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Original Article

What is the Optimal Treatment Regimen of Low-Molecular-Weight Heparin in Coronavirus Disease 2019 Pneumonia?

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Abstract

OBJECTIVE: The optimal anticoagulant treatment regimen in hospitalized coronavirus disease 2019 (COVID-19) patients is uncertain. This study aimed to compare the rates of disease progression and mortality in patients treated with low-molecular-weight heparin (LMWH) according to baseline D-dimer levels and in those who received a fixed-dose regimen irrespective of the D-dimer level.

MATERIAL AND METHODS: This was a retrospective analysis of all patients admitted to a university hospital for COVID-19 pneumonia during a 1-year period. The protocol for D-dimer-driven therapy (on-protocol) was as follows: prophylactic dose when the baseline level is <1000 ng/mL, intermediate dose when the level is between 1000 and 3000 ng/mL, and therapeutic dose when the level is >3000 ng/mL. We compared the progression and mortality rates between the on-protocol and off-protocol treatment groups. The off-protocol group consisted of patients that received a fixed-dose LMWH regimen, which was not in accordance with the defined protocol.

RESULTS: Of 384 patients (mean age 61.5 ± 15.9 years, 216 male), 294 patients with complete data composed the study group, and 174 patients were treated on-protocol and 120 patients were treated off-protocol. The on-protocol group had lower C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and D-dimer levels and higher SpO_2/FiO_2 levels at admission. Disease progression developed in 45/174 on-protocol patients (25.9%) vs. 53/120 off-protocol patients (44.2%) during the follow-up ($P = .001$), and mortality was 29 (16.7%) vs. 32 (26.7%), respectively ($P = .041$). Logistic regression analysis was performed and included age, presence of comorbidities, LMWH regimen, baseline SpO2/FiO2, CRP, and LDH levels as independent variables. The presence of cardiac comorbidity, age, CRP, and LDH levels, but not the LMWH treatment regimen, were associated with both disease progression and mortality.

CONCLUSION: A D-dimer-driven LMWH treatment protocol is not associated with better clinical outcomes in hospitalized COVID-19 patients.

KEYWORDS: Anticoagulants, COVID-19, D-dimer, embolism, treatments
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INTRODUCTION

Several studies and autopsy examinations have shown an elevated incidence of microvascular/macrovascular and venous/arterial thrombosis with embolic events.[1-4] It has been hypothesized that coagulopathy may be caused by the direct viral effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the endothelium or by a strong inflammatory response resulting in sepsis.[5,6] In severe coronavirus disease 2019 (COVID-19) patients, the presence of new thromboembolism and elevated D-dimer levels have been reported to be risk factors associated with mortality.[3,4,7]

D-Dimer is a fibrin degradation product, and its levels are known to be elevated in COVID-19-associated coagulopathy.[8,9] Studies found that higher D-dimer levels are closely related to prognosis and mortality.[2-4,10,11] Although high D-dimer levels were reported to have a high sensitivity and specificity for diagnosing venous thromboembolism in 1 study.[12] This biomarker is considered primarily to be a marker of poor overall outcome rather than a specific predictor of thromboembolic disease in COVID-19.[13,14]

Studies have shown that prophylactic anticoagulants are associated with better clinical outcomes and that treatment at therapeutic doses does not provide any further improvements in outcomes.[12,15-17] Two studies suggest that in noncritically ill hospitalized patients, anticoagulation at the therapeutic dose was associated with better outcomes.[18,19] However, the bleeding risk is expected to be higher at therapeutic doses. In the study of Lopes et al,[15] the bleeding risk was 8% and 2% in the therapeutic and prophylactic anticoagulation groups, respectively [relative risk 3.64 (95% CI, 1.61-8.27), $P = .0010$]. Current guidelines thus recommend anticoagulant therapy at prophylactic doses in patients with moderate-to-severe COVID-19.[2,11] On the other hand, some studies showed that anticoagulation at therapeutic doses is associated with lower mortality in patients with high (sixfold of the upper limit of normal) D-dimer levels and that anticoagulant treatment dosed according to D-dimer levels is associated with improved survival in critically ill COVID-19 patients.[17,18,20] Two cutoff levels

