The Journal of Clinical Pharmacology
2020, 0(0) 1–5

DOI: 10.1002/jcph.1749

Empiric Therapeutic Anticoagulation and Mortality in Critically Ill Patients With Respiratory Failure From SARS-CoV-2: A Retrospective Cohort Study

John Ferguson, MD[1], Stacy Volk, PharmD[2], Thomas Vondracek, PharmD[3], John Flanigan, PharmD[4], and Andrew Chernaik, MD[5]

Abstract

The pathophysiology of respiratory failure associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains under investigation. One hypothesis is that progressive endothelial damage from the virus leads to microvascular thrombosis. It is uncertain if empiric therapeutic anticoagulation provides benefit over standard deep vein thrombosis (DVT) prophylaxis in critically ill patients with SARS-CoV-2. A retrospective cohort study was performed to evaluate adult patients admitted to the intensive care unit at 3 hospitals with polymerase chain reaction-confirmed SARS-CoV-2-associated respiratory failure requiring invasive mechanical ventilation. A Kaplan-Meier survival analysis was used to compare patients who were initiated on therapeutic anticoagulation prior to the time of intubation and those receiving standard DVT prophylaxis doses. The primary outcome was the difference in the 28-day mortality of patients between the 2 groups. Twenty-eight-day mortality did not differ between groups, occurring in 26.1% of patients who received therapeutic anticoagulation and 29.5% of those who received a prophylactic dose only (hazard ratio, 0.52; $P = .055$). There was no difference in 28-day mortality between groups in patients who were admitted with a serum D-dimer $\geq$ 2 µg/mL (hazard ratio, 0.67; $P = .41$). Empiric therapeutic anticoagulation in patients who require invasive mechanical ventilation for confirmed SARS-CoV-2 infection does not improve 28-day mortality compared with standard DVT prophylaxis, even among those with elevated D-dimer levels.

Keywords

ARDS, COVID-19, SARS-CoV-2, therapeutic anticoagulation

The pathophysiology of respiratory failure associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains under investigation. It is hypothesized that direct endothelial damage from the virus progresses to microvascular thrombosis.[1] Activation of coagulation pathways follows because of overproduction of proinflammatory cytokines, including tumor necrosis factor, interleukin 6, and interleukin 1ß, leading to thrombin formation.[2] Progressive microvascular dysfunction in the pulmonary capillaries subsequently leads to disseminated intravascular coagulation, hypoxic vasoconstriction, and tissue injury.[1–3]

Among patients with SARS-CoV-2, levels of D-dimer, fibrin degradation products, and fibrinogen are elevated, whereas prothrombin time is reduced.[4–5] D-dimer is greater in patients with a greater severity of illness.[5] Survivors of SARS-CoV-2 on average have lower D-dimer than nonsurvivors, and those with a D-dimer > 1000 µg/mL have an odds ratio of more than 20 for death.[4]

In critically ill patients with SARS-CoV-2, the incidence of thrombotic complications, even with deep vein thrombosis (DVT) prophylaxis, is estimated to be 28% to 42.7%. These include predominantly pulmonary emboli and dialysis filter clotting.[6–10] Microthrombosis formation has been demonstrated on postmortem pathologic evaluation of patients who developed SARS-CoV-2, and clinically ischemic manifestations of thrombosis occur.[11] Empiric therapeutic anticoagulation improves oxygen delivery and might reduce mortality in critically ill patients.[12]

In the early phase of SARS-CoV-2 infection, our hospital system often implemented an aggressive anticoagulation strategy for patients with respiratory failure requiring admission to an intensive care unit. We hypothesized that therapeutic anticoagulation for

[1]Rocky Mountain Pulmonary and Critical Care, Wheat Ridge, Colorado, USA
[2]Lutheran Medical Center, Wheat Ridge, Colorado, USA
[3]Saint Joseph Hospital, Denver, Denver, Colorado, USA
[4]Good Samaritan Medical Center, Lafayette, Colorado, USA
[5]New West Physicians, Golden, Colorado, USA

Submitted for publication 7 August 2020; accepted 1 September 2020.

Corresponding Author:
John Ferguson, MD, Rocky Mountain Pulmonary and Critical Care. 3555 Lutheran Pkwy., Suite 150, Wheat Ridge, CO 80033
Email: jferguson@rockymtnpulmonary.com

respiratory failure caused by SARS-CoV-2 leads to improved survival in intubated patients.

