Supplemental Section for Methylprednisolone, Venous Thromboembolism, and Association with Heparin to 30 days in Hospital Survival in Severe COVID-19 Pneumonia

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**Figure S1.** Cohort Flow Chart.

**379 received no methylprednisolone**

**380 received no methylprednisolone**

**1121 patients where data abstracted but 759 included in propensity score matched sample**

**Excluded because: 3 < 18 years of age**

**71 pregnant**

**375 used other corticosteroids 92 not inpatient**

**2 duplicates**

**2041 patients ﬂagged in electronic health record in COVID -19**

**164 high dose**

**Methylprednisolone**

**215 low dose**

**Methylprednisolone**

**Table S1.** Baseline Demographics Disease Characteristics on Unmatched Population

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Unmatched No****methylprednisolone (N=645)** | **Unmatched Methylprednisolone (N=476)** | **P Value** |
| Age in years | 64.00(53.00,79.00) | 64.00(56.00,73.00) | 0.6620 |
| Male | 411(63.43) | 219(53.03) | 0.6079 |
| Weight (kg) | 81.20(68.70,90.72) | 83.90(71.10,99.80) | 0.0040 |
| BMI (kg/m2) | 28.18(24.83,31.65) | 29.48(25.94,34.30) | <.0001 |
| Nursing Home | 125(19.38) | 43(10.26) | <.0001 |
| Former/Currentsmoker | 116(19.86) | 96(25.81) | 0.0377 |
| Never smoker | 468(80.14) | 276(74.19) | 0.0377 |
| SOB | 412(63.78) | 334(78.96) | <.0001 |
| Cough | 417(64.75) | 301(71.16) | 0.0327 |
| AMS | 109(17.33) | 46(11.11) | 0.0058 |
| GI | 149(23.17) | 88(20.90) | 0.4077 |
| Anosmia or Ageusia | 10(1.57) | 9(2.20) | 0.4834 |
| Duration of Symptoms prior toadmission | 5.00(2.00,7.00) | 5.00(3.00,7.00) | 0.0165 |
| Diabetes | 214(33.18) | 157(37.20) | 0.1888 |
| COPD | 27(4.19) | 30(7.09) | 0.0506 |
| Asthma | 40(6.22) | 40(9.48) | 0.0569 |
| Cancer | 61(9.46) | 49(11.61) | 0.2594 |
| CAD | 86(13.33) | 67(15.84) | 0.2839 |
| CVA | 28(4.35) | 15(3.55) | 0.6336 |
| CHF | 51(7.96) | 32(7.57) | 0.9071 |
| Arrhythmia | 65(10.12) | 38(8.96) | 0.5967 |
| Renal Failure | 40(6.23) | 33(7.78) | 0.3249 |
| RheumatologicDisease | 15(2.33) | 22(5.20) | 0.0159 |

|  |  |  |  |
| --- | --- | --- | --- |
| qSOFA 0 | 375(59.62) | 225(54.35) | 0.2544 |
| qSOFA 1 | 199(31.64) | 156(37.68) | 0.2544 |
| qSOFA 2 | 51(8.11) | 31(7.49) | 0.2544 |
| qSOFA 3 | 4(0.64) | 2(0.48) | 0.2544 |
| O2 sat < 94% | 305(48.41) | 225(57.25) | 0.0069 |
| Temperature | 99.00(98.00,100.70) | 99.30(98.00,100.80) | 0.0476 |
| Heart Rate | 95.00(82.00,108.00) | 95.00(82.00,108.00) | 0.0581 |
| Respiratory Rate | 19.00(18.00,21.00) | 20.00(18.00,22.00) | 0.0097 |
| Nasal Cannula | 227(82.85) | 137(66.50) | 0.0005 |
| Venti mask | 4(1.46) | 3(1.46) | 0.0005 |
| High Flow | 8(2.92) | 15(7.28) | 0.0005 |
| CPAP | 1(0.36) | 2(0.97) | 0.0005 |
| BPAP | 0(0.00) | 2(0.97) | 0.0005 |
| MechanicalVentilation | 55(10.62) | 138(39.88) | <.0001 |
| WBC | 6.50(5.00,9.10) | 6.50(5.10,9.50) | 0.5947 |
| HGB | 13.40(12.00,14.50) | 13.50(12.20,14.80) | 0.2190 |
| PLT | 200.00(158.00,251.00) | 186.00(147.00,251.00) | 0.0596 |
| ALC | 0.90(0.60,1.20) | 0.79(0.60,1.10) | 0.0007 |
| IL6 | 11.50(5.00,34.00) | 12.00(5.00,32.00) | 0.6607 |
| CRP | 10.91(5.20,20.79) | 13.11(7.09,20.20) | 0.0444 |
| D-Dimer | 1.01(0.64,2.11) | 0.98(0.61,1.89) | 0.7909 |
| Ferritin | 641.89(320.65,1453.60 | 838.96(430.40,1569.80) | 0.0044 |
| Creatinine | 1.00(0.80,1.40) | 1.01(0.80,1.33) | 0.9379 |
| Troponin | 0.03(0.01,0.30) | 0.02(0.01,0.09) | 0.0516 |
| BNP | 103.70(29.85,701.30) | 88.80(26.20,362.00) | 0.1702 |
| Hydroxychloroquine | 463(73.73) | 333(88.33) | <.0001 |
| Azithromycin | 438(70.19) | 277(73.47) | 0.2793 |
| Remdesivir | 4(0.65) | 63(16.80) | 0.0061 |
| Tocilizumab | 31(5.01) | 11(2.94) | <.0001 |
| ConvalescentPlasma | 0(0.00) | 4(28.57) | 0.0002 |
| ECMO | 1(0.17) | 9(2.43) | 0.0011 |
| Dialysis | 19(3.09) | 11(2.92) | 0.8748 |

