Platelet Count Rose While D-Dimer Levels Dropped as Deaths and Thrombosis Declined—An Observational Study on Anticoagulation Shift in COVID-19

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Abstract

Background High levels of D-dimer and low platelet counts are associated with poor outcome in coronavirus disease 2019 (COVID-19). As anticoagulation appeared to improve survival, hospital-wide recommendations regarding higher doses of anticoagulation were implemented on April 9, 2020.

Objectives To investigate if trends in D-dimer levels and platelet counts were associated with death, thrombosis, and the shift in anticoagulation.

Methods Retrospective cohort study of 429 patients with COVID-19 at Karolinska University Hospital. Information on D-dimer levels and platelet counts was obtained from laboratory databases and clinical data from medical records.

Results Thirty-day mortality and thrombosis rates were 19% and 18%, respectively. Pulmonary embolism was common, 65/83 (78%). Increased D-dimer levels in the first week in hospital were significantly associated with death and thrombosis (odds ratio [OR]: 6.06; 95% confidence interval [CL]: 2.10–17.5 and 3.11; 95% CI: 1.20–8.10, respectively). If platelet count increased more than 35×10^9/L per day, the mortality and thrombotic risk decreased (OR: 0.16; 95% CI: 0.06–0.41, and OR: 0.36; 95% CI: 0.17–0.80). After implementation of updated hospital-wide recommendations, the daily mean significantly decreased regarding D-dimer levels while platelet counts rose; −1.93; 95% CI: −1.00–2.87 mg/L FEU (fibrinogen-equivalent unit) and 65; 95% CI: 54–76 $\times 10^9$/L, and significant risk reductions for death and thrombosis were observed; OR: 0.48; 95% CI: 0.25–0.92 and 0.35; 95% CI: 0.17–0.72.

Conclusion In contrast to D-dimer levels, increase of platelet count over the first week in hospital was associated with improved survival and reduced thrombotic risk. The daily mean levels of D-dimer dropped while the platelet counts rose, coinciding with increased anticoagulation and a decline in thrombotic burden and mortality.

Keywords
- COVID-19
- platelet count
- thrombosis
- low-molecular-weight heparin

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Introduction

In the early phase of the coronavirus disease 2019 (COVID-19) pandemic, reports revealed that D-dimer levels in plasma were greatly elevated among the severely ill patients, and that anticoagulation seemed to improve survival.[1,2] The virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was found to trigger thromboinflammation and endothelial damage, leading to an increase in thrombin generation and altered fibrinolysis.[3–6] Platelets appear to be hyperactive and play a pivotal role, but how SARS-CoV-2 interacts with parent cells (megakaryocytes) and/or platelets is under intense research.[7,8]

Mild thrombocytopenia at admission is associated with severe disease and mortality.[9–11] However, the association between the trends of platelet counts over time and unfavorable outcomes is not fully elucidated even though a recent publication has reported that deceased count is associated with mortality.[9,10,12]

In hospitalized COVID-19 patients, venous thromboembolism (VTE) is the most common thrombotic manifestation, with a reported prevalence in the intensive care unit (ICU) population of around 30% in the early phase of the pandemic, dominated by pulmonary embolism (PE).[13–16] The incidence of VTE was then three times higher in COVID-19, compared with other severe respiratory infections.[17] Notably, a high incidence of VTE has been described despite prophylactic anticoagulation treatment in COVID-19.[18] Antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) seems to improve outcome, although final results from large randomized clinical trials to provide guidance on optimal LMWH dosage are still lacking.[19–24] Observational studies have so far reported different results regarding if higher doses of LMWH are efficient to reduce mortality and thrombosis in severe COVID-19, this depending on cohort composition, study design, and outcome, as well as differences in antithrombotic guidelines between institutions.[12,21–23,25] At Karolinska University Hospital, reports of thrombosis despite antithrombotic prophylaxis resulted in hospital-wide recommendations for increased treatment with LMWH in severe COVID-19 (April 9, 2020).[26] These hospital-wide recommendations were consistent with International Society on Thrombosis and Haemostasis (ISTH) guidelines published at the end of May.[27]

Our aim was to see if the dynamics of D-dimer levels and platelet counts during the first week in hospital were associated with death and thrombosis. Further, we investigated if intensified anticoagulation in severe COVID-19 had any effect on D-dimer levels and platelet counts, and if they were related to survival and thrombosis.

Methods

This is a cohort study based on retrospectively collected data from patients with verified COVID-19 at Karolinska University Hospital (Karolinska), Stockholm, Sweden, a tertiary referral hospital. The project was given ethics approval (D-nr 2020–01752) by the Swedish Ethics Review Authority.

The cohort comprised patients admitted to Karolinska's two sites: Huddinge and Solna, between March 5 and April 22, 2020. They were followed from admission until discharge or death, last day of data collection being June 30, 2020. All patients were identified as having COVID-19 by way of at least one interleukin 6 (IL-6) test result recorded in the Karolinska University Laboratory (KUL) database, and SARS-CoV-2 was confirmed with a positive reverse transcription polymerase chain reaction test. IL-6 was included in the centralized COVID biobank and supposed to be assayed in all in-hospital COVID-19 patients. All included patients were older than 18 years of age at admission and assessed as having severe disease defined by SaO2 <94% in room air at sea level.[28,29] Exclusion occurred if follow-up was unknown or if the patient contracted the disease while hospitalized. Patients could have been transferred from another hospital in Stockholm county, but follow-up was exclusive to Karolinska. The referring hospitals are connected to the KUL enabling collection of laboratory information from admittance and through follow-up. Patients admitted to the ICU, a unit where intubation and mechanical ventilation is possible, had respiratory failure and were all assessed by intensivists prior to ICU admission. Ward patients were not transferred to the ICU at any time during their hospital stay.

