



Thrombotic complications and anticoagulation in COVID-19 pneumonia: a New York City hospital experience

Ahmad Hanif¹ · Sumera Khan² · Nikhitha Mantri² · Sana Hanif² · Muhamed Saleh² · Yamini Alla² · Siddharth Chinta² · Nikee Shrestha² · Wenyan Ji³ · Kristopher Attwood³ · Muhammad Adrish⁴ · Kevin R. Jain¹

Received: 27 May 2020 / Accepted: 10 August 2020 / Published online: 17 August 2020
© Springer-Verlag GmbH Germany, part of Springer Nature 2020

Abstract

Infection with SARS-CoV-2 (COVID-19) can cause prothrombotic complications. We aim to study the frequency of thrombotic complications and impact of anticoagulation on outcomes in hospitalized patients. We conducted a retrospective chart review of 921 consecutive patients admitted to our hospital with COVID-19. Patients were divided into four groups depending on whether they were on anticoagulation prior to admission, started anticoagulation during the admission, received prophylactic anticoagulation, or did not receive any anticoagulation. At the time of analysis, 325 patients (35.3%) had died, while 544 patients (59%) had been discharged resulting in inpatient mortality of 37.3%. Male sex, age > 65 years, and high D-dimer at admission were associated with higher mortality. Sixteen patients (1.7%) had venous thromboembolism confirmed with imaging, 11 patients had a stroke, and 2 patients developed limb ischemia. Treatment with therapeutic anticoagulation was associated with improved inpatient mortality compared with prophylactic anticoagulation alone (63% vs 86.2%, $p < 0.0001$) in patients requiring mechanical ventilation. Other outcomes such as rates of liberation from mechanical ventilation and duration of mechanical ventilation were not significantly impacted by the type of anticoagulation.

Keywords COVID-19 · Thrombosis · Anticoagulation · Mortality · Venous thromboembolism

Introduction

The coronavirus pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the disease first appeared in December 2019, it has been spreading rapidly throughout the world. Infection with SARS CoV-2 (COVID-19) can result in a wide range of symptoms [1].

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00277-020-04216-x>) contains supplementary material, which is available to authorized users.

✉ Ahmad Hanif
ahhanif@BronxCare.org

¹ Department of Medicine, Division of Hematology & Oncology, BronxCare Hospital Center, Bronx, NY, USA

² Department of Medicine, BronxCare Hospital Center, Bronx, NY, USA

³ Department of Biostatistics, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

⁴ Department of Medicine, Division of Pulmonary and Critical Care, BronxCare Hospital Center, Bronx, NY, USA

Patients who develop pneumonia usually require admission to hospital for respiratory support and tend to have a poor prognosis. Although initially considered to be a predominantly respiratory infection, COVID-19 has been shown to have multiorgan involvement. A study by Tang et al. showed that elevated D-dimer levels correlate with higher mortality and prophylactic anticoagulation improves outcomes in hospitalized patients [2]. There is growing evidence that COVID-19 produces a procoagulant state with both micro-thrombi and macro-thrombi observed in an autopsy series [3, 4]. The mechanisms behind the thrombotic state induced by COVID-19 are incompletely understood but likely include endothelial dysfunction and platelet activation due to cytokine storm leading to stasis and thrombus formation [5, 6]. Expert guidelines have emerged for anticoagulation management in patients with severe COVID-19; however, there is a paucity of data regarding the efficacy of anticoagulation in these patients [7]. Furthermore, these patients are prone to coagulopathy, which can theoretically increase the risk of bleeding compounded by the use of therapeutic anticoagulation [8, 9].

We at BronxCare Hospital have been employing therapeutic anticoagulation in patients with high clinical suspicion of micro-

thrombotic disease. Here, we report our experience with anticoagulation in a large number of patients treated at a community hospital in New York City. The purpose of this study is to help clarify the risk of prothrombotic complications in patients admitted to the hospital with severe COVID-19 and assess the impact of anticoagulation on outcomes of these patients.

