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Original article

The association of anticoagulation before admission and survival of patients with COVID-19

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ABSTRACT

Background: Severe coronavirus disease 2019 (COVID-19) is associated with systematic coagulopathy which might result in fatality. We aimed to investigate whether systematic anticoagulation before admission with COVID infection was associated with patients' survival.

Methods: We reviewed medical records of 6,095 hospitalized patients with laboratory confirmed COVID-19 from the Mount Sinai Health System. Patients were stratified into two groups: patients with therapeutic anticoagulation before admission (7.9%, N=480), or those without (92.1%, N=5,615). Propensity score matched analysis was conducted to assess the association of anticoagulation before admission and in-hospital mortality (N=296 in each group). Multiple imputation for missing data was conducted.

Results: A total of 480 patients (7.9%) received anticoagulation before admission. Patients with anticoagulation before admission were older (72.1±14.7 years vs. 63.1±17.2 years), and had more comorbidities including chronic pulmonary obstructive disease, hypertension, diabetes, chronic kidney disease, atrial fibrillation, and heart failure (all $p< 0.05$). Notably, patients with anticoagulation before admission had lower D-dimer [1.48 (IQR 0.75, 2.79) μg/mL vs 1.66 (0.89, 3.52) μg/mL, p=0.002]. In a propensity score matched analysis (N=296 in each group), in-hospital mortality was not significantly different in patients with anticoagulation before admission compared to those without (28.4% vs 31.1%, p=0.53). In addition, inverse probability weighted analysis and multiple imputation for missing data did not change the result. Furthermore, these differences were not significant after excluding endotracheal intubation from both groups.

Conclusion: Anticoagulation before admission was not associated with lower risk of in-hospital mortality of COVID-19 patients. Further investigation is needed to confirm these findings.

Introduction

Coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2, has spread all around the world since the first reported case in December 2019 [1,2]. The World Health Organization declared COVID-19 to be a pandemic on March 11, 2020 and as of April 22nd, New York City has become the epicenter [3]. On April 17th, 2021, the number of deaths due to the COVID-19 pandemic exceeded 3 million and the number of COVID-19 cases reached 140 million globally [3]; 31 million of which are from the USA alone.

Inflammation due to COVID-19 causes coagulopathy and micro- or macro-thrombi, which could result in high fatality [4]. Several observational studies suggested potential benefit of therapeutic anticoagulation during hospitalization [5–8]. However, patients with COVID-19 are usually admitted to hospital after several days from onset of symptoms with elevated D-dimer at admission which is considered to be an independent predictor for in-hospital mortality [9,10]. Thus, we hypothesized anticoagulation before admission might decrease the risk of thrombotic events or mortality.

The aim of this study was to investigate the association of therapeutic anticoagulation before admission and mortality of patients with COVID-19.

Methods

This retrospective study was conducted by obtaining the medical records of 6,095 hospitalized patients, in the Mount Sinai

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Health system, with laboratory confirmed COVID-19. Identification of COVID-19 required a nasopharyngeal swab, which was tested using a polymerase chain reaction [11–20]. The decision to admit the patient was largely provider dependent, and not based on any specific predetermined criteria.

Patients' demographics, comorbidities, and clinical outcomes were extracted from electronic medical records. Patients were stratified into groups, those with therapeutic anticoagulation before admission or those without anticoagulation before admission included apixaban, dabigatran, rivaroxaban excluding 2.5 mg as prevention of atherosclerotic cardiovascular events [21], edoxaban, warfarin, and enoxaparin (as therapeutic dose). Anticoagulation during hospitalization included apixaban, rivaroxaban, warfarin, enoxaparin as therapeutic dose, and intravenous continuous unfractionated heparin and argatroban.

