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Research Article

# A Single-Center Retrospective Study of Interventions Associated with Survival in COVID-19 Patients Requiring Invasive Mechanical Ventilation

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## Abstract

The purpose of our study was to identify the association of four interventions (therapeutic anticoagulation, neuromuscular blockade, prone positioning, and corticosteroids) with in-hospital mortality in COVID-19 patients requiring invasive mechanical ventilation (IMV).

This was a retrospective single-center observational study in which all consecutive COVID-19 patients requiring IMV admitted to ICU from February 5th to May 11th, 2020 were included. Kaplan-Meier survival analysis and cox proportional hazard regression were used for statistical analysis.

A total of 113 patients were included: male (76.1%) and mean age 56.5 ± 14.4 years. In-hospital mortality was 65.5%. The study outcome (discharged alive or deceased) was available for 96.5% patients. Early survival advantage seen with systemic corticosteroids and prone positioning in the respective Kaplan-Meier curves was lost at ~50 - 60 days. However, therapeutic anticoagulation and neuromuscular blockade continued to be associated with lower mortality. In the multivariate Cox regression model adjusting for confounders, therapeutic anticoagulation [HR 0.33 (CI 0.14 - 0.74, p = 0.007)] and neuromuscular blockade [HR 0.44 (CI 0.23 - 0.83, p = 0.01)] were independently associated with reduced in-hospital mortality.

In conclusion, therapeutic anticoagulation and neuromuscular blockade were independently associated with improved survival of COVID-19 patients requiring IMV. Notwithstanding the lower sample size and retrospective nature of our study, given that survival benefit associated with systemic corticosteroids was lost at ~50 - 60 days, randomized controlled trials such as RECOVERY should also consider reporting 60- or 75-day mortality, in addition to 30-day mortality (when these data are available).

***Keywords:*** *COVID-19; Invasive Mechanical Ventilation; Anticoagulation; Corticosteroids; Intensive Care Unit*

## Abbreviations

COVID-19: Coronavirus Disease 2019; IMV: Invasive Mechanical Ventilation; IQR: Interquartile Range; HR: Hazard Ratio; CI: Confidence Interval; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; RT-PCR: Reverse Transcription Polymerase Chain Reaction; PEEP: Positive End-Expiratory Pressure; FiO2: Fraction of Inspired Oxygen; Tv: Tidal Volume; APACHE: Acute Physiology of Chronic Health Evaluation; UFH: Unfractionated Heparin; aPTT: Activated Partial Thromboplastin Time; $PaO_2$: Partial Pressure of Arterial Oxygen; P/F: $PaO_2/FiO_2$; SD: Standard Deviation; PH: Proportional Hazard; ANOVA: Analysis of Variance; BMI: Body Mass Index; DM: Diabetes; VTE: Venous Thromboembolism; HTN: Hypertension; COPD: Chronic Obstructive Pulmonary Disease; HIV: Human Immunodeficiency Virus; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; HF: Heart Failure; CVA: Cerebrovascular Accident

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen causing coronavirus disease 2019 (COVID-19), has rapidly spread around the world [1]. As of 06/28/2020, around 10.2 million people have been diagnosed with COVID-19 and 503,000 deaths have been reported worldwide [2].

The clinical course of COVID-19 is highly variable ranging from mild to severe disease depending on host factors. While a majority (~ 80%) of patients develop mild disease, severe illness has been observed in 5 - 14% of cases [3]. While the percentage of patients that require invasive mechanical ventilation (IMV) for respiratory failure is relatively small (~2 - 3%) [1,4], it still accounts for large absolute numbers with overwhelmed intensive care units (ICU) in healthcare systems around the world.

The etiology of respiratory failure in COVID-19 is multifactorial. Acute respiratory distress syndrome (ARDS) is the leading mechanism [5]. In addition, it has been suggested that coagulation derangements resulting in thrombi in pulmonary circulation may play a significant role in respiratory failure. Klok., *et al*. recently demonstrated that 31% of COVID-19 patients requiring ICU care had thrombotic complications, with pulmonary embolism being the prominent diagnosis [6]. Additionally, differences in lung mechanics in these patients from traditional ARDS have been observed [7].

There is a significant evidence that prone positioning [8], neuromuscular blockade [9] and systemic corticosteroids [10] reduce mortality in patients with severe ARDS. However, it is not clear if these treatments have similar effects on patients with COVID-19 compared to traditional ARDS. Data from the recently reported RECOVERY trial [11] suggests that corticosteroids reduce mortality in severe COVID-19 cases.

## Aim of the Study

In this study, we aimed to investigate whether these interventions (therapeutic anticoagulation, neuromuscular blockade, prone positioning, and corticosteroids) are associated with reduced mortality in COVID-19 patients requiring IMV admitted to ICU.

