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Effect of Routine Thromboprophylaxis with Low Molecular Weight Heparin in Hospitalized COVID-19 Patients: A Retrospective Study

Hastanede Tedavi Edilen COVID-19 Hastalarında Rutin Olarak Uygulanan Düşük Moleküler Ağırlıklı Heparin Tromboprofilaksinin Etkisi: Retrospektif Çalışma

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ABSTRACT Objective: Current guidelines recommend thromboprophylaxis with low molecular weight heparin (LMWH) in patients with coronavirus disease-2019 (COVID-19). However, there is no current consensus on the routine application of thromboprophylaxis. This study aimed to evaluate the effect of routine application of LMWH on clinical outcomes including mortality and the need for intensive care unit (ICU) admission in hospitalized COVID-19 patients. **Material and Methods:** All confirmed patients with COVID-19 hospitalized in COVID-19 dedicated wards, from March 15 to May 15, 2020, were included in this retrospective cohort study. Two groups of patients were established, according to the non-routine and routine application of LMWH with therapeutic, weight-based, anticoagulation dosing. Clinical, laboratory and treatment data were collected, analyzed, and compared between the two groups. The initial and extreme values of the laboratory tests were used for analysis. A logistic regression model was developed to assess the factors related to in-hospital adverse outcomes. **Results:** A total of 1,511 patients (797 men, median age 59.0 years) were retrospectively analyzed [group non-routine LMWH (n=828); group routine LMWH (n=683)]. Multivariate logistic regression analysis showed routine use of LMWH, favipiravir administration, extreme values of white blood cell count, neutrophil lymphocyte ratio, and troponin I as factors independently associated with in-hospital adverse outcomes (odds ratio=0.25, 95% confidence interval: 0.83-0.91; p<0.001 for routine use of LMWH). **Conclusion:** In hospitalized COVID-19 patients routine treatment with therapeutic LMWH dosage was associated with a 75% decrease in mortality and need for ICU admission compared with the non-routine administration when adjusted for other variables in this study.

Keywords: COVID-19; venous thrombosis; thrombosis; heparin; low molecular weight heparin

ÖZET Amaç: Mevcut kılavuzlar, koronavirüs hastalığı-2019'lu [coronavirus disease-2019 (COVID-19)] hastalarda düşük moleküler ağırlıklı heparin (DMAH) ile tromboprofilaksi yapılmasını önermektedir. Ancak tromboprofilaksinin rutin uygulanması konusunda güncel bir fikir birliği yoktur. Bu çalışmada, hastanede yatan COVID-19 hastalarında rutin DMAH uygulamasının, mortalite ve yoğun bakım ünitesine (YBÜ) kabul ihtiyacı dâhil klinik sonuçlar üzerindeki etkisini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** 15 Mart 2020-15 Mayıs 2020 tarihleri arasında doğrulanmış COVID-19 tanısı olan tüm hastalar bu retrospektif çalışmaya dâhil edildi. Terapötik, kilo bazlı, antikoagülasyon dozlaması ile LMWH'nin rutin olmayan ve rutin olan uygulamasına göre 2 grup hasta oluşturuldu. Klinik, laboratuvar ve tedavi verileri toplandı, analiz edildi ve 2 grup karşılaştırıldı. Analiz için laboratuvar testlerinin başlangıç ve uç değerleri kullanılmıştır. Hastane içi olumsuz sonuçlarla ilgili faktörleri değerlendirmek için bir lojistik regresyon modeli geliştirildi. **Bulgular:** Toplam 1.511 hasta (797 erkek, medyan yaş 59,0 yıl) geriye dönük olarak analiz edildi [rutin olmayan DMAH grubu (n=828); grup rutin DMAH (n=683)]. Yaptığımız çok değişkenli lojistik regresyon analizi, DMAH'nin rutin kullanımını, favipiravir uygulamasını, lökosit sayımının uç değerini, nötrofil/lenfosit oranını ve troponin I değerini hastane içi olumsuz sonuçlarla ilişkili bağımsız faktörler olduğunu gösterdi (odds oranı=0,25, %95 güven aralığı: 0,83-0,91; p<0,001 DMAH'nin rutin kullanımı için). **Sonuç:** Hastaneye yatması gereken COVID-19 hastalarında, DMAH dozu ile rutin tedavi, bu çalışmada diğer değişkenler için ayarlandığında rutin olmayan uygulamaya kıyasla mortalite ve YBÜ'ye yatış ihtiyacında %75 azalma ile ilişkilendirilmiştir.

