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

Ronaldo C. Go (criticalmd@gmail.com)
Hackensack University Medical Center https://orcid.org/0000-0001-6100-7773
Themba Nyirenda
Hackensack Meridian School of Medicine
Maryam Bojarian
Hackensack University Medical Center
Davood Hosseini
HackensackUMC: Hackensack University Medical Center
Mehek Rahim
HackensackUMC: Hackensack University Medical Center
Kevin Kim
HackensackUMC: Hackensack University Medical Center
Keith M. Rose
Hackensack Meridian School of Medicine

Research Article

Keywords: COVID-19, methylprednisolone, venous thromboembolism, heparin

Posted Date: August 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-845767/v1

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 incidence 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 hazard ratio.

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 [HR =2.92 (95% CI 1.54, 5.55 P< 0.0001)]. The 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 in our institution. It was given as rescue due to concerns of prolonging viral shedding. There was significant heterogeneity in how it was administered. Our study found that low dose methylprednisolone (<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 ($\geq$ 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 and heparin maybe an ideal anti-coagulation because of its anti-thrombotic, anti-inflammatory, and anti-viral properties. However, 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)

There is sparsity in literature on the association of methylprednisolone dose or duration to incidence of VTE and if there was a and heparin to incidence of thrombosis and survival in COVID-19.

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 SpO2 <94% on room air at sea level,

a respiratory rate >30 breaths/min, PaO2/FiO2 <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, C-reactive, Beta natriuretic peptide, C-Reactive Protein, 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 incidence of thromboembolic disease between no methylprednisolone, low dose methylprednisolone, and high dose methylprednisolone 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. 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^2 vs. BMI <30.0 kg/ m^2), sex (M/F), 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 (CRP >20 mg/dL vs CRP ≤20 mg/dL), and quick sequential organ failure assessment or qSOFA (score: 0,1,2,3).(5) 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.

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 NMP and MP group (P<0.0165) and there were more patients on invasive mechanical ventilation in MP group (P>0.0001). MP was generally initiated due to increasing oxygen support.

A propensity score matched sample was constructed out of 759 patients (380 in NMP and 379 in MP). **(Table 1)** An examination of the proportional hazard assumption, MP and Fractional inspired oxygen (FiO2) significantly violated it (both with P<0.0001). Data on P/F ratio was lacking; and FiO2 was used since 95% of patients had this data. **((Figure S1-S20 and Table S1-S13)** 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), MP, high dose methylprednisolone (HDMP), low dose methylprednisolone (LDMP), calcium and initial diastolic blood pressure. All variables with non-proportional hazard were adjusted using FiO2, as indicated above. The Youden Index method yielded a MP dose cut- off of 1.36 mg/kg/day. Low dose methylprednisolone (LDMP) was defined as < 1.36 mg/kg/day and high dose methylprednisolone (HDMP) was defined as ≥ 1.36 mg/kg/day. 215 received LDMP and 164 received HDMP.

Out of 754 patients with evaluable anticoagulation data, 392 (52%) received prophylactic heparin and 232 (30.8%) received therapeutic heparin drip or enoxaparin. 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 for thromboembolic disease (worsening hypoxia, echocardiographic findings of right heart strain, and/or radiographic evidence), although also due to 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 [Low dose methylprednisolone (N=25) and high dose methylprednisolone (N=10)] and 3% of patients who did not receive methylprednisolone (N=12), had deep venous thrombosis [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 DVT/PE (RR=5.46 95% CI 2.87, 10.34 P < 0.0001). The median d-dimer in patients without DVT/PE (0.9775 mcq/mL) and patients with DVT/PE (4.707 mcq/mL) was statistically significant. (P < 0.0003). However, the median d-dimer in the methylprednisolone group with DVT/PE (7.115 mcq/mL) and no methylprednisolone with DVT/PE (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 S14-S18)** Patients who received LD MP and TAc 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 PAc. **(Figure 2)** There was no difference in 30 days in hospital survival between HDMP with PAc or TAc (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 incidence of deep venous thrombosis in patients who received methylprednisolone compared to no methylprednisolone use. This may be due to higher production of procoagulant factors. 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 elevated FVII, FVIII, and FXI while cumulative

evidence suggested lowered levels of VWF and fibrinogen and increased levels of PAI-1. (31) Another possible explanation is that patients who received methylprednisolone had more severe disease, as suggested by higher numbers of patients on invasive mechanical ventilation, compared to NMP group. D-dimers have been used as marker of severity. (32-35) Patients with DVT/PE, regardless of methylprednisolone use, had higher median d-dimers compared to those with no DVT/PE.