According to hospital-wide recommendations, first published online on March 27, COVID-19 patients were recommended to receive antithrombotic prophylaxis with LMWH in-hospital. Revised hospital-wide recommendations on April 9 (presented in ►**Table 1**) included modified recommendations with instructions on who should be considered for enhanced prophylactic treatment (i.e., ICU ward or equivalent, D-dimer levels over 3 mg/L FEU [fibrinogen-equivalent units], fibrinogen over 8 mg/L, coexisting cancer, previous thrombosis, or known thrombophilia), and treatment duration after discharge from hospital.[26] In ICU-specific recommendations (April 3), allowance was given for higher doses of LMWH than for regular prophylaxis, but these were not specified. Patients with diagnosed thrombosis or a strong clinical suspicion of PE received treatment doses of LMWH. Very few patients received unfractionated heparin.

Outcomes

In-hospital death covered patients who died from COVID-19 in hospital. Thrombosis covered venous, arterial, and catheter-related thromboses. VTE included symptomatic PE and/or deep vein thrombosis, diagnosed by either computed tomography or duplex ultrasonography. Strongly suspected clinical PE was defined by stated in free text in the medical records if the patient received full-dose anticoagulation and/or systemic thrombolysis and was clinically too unstable to undergo confirmative examination. Arterial thrombosis was acute ischemic stroke defined as altered focal neurological status and confirmed by typical findings in computed tomography. Acute myocardial infarction was noted if found in the patient medical records as text or as ICD-10 code included in I.21. Catheter-related thromboses were both arterial and venous and verified by duplex ultrasonography.

Table 1 Hospital recommendations on thromboprophylaxis and antithrombotic therapy with LMWH to patients with COVID-19, implemented March 27 and updated April 9, 2020

Regular thromboprophylaxis[a]: all hospitalized patients				
Adm.	Body weight	<50 kg	50–90 kg	<90 kg
Inj., sc	Dalteparin (sc)	2,500 IE qd	5,000 IE qd	75 IE/kg qd
Inj., sc	Tinzaparin (sc)	2,500 IE qd	4,500 IE qd	50 IE/kg qd
Enhanced thromboprophylaxis added after update on April 9[a,b]: to patients with symptoms corresponding to need of ICU care, D-dimer over 3 mg/L FEU, fibrinogen over 8 g/L, cancer, previous thrombosis, or known severe thrombophilia				
Adm.	Body weight	<50 kg	50–90 kg	<90 kg
Inj., sc	Dalteparin	2,500 IE bin	5,000 IE bin	75 IE/kg bin
Inj., sc	Tinzaparin	2,500 IE bin	4,500 IE bin	50 IE/kg bin
Treatment dose[a,b]: to patients with confirmed thrombosis/pulmonary embolism or strong suspicion of thromboembolism				
Adm.				
Inj., sc	Dalteparin	200 IE/kg per day, qd/bin		
Inj., sc	Tinzaparin	175 IE/kg per day, qd/bin		
Infusion	Heparin	400–500 IE/24 h		

Abbreviations: bin, twice daily; FEU, fibrinogen-equivalent unit; ICU, intensive care unit; inj., injection; qd, once daily; sc, subcutaneous.
[a]If platelet count is over 30×10^9/L and no bleeding symptoms.
[b]Dose reduction should be considered if reduced kidney function (eGFR < 30 mL/min).

Data Collection

Descriptive data of the patients were extracted retrospectively from medical records and included information on age, sex, body mass index (BMI), hypertension, diabetes mellitus type 2, chronic obstructive pulmonary disease (COPD), heart disease (i.e., ischemic heart disease, arrhythmia, and cardiomyopathy), continuous treatment with anticoagulants, and time of onset of COVID-19 symptoms. During the study period, we collected information of hospital admission, start of LMWH (prophylactic or treatment dose), maximum dose of LMWH during hospitalization, anticoagulant-related bleeds, thrombotic events, need of mechanical ventilation, in-hospital death, and length of hospital stay. Anticoagulant-related bleeds were noted if found in the medical records and divided into levels of severity of bleeding according to ISTH criteria.[30] Discharge from hospital was either to home or an inpatient rehabilitation facility. From the KUL database, data of D-dimer levels in plasma and platelet counts in blood were collected continuously during the study period or for a maximum of 21 days. Coagulation laboratory parameters were measured at KUL, and automatically analyzed (►**Supplementary Methods**: Laboratory Analysis, available in the online version).

Statistical Methods

Levels

Descriptive data for continuous and categorical variables were summarized as medians with interquartile range (IQR) and counts with percentages (%), respectively.

First levels of D-dimer and platelet counts were only used if they were taken within 3 days from hospital admission. All analysis concerning first levels was adjusted for if LMWH was given the same day as the first level was measured, or after. To analyze speed and direction of change of D-dimer levels and platelet counts, person-specific linear regression models were fitted to D-dimer levels and platelet counts occurring within the first 7 days in hospital. The model used was univariate ordinary least-squares regression.

$$y_i = \beta_0 + \beta_1 * \text{day} + \varepsilon_i$$

where y_i is the outcome, β_0 is the intercept, β_1 the mean increase in y per day (slope), and ε_i the error term. The person-specific slopes and intercepts were used as summary measures to describe the starting levels and speed and direction of change in further analysis. The slopes can be interpreted as the mean change per day for each patient within the first days in hospital. For thrombosis, only information prior to the occurrence was included in the analysis.

Analysis

The relationship of D-dimer levels and platelet count dynamics (first level and estimated slopes) to death and thrombosis was estimated using multivariable logistic regression with robust standard errors. We adjusted for the admission date of each patient to account for the constant improvement in the treatment of COVID-19 patients during the study period.

