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

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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 (hazard ratio, 0.82; corrected CI, 0.61 to 1.05) and propensity score–matching analysis showed an association between aspirin treatment and lower mortality (hazard ratio, 0.48; 95% CI, 0.337 to 0.69).

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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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
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.

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, 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...
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.
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 enoxaparin treatment and 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, 0.373 to 0.81; \( P = 0.002 \)), 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 1. Baseline Characteristics (N = 2,070)**

<table>
<thead>
<tr>
<th>Categories and Variables</th>
<th>Mean ± SD and Median [Interquartile Range] and Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>65 ± 16</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1,218 (58.8%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29 (24–35)</td>
</tr>
<tr>
<td>Never smoking†</td>
<td>882 (46.6%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>381 (18.4%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>665 (32.1%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>512 (24.7%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>539 (26.0%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>283 (13.7%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>749 (36.2%)</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>141 (6.8%)</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>142 (6.9%)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>347 (16.8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>935 (45.2%)</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>127 (6.1%)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>619 (29.9%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>377 (18.2%)</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>201 (9.7%)</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>28 (1.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,549 (74.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,263 (61.0%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>532 (25.7%)</td>
</tr>
<tr>
<td>Depression</td>
<td>542 (26.2%)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>18 (0.9%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>430 (20.8%)</td>
</tr>
<tr>
<td>Number of comorbidities, number</td>
<td>4 [2–7]</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, points</td>
<td>3 [1–6]</td>
</tr>
<tr>
<td>Severity of acute illness during the first 24 h after ICU admission</td>
<td>64 [4–9]</td>
</tr>
<tr>
<td>Sequential Organ Failure Assessment score§</td>
<td>15 [14–15]</td>
</tr>
<tr>
<td>Glasgow Coma Scale score¶</td>
<td>541 (26.1%)</td>
</tr>
</tbody>
</table>

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. ¶Data were missing in 9 patients. ‖Data were missing in 177 patients. ¶¶Data were missing in 177 patients.
Antiviral drugs
- Remdesivir
  - Number of Patients (%): 991 (47.9)
  - Hazard Ratio [95% CI]: 1.06 [0.71–1.58]
  - P Value: 0.770
  - Corrected Hazard Ratio [95% CI]: 1.06 [0.57–1.98]
  - Corrected P Value: > 0.999

- Hydroxychloroquine
  - Number of Patients (%): 706 (34.1)
  - Hazard Ratio [95% CI]: 0.98 [0.64–1.52]
  - P Value: 0.935
  - Corrected Hazard Ratio [95% CI]: 0.98 [0.50–1.94]
  - Corrected P Value: > 0.999

- Atazanavir
  - Number of Patients (%): 162 (7.8)
  - Hazard Ratio [95% CI]: 0.50 [0.39–0.89]
  - P Value: 0.006
  - Corrected Hazard Ratio [95% CI]: 0.50 [0.315–1.07]
  - Corrected P Value: 0.138

Anticoagulants
- Enoxaparin
  - Number of Patients (%): 1,504 (72.7)
  - Hazard Ratio [95% CI]: 0.82 [0.69–0.97]
  - P Value: 0.021
  - Corrected Hazard Ratio [95% CI]: 0.82 [0.61–1.05]
  - Corrected P Value: 0.483

- Heparin
  - Number of Patients (%): 1,086 (52.5)
  - Hazard Ratio [95% CI]: 0.79 [0.66–0.95]
  - P Value: 0.011
  - Corrected Hazard Ratio [95% CI]: 0.79 [0.59–1.05]
  - Corrected P Value: 0.253

- Apixaban
  - Number of Patients (%): 408 (19.7)
  - Hazard Ratio [95% CI]: 0.42 [0.363–0.48]
  - P Value: < 0.001
  - Corrected Hazard Ratio [95% CI]: 0.42 [0.336–0.52]
  - Corrected P Value: < 0.001

Antiplatelet drugs
- Aspirin
  - Number of Patients (%): 1,355 (65.5)
  - Hazard Ratio [95% CI]: 0.72 [0.60–0.87]
  - P Value: < 0.001
  - Corrected Hazard Ratio [95% CI]: 0.72 [0.54–0.96]
  - Corrected P Value: 0.010

- Clopidogrel
  - Number of Patients (%): 181 (8.7)
  - Hazard Ratio [95% CI]: 0.88 [0.53–1.44]
  - P Value: 0.610
  - Corrected Hazard Ratio [95% CI]: 0.88 [0.40–1.91]
  - Corrected P Value: > 0.999

Stereos
- Dexamethasone
  - Number of Patients (%): 831 (40.1)
  - Hazard Ratio [95% CI]: 1.13 [0.70–1.83]
  - P Value: 0.603
  - Corrected Hazard Ratio [95% CI]: 1.13 [0.54–2.39]
  - Corrected P Value: > 0.999

