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Treatments Associated with Lower Mortality among Critically Ill COVID-19 Patients: A Retrospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- While the treatment of critically ill COVID-19 patients has improved, mortality rates remain high

What This Article Tells Us That Is New

- In a retrospective cohort consisting of 2,070 critically ill COVID-19 patients treated in six hospitals, multivariable regression analysis showed lower in-hospital mortality associated with apixaban, aspirin, or enoxaparin treatment
- Propensity score–matching analyses demonstrated lower mortality for patients receiving apixaban (27% [96 of 360] *vs.* 37% [133 of 360]), aspirin (26% [121 of 473] *vs.* 30% [140 of 473]), or enoxaparin (25% [87 of 347) *vs.* 34% [117 of 347]) compared to matched controls

ABSTRACT

Background: Mortality in critically ill COVID-19 patients remains high. Although randomized controlled trials must continue to definitively evaluate treatments, further hypothesis-generating efforts to identify candidate treatments are required. This study's hypothesis was that certain treatments are associated with lower COVID-19 mortality.

Methods: This was a 1-yr retrospective cohort study involving all COVID-19 patients admitted to intensive care units in six hospitals affiliated with Yale New Haven Health System from February 13, 2020, to March 4, 2021. The exposures were any COVID-19–related pharmacologic and organ support treatments. The outcome was in-hospital mortality.

Results: This study analyzed 2,070 patients after excluding 23 patients who died within 24 h after intensive care unit admission and 3 patients who remained hospitalized on the last day of data censoring. The in-hospital mortality was 29% (593 of 2,070). Of 23 treatments analyzed, apixaban (hazard ratio, 0.42; 95% CI, 0.363 to 0.48; corrected CI, 0.336 to 0.52) and aspirin (hazard ratio, 0.72; 95% CI, 0.60 to 0.87; corrected CI, 0.54 to 0.96) were associated with lower mortality based on the multivariable analysis with multiple testing correction. Propensity score–matching analysis showed an association between apixaban treatment and lower mortality (with *vs.* without apixaban, 27% [96 of 360] *vs.* 37% [133 of 360]; hazard ratio, 0.48; 95% CI, 0.337 to 0.69) and an association between aspirin treatment and lower mortality (with *vs.* without aspirin, 26% [121 of 473] *vs.* 30% [140 of 473]; hazard ratio, 0.57; 95% CI, 0.41 to 0.78). Enoxaparin showed similar associations based on the multivariable analysis (hazard ratio, 0.82; 95% CI, 0.69 to 0.97; corrected CI, 0.61 to 1.05) and propensity score–matching analysis (with *vs.* without enoxaparin, 25% [87 of 347] *vs.* 34% [117 of 347]; hazard ratio, 0.53; 95% CI, 0.367 to 0.77).

Conclusions: Consistent with the known hypercoagulability in severe COVID-19, the use of apixaban, enoxaparin, or aspirin was independently associated with lower mortality in critically ill COVID-19 patients.

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A Particular challenge of COVID-19 treatment is the high mortality, especially among critically ill patients. Although the mortality rate was estimated to be ~50% among critically ill COVID-19 patients in the early stage of the pandemic,[1] a study performed at a later stage of the pandemic showed a downward trend of mortality rates from ~44% to ~19%.[2] Effective treatments might be one factor responsible for this decline. Continuous efforts in discovering effective treatments are needed and have been ongoing as evidenced by the recent trials exploring the effectiveness of therapeutic *versus* prophylactic anticoagulation in hospitalized and critically ill patients.[3–5] With the passing of the COVID-19 pandemic's first anniversary and the surge of the Delta variant, a look back at the data accumulated over 1 yr provides an opportunity to identify potentially effective treatments. Such an approach could corroborate established treatments or generate hypotheses for future investigations.

This retrospective cohort study hypothesized that certain treatments would be associated with lower mortality in patients

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treated in intensive care units (ICUs) for COVID-19–related complications. Our objective was to identify the treatments associated with lower COVID-19 mortality based on multivariable analysis. The reproducibility of the associations identified by multivariable analysis was evaluated by propensity score–matching analysis. This study was based on all COVID-19 patients treated in the ICUs in hospitals affiliated with Yale New Haven Health System headquartered in New Haven, Connecticut.

Materials and Methods

Study Design

Yale University's Human Subject Protection Program initially approved this retrospective cohort study and waived informed consent on May 6, 2020 (institutional review board protocol no. 2000028070). The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

This study was based on all patients diagnosed with COVID-19 secondary to a SARS-CoV-2 infection and treated for COVID-19–related complications in the ICUs of six hospitals affiliated with Yale New Haven Health System (*i.e.*, Yale New Haven Hospital, Saint Raphael Campus, Greenwich Hospital, Bridgeport Hospital, Lawrence + Memorial Hospital, and Westerly Hospital). The study period was from February 13, 2020, when the first COVID-19 patient was admitted to the ICU at Yale, to March 4, 2021, when the COVID-19 ICU admission significantly declined. We included all COVID-19 patients admitted to Yale's ICUs during the study period to reflect the experience of treating critically ill COVID-19 patients throughout the first pandemic year.

Study Population

Inclusion criteria for this study included an age of 18 yr or older, a diagnosis of COVID-19 (based on real-time reverse transcription–polymerase chain reaction assay targeting three regions of the SARS-CoV-2 genome, namely orf1ab, spike [S] gene, and nucleocapsid [N] gene), and treatment in one of Yale New Haven Health System's ICUs at any time during the study period. COVID-19 patients who required organ support therapies or intensive monitoring and care were eligible for ICU admission at Yale. No patients were admitted to ICU purely for isolation. The respiratory criteria for ICU admission varied over time: when there were sufficient ICU resources, patients requiring noninvasive ventilation or invasive mechanical ventilation were admitted to the ICU; however, during the case surge, when ICU resources were inadequate, only patients requiring invasive mechanical ventilation were admitted to the ICU. Exclusion criteria for this study were death within 24 h after ICU admission, age of less than 18 yr, and continued hospitalization on the last day of data censoring. Patient care was per the institutional protocols customized for COVID-19 patients and continuously updated based on the evolving evidence.

Variables

The primary outcome was in-hospital mortality, defined as all-cause death that occurred during a patient's hospitalization. Patients were regarded as survivors if they were discharged alive from the hospital or as nonsurvivors if they died during hospitalization. We included patients who were admitted to Yale's ICUs up to March 4, 2021. The relevant information of those patients who remained hospitalized on March 4, 2021, was updated based on the electronic medical records on June 1, 2021 (*i.e.*, the last day of data censoring).

The treatments in this study were any COVID-19–related pharmacologic or organ support intervention instituted during a patient's hospitalization. The pharmacologic treatments included (1) antiviral drugs (*e.g.*, remdesivir and hydroxychloroquine); (2) anticoagulants (*e.g.*, enoxaparin, heparin, and apixaban); (3) antiplatelet agents (*e.g.*, aspirin, clopidogrel, and ticagrelor); (4) steroids (*e.g.*, dexamethasone, methylprednisolone, and hydrocortisone); (5) immunomodulators (*e.g.*, tocilizumab); (6) immunosuppressants (*e.g.*, tacrolimus); (7) vasopressors (*e.g.*, norepinephrine, epinephrine, and dopamine); and (8) uncategorized drugs (*e.g.*, azithromycin, convalescent plasma, and famotidine). Information on drug dose, timing, and duration of treatment was collected. The organ support therapies included (1) conventional oxygen therapy delivered using a regular nasal cannula or face mask; (2) high-flow nasal cannula; 3) bilevel positive airway pressure ventilation; (4) continuous positive airway pressure ventilation; (5) invasive mechanical ventilation; (6) continuous venovenous hemofiltration; and (7) extracorporeal membrane oxygenation.

