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Letter to the Editors-in-Chief

The effect of anticoagulation on clinical outcomes in novel Coronavirus (COVID-19) pneumonia in a U.S. cohort

ABSTRACT

Background: COVID-19 infection is associated with D-dimer elevations, high rates of thrombus formation, and poor clinical outcomes. We sought to determine if empiric therapeutic anticoagulation (AC) affected survival in COVID-19 patients compared to standard prophylactic AC.

Methods: Retrospective analysis of 402 COVID-19 patients hospitalized between March 15 and May 31, 2020 was performed. Clinical outcomes were compared between 152 patients treated with therapeutic AC to 250 patients on prophylactic AC. An elastic net logistic regression was designed to first identify the important variables affecting mortality. These variables were then included as covariates to AC in standard multivariate logistic regression models studying the effect of AC on death. Nonparametric survival analysis was conducted, and Kaplan Meier curves were constructed.

Results: Increased mortality was associated with therapeutic AC [OR 3.42 (2.06, 5.67)]. The log-rank test was statistically significant at p = 0.001 showing higher mortality for patients treated with therapeutic AC compared to prophylactic AC. Subset analysis of critically ill and intubated patients had similar survival curves regardless of AC dose. The log-rank test was not significant even with Prentice modification. For non-ICU patients, the log rank test favoring prophylactic AC disappeared when the analysis was stratified by D-dimer level less or greater than 3 \( \mu \text{g/mL} \). Approximately 9% of patients receiving therapeutic AC experienced clinically significant bleeding or thrombocytopenia, versus 3% in those receiving prophylactic AC.

Conclusions: In our cohort, therapeutic anticoagulation provided no mortality benefit over thromboprophylaxis, independent of co-morbidities or disease severity. More adverse events were observed with therapeutic AC.
Baseline characteristics by anticoagulation status.  

|                     | Prophylactic AC (N = 250) | Therapeutic AC (N = 152) | Total (N = 402) | p value |
|---------------------|----------------------------|--------------------------|-----------------|---------|
| **Sex**             |                            |                          |                 |         |
| Female              | 120 (47.4%)                | 66 (44.3%)               | 186 (46.3%)     | 0.54    |
| Male                | 133 (52.6%)                | 83 (55.7%)               | 216 (53.7%)     |         |
| **Age**             |                            |                          |                 |         |
| <30                 | 12 (4.7%)                  | 4 (2.7%)                 | 16 (4.0%)       | 0.01    |
| 30–39               | 25 (9.9%)                  | 7 (4.7%)                 | 32 (8.0%)       |         |
| 40–49               | 32 (12.6%)                 | 15 (10.1%)               | 47 (11.7%)      |         |
| 50–59               | 48 (19.0%)                 | 29 (19.5%)               | 77 (19.2%)      |         |
| 60–69               | 58 (22.9%)                 | 35 (23.5%)               | 93 (23.1%)      |         |
| 70–79               | 43 (17.0%)                 | 31 (20.8%)               | 74 (18.4%)      |         |
| >80                 | 35 (13.8%)                 | 28 (18.8%)               | 63 (15.7%)      |         |
| **BMI over 30**     |                            |                          |                 |         |
| No                  | 77 (30.4%)                 | 45 (30.2%)               | 122 (30.3%)     | 0.96    |
| Yes                 | 176 (69.6%)                | 104 (69.8%)              | 280 (69.7%)     |         |
| **White**           |                            |                          |                 |         |
| No                  | 235 (92.9%)                | 140 (94.0%)              | 375 (93.3%)     | 0.68    |
| Yes                 | 18 (7.1%)                  | 9 (6.0%)                 | 27 (6.7%)       |         |
| **Hispanic**        |                            |                          |                 |         |
| No                  | 216 (85.4%)                | 128 (85.9%)              | 344 (85.6%)     | 0.88    |
| Yes                 | 37 (14.6%)                 | 21 (14.1%)               | 58 (14.4%)      |         |
| **BMI over 30**     |                            |                          |                 |         |
| No                  | 11 (4.3%)                  | 9 (6.0%)                 | 20 (5.0%)       | 0.45    |
| Yes                 | 242 (95.7%)                | 140 (94.0%)              | 382 (95.0%)     |         |
| **ICU admission**   |                            |                          |                 |         |
| No                  | 214 (84.6%)                | 80 (53.7%)               | 294 (73.1%)     | <0.01   |
| Yes                 | 39 (15.4%)                 | 69 (46.3%)               | 108 (26.9%)     |         |
| **Intubation**      |                            |                          |                 |         |
| No                  | 230 (90.9%)                | 109 (73.2%)              | 339 (84.3%)     | <0.01   |
| Yes                 | 23 (9.1%)                  | 40 (26.8%)               | 63 (15.7%)      |         |
| **Chronic pulmonary** |                           |                          |                 |         |
| disease             |                            |                          |                 | 0.69    |
| Missing             | 8                          | 0                        | 8               |         |
| Yes                 | 182 (74.3%)                | 108 (72.5%)              | 290 (73.6%)     |         |
| **Cancer**          |                            |                          |                 | 0.37    |
| Missing             | 8                          | 0                        | 8               |         |
| Yes                 | 232 (94.7%)                | 144 (96.6%)              | 376 (95.4%)     |         |
| **Cardiovascular**  |                            |                          |                 | <0.01   |
| disease             |                            |                          |                 |         |
| No                  | 157 (62.1%)                | 65 (43.6%)               | 222 (55.2%)     |         |
| Yes                 | 96 (37.9%)                 | 84 (56.4%)               | 180 (44.8%)     |         |
| **Hypertension**    |                            |                          |                 | 0.71    |
| No                  | 77 (30.4%)                 | 48 (32.2%)               | 125 (31.1%)     |         |
| Yes                 | 176 (69.6%)                | 101 (67.8%)              | 277 (68.9%)     |         |
| **Diabetes**        |                            |                          |                 | 0.53    |
| No                  | 144 (56.9%)                | 80 (53.7%)               | 224 (55.7%)     |         |
| Yes                 | 109 (43.1%)                | 69 (46.3%)               | 179 (44.3%)     |         |