There was no direct relationship to the dose of methylprednisolone to incidence of DVT, but patients who received methylprednisolone > 7 days had a higher incidence of DVT. This association with venous thromboembolism may diminish with increasing methylprednisolone use. (16.17) One study had OR of 4.7 for 0-30 days duration trending down to OR 2 for > 1 year duration (16). The duration of methylprednisolone for all our patients was less than 30 days. At that duration, the initial procoagulant effects are overshadowed by the inhibition of platelet aggregation and tissue factor-mediated leukocyte procoagulant. (36,37)

Our study suggested therapeutic heparin was not superior to prophylactic heparin, regardless of the methylprednisolone dose. Most of the patients in the methylprednisolone group require higher oxygen support, and at that time it 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) These benefits maybe too late to be seen once higher level of oxygen support, at least high flow nasal cannula, is required.

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

Use of methylprednisolone is associated with higher incidence of venous thromboembolism.

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.

Declarations

Conflict of Interest: None except Ronaldo C. Go MD has done consulting work for Hoffmann LaRoche.

Ethnics 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 anaylzed 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.

ACKNOWLEDGEMENT

We thank Andrew Ip MD and Steven Goldberg MD for allowing access to database.

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
FiO2	fraction of inspired oxygen
HCQ	Hydroxychloroquine
HMH	Hackensack Meridian Health
HR	hazard ratio
IQR	interquartile range
HDMP	high dose methylprednisolone
LDMP	low dose methylprednisolone
MP	methylprednisolone
NMP	no methylprednisolone
OP	organizing pneumonia
Pac	prophylactic dose of heparin
PAI-1	plasminogen activation factor 1
PaO2	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 wildebrand factor

References

1. WHO Coronavirus (COVID-19) Dashboard. World Health Organization. https://covid19.who.int/. Updated July 2, 2021. Accessed July 4, 2021.
2. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in COVID-19. NEJM. 2020;383:120–8.
3. Hariri LP, North CM, Shih AR, et al. Lung Histopathology in Coronavirus Disease 2018 as Compared with Severe Respiratory Syndrome and H1N1 Influenza. Chest January. 2021;159(1):73–85.
4. Recovery Group. Dexamethasone in Hospitalized Patients with COVID-19. NEJM. February. 25, 2021;384:693–704.
5. Go R, Shah R, Nyirenda T, et al. Methylprednisolone and 60 Day In Hospital Survival in COVID-19 Pneumonia. Critical Care Explorations July. 2021;3:7:e0493. doi:10.1097/CCE.0000000000004932021.
6. Edalatifard M, Akhtari M, Salehi M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: Results from a randomised controlled clinical trial. Eur Respir J. 2020;56:2002808.
7. Pinzón MA, Ortiz S, Holguín H, Betancur JF, Cardona Arango D, Laniado H, Arias Arias C, Muñoz B, Quiceno J, Jaramillo D, Ramirez Z. Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia. PLoS One. 2021 May;25(5):e0252057. 16(.
8. Ko JJ, Wu C, Mehta N, Wald-Dickler N, Yang W, Qiao R. A Comparison of Methylprednisolone and Dexamethasone in Intensive Care Patients With COVID-19. J Intensive Care Med. 2021 Jun;36(6):673–80.
9. Stuijver DJ, Majoor CJ, van Zaane B, et al. Use of oral glucocorticoids and the risk of pulmonary embolism: a population-based case-control study. Chest. 2013 May;143(5):1337–42.
10. Lieber BA, Han J, Appelboom G, et al. Association of Steroid Use with Deep Venous Thrombosis and Pulmonary Embolism in a Neurosurgical Patients: A National Database Analysis. World Neurosurg. 2016 May;89:126–32.
11. Johannesdottir SA, Horvath-Puho E, Dekkers OM, et al. Use of Glucocorticoids and Risk of Venous Thromboembolism. JAMA Intern Med. 2013;173(9):743–52.
12. Van Zaane B, Nur E, Squizzato A, et al. Hypercoagulable state in Cushing's Syndrome: A Systematic Review. The Journal of Clinical Endocrinology Metabolism June. 2009;94(8):2743–50.
13. Stolz E, Klotzsch C, Schlachetzki F, Rahimi A. High dose corticosteroid treatment is associated with an increased risk of developing cerebral venous thrombosis. Eur Neurol. 2003;49:247–8.
14. Miśkiewicz P, Milczarek-Banach J, Rutkowska-Hinc B, Kondracka A, Bednarczuk T. High-dose intravenous methylprednisolone therapy in patients with Graves' orbitopathy is associated with the

