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Therapeutic dosing of low-molecular-weight heparin may decrease mortality in patients with severe COVID-19 infection

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BACKGROUND: Venous thromboembolism or extensive thrombosis is relatively common in patients with severe COVID-19 infection and has been associated with increased mortality. During the current COVID-19 pandemic, several prophylactic doses and types of low-molecular-weight heparin (LMWH) are being used worldwide; however, there are no high-quality studies or recommendations for an optimal prophylactic LMWH dose.

OBJECTIVES: Investigate the relationship between coagulation parameters and the LMWH dose, and mortality and ICU admission in hospitalized patients with severe COVID-19 pneumonia.

DESIGN: Retrospective.

SETTING: Tertiary care hospital.

PATIENTS AND METHODS: Data on clinical features, coagulation parameters and anticoagulant medications of inpatients with severe COVID-19 were collected for the period between 11 March 2020 and 31 April 2020.

MAIN OUTCOME MEASURES: Mortality and ICU admission for prophylactic dose LMWH (0.5 mg/kg twice daily) and therapeutic dose LMWH (1 mg/kg twice daily).

SAMPLE SIZE: 154 cases.

RESULTS: Ninety-eight (63.6%) patients were treated with the LMWH prophylactic dose and 56 (36.4%) patients were treated with the therapeutic dose. Forty-four (44.9%) of 98 patients using the prophylactic dose LMWH died, while 10 (17.9%) of 56 patients using the therapeutic dose LMWH died (*P*=.001). Mortality was 6.4-fold higher in the prophylactic dose LMWH users than in the therapeutic dose LMWH users (OR=6.5, 95% CI: 2.4-17.6, *P*<.001).

CONCLUSIONS: Therapeutic dosing of LMWH may decrease mortality in patients with severe COVID-19 infected pneumonia. More aggressive thromboprophylaxis regimens using higher doses of heparin should be evaluated in prospective studies.

LIMITATIONS: Lack of information about bleeding complications. LMWH was not compared with other anticoagulant therapies. There was no comparison between our two groups on the APACHE score. Used different doses of LMWH in different clinics in our hospital. Single-center, retrospective study.

CONFLICT OF INTEREST: None.

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In late December 2019, pneumonia cases of unknown etiology started to appear in Wuhan, Hubei province, China. Subsequently, a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified, and the disease was named coronavirus disease (COVID-19) by the World Health Organization (WHO).[1] WHO declared COVID-19 a pandemic on March 11, 2020.[2] In Turkey, there were over 150 000 confirmed cases and 4340 deaths reported owing to COVID-19 as of May 26, 2020.[3] SARS-CoV-2 infection has a broad clinical spectrum, ranging from asymptomatic infection and mild upper respiratory tract infection to respiratory failure, severe viral pneumonia, and even death.[4] Common symptoms are fever, cough, myalgia or fatigue, and dyspnea, and less frequent symptoms include headache, diarrhea, hemoptysis, and anosmia.[5]

While the clinical features of COVID-19 are similar to those of severe acute respiratory syndrome (SARS), the fatality of COVID-19 was lower at 2.3% compared with that of SARS and Middle East respiratory syndrome (MERS) (9.5% and 34.4%, respectively). Fortunately, the lower fatality rate of COVID-19 is associated with the fact that most patients experience mild symptoms without lung involvement.[6] However, COVID-19 fatality increases to approximately 14% when only inpatients are examined.[7] In the past, many thrombotic complications have been detected in SARS and MERS infections, including the following: pulmonary embolism, deep vein thrombosis, thrombus-induced multi-organ infarction, ischemic stroke, disseminated intravascular coagulation (DIC), and hematological manifestations such as prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), elevated D-dimer and fibrinogen, thrombocytopenia, presence of anti-cardiolipin antibody, and lupus anticoagulant test positivity.[8] Similarly, thrombotic complications and hematological manifestations were detected in COVID-19. Indeed, Ackermann et al reported that in an autopsy series of acute respiratory distress syndrome (ARDS) in patients with COVID-19 (n=7) and patients with influenza A (H1N1) (n=7), alveolar capillary micro thrombi was nine times more common in COVID-19 than in influenza.[9] Tang and colleagues examined 183 patients with COVID-19, in whom elevated D-dimer levels, fibrin degradation products, and prolonged PT and aPTT were associated with mortality.[10] In another study on 449 patients diagnosed with COVID-19, there was no significant difference in terms of 28-day mortality in the group of patients using heparin compared with the control group. However, when the D-dimer level exceeded the upper limit of the normal by 6-fold, mortality