Anahtar Kelimeler: COVID-19; venöz tromboz; tromboz; heparin; düşük moleküler ağırlıklı heparin

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Coronavirus disease-2019 (COVID-19) is a systemic illness that affects many organs.[1] Different reports demonstrated that coagulation abnormalities such as disseminated intravascular coagulation (DIC) and microvascular thrombosis complicate COVID-19 and significantly affect mortality.[2,3] According to recent studies, 71% of the patients who died from COVID-19 suffered from DIC.[4-6]

Acute respiratory distress syndrome (ARDS) and pulmonary thrombosis may further complicate the course of the disease. The complex mechanism of ARDS and pulmonary thrombosis can partly be explained by hyperactivation of the immune system, endothelial dysfunction, and the hypercoagulative state.

Thromboprophylaxis using low molecular weight heparin (LMWH) is recommended in the guidelines to reduce the adverse effects of hypercoagulation on patients with COVID-19.[7] However, there is no current consensus on the routine application of thromboprpphylaxis.[8]

In this retrospective study, we highlight the effect of LMWH prophylaxis on COVID-19 patients. In addition, we aimed to provide real-world evidence derived from one of our country's most crowded pandemic state hospitals to support future guidelines.

MATERIAL AND METHODS

All patients (a total of 1,511 cases) diagnosed with COVID-19 between March 2020 and May 2020 in our pandemic state hospital were included in this retrospective study. A change in the treatment regimen of the COVID-19 patients in our hospital determined the two groups. At the beginning of the outbreak, routine anticoagulation with LMWH was not administrated unless severe COVID-19 infection or a documented indication such as venous thromboembolism (VTE) or atrial fibrillation (AF) were present. Those patients who did not receive a routine LMWH comprised the first group. Beginning April 13, 2020, according to our institutional guidelines, all hospitalized COVID-19 patients received a routine thromboprophylaxis with LMWH according to their body mass index (BMI) (enoxaparin 4,000 UI if BMI≤35 or 6,000 UI, if BMI>35, subcutaneously twice a day) in the absence of any contraindication. Patients who received a routine LMWH prophylaxis comprised the second group.

Patients with no outcome data in their records or under 18 years of age were also excluded from the study.

Diagnosis of COVID-19 made according to World Health Organization (WHO) interim guidance and confirmed by detection of severe acute respiratory syndrome-coronavirus-2 RNA using reverse transcriptase-polymerase chain reaction of patient nasopharyngeal or oropharyngeal swabs.

Data were gathered from our institutional medical database. The clinical outcomes were followed until the last follow-up date, June 15, 2020. The comorbidities included coronary artery disease (CAD), chronic kidney disease (CKD), hypertension (HTN), diabetes mellitus (DM), peripheral arterial disease, chronic obstructive pulmonary disease (COPD), and cancer. All parameters and outcomes were compared between the two groups.

The initial and extreme values of the laboratory tests were used for analysis. The initial value was the result of the first test after admission. The extreme value referred to the maximum or minimum value of laboratory tests during hospitalization. The absolute neutrophil count was divided by the absolute lymphocyte count to obtain the neutrophil-to-lymphocyte ratio (NLR).