The potential confounders were as follows: (1) the known risk factors for COVID-19 mortality (age, sex, and hypertension); (2) the severity of the acute illness during the first 24 h after ICU admission (Sequential Organ Failure Assessment score, Glasgow Coma Scale score, and invasive mechanical ventilation); (3) the various phases during the first pandemic year, *i.e.*, the first phase (February 1, 2020, to May 31, 2020), the second phase (June 1, 2020, to August 31, 2020), the third phase (September 1, 2020, to November 30, 2020), and the fourth phase (December 1, 2020, to March 4, 2021), with each patient assigned to a phase based on their ICU admission date; (4) the demographics and comorbidities; and (5) the laboratory results and vital signs during the first 24 h after ICU admission.

Data Sources and Measurement

The measurements of all variables of interest were conducted in routine patient care guided by the institutional protocols customized for COVID-19 patients and continuously updated based on the evolving evidence. Patient data were extracted from the electronic medical records by the Joint Data Analytics Team at the Yale Center for Clinical Investigation. This team centralizes and coordinates clinical

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and research analytics and reporting across the Yale New Haven Health System and Yale School of Medicine.

Bias

Efforts were made to minimize selection bias. Our study analyzed all adult COVID-19 patients admitted to the ICUs in six hospitals affiliated with Yale New Haven Health System at any time during the study period. Yale New Haven Health System covers a significant portion of Connecticut and provides a mixture of different levels of care to state residents. As all our patients were treated in hospital settings, missing data were minimized because of standardized electronic methods for data capture and recording. All variables of interest were measured using the same methods across the healthcare system.

Study Size

No statistical power calculation was conducted before the study because we planned to include all COVID-19 patients who had been treated in Yale New Haven Health System's ICUs throughout the entire first pandemic year. The sample size was based on the available cases.

Quantitative Variables

We used original quantitative data collected from electronic medical records, including demographic characteristics, laboratory results, vital signs, drug doses, and treatment timing and duration. We removed data outside of the 0.5 to 99.5 percentile range for vital signs, considering that some of these measurements could be artifacts or outliers.

Statistical Methods

Continuous data are presented as means and SD or median and interquartile range, depending on the normality of distribution, assessed using histograms and Q-Q plots. Categorical data are presented as numbers and percentages. Missing data were not imputed.

Our objective was to identify treatments associated with lower mortality using a multivariable Cox proportional-hazards model. The variables entering the multivariable analysis included all COVID-19–related treatments and the potential confounders described above under "Variables." Only those treatments that were used in at least 5% of patients were included in the analysis. Demographics, comorbidities, laboratory results, and vital signs with a *P* value less than 0.25 in univariate analyses were included in the multivariable analysis. If two variables had an absolute Pearson's or Spearman's rank correlation coefficient greater than 0.5, we included only one variable to avoid collinearity. We excluded variables that had missing data for more than 10% of the patients. Multiple testing correction was performed using the Bonferroni method to reduce the chance of type I errors at the two-sided 0.05 α level. The hypotheses for all COVID-19–related treatments were considered as a family; therefore, the raw *P* value for each treatment was multiplied by the number of treatments being analyzed to derive the corrected *P* value. The association was estimated using hazard ratios and reported with 95% CIs. To account for clustering within hospitals, we used robust sandwich estimators to compute standard errors for the hazard ratios.[6]

We used propensity score–matching analysis to evaluate the reproducibility of the association identified by the multivariable analysis. We divided patients into two cohorts: one cohort received the treatment, and the other cohort did not, with these two cohorts balanced at the baseline level using propensity score matching. The propensity score model included the demographic characteristics, comorbidities, pandemic phase, severity of acute illness (during the first 24 h after ICU admission), laboratory results (during the first 24 h after ICU admission), and vital signs (during the first 24 h after ICU admission). The matched pairs were identified using a one-to-one nearest neighbor caliper of 0 to 0.1 width. The balance between matched pairs was assessed using a standardized 10% difference. Survival was estimated using the product-limit Kaplan–Meier estimator, and the log-rank statistic was used to compare the survival curves. A stratified Cox proportional-hazards model was used in the analysis of the matched pairs.

We additionally explored the factors that could have modified the association identified by the multivariable analysis and evaluated by the propensity score–matching analysis. The method of analysis depended on the characteristics of the treatment associated with lower COVID-19 mortality. If a drug was associated with lowering mortality significantly, we presented the relevant data by dividing the patients into subgroups with different drug doses when feasible. When feasible, we also split the matched pairs derived from the propensity score matching into subgroups with different drug doses to explore the potential factors that might have modified the association.

A data analysis and statistical plan was written and filed with a private entity (institutional review board) before the data were accessed. During the peer-review process, significant modifications were requested and implemented. No minimum clinically meaningful effect size was defined before data access. The propensity score-matched analyses were planned *post hoc*. For a two-tailed hypothesis test, the significance level for each general hypothesis was 0.05. All analyses were performed in R software (version 3.5.3, R Foundation for Statistical Computing, Austria), with packages including sqldf, dplyr, sandwich, survival, survminer, arsenal, mltools, MatchIt, stddiff, and tableone.

Results

Study Population

From February 13, 2020, to March 4, 2021 (1 yr and 3 weeks), a total of 2,096 patients were treated for COVID-19–related complications in Yale New Haven Health System's ICUs (fig. 1). We excluded 23 patients who died within 24 h after ICU admission and 3 patients who remained hospitalized on the last day of data censoring. The final analysis involved 2,070 patients, including 856 (41%) patients admitted to

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ICU during the first phase, 138 (6.7%) patients during the second phase, 400 (19.3%) patients during the third phase, and 676 (32.7%) patients during the fourth phase (fig. S1 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The study population had a mean age of 65 yr (SD, 16 yr; N = 2,070) and a male patient percentage of 58.8% (1,218 of 2,070; table 1 and table S1 in Supplemental Digital Content, http://links.lww.com/ALN/C693).

Descriptive Data

The potential COVID-19–related treatments are presented in table S2 in Supplemental Digital Content (http://links.lww.com/ALN/C693), with most treatments given to less than 5% of the study population. The treatments included in the multivariable analysis are presented in table 2. The potential confounders included in the multivariable analysis are presented in table S3 in Supplemental Digital Content (http://links.lww.com/ALN/C693).

Outcome Data

A total of 593 patients died during hospitalization, and 1,477 patients were discharged from the hospital alive. The all-cause in-hospital mortality was 28.6% (593 of 2,070). The mortality was 31.8% (272 of 856) during the first pandemic phase, 10.1% (14 of 138) during the second pandemic phase, 26.8% (107 of 400) during the third pandemic phase, and 29.6% (200 of 676) during the fourth pandemic phase. The median hospital stay was 16 days (interquartile range, 10 to 27), and the median ICU stay was 6 days (interquartile range, 2 to 13).