HR = Hazard Ratio; CI = Confidence Interval; SOB = Shortness of Breath; AMS = Altered Mental Status; GI = Gastrointestinal Symptoms; PTA = Prior to admission; COPD = Chronic Obstructive Disease; CAD = Coronary Artery Disease; CVA = Cerebrovascular Accident; CHF = Congestive Heart Failure; LFTs = elevated liver function tests; qSOFA = Quick Sepsis Related Organ Failure Assessment; HCQ = Hydroxychloroquine; AZ = Azithromycin; MP = Methylprednisolone; HD MP = High Dose Methylprednisolone; LD MP = Low Dose Methylprednisolone; WBC= White Blood Cells; HGB = Hemoglobin; PLT = Platelet; ALC = Absolute Lymphocyte Count; ECMO = Extracorporeal Membrane Oxygenation

**Figure S2.** Bar plot of COVID-19 Hospitalizations in the 13 HMH Hospitals from March – June 2020. Hackensack University Medical Center (HUM) has 4 hospitals combined.

500

Hospital

BMC JFK OMC RBO RMC HUM JSU PMC RBP SOM

400

300

**Maximum Daily IP Census**

200

100

0

March

April

May

June

**Hospitalization Month**

**Figure S3.** Spaghetti plot of inpatient COVID-19 patients in 13 HMH Hospitals between March to June 2020.



**Table S2.** Univariate and Multivariate Cox Regression Analyses of Propensity Score Matched Population

|  |  |
| --- | --- |
| **Univariate Cox Regression** | **Multivariate Cox Regression** |
| **Comparison** | **HR (95% CI)** | **P-Value** | **Comparison** | **HR (95% CI)** | **P-Value** |  |
| Male vs Female | 1.20 (0.93, 1.56) | 0.1691 | ***Model 1: MP vs NMP*** |  |  |  |
| Age>60 vs <60 | 2.83 (2.05, 3.91) | <.0001 | MP vs NMP | 0.40(0.27,0.59) | <0.0001 |  |
| Current vs Non Smoker | 0.62(0.29, 1.32) | 0.2154 | Nursing home vs Residential | 3.08(1.94,4.89) | >0.0001 |  |
| Former vs Current Smoker | 1.21(0.91, 1.61) | 0.1934 | CAD vs None | 2.12(1.38,3.27) | 0.0006 |  |
| Nursing Home vs Residential | 2.81(1.99, 3.96) | <.0001 | Invasive Mechanical Ventilation vs None | 2.87(1.64,5.02) | 0.0002 |  |
| ***Symptoms*** |  |  | Non-Mechanical Ventilation Oxygen Support vs None | 1.11(0.60,2.05) | 0.7483 |  |
| Fever vs None | 0.88 (0.67, 1.15) | 0.3445 | ***Model 2: Dose (LD or HD) vs NMP*** |  |  |  |
| SOB vs None | 1.18 (0.91, 1.53) | 0.2233 | HD MP vs NMP | 0.48(0.30,0.77) | 0.0025 |  |
| Cough vs None | 0.79 (0.61, 1.01) | 0.0641 | LD MP vs NMP | 0.35(0.22,0.53) | <0.0001 |  |
| AMS vs None | 3.14(2.32, 4.26) | <.0001 | Nursing Home vs Residential | 2.95(1.83,4.76) | <0.0001 |  |
| GI vs None | 0.66(0.47, 0.93) | 0.0185 | CAD vs None | 2.22 (1.44,3.42) | 0.0003 |  |
| Anosmia or Ageusia vsNone | NA | <.0001 | Invasive Mechanical Ventilation vs None | 2.77(1.58,4.86) | 0.0004 |  |