## Materials and Methods

### Study design and participants

This retrospective study was conducted at Jacobi Medical Center in Bronx, New York. Jacobi is a 457-bed municipal hospital operated by New York City Health and Hospitals Corporation (NYCHHC) in affiliation with the Albert Einstein College of Medicine. Jacobi has 12 medical ICU beds, but during the pandemic the capacity was expanded to ~72 beds by including beds from the coronary care unit, surgical, burn, and pediatric ICUs. Consecutive adult patients (age ≥ 18 years) that required IMV and admission to ICU due to acute hypoxic

respiratory failure secondary to reverse transcription polymerase chain reaction (RT-PCR) confirmed COVID-19 were included in the study. The enrollment period was February 5th to May 11th, 2020. Eleven patients were excluded from the study because they were on airway pressure release ventilation, thereby lacking some ventilator parameters required for our analysis. The study was approved by the institutional review board of the Albert Einstein College of Medicine (2020-11757) and the respective committee of NYCHHC/Jacobi.

### Data extraction

Data on demographics, prior medical history, vital signs, average ventilator settings [PEEP, $FiO_2$ and tidal volume (Tv)] within 24 hours of diagnosis of acute respiratory failure and parameters needed to calculate Acute Physiology and Chronic Health Evaluation (APACHE) II were collected.

### Interventions

**Therapeutic anticoagulation:** Patients without contraindication for anticoagulation (platelet count > 50,000/µl, no history of Child-Pugh C liver disease, and no evidence of bleeding) received full dose anticoagulation [enoxaparin 1 mg/kg every 12-hour or 1.5 mg/kg every 24-hour, apixaban 5 mg every 12-hour, or unfractionated heparin (UFH) infusion targeting activated partial thromboplastin time (aPTT) 1.5 - 3 times baseline] if they had documented venous thromboembolic disease and/or a D-dimer > 3000 ng/ml. Patients were included in the therapeutic anticoagulation group if they received anticoagulation for more than 24 hours during the hospital course.

**Prone-positioning:** Prone position for management of refractory hypoxia was done at the discretion of intensivist for patients in ARDS with P/F ratio < 150 while on PEEP ≥ 5 $cmH_2O$ [12]. Identified patients were in a complete prone position for 14 - 18 consecutive hours for each session. During the pandemic, a sudden surge of patients admitted with ARDS outpaced our capacity to prone sedated patients on IMV, and thereby provided us with patients with nearly matched baseline characteristics (Table 1) for studying the association of prone position with survival. Average P/F ratio was < 150 in the first 24 hours of IMV initiation in 40 (80%) patients in the prone group and 32 (50.8%) patients in the supine group.

**Corticosteroids:** Patients were included in the corticosteroid group if they received at least one dose of any systemic corticosteroids (hydrocortisone, dexamethasone, or methylprednisolone).

**Neuromuscular blockade:** Cisatracurium or rocuronium was used for neuromuscular blockade to maintain ventilator synchrony. The decision to proceed with neuromuscular blockade was based on intensivist's discretion and was dependent on the assessment of ventilator asynchrony in patients with moderate to severe ARDS [9]. Patients who received neuromuscular blockade only for intubation were not included in neuromuscular blockade group.

### Outcomes and statistical analysis

The endpoint was in-hospital mortality. Continuous data are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) and categorical data as relative frequencies. The comparison between intervention and non-intervention groups were performed with student t-test for normal distribution and with K-Wallis test for skewed distribution. Relative frequencies were compared using the Chi-square test. Kaplan-Meier survival analysis was performed individually for the interventions. Log-rank test was performed. Cox proportional hazard (PH) assumptions were tested using Schoenfeld individual test. For interventions fulfilling Cox PH regression assumptions, Cox regression was performed with univariate variables. In the multivariable model, clinically significant variables were predefined and included as covariates due to their known association with mortality. Covariates not fulling the PH assumptions were included as stratification variables to account for the confounding effect on the study variable. Effect of interaction between the stratifica-

tion variables and main effect variables was studied by comparing models using ANOVA. P-value < 0.05 was considered as statistically significant. Statistical analysis was performed using the Microsoft Excel (2019) and RStudio (Version1.2.5033).

## Results

113 consecutive patients were enrolled: 76.1% male, 38.9% African American, mean age 56.5 ± 14.4 years, and BMI 32.1 ± 8.8 kg/$m^2$. Hypertension and diabetes (DM) were present in 66 (58.4%) and 67 (69.3%) patients, respectively. Median P/F ratio in the first 24 hours after initiation of IMV was 125 [IQR 99 - 189]. APACHE II was 26.9 ± 8.9. Median length of stay was 18 [IQR 9 - 30] days (Table 1). In-hospital mortality was seen in 74 of 113 patients (65.5%); 81.3% for patients ≥ 65 years and 59.3% for patients < 65 years. Only 4 (3.53%) patients remained hospitalized at the time of final analysis.