Treatments Associated with Lower Mortality

The following treatments were associated with lower mortality based on the multivariable analysis: atazanavir (hazard ratio, 0.58; 95% CI, 0.393 to 0.89; $P = 0.006$), enoxaparin (hazard ratio, 0.82; 95% CI, 0.69 to 0.97; $P = 0.021$), heparin (hazard ratio, 0.79; 95% CI, 0.66 to 0.95; $P = 0.011$), apixaban (hazard ratio, 0.42; 95% CI, 0.363 to 0.48; $P < 0.001$), aspirin (hazard ratio, 0.72; 95% CI, 0.60 to 0.87; $P < 0.001$), famotidine (hazard ratio, 0.364; 95% CI, 0.174 to 0.76; $P = 0.008$), and conventional oxygen therapy (hazard ratio, 0.51; 95% CI, 0.327 to 0.81; $P = 0.004$; table 2). The results of the 23 hypotheses, corresponding to all treatments included in the multivariable analysis, were corrected using the Bonferroni method. After multiple testing correction, only apixaban (corrected CI, 0.336 to 0.52; corrected $P < 0.001$) and aspirin (corrected CI, 0.54 to 0.96; corrected $P = 0.010$) remained significantly associated with lower mortality. The results of the univariate analyses are presented in table S4 in Supplemental Digital Content (http://links.lww.com/ALN/C693).

Propensity Score–matching Analysis for Apixaban

The association between apixaban and mortality was further evaluated using propensity score–matching analysis as this association remained significant after the multivariable analysis with multiple testing correction. The propensity score matching generated two well balanced cohorts: one comprising 360 patients who received apixaban treatment and the other comprising 360 patients who never received apixaban treatment (table 3 and table S5 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The mortality was 26.7% (96 of 360) in patients treated with apixaban and 36.9% (133 of 360) in patients not treated with apixaban. Apixaban treatment had a significant association with lower mortality (hazard ratio, 0.48; 95% CI, 0.337 to 0.69; $P < 0.001$), reflecting a 52% lower mortality risk in apixaban-treated patients compared to patients never treated with apixaban. The respective survival probabilities

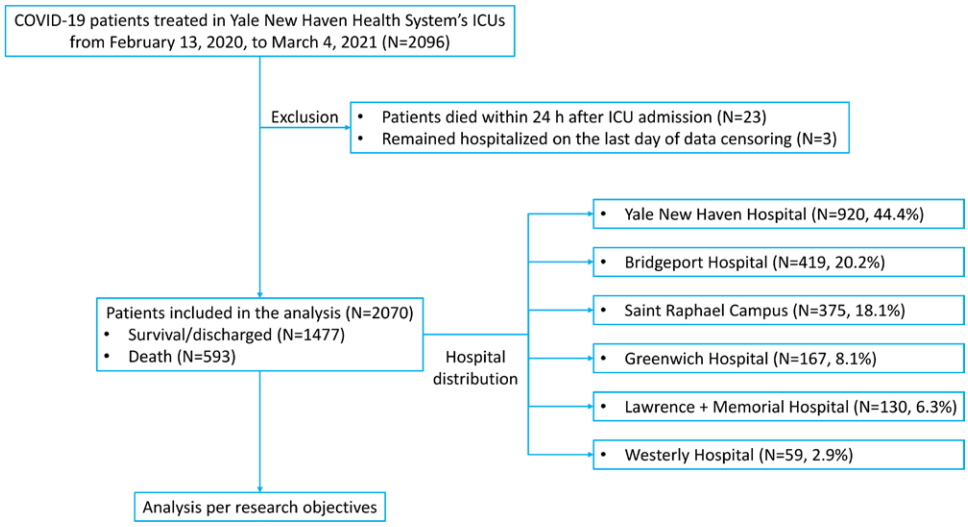

Fig. 1. Patients and analyses. ICU, intensive care unit.

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Table 1. Baseline Characteristics (N = 2,070)

Categories and Variables	Mean ± SD and Median [Interquartile Range] and Number of Patients (%)
Demographics	
Age, yr	65 ± 16
Sex (male)	1,218 (58.8%)
Body mass index, kg/m^2*	29 [24–35]
Never smoking†	882 (46.6%)
Comorbidities	
Myocardial infarction	381 (18.4%)
Congestive heart failure	665 (32.1%)
Peripheral vascular disease	512 (24.7%)
Cerebrovascular disease	539 (26.0%)
Dementia	283 (13.7%)
Chronic obstructive pulmonary disease	749 (36.2%)
Rheumatic disease	141 (6.8%)
Peptic ulcer disease	142 (6.9%)
Liver disease	347 (16.8%)
Diabetes	935 (45.2%)
Paraplegia	127 (6.1%)
Renal disease	619 (29.9%)
Malignancy	377 (18.2%)
Metastatic cancer	201 (9.7%)
Human immunodeficiency virus infection	28 (1.4%)
Hypertension	1,549 (74.8%)
Hyperlipidemia	1,263 (61.0%)
Anxiety	532 (25.7%)
Depression	542 (26.2%)
Immunosuppression	18 (0.9%)
Asthma	430 (20.8%)
Number of comorbidities, number	4 [2–7]
Charlson Comorbidity Index, points	3 [1–6]
Severity of acute illness during the first 24 h after ICU admission	
Sequential Organ Failure Assessment score‡	6 [4–9]
Glasgow Coma Scale score§	15 [14–15]
Invasive mechanical ventilation	541 (26.1%)

Refer to table S1 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for laboratory results and vital signs acquired during the first 24 h after ICU admission.

*Data were missing in 9 patients. †Data were missing in 177 patients. ‡Data were missing in 114 patients. §Data were missing in 927 patients.

ICU, intensive care unit.

of patients who received and did not receive apixaban treatment are presented in figure 2A. An additional stratified multivariable Cox regression analysis based on the matched cohorts also showed a significant association between apixaban treatment and lower mortality (hazard ratio, 0.388; 95% CI, 0.254 to 0.59; $P < 0.001$), with the covariates including enoxaparin, aspirin, and dexamethasone.

Propensity Score–matching Analysis for Enoxaparin

Enoxaparin was the anticoagulant of choice for hospitalized COVID-19 patients during this pandemic. In total, 72.7% of our patients received enoxaparin, whereas only 19.7% received apixaban. The multivariable analysis suggested an association between enoxaparin treatment and lower mortality, although this association was no longer significant after multiple testing correction (table 2). This result might be due to overcorrection. To further explore this association, we used propensity score–matching analysis to estimate the association between enoxaparin and mortality.

The propensity score matching generated two well balanced cohorts: one comprising 347 patients who received enoxaparin treatment and the other comprising 347 patients who never received enoxaparin treatment (table 4 and table S6 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The mortality was 25.1% (87 of 347) in patients treated with enoxaparin and 33.7% (117 of 347) in patients never treated with enoxaparin. Enoxaparin treatment had a significant association with lower mortality (hazard ratio, 0.53; 95% CI, 0.367 to 0.77; $P < 0.001$), reflecting a 47% lower mortality risk in enoxaparin-treated patients compared to patients never treated with enoxaparin. The respective survival probabilities of patients who received and did not receive enoxaparin are presented in figure 2B. An additional stratified multivariable Cox regression analysis based on the matched cohorts also showed a significant association between enoxaparin treatment and lower mortality (hazard ratio, 0.55; 95% CI, 0.373 to 0.81; $P = 0.002$), with the covariates including apixaban, aspirin, and dexamethasone.

Propensity Score–matching Analysis for Aspirin

The association between aspirin and mortality was further evaluated using propensity score–matching analysis because this association remained significant after the multivariable analysis with multiple testing correction. The propensity score matching generated two well balanced cohorts: one comprising 473 patients who received aspirin treatment and the other comprising 473 patients who never received aspirin treatment (table 5 and table S7 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The mortality was 25.6% (121 of 473) in patients treated with aspirin and 29.6% (140 of 473) in patients not treated with aspirin. Aspirin treatment had a significant association with lower mortality (hazard ratio, 0.57; 95% CI, 0.41 to 0.78; $P < 0.001$), reflecting a 43% lower mortality risk in aspirin-treated patients compared to patients never treated with aspirin. The respective survival probabilities of patients who received and did not receive aspirin treatment are presented in figure 2C. An additional stratified multivariable Cox regression analysis based on the matched cohorts also showed a significant association between aspirin treatment and lower mortality (hazard ratio, 0.61; 95% CI, 0.43 to 0.86; $P = 0.005$), with the covariates including apixaban, enoxaparin, and dexamethasone.