Differences in baseline characteristics between groups were evaluated using analysis of variance for continuous variables and the χ^2 test for categorical variables. Continuous variables are presented as mean ± standard deviation or median [interquartile range] depending on what is appropriate for the data distribution, and categorical variables were expressed as percentages. All vital signs were recorded at time of admission. The primary outcome of interest was in-hospital mortality. Bleeding events were defined through ICD-10 codes. A propensity score analysis was performed to adjust baseline characteristics between those with therapeutic anticoagulation before admission or those without. A 1:1 match was performed using a nearest neighbor match within a caliper 0.2 of the standard deviation of the logit of the propensity score [22]. The following variables were used to estimate propensity score: age, sex, race, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, obesity, hypertension, diabetes mellitus, chronic kidney disease, human immunodeficiency virus, cancer, atrial fibrillation, heart failure, alcoholic/non-alcoholic liver disease [23,24]. In addition, we also performed an inverse probability weighted analysis (IPTW) with 5% truncated weights [25]. Finally, we performed a multiple imputation for missing data of C-reactive protein, D-dimer, hemoglobin, lactate dehydrogenase, serum creatinine, troponin-I, and white blood cell count. The percentage of missing data was the following: C reactive protein: 19.6%, D-dimer: 22.7%, hemoglobin: 3.7%, lactate dehydrogenase: 27.1%, serum creatinine: 4.4%, troponin-I: 13.3%, white blood cell count: 3.7%.

As sensitivity analyses, we did subgroup analyses excluding patients with endotracheal intubation. A subgroup analysis of patients with heart disease (atrial fibrillation or heart failure) was also conducted. Furthermore, we assessed the effect of continuation versus discontinuation of therapeutic anticoagulation among patients with anticoagulation before admission. All statistical calculations and analyses were performed on R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria) with packages of matchit and mice. Values of $p<0.05$ were considered statistically significant.

This study was approved by the institutional review board (#2000495) and conducted in accordance with the principles of the Declaration of Helsinki. The waiver of patients' informed consent was also approved by the institutional review board.

Results

Of the 6,095 patients admitted due to COVID-19, 480 (7.9%) had anticoagulation therapy before admission. Baseline characteristics and vital signs across study groups are reported in Table 1. Patients with anticoagulation before admission were older (72.1±14.7 years vs. 63.1±17.2 years), and had more comorbidities including asthma, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, chronic kidney disease, atrial fibrillation, and heart failure (all comparisons $p<0.05$) (Table 1). Vital signs at admission were similar for both groups except temperature at admission (Table 1). Lengths of hospital stay were similar between the two groups [with anticoagulation before admission versus those without; 6.0 (3.0, 12.0) versus 6.0 (3.0, 11.0) days, $p=0.058$].

Notably, patients with anticoagulation before admission had lower D-dimer [1.48 (0.75, 2.79) μg/mL vs 1.66 (0.89, 3.52) μg/mL, $p=0.002$] compared to those without. In addition, patients with anticoagulation before admission had lower hemoglobin and higher troponin I and creatinine (Table 1). Proportions of bleeding events, endotracheal intubation, and in-hospital death were significantly higher in patients with anticoagulation before admission compared to those without (Table 2).

After matching by propensity score (N=296 in each group), good balance between groups was achieved with standardized difference between groups mostly less than 10% (Table 1). Interestingly, in propensity score matched analysis, patients with anticoagulation before admission had lower D-dimer [1.52 (0.81, 2.85) μg/mL vs 1.85 (0.99, 3.74) μg/mL, $p=0.002$) compared to those without. In-hospital mortality was not significantly different in patients with anticoagulation before admission compared to those without (28.4% vs 31.1%, $p=0.53$) (Table 2). IPTW analysis showed similar results [odds ratio (95% confidential interval): 1.02 (0.97-1.07), $p=0.45$]. Furthermore, multiple imputation for missing data did not change the result [odds ratio (95% confidential interval): 0.95 (0.68-1.31), $p=0.74$]. In addition, these differences were not significant after excluding patients with endotracheal intubation from both groups (N=5,318, 265 pairs; 23.8% vs. 27.2%, $p=0.43$). Intensive care unit (ICU) admission rate and endotracheal intubation rate were significantly lower in patients with anticoagulation prior to admission, respectively (16.2% vs 25.0%, $p=0.011$; 10.1% vs 19.6%, $p=0.002$) (Table 2).