Methods

The study was approved by the institutional review board. We conducted a retrospective chart review of all adult patients who were admitted to BronxCare Hospital Center between March 15 and April 14 of 2020 with a diagnosis of COVID-19 pneumonia. Patients who were discharged from emergency room and who were admitted for reasons other than COVID-19 pneumonia were excluded from the study. Patients were divided into 4 cohorts: those receiving therapeutic anticoagulation prior to admission (Prior_AC), those started on therapeutic anticoagulation during the admission (New_AC), those who received prophylactic anticoagulation only during the hospital stay (Prophy), and patients who did not receive any anticoagulation (No_AC). Patient demographics, anticoagulation status, results of coagulation tests, and outcomes including inpatient mortality, dependency on mechanical ventilation, clinically significant bleeding, and length of stay were recorded and herein reported. Clinically significant bleeding was defined as any bleeding requiring or resulting in red cell transfusion, cessation of anticoagulation, or administration of reversal agents. Thrombotic complications were defined as imaging-confirmed venous thromboembolism, stroke, or limb ischemia. Peak D-dimer level was defined as the highest level of D-dimer level obtained at any point during the admission.

Statistical analysis

Patient characteristics were summarized by group using the median for continuous variables and frequencies for categorical variables. Comparisons were made using the Kruskal–Wallis and Fisher's exact tests, as appropriate. Binary outcomes (e.g. mortality) were compared between group using Fisher's exact test or using logistic regression models for continuous measures (e.g. D-dimer levels). Time-to-event outcomes (e.g. duration of ventilation) were compared using the log-rank test. All analyses were conducted in SAS v9.4 (Cary, NC) at a significance level of 0.05.

Results

A total of 1308 patients were reviewed. All patients had confirmation of COVID-19 infection by RNA detection of

SARS-CoV-2 by nasopharyngeal swab. Three hundred eighty-seven patients were excluded of which 377 patients were not admitted to the hospital, 5 patients with age less than 18 years, 4 patients admitted for reasons other than COVID-19 pneumonia, and 1 patient was transferred to another hospital. Nine hundred twenty-one patients were included in the analysis. Thirty-three patients were on therapeutic anticoagulation prior to admission and were continued on it during hospital stay (28 on direct oral anticoagulants (DOAC) and 5 on warfarin). One hundred ninety-one patients were started on therapeutic anticoagulation during hospital admission. Out of these 191 patients, 102 were started on a DOAC, 68 on low molecular weight heparin and 21 on unfractionated heparin. One hundred seventy-two patients (90%) were started on anticoagulation due to high clinical suspicion of microthrombotic disease, while 19 patients (10%) were started due to thrombotic complications. Six hundred seventy-two patients received only prophylactic anticoagulation during admission, and 25 patients did not receive any anticoagulation. There were no significant differences in age, sex, and BMI among the groups (see Table 1). Patients in New_AC group had a higher D-dimer level at admission and peak D-dimer during admission compared with other groups.

At the time of analysis, 325 patients (35.3%) had died, while 544 patients (59%) had been discharged resulting in inpatient mortality of 37.3%. Age greater than 65 years was associated with higher mortality. Female sex was protective, 29.1% vs 61% (OR 0.64, 95% CI: 0.48–0.85, $p = 0.0023$). Patients in Prophy group had lower mortality compared with New_AC group (32.4% vs 45%, $p = 0.0014$); mortality was not significantly different between other groups. However, among the patients requiring mechanical ventilation, patients who were started on therapeutic anticoagulation had lower inpatient mortality compared with those who were continued on prophylactic anticoagulation (63% vs 86.2%, $p < 0.0001$). Of the 323 patients (35.1%) who were started on mechanical ventilation, patients in New_AC group were more likely to have received mechanical ventilation during hospital admission (119 of 191, 63% $p < 0.001$). At the time of analysis, 53 patients (16.4%) were successfully liberated from mechanical ventilation; rates were not significantly different between groups. The duration of mechanical ventilation was similar among the groups. Length of hospital stay was significantly higher in the New_AC group (11 days) compared with other 3 groups (Prior_AC: 7.7 days, Prophy: 5.7 days, No_AC: 5.2 days; $p < 0.0001$). The outcome results are summarized in Table 2.

Out of 921 patients 16 patients (1.7%) had venous thromboembolism (VTE) confirmed with imaging, 11 patients had an ischemic stroke, and 2 patients developed limb ischemia. On univariate analysis, the D-dimer levels at admission and peak D-dimer levels were associated with higher inpatient mortality, rate of intubation, and thrombotic complications.