| Duration of Symptoms PTA > 7 vs < 7 days | 0.61 (0.41, 0.91) | 0.0143 | Non-Mechanical Ventilation Oxygen Support vs None | 1.13(0.61,2.09) | 0.6992 |  |
| ***Comorbidities*** |  |  |  |  |  |  |
| Diabetes vs None | 1.06 (0.82, 1.37) | 0.6503 |  |  |  |  |
| COPD vs None | 2.44 (1.64, 3.63) | <.0001 |  |  |  |  |
| Asthma vs None | 0.89 (0.56,1.41) | 0.6042 |  |  |  |  |
| COPD/Asthma vs None | 1.49(1.07, 2.05) | 0.0169 |  |  |  |  |
| Hypertension vs None | 2.12 (1.60, 2.81) | <.0001 |  |  |  |  |
| Cancer vs None | 2.08 (1.46, 2.97) | <.0001 |  |  |  |  |
| CAD vs None | 2.09 (1.56, 2.79) | <.0001 |  |  |  |  |
| CVA vs None | 2.24 (1.44, 3.50) | 0.0004 |  |  |  |  |
| CHF vs None | 2.12 (1.41, 3.21) | 0.0004 |  |  |  |  |
| Arrhythmia vs None | 2.07 (1.43, 2.98) | 0.0001 |  |  |  |  |
| Renal Failure vs None | 1.95 (1.37, 2.78) | 0.0002 |  |  |  |  |
| Dialysis vs None | 0.74 (0.39, 1.43) | 0.3726 |  |  |  |  |
| Elevated LFTS vs None | 1.03 (0.80, 1.33) | 0.8142 |  |  |  |  |
| ***Oxygen Support*** |  |  |  |  |  |  |
| Low Oxygen Saturation vs None | 0.99 (0.77, 1.28) | 0.9307 |  |  |  |  |
| Invasive Mechanical Ventilation vs None | 1.62 (1.16, 2.27) | 0.0051 |  |  |  |  |
| Non-Mechanical Ventilation Oxygen Support Vs None | 0.98 (0.64, 1.50) | 0.9233 |  |  |  |  |
| ***qSOFA*** |  |  |  |  |  |  |
| qSOFA 3 vs 0 | 10.23 (5.00, 20.96) | <.0001 |  |  |  |  |
| qSOFA 2 vs 0 | 3.64 (2.41, 5.50) | <.0001 |  |  |  |  |
| qSOFA 1 vs 0 | 1.42 (1.07, 1.90) | 0.0169 |  |  |  |  |
| ***COVID-19 Treatment*** |  |  |  |  |  |  |
| Hydroxychloroquine vs None | 0.41 (0.30, 0.56) | <.0001 |  |  |  |  |
| Azithromycin vs None | 0.64 (0.49, 0.84) | 0.0012 |  |  |  |  |
| HCQ and Az vs None | 0.89 (0.19, 4.26) | 0.8860 |  |  |  |  |
| Remdesivir vs None | 0.78 (0.34, 1.81) | 0.5637 |  |  |  |  |
| Tocilizumab vs None | 0.68 (0.47, 0.98) | 0.0407 |  |  |  |  |
| Convalescent Plasma vs None | 0.23 (0.03, 1.74) | 0.1558 |  |  |  |  |
| ***Methylprednisolone*** |  |  |  |  |  |  |
| ***Dose*** |  |  |  |  |  |  |
| MP vs NMP | 0.44 (0.33, 0.60) | <.0001 |  |  |  |  |
| HD MP vs NMP | 0.61 (0.44, 0.85) | 0.0033 |  |  |  |  |
| LD MP vs NMP | 0.34 (0.24, 0.48) | <.0001 |  |  |  |  |

**Figure S4.** Boxplot of fraction of inspired oxygen (FiO2) reported on COVID-19 patients NMP, LD MP, and HD MP.



**Figure S5.** Plot of differences Methylprednisolone – No Methylprednisolone in hospitalized COVID-19 patients. The plot shows that the differences were very close to zero as were the Logit propensity scores.