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for D-dimer, 1000 and 3000 ng/mL, were used in previous studies and have also been used in this study. The 2 earlier studies showed that an admission D-dimer level above 1000 ng/mL was an independent risk factor for mortality[18] and that treatment with therapeutic-dose low-molecular-weight heparin (LMWH) was associated with improved survival only in patients with D-dimer levels sixfold above the upper limit of normal (3000 ng/mL in the case of our institution).[17]

In this study, we aimed to determine whether D-dimer-driven LMWH treatment or prophylactic LMWH treatment is more effective in preventing disease progression and mortality.

MATERIAL AND METHODS

This was a retrospective analysis of the hospital records of all patients admitted to a tertiary-care center of Ege University Faculty of Medicine with a diagnosis of COVID-19 pneumonia between May 2020 and April 2021. All patients presented with acute-onset fever and/or pulmonary symptoms and had radiographic evidence of pneumonia, i.e., presence of new pulmonary infiltrates, including ground-glass opacities, interstitial infiltrates, and consolidation. They all needed supplemental oxygen therapy. All relevant clinical data of the patients were retrieved from an electronic database, which was developed at the beginning of the pandemic and included data on patient demographics, symptoms, clinical, laboratory, and radiographic findings, treatment, and clinical outcomes.

The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments, and it was approved by Institutional Ethics Committee of Ege University Faculty of Medicine (20-5T/48). Written informed consent was obtained from all patients during the time they were hospitalized for their clinical data to be registered in the database and used anonymously for scientific purposes.

The Study Population

A total of 384 patients who were admitted to a single tertiary-care center with a diagnosis of COVID-19 pneumonia were initially included in the study. Of these, 36 patients whose initial or follow-up D-dimer levels were not recorded, 54 patients who were not treated with any anticoagulant agent, and 11 and 8 patients who were already receiving aspirin or an oral anticoagulant, respectively, were excluded. Thus, the data from 294 patients who received low-molecular-weight heparin treatment and for whom all relevant data were available were analyzed.

Anticoagulant Treatment Regimens

An anticoagulant treatment protocol was established in the department early in the pandemic following the publication of reports of coagulopathy associated with COVID-19. Thus, the prophylactic dose of enoxaparin was given to patients whose admission D-dimer level was below 1000 ng/mL, the intermediate (twice the prophylactic) dose was given to patients with D-dimer levels between 1000 and 3000 ng/mL, and the therapeutic dose was administered to patients when the initial D-dimer level exceeded 3000 ng/mL.

Main Points

- The presence of cardiac comorbidity, age, C-reactive protein, and lactate dehydrogenase levels were associated with both disease progression and mortality.
- Low-molecular-weight heparin treatment regimens were not associated with both disease progression and mortality.

The patients were treated according to this locally developed protocol (n = 174) or the enoxaparin dose was determined off-protocol at the discretion of the attending physicians (n = 120). The off-protocol group was divided into 2 subgroups: undertreatment group (n = 54)—patients with a D-dimer level higher than 1000 ng/mL who received the prophylactic dose, and overtreatment group (n = 66)—patients with a D-dimer level lower than 1000 ng/mL who received intermediate or therapeutic dose.

Assessment of Clinical Outcomes

We compared the clinical outcomes according to the LMWH treatment regimen. The 2 co-primary outcomes were inhospital mortality and disease progression. The disease progression was assessed using the Ordinal Scale for Clinical Improvement.[21] We also analyzed, as a secondary outcome, the safety of these regimens, namely bleeding events associated with LMWH treatment, by comparing the need for blood transfusions and hemoglobin levels at admission and discharge.