Exploratory Analysis

Association Modification by Apixaban Dose. Apixaban was administered in two different doses: a prophylactic dose (2.5 or 5 mg two times daily) in 80% (328 of 408) of patients and a therapeutic dose (10 mg two times daily) in 20% (80 of

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Table 2. Association between Treatment and Mortality Based on Multivariable Analysis (N = 1,656)

Categories and Treatments	Number of Patients (%)*	Multiple Testing Uncorrected		Multiple Testing Corrected†	
		Hazard Ratio [95% CI]	*P* Value	Hazard Ratio [Corrected CI]	*P* Value
Antiviral drugs					
Remdesivir	991 (47.9)	1.06 [0.71–1.58]	0.770	1.06 [0.57–1.98]	> 0.999
Hydroxychloroquine	706 (34.1)	0.98 [0.64–1.52]	0.935	0.98 [0.50–1.94]	> 0.999
Atazanavir	162 (7.8)	0.58 [0.393–0.89]	0.006	0.58 [0.315–1.07]	0.138
Anticoagulants					
Enoxaparin	1,504 (72.7)	0.82 [0.69–0.97]	0.021	0.82 [0.61–1.05]	0.483
Heparin	1,086 (52.5)	0.79 [0.66–0.95]	0.011	0.79 [0.59–1.05]	0.253
Apixaban	408 (19.7)	0.42 [0.363–0.48]	< 0.001	0.42 [0.336–0.52]	< 0.001
Antiplatelet drugs					
Aspirin	1,355 (65.5)	0.72 [0.60–0.87]	< 0.001	0.72 [0.54–0.96]	0.010
Clopidogrel	181 (8.7)	0.88 [0.53–1.44]	0.610	0.88 [0.40–1.91]	> 0.999
Steroids					
Dexamethasone	831 (40.1)	1.13 [0.70–1.83]	0.603	1.13 [0.54–2.39]	> 0.999
Methylprednisolone	561 (27.1)	0.91 [0.81–1.03]	0.123	0.91 [0.76–1.09]	> 0.999
Hydrocortisone	264 (12.8)	1.29 [1.02–1.62]	0.030	1.29 [0.89–1.88]	0.690
Immunomodulators					
Tocilizumab	925 (44.7)	1.03 [0.86–1.23]	0.738	1.03 [0.78–1.37]	> 0.999
Vasopressors					
Norepinephrine	890 (43.0)	1.38 [1.07–1.77]	0.012	1.38 [0.93–2.04]	0.276
Epinephrine	178 (8.6)	1.62 [1.37–1.92]	< 0.001	1.62 [1.24–2.11]	< 0.001
Uncategorized drugs					
Azithromycin	327 (15.8)	0.78 [0.55–1.10]	0.156	0.78 [0.46–1.33]	> 0.999
Convalescent plasma	317 (15.3)	0.90 [0.77–1.05]	0.193	0.90 [0.71–1.15]	> 0.999
Famotidine	132 (6.4)	0.364 [0.174–0.76]	0.008	0.364 [0.114–1.15]	0.184
Organ support therapies					
Conventional oxygen therapy	1,898 (91.7)	0.51 [0.327–0.81]	0.004	0.51 [0.253–1.05]	0.092
High-flow nasal cannula	1,070 (51.7)	0.81 [0.61–1.08]	0.146	0.81 [0.52–1.26]	> 0.999
Bilevel positive airway pressure ventilation	473 (22.9)	1.45 [0.98–2.15]	0.066	1.45 [0.78–2.68]	> 0.999
Continuous positive airway pressure ventilation	234 (11.3)	0.83 [0.68–1.02]	0.076	0.83 [0.61–1.14]	> 0.999
Invasive mechanical ventilation	888 (42.9)	1.01 [0.91–1.13]	0.791	1.01 [0.86–1.20]	> 0.999
Continuous veno-venous hemofiltration	116 (5.6)	1.26 [0.89–1.77]	0.194	1.26 [0.73–2.15]	> 0.999

All treatments included in this table were entered into a multivariable regression model simultaneously. The multivariable model included the following variables: all treatments listed in this table and all potential confounders listed under "Multivariable Analysis" in table S3 in Supplemental Digital Content (http://links.lww.com/ALN/C693). Refer to table S4 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for the results of the association between each treatment and mortality based on univariate analysis. Refer to table S3 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for the results of the associations between each potential confounder and mortality based on univariate and multivariable analysis.

*The denominator for percentage calculation was 2,070. †The CI of hazard ratio and *P* value were corrected for multiple testing using the Bonferroni method. The 23 hypotheses for all treatments included in this table were regarded as one family. The corrected *P* value is equal to the uncorrected *P* value multiplied by 23.

408) of patients (table S8 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The 360 matched pairs based on apixaban treatment were split into two subgroups: one subgroup had patients treated with prophylactic apixaban *versus* matched patients never treated with apixaban (N, 287 *vs*. 287), whereas the other subgroup had patients treated with therapeutic apixaban *versus* matched patients never treated with apixaban (N, 73 *vs*. 73; table S9 in Supplemental Digital Content, http://links.lww.com/ALN/C693). Prophylactic apixaban was associated with lower mortality (30.7% *vs*. 38.0%; hazard ratio, 0.50; 95% CI, 0.340 to 0.73; $P < 0.001$), whereas therapeutic apixaban was not associated with lower mortality (11.0% *vs*. 32.9%; hazard ratio, 0.385; 95% CI, 0.137 to 1.08; $P = 0.069$).

Association Modification by Enoxaparin Dose. Enoxaparin was administered in two different doses: a prophylactic dose (40 mg one time daily or 0.5 mg/kg two times daily) in 79.3% (1,192 of 1,504) of patients and a therapeutic dose (1 mg/kg two times daily) in 20.7% (312 of 1,504) of patients (table S10 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The 347 matched pairs per enoxaparin treatment were split into two subgroups: one subgroup had patients treated with prophylactic enoxaparin *versus* matched patients never treated with enoxaparin (N, 289 *vs*. 289), whereas the other subgroup had patients treated with therapeutic enoxaparin *versus* matched patients never treated with enoxaparin (N, 58 *vs*. 58; table S11 in Supplemental Digital Content, http://links.lww.com/ALN/C693). Prophylactic and therapeutic enoxaparin were both associated with lower mortality (25.6% *vs.* 31.8%; hazard ratio, 0.65; 95% CI, 0.43 to 0.97; $P = 0.036$ and 22.4% *vs.* 43.1%; hazard ratio, 0.191; 95% CI, 0.066 to 0.55; $P = 0.002$, respectively).