### Therapeutic anticoagulation

A total of 82 (72.6%) patients received therapeutic anticoagulation and remaining 31 (27.4%) were on prophylactic anticoagulation. D-dimer values were available for 108 patients, 81 patients in therapeutic anticoagulation group, and 27 in prophylaxis group. Peak D-dimer > 3,000 ng/ml was seen in 88.9% (72 of 81) of patients in anticoagulation group and 70.4% (19 of 27) in prophylaxis group (p = 0.02). Median peak D-dimer levels were 9,619 ng/ml (IQR 5,073 - 35,424) in anticoagulation group vs. 5,196 ng/ml (IQR 2,544 - 13,046) in prophylaxis group (p < 0.01).

Of 82 patients in therapeutic anticoagulation group, 35 (42.7%) received it solely based on peak D-dimer > 3,000 ng/ml. 37 (51.4%) had peak D-dimer > 3,000 ng/ml and either a pre-existing or newly diagnosed condition requiring therapeutic anticoagulation [e.g. atrial fibrillation, venous thromboembolism (VTE)]. One patient did not have a documented D-dimer value but was anticoagulated for newly diagnosed VTE. Of the remaining 9 patients with peak D-dimer < 3,000 ng/ml, 3 had pre-existing condition requiring therapeutic anticoagulation, 2 patients had newly diagnosed VTE and 4 were anticoagulated for suspicion of PE but inability to obtain the test due to infection control reasons.

Parameters including age, gender, race, BMI, comorbidities, APACHE II, Tv, and median P/F ratio were not different between therapeutic and prophylactic anticoagulation groups (Table 1). However, mean PEEP was higher (13.9 vs. 11.8 $cmH_2O$, p = 0.01) in the therapeutic anticoagulation group.

