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Prophylactic versus therapeutic anticoagulation for survival of patients with COVID-19 on steroid

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Abstract

Previous observational and randomized studies suggested potential benefit of therapeutic anticoagulation during hospitalization, but this treatment remains controversial. As of June 30th 2021, steroids is the standard treatment of COVID patients. We aimed to investigate the association of prophylactic and therapeutic anticoagulation with mortality for patients with COVID-19 who were treated with steroids. We retrospectively reviewed the medical records of 2533 patients discharged between March 1st, 2020 and March 30th, 2021, with laboratory-confirmed COVID-19 in the Mount Sinai Health System and treated with steroids. We evaluated the effect of therapeutic versus prophylactic anticoagulation on the outcomes using propensity score analyses. Subgroup analyses were conducted by stratification of patients by endotracheal intubation. Among the 2533 eligible patients, 465 (18.4%) received therapeutic anticoagulation. After 1:1 propensity score matching (N = 383 pairs), in-hospital mortality was similar between those with therapeutic versus prophylactic anticoagulation (36.0% versus 30.0%, P = 0.091). In-hospital mortality regardless of endotracheal intubation were not significantly different between the two groups. Therapeutic anticoagulation was not associated with reduced or increased risk of in-hospital mortality in patients with COVID-19 treated with steroids.

Keywords COVID-19 · Mortality · Hemoglobin drop · Acute kidney injury

Highlights

- We investigated 2533 COVID-19 patients treated with steroids.
- We evaluated the effect of therapeutic versus prophylactic anticoagulation.
- After adjustments, in-hospital mortality was similar (36.0% versus 30.0%, P = 0.091).
- Therapeutic anticoagulation was not associated with better or worse mortality.

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Introduction

Previous observational and randomized studies suggested potential benefit of therapeutic anticoagulation during hospitalization, but this treatment remains controversial [1, 2]. As of June 30th 2021, steroids are the standard treatment of COVID-19 patients to reduce inflammation and cytokine storm associated with COVID-19 [3–5]. Initially, therapeutic anticoagulation seems to be preferred because COVID-19 causes inflammation and thrombosis, however, steroids were not frequently used in the initial phase of pandemic [6]. Therefore, we hypothesized that the results might be different if we selected patients who have been treated with steroid for COVID-19 and patients who needs steroids for

other underlying diseases. Herein, we aimed to investigate the association of prophylactic and therapeutic anticoagulation with mortality for patients with COVID-19 who were treated with steroids.

Methods

This retrospective study was conducted by review of the electronic medical records for 9965 patients with laboratory confirmed COVID-19 hospitalized in the Mount Sinai Health system between March 1st 2020 and March 30th 2021 [7–10]. Identification of COVID-19 was based on a nasopharyngeal swab, which was tested using a polymerase chain reaction. For the purpose of this study (examine the effectiveness of therapeutic versus prophylactic anticoagulation among patients on steroids), we limited our cohort to patients who were treated with steroids within 2 days of admission (n = 3984). We showed patients' baseline characteristics and in-hospital outcomes who were not treated with steroids in supplemental Table 1. Steroids were defined as treatment with systemic betamethasone, dexamethasone, hydrocortisone, prednisone, prednisolone, and methylprednisolone. We excluded patients age < 18 years old (n = 9) and those who were transferred to other facilities (n = 86). Then, we excluded 517 patients who were discharged within two days of admission (dead or alive) to mitigate the selection bias. We also limited the analysis to patients who received therapeutic or prophylactic anticoagulation within 2 days of admission to investigate the initial treatment choice for COVID-19 patients (n = 3110). Moreover we excluded patients with both prophylactic and therapeutic anticoagulation within 2 days of admission (n = 343). Finally, we excluded patients with atrial fibrillation (n = 207) and acute venous thromboembolism during hospitalization (n = 27) since these patients needed therapeutic anticoagulation unrelated to COVID treatment, resulting in the final cohort of 2533 patients. Therapeutic anticoagulation was defined as apixaban, dabigatran, rivaroxaban (excluding 2.5 mg as prevention of atherosclerotic cardiovascular events) [11], edoxaban, warfarin, and enoxaparin (as therapeutic dose), intravenous continuous unfractionated heparin, and argatroban. Prophylactic anticoagulation was defined as subcutaneous heparin or enoxaparin in prophylactic dose.