- a Pearson’s Chi-squared test.  
- b Trend test for ordinal variables.

The initial survival curve showed significant difference between patients receiving therapeutic and prophylactic AC, the survival benefit disappeared once adjusted for disease severity, by performing subset analysis on critically ill requiring ICU admission (further stratified by intubation status) and non-critically ill patients. No statistical difference was found in either of the survival curves (Fig. 1). While our cohort of patients who were intubated and treated with therapeutic AC appeared to have a slightly higher survival probability as compared to patients who were on prophylactic AC, it was only seen during the first few days of AC treatment. This benefit disappeared after 4 days. Our median duration for therapeutic AC (7.2 days) was longer than the Mt. Sinai cohort (median duration of therapeutic AC = 3 days). Our results suggest that the survival benefit highlighted by Paranjbpe, et al. may represent a timing bias for effect of AC on survival for intubated patients [7].

Non-critically ill patients were examined as a whole and stratified based on D-dimer level. Fig. 1 illustrates all non-critically ill patients and shows a p value of 0.006 for the log-rank test, favoring prophylactic dose AC. This trend disappeared when the analysis was stratified by D-dimer level less or greater than 3 μg/mL. To our knowledge, ours is the first study that utilizes D-dimer for disease severity to stratify non-critically ill patients and compare the effect of therapeutic AC to prophylactic AC on in-hospital mortality.

Clinically significant adverse outcomes were defined as hemorrhage resulting in a decrease in hemoglobin greater than 2 g/dL with transfusion requirements, or a clinically significant decrease in platelet count (based on judgement of treating provider) resulting in discontinuation of any form of AC. Approximately 9% of our patients receiving therapeutic AC experienced clinically significant adverse events resulting in discontinuation of treatment; 11 patients had clinically significant bleeding while 3 patients developed clinically significant thrombocytopenia. This contrasts with the 3% risk seen in those patients receiving prophylactic AC. Our overall bleeding rate of 7.2% is higher than previously reported [7,8]. Out of the 11 patients in our therapeutic AC cohort who had clinically significant bleeding, 9 were critically ill and 3 of these patients had significant bleeding associated with ECMO. We suspect our higher bleeding rates are driven by this observation, when contrasting critically ill versus non-critically ill COVID-19 patients [9].