Methods

Data Selection and Protocol

Ethics approval was obtained for this study through the local institutional review board (IRB). A retrospective cohort of adult patients admitted to the intensive care unit at 3 hospitals between March 15, 2020, and May 8, 2020, was evaluated after IRB approval was granted. Patients with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 respiratory failure necessitating invasive mechanical ventilation were included in the study. Patients who received empiric therapeutic anticoagulation prior to the time of intubation were included in the study group. Therapeutic anticoagulation was administered as either a continuous infusion of heparin dose-adjusted based on unfractionated heparin level or by subcutaneous 1 mg/kg twice daily or 1.5 mg/kg daily low-molecular-weight heparin (LMWH). LMWH dose adjustments were made based on anti-Xa levels in the event of renal insufficiency. Patients who were receiving oral anticoagulation prior to admission and remaining on anticoagulation were included in the therapeutic anticoagulation group. All patients in the control group received DVT chemoprophylaxis in the form of enoxaparin 40 mg subcutaneously daily, enoxaparin 30 mg twice daily, enoxaparin 0.5 mg/kg twice daily, or heparin 5000 units subcutaneously 2 or 3 times daily. Adjuvant therapies were administered at the discretion of the treating physician based on preferences and drug availability. A small number of patients were concurrently enrolled in a placebo-matched trial of sarilumab at the discretion of the treatment team.

Statistical Analysis

Statistics were performed using Stata version 15.1. The null hypothesis for all comparisons was determined to be a lack of difference. A 2-tailed α of 0.05 was specified for statistical significance. Kaplan-Meier survival analysis was performed at 28 days for all patients and for the prespecified cohort of patients with a baseline D-dimer > 2 μg/mL. Proportional Cox hazard ratio was used to compare survival between groups. Multivariate logistic regression analysis was performed using adjuvant treatment as independent variables to model survival.

Results

Demographics

One hundred and forty-one patients were identified among 3 hospitals in the same hospital system who required intubation for acute respiratory failure in the setting of confirmed SARS-CoV-2 by nasal/oral PCR. Forty-six patients received therapeutic anticoagulation, whereas 95 did not. Baseline demographics, comorbidities, and laboratory investigations were similar between groups (Table 1). A greater number of patients who were treated with therapeutic-dose anticoagulation received adjuvant convalescent plasma, whereas fewer patients received either adjuvant hydroxychloroquine or azithromycin (Table 1).

Table 1. Baseline Characteristics

	Therapeutic Dose Anticoagulation (n = 46)	Prophylactic Dose Anticoagulation (n = 95)	*P*
Demographics			
Age	65 (56-73)	63 (52-71)	.36
Male, n (%)	24 (52.2)	54 (56.8)	.60
Body mass index (kg/m^2)	30.1 (26.3-33.9)	30.7 (26.6-37.0)	.55
Diabetes mellitus, n (%)	13 (28.3)	21 (22.1)	.42
Laboratory values			
D-dimer (<0.50 μg/mL)	1.47 (0.92-3.02)	1.68 (0.95-3.14)	.76
Prothrombin time (11.5-15.5 seconds)	14.0 (13.2-16)	14.3 (13.4-15.2)	.71
Partial thromboplastin time (23-36 seconds)	38.5 (31.4-45)	37.3 931.7-41.9)	.91
C-reactive protein (<3 mg/L)	120 (43.6-200.5)	132.5 (104-179)	.24
Serum creatinine (0.7-1.3 mg/dL)	1.08 (0.94-1.47)	1.05 (0.81-1.32)	.21
Fibrinogen (200-475 mg/dL)	644.5 (489.5-762.55)	681 (601-708)	.79
Adjuvant treatment			
Hydroxychloroquine, n (%)	25 (54.3)	75 (78.9)	.003
Azithromycin, n (%)	22 (47.8)	66 (69.4)	.01
Convalescent plasma, n (%)	15 (32.6)	13 (13.7)	.01
Sarilumab/placebo,[a] n (%)	2 (4.3)	23 (24.2)	.004
Remdesivir,[a] n (%)	7 (15.2)	13 (13.7)	.80

Laboratory variables are expressed as median with interquartile range.
[a]Twenty-five patients (17.6%) were enrolled in a placebo-controlled study with sarilumab.

Mortality

The 28-day mortality was 26.1% (95%CI, 12.9%-39.3%) in patients who received therapeutic anticoagulation and 29.5% (95%CI, 20.2%-38.8%) in those who received a prophylaxis dose for DVT prevention (HR, 0.52; 95%CI, 0.26-1.04; $P = .055$); see Figure 1. In a multivariate logistic regression analysis, empiric therapeutic anticoagulation was associated with an odds ratio of death at 28 days of 0.73 (95%CI, 0.33-1.76), $P = .48$.

