Received: 15 May 2020 | Revised: 21 May 2020 | Accepted: 23 May 2020

DOI: 10.1002/rth2.12398

COMMENTARY

rpth research & practice in thrombosis & haemostasis

Anticoagulation, immortality, and observations of COVID-19

Jason H. Maley MD[1] | Camille R. Petri MD[1] | Laura N. Brenner MD[1] | Raghu R. Chivukula MD, PhD[1] | Tiara F. Calhoun MD[2] | Vladimir Vinarsky MD[1] | Charles Corey Hardin MD, PhD[1]

[1]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, MA, USA

[2]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

Correspondence: Jason H. Maley, Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, 55 Fruit Street, Bulfinch 148, Boston, MA 02114, USA.

Email: jmaley@partners.org

Twitter: @JHMaley

The current coronavirus disease 2019 (COVID-19) pandemic has produced an understandable sense of urgency among clinicians and researchers to develop, deploy, and report novel treatment strategies. Many centers are therefore using off-label therapies and reporting early observational results of their experiences.[1-3] A similar situation arose during the 2014 outbreak of Ebola virus disease (EVD).[4] As discussed by Kalil,[5] that outbreak also generated intense interest in providing novel therapies outside the context of randomized controlled trials (RCTs). In fact, controversy erupted over whether RCTs were ethical given the urgent circumstances.[5] Ultimately, only 1 RCT was conducted, and no evidence-supported therapies were available at the time of the next outbreak of EVD in 2019.

For COVID-19, anticoagulation, in the absence of documented thrombosis, is one approach that has gained attention as a result of observational reports. Interest in the use of anticoagulation as a therapy for severe COVID-19 was first prompted by reports that biomarkers associated with thrombosis, such as D-dimer, are frequently elevated.[6] Additionally, multiple investigators reported an elevated rate of thrombotic events among patients with severe COVID-19 (ranging from 7% to >30%), and an association between elevated D-dimer and mortality.[7-10] In response, clinicians have advocated for protocols ranging from prophylactic anticoagulation to full-dose therapeutic anticoagulation, either in all patients or triggered by biomarkers.[11,12] To date, no RCTs of specific anticoagulation strategies have been reported, though many are under way.[13]

This is the context in which a research letter by Paranjpe and colleagues[2] was published online May 5, 2020, in the *Journal of the American College of Cardiology*. The authors report a retrospective cohort study examining the association between therapeutic anticoagulation and in-hospital mortality among patients with COVID-19. Of 2773 patients in the cohort who were treated within the Mount Sinai Health System in New York, 28% received some form of systemic anticoagulation during their hospital stay. The median time from admission to start of therapy was 2 days (interquartile range [IQR], 0-5 days) and median time on therapy was 3 days (IQR, 2-7 days). Mortality was similar among patients who received therapeutic anticoagulation (22.5%) and those who did not (22.8%). Patients who received therapeutic anticoagulation were more likely to require invasive mechanical ventilation (29.8% vs 8.1%; $P < .001$). In-hospital mortality was 62.7% (median survival, 9 days) among mechanically ventilated patients who did not receive anticoagulation. In contrast, in-hospital mortality was 29.1% among ventilated patients receiving anticoagulation. Rates of major bleeding between anticoagulated (3%) and nonanticoagulated (2%) patients were similar.

This report has gained substantial attention in the press, with some stories promoting this work as possible evidence of a causal link between anticoagulation and improved survival.[14] However, this study by Paranjpe and colleagues[2] has several important limitations that must be considered when interpreting these data. Among these limitations are confounding by indication, additional unmeasured confounders, and, most importantly, immortal time bias.

First, as with any observational study of a therapeutic intervention, we must consider the role of confounding, including confounding by indication and additional unmeasured confounders.