In the subgroup analysis of patients with heart disease, in-hospital mortality was not significantly different in patients with anticoagulation before admission (N=218) versus those without (N=438) (38.5% versus 35.1%, $p=0.44$). Among patients with anticoagulation before admission, there was no difference in mortality with respect to continuation (N=359) versus discontinuation (N=121) of therapeutic anticoagulation (30.6% versus 34.7%, $p=0.47$).

Discussion

The salient findings are the following: 1) Patients with anticoagulation before admission are older and have higher rates of comorbidities compared to those without; 2) Patients with anticoagulation before admission had lower D-dimer compared to those without; 3) Anticoagulation before admission was not associated with in-hospital mortality.

Thromboembolic disease due to coagulopathy is a major complication of COVID-19 as has been shown in prior observational research, including autopsy studies [6, 26-33]. The recent observational study suggested potential benefit of anticoagulation during hospitalization, especially of therapeutic anticoagulation [7]. However, despite anticoagulation therapy during hospitalization, high mortality among patients with COVID-19 was still observed [5]. Given high D-dimer at admission, macrothrombi could be present at initial presentation [10,26,32,34]. Therefore, next step of anticoagulation for prevention of coagulopathy would be anticoagulation before admission. Herein, we conducted the study investigating the effect of anticoagulation before admission.

We showed that patients with anticoagulation before admission compared to those without anticoagulation before admission had lower level of D-dimer which is considered to be a risk factor of poor outcomes [10,35]. We consider therapeutic anticoagulation before admission can also be considered as a treatment

Table 1
Baseline characteristics and treatments with and without anticoagulation before admission, all hospitalizations and propensity matched hospitalization.