We reviewed patients' electronic medical records and extracted demographics, comorbidities, vital signs, laboratory data, and clinical outcomes. Patients were stratified into two groups, those with therapeutic or prophylactic anticoagulation. Comorbidities were characterized based on the ICD 10 codes. All vital signs and blood tests were recorded at the time of admission. The primary outcome of interest was the in-hospital mortality. Secondary outcomes are acute kidney injury, liver injury, hemoglobin drop, transfusion of red blood cell. Hemoglobin drop was defined as hemoglobin decline by more than 3 g/dL and acute kidney injury was defined as any increase of creatinine by more than 0.3 mg/dL or to more than 1.5 times baseline [12]. Liver injury was defined as ALT more than 5 × upper normal limit (46 U/L).

Continuous variables are presented as mean ± standard deviation or median [interquartile range] depending on the data distribution, and categorical variables were expressed as percentages. Differences in baseline characteristics between groups were evaluated, using the χ^2 test for categorical variables, and t-test or Wilcoxon test for continuous variables. We performed 1:1 match using the nearest neighbor with a caliper equal to 0.2 of the standard deviation of the logit of the propensity score [13]. The following variables were used to estimate propensity score: age, sex, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, obesity, hypertension, diabetes mellitus, cancer, atrial fibrillation, coronary artery disease, heart failure, estimated glomerular filtration rate (eGFR), blood urea nitrogen, white blood cell count, and hemoglobin, vital signs, tocilizumab, remdesivir, and treatment with convalescent plasma [5, 9, 14, 15]. The Modification of Diet in Renal Disease equation was used to estimate eGFR [12, 16].

In addition, as a sensitivity analysis, we performed inverse probability treatment weighted (IPTW) analysis to estimate the association of anticoagulation with in-hospital mortality. We imputed missing data using mice package (R software) and repeated propensity score matched and IPTW analysis.

We compared the in-hospital mortality between the propensity-score-matched patients with therapeutic versus prophylactic anticoagulation in the following subgroups: patients on endotracheal intubation, patients who did not have endotracheal intubation; patients were matched by re-estimated propensity score in each subgroup.

All statistical analyses were performed using R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria). P-values < 0.05 considered statistically significant.

Results

Among the 2533 eligible patients, 465 (18.4%) received therapeutic anticoagulation. The patients with therapeutic anticoagulation were older and had more comorbidities (Table 1) as compared to patients with prophylactic anticoagulation. Notably, patients with therapeutic anticoagulation strategies had higher d-dimer at admission than those with prophylactic anticoagulation. Table 2 showed crude in-hospital outcomes. Patients on therapeutic anticoagulation had lower in-hospital mortality compared to those who were not

Table 1 Baseline characteristics and in-hospital outcomes of patients admitted with COVID 19 by anticoagulation therapy (prophylactic versus therapeutic) before and after matching by propensity score