Table 1 Baseline characteristics and outcomes by type of anticoagulation

Variable	All <i>n</i> = 921 (%)	Prior_AC <i>n</i> = 33 (%)	Prophy <i>n</i> = 672 (%)	New_AC <i>n</i> = 191 (%)	No_AC <i>n</i> = 25 (%)	<i>p</i> -value	
Age (year, median)	62.0	68.0	62.0	62.0	64.0	0.303	
Sex	Female	347 (37.7)	13 (39.4)	259 (38.5)	68 (35.6)	7 (28)	0.677
	Male	574 (62.3)	20 (60.6)	418 (61.5)	123 (64.4)	18 (72)	
Race	Black	260 (33.8)	17 (56.7)	181 (32.4)	55 (34.2)	7 (36.8)	0.210
	Asian	17 (2.2)		11 (2)	5 (3.1)	1 (5.3)	
	Hispanic	472 (61.4)	13 (43.3)	350 (62.6)	99 (61.5)	10 (52.6)	
	Caucasian	20 (2.6)		17 (3)	2 (1.2)	1 (5.3)	
BMI (kg/m ² , mean)	30.4	30.1	30.5	30.6	27.5	0.231	
D-dimer at admission (ng/mL, mean)	3190	2149	2550	5217	2990	< 0.001	
Peak D-dimer level (ng/mL, mean)	6206	4231	3652	14317	3173	< 0.001	
Intubated	323 (35.1)	11 (33.3)	188 (28)	119 (62.6)	2 (20)	< 0.001	
Successfully extubated [†]	53 (16.4)	2 (18.1)	24 (12.7)	27 (22.6)	0	0.077	
Median days on mechanical ventilation (Range) [‡]	4 (1–14)	3	3	4	0	0.834	
Intra-hospital bleeding	35 (4.1)	3 (10)	11 (1.7)	19 (11.4)	2 (10.5)	< 0.001	
Length of stay (days, median) [*]	9.0	8.8	7.4	15.3	5.6	< 0.001	

Abbreviations: *Prior_AC* patients on anticoagulation prior to admission and continued during hospitalization, *Prophy* patients who received only prophylactic anticoagulation, *New_AC* patients who were started on therapeutic anticoagulation during hospitalization, *No_AC* patients who did not receive any anticoagulation, *BMI* body mass index

[†] Percentages are calculated for intubated patients only

[‡] Only in extubated patients

^{*} Only in patients who were discharged from the hospital

These associations are summarized in Table 3. None of the patients in *Prior_AC* group had thrombotic complications. Thirty-five patients (4.1%) had clinically significant bleeding; patient in *Prophy* group had less incidence of bleeding complications (1.7%) compared with other groups. Among these 35 patients, 18 required transfusion support, 4 were given reversal agents, and there were 2 deaths attributed to bleeding. On univariate analysis, starting therapeutic anti-coagulation during admission and peak D-dimer levels, but not D-dimer levels at admission, was associated with risk of bleeding (see Table 3).

Discussion

Thrombotic complication, both macro- and micro-thrombotic, is a major concern among physicians involved in the treatment of patients admitted to the hospital with COVID-19. Our study describes the outcomes of 921 predominantly Hispanic and Black patients stratified by the type of anticoagulation received during the hospital admission. We analyzed a group of patients already on therapeutic anticoagulation at admission for various reasons, as a surrogate for starting anticoagulation early in the disease process. As previously described, male sex is associated with higher infection rate and worse mortality [10, 11]. We noticed a higher mortality rate in our population,

which is consistent with previous analyses showing Black and Hispanic patients have worse outcomes with COVID-19 [12, 13]. Our results show that patients on therapeutic anticoagulation had a higher mortality compared with patients on prophylactic anticoagulation. This is expected as patients who are started on therapeutic anticoagulation are generally sicker with higher D-dimer levels. This is evidenced by the higher D-dimer level at admission and higher peak D-dimer in these patients. When the analysis is limited to patients requiring mechanical ventilation, patients with therapeutic anticoagulation did better in terms of inpatient mortality. Recently, another study from a neighboring New York City hospital also found improved mortality with anticoagulation (29.1% vs 62.7%) in 395 intubated patients [14].