To continue we investigate the effect of protocol change, i.e., the modified antithrombotic hospital-wide recommendations, published on April 9, 2020 (►**Supplementary Methods**, available in the online version). A random intercept linear mixed effects regression model was applied to calculate the daily means of D-dimer levels and platelet counts among patients during their first 7 days at hospital. Person-specific random intercepts were used to take into account

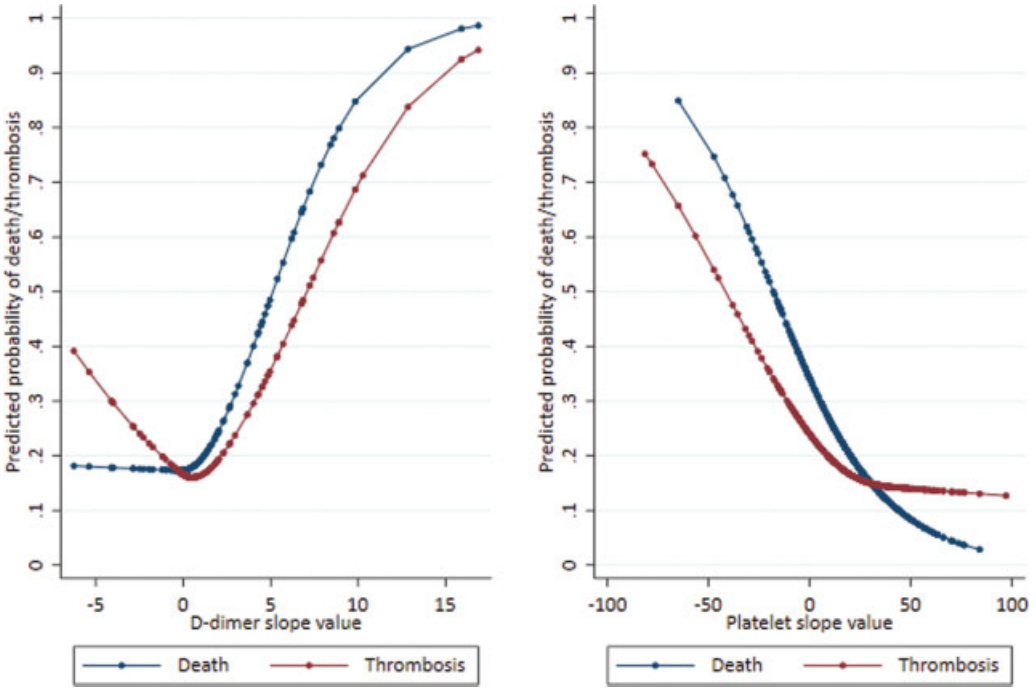

Fig. 1 The predicted probability of death and thrombosis regarding the different slopes (rate of change in levels) of D-dimer levels and platelet counts during the first week in hospital in patients with COVID-19. The *blue line* is the predicted probability of death and the *red line* is for thrombosis in connection with the different slopes of biomarker levels during the first week in hospital (rate of change in levels; β-coefficients estimated by linear regression); D-dimer level (**A**) and platelet count (**B**). The *y*-axis is the predicted probability of death and thrombosis, the *x*-axis in (**A**) is the D-dimer slope (β-coefficients) and in (**B**) the change in mean daily platelet count. Modeling was performed by applying logistic regression and restricted cubic splines with three knots.

the differences in disease severity at hospital admission and to control for the intra-person correlation. Probability of death and thrombosis before versus after protocol change was estimated using logistic regression.

Interrupted time series regression was also used to further investigate the effect of protocol change. The model was mixed effects linear regression with random intercept and the parameter of interest was the interaction of time and time period after protocol change, which can be interpreted as the difference in speed of change in the outcome variable before and after protocol change. For the whole cohort, all models were adjusted for established risk factors associated with the severity of COVID-19, i.e., age, sex, diabetes mellitus type 2, heart disease, and COPD. BMI was not used because of too much missing data. We also adjusted for continuous treatment with DOACs or warfarin, hypothesizing a protecting effect on the outcomes.[31]

Graphs

Graphs were produced using predictions from unadjusted linear regression (►**Fig. 1**) and logistic regression models (►**Fig. 2**). The dynamics of change in D-dimer levels and platelet counts were allowed to be nonlinear using restricted cubic splines with three knots. For the linear regression model, clustered robust standard errors were used to account for the intra-person correlation.

The analysis was performed using Stata, version 15 (StataCorp, 2017, Stata Statistical Software: Release 15; College Station, Texas, StataCorp LLC). *p*-Values smaller than 0.05 were considered statistically significant.

Results

During the study period, March 5 to April 22, 429 patients with severe COVID-19 were admitted to Karolinska and included in the final cohort (►**Supplementary Fig. S1**, available in the online version). The median age was 59 years (IQR: 50–66). Thirty-seven percent were women in the total cohort, the figure being 21% in the ICU group (►**Table 2**).

Days in Hospital, Death, and Thrombosis

COVID-19 patients were hospitalized for a median period of 15 days (IQR: 8–27). Ninety-four patients died from COVID-19 at hospital, with a 19% case-fatality rate in 30 days and a cumulative incidence of 22%. Thrombotic events had a 30-day incidence of 18% and were six times more frequent in patients at the ICU compared with the ward (cumulative incidence of 30% (83/429) and 5% (9/183), respectively). The most common thrombotic event was PE, found in 65 patients (15 ICU patients diagnosed by high clinical likelihood of PE, but judged too unstable to undergo further examination). Arterial thrombosis occurred in five patients (►**Table 3**).