in the heparin group was significantly lower; however, the heparin dose was not specified in this study.[11] The European Society of Cardiology designed a patient-specific anticoagulation regimen for COVID-19, wherein the therapeutic dose of the anticoagulant (1 mg/kg twice daily) is recommended when there is a high risk of thromboembolism with no intensive care unit (ICU) admission or a low risk of thromboembolism with D-dimer levels >3000 mcg/L. If thromboembolism is detected on ultrasound, the therapeutic dose should be continued; if it is not detected, 40 mg twice daily of enoxaparin is recommended.[12] The American Society of Hematology recommended pharmacologic thromboprophylaxis in hospitalized patients with COVID-19; however, there were insufficient data on the optimal use of the therapeutic dose for low-molecular-weight heparin (LMWH). Nevertheless, there are currently many ongoing randomized controlled trials investigating the use of different heparin doses in patients with COVID-19.[13] Thachil reported that heparin in patients with COVID-19 has potential anticoagulant, anti-inflammatory, and endothelial protective effects and that heparin decreased ARDS, increased oxygenation, and may also have antiviral effects.[14] During the current COVID-19 pandemic, several prophylactic doses and types of LMWH are being used worldwide; however, there are no high-quality evidence studies or recommendation for the optimal prophylactic LMWH dose.[15]

The aim of this study was to investigate the relationship between coagulation parameters and the LMWH dose, and mortality and ICU admission in hospitalized patients with severe COVID-19 pneumonia.

PATIENTS AND METHODS

Patients with severe COVID-19 pneumonia were included in this retrospective study. Patients were treated at the Sultan 2 Abdulhamid Han Training and Research Hospital in Istanbul, Turkey, between March 11, 2020 and April 31, 2020. The study was approved by the Ethics Committee of the Umraniye Training and Research Hospital in Istanbul (approval number 183, date 13/05/2020). The exclusion criteria included the following: age <18 years, bleeding diathesis, hospital stay <5 days, lack of information about laboratory tests and anticoagulant treatment, mild COVID-19 pneumonia, and use of anticoagulant for other indications prior to hospital admission (atrial fibrillation, pulmonary embolism, and others.). Severe COVID-19 pneumonia was defined according to the following criteria of the Republic of Turkey Ministry of Health COVID-19 guidelines: a) tachypnea (>30/min.); b) SpO$_2$ <90%; c) poor prognostic criteria (lymphocyte count <800/µL or

C-reactive protein >40 mg/L or ferritin >500 ng/mL or D-dimer >1000 µg/L); d) bilateral diffuse pneumonia on chest radiography or lung computed tomography; e) no requirement for invasive or non-invasive mechanical ventilation; and f) clinical presentation unrelated to ARDS on hospital admission (**Table 1**). The diagnosis of SARS-CoV-2 was confirmed using real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) performed for the nasopharyngeal and oropharyngeal swab samples.[16] Age, gender, ICU admission, length of hospital stay, D-dimer (normal range <500 µg/L), international normalized ratio (INR) (normal range 0.8–1.2), aPTT (normal range 18.7–32.7 s), and platelet count (normal range 150–450×10⁹/L) data were collected. In our hospital, we have 10 different clinics,

Table 1. The criteria for severe COVID-19 pneumonia.

- Tachypnea (>30/min.)
- sPO₂ <90%
- Poor prognostic criteria (lymphocyte count <800/µL or C-reactive protein
- >40 mg/L or ferritin>500 ng/mL or D-dimer >1000 µg/L)
- Bilateral diffuse pneumonia in chest radiography or lung CT
- Not requiring invasive or non-invasive mechanical ventilation
- Clinical presentation unrelated to ARDS on hospital admission

sPO₂: oxygen saturation, CT: computed tomography, ARDS: acute respiratory distress syndrome

Table 2. Characteristics of patients with severe COVID-19 by survival status.

