

# Methylprednisolone, Venous Thromboembolism, and Association with Heparin to 30 Days in Hospital Survival in Severe COVID-19 Pneumonia

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## Research Article

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# Abstract

## BACKGROUND

Mortality in severe COVID-19 pneumonia is associated with thrombo-inflammation. Corticosteroids are given to attenuate the inflammation, but they are associated with thrombosis. The aims of this study were to determine the risk of venous thromboembolism between no methylprednisolone and methylprednisolone (dose versus duration) and to evaluate the synergistic dose-dependent association of heparin and methylprednisolone to 30 days in hospital survival.

## METHODS

This was a secondary analysis of a retrospective cohort. Patients included in this study were older than 18 years of age and admitted for severe COVID-19 pneumonia between March to June 2020 in 13 hospitals in New Jersey, United States. A propensity score analysis between administration of methylprednisolone and no methylprednisolone was fitted for 11 variables and Youden Index Method was used to determine cut-off between low dose and high dose methylprednisolone. Multivariate cox regression was performed to assess risk.

## RESULTS

In 759 patients, the incidence of venous thromboembolism was 9% of patients who received methylprednisolone and 3% of patients who did not receive methylprednisolone with a [RR =2.92 (95% CI 1.54, 5.55 P< 0.0001)]. There was a higher incidence of mechanical ventilation in the methylprednisolone group. The median d-dimer between patients with venous thromboembolism was higher compared to those without (P<0.0003). However, the d-dimer was not statistically significant between those who had venous thromboembolism between methylprednisolone and no methylprednisolone groups. (P 0.40). There was no higher risk in high dose versus low dose [RR=0.524 (95% CI 0.26, 1.06 P 0.4)]; however, the risk for DVT/PE between methylprednisolone for > 7 days and ≤ 7 days was statistically significant. (RR=5.46 95% CI 2.87, 10.34 P < 0.0001). Patients who received low dose and therapeutic heparin had a trend towards higher risk of mortality compared to prophylactic heparin (HR=1.81 95% CI 0.994 to 3.294) (P=0.0522). There was no difference in 30 days in hospital survival between high dose with prophylactic or therapeutic heparin (HR=0.827 95% CI 0.514 to 1.33) (P=0.4335).

## CONCLUSIONS

Methylprednisolone for > 7 days had a higher association of venous thromboembolism. There was no added benefit of therapeutic heparin to methylprednisolone on mechanically ventilated patients.

## Introduction

As of July 2, 2021, there has been 182,319,261 coronavirus disease 2019 (COVID-19) cases and 3,954,324 deaths worldwide. (1) It is a biphasic disease, with predominant viral shedding during the first

week and hyperinflammation during the second week. The main cause of mortality is acute respiratory distress syndrome (ARDS). Lung histologic studies show severe endothelial damage, diffuse alveolar damage, thrombosis in situ, intussusceptive angiogenesis, and patterns of organizing pneumonia (OP) and / or acute fibrosing organizing pneumonia (AFOP). (2,3) There is a higher degree of thrombosis compared to ARDS secondary to influenza. (2,3)

Corticosteroids were considered for their anti-inflammatory and anti-fibrotic effect and due to the Recovery study, has become standard of care. (4) During the initial pandemic surge, we used methylprednisolone as a rescue due to concerns of prolonging viral shedding. There was significant heterogeneity in how it was administered. Our initial study found that low dose (LDMP) (<1.36 mg/kg of actual body weight/day), administered >7 days from onset of symptoms was associated with prolonged survival and no additional benefit with high dose (HDMP) ( $\geq$  1.36 mg/kg of actual body weight/day). (5) Several studies on high dose methylprednisolone suggested mortality benefit although their definition of high dose fits our weight-based definition of low dose. (6-8)