Mild COVID-19 was defined as a symptomatic disease with no radiographic evidence of pneumonia. During the clinical assessment, moderate COVID-19 disease was defined as evidence of lower respiratory tract disease with SpO_2 ≥94% without oxygen supplementation. The presence of any of the following was defined as severe COVID-19: SpO_2 <94; respiratory rate with ≥30 breaths per minute; the ratio of partial arterial oxygen pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2) <300 mmHg; >50% lesion showed by the chest computerized tomography scan; respiratory failure necessitating mechanical ventilation or intensive care unit (ICU) monitoring. In-hospital mortality and a need for ICU admission were defined as the adverse clinical endpoints.

This study complies with the 1975 Declaration of Helsinki and was approved by our institution's ethics committee (Şişli Etfal Training and Research Hospital Clinical Research Ethics Committee, date: May 5, 2020, no. 2763), which waived the need for informed consent.

STATİSTİCAL ANALYSİS

Categorical variables were defined as numbers and percentages. Continuous variables were presented as mean±standard deviation or median and interquartile range based on the distribution pattern, which was assessed using Kolmogorov-Smirnov test. Either t-test or Mann-Whitney U test was used to compare continuous variables between the two groups. Categorical variables were compared using the chi-square test. To evaluate the factors related to adverse clinical endpoints, we developed a logistic regression model in which age, gender, routine use of LMWH, CKD, COPD, favipiravir administration, maximum leucocyte count, maximum NLR, and maximum troponin were included as covariates. When constructing the multivariate model, covariates with statistical significance or clinical significance in univariate analysis were included. Model fit was evaluated using C statistics. Statistical significance was defined with a two-tailed p value of <0.05. Data analysis was performed using SPSS version 20.0 software (SPSS Inc, Chicago, Illinois).

RESULTS

A total of 1,511 consecutive patients were diagnosed with COVID-19 and hospitalized in the general COVID-19 dedicated wards with a median age of 59.0 (47.0-71.0) years, including 717 (47.3%) females and 797 (52.7%) males were included in the study. According to the grouping criteria mentioned above, there were 828 non-routine LMWH cases and 683 routine LMWH cases. Characteristics of patients in both groups are listed in Table 1. Patients in the group in which LMWH thromboprophylaxis was

TABLE 1: Clinical and demographic features of study population according to application strategy of LMWH prophylaxis.

	Non-routine LMWH (n=828)	Routine LMWH (n=683)	p value
Age (years)	56 (46-69)	61 (48-73)	<0.001
Gender			
Female	368 (44.4%)	346 (50.7%)	0.016
Male	460 (55.6%)	337 (49.3%)	
Comorbidities			
Hypertension	269 (32.5%)	297 (43.5%)	<0.001
CAD	75 (9.1%)	136 (19.9%)	<0.001
COPD	82 (9.9%)	105 (15.4%)	<0.001
Smoker	34 (4.1%)	47 (6.9%)	0.017
Diabetes mellitus	175 (21.1%)	185 (27.1%)	0.007
Chronic kidney disease	28 (3.4%)	47 (6.9%)	0.002
Malignancy	27 (3.3%)	34 (5.0%)	0.091
Peripheral arterial disease	11 (1.3%)	10 (1.5%)	0.823
In-hospital medications			
LMWH	291 (35.1%)	591 (86.5%)	<0.001
Hydroxychloroquine	769 (92.9%)	621 (90.9%)	0.164
Favipiravir	82 (9.9%)	95 (13.9%)	0.016
Azithromycin	261 (31.5%)	217 (31.8%)	0.917
Oseltamivir			
In-hospital outcomes	18 (2.2%)	2 (0.3%)	0.001
Length of hospital stay (days)	7 (5-10)	7 (5-10)	0.794
ICU admission	69 (8.3%)	32 (4.7%)	0.005
In-hospital mortality	29 (3.5%)	9 (1.3%)	0.007

LMWH: Low molecular weight heparin; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit.

routinely administered were elderly with a higher incidence of HTN, CAD, COPD (p<0.001 for all), DM (p=0.007), and CKD (p=0.002) history.