| | All patients | Prone positioning | | | Corticosteroid use | | | Neuromuscular blockade use | | | Anticoagulation use | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N = 113 | Yes N = 50 | No N = 63 | p-value | Yes N = 58 | No N = 55 | p-value | Yes N = 70 | No N = 43 | p-value | Therapeutic N = 82 | Prophylactic N = 31 | p-value |
| Male sex-n (%) | 87 (76.1) | 41 (82) | 45 (78) | 0.28 | 44 (76) | 42 (76) | 1 | 54 (77) | 32 (74) | 0.92 | 64 (78) | 22 (71) | 0.59 |
| Age (years) Mean (SD) | 56.5 (14.4) | 56 (11.8) | 56.8 (16.3) | 0.76 | 55.4 (14.9) | 57.6 (14) | 0.41 | 53.8 (14.3) | 60.8 (13.6) | 0.01 | 56.4 (14.3) | 56.6 (14.9) | 0.94 |
| Race – n (%) | | | | | | | | | | | | | |
| African American | 44 (38.9) | 10 (20) | 34 (54) | <0.01 | 22 (37.9) | 22 (40) | 0.81 | 25 (36) | 19 (44) | 0.75 | 27 (33) | 17 (55) | 0.13 |
| Hispanic/ Latino | 38 (33.6) | 24 (48) | 14 (22) | | 18 (31) | 20 (36) | | 25 (36) | 13 (30) | | 29 (35) | 9 (29) | |
| Caucasian | 4 (3.5) | 1 (2) | 3 (5) | | 2 (35) | 2 (3.6) | | 2 (3) | 2 (5) | | 4 (5) | 0 (0) | |
| Other | 27 (23.9) | 15 (30) | 12 (19) | | 16 (28) | 11 (20) | | 18 (26) | 9 (21) | | 22 (27) | 5 (16) | |
| BMI -kg/$m^2$ Mean (SD) | 32.1 (8.8) | 32.2 (7.3) | 31.9 (10) | 0.87 | 33.5 (8.6) | 30.9 (9) | 0.07 | 33.2 (9.2) | 30.3 (8) | 0.06 | 32.5 (9.2) | 30.9 (8.0) | 0.37 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Comorbidity -n (%) | | | | | | | | | | | | |
| HTN | 66 (58.4) | 28 (56) | 38 (60) | 0.79 | 37 (64) | 29 (52) | 0.31 | 39 (56) | 27 (63) | 0.59 | 49 (60) | 17 (55) | 0.79 |
| DM | 67 (69.3) | 30 (60) | 37 (59) | 1 | 38 (66) | 29 (52) | 0.23 | 39 (56) | 28 (65) | 0.43 | 48 (59) | 19 (61) | 0.96 |
| COPD | 7 (6.2) | 2 (4) | 5 (8) | 0.64 | 3 (5) | 4 (7) | 0.94 | 2 (3) | 5 (12) | 0.14 | 5 (5) | 2 (7) | 1 |
| HIV | 2 (1.8) | 0 (0) | 2 (3) | 0.58 | 1 (2) | 1 (2) | 1 | 2 (3) | 0 (0) | 0.07 | 1 (1) | 1 (3) | 1 |
| CAD | 8 (7.1) | 5 (10) | 3 (5) | 0.28 | 5 (9) | 3 (6) | 0.51 | 2 (3) | 5 (12) | 0.14 | 5 (6) | 3 (10) | 0.51 |
| CKD | 4 (3.5) | 1 (2) | 3 (5) | 0.43 | 1 (2) | 3 (6) | 0.28 | 3 (4) | 3 (7) | 0.12 | 3 (4) | 1 (3) | 0.91 |
| HF | 5 (4.4) | 1 (2) | 4 (6) | 0.26 | 3 (5) | 2 (4) | 0.93 | 1 (1) | 3 (7) | 0.30 | 4 (5) | 1 (3) | 0.7 |
| CVA | 7 (6.2) | 2 (4) | 5 (8) | 0.39 | 4 (7) | 3 (6) | 0.75 | 2 (3) | 4 (9) | 0.28 | 5 (6) | 2 (7) | 0.94 |
| Smoking | 13 (11.5) | 5 (10) | 8 (13) | 0.66 | 5 (9) | 8 (15) | 0.32 | 3 (4) | 7 (16) | 0.21 | 10 (12) | 3 (10) | 0.71 |
| | | | | | | | | 6 (9) | | | | | |
| APACHE II Mean (SD) | 26.9 (8.9) | 26.5 (8.2) | 27.2 (9.5) | 0.76 | 26.5 (9) | 27.4 (8.9) | 0.6 | 26.2 (9) | 28.1 (8.7) | 0.29 | 27.3 (8.7) | 25.8 (9.6) | 0.49 |
| P/F ratio Median (IQR) | 125 [99-189] | 107 [91-139] | 150 [107-221] | <0.01 | 118 [99-167] | 141 [101-221] | 0.27 | 115 [99-167] | 147 [107-232] | 0.03 | 125 [100-176] | 133 [100-223] | 0.55 |
| $FiO_2$ (%) Mean (SD) | 82.3 (20.4) | 90.2 (13.9) | 76.0 (22.5) | <0.01 | 87.8 (17.7) | 76.5 (21.6) | <0.01 | 85 (19.9) | 77.8 (21) | 0.07 | 83.8 (19.6) | 78.1 (22.2) | 0.21 |
| Tidal volume-ml/kg IBW Mean (SD) | 6.71 (1.2) | 6.69 (1.1) | 6.73 (1.2) | 0.86 | 6.7 (1.3) | 6.75 (1.1) | 0.94 | 6.69 (1.2) | 6.7 (1.2) | 0.83 | 6.7 (1.2) | 6.75 (1.1) | 0.82 |
| PEEP ($cmH_2O$) | 13.3 (3.9) | 15.1 (3.2) | 12 (3.8) | <0.01 | 14.3 (3.9) | 12.3 (3.5) | <0.01 | 14.4 (3.6) | 11.5 (3.7) | <0.01 | 13.9 (3.8) | 11.8 (3.8) | 0.01 |
| Length of stay -days Median [IQR] | 18 [9-30] | 21.5 [15-41.5] | 14 [8-24.5] | <0.01 | 21.5 [12.3-30] | 14 [7-25.5] | <0.01 | 21 [11.5-32.3] | 13 [8.5-22] | 0.01 | 21 [11-36.8] | 13 [7-17.5] | <0.01 |
| Prone positioning n (%) | 50 (44.2) | | | | 35 (60) | 15 (27) | <0.01 | 38 (54) | 12 (28) | <0.01 | 44 (54) | 6 (19) | <0.01 |
| Corticosteroid use n (%) | 58 (51.3) | 35 (70) | 23 (37) | <0.01 | | | | 43 (61) | 15 (35) | <0.01 | 52 (63) | 6 (19) | <0.01 |
| Neuromuscular blockade agent use n (%) | 70 (61.9) | 38 (76) | 32 (51) | <0.01 | 43 (74) | 27 (49) | <0.01 | | | | 54 (66) | 16 (52) | 0.16 |
| Anticoagulation use n (%) | 82 (72.6) | 44 (88) | 38 (60) | <0.01 | 52 (90) | 30 (55) | <0.01 | 54 (77) | 28 (65) | 0.16 | | | |

***Table 1:*** *Baseline characteristics and clinical features in various intervention groups.*

*HTN: Hypertension; DM: Diabetes; COPD: Chronic Obstructive Pulmonary Disease; HIV: Human Immunodeficiency Virus; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; HF: Heart Failure; CVA: Cerebrovascular Accident; APACHE II: Acute Physiology and Chronic Health Evaluation; P/F Ratio:* Ratio *of Partial Pressure of Arterial Oxygen ($PaO_2$ in mmHg) to Fraction of Inspired Oxygen ($FiO_2$ Expressed as a Fraction); PEEP: Positive End-Expiratory Pressure.*

There was a significant difference in the Kaplan-Meier survival curves between therapeutic anticoagulation vs. prophylactic anticoagulation groups (log-rank p = 0.002) (Figure 1A). Univariate cox regression analysis for in-hospital mortality showed a significant decrease in mortality in the therapeutic anticoagulation group [HR 0.47 (CI 0.28 - 0.78, p = 0.003)] (Table 2). In the fully adjusted model, the therapeutic anticoagulation group continued to have lower mortality [HR 0.33 (CI 0.14 - 0.74, p = 0.007)] (Table 2).