All relevant laboratory findings, including D-dimer, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and SpO_2/FiO_2 levels at admission and follow-up (days 3-5 of hospitalization), were recorded and analyzed.

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences Statistics 23.0 for Windows packaged software (IBM Corp.; Armonk, NY, USA). Numerical variables were summarized with mean ± SD and categorical variables with frequency and percentage. The significance of differences among groups was assessed by the Student's *t*-test, Mann–Whitney *U-test*, 1-way analysis of variance, or Kruskal–Wallis *H* test for continuous variables and analysis of categorical variables was examined by the chi-square test. Pearson or Spearmen correlation analysis were used to determine the relationship between parameters. A value of $P < .05$ was considered significant for all statistical analyses.

As the 2 treatment groups were not similar in terms of baseline disease severity and inflammatory biomarkers, logistic regression analysis and propensity-matched analysis were performed to analyze the effect of different treatment regimens on mortality. To that end, receiver operating characteristic curves were first built for age, LDH, and CRP levels. With these analyses, threshold values were determined (62.5 years, 418.5 U/L, and 51.6 mg/dL for age, LDH, and CRP, respectively). Propensity score matching (PSM) was performed to avoid confounding bias in the analysis investigating the association between protocol adherence and mortality. The propensity score was calculated by using logistic regression to estimate the probability of mortality with the age, CRP, and cardiac morbidity-independent

Table 1. Demographic, Clinical Characteristics, and Laboratory Findings of the Study Population and the 2 Treatment Groups at Admission

	Total (n = 294)	On-Protocol (n = 174)	Off-Protocol (n = 120)	*P*
Male, n (%)	168 (57.1)	93 (53.4)	75 (46.6)	.15
Negative PCR, n (%)	52 (17.7)	31 (17.8)	21 (17.5)	1.0
Age, mean ± SD	62.4 ± 15.9	59.5 ± 16.6	66.7 ± 13.7	<.001
Cardiovascular comorbidity, n (%)	46 (15.6)	17 (9.8)	29 (24.2)	.001
SpO_2/FiO_2, mean ± SD	348.6 ± 113.8	364.0 ± 112.1	326.2 ± 112.9	<.001
CRP (mg/L), mean ± SD	88.0 ± 75.3	76.4 ± 69.1	104.9 ± 80.9	.001
Ferritin (µg/L), median (minimum–maximum)	464.0 (187.0-777.0)	426.0 (4.2-2891.0)	561.5 (43.8-10 265.0)	.08
LDH (U/L), mean ± SD	341.7 ± 191.5	310.8 ± 137.6	390.2 ± 247.0	.007
D-Dimer (µg/L), mean ± SD	1455.6 ± 1332.5	1182.9 ± 1044.7	1850.9 ± 1587.1	.001

CRP, C-reactive protein; LDH, lactate dehydrogenase; PCR, polymerase chain reaction.

variables. The 1 : 2 propensity matching without replacement was performed by using an optimal pair-matching algorithm. Standardized mean difference (SMD) was used for the assessment of balance after PSM. We assessed the balance of confounding between the matched data of the survivors and non-survivors according to the criterion of an SMD less than 0.1.

RESULTS

We collected data from 384 patients who were hospitalized in the ward or intensive care unit between May 2020 and April 2021. Of these, 294 patients who met the inclusion and exclusion criteria and had complete data composed the study group. The demographic features and admission values of relevant laboratory parameters are shown in Table 1. Of these patients, 97 (33%) had a progressive course during their follow-up in the hospital. The mortality rate was 20.7% (61 of 294 patients).

A total of 174 patients received LMWH according to the study protocol, and the remaining 120 patients were treated off-protocol. The CRP, ferritin, LDH, and D-dimer levels at admission were lower in the on-protocol group as compared to the off-protocol group. Similarly, SpO_2/FiO_2 levels were higher in the on-protocol group (Table 1).