Antithrombotic Treatment with Low-Molecular-Weight Heparin and Bleeding during Treatment

Three hundred and sixty-seven patients were treated with LMWH, with more than half receiving an intermediate or full dose, escalating from the initial prophylactic dose (►**Table 3** and ►**Fig. 2**). At the ICU, almost all (240/246) patients received antithrombotic treatment, in contrast to those

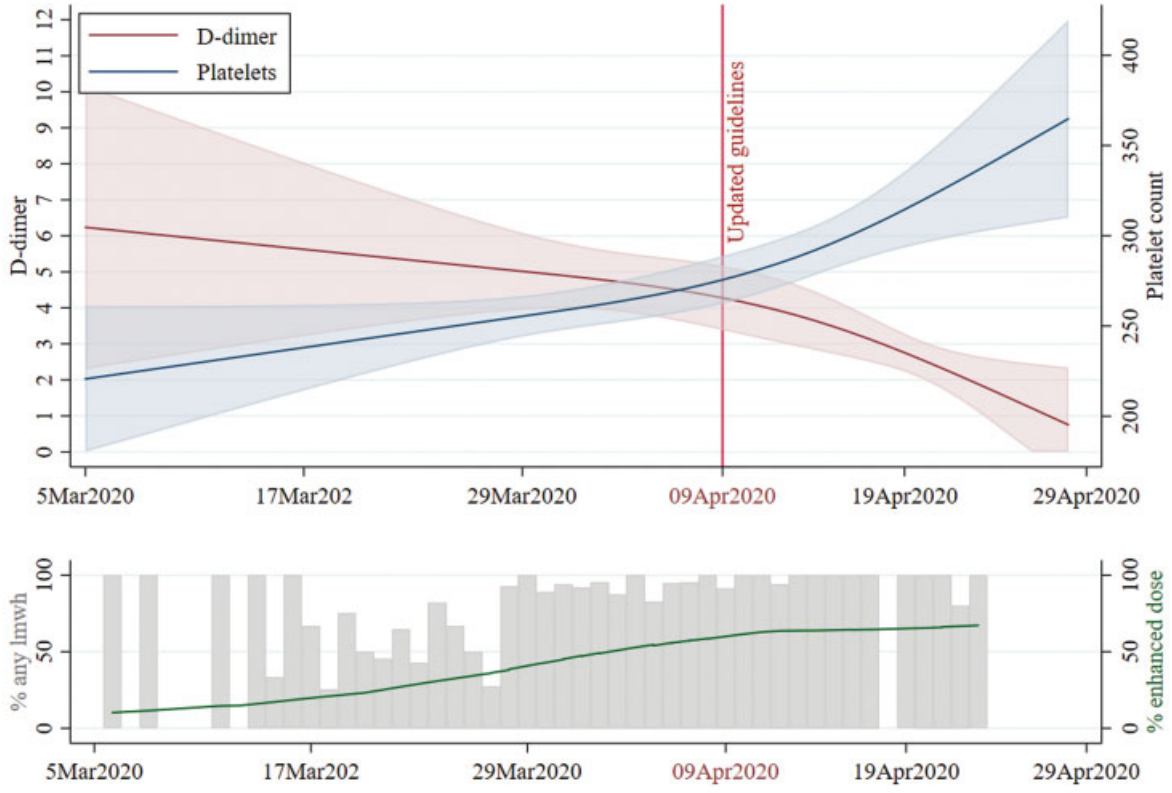

Fig. 2 Predicted daily mean D-dimer level and platelet count from March 5 to April 4, 2020 on patients with COVID-19. Prediction was based on measurements every given day on patients treated within the first 7 days at hospital; the *red line* represents D-dimer level and the *blue line* platelet count. The *shaded areas* are 95% confidence intervals. The *green line* is the lowest smoothed day-specific mean percentage of patients admitted that day, receiving either intensified prophylactic treatment or full-dose with LMWH (enhanced dose) at any time during their hospital stay. Modeling was performed by using linear regression with clustered robust standard errors. Restricted cubic splines with three knots were used to allow flexibility over time. LMWH, low-molecular-weight heparin.

outside the ICU, where only 69% received such treatment. Bleeding after antithrombotic treatment occurred only in ICU patients (cumulative incidence: 11%). According to ISTH classification, 24 of 27 bleeds were categorized as clinically relevant and 22 of them occurred during intermediate- or full-dose regimens with LMWH.[30] Prior to the bleeds, eight patients received infusion with heparin, two patients had been given central thrombolytic treatment and seven, platelet inhibitors. Fifteen of the patients suffered from a thrombotic event prior to their bleed. Four bleeds were intracranial after ischemic stroke, classified as major (►**Table 3**).

Associations between D-Dimer Levels, Platelet Counts, Death, and Thrombosis

D-Dimer levels and platelet counts (first levels at hospital, peak levels, and day of peak) are presented in ►**Table 4**. We performed logistic regression analysis to assess if the risk of death and thrombosis was associated with the first D-dimer level and platelet count in hospital. Whereas the first D-dimer level at hospital was significantly associated with thrombosis (odds ratio [OR]: 1.10; 95% confidence interval [CI]: 1.04–1.16), it was not associated with death (►**Table 4**). If categorized, the OR for thrombosis would increase with each category compared with the lowest D-dimer level percentile (≤0.96 mg/L FEU), first being significant at levels three times higher than normal (<0.5 mg/L FEU). Regarding death, the OR increased compared with the lowest D-dimer level percentile up to 4.1 mg/L FEU, only significantly associated in the stratum 1.69–4.1 mg/L FEU (OR: 2.79; 95% CI: 1.30–5.93). Both death and thrombosis were associated with peak D-dimer levels (OR: 1.07; 95% CI: 1.05–1.10 and 1.09; 95% CI: 1.06–1.11, respectively). We found no significant associations with either the first or the peak platelet count in relation to death and thrombosis (►**Table 4**).

We conclude that the higher the D-dimer level was, the higher the risk was for thrombosis, in contrast to the risk of death where higher levels were not associated with increased risk. First and peak levels of platelet count were not good markers. This is well illustrated in ►**Supplementary Fig. S2** (available in the online version) showing the probability for death and thrombosis in relation to D-dimer level and platelet count.