Two hundred and nighty-one (35.1%) and 591 (86.5%) patients received LMWH in non-routine LMWH and routine LMWH groups, respectively (p<0.001). While 82 (9.9%) patients received favipiravir and 18 (2.2%) received oseltamivir in the non-routine group, 95 (13.9%) received favipiravir and 2 (0.3%) received oseltamivir in the routine group (p=0.016 and p=0.001 respectively). No significant difference was observed between the two groups in terms of azithromycin and hydroxychloroquine use.

Figure 1 and Figure 2 shows the comparison of the initial laboratory values of D-dimer level, and NLR within both groups according to whether LMWH was used or not. All values were statistically significant in the non-routine LMWH group (p<0.001 for all), whereas the difference was not significant in the routine LMWH group (p=0.078 and p=0.245, respectively).

Figure 3 displays the rates of adverse events among the groups. The non-routine LMWH group had a significantly higher prevalence of hospital mortality and need for ICU admission than the routine LMWH group (3.15% vs. 1.3%, p=0.007 and 8.3% vs. 4.7%, p=0.005 respectively).

While initial laboratory values including white blood cell (WBC) count, neutrophil count, platelet count, activated partial thromboplastin time (aPTT), international normalized ratio (INR), troponin I (p<0.001, for all), prothrombin time (PT) (p=0.018), and creatinine level (p=0.024) were higher in routine LMWH group, lymphocyte count (p=0.003), PT (p=0.018), and creatinine level (p=0.024) were lower. In the extreme laboratory values, while WBC, aPTT, PT, INR, urea (p<0.001, for all), neutrophyl count (p=0.012), lymphocyte count (p=0.034), NLR (p=0.027), D-dimer (p=0.003), and troponin I (p=0.008) levels were higher in routine LMWH group, hemoglobin, ferritin and urea levels (p<0.001, for all) were lower (Table 2).

Table 3 shows the results of univariate and multivariate logistic regression analysis. The univariate analysis showed that the age, gender, routine LMWH

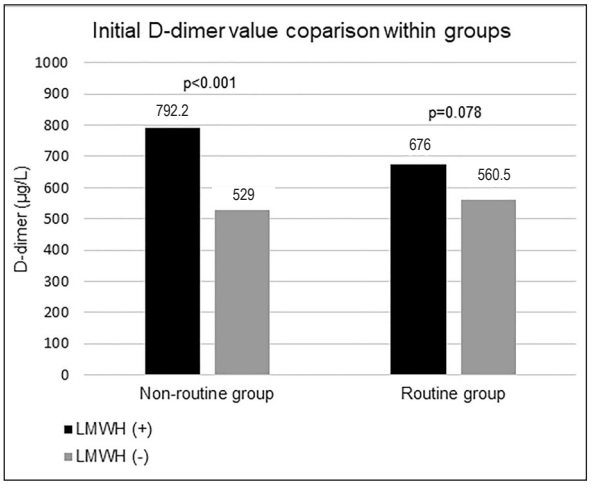

FIGURE 1: A paired bar chart showing the comparison of initial D-dimer values within groups.
LMWH: Low molecular weight heparin.

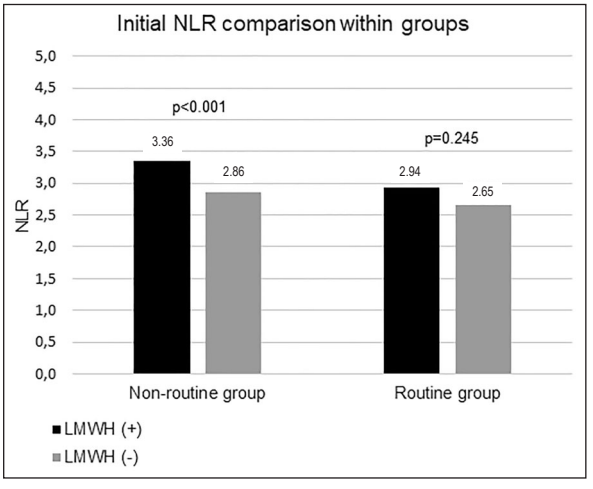

FIGURE 2: A paired bar chart showing the comparison of initial neutrophil-lymphocyte ratios within groups.
NLR: Neutrophil-lymphocyte ratio; LMWH: Low molecular weight heparin.