| | Univariable Models HR (95% CI)[a] | p value[b] | Multivariable Models | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Model 1[j] HR (95% CI)[a] | p value[b] | Model 2[k] HR (95% CI)[a] | p value[b] | Model 3[l] HR (95% CI)[a] | p value[b] | Model 4[m] HR (95% CI)[a] | p value[b] |
| Anticoagulation use[c] | 0.47 (0.28-0.78) | 0.003 | 0.49 (0.29-0.82) | 0.006 | 0.47 (0.28-0.80) | 0.005 | 0.47 (0.28-0.80) | 0.005 | 0.33 (0.14-0.74) | 0.007 |
| Neuromuscular blockade use[d] | 0.60 (0.38-0.96) | 0.03 | 0.64 (0.39-1.03) | 0.06 | 0.61 (0.37-1.003) | 0.05 | 0.59 (0.35-0.97) | 0.04 | 0.44 (0.23-0.83) | 0.01 |
| Age[e] | 1.75 (1.09-2.81) | 0.02 | | | 1.52 (0.90-2.57) | 0.11 | 1.57 (0.92-2.68) | 0.09 | 1.02 (0.53-1.95) | 0.94 |
| Sex[f] | 0.57 (0.31-1.04) | 0.07 | | | 0.59 (0.32-1.1) | 0.09 | 0.62 (0.33-1.19) | 0.15 | 0.98 (0.46-2.05) | 0.95 |
| BMI[g] | 1.02 (0.64-1.61) | 0.93 | | | 1.33 (0.81-2.19) | 0.26 | 1.26 (0.76-2.15) | 0.37 | 0.79 (0.43-1.44) | 0.44 |
| Hypertension | 1.24 (0.78-1.99) | 0.36 | | | 1.29 (0.76-2.17) | 0.34 | 1.28 (0.76-2.15) | 0.35 | 1.71 (0.89-3.29) | 0.10 |
| Diabetes Mellitus | 0.69 (0.44-1.11) | 0.13 | | | 0.61 (0.38-0.99) | 0.049 | 0.61 (0.37-0.99) | 0.04 | 0.14 (0.07-0.26) | <0.01 |
| P/F ratio[h] | 0.91 (0.58-1.44) | 0.70 | | | | | 0.82 (0.50-1.34) | 0.43 | 0.39 (0.21-0.74) | 0.03 |
| Tidal Volume[i] | 0.77 (0.49-1.22) | 0.27 | | | | | 0.91 (0.56-1.49) | 0.71 | 0.38 (0.21-0.67) | <0.01 |

***Table 2:*** *Cox proportional hazard regression for in-hospital mortality.*

*a: Hazard ratio (95% confidence interval).*

*b: p value for Wald $\chi 2$ test of $\beta$ coefficient in the Cox proportional hazards (PH) regression model.*

*c : Anticoagulation use (Therapeutic compared to prophylactic use).*

*d: Neuromuscular blockade (NM) use (NM group compared to no NM group).*

*e: Age (Age above the median compared to age below the median).*

*f: Sex (Female compared with male).*

*g: Body Mass Index (kg/m2) (BMI above the median compared to BMI below the median).*

*h: Ratio of arterial oxygen partial pressure (PaO2 in mmHg) (P/F ratio above the median compared to below the median).*

*i: Tidal volume in ml per kilogram of ideal body weight (TV per kg IBW above the median compared to below the median).*

*j: Model 1: includes the interventions with statistically significant p values on univariate Cox PH model.*

*k: Model 2: in addition to Model 1 also includes baseline patient characteristics: age, sex, BMI, HTN, DM due to association with mortality in previous studies published on COVID 19.*

*l: Model 3: in addition to Model 2, it includes P/F ratio and TV/ kg IBW, which are confounders known to effect mortality in intubated patients. All the variables included in the analysis met the Cox PH assumption on testing with Schoenfeld individual test.*

*m: Model 4: Model 3 does not include prone positioning, corticosteroid use, APACHE II score (higher than median compared to lower than median) as these variables did not fulfil the Cox PH assumption. Stratified Cox PH model was performed and compared to Stratified Cox PH model including interaction between the stratification variables and other variables included in Model 3. ANOVA comparing the models showed that Model with interactions had significant difference ($p < 0.01$). Therefore, the final model which is shown here is: Model 4, which is the Stratified Cox PH model which includes interactions between proning, corticosteroid use and APACHE II score and all other variables in Model 3.*

Blood transfusion was required in 47.1% of patients in the therapeutic anticoagulation group and 16.1% in the prophylactic anticoagulation group. No intracranial hemorrhage was reported in either group. Gastrointestinal tract was the most common site of bleeding, identified in 12 of 16 patients as a major bleeding source.

