the last months of the COVID-19 pandemic with a low proportion of patients who were unavailable for analysis. With regard to the causes of death, we based our report on clinical assessment because no autopsies of COVID-19 patients were performed during the study. We are aware of the fact that some hemorrhagic or thrombotic events can be masked by COVID-19 presentation, that is, by severe pneumonia. Acute PE and DVT could be underrepresented in our patient group, since DVT is asymptomatic in approximately half of the patients. In many cases, fatal PE could be the first and the only sign of VTE.[17]

In conclusion, our single-center experience indicates that to achieve a relatively low risk of arterial and venous thromboembolic events in hospitalized COVID-19 patients, a locally approved thromboprophylaxis protocol with varying LMWH dosage regimens could be useful in everyday practice and such strategy should be encouraged, while awaiting the results of randomized trials. Given that the most recent data suggest that therapeutic anticoagulation should be considered in most non-ICU hospitalized COVID-19 patients, it should be highlighted that the protocols regarding the use of heparins in this disease should be regularly updated.

ARTICLE INFORMATION

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