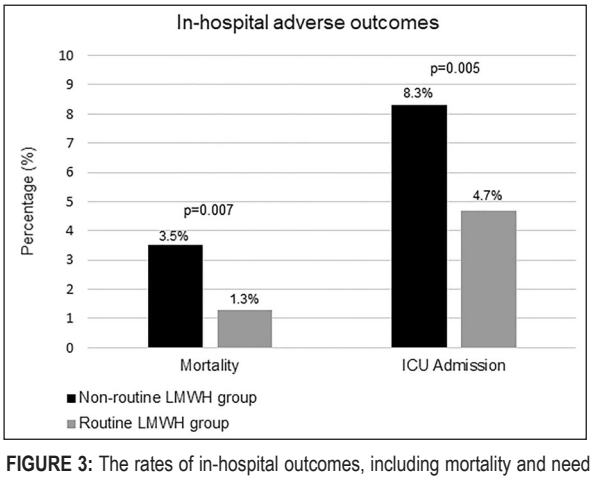

FIGURE 3: The rates of in-hospital outcomes, including mortality and need for ICU admission among the groups.
ICU: Intensive care unit; LMWH: Low molecular weight heparin.

TABLE 2: Laboratory findings of study population according to application strategy of LMWH prophylaxis.

	Non-routine LMWH (n=828)	Routine LMWH (n=683)	p value
Admission laboratory findings			
White blood cell count (x109/L)	5.9 (4.6-7.6)	6.7 (5.0-9.1)	<0.001
Neutrophil (x109/L)	3.9 (2.8-5.5)	4.3 (3.0-6.6)	<0.001
Lymphocyte (x109/L)	1.32 (0.97-1.76)	1.43 (0.99-2.01)	0.003
NLR	2.85 (1.88-4.73)	2.93 (1.92-5.18)	0.295
Hemoglobin (g/dL)	13.2 (12.0-14.4)	12.7 (11.2-14.0)	<0.001
Platelet count (x109/L)	193 (158-248)	211 (172-261)	<0.001
D-dimer (µg/L)	600 (383-999)	659 (411-1,185)	0.053
aPTT (sec)	24.7 (23.2-26.5)	25.3 (23.6-27.7)	<0.001
PT (sec)	12.4 (11.6-13.6)	12.6 (11.8-13.9)	0.018
INR	1.06 (0.99-1.14)	1.08 (1.01-1.18)	<0.001
Ferritin (µg/L)	180 (87-368)	126 (54-290)	<0.001
Fibrinogen (mg/dL)	367 (311-417)	367 (305-426)	0.710
Troponin I (ng/dL)	4.7 (2.8-10.2)	5.9 (3.1-14.72)	<0.001
CRP (mg/L)	52 (16-105)	39 (11-106)	0.199
Urea (mg/dL)	30 (23-41)	34 (25-52)	<0.001
Creatinine (mg/dL)	0.82 (0.69-0.98)	0.85 (0.68-1.09)	0.024
Extreme laboratory findings*			
White blood cell count (x109/L)	7.6 (6.0-9.8)	8.37 (6.4-11.6)	<0.001
Neutrophil (x109/L)	4.1 (2.9-5.6)	4.2 (3.1-6.4)	0.012
Lymphocyte (x109/L)	1.04 (0.72-1.48)	1.09 (0.75-1.63)	0.034
NLR	4.15 (2.57-7.53)	4.49 (2.68-9.11)	0.027
Hemoglobin (g/dL)	13.8 (12.6-14.9)	13.3 (11.9-14.6)	<0.001
Platelet count (x109/L)	275 (212-360)	274 (213-349)	0.858
D-dimer (µg/L)	759 (475-1,620)	922 (527-1,890)	0.003
aPTT (sec)	25.2 (23.7-27.4)	26.0 (24.1-28.8)	<0.001
PT (sec)	12.8 (11.8-14.0)	13.1 (12.1-14.6)	<0.001
INR	1.08 (1.01-1.19)	1.12 (1.03-1.23)	<0.001
Ferritin (µg/L)	212 (99-506)	156 (64-386)	<0.001
Fibrinogen (mg/dL)	373 (321-426)	367 (302-417)	0.030
Troponin I (ng/dL)	5.6 (3.1-14.5)	6.8 (3.6-19.1)	0.008
CRP (mg/L)	58 (17-123)	40 (11-113)	0.080
Urea (mg/dL)	36 (28-51)	40 (30-65)	<0.001
Creatinine (mg/dL)	0.91 (0.76-1.11)	0.92 (0.74-1.21)	0.362