increased activity of factor VIII. J Endocrinol Invest. 2019;42(2):217–25. doi:10.1007/s40618-018-0907-z.

15. Høgevold HE, Høiseth A, Reikerås O. Effect of high-dose corticosteroids on the incidence of deep vein thrombosis after total hip replacement. Arch Orthop Trauma Surg. 1991;111(1):29–31.
16. Huerta C, Johansson S, Wallander MA, García Rodríguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med. 2007 May 14;167(9):935 – 43.
17. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, et al. Use of Glucocorticoids and Risk of Venous Thromboembolism: A Nationwide Population-Based Case-Control Study. JAMA Intern Med. 2013;173(9):743–52.
18. Sarfraz A, Sarfraz Z, Abdul A, et al. Venous Thromboembolism, Corticosteroids and COVID-19: A Systematic Review and Meta-Analysis. Clinical Applied thrombosis/Hemostasis. 2021;27:1–7.
19. Longchamp G, Manzocchi-Besson S, Longchamp A, Righini M, Robert-Ebadi H, Blondon M. Proximal deep vein thrombosis and pulmonary embolism in COVID-19 patients: a systematic review and meta-analysis. Thromb J. 2021 Mar 9;19(1):15. doi: 10.1186/s12959-021-00266-x.
20. Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, Le Mao R, Rodríguez C, Hunt BJ, Monreal M. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. Chest. 2021 Mar;159(3):1182–1196. doi: 10.1016/j.chest.2020.11.005.
21. Vaughn VM, Yost M, Abshire C, et al. Trends in Venous Thromboembolism Anticoagulation in Patients Hospitalized With COVID-19. JAMA Netw Open. 2021;4(6):e2111788.
22. Tacquard C, Mansour A, Godon A. Impact of High-Dose Prophylactic Anticoagulation in Critically Ill Patients With COVID-19 Pneumonia. Chest. 2021 Jun;159(6):2417–27.
23. INSPIRATION Investigators. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA. 2021;325(16):1620–30. doi:10.1001/jama.2021.4152.
24. Al-Samkari H, Gupta S, Leaf RK, et al. Thrombosis, Bleeding and the Observational Effect of Early Therapeutic Anticoagulation on Survival in Critically Ill Patients with COVID-19. Ann Intern Med. 2021;174:622–32.
25. REMAP-CAP Investigators; ACTIV-4a Investigators; Investigators ATTACC, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Aug 4. doi:10.1056/NEJMoa2103417.
26. ATTACC Investigators; ACTIV-4a Investigators; Investigators REMAP-CAP, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med. 2021 Aug 4. doi:10.1056/NEJMoa2105911.
27. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: Reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014;33:1242–58.

28. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80:557–72.
29. Heaton JH, Nebes VL, O'dell LG, et al. Glucocorticoid and cyclic nucleotide regulation fo plasminogen activator and plasminogen actiator-inhibitor gene expression in primary cutres of rat hepatocytes. Mol Endocrinol. 1989;3:185–92.
30. Huang LQ, Whitworth JA, Chesterman CN. Effects of cyclosporin A and dexamethasone on haemostatic and vasoactive functios of vascular endothelial cells. Blood Coagul Fibrinolysis. 1995;6:438–45.
31. Morage PE, Aubert J, Peiretti F, et al. Glucocorticoids and Insulin promote plasminogen activator inhibitor I production by human adipose tissue. Diabetes. 1999;48:890–5.
32. Li Y, Zhao K, Wei H, Chen W, Wang W, Jia L, Liu Q, Zhang J, Shan T, Peng Z, Liu Y, Yan X. Dynamic relationship between D-dimer and COVID-19 severity. Br J Haematol. 2020 Jul;190(1):e24–7. doi:10.1111/bjh.16811.
33. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020 Nov;195:219–25. doi:10.1016/j.thromres.2020.07.0.
34. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. j intensive care. 2020;8:49. https://doi.org/10.1186/s40560-020-00466-z.
35. Short SAP, Gupta S, Brenner SK, Hayek SS, Srivastava A, Shaefi S, Singh H, Wu B, Bagchi A, Al-Samkari H, Dy R, Wilkinson K, Zakai NA, Leaf DE; STOP-COVID Investigators. d-dimer and Death in Critically Ill Patients With Coronavirus Disease 2019. Crit Care Med. 2021 May 1;49(5):e500-e511.
36. Squizzato A, Gerdes VE, Ageno W, Büller HR. The coagulation system in endocrine disorders: a narrative review. Intern Emerg Med. 2007;2(2):76–8317657422.
37. Brotman DJ, Girod JP, Posch A, et al. Effects of short-term glucocorticoids on hemostatic factors in healthy volunteers. Thromb Res. 2006;118(2):247–5216005496.
38. K SY, Jin W, Sood A, et al. Glycosaminoglycan binding motif at S1/S2 proteolytic cleavage site on spike glycoprotein may facilitate novel coronavirus (SARS-CoV-2) host cell entry. *Biorxiv*. 2020.04.14.041459.
39. Yu M, Zhang T, Zhnag W, et al. Elucidating the interactions between Heparin/Heparan Sulfate and SARS-CoV-2 related proteins – an important strategy for developing novel therapeutics for the COVID-19 Pandemic. *Front Mol Biosci*. 25 January 21. 7:628551.
40. Clausen TM, Sandoval DR, Spliid CB, et al. SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. Cell. 2020;183(4):1043–57.e15. doi:10.1016/j.cell.2020.09.033.
41. Buijsers B, Yanginlar C, Maciej-Hulme ML, et al. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19. *EbioMedicine*. August 25, 2020. DOI://https://doi.org/10.1016/j.ebiom.2020.102969.

Tables

Table 1. Characteristics of hospitalized COVID-19 patients treated with or without Methylprednisolone (n=759)

	No Methylprednisolone (n=380)	Methylprednisolone (n=379)	
Level	Count (%)	Count (%)	P-Value
Age in years	65 (54,80)	64(55,74)	0.0230
Age ≥ 60 years	254(66.67)	244(64.55)	0.2436
Male	237(62.20)	242(64.02)	0.5775
Weight (kg)	81.67(70.30,96.00)	83.90(71.70,99.80)	0.8758
BMI (kg/m^2)	29.82(25.51,32.81)	29.76(25.82,34.44)	0.0413
BMI ≥ 30 kg/m^2	179(46.98)	181(47.88)	0.6767
Black	58(15.30)	44(11.80)	0.2500
White	178(46.97)	160(42.90)	0.2500
Asian/Indian	25(6.60)	133(35.66)	0.2500
Hispanic	118(31.13)	181(47.88)	0.2500
Non-smoker	278(78.31)	251(74.04)	0.2334
Smoker (Former or Current)	77(21.69)	88(25.96)	0.2334
Fever	250(65.79)	294(77.78)	**0.0003**
Shortness of breath	248(65.09)	298(79.05)	**<.0001**
Cough	242(63.68)	270(71.43)	**0.0191**
Altered Mental Status	63(16.54)	41(10.85)	**0.0032**
GI	76(20.00)	81(21.49)	0.5211
Anosmia or Ageusia	6(1.59)	9(2.45)	0.5930
Duration of Symptoms PTA	5.00(2.00,7.00)	5.00(3.00,7.00)	0.0699
Duration>7 days	59(18.91)	75(21.99)	0.2864
Diabetes	143(37.53)	138(36.51)	0.6521
COPD	20(5.25)	28(7.41)	0.2482
Asthma	24(6.30)	37(9.81)	0.0741
Hypertension	225(59.06)	219(57.94)	0.5525
Cancer	43(11.29)	43(11.38)	0.9013