The rate of clinical worsening was lower in patients who received on-protocol LMWH treatment (n = 45/174, 25.9%) as compared to patients treated off-protocol (n = 53/120, 44.2%) (*P* = .001). Similarly, fewer patients in the on-protocol group died (n = 29, 16.7%) as compared to the off-protocol group (n = 32, 26.7%) (*P* = .41) (Table 2). However, patients who had a progressive clinical course had higher follow-up D-dimer levels. Similarly, levels of CRP and ferritin at admission and follow-up were higher in patients whose clinical status worsened during the follow-up and in those who died, indicating that the difference in the 2 co-primary outcomes may be due to differences in the severity of disease in the 2 treatment groups (Table 3).

The mortality rates were similar in the overtreatment (n = 14/66, 21.2%) and undertreatment subgroups (n = 18/54, 33.3%) (*P* = .151). The rates of disease progression were also similar in the 2 subgroups (45.4% and 40.7%, respectively, *P* = .580) (Table 2).

Although on-protocol LMWH treatment appeared to be associated with better clinical outcomes, the severity of COVID-19 was not similar in the 2 treatment groups. In order to adjust for the confounding effect of less severe disease in the on-protocol group, 2 statistical analyses were performed. First, logistic regression analysis showed that mortality was associated with the presence of cardiac comorbidities, old age, high CRP, and LDH level but not with the dose of LMWH treatment (Table 4). Similarly, after PSM, there was no difference between the on-protocol and off-protocol groups in terms of mortality rate (n = 29/90, 32.2% vs. n = 31/90, 34.4%, respectively) (Table 5).

With regard to the safety of the different LMWH regimens, there was no difference in the percentage of patients who

Table 2. Progression and Mortality Rates Between On-Protocol and Off-Protocol Groups Together with the Overtreatment and Undertreatment Subgroups

	On-Protocol (n = 174)	Off-Protocol (n = 120)	*P*	Overtreatment (n = 66)	Undertreatment (n = 54)	*P*
Patients with a progressive course, n (%)	45 (25.9)	53 (44.2)	.001	30 (45.4)	22 (40.7)	.58
Patients who died, n (%)	29 (16.7)	32 (26.7)	.041	14 (21.2)	18 (33.3)	.15

Table 3. Laboratory Findings at Admission in Coronavirus Disease 2019 Patients According to Their Clinical Outcomes

	Patients with Progressive Course	Patients with Clinical Improvement	*P*
D-Dimer (mg/L), mean ± SD	1555.3 ± 1414.3	1301.0 ± 1233.4	.054
CRP (mg/L), mean ± SD	109.3 ± 77.8	69.3 ± 69.1	<.001
Ferritin (µg/L), median (minimum–maximum)	603.5 (32.9-10 265.0)	320 (4.2-4609.0)	<.001
	Patients Who Died	**Patients Who Survived**	
D-Dimer (mg/L), mean ± SD	1910.3 ± 1552.3	1254.1 ± 1195.7	<.001
CRP (mg/L), mean ± SD	115.8 ± 80.6	72.8 ± 70.0	<.001
Ferritin (µg/L), median (minimum–maximum)	618.0 (32.9-10 265.0)	353.0 (4.21-4609.0)	.001

CRP, C-reactive protein.

Table 4. Multivariate Logistic Regression Analysis for Mortality

	Odds Ratio	(95% CI)	*P*
Age > 62.5	5.3	2.5-11.1	<.001
LDH > 418.5	4.3	2.3-8.2	<.001
CRP > 51.645	3.4	1.7-6.9	<.001
Cardiac comorbidities	2.6	1.1-5.9	<.001

CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 5. Mortality Rates in the 2 Treatment Groups after Propensity Score Matching

	On-Protocol (n = 90)	Off-Protocol (n = 90)	*P*
Patients who died, n (%)	29 (32.2)	31 (34.4)	.87
Patients who survived, n (%)	61 (67.8)	59 (65.6)	

needed blood transfusions. The overtreatment subgroup showed a larger, but clinically modest decrease in hemoglobin levels (Table 6).