**Standardized Mean Differences**

crpd1High

LowOxygen

renal\_failure

respRate\_high

cancer

hypertension

diabetes

sex

OlderAge

ObesityStatus

Logit Prop Score

-1.0 -0.5 0.0 0.5 1.0

Difference (Treated - Control)

All Obs Region Obs Matched Obs Negligible differences

**Figure S6.** Comparison Boxplots of distributions of Logit of Propensity Scores for MP– NMP treated COVID-19 patients. The boxplots show that the two distributions are well balanced for the MP-NMP matched observations.

**Distribution of LPS**

Matched

Treated (Methylpredn = Methylprednisolone) Control (Methylpredn = None) dnisolone)

Region

Observations

All

-2 -1 0 1

Logit of Propensity Score

**Figure S7.** LPS Cloud Plots showing Distributions of Logit of Propensity Scores for MP and NMP treated COVID-19 patients. The propensity matching procedure failed to match only 8 of the methylprednisolone patients with any of patients who did not receive methylprednisolone during their COVID-19 hospitalization.

Taken together, Table S1 and Table S2 and Figures S1-S3 show that that propensity matched sample of 384 pairs yielded reasonably well-balanced distributions to conduct subsequent analyses.

**LPS Clouds**

Treated

Observations

Control

-2 -1 0 1

Logit of Propensity Score

Outside Support Region Support Region (Not Matched) Matched Obs

**Figure S8.** A plot of log cumulative hazard function (-log (survival function)) by time for MP and NMP treated COVID-19 patients. The plot showed that cumulative hazard function made a sharp increase by day 40 and the no methylprednisolone cohort had a mild slowing rate around 30 days. This graph indicates that the methylprednisolone the proportional hazard assumption may not been satisfied.

**Negative Log of Estimated Survivor Functions**

1.5

1.0

-log(Survival Probability)

0.5

0.0

0 10 20 30 40 50 60

Days

Treatment MP NMP

**Figure S9.** A plot of log cumulative hazard function (-log (survival function)) by log(time) in MP and NMP treated COVID-19 patients. The shows that hazard in the methylprednisolone cohort were increasing more rapidly after 2 (log (Days)) indicating there was a possible interaction between methylprednisolone and days since admission.

**Log of Negative Log of Estimated Survivor Functions**

0

-2

log[-log(Survival Probability)]

-4

-6

0 1 2 3 4

log(Days)

Treatment MP NMP

**Figure S10**. The plot of log(cumulative hazard)(-negative survival)) by days for the NMP , LD MP and HD MP treated COVID-19 patients. The graph show that cumulative hazard in HD and LD methylprednisolone were increase and in particular the HD MP was increasing much faster than LD after 40 days, this suggest that the proportional hazard assumption may not have been met.

**Negative Log of Estimated Survivor Functions**

2.0

1.5

1.0

-log(Survival Probability)

0.5

0.0

0 10 20 30 40 50 60

Days

Dose HD MP LD MP NMP

**Figure S11.** The plot of log cumulative hazard (-negative survival) by log (days) in NMP , LD MP , HD MP treated COVID-19 patients. show that cumulative hazard in HD and LD methylprednisolone were increase and in particular the HD MP was increasing much faster than LD after 2 log days, and by 3 log days, the HD MP and NMP are the same path while LD increased slowly before increasing faster before 4 log days. This suggest that the proportional hazard assumption may not have been met.

**Log of Negative Log of Estimated Survivor Functions**

0

-2

log[-log(Survival Probability)]

-4

-6

0 1 2 3 4

log(Days)

Dose HD MP LD MP NMP

In the following, we examined the proportional assumption using a formal test of Supremum test of proportionality, Lin, Wei, Ying (1993). Table S3 is a summary of all the covariates that were indicated to failed to satisfy the proportional based on the Supremum test. Tables S4 – S10 contain the results of the test for each variable included in the propensity matched cohort.

**Figure S14**. Plot of observed standardized score process of methylprednisolone vs. 20 simulated realizations. The plot shows that with the first 20 of 1,000 simulated realizations(depicted by thin dotted line) conducted here, the observed MP process (depicted by the thick solid line) exhibited significant deviation from the paths of simulations within the first 20 days since the COVID-19 admission and then thereafter the MP process was more typical with simulated realization. Over the 1000 simulated realization, the supremum test reported an absolute maximum value of 2.2103 with p-value of <0.0001. Thus, the test indicated that methylprednisolone administration significantly violated the proportional hazards assumption.