### Prone positioning

A total of 50 (44.2%) patients were included in the prone positioning group. Patients were included in the prone group if they underwent at least one session of prone positioning. Median number of proning sessions were 3.5 [IQR 2 - 5]. Parameters including age, BMI, comorbidities, APACHE II, Tv were not different between prone and supine groups (Table 1). However, median P/F ratio was lower (107 vs. 150, $p < 0.01$) and mean PEEP was higher (15.1 vs. 12 $cmH_2O$, $p < 0.01$) in the prone group. This is attributable to the fact that patients with P/F ratio less than 150 were considered eligible for prone positioning. Despite African American being predominant race in our cohort (44 of 113 patients, 38.9%), they constituted smaller fraction 20% (10 of 50 patients) of the prone group. This difference could be explained by lower proportion of African American with mean P/F ratio < 150 compared to other racial groups. P/F ratio < 150 was seen in 54.5% African American, 73.6% Hispanic, 75% Caucasian, and 62.9% others.

Log-rank analysis performed on Kaplan-Meier curve comparing the survival in prone vs. the supine groups had a p-value 0.14, indicating no difference in survival between the groups (Figure 1B). Data for prone positioning did not fulfill Cox PH assumption, hence was not included in the final multivariate Cox PH regression model.

### Corticosteroids

A total of 58 (51.3%) patients received systemic corticosteroids. Majority of patients 56 (96.6%) were treated with methylprednisolone, 1 (1.7%) with both methylprednisolone and hydrocortisone, and 1 (1.7%) with dexamethasone. Median days of corticosteroid treatment was 6 [IQR 4 - 9]. Patients were treated with a dose equivalent to 40 - 200 mg of methylprednisolone per day.

Parameters including age, gender, race, BMI, comorbidities, APACHE II, Tv and median P/F ratio were not different between corticosteroid and no corticosteroid groups (Table 1). However, mean PEEP was higher (14.3 vs. 12.3 $cmH_2O$, $p < 0.01$) in the corticosteroid group. Log-rank analysis performed on Kaplan-Meier curve comparing the survival of patients who received corticosteroids with those who did not, revealed a p-value of 0.04. However, visual inspection of the Kaplan-Meier curve indicated that corticosteroids may offer a short-term benefit up to ~60 days, but do not provide long-term advantage. It is well known that the p-value obtained by the log-rank test may not be reliable if the survival curves cross (Figure 1C). In addition, data for corticosteroids did not fulfill the Cox PH assumptions based on Schoenfeld individual test.

### Neuromuscular blockade

A total of 70 (61.9%) patients undergoing IMV received neuromuscular blockade. Parameters including gender, race, BMI, comorbidities, APACHE II, Tv and median P/F ratio were not different between neuromuscular blockade and no neuromuscular blockade groups (Table 1). However, age (53.8 vs. 60.8 years, $p = 0.01$) and P/F ratio (115 vs. 147, $p = 0.03$) were lower and mean PEEP was higher (14.4 vs. 11.5 $cmH_2O$, $p < 0.01$) in the neuromuscular blockade group.

There was a significant difference in the Kaplan-Meier survival curves between neuromuscular blockade vs. non neuromuscular blockade groups (log-rank p-value = 0.003) (Figure 1D). Univariate and multivariate cox regression analysis for in-hospital mortality showed a significant decrease in mortality in the neuromuscular blockade group [HR 0.60 (CI 0.38-0.96, $p = 0.03$)], and [HR 0.44 (CI 0.23 - 0.83, $p = 0.01$)], respectively (Table 2).