Trend Analysis of D-Dimer Levels and Platelet Counts in the First Week at Hospital, and Their Association with Death and Thrombosis

To understand the direction and velocity of change, dynamics, and their implications as regards D-dimer levels and platelet counts during the first 7 days at hospital, we

Table 2 Admission characteristics, subgrouped to level of care

Variables	All $N = 429$	ICU $N = 246$	Ward $N = 183$[a]
Median age, y (IQR)	59 (50–66)	59 (51–64)	60 (46–69)
19–39 years of age	41 (9.6)	19 (7.7)	22 (12)
40–69 years of age	316 (74)	198 (80)	118 (65)
70–93 years of age	72 (17)	29 (12)	43 (23)
Women	159 (37)	50 (21)	109 (60)
Median BMI, kg/m^2 (IQR)[b]	29.0 (26.1–32.5)	29.0 (26.4–31.9)	28.4 (26.0–32.9)
Severe obesity (BMI 35 or more)	48 (14)	24 (12)	24 (13)
Hypertension	163 (38)	95 (38)	68 (37)
Diabetes mellitus type 2	117 (27)	68 (28)	58 (32)
Heart disease[c]	68 (16)	25 (10)	43 (23)
Chronic obstructive pulmonary disease	73 (17)	43 (17)	30 (16)
Anticoagulant treatment	19 (4.4)	5 (2.0)	17 (9)
In age group 70 years and older	11 (2.6)	2 (0.8)	9 (5)
Median days with Covid-19 symptoms (IQR)	7 (5–10)	7 (6–11)	7 (5–10)

Abbreviations: BMI, body mass index; ICU, intensive care unit; IQR, interquartile range.
Note: All data are presented as count and percentage (%) unless otherwise noted.
[a]35 patients restricted to ward.
[b]Missing results in 22% of cases.
[c]Includes ischemic heart disease, arrhythmia, and cardiomyopathy.

calculated a slope based on the rate of change in levels. This was followed by predicting the probabilities of death and thrombosis in relation to the rate of change in D-dimer levels and platelet counts, graphically illustrated in ►**Fig. 1**. The probabilities of death and thrombotic events increased with a faster increase of D-dimer levels in plasma. The probability of death seemed to increase even faster than that of thrombosis. To further investigate this, we categorized patients into: no or minor change, increase or decrease in slope. We could confirm that a mean increase in slope of more than 0.05 mg/L FEU per day was significantly associated with both death and thrombosis (OR: 6.06; 95% CI: 2.10–17.5 and 3.12; 95% CI: 1.12–8.11) compared with no change (►**Table 4**). This corresponded to an estimated cumulative incidence of death of 29.5% if the slope increased compared with 11.5% if there was no change in D-dimer levels. For thrombosis, the cumulative incidence rates were 26.5 and 9.4%, respectively. In sensitivity analysis, we divided the intercept in the regression models at the 75th percentile. We observed that an even decrease in slope was associated with death and thrombosis when the intercept was high compared with the reference with minor change or decrease at a lower intercept. However, this group with decreasing D-dimer levels from a high starting point was very small, which resulted in uncertain estimates and wide CIs (data not presented). Still, this was visualized in ►**Fig. 1**, where a decrease in D-dimer levels also seemed to affect the probabilities of thrombosis and death.

Rate of change in platelet counts during the first week at hospital was striking. The faster the platelet counts increased, the lower the probability of dying or having a thrombotic event, as graphically presented in ►**Fig. 1**. This was well supported by the results of regression analysis; a mean increase of more than 35×10^9/L platelets per day decreased the risks of death (OR: 0.16; 95% CI: 0.06–0.41) and thrombosis (OR: 0.36; 95% CI: 0.17–0.80) compared with no change or a decrease in slope. For platelet counts with a daily mean increase of $10–35 \times 10^9$/L, the ORs were 0.48 (95% CI: 0.27–0.85) and 0.47 (95% CI: 0.26–0.85) for death and thrombosis, respectively (►**Table 4**). The importance of increasing platelets was further indicated by the calculated cumulative incidence of death of 15.8% for patients with a daily mean increase in platelets of 10×10^9/L or more compared with 39.1% for patients with no change or decrease. Corresponding cumulative incidence rates of thrombosis were 15.6 versus 28.4%. There was no significant interaction between the first platelet count at hospital and how fast the platelet count increased per day (data not presented), this might indicate that the dynamics were independent of the first level. To summarize, the rate of increase in platelet count demonstrated an impressive association with risk reduction in both thrombosis and death. The pattern of D-dimer levels was less robust due to a lower number of observations compared with platelet counts (►**Fig. 1** and ►**Table 4**).

Comparison between the Time Periods Before and After the Modification of Antithrombotic Hospital-Wide Recommendations

The daily mean levels of D-dimer and platelet counts were estimated, illustrated graphically in ►**Fig. 2**. Added to the figure is the lowest smoothed percentage of patients admitted daily who were given high antithrombotic prophylactic