	Before propensity score matching				After propensity score matching		
	Patients with prophylactic anticoagulation N = 2068	Patients with therapeutic anticoagulation N = 465	P value	SMD	Patients with prophylactic anticoagulation N = 383	Patients with therapeutic anticoagulation N = 383	SMD
Age (years), mean (SD)	64.52 (16.00)	68.20 (14.94)	< 0.001	0.237	66.98 (14.81)	68.23 (15.18)	0.083
Male, n (%)	1146 (55.4)	268 (57.6)	0.413	0.045	244 (63.7)	226 (59.0)	0.097
Comorbidities							
Asthma, n (%)	159 (7.7)	22 (4.7)	0.033	0.123	15 (3.9)	19 (5.0)	0.051
COPD, n (%)	99 (4.8)	32 (6.9)	0.084	0.089	29 (7.6)	23 (6.0)	0.062
Hypertension, n (%)	687 (33.2)	174 (37.4)	0.094	0.088	141 (36.8)	144 (37.6)	0.016
Diabetes mellitus, n (%)	447 (21.6)	119 (25.6)	0.072	0.094	98 (25.6)	100 (26.1)	0.012
Obstructive sleep apnea, n (%)	55 (2.7)	11 (2.4)	0.843	0.019	12 (3.1)	10 (2.6)	0.031
Obesity	189 (9.1)	38 (8.2)	0.569	0.034	38 (9.9)	34 (8.9)	0.036
HIV, n (%)	36 (1.7)	6 (1.3)	0.627	0.037	9 (2.3)	6 (1.6)	0.057
Cancer, n (%)	150 (7.3)	42 (9.0)	0.225	0.065	42 (11.0)	38 (9.9)	0.034
Heart failure, n (%)	104 (5.0)	38 (8.2)	0.011	0.127	27 (7.0)	27 (7.0)	< 0.001
Coronary artery disease, n (%)	226 (10.9)	85 (18.3)	< 0.001	0.209	70 (18.3)	68 (17.8)	0.014
Vital signs							
Temperature, median [IQR]	37.89 [37.33, 38.83]	38.11 [37.44, 38.89]	0.025	0.058	38.22 [37.39, 39.06]	38.17 [37.44, 38.89]	0.011
Heart rate (/min), median [IQR]	95.00 [83.00, 107.00]	95.00 [83.00, 110.00]	0.45	0.086	95.00 [82.00, 109.00]	94.00 [82.00, 109.00]	0.007
Respiratory rate (/min), median [IQR]	20.00 [18.00, 22.00]	20.00 [18.00, 26.00]	< 0.001	0.324	20.00 [18.00, 24.00]	20.00 [18.00, 24.50]	0.019
Systolic blood pressure (mmHg), median [IQR]	131.00 [117.00, 146.00]	130.00 [116.75, 146.00]	< 0.001	0.01	129.00 [115.00, 144.00]	130.00 [115.00, 146.00]	0.078
Diastolic blood pressure (mmHg), median [IQR]	76.00 [67.00, 85.00]	74.00 [66.00, 84.00]	< 0.001	0.09	74.00 [66.00, 84.00]	4.00 [66.00, 83.00]	0.001
O_2 saturation (%), median [IQR]	90.00 [83.00, 92.00]	84.00 [70.00, 90.00]	< 0.001	0.347	87.00 [75.00, 91.00]	85.00 [73.50, 90.00]	0.025
Blood tests							
White blood cell (K/μL), median [IQR]	6.80 [5.14, 9.50]	8.20 [6.00, 11.70]	< 0.001	0.23	7.30 [5.60, 10.30]	7.90 [5.91, 10.80]	0.007
Hemoglobin (g/dL), median [IQR]	13.40 [12.10, 14.60]	12.90 [11.30, 14.40]	< 0.001	0.236	13.10 [11.70, 14.40]	12.90 [11.40, 14.40]	0.074
eGFR (mL/min/1.73m^2), median [IQR]	75.91 [52.13, 96.34]	61.46 [33.47, 83.92]	< 0.001	0.273	68.05 [39.22, 90.97]	61.67 [34.21, 85.50]	0.077
Blood urea nitrogen (mg/dL), median [IQR]	17.00 [12.00, 26.00]	23.00 [15.00, 39.00]	< 0.001	0.4	20.00 [13.50, 36.50]	22.00 [15.00, 37.00]	0.003
Aspartate aminotransferase, (U/L), median [IQR]	43.00 [28.00, 64.75]	44.00 [29.00, 67.50]	0.52	0.108	47.00 [30.00, 68.50]	42.50 [29.00, 68.00]	0.085

Table 1 (continued)