Non-COVID-19 studies have suggested a corticosteroid associated coagulopathy due to high levels of Factor VIII, Factor IX, and von Willebrand factor (vWF) and enhanced thrombin generation. (9-12) Some studies suggest that higher doses of methylprednisolone were associated with higher rates of thrombosis. (13-15) Two studies suggest that risk of venous thromboembolism (VTE) decreases with duration of use (16,17) A recent meta-analysis in COVID-19 suggested an association of VTE with corticosteroids, although the association may also be due to severity of underlying disease. (18) There was significant heterogeneity in corticosteroid administration, and they were not able to assess which regimen was associated with higher risk. (18)

The incidence of VTE in COVID-19 ranges 1.31%-17%. (19-21) Higher risk of thrombotic complications may suggest benefit from higher doses of anticoagulation. Heparin maybe an ideal anti-coagulation because of its anti-thrombotic, anti-inflammatory, and anti-viral properties. One observational study showed that intermediate to high prophylactic dose reduced the incidence of thrombotic complications. (22) Another study showed that intermediate to higher prophylactic doses reduced thrombotic complications but were not associated with improved mortality. (23) Early therapeutic anticoagulation in critically ill patients have failed to show improved survival. (24,25) Therapeutic anticoagulation was shown to improve survival in patients who are not critically ill or on nasal cannula. (26)

Since mortality in COVID-19 ARDS is associated with thrombo-inflammation, there may be a synergistic, dose dependent association with prolonged in hospital survival with methylprednisolone and heparin. Currently, there is sparsity in literature regarding this outcome.

## Methodology

## Eligibility criteria

We performed a comprehensive review of real-world data collected within Hackensack Meridian Health (HMH), a NJ health network comprising of thirteen hospitals. Data was obtained from electronic health records (EHR) in patients with COVID-19. We included only adult patients, hospitalized for at least 2 days between March 1, 2020, and June 15, 2020 with a positive SARS-CoV-2 PCR and diagnosed with severe pneumonia, defined as SpO<sub>2</sub> <94% on room air at sea level, a respiratory rate >30 breaths/min, PaO<sub>2</sub>/FiO<sub>2</sub> <300 mm Hg, or lung infiltrates >50%. We excluded pregnant patients. Approval was obtained by the Hackensack Meridian Health Institutional Review Board (study #Pro2020-0485) and the study was also registered on ClinicalTrials.gov as a prospective observational database (NCT04347993).

## Data collection process and data items

Age, gender, race, ethnicity, and sex were self-reported. Weight and height were measured. Comorbidities were defined prior to COVID-19 and included cardiovascular disease, lung disease, diabetes mellitus, neurologic disease, cancer, and renal disease. SARS-CoV-2 was detected by nasal PCR. Routine blood work included complete blood count (CBC), complete metabolic profile (CMP), magnesium, phosphate, troponin, arterial blood gases, Beta natriuretic peptide, C-Reactive Protein (CRP), D-dimer, ferritin, and interleukin 6. Demographics, clinical characteristics, laboratory values, treatments, and outcomes were manually abstracted. Data was entered and maintained using REDCap (Research Electronic Data Capture) hosted by HMH. Data abstraction occurred daily from June 1, 2020, to December 1, 2020.

## Outcomes

The primary outcomes were the risk of thromboembolic disease between no methylprednisolone and methylprednisolone (dose versus duration) and the association of methylprednisolone with or without therapeutic dose of heparin and 30-days in hospital survival.

## Data Analysis

A one-to-one propensity score matched design between those treated with no methylprednisolone and those treated with methylprednisolone was constructed.<sup>(5)</sup> Patients were matched based variables associated with mortality such as on age groups (age ≥60 years vs. age <60 years), obesity (BMI ≥30.0 kg/m<sup>2</sup> vs. BMI <30.0 kg/m<sup>2</sup>), sex (Male/Female), diabetes (Yes/No), hypertension (Yes/No), cancer (Yes/No), respiratory rate (respiratory rate >22 vs <22), renal failure (Yes/No), low oxygen (oxygenation <94% vs. oxygenation ≥94%), CRP (>20 mg/dL vs ≤20 mg/dL), and quick sequential organ failure assessment or qSOFA (score: 0,1,2,3).<sup>(5)</sup> A nearest-neighbor (greedy match) used a caliper of 0.20 to obtain the matched sample. We performed a post-match assessment of how distribution of propensity scores (or logit of propensity scores) and the adjusted variables are balanced between the no methylprednisolone and methylprednisolone using standardized difference and variance ratio and graphical displays produced by the ASSESS statement of PROC PSMATCH in SAS 9.4. <sup>(5)</sup>