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Table 3. Cohort Characteristics before and after Propensity Score Matching Based on Apixaban Treatment

	Before Propensity Score Matching			After Propensity Score Matching		
Categories and Treatments	**Apixaban Used (N = 408)***	**Apixaban Not Used (N = 1,662)***	**Standardized Difference**	**Apixaban Used (N = 360)***	**Apixaban Not Used (N = 360)***	**Standardized Difference**
Demographics						
Age, yr	70 ± 12	64 ± 16	0.454	70 ± 12	70 ± 14	0.001
Sex (male)	248 (60.8%)	970 (58.4%)	0.049	216 (60.0%)	205 (56.9%)	0.062
Body mass index, kg/m^2	29 [24–34]	29 [25–35]	0.078	29 [24–34]	28 [24–34]	0.039
Never smoking	144 (37.6%)	738 (48.9%)	0.229	134 (37.2%)	136 (37.8%)	0.011
Hospital						
Yale New Haven Hospital	173 (42.4%)	747 (44.9%)	0.147	156 (43.3%)	156 (43.3%)	0.056
Bridgeport Hospital	72 (17.6%)	347 (20.9%)		64 (17.8%)	67 (18.6%)	
Saint Raphael Campus	32 (7.8%)	135 (8.1%)		20 (5.6%)	22 (6.1%)	
Greenwich Hospital	28 (6.9%)	102 (6.1%)		24 (6.7%)	20 (5.6%)	
Lawrence + Memorial Hospital	87 (21.3%)	288 (17.3%)		80 (22.2%)	80 (22.2%)	
Westerly Hospital	16 (3.9%)	43 (2.6%)		16 (4.4%)	15 (4.2%)	
Comorbidities						
Myocardial infarction	118 (28.9%)	263 (15.8%)	0.318	109 (30.3%)	105 (29.2%)	0.024
Congestive heart failure	199 (48.8%)	466 (28.0%)	0.436	184 (51.1%)	181 (50.3%)	0.017
Peripheral vascular disease	141 (34.6%)	371 (22.3%)	0.274	130 (36.1%)	121 (33.6%)	0.052
Cerebrovascular disease	137 (33.6%)	402 (24.2%)	0.208	121 (33.6%)	125 (34.7%)	0.023
Dementia	57 (14.0%)	226 (13.6%)	0.011	50 (13.9%)	53 (14.7%)	0.024
COPD	178 (43.6%)	571 (34.4%)	0.191	165 (45.8%)	168 (46.7%)	0.017
Rheumatic disease	40 (9.8%)	101 (6.1%)	0.138	38 (10.6%)	36 (10.0%)	0.018
Peptic ulcer disease	28 (6.9%)	114 (6.9%)	< 0.001	25 (6.9%)	22 (6.1%)	0.034
Liver disease	77 (18.9%)	270 (16.2%)	0.069	66 (18.3%)	72 (20.0%)	0.042
Diabetes	206 (50.5%)	729 (43.9%)	0.133	190 (52.8%)	184 (51.1%)	0.033
Paraplegia	30 (7.4%)	97 (5.8%)	0.061	28 (7.8%)	27 (7.5%)	0.010
Renal disease	178 (43.6%)	441 (26.5%)	0.364	164 (45.6%)	165 (45.8%)	0.006
Malignancy	91 (22.3%)	286 (17.2%)	0.128	86 (23.9%)	83 (23.1%)	0.020
Metastatic cancer	48 (11.8%)	153 (9.2%)	0.084	48 (13.3%)	44 (12.2%)	0.033
HIV infection	6 (1.5%)	22 (1.3%)	0.013	6 (1.7%)	5 (1.4%)	0.023
Hypertension	334 (81.9%)	1,215 (73.1%)	0.211	304 (84.4%)	308 (85.6%)	0.031
Hyperlipidemia	292 (71.6%)	971 (58.4%)	0.278	270 (75.0%)	262 (72.8%)	0.051
Anxiety	100 (24.5%)	432 (26.0%)	0.034	87 (24.2%)	91 (25.3%)	0.026
Depression	119 (29.2%)	423 (25.5%)	0.083	110 (30.6%)	107 (29.7%)	0.018
Immunosuppression	3 (0.7%)	15 (0.9%)	0.019	3 (0.8%)	2 (0.6%)	0.033
Asthma	94 (23.0%)	336 (20.2%)	0.069	88 (24.4%)	85 (23.6%)	0.020
Number of comorbidities, number	6 [3–8]	4 [2–6]	0.420	6 [4–8]	6 [3–8]	0.025
Charlson Comorbidity Index, points	4 [2–7]	2 [1–5]	0.368	5 [2–7]	4 [2–7]	0.029
Severity of acute illness during the first 24 h after ICU admission						
SOFA score	7 [5–9]	6 [4–9]	0.187	7 [5–9]	6 [5–9]	0.018
Glasgow Coma Scale score	15 [14–15]	15 [14–15]	0.012	15 [14–15]	15 [14–15]	0.009
Invasive mechanical ventilation	106 (26.0%)	435 (26.2%)	0.004	91 (25.3%)	94 (26.1%)	0.019
Pandemic phase†						
First phase	168 (41.2%)	688 (41.4%)	0.121	136 (37.8%)	127 (35.3%)	0.053
Second phase	19 (4.7%)	119 (7.2%)		17 (4.7%)	17 (4.7%)	
Third phase	88 (21.6%)	312 (18.8%)		83 (23.1%)	87 (24.2%)	
Fourth phase	133 (32.6%)	543 (32.7%)		124 (34.4%)	129 (35.8%)	

Refer to table S5 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for laboratory results and vital signs before and after propensity score matching per apixaban treatment.

*Data are expressed as mean ± SD, median [interquartile range], or number (%). †The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020. Accordingly, we divided the first year of the pandemic into four stages: the first phase from February 1, 2020, to May 31, 2020 (including the early cases happened before March 11, 2020); the second phase from June 1, 2020, to August 31, 2020; the third phase from September 1, 2020, to November 30, 2020; and the fourth phase from December 1, 2020, to March 11, 2021. We divided the pandemic into different phases to account for the chronological effect of different treatments.

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Association Modification by Aspirin Dose. Aspirin was administered in two different doses: a low dose (81 mg one time daily) in 89.2% (1,209 of 1,355) of patients and a high dose (300/325 mg one time daily) in 10.8% (146 of 1,355) of patients (table S12 in Supplemental Digital Content, http://links.lww.com/ALN/C693). The 473 matched pairs based on aspirin treatment were split into two subgroups: one subgroup had patients treated with low-dose aspirin *versus* matched patients never treated with aspirin (N, 422 *vs.* 422), whereas the other subgroup had patients