	Non-survivor (n=54)[a]	Survivor (n=100)[a]	P value[b]
Gender			
Female	18 (33%)	40 (40%)	0.5
Male	36 (67%)	60 (60%)	
Age (years)	66 (57, 80)	55 (48, 66)	<.001
Comorbidities	50 (92.6%)	51 (51.0%)	<.001
D-dimer (µg/L)	1990 (649, 4055)	587 (304, 1415)	<.001
INR	1.17 (1.10, 1.30)	1.11 (1.07, 1.17)	<.001
aPTT (sec)	27.5 (24.1, 30.9)	24.4 (23.2, 25.4)	<.001
Platelet (×10⁹/L)	167 (133, 230)	196 (156, 248)	.086
LMWH dose			
Prophylactic	44 (81%)	54 (54%)	.001
Therapeutic	10 (19%)	46 (46%)	
Hospital stay	10 (7, 16)	12 (10, 16)	.038
ICU admission	52 (96%)	22 (22%)	<.001

[a]Data are median (IQR); n (%) [b]Statistical tests: Wilcoxon rank-sum test; chi-square test of independence. LMWH: low-molecular-weight heparin, INR: international normalized ratio, aPTT: activated partial thromboplastin time.

and owing to the lack of information about thromboprophylaxis, different LMWH doses were used in severe COVID-19 pneumonia. Patients were divided into two groups based on LMWH (enoxaparin) use: prophylactic dose (0.5 mg/kg twice daily) and therapeutic dose (1 mg/kg twice daily).

Normally and abnormally distributed quantitative variables were compared using the Student's *t* test and Mann–Whitney U test, respectively. Categorical variables were compared using the chi-square test. The results were presented as the mean and standard deviation, median and interquartile range, or frequency and percentage, wherever appropriate. Categorical and consecutive variables were evaluated using univariate logistic regression analysis for their ability to predict mortality. A *P* value <.05 was considered significant. Data were analyzed using www.e-picos.com (MedicReS, New York, New York, United States, and MedCalc statistical software version 16.4.3 (Ostend, Belgium) and IBM SPSS (Armonk, New York, United States: IBM Corp) version 21.

RESULTS

Ninety-six (62.3%) of the 154 patients with severe COVID-19 pneumonia were men and 58 (37.7%) were women. The ages of the participants ranged between 23 and 96 years, with a median (IQR) age of 60.0 (20.5) years. The median (IQR) age of the patients who survived was 55.0 (18.8) years, whereas those who died were 66.0 (23) years of age (P<.001) (**Table 2**), with no statistically significant difference by gender. Nonsurvivors had more comorbidities than survivors (P<.001). Comorbid diseases included hypertension (n=66, 43%), diabetes mellitus (n=35, 23%), heart disease (n=35, 23%), pulmonary disease (n=25, 16%) and kidney disease (n=8). The median (IQR) length of hospital stay was longer in survivors (P=.038).

Appropriate antiviral (favipiravir or lopinavir-ritonavir) and supportive treatment (no steroids) was initiated in all patients after admission. Seventy-four (48.1%) patients were admitted to the ICU during the treatment period, whereas 80 (51.9%) patients were not admitted to the ICU (**Table 3**). Seventy percent of non-survivors were admitted to the ICU compared to 2.5% of the survivors (P<.001). Forty-four of the 98 (63.6%) patients treated with the prophylactic dose died, whereas 10 of the 56 (36.4%) patients treated with the therapeutic dose died. Fewer patients who received the LMWH therapeutic dose died than did those who received the prophylactic dose (n=10, 17.9% vs n=44, 44.9%, respectively). Age, D-dimer, INR, and aPTT were higher in the non-survivors than in the survivors, and the differ-

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ences were statistically significant (**Table 2**). The platelet count was lower in the non-survivors but the difference was not statistically significant compared with the survivors.

For patients with ICU admission, D-dimer levels, INR, and aPTT were statistically greater compared with patients not admitted to the ICU. ICU admissions were more often males (n=50, 52.1% vs n=24, 41.3%), but the difference between genders was not statistically significant. There was no relationship between the LMWH dose and ICU admission (*P*=.71) (**Table 3**). There was no statistically significant relationship between D-dimer levels and LMWH dose in terms of mortality (*P*=.19) (**Table 4**). In a multiple logistic regression model, age, comorbidities, LMWH prophylactic dose, D-dimer, aPTT, and platelets were statistically significant for the dependent variable, mortality (**Table 5**). Mortality was 6.5-fold higher in the prophylactic dose group than in the therapeutic dose group (95% CI, 2.4-17.6).