We recognize that our study has some limitations. We are unable to derive causality given the observational nature of the study. Further, our patients were not uniformly selected for therapeutic AC based on D-dimer or critical illness. Therapeutic AC was empirically initiated for ICU patients regardless the level of specific biomarker and critical illness was determined by bed location (ICU vs Medicine floor) without additional metrics to measure concurrently for disease severity.

Our analysis, however, identified no evidence that therapeutic AC empirically prescribed to patients with severe COVID-19 infection provides any mortality benefit over standard thromboprophylaxis, even after controlling for confounders including disease severity and comorbidities. We identified the degree of severity of infection as the primary driver of mortality, which was unaffected by the initiation of therapeutic AC.

Further, empiric initiation of therapeutic anticoagulation is not without serious consequences as there were significant hematologic adverse events in COVID-19 patients treated with therapeutic AC compared to usual thromboprophylaxis. Randomized prospective clinical trials are needed to ascertain the appropriate indications, patient selection, and dosing of AC in COVID-19 infection [10]. Future directions of study should consider the role of biomarkers of inflammation and coagulopathy in guiding therapeutic decisions. Despite the conduct power analysis. Power analysis conducted on the multivariate Cox model indicated a beta error of 13%.
limitations, our study provides important insight regarding the use of anticoagulation for COVID-19 patients. These findings may help inform clinical practice in this ongoing global crisis.

CRediT authorship contribution statement

L. Lynn, MD: Collected the data, contributed to the interpretation of the results, took the lead in writing the manuscript, provided critical feedback, helped shape the analysis and manuscript.

J. A. Reyes, MD MPH: Helped conceive the original idea and research plan, collected the data, contributed to the interpretation of the results, provided critical feedback, helped shape the analysis and manuscript.

K. Hawkins, MD: Contributed to the interpretation of the results, provided critical feedback, helped shape the analysis and manuscript.

A. Panda MS: Verified the analytical methods, contributed to the interpretation of the results, provided critical feedback.

L. Linville, MD: Collected the data. Discussed the results and contributed to the final manuscript.

Fig. 1. Survival curves for critically ill and non-critically ill patients.
W. Aldhahri, MD: Collected the data. Discussed the results and contributed to the final manuscript.
G. Kango, MD: Collected the data. Discussed the results and contributed to the final manuscript.
S. Shah, MD: Collected the data. Discussed the results and contributed to the final manuscript.
S. Ayanian, MD MS: Helped conceive the original idea and research plan, processed the experimental data, performed the analysis, contributed to the interpretation of the results, provided critical feedback, helped shape the analysis and manuscript.
K. Teufel, MD: Helped conceive the original idea and research plan, collected the data, contributed to the interpretation of the results, provided critical feedback, helped shape the analysis and manuscript.

Declaration of competing interest

The authors have no conflict of interest to disclose.

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Lei Lynn*a, Juan A. Reyes*a, Katrina Hawkinsb, Arjun Pandac, Laura Linvilleb, Walaa Aldhahrib, Ghazal Kangob, Sneha Shahb, Shant Ayanian, Karolyn Teufela

a Division of Hospital Medicine, The George Washington University School of Medicine and Health Sciences, The GW Medical Faculty Associates, Washington, DC, United States of America
b Department of Anesthesiology and Critical Care Medicine, The George Washington University School of Medicine and Health Sciences, The GW Medical Faculty Associates, Washington, DC, United States of America
c Department of Medicine, The George Washington University School of Medicine and Health Sciences, The GW Medical Faculty Associates, Washington, DC, United States of America

* Corresponding authors: 900 23rd St NW, Washington, DC 20037, United States of America.

E-mail addresses: Ldu@mfa.gwu.edu (L. Lynn), jreyes@mfa.gwu.edu (J.A. Reyes).