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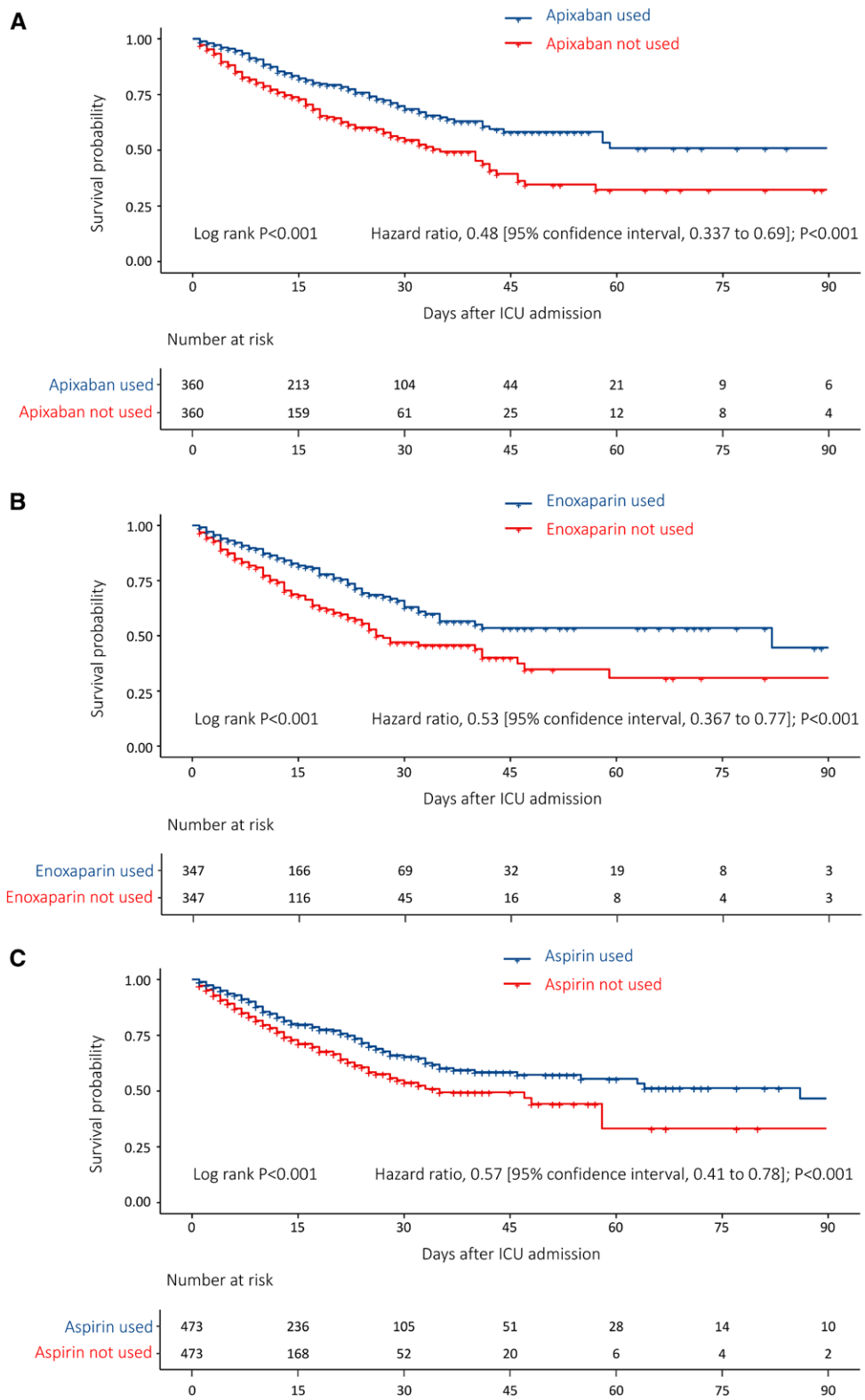

Fig. 2. Survival probability for patients treated and not treated with apixaban (*A*), enoxaparin (*B*), and aspirin (*C*). The patients are matched using propensity score matching. ICU, intensive care unit.

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Table 4. Cohort Characteristics before and after Propensity Score Matching Based on Enoxaparin Treatment

	Before Propensity Score Matching			After Propensity Score Matching		
Categories and Treatments	**Enoxaparin Used (N = 1,504)***	**Enoxaparin Not Used (N = 566)***	**Standardized Difference**	**Enoxaparin Used (N = 347)***	**Enoxaparin Not Used (N = 347)***	**Standardized Difference**
Demographics						
Age, yr	64 ± 16	68 ± 18	0.214	69 ± 16	68 ± 15	0.086
Sex (male)	904 (60.1%)	314 (55.5%)	0.094	186 (53.6%)	189 (54.5%)	0.017
Body mass index, kg/m^2	29 [25–35]	29 [24–35]	0.018	28 [24–35]	29 [24–35]	0.064
Never smoking	665 (48.9%)	217 (40.7%)	0.165	135 (38.9%)	141 (40.6%)	0.035
Hospital						
Yale New Haven Hospital	643 (42.8%)	277 (48.9%)	0.332	173 (49.9%)	173 (49.9%)	0.022
Bridgeport Hospital	279 (18.6%)	140 (24.7%)		79 (22.8%)	80 (23.1%)	
Saint Raphael Campus	146 (9.7%)	21 (3.7%)		17 (4.9%)	16 (4.6%)	
Greenwich Hospital	107 (7.1%)	23 (4.1%)		13 (3.7%)	14 (4.0%)	
Lawrence + Memorial Hospital	280 (18.6%)	95 (16.8%)		56 (16.1%)	55 (15.9%)	
Westerly Hospital	49 (3.3%)	10 (1.8%)		9 (2.6%)	9 (2.6%)	
Comorbidities						
Myocardial infarction	208 (13.8%)	173 (30.6%)	0.411	96 (27.7%)	94 (27.1%)	0.013
Congestive heart failure	375 (24.9%)	290 (51.2%)	0.563	167 (48.1%)	157 (45.2%)	0.058
Peripheral vascular disease	299 (19.9%)	213 (37.6%)	0.400	127 (36.6%)	115 (33.1%)	0.073
Cerebrovascular disease	328 (21.8%)	211 (37.3%)	0.344	124 (35.7%)	121 (34.9%)	0.018
Dementia	196 (13.0%)	87 (15.4%)	0.067	55 (15.9%)	48 (13.8%)	0.057
COPD	482 (32.0%)	267 (47.2%)	0.313	157 (45.2%)	164 (47.3%)	0.040
Rheumatic disease	90 (6.0%)	51 (9.0%)	0.115	23 (6.6%)	30 (8.6%)	0.076
Peptic ulcer disease	89 (5.9%)	53 (9.4%)	0.13	29 (8.4%)	31 (8.9%)	0.021
Liver disease	243 (16.2%)	104 (18.4%)	0.059	62 (17.9%)	64 (18.4%)	0.015
Diabetes	627 (41.7%)	308 (54.4%)	0.257	174 (50.1%)	179 (51.6%)	0.029
Paraplegia	74 (4.9%)	53 (9.4%)	0.173	27 (7.8%)	25 (7.2%)	0.022
Renal disease	322 (21.4%)	297 (52.5%)	0.68	150 (43.2%)	146 (42.1%)	0.023
Malignancy	253 (16.8%)	124 (21.9%)	0.129	87 (25.1%)	83 (23.9%)	0.027
Metastatic cancer	130 (8.6%)	71 (12.5%)	0.127	46 (13.3%)	45 (13.0%)	0.009
HIV infection	19 (1.3%)	9 (1.6%)	0.028	6 (1.7%)	5 (1.4%)	0.023
Hypertension	1,058 (70.3%)	491 (86.7%)	0.408	299 (86.2%)	295 (85.0%)	0.033
Hyperlipidemia	859 (57.1%)	404 (71.4%)	0.301	245 (70.6%)	246 (70.9%)	0.006
Anxiety	364 (24.2%)	168 (29.7%)	0.124	104 (30.0%)	108 (31.1%)	0.025
Depression	353 (23.5%)	189 (33.4%)	0.221	107 (30.8%)	112 (32.3%)	0.031
Immunosuppression	13 (0.9%)	5 (0.9%)	0.002	7 (2.0%)	5 (1.4%)	0.044
Asthma	282 (18.8%)	148 (26.1%)	0.178	82 (23.6%)	90 (25.9%)	0.053
Number of comorbidities, number	4 [2–6]	6 [4–8]	0.665	6 [3–8]	5 [3–8]	0.019
Charlson Comorbidity Index, points	2 [1–5]	5 [2–7]	0.623	4 [2–7]	4 [2–7]	0.033
Severity of acute illness during the first 24 h after ICU admission						
SOFA score	6 [4–8]	7 [4–10]	0.208	6 [4–9]	6 [4–9]	0.008
Glasgow Coma Scale score	15 [14–15]	15 [14–15]	0.055	15 [14–15]	15 [14–15]	0.048
Invasive mechanical ventilation	401 (26.7%)	140 (24.7%)	0.044	79 (22.8%)	83 (23.9%)	0.027
Pandemic phase†						
First phase	659 (43.8%)	197 (34.8%)	0.227	103 (29.7%)	108 (31.1%)	0.046
Second phase	83 (5.5%)	55 (9.7%)		33 (9.5%)	31 (8.9%)	
Third phase	291 (19.3%)	109 (19.3%)		79 (22.8%)	74 (21.3%)	
Fourth phase	471 (31.3%)	205 (36.2%)		132 (38.0%)	134 (38.6%)	

Refer to table S6 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for laboratory results and vital signs before and after propensity score matching per enoxaparin treatment.