Categorical variables were presented as frequency and percentage. Continuous variables were presented as median and interquartile range (IQR). Shapiro-Wilk test was used to assess normality of continuous variables. Time to events such as in-hospital survival, start of mechanical ventilation, and discharge were obtained using Kaplan-Meier method which reported median (95% confidence interval), 30 days survival rates (95% CI), and the intervals were calculated using the arcsine-square root transformation method. Comparison of the propensity matched samples was performed using stratified log-rank test based on quintiles of the propensity scores as the strata. To examine association of risk factor of interest, methylprednisolone treatment, Cox proportional hazard regression analysis with robust covariance (26) (sandwich estimator) to account paired observations was used conducted and hazard ratios, (95% CIs) and p-values were reported in all univariable and multivariable analysis from PROC PHREG. The proportional hazard (PH) assumption, critical in Cox regression, was evaluated using a Kolmogorov-type supremum test (27) in ASSESS statement of PROC PHREG. If the PH assumption was violated, then a continuous variable which also violated the PH and its interaction with time were included in the model to adjust for the significant interaction with time to the risk of in-hospital mortality. (28)

## Results

Between March 4 and June 15, 2020, 2041 patients were flagged in the electronic health record with a diagnosis of COVID-19 and pneumonia. A total of 539 patients were excluded based on eligibility criteria (< 18 years of age, pregnant, received other formulations of corticosteroids, or hospitalized for less than 2 days). Thus, 1121 patients had their data abstracted. In the unmatched population, the median duration of symptoms prior to admission was 5 days in the no methylprednisolone and methylprednisolone group ( $P < 0.0165$ ) and there were more patients on invasive mechanical ventilation in methylprednisolone group ( $P > 0.0001$ ). At that time, methylprednisolone was given as rescue to patients with increasing oxygen support.

A propensity score matched sample was constructed out of 759 patients (380 in no methylprednisolone and 379 in methylprednisolone). (5) **(Table 1 and S2 and Figure S1)** An examination of the proportional hazard assumption, methylprednisolone, and Fractional inspired oxygen ( $FiO_2$ ) significantly violated it (both with  $P < 0.0001$ ). Data on P/F ratio was lacking; and  $FiO_2$  was used since 95% of patients had this data. (5) The supremum test also indicated that non-proportionality was observed in other variables such as nursing home, lack of taste or smell,  $WBC < 11,000$  cells/ml, creatinine  $> 1.5$  ng/mL, respiratory rate  $> 22$  bpm, hydroxychloroquine (HCQ), methylprednisolone, HDMP, LDMP, calcium and initial diastolic blood pressure. All variables with non-proportional hazard were adjusted using  $FiO_2$ , as indicated above.

Out of 754 patients with evaluable anticoagulation data, 392 (52%) received prophylactic heparin (Pac) and 232 (30.8%) received therapeutic heparin drip or enoxaparin (Tac). 130 (17.2%) patients did not receive any anticoagulation therapy. 36 patients (27.27%) who received no anticoagulation, 88 patients (22.39%) who received prophylactic heparin, and 117 (50%) who received therapeutic heparin expired. ( $P < 0.0001$ ). Therapeutic anticoagulation was mostly initiated due to clinical suspicion or confirmation of VTE [worsening hypoxia or echocardiographic findings of right heart strain and/or radiographic

evidence of deep venous thrombosis (DVT) or pulmonary embolism (PE)], atrial fibrillation, or acute coronary syndrome. Therefore, there was a higher proportion of patients on oxygen support who also received therapeutic heparin.