Confounding by indication occurs because clinicians chose to prescribe anticoagulation for some hospitalized patients based on a clinical indication. Conversely, patients who did not receive anticoagulation either did not have a clinical indication or may have had a contraindication such as advanced age, prior hemorrhage, or other bleeding risk factors. The first step in assessing the potential role and magnitude of this confounding is to understand the inherent differences between those patients exposed to the intervention of interest and those not exposed. Put simply, researchers and readers must ask the question: Why did clinicians choose to treat some patients with anticoagulation and not others? The authors do not provide any baseline patient characteristics or subgroup characteristics among mechanically ventilated patients who did and did not receive anticoagulation. We are not provided data on the clinical indications for anticoagulation in this cohort, institutional protocols, or diagnoses of thrombosis. Thus, readers unfortunately have no opportunity to understand why some patients were treated and some were not.

Additionally, it is notable that the reported mortality in the treated group is similar to mortality in several cohorts of critically ill patients with COVID-19.[15,16] Yet mortality in the untreated group is strikingly high. This raises concern for marked differences between the 2 groups, beyond simply their indication for anticoagulation. Therefore, even if the authors had provided characteristics of the groups and incorporated these into the analysis, additional unmeasured confounders likely preclude correct effect estimates. We are again limited in our ability to directly understand the groups, as the authors do not provide patient characteristics or description of the severity of respiratory failure.

Finally, and most importantly, immortal time bias certainly contributes to the observed treatment effect and may be the fatal flaw of this study.[17] Immortal time refers to the time period in observational studies between patients entering into a cohort and ultimately receiving an exposure of interest (Figure 1). For example, in the current study, patients enter into the cohort at the time of hospital admission. However, most patients in the cohort do not receive anticoagulation until days later. During this period between admission and anticoagulation, death cannot occur in the treatment group because those patients must, by design, survive long enough to receive treatment. In other words, the patients who survive to receive treatment are "immortal" between admission and treatment. Outcomes, such as death, that occur among patients during this immortal time can be attributed to only the "no anticoagulation" group. In the study by Paranjpe and colleagues,[2] the median time from admission to start of anticoagulation was 2 days (IQR, 0-5 days). Therefore, 50% of the treated cohort had 2 days of immortal time and 25% had at least 5 days. Once they receive treatment, these patients are classified as part of the anticoagulation treatment group, and anticoagulation "gets the credit" for their accumulated survival prior to treatment despite playing no role in that survival. In this manner, immortal time bias favors the treatment group in time-to-event analyses and mortality rates. Patients in this group accrue survival time and must be well enough to survive the duration of time between entry into the cohort and receipt of treatment.

Given that the authors do not provide characteristics of the patients in each group, we can look to the Kaplan-Meier survival curve provided in the manuscript to generate some hypotheses about bias. It is striking that by day 5 of admission, approximately 25% of patients in the "no anticoagulation" group have died. Yet the anticoagulation group remains, nearly universally, alive through day 5, at which point deaths begin to occur. Why? Immortal time bias may explain this observation. A patient who survived 5 days, then subsequently received anticoagulation, is assigned to the anticoagulation treatment group. Yet anticoagulation was not related to those 5 days of survival prior to treatment, as discussed earlier.

A related limitation of the study is the use of "days of anticoagulation" as an exposure in the survival model. A patient must be alive to receive the exposure, anticoagulation. If a patient lives longer, they receive more days of anticoagulation regardless of why they lived longer. This is a self-fulfilling prophecy. Patients who continue to be alive in the cohort receive more anticoagulation, and therefore the model associates more days of anticoagulation with lower daily hazard of death. For example, one could similarly examine the number of daily progress notes written for a patient and find that more cumulative daily progress notes are associated with lower risk of death—this is simply a function of more opportunity for exposure.