*Data are expressed as mean ± SD, median [interquartile range], or number (%). †The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020. Accordingly, we divided the first year of the pandemic into four stages: the first phase from February 1, 2020, to May 31, 2020 (including the early cases happened before March 11, 2020); the second phase from June 1, 2020, to August 31, 2020; the third phase from September 1, 2020, to November 30, 2020; and the fourth phase from December 1, 2020, to March 11, 2021. We divided the pandemic into different phases to account for the chronological effect of different treatments.

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

treated with high-dose aspirin *versus* matched patients never treated with aspirin (N, 51 *vs.* 51; table S13 in Supplemental Digital Content, http://links.lww.com/ALN/C693). Low-dose aspirin was associated with lower mortality (24.6% *vs.* 30.6%; hazard ratio, 0.53; 95% CI, 0.375 to 0.74; $P < 0.001$), whereas high-dose aspirin was not associated with lower mortality (33.3% *vs.* 21.6%; hazard ratio, 1.14; 95% CI, 0.41 to 3.15; $P = 0.796$).

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Table 5. Cohort Characteristics before and after Propensity Score Matching Based on Aspirin Treatment

Categories and Treatments	Before Propensity Score Matching			After Propensity Score Matching		
	Aspirin Used (N = 1,355)*	Aspirin Not Used (N = 715)*	Standardized Difference	Aspirin Used (N = 473)*	Aspirin Not Used (N = 473)*	Standardized Difference
Demographics						
Age, yr	67 ± 14	62 ± 18	0.272	64 ± 16	64 ± 18	0.007
Sex (male)	810 (59.8%)	408 (57.1%)	0.055	273 (57.7%)	260 (55.0%)	0.055
Body mass index, kg/m^2	29 [25–35]	28 [24–35]	0.041	28 [24–34]	28 [24–35]	0.044
Never smoking	555 (44.7%)	327 (50.2%)	0.109	213 (45.0%)	228 (48.2%)	0.064
Hospital						
Yale New Haven Hospital	612 (45.2%)	308 (43.1%)	0.240	214 (45.2%)	205 (43.3%)	0.089
Bridgeport Hospital	242 (17.9%)	177 (24.8%)		106 (22.4%)	102 (21.6%)	
Saint Raphael Campus	97 (7.2%)	70 (9.8%)		34 (7.2%)	39 (8.2%)	
Greenwich Hospital	97 (7.2%)	33 (4.6%)		17 (3.6%)	24 (5.1%)	
Lawrence + Memorial Hospital	262 (19.3%)	113 (15.8%)		88 (18.6%)	90 (19.0%)	
Westerly Hospital	45 (3.3%)	14 (2.0%)		14 (3.0%)	13 (2.7%)	
Comorbidities						
Myocardial infarction	299 (22.1%)	82 (11.5%)	0.287	69 (14.6%)	66 (14.0%)	0.018
Congestive heart failure	472 (34.8%)	193 (27.0%)	0.170	150 (31.7%)	147 (31.1%)	0.014
Peripheral vascular disease	364 (26.9%)	148 (20.7%)	0.145	130 (27.5%)	118 (24.9%)	0.058
Cerebrovascular disease	378 (27.9%)	161 (22.5%)	0.124	133 (28.1%)	118 (24.9%)	0.072
Dementia	174 (12.8%)	109 (15.2%)	0.069	72 (15.2%)	75 (15.9%)	0.018
COPD	501 (37.0%)	248 (34.7%)	0.048	186 (39.3%)	183 (38.7%)	0.013
Rheumatic disease	93 (6.9%)	48 (6.7%)	0.006	37 (7.8%)	34 (7.2%)	0.024
Peptic ulcer disease	83 (6.1%)	59 (8.3%)	0.082	38 (8.0%)	41 (8.7%)	0.023
Liver disease	216 (15.9%)	131 (18.3%)	0.063	83 (17.5%)	88 (18.6%)	0.027
Diabetes	640 (47.2%)	295 (41.3%)	0.120	212 (44.8%)	215 (45.5%)	0.013
Paraplegia	84 (6.2%)	43 (6.0%)	0.008	32 (6.8%)	31 (6.6%)	0.008
Renal disease	441 (32.5%)	178 (24.9%)	0.170	155 (32.8%)	134 (28.3%)	0.096
Malignancy	240 (17.7%)	137 (19.2%)	0.037	114 (24.1%)	101 (21.4%)	0.066
Metastatic cancer	117 (8.6%)	84 (11.7%)	0.103	52 (11.0%)	55 (11.6%)	0.020
HIV infection	15 (1.1%)	13 (1.8%)	0.059	10 (2.1%)	11 (2.3%)	0.014
Hypertension	1,049 (77.4%)	500 (69.9%)	0.171	370 (78.2%)	362 (76.5%)	0.040
Hyperlipidemia	893 (65.9%)	370 (51.7%)	0.291	296 (62.6%)	286 (60.5%)	0.043
Anxiety	350 (25.8%)	182 (25.5%)	0.009	138 (29.2%)	138 (29.2%)	< 0.001
Depression	365 (26.9%)	177 (24.8%)	0.050	141 (29.8%)	135 (28.5%)	0.028
Immunosuppression	16 (1.2%)	2 (0.3%)	0.106	3 (0.6%)	2 (0.4%)	0.029
Asthma	277 (20.4%)	153 (21.4%)	0.024	109 (23.0%)	113 (23.9%)	0.020
Number of comorbidities, number	4 [2–7]	4 [2–6]	0.181	4 [2–7]	4 [2–7]	0.048
Charlson Comorbidity Index, points	3 [1–6]	2 [1–6]	0.069	3 [1–6]	3 [1–6]	0.038
Severity of acute illness during the first 24 h after ICU admission						
SOFA score	6 [4–9]	6 [4–9]	0.030	6 [4–9]	6 [4–9]	0.051
Glasgow Coma Scale score	15 [14–15]	15 [14–15]	0.130	15 [14–15]	15 [14–15]	0.057
Invasive mechanical ventilation	326 (24.1%)	215 (30.1%)	0.136	125 (26.4%)	122 (25.8%)	0.014
Pandemic phase†						
First phase	400 (29.5%)	456 (63.8%)	0.808	250 (52.9%)	249 (52.6%)	0.010
Second phase	77 (5.7%)	61 (8.5%)		41 (8.7%)	42 (8.9%)	
Third phase	326 (24.1%)	74 (10.3%)		65 (13.7%)	66 (14.0%)	
Fourth phase	552 (40.7%)	124 (17.3%)		117 (24.7%)	116 (24.5%)	

Refer to table S7 in Supplemental Digital Content (http://links.lww.com/ALN/C693) for laboratory results and vital signs before and after propensity score matching per aspirin treatment.

*Data are expressed as mean ± SD, median [interquartile range], or number (%). †The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020. Accordingly, we divided the first year of the pandemic into four stages: the first phase from February 1, 2020, to May 31, 2020 (including the early cases happened before March 11, 2020); the second phase from June 1, 2020, to August 31, 2020; the third phase from September 1, 2020, to November 30, 2020; and the fourth phase from December 1, 2020, to March 11, 2021. We divided the pandemic into different phases to account for the chronological effect of different treatments.