*All extreme values are maximum, while that of lymphocytes is minimum; LMWH: Low molecular weight heparin; NLR: Neutrophil lymphocyte ratio; aPTT: Activated partial thromboplastin time; PT: Prothrombin time; INR: International normalized ratio; CRP: C-reactive protein.

usage, CKD, favipiravir administration, and extreme laboratory values including D-dimer, ferritin, fibrinogen, C-reactive protein, and troponin I levels, NLR, and WBC and lymphocyte counts were associated with adverse events including in-hospital mortality and need for ICU admission. Subsequently, by adding COPD to all the above parameters with statistical significance in the univariate analysis, including age, gender, routine use of LMWH, CKD, COPD, favipiravir administration, extreme values of WBC count, NLR, and troponin I level were incorporated into a multivariate logistic regression model for in-depth analysis. Among these variables, routine use of LMWH, favipiravir administration, and extreme values of WBC count, NLR, and troponin I were identified as independent predictors of adverse clinical endpoints. The predictive capability of our model was assessed using C statistic and found to have an excellent discriminative capacity in predicting the adverse events (area under the curve: 0.87, 95% confidence interval 0.83 to 0.91; $p<0.001$).

TABLE 3: Univariate and multivariate predictors of intensive care unit admission and in-hospital mortality.

	Univariate		Multivariate	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Routine LMWH	0.53 (0.34-0.81)	0.004	0.25 (0.14-0.44)	<0.001
Age	1.02 (1.01-1.04)	<0.001	1.001 (0.98-1.02)	0.87
Male gender	1.95 (1.27-3.00)	0.002	1.17 (0.69-2.00)	0.54
Diabetes mellitus	1.10 (0.69-1.74)	0.68		
Hypertension	1.40 (0.93-2.10)	0.10		
Smoker	1.11 (0.47-2.61)	0.80		
Coronary artery disease	0.89 (0.49-1.63)	0.71		
Chronic kidney disease	2.84 (1.48-5.47)	0.002	1.76 (0.76-4.10)	0.18
COPD	0.94 (0.50-1.75)	0.84	1.08 (0.51-2.28)	0.83
Malignancy	1.84 (0.81-4.17)	0.13		
PAD	1.46 (0.33-6.37)	0.61		
Favipiravir	4.90 (3.15-7.63)	<0.001	3.42 (1.97-5.93)	<0.001
D-dimer (max)	1.001 (1.001-1.002)	<0.001		
Ferritin (max)	1.001 (1.001-1.002)	<0.001		
Fibrinogen (max)	1.58 (1.28-1.95)	<0.001		
WBC count (max)	1.21 (1.17-1.25)	<0.001	1.13 (1.08-1.18)	<0.001
Lymphocyte (min)	0.02 (0.01-0.05)	<0.001		
NLR (max)	1.11 (1.09-1.13)	<0.001	1.05 (1.03-1.07)	<0.001
CRP (max)	1.008 (1.005-1.011)	<0.001		
Troponin I (max)	1.001 (1.001-1.002)	<0.001	1.001 (1.001-1.002)	0.01