9% of patients who received methylprednisolone [LDMP (N=25) and HDMP (N=10)] and 3% of patients who did not receive methylprednisolone (N=12), had VTE [RR = 2.92 (95% CI 1.54, 5.55 P< 0.0001)]. The relative risk between HDMP vs LDMP [RR=0.524 (95% CI 0.26, 1.06 P=0.4)] was not statistically significant. **(Table 2 and 3)** Patients who received methylprednisolone for > 7 days (N=24) and ≤ 7 days (N = 11) had VTE (RR=5.46 95% CI 2.87, 10.34 P < 0.0001). The median d-dimer in patients without VTE (0.9775 mcq/mL) and patients with VTE (4.707 mcq/mL) was statistically significant. (P < 0.0003). However, the median d-dimer in the methylprednisolone group with VTE (7.115 mcq/mL) and no methylprednisolone with VTE (5.37) was not statistically significant. (P=0.40)

In patients who received prophylactic heparin only, 14 patients (16.09%) with no oxygen support, 11 patients (10.19%) with non-invasive oxygen support, and 17 patients (89.47%) with invasive oxygen support or mechanical ventilation expired (P<0.0001). In patients who received methylprednisolone and prophylactic heparin, 10 patients (16.67%) with no oxygen support, 6 patients (8.70%) with non-invasive oxygen support, and 30 patients (61.22%) with invasive oxygen support expired. (P<0.0001). In patients who received methylprednisolone and therapeutic heparin, 6 patients (25%) with no oxygen support, 9 patients (45%) with non-invasive oxygen support, and 11 patients (78.57%) with invasive oxygen support or mechanical ventilation expired. (P=0.0059). **(Table S3-S6)** Patients who received LD MP and therapeutic heparin had a trend towards higher risk of in hospital mortality (HR=1.81 95% CI 0.994 to 3.294) (P=0.0522) compared to LDMP and prophylactic heparin. **(Figure 2)** There was no difference in 30 days in hospital survival between HDMP with prophylactic or therapeutic heparin (HR=0.827 95% CI 0.514 to 1.33) (P=0.4335). **(Figure 3)**. There were 5 patients who had bleeding episodes. Heparin was stopped but the main cause of mortality for all patients was ARDS.

## Discussion

There was a higher risk of venous thromboembolism in patients who received methylprednisolone compared to no methylprednisolone use. This may be due to higher production of procoagulant factors from corticosteroids. Cushing's syndrome, which is due to excess levels of endogenous glucocorticoids, is associated with elevated levels of procoagulant Factor VIII, Factor IX and von Willebrand Factor. (29-31) In vitro studies of exogenous corticosteroids revealed increased synthesis and secretion of VWF and plasminogen-activator-1 (PAI-1). One study suggested corticosteroids had elevated FVII, FVIII, and FXI while cumulative evidence suggested lowered levels of VWF and fibrinogen and increased levels of PAI-1. (31) It is interesting to note that the pulmonary pathologic studies that showed higher levels of thrombosis with COVID-19 compared to Influenza had patients that were treated with corticosteroids. (2,3)

Another possible explanation is that the association of methylprednisolone with VTE maybe due to the severity of underlying inflammatory disease. This maybe suggested higher Median CRP and higher oxygen support in the methylprednisolone group compared to no methylprednisolone group.

One of the strengths of this study is that we were able to determine which methylprednisolone variable was associated with VTE. HD MP was not associated with higher risk of VTE compared to LD MP, but methylprednisolone > 7 days had a higher risk of VTE compared to  $\leq$  7 days. This association with VTE may diminish with increasing methylprednisolone use. (16,17) At >1 year duration, the initial procoagulant effects are overshadowed by the inhibition of platelet aggregation and tissue factor-mediated leukocyte procoagulant. (16,17,32,33) However, all our patients required < 30 days of corticosteroids.