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Discussion

Key Results

This retrospective cohort study examined 2,070 patients treated for COVID-19–related complications in the ICUs in six hospitals affiliated with one healthcare system throughout the first pandemic year. The results suggested that among the multiple COVID-19–related treatments, anticoagulants (i.e., apixaban and enoxaparin) and antiplatelet therapy (i.e., aspirin) were associated with lower in-hospital mortality. Analyses based on propensity score matching suggested that patients

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treated with apixaban were associated with a 52% lower mortality risk than patients who never received apixaban, patients treated with enoxaparin were associated with a 47% lower mortality risk compared to patients who never received enoxaparin, and patients treated with aspirin were associated with a 43% lower mortality risk compared to patients who never received aspirin. It is worth noting that patients treated with apixaban were older and had more comorbidities than patients who never received apixaban treatment in our study population. Moreover, therapeutic anticoagulants were used for imaging-confirmed venous thromboembolism (i.e., patients were likely sicker). Nevertheless, we still observed an association between apixaban/enoxaparin/aspirin and lower mortality among critically ill COVID-19 patients.

Interpretation

Although abundant treatments were applied to our patients throughout the first pandemic year, our study finds that apixaban, enoxaparin, and aspirin, rather than the previously reported treatments like remdesivir,[7,8] dexamethasone,[9] hydroxychloroquine,[10] convalescent plasma,[11] and famotidine,[12] are associated with lower COVID-19 mortality. In hospitalized COVID-19 patients, four different meta-analyses indicated that venous thromboembolism occurred in 24 to 31% of patients, pulmonary embolism occurred in 12 to 19%, and deep venous thrombosis occurred in 12 to 20%.[13–16] The incidence of venous thromboembolism was much higher in COVID-19 patients admitted to the ICU than those hospitalized on the ward (30% *vs.* 13%).[16] Patients with severe COVID-19 had an almost four-fold increased risk of venous thromboembolism compared to patients with nonsevere COVID-19.[14] Therefore, the existing evidence advocates a more proactive strategy of systemic anticoagulation therapy in hospitalized COVID-19 patients.

Several studies examined the use of systemic anticoagulants in hospitalized COVID-19 patients.[17,18] A retrospective cohort study involving 4,389 hospitalized COVID-19 patients showed that therapeutic and prophylactic anticoagulation is associated with lower mortality when compared to no anticoagulation therapy.[19] However, that study did not distinguish different anticoagulants and was not explicitly investigating critically ill patients. Another retrospective cohort study involving 3,625 hospitalized COVID-19 patients showed that the prophylactic use of apixaban or enoxaparin was associated with lower in-hospital mortality.[20] The study also showed that apixaban's therapeutic use was associated with lower mortality, although it was not more beneficial than prophylactic use. However, that study was only based on propensity score–matching analysis and only considered the last anticoagulant order in the first 48 h after hospital admission. Therefore, it did not control the confounding exerted by other COVID-19–related treatments, unlike the multivariable analysis used in our study, and it could not tell what would have happened if an anticoagulant had been given after the first 48 h of hospital admission. Moreover, the study involved all hospitalized patients, including patients requiring ICU-level care, and covered a short period (from March 1, 2020, to April 26, 2020; less than 2 months during the early stage of the pandemic); therefore, it may provide a different insight compared to our study, which focuses on ICU patients and spans the entire first pandemic year.

Three international trials compared the effectiveness of therapeutic-dose anticoagulation with heparin *versus* usual pharmacologic thromboprophylaxis.[3,4] These trials discontinued the enrollment of noncritically ill patients (defined as an absence of critical care-level organ support at enrollment) because of therapeutic anticoagulation's superiority in reducing the need for organ support over 21 days.[3] These trials also discontinued the enrollment of critically ill patients because of therapeutic anticoagulation's futility in reducing the need for organ support over 21 days.[4] These trials did not find an in-hospital mortality difference between different anticoagulation treatments.[3,4] A separate multicenter trial performed in hospitalized COVID-19 patients with elevated D-dimer did not find a difference between therapeutic and prophylactic anticoagulation.[5] However, the result of this trial is challenging to interpret because the primary outcome was defined as a hierarchical composite of time to death, duration of hospitalization, or duration of supplemental oxygen use over 30 days.[5] This trial also did not find a mortality difference between different anticoagulation treatments. Overall, the available evidence showed no mortality difference between therapeutic and prophylactic anticoagulation among hospitalized and critically ill COVID-19 patients. The discrepancy in the results of nonmortality outcome measures among these studies remains to be reconciled.

Although lacking in some details, the current anticoagulation recommendations have primarily focused on the use of enoxaparin.[18] Our findings support this practice. However, our important finding is the robust association between the use of apixaban and lower mortality in critically ill COVID-19 patients, which is consistent with early cohort studies suggesting an association between apixaban treatment and lower mortality in hospitalized COVID-19 patients.[20,21] As a commonly used direct factor Xa inhibitor, apixaban has anticoagulant, anti-inflammatory, and antiviral effects.[22] A previous virology investigation suggested that the inhibition of coagulation factor Xa–mediated cleavage and the subsequent activation of the viral spike protein leads to an impaired fusion of the viral envelope with host cells and, consequently, reduces the infectivity of the SARS virus.[23] This finding offers a mechanism that could explain our observed associations. We note that we did not find an association between the use of rivaroxaban (with a mechanism similar to apixaban) and mortality. The reasons for this finding remain to be elucidated but may be related to the small number of patients who received rivaroxaban treatment (3.4%, 70 of 2,070) in our study population. It should also be noted that the concurrent use of direct oral anticoagulants, including apixaban and antiviral drugs in COVID-19

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patients, can lead to an alarming increase in plasma anticoagulant levels and may increase the risk of bleeding.[24]

The association between aspirin treatment and lower COVID-19 mortality identified by our study is consistent with the literature based on large patient cohorts.[25–28] This association was also corroborated by meta-analyses.[29]

Limitations

This study has several limitations. First, although this cohort study is based on data collected from electronic medical records for all patients treated within a predefined time window across a relatively homogeneous healthcare system, there may still be imprecise information and patient selection bias, especially considering the dramatic toll on the healthcare system caused by the pandemic. Second, our study may be limited by confounding by indication as a retrospective cohort study. Although multivariable analysis and analysis based on propensity score matching were performed, residual bias and a lack of control for unmeasured confounders may still exist. Third, there is a possibility of an immortal time bias or other similar biases related to ignoring differences in timing before treatment because certain medications were not administered until a particular time in the disease course. Fourth, caution is needed when interpreting the data concerning the comparisons of prophylactic and therapeutic anticoagulants with their counterparts because these analyses were not powered to differentiate between different drug doses. Fifth, we conducted a complete case analysis and chose not to impute missing data. Although other approaches dealing with missing data were possible, we excluded patients from specific analyses if the data were missing. Last, as a study based on the experiences of the first pandemic year, the results may not be entirely applicable to future cases, for reasons that include viral mutation, different vulnerable populations, vaccination rates, and the evolution of our knowledge of and measures for treating the disease.

Conclusions

We performed a retrospective cohort study involving all patients treated in a healthcare system's ICUs for COVID-19–related complications throughout the first pandemic year to explore the treatments associated with lower mortality. Consistent with the known hypercoagulability in severe COVID-19, our study showed that the use of apixaban, enoxaparin, or aspirin was independently associated with lower mortality among critically ill COVID-19 patients. The reproducibility of this finding and the ideal dose, timing, and duration of treatment require further elucidation in future studies.

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Competing Interests

Dr. Meng received consulting fees from Edwards Lifesciences, Irvine, California. The other authors declare no competing interests.

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