Table 3 Outcomes within 7 and 30 days, antithrombotic treatment, and bleeding

Outcomes, subgrouped to level of care	All ($N = 429$)	ICU ($N = 246$)	Ward ($N = 183$[a])
Median days of in-hospital stay (IQR)	15 (8–27)	23 (16–37)	8 (5–13)
Patients discharged within 7 days	93 (22)	13 (5.3)	80 (44)
Patients discharged within 30 days	337 (79)	158 (64)	179 (98)
In-hospital death	94 (22)	73 (30)	21 (11)
Within 7 days	23 (5.4)	12 (4.9)	11 (6.0)
Within 30 days	80 (19)	60 (24)	20 (11)
Thrombosis	83 (19)	74 (30)	9 (4.8)
Within 7 days	31 (7.2)	23 (9.3)	8 (4.4)
Within 30 days	77 (18)	68 (28)	9 (4.9)
Venous thromboembolism	72 (17)	65 (26)	7 (3.8)
Pulmonary embolism[b]	65 (15)	58 (24)	7 (3.8)
Arterial thrombosis[c]	5 (1.1)	4 (1.6)	1 (0.5)
Catheter-related thrombosis	6 (1.4)	5 (2.0)	1 (0.5)
Mechanical ventilation	212 (49)	212 (86)	0
Within 7 days	202 (95)	202 (82)	0
Within 30 days	212 (100)	212 (100)	0
Antithrombotic treatment with LMWH	367 (87)	240 (100)	127 (69)
Intermediate or full dose	210 (57)	183 (76)[d]	27(15)[e]
Standard prophylactic dose only	156 (43)	57 (24)	99 (54)
Bleeding on antithrombotic treatment[f]	27 (6.3)	27 (11)	0
Fatal	1	1	0
Major[g]	10	10	0
Clinically relevant minor	13	13	0

All data are presented as count and percentage (%) unless otherwise noted. IQR is inter-quartile range
[a]Thirty-five patients restricted to ward care level.
[b]Fifteen were clinically strongly suspected but not confirmed at ICU, given full-dose anticoagulant treatment, and four patients received thrombolysis
[c]Four patients had ischemic stroke and one critical ischemia in the left leg.
[d]Fifteen patients treated with unfractionated heparin.
[e]Three remained on DOAC.
[f]Four ICU patients received blood transfusion.
[g]Four patients had intracranial bleeding after ischemic stroke.

doses or a treatment dose of LMWH that could have been increased during their hospital stay. Modified hospital-wide recommendations on anticoagulation with added enhanced prophylactic doses were published on April 9, 2020 (►**Table 1**). We investigate if this modification had any effect on average D-dimer levels and platelet counts among patients. For each patient, the levels from the first 7 days in hospital were included in the analysis. When comparing the time periods before and after the modification, the daily mean levels changed significantly after April 9; D-dimer levels decreased in plasma by 1.93 mg/L FEU (1.00–2.87) mg/L FEU and platelet counts increased by 65 (54–76) $\times 10^9$/L on average. Interrupted time series regression analysis estimated the difference in the rate of change (β-coefficients) before and after the protocol change to be −0.13 for D-dimer (95% CI: −0.32–0.06) and 5.95 for platelet counts (95% CI: 4.03–7.87).

When comparing the cumulative incidence of death and thrombosis before and after the shift in the hospital's anticoagulation recommendation on April 9, 24.5% died before compared with 13.5% after the shift. For thrombosis, the cumulative incidence rates were 21.6 versus 11.5%. This corresponded to a significant risk reduction for death and thrombosis if the patient was admitted after the modification of hospital-wide recommendations (OR: 0.48; 95% CI: 0.25–0.92 and 0.35; 95% CI: 0.17–0.72).

Discussion

We found that the dynamics of platelet counts in combination with D-dimer levels were associated with death and thrombosis in our cohort of 429 severely ill patients with COVID-19. As faster the platelet counts increased, the more the risk declined. A trend analysis of daily mean levels

Table 4 D-Dimer and platelet count levels in association with death and thrombosis

	All	Death				Thrombosis[a]			
	N = 429	*N* = 94	OR(a)	[95% CI]	*p*	*N* = 83	OR(a)	[95% CI]	*p*
D-Dimer levels in plasma (mg/L FEU)									
First level at hospital[b], median (IQR)	0.96 (1.70–0.59)	1.27 (0.77–2.80)	0.99	[0.95–1.03]	ns	1.29 (0.76–3.95)	1.10	[1.04–1.16]	***
0th–50th percentile (0–0.95 mg/L FEU)	179 (42)	24 (26)	ref.			25 (30)	ref.		
50th-75th percentile (0.96–1.68 mg/L FEU)	90 (21)	21 (22)	1.52	[0.73–3.16]	ns	15 (18)	1.15	[0.55–2.40]	ns
75th-90th percentile (1.69–4.1 mg/L FEU)	53 (12)	20 (21)	2.79	[1.30–5.93]	**	15 (18)	2.58	[1.20–5.55]	**
90th-100th percentile (4.2–35 mg/L FEU)	37 (8)	13 (14)	1.95	[0.79–4.83]	ns	17 (20)	4.80	[2.09–11.0]	***
Missing levels	70 (16)	16 (17)	1.33	[0.66–2.92]	ns	11 (13)	1.07	[0.45–2.55]	ns
Peak level, median (IQR)	3.85 (1.25–10.6)	11.8 (3.70–34)	1.07	[1.05–1.10]	***	13.0 (5.45–35)	1.09	[1.06–1.11]	***
Day at peak level	6 (2–11)	5 (3–10)				5 (2–7.5)			
Slope (β) from admission to 7 days									
No change	70 (16)	12 (13)	ref.			10 (12)	ref.		
Decrease in slope	65 (15)	4 (4)	2.36	[0.73–7.69]	ns	6 (7)	1.64	[0.54–4.92]	ns
Increase in slope	190 (44)	56 (60)	6.06	[2.10–17.5]	***	50 (60)	3.05	[1.17–7.91]	*
Missing	104 (24)	22 (23)	2.38	[0.72–7.87]	ns	17 (21)	1.18	[0.64–5.54]	ns
Platelet counts in blood ($\times 10^9$/L)									
First count at hospital[a], median (IQR)	201 (159–260)	191 (151–255)				220 (164–279)			
Less than 150 $\times 10^9$/L	80 (19)	22 (24)	1.44	[0.77–2.70]	ns	14 (17)	0.91	[0.46–1.80]	ns
150–350 $\times$ 10^9/L	320 (75)	68 (72)	ref.			59 (71)	ref.		
Over 350 $\times$ 10^9/L	27 (6)	3 (4)	0.37	[0.77–2.70]	ns	9 (11)	2.30	[0.90–5.84]	ns
peak count, median (IQR)	460 (334–577)	408 (288–506)	1.00	[1.00–1.00]	***	420 (317–528)	1.0	[1.00–1.00]	ns
Day at peak count	9 (5–13)	8.5 (4–13)				7 (2–12)			
Slope (β) from admission to 7 days									
No change or decrease in slope	110 (26)	43 (46)	ref.			31 (37)	ref.		
Mean increase on 10–35 $\times$ 10^9/L platelets per day	219 (51)	44 (47)	0.48	[0.27–0.85]	*	36 (43)	0.47	[0.26–0.85]	*
Mean increase more than 35 $\times$ 10^9/L platelets per day	97 (23)	6 (6)	0.16	[0.06–0.41]	***	13 (16)	0.36	[0.17–0.80]	*