Regardless of methylprednisolone use or not, patients with VTE had higher median d-dimers compared to those with no VTE. This suggest that elevated d-dimer is independently associated with VTE. (34,37)

Our study suggested therapeutic heparin was not superior to prophylactic heparin, regardless of the methylprednisolone dose to 30 days in hospital survival. Like methylprednisolone, therapeutic heparin was more prevalent in patients already on higher oxygen support. At that time, benefits of therapeutic heparin may be too late. (24,25) Heparin has multiple non-anticoagulant mechanisms that maybe beneficial in COVID-19 earlier in disease course. It is an analogue of haparan sulphate. This is a cofactor that is required by ACE-2 mediated entry of SARS-COV-2 into the cell. Therefore, heparin may block binding of the virus into the cell. (38-40) This anti-viral affect might be more beneficial if given during the first week of illness when viral shedding is at its peak. Heparan sulphate provides a negatively charge dependent function of the glycocalyx and is degraded by heparanase. (41) Heparanase is increased in COVID-19 and contributes to endothelial dysfunction with increased leakage. Heparin inhibits heparanase. Heparin also neutralizes cytokine and chemokine synthesis and function, complement activation, and histones which are responsible for apoptosis. (41)

## Limitations

Our study has several limitations. First, since it is an observational study, we cannot draw causal inferences due to known and unknown confounders. However, propensity matching was employed to limit the known confounders. Second, misclassification of data is possible due to manual extraction of structured and unstructured data from medical health records. Third, there was also a higher prevalence of invasive mechanical ventilation, and benefits of therapeutic heparin with methylprednisolone for patients on nasal cannula could not be seen.

## Conclusions

Duration > 7 days of methylprednisolone is associated with higher risk of venous thromboembolism. This maybe due to methylprednisolone or severity of underlying inflammatory disease. There was no

synergistic benefit of methylprednisolone and therapeutic heparin for severe COVID-19. Therapeutic heparin should be reserved for patients with radiographic evidence of venous thrombo-embolic disease.

## Abbreviations

AFOP	acute fibrinous organizing pneumonia
ARDS	acute respiratory distress syndrome
BMI	body mass index
CBC	complete blood count
CI	confidence interval
CMP	complete metabolic profile
Covid-19	coronavirus disease 2019
CRP	c-reactive protein
EHR	Electronic Health Record
FiO <sub>2</sub>	fraction of inspired oxygen
HCQ	Hydroxychloroquine
HMH	Hackensack Meridian Health
HR	hazard ratio
IQR	interquartile range
HDMP	high dose methylprednisolone
LDMP	low dose methylprednisolone
OP	organizing pneumonia
Pac	prophylactic dose of heparin
PAI-1	plasminogen activation factor 1
PaO <sub>2</sub>	partial pressure of arterial oxygen
qSOFA	quick sequential organ failure assessment

RR relative risk

SARS-COV-2 severe acute respiratory syndrome coronavirus 2

SpO2 oxygen saturation

Tac therapeutic dose of heparin

vWF von willebrand factor

## Declarations

### Ethics approval and consent to participate

We obtained ethics approval and waiver of consent [45 CFR 46.116 (d)] since this is retrospective, some of the patients have expired and there was minimal risk.

### Consent for publication

N/A

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

There are no competing interests.

### Funding

There was no funding.

### Authors' contributions

RCG analyzed data and interpreted data and was the major contributor to writing the manuscript. TN performed and analyzed data and was a contributor to writing. MB, KK, MR, DKH, and KMR performed data entry and contributed to writing the manuscript.

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## Tables

Please see the supplementary files section to view the tables.