CI: Confidence interval; LMWH: Low molecular weight heparin; COPD: Chronic obstructive pulmonary disease; PAD: Peripheral arterial disease; WBC: White blood cell; NLR: Neutrophil lymphocyte ratio; CRP: C-reactive protein.

DISCUSSION

In this article, we evaluated the effect of routine anticoagulation with LMWH in all hospitalized patients without stratifying the severity of COVID-19 disease. Given the marked decrease in in-hospital adverse events, our clinical pathway suggested that all hospitalized COVID-19 patients with a low risk of bleeding should receive thromboprophylaxis with LMWH.

The management of coagulation disorders associated with COVID-19 is very challenging and still needs close monitoring, according to the growing clinical experience.[9] A hypercoagulable state predisposing to arterial thrombosis and VTE (especially pulmonary embolism) has been described in the early clinical reports of COVID-19 infection.[10] In patients that develop ARDS, the prevalence of a coagulation disorder may be as high as 25%. It may lead to higher complication rates and poor outcomes, including the need for ICU admission, the necessity of mechanical ventilation, and death.[11,12] COVID-19 related coagulopathy is assumed to occur due to the interactions of the coagulation system with the inflammatory and immune systems, revealing a cytokine increase called a "cytokine storm" related with hyper inflammation, coagulation, and platelet activation.[13] On admission, elevated D-dimer levels are significantly correlated with a roughly fivefold increase in mortality compared to normal levels in COVID-19 patients.[14] Therefore, anticoagulant strategies to prevent or treat VTE in outpatients and hospitalized patients with proven COVID-19 infection still receive considerable attention. Thromboprophylaxis using subcutaneous LMWH or unfractionated heparin is recommended for hospitalized patients in current guidelines.[15,16] Due to the high rates of VTE events under the well-known standard prophylactic dose therapy, interest in higher-dose prophylaxis or therapeutic-dose anticoagulation has increased among COVID-19 patients.[17,18]

COVID-19 infection causes a systemic inflammatory response with elevated levels of proinflammatory cytokines and endothelial dysfunction.[19]

Endothelial injury activated by the binding of the virus to the angiotensin-2 receptor of the endothelial cells combined with the resultant increased systemic inflammation leads to a prothrombotic endothelial dysfunction.[20] This thromboinflammation in the setting of COVID-19 is strongly related to mortality.[21,22]{Rentsch, 2021 #1488}{Rentsch, 2021 #1554} Finding of microvascular thrombosis in the pulmonary vessels, as well as preliminary evidence of improved survival in severe patients receiving anticoagulants, shifted the attention of researchers to the role of thrombosis in the pathogenesis and treatment of COVID-19.[23]

Given the thrombotic burden of COVID-19, thromboprophylaxis using LMWH is considered a therapeutic primacy and is recommended by several guidelines from international scientific communities.[16,24] However, these studies have had various results. Variations in reported associations likely derive from the form, dosage, and timing of anticoagulation. Additionally, it is also a matter of debate whether the patient population to be anticoagulated is severe and critical or all COVID-19 patients. In an expert consensus statement, LMWH thromboprophylaxis was recommended in severe COVID-19 patients and mild/moderate COVID-19 patients having a high or moderate thromboembolism risk.[25] In a study, LMWH treatment was shown to be associated with better prognosis in severe COVID-19 patients with a sepsis-induced coagulopathy score ≥4 or markedly elevated D-dimmer levels. Conversely, no difference was found in 28-day mortality for the general COVID-19 patients on heparin therapy.[5] However, this study was conducted at the beginning of the COVID-19 breakdown and did not analyze other variables. Moreover, they compared LMWH vs. no-LMWH strategy and included only the severely ill COVID-19 patients.