Interestingly, patients who were continued on therapeutic anticoagulation at admission did not differ from other groups in terms of outcomes, suggesting that early anticoagulation in these patients may not be relevant. However, the number of patients in this group was small, and therefore, definitive conclusions cannot be drawn. Predictably, the rates of mechanical ventilation and length of stay were higher in the *New_AC* group but not significant among other groups, again owing to the higher severity of disease in these patients. Other outcomes such as rates of liberation from mechanical ventilation and duration of mechanical ventilation were not significantly impacted by the type of anticoagulation.

Table 2 Determinants of inpatient mortality

Variables		Number	Dead	Inpatient mortality [§] (%)	p-value
Age (year)	< 55	267	42	15.7	< 0.001
	55–65	247	76	30.8	
	> 65	407	207	50.9	
Sex	Female	347	101	29.1	0.002
	Male	574	224	39.0	
Race	Black	260	95	36.5	0.29
	Hispanic	472	171	36.2	
	Asian	17	5	29.4	
	Caucasian	20	3	15.0	
	Unknown	152	51	33.6	
BMI (kg/m ²) [†]	< 25	198	74	37.4	0.17
	25–30	326	132	40.5	
	> 30	392	116	29.6	
Anticoagulation groups	Prior_AC	33	14	42.4	0.0014 [‡]
	Prophy	672	218	32.4	
	New_AC	191	86	45.0	
	None	25	7	28.0	
Anticoagulation groups (Only intubated patients)	Prior_AC	11	10	90.9	< 0.001*
	Prophy	188	162	86.2	
	New_AC	119	75	63	
	None	5	5	100	
Total		921	325	35.3	

Abbreviations: *Prior_AC* patients on anticoagulation prior to admission and continued during hospitalization, *Prophy* patients who received only prophylactic anticoagulation, *New_AC* patients who were started on therapeutic anticoagulation during hospitalization, *No_AC* patients who did not receive any anticoagulation, *BMI* body mass index

[§] Calculated at the time of analysis. Included patients who are not yet discharged

[†] BMI was unknown for some patients

[‡] *p*-value obtained through pair-wise comparisons is only significant for Prophy vs New_AC

**p*-value obtained through pair-wise comparisons is only significant for New_AC vs Prophy

The rate of VTE in our patients was 1.7%, which is higher than usual hospitalizations, but other studies have reported a much higher incidence of VTE in patients with COVID-19

[15, 16]. There is a significant potential for under-diagnosis of VTE due to a higher threshold to obtain radiographic imaging in these patients secondary to concern for spread of infection. The

Table 3 Univariate analysis of outcomes with D-dimer as predictor

	Outcomes	Odds ratio (95% CI)	p-value
D-dimer at admission	Inpatient mortality	1.71 (1.35–2.16)	< 0.001
	Need for mechanical ventilation	1.2 (1.03–1.45)	0.02
	Successful extubation*	0.09 (0.01–1.29)	0.08
	Thrombotic complications	1.23 (1.00–1.51)	0.05
	Bleeding	1.13 (0.84–1.52)	0.41
Peak D-dimer	Inpatient mortality	1.69 (1.37–2.07)	< 0.001
	Need for mechanical ventilation	2.00 (1.59–2.52)	< 0.001
	Successful extubation*	1.02 (0.76–1.36)	0.91
	Thrombotic complications	1.21 (0.99–1.49)	0.067
	Bleeding	1.30 (1.01–1.68)	0.04

Abbreviations: *CI* confidence interval

*In the intubated patients only

study by Middeldorp et al. employed screening for asymptomatic patients, which also resulted in higher percentage of confirmed cases [16]. The risk of stroke in these patients has been demonstrated in previous studies and again found in our patient population as well [17, 18]. Patients who developed thrombotic complications had a higher D-dimer level at admission. It is hard to say if the high D-dimer in these patients was due to the thrombosis itself or a manifestation of the severity of the disease, but the very high D-dimer levels observed in these patients suggest that patients with higher severity of the disease are at higher risk for thrombotic events. None of the patients already on anticoagulation experienced thrombotic complications. This points towards a potential benefit for early anticoagulation. On the other hand, patients who were on only on prophylactic anticoagulation had less clinically significant bleeding. Zhang et al. recently reported the predictive value of D-dimer at admission for inpatient mortality [19]. Our study showed similar findings where D-dimer levels were predictive of inpatient mortality, need for mechanical ventilation, and thrombotic complications. There were also strong associations between peak D-dimer levels and need for mechanical ventilation. These findings suggest that D-dimer is a useful marker for gauging the severity of the disease and could be followed to predict adverse outcomes including the need for mechanical ventilation. During times of hospital overload, this knowledge can be a handy tool for rapid triage of patients with COVID-19.