	Before propensity score matching				After propensity score matching		
	Patients with prophylactic anticoagulation N = 2068	Patients with therapeutic anticoagulation N = 465	P value	SMD	Patients with prophylactic anticoagulation N = 383	Patients with therapeutic anticoagulation N = 383	SMD
Alanine Aminotransferase, (U/L), median [IQR]	31.00 [20.00, 51.00]	30.00 [18.00, 57.00]	0.67	0.106	33.00 [20.00, 56.00]	31.00 [18.00, 57.00]	0.043
C reactive protein (mg/L), median [IQR]	85.60 [42.41, 150.30]	126.66 [59.77, 214.30]	< 0.001	0.393	105.50 [48.65, 194.25]	117.20 [55.66, 207.17]	0.064
D-Dimer (μg/mL), median [IQR]	1.15 [0.69, 2.00]	1.67 [0.83, 3.18]	< 0.001	0.334	1.39 [0.74, 2.75]	1.64 [0.81, 3.17]	0.065
PT-INR, median [IQR]	1.10 [1.00, 1.20]	1.20 [1.10, 1.30]	< 0.001	0.423	1.10 [1.00, 1.20]	1.20 [1.10, 1.30]	0.346
APTT (second), median [IQR]	32.40 [29.40, 35.90]	33.30 [29.60, 39.00]	< 0.001	0.267	33.40 [30.20, 36.68]	33.60 [29.90, 39.20]	0.165
Treatment							
Use of tocilizumab, n (%)	61 (2.9)	32 (6.9)	< 0.001	0.183	21 (5.5)	23 (6.0)	0.022
Use of remdesivir, n (%)	887 (42.9)	154 (33.1)	< 0.001	0.202	141 (36.8)	129 (33.7)	0.066
Convalescent Plasma, n (%)	430 (20.8)	141 (30.3)	< 0.001	0.22	127 (33.2)	113 (29.5)	0.079

APTT activated partial thromboplastin time, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *IL-6* interleukin-6, *IQR* interquartile range, *PT-INR* prothrombin time and international normalized ratio, *SD* standard deviation, *SMD* standardized mean difference

Table 2 In-hospital outcomes for patients with prophylactic vs. therapeutic anticoagulation

	Before propensity score matching			After propensity score matching		
	Patients with prophylactic anticoagulation N = 2068	Patients with therapeutic anticoagulation N = 465	P value	Patients with prophylactic anticoagulation N = 383	Patients with therapeutic anticoagulation N = 383	P value
In-hospital mortality	424 (20.5)	173 (37.2)	< 0.001	115 (30.0)	138 (36.0)	0.091
ICU admission	461 (22.3)	194 (41.7)	< 0.001	131 (34.2)	150 (39.2)	0.177
Endotracheal intubation	268 (13.0)	134 (28.8)	< 0.001	78 (20.4)	100 (26.1)	0.072
Acute kidney injury			< 0.001			0.451
No acute kidney injury	1603 (77.6)	277 (59.6)		255 (66.6)	235 (61.4)	
Stage 1	158 (7.6)	49 (10.5)		35 (9.1)	39 (10.2)	
Stage 2	56 (2.7)	28 (6.0)		15 (3.9)	21 (5.5)	
Stage 3	249 (12.1)	111 (23.9)		78 (20.4)	88 (23.0)	
Liver injury	268 (13.0)	134 (28.8)	< 0.001	78 (20.4)	100 (26.1)	0.072
Hemoglobin drop > 3 g/dL	306 (14.8)	105 (22.6)	< 0.001	77 (20.1)	79 (20.6)	0.929
Transfusion of red blood cell	94 (4.5)	52 (11.2)	< 0.001	23 (6.0)	37 (9.7)	0.080

treated with prophylactic anticoagulation. They also experienced higher AKI and liver injury, hemoglobin drop > 3 g/dL, and transfusion (Table 2).