**Checking Proportional Hazards Assumption for Methylprednisolone**

**Observed Path and First 20 Simulated Paths**

1

Pr > MaxAbsVal: <.0001

(1000 Simulations)

0

Standardized Score Process

-1

-2

0 10 20 30 40 50 60

Days

**Figure S15**. Plot of observed standardized score process of methylprednisolone (MP) dose level (NMP, LD, HD) vs. 20 simulated realizations. The plot shows that with the first 20 of 1,000 simulated realizations(depicted by thin dotted line) conducted here, the observed MP dose process (depicted by the thick solid line) exhibited significant deviation from the paths of simulations within the first 20 days since the COVID-19 admission and then thereafter the MP dose process was more typical with simulated realizations. Over the 1000 simulated realization, the supremum test reported an absolute maximum value of 2.360 with p-value of <0.0001. Thus, the test indicated that methylprednisolone dose level significantly violated the proportional hazards assumption.

**Checking Proportional Hazards Assumption for MethylprednisoloneDose**

**Observed Path and First 20 Simulated Paths**

1

Pr > MaxAbsVal: <.0001

(1000 Simulations)

0

Standardized Score Process

-1

-2

0 10 20 30 40 50 60

Days

**Figure S16**. Plot of observed standardized score process of FiO2 (%) vs. 20 simulated realizations. The plot shows that with the first 20 of 1,000 simulated realizations(depicted by thin dotted line) conducted here, the observed FiO2 process (depicted by the thick solid line) exhibited significant deviation from the paths of simulations within the first 20 days since the COVID-19 admission and then thereafter the FiO2 process was more typical with simulated realizations.

Over the 1000 simulated realization, the supremum test reported an absolute maximum value of 2.4993 with p-value of <0.0001. Thus, the test indicated that FiO2 level significantly violated the proportional hazards assumption.

**Checking Proportional Hazards Assumption for FiO2**

**Observed Path and First 20 Simulated Paths**

2

Pr > MaxAbsVal: <.0001

(1000 Simulations)

1

Standardized Score Process

0

-1

0 10 20 30 40 50 60

Days

|  |
| --- |
| **Table S3**. Assessment of the Proportional Hazards Assumptions in Baseline Characteristics in COVID-19 Patients |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| **Nursing Home** | **1.4886** | **1000** | **19** | **0.0110** |
| **Anosmia or Ageusia** | **0.0030** | **1000** | **19** | **<.0001** |
| **WBC lower** | **2.3013** | **1000** | **19** | **<.0001** |
| **Creatinine high** | **1.2404** | **1000** | **19** | **0.0400** |
| **Respiratory Rate high** | **1.3106** | **1000** | **19** | **0.0420** |
| **Hydroxychloroquine** | **1.6164** | **1000** | **19** | **0.0020** |
| **Methylprednisolone** | **2.2103** | **1000** | **19** | **<.0001** |
| **HD/LD/No Methylprednisolone** | **2.3601** | **1000** | **19** | **<.0001** |
| **Fi02** | **2.4993** | **1000** | **19** | **<.0001** |
| **qSOFA** | **1.5330** | **1000** | **19** | **0.0200** |
| **Calcium** | **1.3128** | **1000** | **19** | **0.0360** |
| **Initial BP (diastolic)** | **1.4722** | **1000** | **19** | **0.0330** |
| Supremum Test for Proportional Hazard Assumption. Any P<0.05 was Statistically Significant. |

**Table S4.** Assessment of the Proportional Hazards Assumptions for the Demographic and comorbidities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| Sex | 0.8227 | 1000 | 19 | 0.3490 |
| Older age | 1.0353 | 1000 | 19 | 0.1520 |
| Obesity status | 1.1676 | 1000 | 19 | 0.0660 |
| Form current Smoker | 0.6363 | 1000 | 19 | 0.6040 |
| Is Smoker | 0.5641 | 1000 | 19 | 0.7890 |
| **Nursing Home** | **1.4886** | **1000** | **19** | **0.0110** |
| Fever | 0.3243 | 1000 | 19 | 0.9880 |
| SOB | 1.0332 | 1000 | 19 | 0.1350 |
| Cough | 0.9889 | 1000 | 19 | 0.1750 |
| AMS Symptoms | 1.1986 | 1000 | 19 | 0.0530 |
| GI | 0.6098 | 1000 | 19 | 0.6500 |
| **Anosmia or Ageusia** | **0.0030** | **1000** | **19** | **<.0001** |
| Symptoms>7days | 0.5481 | 1000 | 19 | 0.7380 |
| Duration symptom Cat | 0.8762 | 1000 | 19 | 0.2280 |
| Diabetes | 0.6145 | 1000 | 19 | 0.6330 |
| COPD\_O2 | 0.6974 | 1000 | 19 | 0.4280 |
| COPD | 0.2846 | 1000 | 19 | 0.9930 |
| Asthma | 0.5324 | 1000 | 19 | 0.7420 |
| COPD/asthma | 0.3837 | 1000 | 19 | 0.9530 |
| Hypertension | 0.9271 | 1000 | 19 | 0.2310 |
| Cancer | 1.0278 | 1000 | 19 | 0.1280 |
| Coronary | 0.8326 | 1000 | 19 | 0.3160 |
| Coronary Stroke | 1.1629 | 1000 | 19 | 0.0920 |
| Coronary Heart | 0.9956 | 1000 | 19 | 0.1510 |
| Coronary Arrhythmia | 0.8273 | 1000 | 19 | 0.2920 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| Renal Failure | 0.5449 | 1000 | 19 | 0.7580 |
| Renal Failure Dialysis | 0.6128 | 1000 | 19 | 0.5880 |
| Rheumatic disease disorder | 0.6623 | 1000 | 19 | 0.5470 |
| Supremum Test for Proportional Hazard Assumption. Any P<0.05 was Statistically Significant. |