DISCUSSION

SARS-CoV-2 acts by binding to the angiotensin converting enzyme (ACE) 2 receptor protein on the host cell surface using the viral spike (S) protein. The ACE-2 protein is mainly distributed in the heart, lungs, kidneys, testicles, and digestive tract. Owing to this distribution, coronavirus can spread to many organs and cause the release of many proinflammatory cytokines, leading to cell death and organ damage, which can ultimately result in multiple organ dysfunction syndrome. Therefore, the microvascular system is damaged, causing an abnormal activation of the coagulation system, leading to generalized small vessel vasculitis and extensive microthrombosis.[17] The interaction between the ACE-2 receptor and SARS-CoV-2 has been reported to cause endothelial damage with a 5-fold increase in the von Willebrand factor.[18] According to the International Society of Thrombosis and Haemostasis (ISTH), patients with severe COVID-19 usually present with single organ failure at the beginning of the disease, such as respiratory failure, and some patients may develop multiple organ damage in advanced stages. The main reason for multiple organ damage is reported to be the development of coagulopathy.[19]

Tang and colleagues reported that approximately 71% (15/21) of patients with COVID-19 who died had overt DIC in the late stages of the disease, according to the ISTH DIC criteria.[10] In a recently published study, COVID-19 showed properties similar to those of macrophage activation syndrome in terms of lung injury and microvascular thrombosis. Although overt DIC was observed in the late stages of the disease, typical overt

DIC was not observed in the early stages. Lung limited vascular immunopathology caused by COVID-19 has been named diffuse pulmonary intravascular coagulopathy, in which D-dimer and cardiac enzyme concentrations increased while fibrinogen and platelet levels were normal.[20] The aforementioned clinical signs show the aggressive thrombotic burden in patients with COVID-19.

Pharmacological prophylaxis with LMWH (such as enoxaparin) to prevent venous thromboembolism in patients admitted to the hospital with COVID-19 was recommended by WHO.[21] However, there is no evidence from the literature about the optimal dose regimen.

Table 3. Characteristics of patients with severe COVID-19 by ICU admission during the treatment period.

	No ICU admission (n=80)[a]	ICU admission (n=74)[a]	*P* value[b]
Gender			
Female	34 (42%)	24 (32%)	0.3
Male	46 (57%)	50 (68%)	
Age (years)	58 (50, 67)	63 (53, 78)	.051
Comorbidities	43 (53.8%)	58 (78.4%)	
D-dimer (µg/L)	594 (304, 1310)	1425 (348, 3218)	.003
INR	1.10 (1.06, 1.17)	1.17 (1.09, 1.28)	.002
aPTT (sec)	24.3 (23.3, 25.3)	25.9 (23.8, 28.6)	<.001
Platelet (×10⁹/L)	198 (158, 249)	176 (139, 229)	0.10
LMWH dose			
Prophylactic	52 (65%)	46 (62%)	0.8
Therapeutic	28 (35%)	28 (38%)	
Mortality			
Non-survivor	2 (2.5%)	52 (70%)	<.001
Survivor	78 (98%)	22 (30%)	
Hospital stay	11 (9, 15)	12 (8, 17)	0.5

[a]Data are median (IQR); n (%) [b]Statistical tests: Wilcoxon rank-sum test; chi-square test of independence. LMWH: low-molecular-weight heparin, INR: international normalized ratio, aPTT: activated partial thromboplastin time.

Table 4. D-dimer levels by dose level of low-molecular-weight heparin in non-survivors (n=54).

D-dimer (µg/L)	Prophylactic (n=44)	Therapeutic (n=10)	*P* value[a]
<1000	15 (34.1%)	2 (20%)	.19
1000-3000	13 (29.5%)	6 (60%)	
>3000	16 (36.4%)	2 (20%)	

[a]Statistical test: Chi-square test of independence.

Table 5. Multiple logistic regression analysis with mortality as dependent variable (n=154).

	β coefficient	SE	P value	Odds ratio	95% CI Lower	95% CI Upper
Age	.038	.017	.028	1.039	1.004	1.075
Comorbidities	2.342	.712	.001	10.398	2.578	41.947
LMWH prophylactic dose	1.871	.509	.001	6.495	2.393	17.627
D-dimer	.001	.001	.021	1.001	1.001	1.001
INR	1.604	1.522	.292	4.975	.252	98.240
aPTT	.104	.050	.038	1.110	1.006	1.225
Platelet	-.007	.003	.028	.993	.987	.999
Intercept	-9.764	2.476	.001			

The model was statistically significant, $\chi^2(4)$=79.658, P<.001 and explained 55.6% (Nagelkerke R^2) of the variance in mortality.