In the prespecified subgroup with a serum D-dimer ≥ 2 μg/mL, the 28-day mortality was 25% (95%CI, 6.3%-43.7%) in patients who received therapeutic anticoagulation (n = 24) and 23.8% (95%CI, 13.1%-34.6%)

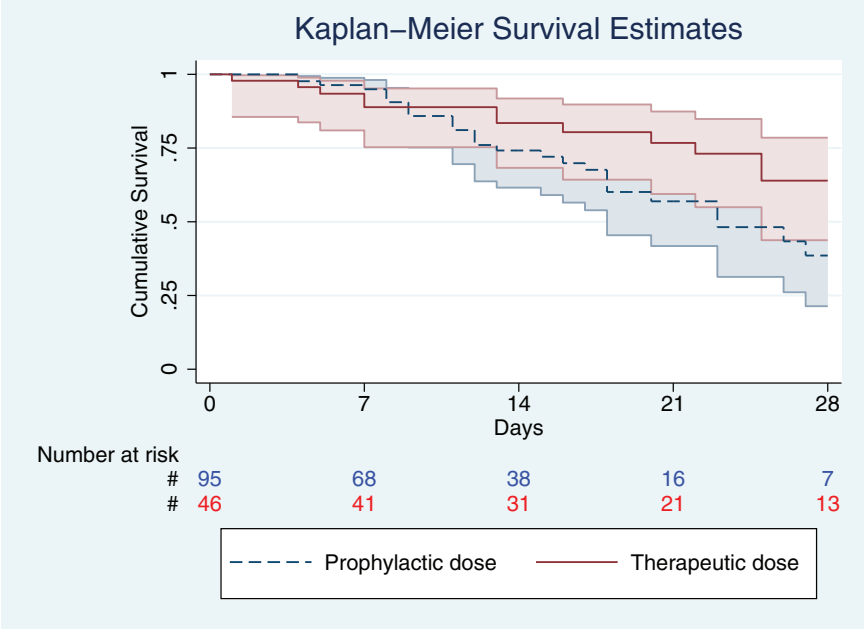

Figure 1. Kaplan-Meier survival curve at 28 days in all patients.

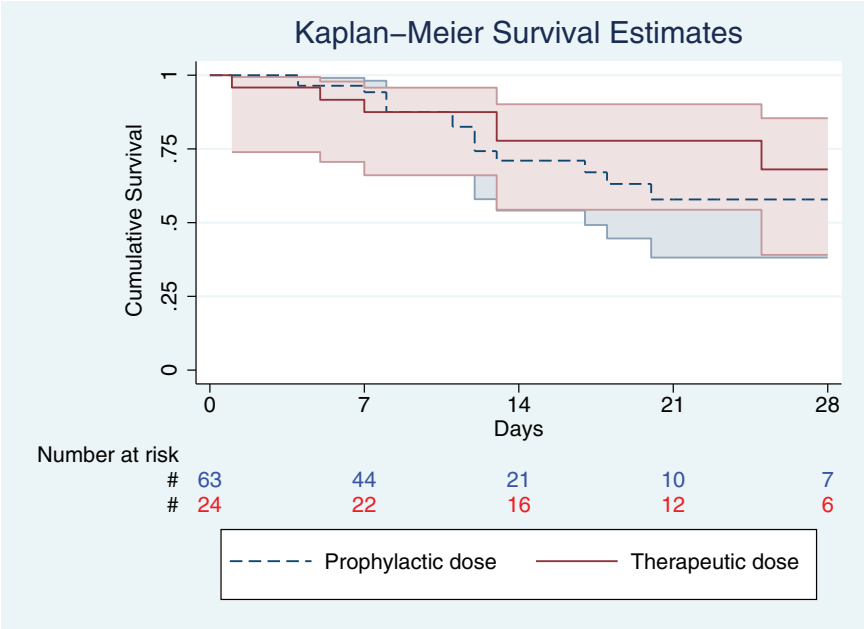

Figure 2. Kaplan-Meier survival curve at 28 days in patients with admission D-dimer > 2 μg/mL.

in those who received a prophylactic dose for DVT prevention (n = 63): HR, 0.67; 95%CI, 0.26%-1.74%; $P = .41$ (Figure 2).

Adverse Events

Twelve patients who received empiric therapeutic anticoagulation (25.5%) required a packed red blood cell (PRBC) transfusion for a hemoglobin below 7 g/dL, whereas 8 who were treated with DVT prophylaxis alone (7.6%) received a PRBC transfusion ($P = .01$). Patients who received therapeutic anticoagulation experienced 5 episodes of clinically apparent bleeding: 3 gastrointestinal events, 1 muscle hematoma, and 1 intracranial event. Those who received prophylactic-dose anticoagulation experienced 4 episodes of clinically apparent bleeding: 3 gastrointestinal events

and 1 tracheal bleeding event. There were no fatal bleeding events in either group.