	All hospitalizations			Propensity matched hospitalizations			
	Without anticoagulation before admission (n=5,615)	With anticoagulation before admission (n=480)	*p*-value	Without anticoagulation before admission (n=296)	With anticoagulation before admission (n=296)	*p*-value	SMD
Age, (mean, SD), years	63.1 (17.2)	72.1 (14.7)	<0.001	70.8 (14.9)	70.8 (15.0)	0.98	0.002
Race, n (%)WhiteAfrican American HispanicAsianOther			<0.001			0.73	0.12
	1,234 (22.0)	169 (35.2)		98 (33.1)	103 (34.8)		
	1,397 (24.9)	124 (25.8)		73 (24.7)	70 (23.6)		
	1,578 (28.1)	93 (19.4)		49 (16.6)	58 (19.6)		
	275 (4.9)	19 (4.0)		19 (6.4)	14 (4.7)		
	1,131 (20.1)	75 (15.6)		57 (19.3)	51 (17.2)		
Male, n (%)	3,162 (56.3)	264 (55.0)	0.61	177 (59.8)	171 (57.8)	0.68	0.041
Asthma, n (%)	267 (4.8)	37 (7.7)	0.006	10 (3.4)	20 (6.8)	0.092	0.15
COPD, n (%)	190 (3.4)	47 (9.8)	<0.001	30 (10.1)	37 (12.5)	0.44	0.075
Hypertension, n (%)	1,754 (31.3)	262 (54.6)	<0.001	155 (52.4)	155 (52.4)	1.00	<0.001
Diabetes mellitus, n (%)	1,178 (21.0)	154 (32.1)	<0.001	87 (29.4)	89 (30.1)	0.93	0.015
Chronic Kidney Disease, n (%)	565 (10.1)	114 (23.8)	<0.001	77 (26.0)	72 (24.3)	0.71	0.039
Obstructive Sleep Apnea, n(%)	96 (1.7)	29 (6.1)	<0.001	14 (4.7)	17 (5.7)	0.71	0.046
Obesity, n (%)	416 (7.4)	65 (13.5)	<0.001	34 (11.5)	38 (12.8)	0.71	0.041
HIV, n (%)	96 (1.7)	9 (1.9)	0.94	3 (1.0)	6 (2.0)	0.50	0.083
Cancer, n (%)	400 (7.1)	63 (13.1)	<0.001	38 (12.8)	43 (14.5)	0.63	0.049
Atrial fibrillation, n (%)	210 (3.8)	171 (36.2)	<0.001	95 (32.1)	99 (33.4)	0.79	0.029
Heart Failure, n (%)	285 (5.1)	123 (26.0)	<0.001	63 (21.3)	65 (22.0)	0.92	0.016
Alcoholic/Non-alcoholic liver disease, n (%)	127 (2.3)	7 (1.5)	0.34	6 (2.0)	5 (1.7)	1.00	0.025
Temperature, (median [IQR])	37.2 [36.9, 37.7]	37.1 [36.8, 37.5]	<0.001	37.3 [36.9, 37.7]	37.2 [36.9, 37.5]	0.026	-
Heart Rate, (median [IQR])	95.7 [87.0, 105.9]	95.2 [85.3, 105.6]	0.30	97.2 [87.0, 109.5]	95.0 [86.0, 105.2]	0.078	-
Systolic Blood Pressure, (median [IQR])	137.0 [126.3, 149.0]	138.2 [128.7, 150.3]	0.27	141.3 [128.9, 152.2]	138.0 [129.0, 150.1]	0.10	-
Diastolic Blood Pressure, (median [IQR])	79.0 [73.8, 84.6]	78.5 [73.0, 84.9]	0.80	79.0 [73.8, 84.6]	78.5 [73.0, 84.9]	0.80	-
Respiratory rate /min. (median [IQR])	20.1 [19.0, 24.3]	20.3 [19.3, 23.4]	0.49	20.7 [19.3, 26.6]	20.4 [19.4, 23.9]	0.23	-
Oxygen Saturation, %, (median [IQR])	93.0 [90.8, 95.2]	93.1 [91.0, 94.7]	0.57	92.3 [90.0, 94.5]	93.0 [90.9, 94.5]	0.083	-
White blood cell, K/μL, (median [IQR])	7.6 [5.6, 10.7]	7.5 [5.4, 10.6]	0.24	7.7 [5.4, 10.9]	7.40 [5.40, 10.7]	0.73	-
Hemoglobin, g/dL (median [IQR])	13.3 [11.8, 14.6]	12.4 [10.5, 14.0]	<0.001	12.9 [11.3, 14.4]	12.4 [10.8, 14.0]	0.007	-
Creatinine, (median [IQR])	1.01 [0.79, 1.56]	1.26 [0.90, 2.10]	<0.001	1.28 [0.90, 2.30]	1.23 [0.86, 1.99]	0.26	-
Lactate dehydrogenase, U/L (median [IQR])	421.0 [314.0, 574.0]	405.0 [305.0, 574.0]	0.35	422.0 [311.0, 564.3]	417.0 [308.0, 584.8]	0.87	-
C-reactive protein, mg/L (median [IQR])	113.0 [53.1, 199.5]	93.8 [39.0, 177.1]	<0.001	107.8 [57.4, 182.6]	102.0 [40.7, 185.0]	0.18	-
D-dimer, μg/mL (median [IQR])	1.66 [0.89, 3.52]	1.48 [0.75, 2.79]	0.002	1.85 [0.99, 3.74]	1.52 [0.81, 2.85]	0.002	-
Troponin I, ng/mL (median [IQR])	0.02 [0.01, 0.06]	0.03 [0.01, 0.10]	<0.001	0.04 [0.01, 0.11]	0.03 [0.01, 0.08]	0.13	-
Therapeutic anticoagulation during hospitalization, n (%)	1,609 (28.7)	359 (74.8)	<0.001	147 (49.7)	241 (81.4)	<0.001	-
Prophylactic anticoagulation during hospitalization, n (%)	3,900 (69.5)	116 (24.2)	<0.001	144 (48.6)	51 (17.2)	<0.001	-
Steroid during hospitalization, n (%)	1,703 (30.3)	187 (39.0)	<0.001	119 (40.2)	138 (46.6)	0.14	-
Use of tocilizumab, n (%)	255 (4.5)	20 (4.2)	0.79	15 (5.1)	19 (6.4)	0.60	-

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; SMD, standardized mean differences.

Table 2
In-hospital outcomes with and without anticoagulation before admission, all hospitalizations and propensity matched hospitalization.