Chinese expert consensus recommended unfractionated heparin instead of LMWH, as unfractionated heparin has the advantages of a short half-life, convenient monitoring, and can be neutralized with protamine. LMWH is only recommended in mild or moderate coagulation dysfunction in patients with COVID-19 with the dose of 1 mg/kg twice daily.[17] In another study, LMWH was suggested as the first option instead of unfractionated heparin (UFH), as UFH requires more frequent injections and increases the risk of transmission of SARS-Cov-2; indeed, this study reported that high-dose thromboprophylaxis may be required in patients with severe COVID-19, and randomized controlled studies are ongoing.[22] In another ongoing randomized controlled trial, Marietta and colleagues aim to compare the efficacy and safety of high (70 IU/kg twice daily enoxaparin) versus low (4000 IU once a day) LMWH dosages in hospitalized patients with severe COVID-19 pneumonia not requiring invasive mechanical ventilation.[23] Khan et al reported the use of 1.5 mg/kg enoxaparin once a day in patients with D-dimer levels >1000 µg/L in the ICU.[18] In our hospital, LMWH (enoxaparin) is often used in VTE prophylaxis. Different doses of LMWH were used in patients with COVID-19 admitted to our hospital owing to the lack of sufficient data on the dose of enoxaparin. In the current study, the relationship between the prophylactic dose (0.5 mg/kg twice daily) and therapeutic dose (1 mg/kg twice daily), and mortality was retrospectively investigated, and we verified that the use of the therapeutic dose LMWH reduced mortality in patients with severe COVID-19. In a multiple logistic regression analysis, the use of the LMWH prophylactic dose was associated with a 6.5-fold increased risk of mortality compared with the therapeutic dose when adjusted for other variables. There was no significant relationship between ICU admission and the LMWH dose.

Per a recently published clinical guideline, the use of enoxaparin 1 mg/kg twice daily is recommended in patients with a D-dimer level >3000 µg/L and weight <100 kg.[24] Tang and colleagues found that mortality decreased significantly in those using heparin when the D-dimer level was >3000 µg/L.[11] In a recently published study of 71 patients, 16 developed VTE (22.5%) and 7 developed pulmonary embolism (10%) despite adequate thromboprophylaxis. The positive predictive value of a D-dimer level ≥3000 µg/L for venous thromboembolism was 80%. These authors suggest that D-dimer levels should guide more aggressive thromboprophylaxis regimens using higher doses of heparin.[25] In our study, the mortality rate of patients from both the prophylactic and therapeutic groups was similar when patients were classified by D-dimer results. The reason for this was thought to be owing to the low mortality rate (n=10) of patients receiving the therapeutic dose. This relationship should be assessed with a larger patient population in future studies.

Lippi et al assessed four studies that investigated the association between D-dimer levels and mortality; all were significant results.[26] In our study, the D-dimer level was significantly higher in the non-survivor group than in the survivor group. Although the D-dimer level was associated with mortality in the multivariate logistic regression analysis (P=.021), odds ratio was very close to 1 (OR=1.001). It was thought that this may be because of the wide range of D-dimer levels, specifically from 12.2 to 32300.

Bikdeli et al reported that the hemostasis parameters of patients with COVID-19 were variably associated with prolongation of INR, and variably by a trend of shortened aPTT.[27] In our study, these parameters were

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higher in the non-survivors group than in the survivors group and were associated with mortality in the multivariate analysis.

Lippi et al reported in their meta-analysis that a low platelet count was associated with an increased risk of severe disease and mortality in patients with COVID-19.[28] In our study, although the platelet count levels were lower in the non-survivors group, there was no significant relationship in comparison with the survivor group. In the multivariate analysis, platelet count levels were associated with mortality. In a recently published article, active arterial bleeding required radiological embolization using LMWH in two patients with COVID-19.[29]

The most important limitation of this study was the lack of information about bleeding complications. Second, LMWH was not compared with other anticoagulant therapies. Third, there was no comparison of APACHE scores. Fourth, a possible source of bias exists in the fact that we used different doses of LMWH in different clinics in our hospital because of the lack of information on adequate thromboprophylaxis in patients with COVID-19. Furthermore, this was a single-center, retrospective study.

Patients in the non-survivor group were older than those in the survivor group and had more comorbidities. Despite these limitations, as our knowledge of the COVID-19 pandemic is increasing daily, we believe that the results of the current study have specific clinical significance.

In conclusion, venous thromboembolism is a key interest in patients with severe COVID-19 who are hospitalized, even in those undergoing thromboprophylaxis. More aggressive thromboprophylaxis regimens using higher doses of heparin should be evaluated in prospective studies. Moreover, the dose of LMWH should be adjusted based on the risk of bleeding (e.g., coagulation parameters, renal function, age, and data on previous bleeding).

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