Discussion

In a multicenter retrospective cohort of patients who required invasive mechanical ventilation for SARS-CoV-2 infection, therapeutic-dose anticoagulation did not improve mortality at 28 days compared with DVT prophylactic dosing alone.

A similar retrospective cohort evaluated 449 patients, 99 of whom were treated with prophylactic-dose anticoagulation.[13] There was no difference in 28-day mortality between patients receiving anticoagulation and those who did not. However, in those with elevated sepsis-induced coagulopathy scores or D-dimer levels greater than 6 times the upper limit of normal, the 28-day mortality was reduced with the use of prophylactic-dose anticoagulation.[13] Unlike the control group of this study, which received no amount of anticoagulation, all the patients in our cohort who did not receive therapeutic anticoagulation received some form of chemical DVT prophylaxis.

In contrast to our findings, another retrospective cohort study demonstrated that among 395 patients who required mechanical ventilation, the median survival was 21 days when receiving therapeutic anticoagulation, compared with 9 days in those who received standard care, including DVT chemoprophylaxis.[14] The inhospital mortality in the cohort receiving therapeutic anticoagulation was similar to ours (29.1% vs 30.4%); however, the mortality in the patients not receiving therapeutic anticoagulation was much higher than our own (62.7% vs 33.7%).

There are notable limitations in interpretation of our results. First, we did not evaluate all general medical ward patients who received empiric therapeutic anticoagulation. Whether empiric anticoagulation at the time of diagnosis reduces progression to intubation is uncertain. We chose time zero to be the day of intubation rather than hospital admission. Second, there was a difference between groups in adjuvant therapies administered. Based on available data, however, the difference in utilization of hydroxychloroquine is likely insignificant.[15] More patients who received therapeutic anticoagulation received convalescent plasma than those who received only prophylactic-dose anticoagulation, but this is also unlikely to have affected mortality among this cohort that required invasive mechanical ventilation.[16,17] These decisions were made by individual provider preferences rather than severity of illness, as all treated patients were critically ill with similar baseline characteristics. Last, because of the prolonged duration of illness associated with SARS-CoV-2 infection, 28-day mortality may be an insufficient length of time to recognize significant differences in outcomes.

Conclusions

In summary, patients who had acute respiratory failure requiring intubation because of SARS-CoV-2 infection showed no difference in 28-day mortality from time of intubation when empirically treated with therapeutic-dose anticoagulation compared with standard DVT prophylactic doses, even among those with D-dimer levels greater than 2 μg/mL. Although there were no deaths associated with bleeding complications, there was a significant increase in the number of patients who required transfusions among those who received therapeutic anticoagulation.

Conflicts of Interest

There are no conflicts of interest to report by any author.

Funding

There was no funding for this research.

Data Availability Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Statement of Authorship

All authors contributed to this study.

References

1. Varga Z, Flammer A, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020:395(10234):1417-1418.
2. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med*. 2020;8(6):e46-47.
3. Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect*. 2020;9(1):727-732.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
5. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020;58(7):1116-11120.
6. Maatman T, Farid J, Feizpour C, et al. Routine venous thromboembolism prophylaxis may be inadequate in the hypercoagulable state of severe coronavirus disease 2019. *Crit Care Med*. 2020;48(9):e783-e790. https://doi.org/10.1097/CCM.0000000000004466.
7. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter

prospective cohort study. *Intensive Care Med*. 2020;46(6):1089-1098.
8. Chen J, Wang X, Zhang S. Findings of acute pulmonary embolism in COVID-19 patients. *Lancet Infect Dis.* 2020;190: 58-59. https://doi.org/10.2139/ssrn.3548771.
9. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-147.
10. Thomas W, Varley J, Johnston A, et al. Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. *Thromb Res*. 2020;191:76-77.
11. Luo W, Yu H, Gou J, et al. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints.* 2020;2020020407.
12. Negri EM, Piloto BM, Morinaga LK, et al. Heparin therapy improving hypoxia in COVID-19 patients—a case series. *Preprints.* 2020. https://doi.org/10.1101/2020.04.15. 20067017. Accessed June 1, 2020.
13. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020;18(5):1094-1099.
14. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID19. *J Am Coll Cardiol*. 2020;76(1):122-124.
15. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. 2020;382(25):2411-2418.
16. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-10: a randomized clinical trial. *JAMA*. 2020;324(5):1-11.
17. Joyner, MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medrxiv*. 2020. https: //doi.org/10.1101/2020.08.12.20169359.