DISCUSSION

This study provides evidence that LMWH treatment at prophylactic doses results in similar clinical outcomes to D-dimer-driven doses in COVID-19 patients. This is an important finding as it may reduce the cost of treatment and the burden on healthcare systems. The study showed that LMWH at prophylactic doses resulted in similar rates of disease progression and mortality compared to D-dimer-driven doses. This suggests that there is no clinical benefit to higher D-dimer-driven doses and indicates that clinicians can safely reduce the dose of LMWH and still achieve the same clinical outcomes. The study also showed that the 2 treatment regimens resulted in similar rates of bleeding events, except that the use of higher doses was associated with larger decreases in hemoglobin levels. Even though this decrease was clinically modest, it must be taken into account in view of the lack of superiority in the clinical effectiveness of higher doses.

Adjustment of LMWH dosing according to D-dimer levels is legitimate as high D-dimer levels have been found to be associated with mortality[21] and shown in some studies to be related to the extent of pulmonary embolism.[22] The current study also found that D-dimer levels both at admission and at follow-up were related to the disease course. The cutoff level of 3000 ng/mL was chosen because levels above this threshold have been found to be associated with both the presence of pulmonary embolism and evidence of benefit from anticoagulant treatment at therapeutic doses.[17,23] The rationale for the cutoff level of 1000 ng/mL was that this was shown in early studies to be an independent predictor of mortality in COVID-19 patients.[24] Thus, D-dimer-driven dosing of LMWH appeared to be a more logical and personalized approach to deal with coagulopathy and its related consequences. In support of this view, an earlier study, which included critically

Table 6. Difference in Hemoglobin Levels Between Admission and Discharge and Need for Blood Transfusion in the Treatment Groups

	On-Protocol (n = 154)	Overtreatment (n = 53)	Undertreatment (n = 46)	*P*
The difference in hemoglobin levels between admission and discharge*, mean ± SD	−0.27 ± 1.11	−0.50 ± 1.3	−0.25 ± 1.0	.028
	On-Protocol (n = 174)	**Overtreatment (n = 66)**	**Undertreatment (n = 54)**	***P***
Patients who received blood transfusion, n (%)	20 (11.5)	13 (19.7)	8 (14.8)	.27

*Patients who received blood transfusions were excluded from the analysis.

ill COVID-19 patients only and which used the same cut-off levels and treatment doses, found that the D-dimer-driven regimen was associated with a lower rate of mortality.[18] In the current study, although the clinical outcomes, i.e., disease progression and mortality, appeared to be better with a D-dimer-driven LMWH treatment regimen, propensity-matched analysis of the data showed similar effectiveness compared to the prophylactic LMWH. Similarly, logistic regression analysis demonstrated that independent predictors of outcome were older age, cardiac comorbidity, and high levels of CRP and LDH at admission but not the LMWH treatment regimen. These findings differed from the previous study in ICU patients. This may be related to the differences in the severity of inflammation and coagulopathy in the 2 study populations.

The main strength of this study is that it included all patients who met the inclusion and exclusion criteria. This comprised a significant proportion of all patients admitted to the hospital for COVID-19. Thus, the findings should be generalizable. The main limitation, on the other hand, was that the 2 treatment groups were not similar in terms of laboratory findings (possibly reflecting disease severity) at admission. However, 2 separate statistical analyses were performed, namely propensity-matched analysis and logistic regression analysis, to account for these differences.

In conclusion, this study shows that prophylactic doses of LMWH result in similar clinical outcomes to D-dimer-driven doses in COVID-19 patients, with the added benefit of a lower risk of bleeding events.

Ethics Committee Approval: This study was approved by Ethics Committee of Ege University (Approval No: 20-5T/48, Date: 15.05.2020).

Informed Consent: Written informed consent was obtained from all patients during the time they were hospitalized for their clinical data to be registered in the database and used anonymously for scientific purposes.

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