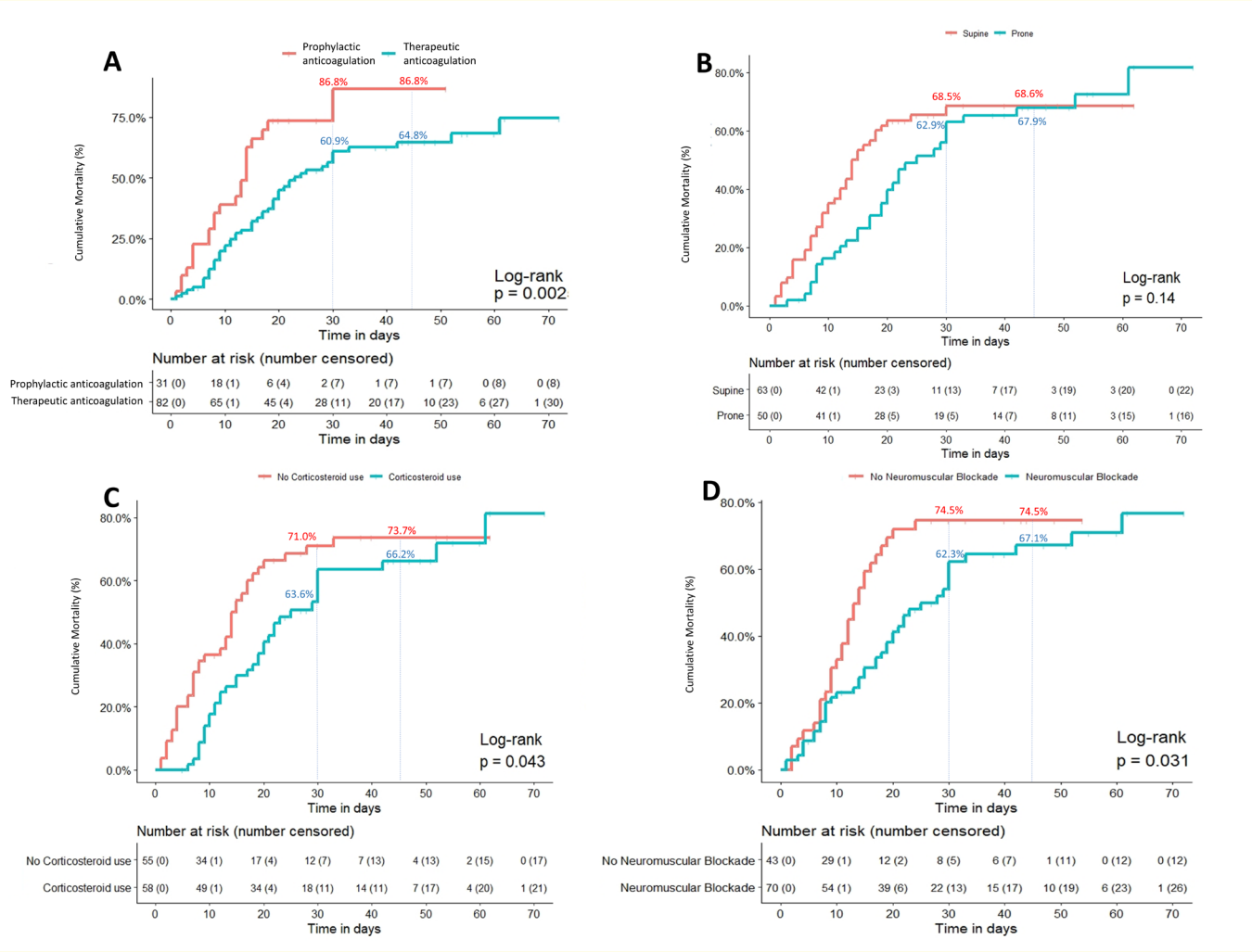


***Figure 1:*** *Kaplan-Meier cumulative incidence curve for mortality in each intervention arm. 30 and 45-day mortality estimate is represented on the curve. A Therapeutic anticoagulation vs. Prophylactic anticoagulation In-hospital mortality was 62% (51 of 82) in therapeutic anticoagulation and 74% (23 of 31) in prophylactic anticoagulation. B Prone vs. Supine In-hospital mortality was 66% (33 of 50) in prone and 65% (41 of 63) in supine group C Corticosteroids vs. No corticosteroids In-hospital mortality was 62% (36 of 58) in corticosteroid and 69% (38 of 55) in no corticosteroid group D Neuromuscular blockade vs. No neuromuscular blockade In-hospital mortality was 61% (43 of 70) in neuromuscular blockade and 72% (31 of 43) in no neuromuscular blockade group.*
*Number censored represents patients who are alive on the last day of individual follow-up (discharged patients and 4 patients that were still in hospital as of 6/18/2020).*

## Discussion

Our study described the baseline characteristics and outcomes of 113 COVID-19 patients requiring IMV in a safety net hospital that predominantly serves the African American and the Hispanic population. This is the first study that has performed evaluation of vari-

ous interventions including therapeutic anticoagulation, prone positioning, corticosteroids, and neuromuscular blockade in COVID-19 patients on IMV. A notable strength of our study is that it has a long follow-up (up to 72 days) for intubated patients receiving intensive care with COVID-19 infection, with 96.5% of patients having met the study outcome (discharged alive or in-hospital mortality) at the time of final analysis. There are some important aspects to be considered while weighing the data reported in this study with that reported in others, as discussed below for each intervention.

This in-hospital mortality of 65.5% is the closest approximation of actual mortality in COVID-19 patients on IMV. Mean APACHE II in our cohort was 26.9 ± 8.9, which correlates with 55% in-hospital mortality in non-operative patients [13]. Mortality rate ranging from 24.5 - 96.9% has been reported in critically ill COVID-19 patients [5,14-17]. While only a fraction of the study population (20.2 - 79%) was on IMV in prior studies [5,14-16], the novelty of our study is that we exclusively focused on the outcomes of COVID-19 patients receiving IMV. Additionally, availability of final outcome in the majority (96.5%) of patients addresses a critical knowledge gap from the prior studies evaluating mortality as anywhere from 29 - 72% of the study population remained in the hospital at the time of their mortality analysis [5,14-16]. It should also be noted, however, that ours is a public safety-net hospital with a high proportion of patients with uncontrolled co-morbidities, and also that we had a massive surge of patients during the NYC peak of COVID-19.