Abbreviations: CI, confidence interval; FEU, fibrinogen-equivalent unit; IQR, interquartile range; OR; odd ratio, (a): adjusted for age, sex, heart disease, diabetes mellitus type 2, chronic obstructive pulmonary disease, anticoagulant treatment, date on admission and when LMWH was given in relation to either first D-dimer level measurements or platelet count.

Note: All data are presented as count and percentage (%) unless otherwise noted. *p*-Values are marked with * for <0.05, ** for <0.01, and *** for <0.005.

[a]Only information prior to thrombosis was included in the analysis.

[b]Within first 3 days.

graphically shows a gradually decreasing D-dimer levels and increasing platelet counts among patients over the course of the study period. These changes in levels significantly coincided with the implementation of hospital-wide recommendations of intensified anticoagulation and decreased relative risks of mortality and thrombosis.

Our study population is similar in characteristics to previous studies of patients with severe COVID-19 infections during the first phase of the pandemic in Europe.[14,18,32,33] Similarities included thrombotic events were six times more frequent in ICU patients versus patients treated at the general ward and the most common thrombotic event, by far, was PE, found in 25% of the ICU patients.[12,14,18,23,33] In contrast to previous studies, we have completed follow-up of all patients until hospital discharge or death. This may explain why we at the ICU experienced a higher cumulative death rate of 30%, of whom 84% died within 30 days, compared with rates of 13 to 24% in previous studies, all with shorter follow-up times.[14,34]

Bleeding has been reported as a spontaneous event or an unwanted complication of anticoagulation treatment in COVID-19 cases, with a prevalence rate of 2 to 21%. The wide range has been explained by the dosage of anticoagulation and the combination with platelet inhibitors or fibrinolytic therapy, but also by more frequently reported bleeds among mechanically ventilated ICU patients.[2,19,35] This was also seen in the current cohort; bleeds occurred only in the ICU-treated patients, with a cumulative incidence of 11%, and the majority had experienced a thrombotic event before the bleed (►**Table 3**). Our results support theories of COVID-19 coagulopathy without prominent bleeding.[36,37] Taken together, bleeding manifestations seem to be a later complication of severely ill ICU-treated COVID-19 patients, typically in combination with antithrombotic treatment other than LMWH alone.

In our cohort, we observed the same pattern with elevated first D-dimer levels and peak as in previous studies (►**Table 4**).[32,38,39] The higher the first D-dimer level was in hospital, the higher the risk was for thrombosis, in contrast to the risk of death where levels over 4.1 mg/L FEU did not associate with increased risk (►**Table 4**). More information was provided when studying the dynamics in D-dimer levels over the first week. Even if the patient had a low first D-dimer level, a fast increase would indicate a higher risk of thrombosis and death than unchanged levels. We could also note that if a patient's D-dimer level dropped from a higher starting point, the increased risk may remain, but this needs to be confirmed in other studies. This highlights that first D-dimer levels are far better assessed in regard to the following levels to truly estimated risk of death and thrombosis. The slope might indicate an ongoing thromboinflammatory process that gets out of control in patients with potential risk factors. In other studies, with thromboelastography, delayed or absent fibrinolysis was found as a sign of this disturbance of normal anticoagulation.[37,40,41]

In contrast to previous studies, first platelet count was not a good risk marker of death and thrombosis in our cohort as we found no association with thrombocytopenia.[11,42] Again, studying the dynamics in the first week in hospital provided much more captivating results. A fast increase of more than 35×10^9/L platelets per day demonstrated a robust association with a large risk reduction for both thrombosis and death (►**Table 4** and ►**Fig. 1**). If used as a dynamic risk marker, the platelet count may remain within the reference range but still be of high clinical value and should not be disregarded. Platelets appear to be hyperactive and play a key role, but how SARS-CoV-2 interacts with the megakaryocytes and/or platelets is still unknown.[8] The thrombi seen at autopsy are platelet-rich, indicating that consumption could be a plausible explanation, but other reasons such as increased platelet clearance and/or an impaired immune response in host-defense also contribute to an inability to increase platelet counts.[9,11,43,44] On the whole, dynamics of D-dimer levels and platelet counts have not previously been assessed in depth in this context and our findings emphasize to use them both as dynamic markers in severe COVID-19 and to not only focus on first levels.