	All hospitalizations			Propensity matched hospitalizations		
	Without anticoagulation before admission (n=5,615)	With anticoagulation before admission (n=480)	*p*-value	Without anticoagulation before admission (n=296)	With anticoagulation before admission (n=296)	*p*-value
Bleeding events, n (%)	158 (2.8)	40 (8.3)	<0.001	15 (5.1)	25 (8.4)	0.14
Transfusion of red blood cell, n (%)	142 (2.5)	19 (4.0)	0.084	11 (3.7)	10 (3.4)	1.00
Intensive care unit, n (%)	1,050 (18.7)	72 (15.0)	0.052	74 (25.0)	48 (16.2)	0.011
Endotracheal intubation, n (%)	737 (13.1)	40 (8.3)	0.003	58 (19.6)	30 (10.1)	0.002
In-hospital death, n (%)	1,328 (23.7)	152 (31.7)	<0.001	92 (31.1)	84 (28.4)	0.53

option. In this study, we could not reveal the survival benefit of anticoagulation before admission. Since anticoagulation before admission was not prescribed for COVID, but for atrial fibrillation, venous thromboembolism and valvular heart disease, especially post-surgery (e.g. for patients who had a mechanical valve), multiple comorbidities in patients with anticoagulation might reduce the effect of anticoagulation before admission despite rigorous adjustment. After propensity matching, ICU admission rate and endotracheal intubation rate during hospital stay were significantly lower in patients with anticoagulation prior to admission. Anticoagulation prior to admission has the potential to prevent venous thromboembolism (VTE) on admission and the rate of therapeutic anticoagulation during hospitalization was significantly higher in patients with anticoagulation prior to admission compared to those without after propensity matching. These patients who were continued on therapeutic anticoagulation are potentially less susceptible to develop VTE events or microthrombosis during hospital stay, which could contribute to lower incidence of ICU admission and endotracheal intubation. However, as a limitation in a retrospective observational study without each patient's chart review, we were not able to demonstrate causal relationship between these outcomes and VTE events during hospitalization.

Recently, Corrochano et al. studied 28-day post admission mortality and ICU admission as outcomes among patients who received anticoagulation or antiplatelet therapy prior to admission, which showed that prior anticoagulation use was associated with significantly lower ICU admission rate, however, there was no mortality benefit [36]. While our study demonstrated similar results regarding these same outcomes, we further studied the mortality benefit of prior anticoagulation use among patients who were not intubated during hospitalization and among patients who had cardiac conditions, which still showed no mortality benefit with prior anticoagulation use among these subgroups.

There is an ongoing randomized trial of low molecular weight heparin for ambulatory patients with COVID-19 [24,37] and several ongoing randomized trials of therapeutic anticoagulation targeting hospitalized patients with COVID-19, demonstrating conflicting results [38–42]. Although we could not show the benefit of anticoagulation before admission, further investigation with randomized controlled trials regarding anticoagulation therapy at the time of onset of COVID-19 is needed.

Our study is not without limitations. First, this is an observational study. Despite good balance between anticoagulation and patients without anticoagulation therapy in available patients' baseline characteristics such as age, race, sex, comorbidities, and vital signs, we could not fully adjust for not reported characteristics such as frailty [43] or unobserved confounders such as sequential organ failure assessment score [31]. Second, we do not have complete information on the indication for anticoagulation before admission, such as history of VTE, other thrombus, and valvular surgery. In addition, we did not perform a manual chart review which might affect our findings such as the duration of symptoms at the time of hospital admission which matters since hypercoagulability may have already started at the time of symptom onset. Finally, there was discrepancy in the proportion of patients with atrial fibrillation among patients without anticoagulation before and after propensity score matching, which could be a source of bias and likely reduced the power to detect a difference in the in-hospital death. However, IPTW analysis showed the robustness of our results.

In conclusion, anticoagulation before admission was not associated with in-hospital mortality of COVID-19 patients. Further investigation with a randomized controlled trial of anticoagulation at the onset of symptoms of COVID-19 is needed to confirm these findings.

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None.

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Author contributions

TK, MT, NE, had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: TK

Data Curation: TK, MT, NE

Acquisition, analysis, or interpretation of data: TK, MT, NE

Drafting of the manuscript: TK

Critical revision of the manuscript for important intellectual content: TK, MT, NE

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