### Systemic anticoagulation

COVID-19 associated coagulopathy has been postulated to account for VTE and multiorgan dysfunction that is common in severe COVID-19 patients [18-20]. Our findings suggest a mortality benefit with therapeutic anticoagulation in the specific cohort of IMV patients. A similar outcome has been described in a broader hospitalized COVID-19 population that included some patients requiring IMV [21]. Our data is limited by the retrospective observational nature and limited radiologic confirmation of VTE. Many patients were anticoagulated based on elevated D-dimer per institutional protocol. Blood transfusions may partially be attributed to anemia of critical illness, with 10% of patients identified to have a gastrointestinal bleeding. There were no major intracranial bleeds. Prospective trials are needed to determine safety and to validate survival advantage conferred by full dose anticoagulation in COVID-19 patients requiring IMV. Although widely considered 'standard of care' in severe COVID-19 management currently (and rightly so), prospective trials are still needed to further validate the survival advantage conferred by full-dose anticoagulation in COVID-19 patients requiring IMV.

### Prone positioning

Prone positioning has been shown to reduce mortality in patients with severe ARDS requiring IMV [8,22,23]. Small preliminary studies have evaluated the safety of prone position in COVID-19 on IMV [24] and a study by Thompson., *et al*. demonstrated improved oxygenation in awake spontaneously breathing patients with proning [25]. To the best of our knowledge, the effect of proning on mortality of COVID-19 requiring IMV has not been evaluated. In our study, 106 (93.8%) patients met Berlin criteria for ARDS with P/F ratio < 300 and diffuse bilateral infiltrates on chest radiograph [13] and 72 (63.7%) patients had P/F ratio < 150. Kaplan-Meier survival curve from this study showed a short-term mortality benefit but no long-term survival advantage. However, it must be noted that those who received the prone positioning intervention in this cohort of patients had worse respiratory parameters in the first 24 hours of IMV initiation. Considering all factors, particularly that proned patients had an early survival advantage despite worse respiratory parameters,the data indicate that prone positioning may have an overall beneficial effect in COVID-19 patients in severe ARDS, but the magnitude of possible benefit appears to bemodest. Pathophysiological differences such as higher incidence and severity of thrombotic pulmonary disease [26,27] may make proning less effective in COVID-19 patients.

### Systemic corticosteroids

Patients who received systemic corticosteroids had short-term survival benefit in our study lasting up to ~60 days. However, overall, in-hospital mortality was not different between the groups. RECOVERY trial evaluating the efficacy of low dose dexamethasone for hospitalized COVID-19 patients in the United Kingdom [11] showed reduced mortality in dexamethasone-treated COVID-19 patients requiring IMV. The median duration of dexamethasone in the RECOVERY trial was 6 days comparable to our study. There are several reasons

for the different findings in our study: 1) This is a retrospective study in a much smaller cohort of patients; the RECOVERY trial was a randomized, controlled, open-label trial which included 1007 patients on IMV. 2) The RECOVERY trial reported 28-day mortality, and as we alluded earlier, we did see reduced mortality in the corticosteroid group earlier in the course after initiation of IMV, but there was no sustained benefit with long-term follow-up. 30-day mortality in our cohort was 63.6% for patients that received corticosteroids, and 71% for patients that did not. 3) Most patients in our study were treated with methylprednisolone. It is not clear if methylprednisolone has similar benefits compared to dexamethasone in COVID-19. 4) Population differences between the studies such as a much higher proportion of patients with DM (69.3%) in our study, compared to the RECOVERY trial (~25% patients with DM). Considering all the above factors, while it may still be beneficial to administer dexamethasone to COVID-19 patients requiring IMV, long-term follow-up data form the RECOVERY trial (60- or 75-day mortality) is warranted. This is particularly important given that many COVID-19 patients requiring IMV have a prolonged ICU course.

**Neuromuscular blockade**

The patients who received neuromuscular blockade had more severe disease as reflected in the need for higher PEEP and lower P/F ratio at IMV initiation. After adjusting for factors which account for differences in severity of disease, neuromuscular blockade had survival benefit in our cohort of COVID-19 patients requiring IMV. These findings are consistent with improved survival with neuromuscular blockade in patients with moderate to severe ARDS reported in study by Papazian., *et al* [9]. Given these findings, the need for neuromuscular blockade in COVID-19 patients on IMV should be assessed and encouraged on a case-by-case basis based on ventilator asynchrony.

## Conclusion

The main findings can be summarized as follows: i) in-hospital mortality of our cohort of severe COVID-19 patients on IMV in ICU was 65.5%, with 96.5% of patients having met the study outcome (discharged alive or in-hospital mortality) at the time of final analysis; ii) therapeutic anticoagulation and neuromuscular blockade were independently associated with lower in-hospital mortality; and iii) despite the trend toward improved survival earlier in the course after initiation of IMV, prone positioning and corticosteroids were not associated with long-term survival benefit in this single-center retrospective study.

## Conflict of Interest

No disclosure to declare.

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