**Table S5**. Assessment of the Proportional Hazards Assumptions for the dichotomized lab values and respiratory rate

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| **WBC lower** | **2.3013** | **1000** | **19** | **<.0001** |
| HBG lower norm | 1.1560 | 1000 | 19 | 0.0730 |
| Platelet lower norm | 0.6383 | 1000 | 19 | 0.5980 |
| Abs lymphocyte lower norm | 0.6654 | 1000 | 19 | 0.4550 |
| IL-6 high | 1.1596 | 1000 | 19 | 0.0830 |
| CRP d1 High | 0.9503 | 1000 | 19 | 0.2040 |
| Ferritin high | 0.5388 | 1000 | 19 | 0.7860 |
| D-dimer categ | 0.9539 | 1000 | 19 | 0.2180 |
| **Creatinine high** | **1.2404** | **1000** | **19** | **0.0400** |
| **Respiratory Rate high** | **1.3106** | **1000** | **19** | **0.0420** |
| Supremum Test for proportional hazard assumption. Any p<0.05 was statistically significant. |

**Table S6.** Assessment of the Proportional Hazards Assumptions for therapy for COVID-19

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| **HCQ** | **1.6164** | **1000** | **19** | **0.0020** |
| Azithromycin | 0.8226 | 1000 | 19 | 0.3600 |
| HCQ and AZ | 0.7439 | 1000 | 19 | 0.2570 |
| Remdesivir | 0.7195 | 1000 | 19 | 0.4200 |
| Tocilizumab | 0.7093 | 1000 | 19 | 0.4830 |
| SAR | 0.8885 | 1000 | 19 | 0.2530 |
| Convalescent Plasma | 0.4901 | 1000 | 19 | 0.3390 |
| **Methylprednisolone** | **2.2103** | **1000** | **19** | **<.0001** |
| **HD/LD/No Methylprednisolone** | **2.3601** | **1000** | **19** | **<.0001** |
| Supremum Test for proportional hazard assumption. Any p<0.05 was statistically significant |

**Table S7.** Assessment of the Proportional Hazards Assumptions for clinical presentation parameters

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| Elevated LFTs | 0.8344 | 1000 | 19 | 0.3650 |
| Low Oxygen | 0.9414 | 1000 | 19 | 0.2120 |
| Supplemental Oxygen | 0.8402 | 1000 | 19 | 0.3030 |
| **FiO2** | **2.4993** | **1000** | **19** | **<.0001** |
| **qSOFA** | **1.5330** | **1000** | **19** | **0.0200** |
| Fever Temp | 0.7363 | 1000 | 19 | 0.5400 |
| Intubated | 1.0596 | 1000 | 19 | 0.1160 |
| Mechanical ventilation | 0.5595 | 1000 | 19 | 0.5940 |
| Supremum Test for proportional hazard assumption. Any p<0.05 was statistically significant. |