Observational research plays an important role in understanding the benefits and risks of treatments, particularly when clinical trials are not feasible. While it is essential to explore treatment approaches to COVID-19 in a timely manner, rapid publication of early observational data and amplification of these data in the press may also be detrimental if study limitations are not fully explored. Unfortunately, flawed analyses have appeared in many studies during the COVID-19 pandemic, often gaining widespread publicity. Some examples,

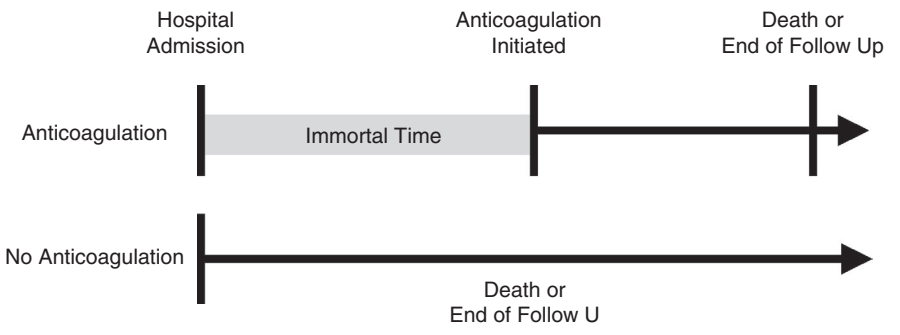

FIGURE 1 Immortal time accumulates between hospital admission and start of therapy for patients who ultimately join the treatment group, while outcomes among patients who do not receive treatment can occur immediately after hospital admission

susceptible to the biases we have discussed, include a small, uncontrolled study of hydroxychloroquine and azithromycin[3]; a report of remdesivir compassionate use[1]; and a retrospective study of interleukin-1 blockade.[18] Fortunately, there are also many ongoing RCTs of therapies for COVID-19, including anticoagulation, which will help determine the utility of these treatments. We eagerly await these data.

RELATIONSHIP DISCLOSURE

Dr Hardin reports receiving research funding from AstraZeneca. All other authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception, drafting, and final editing of this manuscript.

TWITTER

Jason H. Maley @JHMaley
Camille R. Petri @snurpycp
Laura N. Brenner @LauraNBrenner
Raghu R. Chivukula @chivukula_raghu
Tiara F. Calhoun @tiaraforsyth
Vladimir Vinarsky @vinarsky
Charles Corey Hardin @CoreyHardin2

REFERENCES

1. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020.
2. Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg BS, Levin MA, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020.
3. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020:105949.
4. 2014-2016 Ebola Outbreak in West Africa | History | Ebola (Ebola Virus Disease) | CDC [Internet]; 2020 . [Accessed 2020 May 8] Available from https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html
5. Kalil AC. Treating COVID-19-Off-label drug use, compassionate use, and randomized clinical trials during pandemics. JAMA. 2020;323(19):1897.
6. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020.
7. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020.
8. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med. 2020.
9. Klok FA, Kruip MJH, van der Meer NJM, Arbous MS, Gommers D, Kant KM. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID- 19: an updated analysis. Thromb Res. 2020;19:148–50.
10. Longchamp A, Longchamp J, Manzocchi-Besson S, Whiting L, Haller C, Jeanneret S, et al. Venous thromboembolism in critically ill patients with Covid- 19: results of a screening study for deep vein thrombosis. Res Pract Thromb Haemost. 2020.
11. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18:1094–9.
12. Cattaneo M, Bertinato EM, Birocchi S, Brizio C, Malavolta D, Manzoni M, et al. Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified? Thromb Haemost. 2020.
13. Search of: anticoagulation | COVID - List Results - ClinicalTrials.gov [Internet]. [Accessed 2020 May 13] Available from https://clinicaltrials.gov
14. Rodriguez A. Blood thinners could improve survival chances for sickest coronavirus patients, study says [Internet]. USA TODAY. USA TODAY; 2020. [Accessed 2020 May 14] Available from https://www.usatoday.com/story/news/health/2020/05/08/blood-thinners-and-covid-19-sickest-coronavirus-patients-may-benefit/3096262001/
15. Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med. 2020.
16. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323(20):2052.
17. Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Safety. 2007;16(3):241–9.
18. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325–e331.

How to cite this article: Maley JH, Petri CR, Brenner LN, et al. Anticoagulation, immortality, and observations of COVID-19. *Res Pract Thromb Haemost*. 2020;4:674–676. https://doi.org/10.1002/rth2.12398