## Figures

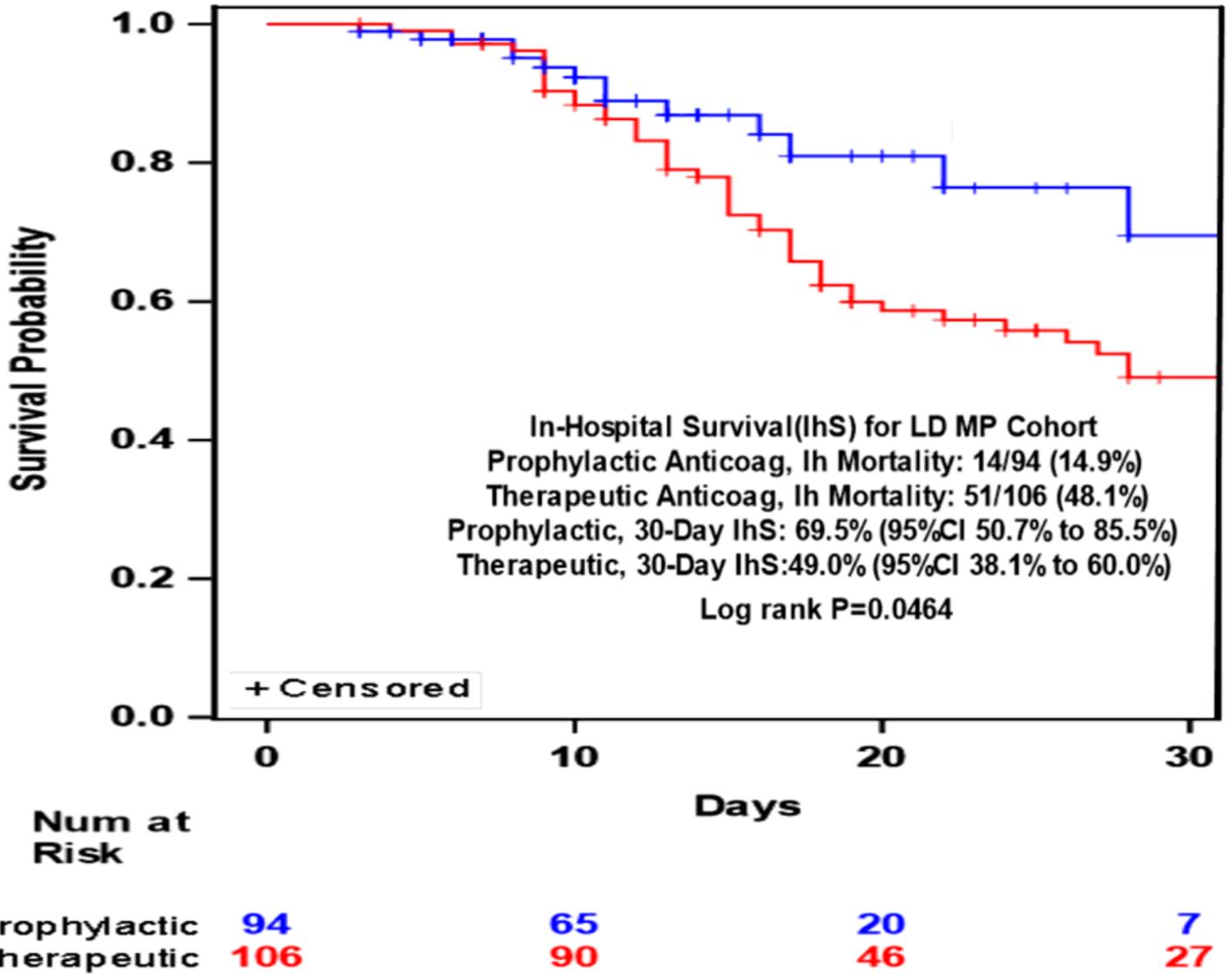


Figure 1

Kaplan Meier plot of LDMP with prophylactic heparin versus therapeutic heparin and 30 days in hospital survival.