**Table S8.** Assessment of the Proportional Hazards Assumptions for labs (continuous) form

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| White Blood Cells | 0.7495 | 1000 | 19 | 0.1300 |
| Abs. neutrophil count | 0.9530 | 1000 | 19 | 0.2840 |
| Abs. lymphocyte count | 0.9140 | 1000 | 19 | 0.2870 |
| Abs. Neutrophil/Lymphocyte Ratio | 0.8075 | 1000 | 19 | 0.3350 |
| Platelets | 0.8027 | 1000 | 19 | 0.4820 |
| HGB | 1.0019 | 1000 | 19 | 0.3350 |
| LDH | 0.5495 | 1000 | 19 | 0.8100 |
| Ferritin | 0.9932 | 1000 | 19 | 0.1850 |
| D-dimer | 0.4179 | 1000 | 19 | 0.8120 |
| C-reactive Protein | 0.6009 | 1000 | 19 | 0.6370 |
| Troponin | 0.6315 | 1000 | 19 | 0.3740 |
| BNP | 0.8043 | 1000 | 19 | 0.0980 |
| Creatinine | 0.8413 | 1000 | 19 | 0.1350 |
| AST | 0.5009 | 1000 | 19 | 0.5200 |
| ALT | 0.4692 | 1000 | 19 | 0.6730 |
| Bilirubin | 0.1955 | 1000 | 19 | 0.5030 |
| Supremum Test for proportional hazard assumption. Any p<0.05 was statistically significant. |

**Table S9.** Assessment of the Proportional Hazards Assumptions for the inflammatory markers

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| IL-6 on Admission | 0.4438 | 1000 | 19 | 0.6970 |
| IL-6 Recent | 0.4438 | 1000 | 19 | 0.6970 |
| CK | 0.7009 | 1000 | 19 | 0.1930 |
| La | 0.8184 | 1000 | 19 | 0.3190 |
| Potassium | 0.8724 | 1000 | 19 | 0.2810 |
| Magnesium | 0.6025 | 1000 | 19 | 0.5370 |
| Phosphate | 0.4909 | 1000 | 19 | 0.3360 |
| **Calcium** | **1.3128** | **1000** | **19** | **0.0360** |
| Sodium | 0.3766 | 1000 | 19 | 0.8310 |
| BUN | 0.4980 | 1000 | 19 | 0.5620 |
| HCT | 0.7023 | 1000 | 19 | 0.6600 |
| Glucose | 0.4796 | 1000 | 19 | 0.5520 |
| Total bilirubin | 0.3156 | 1000 | 19 | 0.7450 |
| Supremum Test for proportional hazard assumption. Any p<0.05 was statistically significant. |

**Table S10.** Assessment of the Proportional Hazards Assumptions for the vitals

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Max Abs Value | Replications | Seed | P-Value |
| Initial temperature | 0.5519 | 1000 | 19 | 0.7350 |
| Initial Heart rate | 0.3960 | 1000 | 19 | 0.9890 |
| Initial BP (Systolic) | 0.7093 | 1000 | 19 | 0.6500 |
| **Initial BP (diastolic)** | **1.4722** | **1000** | **19** | **0.0330** |
| Mean arterial pressure | 1.2078 | 1000 | 19 | 0.1220 |
| Initial Respiratory Rate | 0.4505 | 1000 | 19 | 0.5730 |
| Height (cm) | 0.5232 | 1000 | 19 | 0.7760 |
| Weight(kg) | 0.9904 | 1000 | 19 | 0.1310 |
| BMI kg/m2 | 1.0447 | 1000 | 19 | 0.1000 |
| Diagnosis age years | 1.3620 | 1000 | 19 | 0.0500 |
| Supremum Test for proportional hazard assumption. Any p<0.05 was statistically significant. |

**Table S11**. Univariate\* Cox Regression Analysis of In-hospital Mortality in COVID-19 Patients

\* univariate associations were reported for covariate that satisfied the proportional hazard assumption with since admission to COVID-19 hospitalization. Variables which demonstrated that the NPH assumption was violated were adjusted by inclusion of an interaction of FiO2 and time, and FiO2 in the model.