- Methylprednisolone
  - Number of Patients (%): 561 (27.1)
  - Hazard Ratio [95% CI]: 0.91 [0.81–1.03]
  - P Value: 0.123
  - Corrected Hazard Ratio [95% CI]: 0.91 [0.76–1.09]
  - Corrected P Value: > 0.999

- Hydrocortisone
  - Number of Patients (%): 264 (12.8)
  - Hazard Ratio [95% CI]: 1.29 [1.02–1.62]
  - P Value: 0.030
  - Corrected Hazard Ratio [95% CI]: 1.29 [0.89–1.88]
  - Corrected P Value: 0.690

Immunomodulators
- Tocilizumab
  - Number of Patients (%): 925 (44.7)
  - Hazard Ratio [95% CI]: 1.03 [0.86–1.23]
  - P Value: 0.738
  - Corrected Hazard Ratio [95% CI]: 1.03 [0.78–1.37]
  - Corrected P Value: > 0.999

Vasopressors
- Norepinephrine
  - Number of Patients (%): 1,178 (56.0)
  - Hazard Ratio [95% CI]: 1.38 [1.07–1.77]
  - P Value: 0.012
  - Corrected Hazard Ratio [95% CI]: 1.38 [0.93–2.04]
  - Corrected P Value: > 0.999

- Epinephrine
  - Number of Patients (%): 187 (8.6)
  - Hazard Ratio [95% CI]: 1.62 [1.37–1.92]
  - P Value: < 0.001
  - Corrected Hazard Ratio [95% CI]: 1.62 [1.24–2.11]
  - Corrected P Value: < 0.001

Uncategorized drugs
- Azithromycin
  - Number of Patients (%): 327 (15.8)
  - Hazard Ratio [95% CI]: 0.78 [0.55–1.10]
  - P Value: 0.156
  - Corrected Hazard Ratio [95% CI]: 0.78 [0.46–1.33]
  - Corrected P Value: > 0.999

- Convalescent plasma
  - Number of Patients (%): 317 (15.3)
  - Hazard Ratio [95% CI]: 0.90 [0.77–1.05]
  - P Value: 0.193
  - Corrected Hazard Ratio [95% CI]: 0.90 [0.71–1.15]
  - Corrected P Value: > 0.999

- Famotidine
  - Number of Patients (%): 132 (6.4)
  - Hazard Ratio [95% CI]: 0.364 [0.174–0.76]
  - P Value: 0.008
  - Corrected Hazard Ratio [95% CI]: 0.364 [0.114–1.15]
  - Corrected P Value: 0.184

Organ support therapies
- Conventional oxygen therapy
  - Number of Patients (%): 1,898 (91.7)
  - Hazard Ratio [95% CI]: 0.51 [0.327–0.81]
  - P Value: 0.004
  - Corrected Hazard Ratio [95% CI]: 0.51 [0.253–1.05]
  - Corrected P Value: 0.092

- High-flow nasal cannula
  - Number of Patients (%): 1,070 (51.7)
  - Hazard Ratio [95% CI]: 0.81 [0.61–1.08]
  - P Value: 0.146
  - Corrected Hazard Ratio [95% CI]: 0.81 [0.52–1.26]
  - Corrected P Value: > 0.999

- Bilevel positive airway pressure ventilation
  - Number of Patients (%): 473 (22.9)
  - Hazard Ratio [95% CI]: 1.45 [0.98–2.15]
  - P Value: 0.066
  - Corrected Hazard Ratio [95% CI]: 1.45 [0.78–2.68]
  - Corrected P Value: > 0.999

- Continuous positive airway pressure ventilation
  - Number of Patients (%): 234 (11.3)
  - Hazard Ratio [95% CI]: 0.83 [0.68–1.02]
  - P Value: 0.076
  - Corrected Hazard Ratio [95% CI]: 0.83 [0.61–1.14]
  - Corrected P Value: > 0.999

- Invasive mechanical ventilation
  - Number of Patients (%): 868 (42.9)
  - Hazard Ratio [95% CI]: 1.01 [0.91–1.13]
  - P Value: 0.791
  - Corrected Hazard Ratio [95% CI]: 1.01 [0.86–1.20]
  - Corrected P Value: > 0.999

- Continuous veno-venous hemofiltration
  - Number of Patients (%): 116 (3.2)
  - Hazard Ratio [95% CI]: 1.26 [0.89–1.77]
  - P Value: 0.194
  - Corrected Hazard Ratio [95% CI]: 1.26 [0.73–2.15]
  - Corrected P Value: > 0.999

**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, 287 vs. 289), whereas the other subgroup had patients treated with therapeutic enoxaparin versus matched patients never treated with enoxaparin (N, 73 vs. 73). 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 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...
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.
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).
Treatments Associated with Lower COVID-19 Mortality

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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...
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
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 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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References