The WHO interim guidance statement recommends using prophylactic anticoagulation rather than therapeutic dosing in hospitalized patients with COVID-19, without a proven indication for a higher anticoagulation dose.[7] However, consistently reported thromboembolic complications occurring despite using a prophylactic dose of LMWH had led many centers to reassess thromboprophylaxis and increase the dose from prophylactic to therapeutic intensity anticoagulation individually, taking into account D-dimer and fibrinogen levels and other risk factors as well as BMI.[9] Canoglu and Saylan retrospectively investigated the relationship between the prophylactic dose and therapeutic dose of LMWH and verified that the using a therapeutic dose reduces mortality in severe COVID-19 patients.[26] Paolisso et al. evaluated the different dose regimens of LMWH therapy in both severe and non-severe hospitalized COVID-19 patients and demonstrated that intermediate LMWH dosage (enoxaparin 40-60 mg, subcutaneously every 12h) improved the prognosis both in both groups.[27] Gavioli et al. recommend placing all hospitalized COVID-19 patients on LMWH or heparin during admission. Moreover, if a patient was on oral anticoagulation therapy before the onset of COVID-19 (for a different indication, i.e., AF) must be switched to LMWH for its anti-inflammatory properties.[28] So far, no studies assess the efficacy and safety of routine anticoagulation using a therapeutic dose of LMWH therapy in all patients hospitalized with COVID-19 disease.

In patients diagnosed with COVID-19, D-dimer level and NLR are commonly elevated and correlated with the severity of the disease.[29,30] The indications for LMWH application were different from each other in the two groups. Therefore, we compared the baseline laboratory values of D-dimer level and NLR within the groups to demonstrate this distinction. We found that NLR and D-dimer values of patients who received LMWH were significantly elevated in the non-routine group than in those who did not take LMWH, while no difference was found in the routine group.

The mortality and ICU admission rates were lower in patients with the routine administration of LMWH even though their mean age and rate of comorbid diseases were higher at the time of diagnosis than in the other group. Similarly, the multiple logistic regression model showed that routine treatment of patients with therapeutic LMWH dose was related to a 75% decrease in mortality and need for ICU admission compared with the non-routine administration when adjusted for other variables in this study. Pulmonary micro thrombosis and disseminated inter-

vascular coagulation are possible pathophysiological events leading to a poor prognosis in COVID-19 patients.[17,31,32] Therefore, the observed protective association between LMWH and mortality in our study could be related to the preventive effect of LMWH on those conditions. In addition, this beneficial effect might also be attributable to LMWH's anti-inflammatory and anti-viral effects.[33,34] Moreover, anti-inflammatory effects of heparin in the airway and vasculature are well known, which could beneficially impact inflammation related to COVID-19.

This study has several limitations. First, this is a single-center, retrospective, observational study. Second, a potential cause of bias exists due to the hospitalization of mild, moderate, and severe COVID-19 positive cases at the beginning of the study, while only moderate and severe patients were hospitalized due to the overload in the health system in the following period. Nonetheless, as this study included a large patient population, we believe that our results have particular clinical significance.

CONCLUSION

In conclusion, our study demonstrated that mortality and the need for ICU admission might be reduced by implementing routine therapeutic-dose anticoagulation using LMWH among hospitalized COVID-19 patients. Upcoming research should focus on the validation of these results in randomized controlled trials.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Tolga Demir; **Design:** Tolga Demir, Macit Bitargil; **Control/Supervision:** İsmail Koramaz; **Data Collection and/or Processing:** Helin El Kılıç, Hakkı Kürşat Çetin; **Analysis and/or Interpretation:** Kudret Keskin; **Literature Review:** Nilüfer Bektaş; **Writing the Article:** Tolga Demir; Critical Review: Macit Bitargil.*

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