Cerebrovascular Accident	18(4.74)	14(3.70)	0.3692
Coronary Artery Disease	29(7.61)	28(7.41)	0.8886
Arrhythmia	41(10.79)	30(7.94)	0.1213
Renal Failure	28(7.35)	31(8.20)	0.6682
Rheumatologic disorder	10(2.62)	19(5.04)	0.0588
qSOFA 0	224(58.49)	222(58.42)	0.7647
qSOFA 1	130(33.94)	130(34.21)	0.7647
qSOFA 2	28(7.31)	26(6.84)	0.7647
qSOFA 3	1(0.26)	2(0.53)	0.7647
Temperature	98.80(97.70,100.40)	99.30(98.00,100.70)	0.1284
Heart Rate	95.00(84.00,108.00)	97.00(86.00,108.00)	0.1438
Arterial pressure	92.33(83.33,100.50)	90.67(81.83,99.33)	0.0870
Respiratory Rate	19.00(18.00,22.00)	20.00(18.00,22.00)	0.3231
O2 Sat <94%	215(56.43)	217(57.41)	0.6733
Nasal Cannula	160(82.05)	131(65.83)	0.2500
High Flow	6(3.08)	15(7.54)	0.2500
CPAP	1(0.51)	2(1.01)	0.2500
BiPAP	0(0.00)	2(1.01)	0.2500
Non-rebreather	26(13.33)	46(23.12)	0.2500
Mechanical Ventilation	35(11.15)	129(39.33)	**<.0001**
WBC	6.65(5.10,9.20)	6.50(5.10,9.50)	1.0000
HGB	13.40(12.30,14.50)	13.50(12.20,14.70)	0.6746
PLT	203.00(161.00,257.00)	189.00(147.00,252.00)	0.2736
ALC	0.90(0.60,1.30)	0.80(0.60,1.10)	**0.0031**
IL6	12.00(5.00,39.00)	15.00(5.00,36.00)	0.2678
CRP	9.88(4.99,17.31)	12.67(6.84,19.08)	**0.0047**
D-dimer	1.09(0.65,2.20)	1.44(0.72,3.13)	0.1155
Ferritin	729.50(325.50,1404.00)	867.00(418.00,1548.00)	0.0675
Creatinine	1.01(0.80,1.50)	1.01(0.80,1.35)	0.2630

Troponin	0.03(0.01,0.30)	0.02(0.01,0.09)	0.0732
BNP	131.85(40.30,1000.55)	88.80(26.20,362.00)	0.2110
Hydroxychloroquine	269(71.93)	317(88.55)	**<.0001**
Azithromycin	255(68.55)	264(73.54)	0.0728
Remdesivir	3(0.82)	10(2.82)	**0.0196**
Tocilizumab	13(3.53)	63(17.65)	**<.0001**
Convalescent Plasma	0(0.00)	4(28.57)	**<.0001**

Table 2. Differences in rates of DVT/PE across the Methylprednisolone Administration

Outcome	NMP	MP	P value
DVT	9 (2.33)	34 (9.07)	
PE	3 (0.78)	1 (0.27)	<.0001
None	375 (96.90)	340 (90.67)	

Table 3. Differences in rates of DVT/PE across the Methylprednisolone Dose Levels