To continue, there was a considerable difference in patients' daily mean of D-dimer levels and platelet count in the first week in hospital after the hospital-wide recommendations of intensified anticoagulation was implemented in April 9. In patients admitted after April 9, the risks of thrombosis and death were significantly reduced in comparison with patients admitted earlier and this decrease was confirmed in a large Swedish study.[45] As visualized in the graph in ►**Fig. 2**, the changes in D-dimer levels and platelet counts began before the hospital-wide recommendations of intensified anticoagulation was published, indicating that a combination of factors contributed to these changes during the study period. The gained experience over time, i.e., improved general care, ventilation adjustment as well as fewer patients intubated, contributed to an improved outcome in hospital in cases of severe COVID-19 in the first phase of the pandemic. Antiviral medication and cortisone could theoretically have had some impact but were not systematically given to patients at Karolinska with severe COVID-19 at that time.[46,47] In numbers, only 14 patients were given Remdesivir (10 in ICU, 4 in ward) and none of the patients received dexamethasone. Undoubtedly, the new hospital-wide recommendations of enhanced prophylaxis with LMWH coincided with the improved outcome pattern with a decline in risk of both death and thrombosis. Previous studies have pointed in different directions, both in line with our results and the opposite. This discrepancy depends on several factors, most importantly heterogeneity between studies, and their results are, therefore, unsuited to compare with ours.[12,21–23] We chose to compare time periods before and after hospital-wide guideline modification, using our updated recommendations as a proxy for true dose escalation. We also show how the use of higher maximum doses than ordinary prophylaxis increased over time in ►**Fig. 2**. This gave us an opportunity to evaluate the effect of anticoagulation with an alternative approach generating supporting evidence of the importance of anticoagulant in treatment of thromboinflammation in COVID-19, strengthened by the impact on D-dimer levels and platelet count.[48]

LMWH does not only halter thrombin generation but also seem to have nonanticoagulant effects, favorable in treatment of COVID-19.[48] Studies have suggested that LMWH may inhibit heparinase that contributes to vascular leakage and inflammation in COVID-19.[49] Further, in vitro study of plasma from COVID-19 patients found an activation of platelets and neutrophils and formations of neutrophil extracellular traps (NETs), whereas NETs correlated with thrombosis and were blocked by LMWH but not by aspirin or dipyridamole.[50] Aspirin has been found to have some favorable effect in COVID-19, but we are still awaiting results from randomized control trials.[21]

Strengths and Limitations

This study has several strengths, with a relatively large single-center cohort, including patients in both the ICU and wards, with complete information and follow-up until discharge or in-hospital death. In total, the cohort generated 8,534 hospital days, and the data were collected systematically including by reviewing the medical records on a daily to weekly basis during follow-up. We have in our statistical analysis been vigilant with the effect that the gained experienced over time had in the early phase of the pandemic on both mortality and thrombotic events. A couple of different approaches were utilized to address this effect in our analysis. First, we cautiously adjusted to admission date for each patient in our regression analysis. Second, when evaluating the influence on our hospital-wide recommendations for intensified anticoagulation, we added interrupted time series regression. However, there are limitations in the study that must be considered. We identified our patients as those having IL-6 results in the KUL database, being a test included in the centralized COVID biobank and supposed to be performed in all cases of severely ill in-hospital COVID-19 patients. Even so we may have missed some patients. We also observed a noticeable amount of missing D-dimer levels within the first 3 days at hospital. Instead of imputing values, we decided to keep the patients with missing data in the analysis, categorizing the patients with missing D-dimer levels to their own group. We did not find any significant association with either death or thrombosis comparing the group with missing data with the reference group (►**Table 4**). This supports the hypothesis that the missing results occurred at random and the group with missing levels had little effect on the outcome of the analysis, except with losing statistical power. In contrast, we had neglectable number of missing results for platelet count. We only report the highest-dose LMWH given to each patient, a consequence of limited information of exact date of dose escalation in many patients. Of course, this restricted us to go further into our analysis of anticoagulation, but we have cautiously adjusted for timing of the first given dose in relation to sampling regarding D-dimer level and platelet count. Finally, we cannot ignore residual confounding influencing our results regarding the effect on the use of intensified anticoagulation. Nevertheless, this study is observational, so only associations can be established and not causalities. Implications for future research are, foremost, randomized controlled trials regarding anticoagulant treatment doses and treatment periods.

Conclusion

D-Dimer levels and platelet counts are key markers of thromboinflammation and severity in COVID-19. From our study we suggest following the rate of change of levels during the first week in hospital in connection with risk prediction of death and thrombosis. When the daily mean platelet counts increased and levels of D-dimer levels decreased during the study period, the thrombotic burden and deaths declined. This coincided with the introduction of a higher dosage of anticoagulation to patients with severe COVID-19, underscoring anticoagulation as a treatment cornerstone and the need for dose adjustment in relation to disease severity.

What is known about this topic?

- High level of D-dimers is associated with death and thrombosis in COVID-19.
- Platelets seem to play a pivotal role in pathogenesis of severe COVID-19.
- Thrombosis prophylaxis with low-molecular-weight heparin (LMWH) appears to improve survival; randomized clinical trials are lacking providing guidance on optimal dosage.

What does this paper add?

- The rate of change in platelet count in consort with D-dimer over the first week in hospital was associated with poor outcome in COVID-19, supporting platelets' pivotal role.
- Recommendations on intensified anticoagulation with LMWH were significantly associated with a drop in daily mean values of D-dimers while the platelet count rose. This also coincided with a risk reduction in mortality and thrombosis.

Author Contributions

A. Sjöström, J. Antovic, and M. Bruzelius designed the study. A. Sjöström and J. D. Wersäll collected the data. A. Sjöström, M. Bruzelius, and A. Warnqvist performed data analysis and interpretation. A. Sjöström and M. Bruzelius drafted the first version of the manuscript. All authors contributed to the text and critically reviewed the final version of the article and they approved it for publication.

Data Sharing

The data that support the findings of this study are available on reasonable request from the corresponding author.

Conflict of Interest

J.A. has received research grants from Shire, honoraria from Stago, Siemens, Sysmex, Roche, Baxter, and Sobi, and acts on advisory boards for Sobi and Novo Nordisk. M.B.

acts on the advisory board for CSL Behringer and Sobi and has had consultant assignments for Novo Nordisk and received lecturer honoraria from Sobi.A.O. and M.B. were both supported by funds from Stockholm County Council. A.O. was supported by Swedish Carnegie Hero Funds. A.S., J.D.W., A.W., A.Å., and M.M. declare no competing financial interests.

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