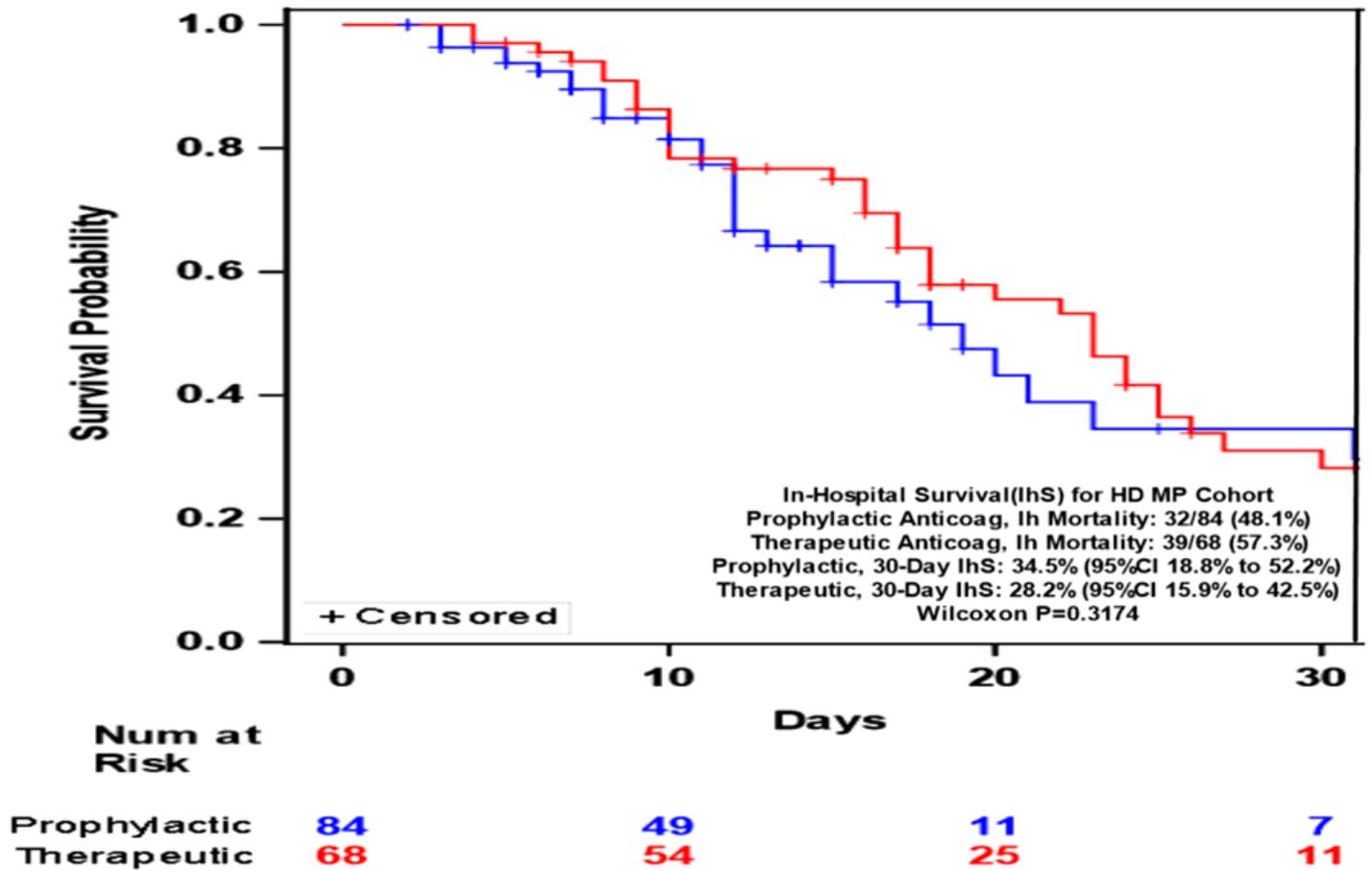


Figure 2

Kaplan Meier Plot of HDMP with prophylactic heparin versus therapeutic heparin and 30 days in hospital survival.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [BMCSupplementalMPThrombosisHeparin.docx](#)
- [Tables.docx](#)