Outcome	NMP	LD MP	HD MP	P value
DVT	9 (2.33)	25 (11.74)	9 (5.56)	
PE	3 (0.78)	0 (0.0)	1 (0.62)	<.0001
None	375 (96.90)	188 (88.26)	152 (93.83)	

Figures

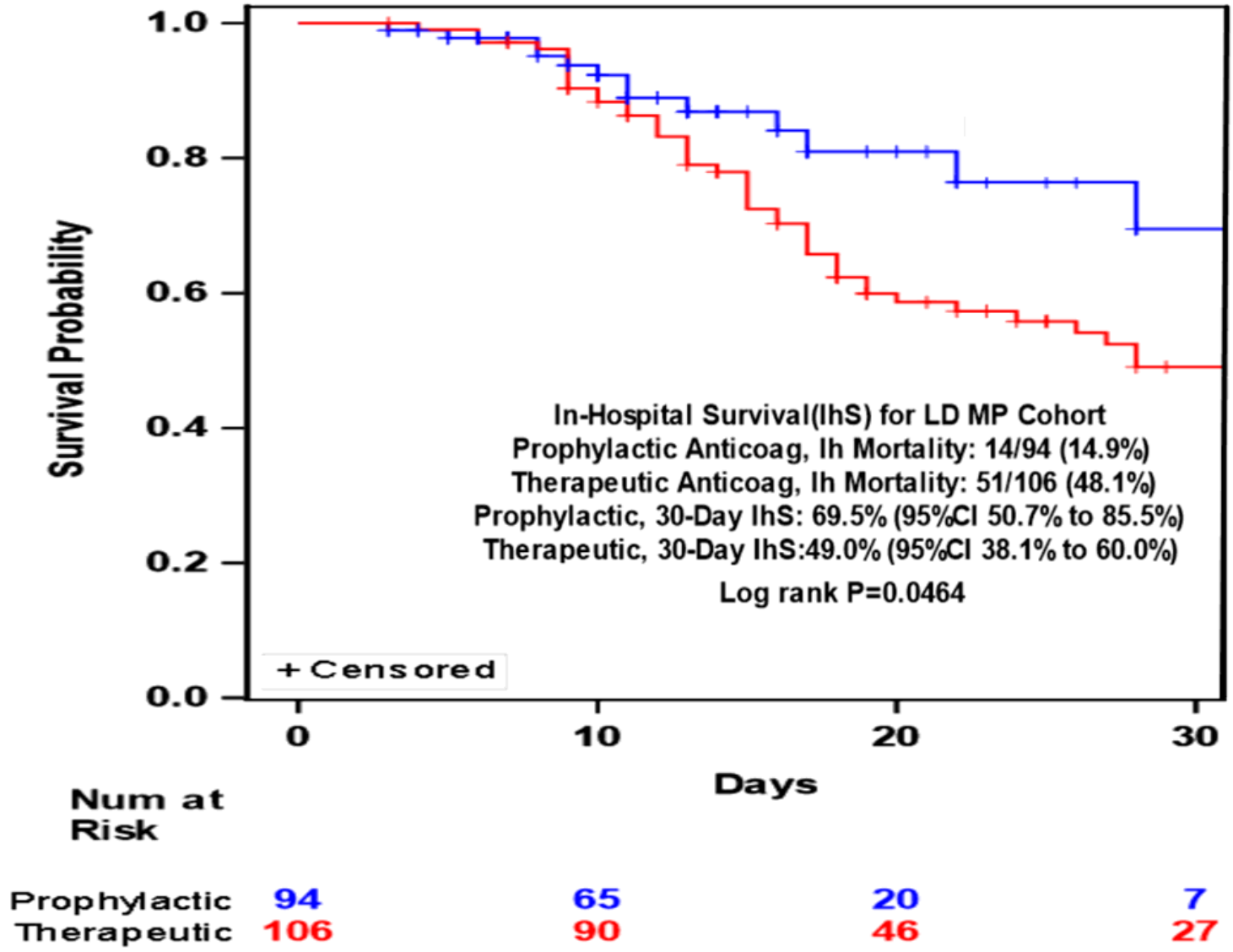

Figure 1