Our study has several limitations; it is a retrospective series, and thus, the results need to be validated in a prospective research study. The exact timing of anticoagulation relative to the clinical adverse events in our patients is not examined, and therefore, its full impact is difficult to predict. A more extensive study with deep collection of data regarding comorbid conditions and their severity will be helpful to delineate the exact correlation of anticoagulation with outcomes.

Conclusion

Our retrospective study involving a predominantly minority patient population showed that hospitalized patients with COVID-19 are at risk for developing thrombotic complications, such as VTE, stroke, and limb ischemia. In our analysis, higher D-dimer levels at admission and peak D-dimers were associated with worse outcomes and can be used to select patients at risk of adverse events. Patients requiring mechanical ventilation carry a poor prognosis, and therapeutic anticoagulation may be of value in these patients. Further prospective studies with greater number of patients can help clarify the role of anticoagulation in patients with COVID-19

Contributions AH, MA, and KJ created and designed the study. AH, SK, NM, SH, MS, YA, SC, and NS collected the data. All authors contributed to writing and revising the manuscript.

Compliance with ethical standards

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

Ethical approval The study was approved by Institutional Review Board of BronxCare Hospital Center. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Code availability Not applicable

References

- Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al (2020) Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 382(18):1708–1720
- Tang N, Bai H, Chen X, Gong J, Li D, Sun Z (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 18(5):1094–1099
- Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS (2020) Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans [Internet]. *Pathology*. [cited 2020 Apr 15]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2020.04.06.20050575>
- Wichmann D, Sperhake J-P, Lütgehetmann M, et al (2020) Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. *Ann Intern Med*. <https://doi.org/10.7326/M20-2003>
- Connors JM, Levy JH (2020) COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. <https://doi.org/10.1182/blood.2020060000>
- Tapper H, Herwald H (2000) Modulation of hemostatic mechanisms in bacterial infectious diseases. *Blood*. 96(7):2329–2337
- Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M et al (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 18(5):1023–1026
- Connell NT, Battinelli EM, Connors JM (2020) Coagulopathy of COVID-19 and antiphospholipid antibodies. *J Thromb Haemost JTH*. <https://doi.org/10.1111/jth.14893>
- Mucha SR, Dugar S, McCrae K, et al (2020) Coagulopathy in COVID-19. *Cleve Clin J Med*. <https://doi.org/10.3949/ccjm.87a.ccc024>
- Jin J-M, Bai P, He W, Wu F, Liu X-F, Han D-M et al (2020) Gender differences in patients with COVID-19: focus on severity and mortality. *Front Public Health* [Internet]. [cited 2020 May 23];8. Available from: <https://www.frontiersin.org/articles/10.3389/fpubh.2020.00152/full>
- Meng Y, Wu P, Lu W, Liu K, Ma K, Huang L et al (2020) Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: a retrospective study of 168 severe patients. *PLoS Pathog* 16(4):e1008520
- Laurencin CT, McClinton A (2020) The COVID-19 Pandemic: a Call to Action to identify and address racial and ethnic disparities. *J Racial Ethn Health Disparities* 7(3):398–402
- Azar KMJ, Shen Z, Romanelli RJ, Lockhart SH, Smits K, Robinson S et al (2020) Disparities in outcomes among COVID-19 patients in a large health care system in California. *Health Aff Proj Hop* 1013777hlthaff202000598

14. Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg BS, Levin MA, et al (2020) Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol* [Internet]. [cited 2020 May 23]; Available from: <https://www.onlinejacc.org/content/early/2020/05/05/j.jacc.2020.05.001>
15. Venous thromboembolism in adult hospitalizations—United States, 2007–2009 [Internet]. [cited 2020 May 23]. Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6122a1.htm>
16. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA et al (2020) Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*
17. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP et al (2020) Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 382(20):e60
18. Mao L, Wang M, Chen S, He Q, Chang J, Hong C et al (2020) Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *medRxiv*. 25;2020.02.22.20026500.
19. Zhang L, Yan X, Fan Q, et al (2020) D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost JTH*. <https://doi.org/10.1111/jth.14859>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.