After matching by propensity score (N = 383 in each group), baseline characteristics and in-hospital treatments were well balanced, with standardized differences of < 0.10 (Table 1). In-hospital mortality was not significantly

Table 3 In hospital mortality for subgroups of patients' stratified by endotracheal intubation

	Before propensity score matching in each subgroup			After matching by propensity score in each subgroup		
	Patients with prophylactic anticoagulation	Patients with therapeutic anticoagulation	P value	Patients with prophylactic anticoagulation	Patients with therapeutic anticoagulation	P value
Patients without endotracheal intubation	N = 268 219 (81.7%)	N = 134 98 (73.1%)	0.063	N = 89 71 (79.8%)	N = 89 65 (73.0%)	0.38
Patients with endotracheal intubation	N = 1800 205 (11.4%)	N = 331 75 (22.7%)	< 0.001	N = 286 59 (20.6%)	N = 286 68 (23.8%)	0.42

different between patients with therapeutic anticoagulation and those with prophylactic anticoagulation (Table 2). In addition, ICU admission, endotracheal intubation, acute kidney injury, liver injury, hemoglobin drop > 3 g/dL, and transfusion were not significantly different. Furthermore, IPTW and multiple imputation for missing data did not change the result (therapeutic versus prophylactic; odds ratio [95% confidential interval] 1.06 [0.81–1.39], P = 0.67]; 1.07 [0.77–1.50], P = 0.68, respectively).

Subgroup analyses are shown in Table 3. Patients with therapeutic anticoagulation did not have significantly different in-hospital mortality compared to those with prophylactic anticoagulation in the subgroup of patients with or without endotracheal intubation (Table 3).

Discussion

In this study, we could not reveal the survival benefit of therapeutic anticoagulation over prophylactic anticoagulation. Previous observational data demonstrated no significant different mortality between these treatments [1] and our data validated the results among patients with the current standard treatment of steroids. Although COVID-19 triggers hypercoagulable state, therapeutic anticoagulation was not proven to reduce in-hospital mortality with the treatment by steroids.

Thromboembolism due to COVID-19 related coagulopathy is the major complication [17–25]. Herein, in the early phase of pandemic, therapeutic dose of anticoagulation was associated with a decreased risk of mortality [1, 6]. However, given the data in the early phase of pandemic, the use of steroids were not clear. Steroids were proven to be effective to decrease the risk of death due to COVID-19 since they reduce cytokine storm [3–5]. Our study showed that no benefit was observed in therapeutic anticoagulation over prophylactic anticoagulation for COVID-19 patients with steroids, which could be interpreted that steroid and prophylactic anticoagulation is usually enough to treat COVID-19 patients.

There are several ongoing randomized trials of therapeutic anticoagulation targeting hospitalized patients with COVID-19, demonstrating conflicting results [26–30], which will further elucidate which anticoagulation is necessary for COVID-19 patients, especially treated with steroids. Interestingly, the recent report demonstrated no benefit of therapeutic anticoagulation for critically ill patients with COVID-19, which supported our findings [31], however, therapeutic anticoagulation was shown to be beneficial for non-critically ill patients with COVID-19 in organ support-free days, but not for survival until hospital discharge [32]. Further investigation is warranted.

Our study has several limitations. First, this is a retrospective observational study. Despite rigorous adjustments including multiple imputation for missing data and propensity score analyses, we could not exclude unmeasured confounders. Second, we do not have complete information on the indication for therapeutic anticoagulation, including history of venous thromboembolism, other thrombi, and mechanical valvular surgery.

In conclusion, prophylactic versus therapeutic anticoagulation showed similar in-hospital mortality of COVID-19 patients treated with steroids. Our data supports prophylactic anticoagulation for COVID-19 patients treated with steroids.

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Author contributions TK, MT, NE, had full access to all the data in the study and takes 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: All authors. Drafting of the manuscript: TK. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: TK, MT. Administrative, technical, or material support: NE. Study supervision: NE.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the institutional review boards of Icahn School of Medicine at Mount Sinai (#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 boards.

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