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

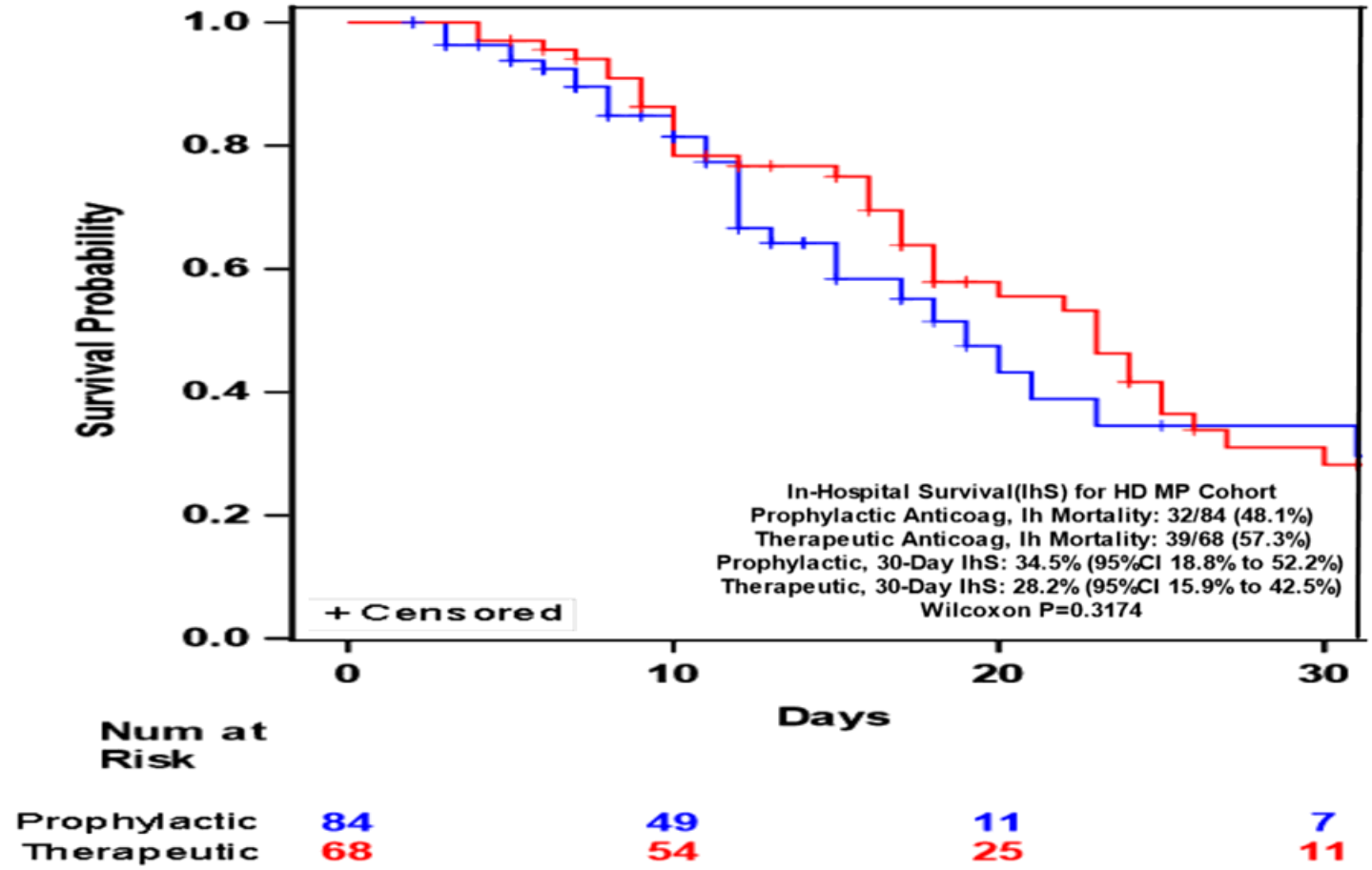

Figure 2

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.

- SupplementalBMCMPThrombosis.docx