|  |  |  |
| --- | --- | --- |
| Comparison Effect | HR (95% CI) | P-Value |
| Male vs Female | 1.20 (0.93, 1.56) | 0.1691 |
| **Age>60 vs <60** | **2.83 (2.05, 3.91)** | **<.0001** |
| Current vs Non-Smoker | 0.62(0.29, 1.32) | 0.2154 |
| Former vs Current Smoker | 1.21(0.91, 1.61) | 0.1934 |
| **Nursing Home vs Home** | **2.81(1.99, 3.96)** | **<.0001** |
| *Symptoms* |  |  |
| Fever vs None | 0.88 (0.67, 1.15) | 0.3445 |
| SOB vs None | 1.18 (0.91, 1.53) | 0.2233 |
| Cough vs None | 0.79 (0.61, 1.01) | 0.0641 |
| **AMS vs None** | **3.14(2.32, 4.26)** | **<.0001** |
| **GI vs None** | **0.66(0.47, 0.93)** | **0.0185** |
| **Anosmia or Ageusia vs None** | **NA** | **<.0001** |
| **Duration of Symptoms PTA > 7 vs < 7 days** | **0.61 (0.41, 0.91)** | **0.0143** |
| Diabetes vs None | 1.06 (0.82, 1.37) | 0.6503 |
| **COPD vs None** | **2.44 (1.64, 3.63)** | **<.0001** |
| Asthma vs None | 0.89 (0.56,1.41) | 0.6042 |
| **COPD/Asthma vs None** | **1.49(1.07, 2.05)** | **0.0169** |
| **Hypertension vs None** | **2.12 (1.60, 2.81)** | **<.0001** |
| **Cancer vs None** | **2.08 (1.46, 2.97)** | **<.0001** |
| **CAD vs None** | **2.09 (1.56, 2.79)** | **<.0001** |
| **CVA vs None** | **2.24 (1.44, 3.50)** | **0.0004** |
| **CHF vs None** | **2.12 (1.41, 3.21)** | **0.0004** |
| **Arrhythmia vs None** | **2.07 (1.43, 2.98)** | **0.0001** |
| **Renal Failure vs None** | **1.95 (1.37, 2.78)** | **0.0002** |
| Dialysis vs None | 0.74 (0.39, 1.43) | 0.3726 |
| *Presentations Characteristics* |  |  |
| Elevated LFTS vs None | 1.03 (0.80, 1.33) | 0.8142 |
| Low Oxygen Saturation vs None | 0.99 (0.77, 1.28) | 0.9307 |
| **Mechanical Ventilation vs None** | **1.62 (1.16, 2.27)** | **0.0051** |
| Non-Mechanical Ventilation Oxygen Support Vs None | 0.98 (0.64, 1.50) | 0.9233 |
| qSOFA 3 vs 0 | 10.23 (5.00, 20.96) | <.0001 |
| **qSOFA 2 vs 0** | **3.64 (2.41, 5.50)** | **<.0001** |

|  |  |  |
| --- | --- | --- |
| Comparison Effect | HR (95% CI) | P-Value |
| **qSOFA 1 vs 0** | **1.42 (1.07, 1.90)** | **0.0169** |
| **Hydroxychloroquine vs None** | **0.41 (0.30, 0.56)** | **<.0001** |
| **Azithromycin vs None** | **0.64 (0.49, 0.84)** | **0.0012** |
| HCQ and Az vs None | 0.89 (0.19, 4.26) | 0.8860 |
| Remdesivir vs None | 0.78 (0.34, 1.81) | 0.5637 |
| **Tocilizumab vs None** | **0.68 (0.47, 0.98)** | **0.0407** |
| Convalescent Plasma vs None | 0.23 (0.03, 1.74) | 0.1558 |
| **Methylprednisolone** |  |  |
| *Dose* |  |  |
| **MP vs NMP** | **0.44 (0.33, 0.60)** | **<.0001** |
| **HD MP vs NMP** | **0.61 (0.44, 0.85)** | **0.0033** |
| **LD MP vs NMP** | **0.34 (0.24, 0.48)** | **<.0001** |
| *Level of Oxygen Support Vs MP Dose* |  |  |
| No oxygen support in HD MP vs NMP | 0.96 (0.49, 1.86) | 0.8940 |
| No oxygen support in LD MP vs NMP | 0.25 (0.10, 0.62) | **0.0028** |
| Oxygen support in HD MP vs NMP | 0.50 (0.24, 1.06) | 0.0701 |
| Oxygen support in LD MP vs NMP | 0.08 (0.02, 0.28) | **<.0001** |
| Mechanical Ventilation in HD MP vs NMP | 0.39 (0.23, 0.65) | **0.0003** |
| **Mechanical Ventilation in LD MP vs NMP** | **0.34 (0.20, 0.57)** | **<.0001** |

HR = Hazard Ratio; CI = Confidence Interval; SOB = Shortness of Breath; AMS = Altered Mental Status; GI = Gastrointestinal Symptoms; PTA = Prior to admission; COPD = Chronic Obstructive Disease; CAD = Coronary Artery Disease; CVA = Cerebrovascular Accident; CHF

= Congestive Heart Failure; LFTs = elevated liver function tests; SOFA = Sequential Organ Failure Assessment; HCQ = Hydroxychloroquine; AZ = Azithromycin; MP = Methylprednisolone; HD MP = High Dose Methylprednisolone; LD MP = Low Dose Methylprednisolone

**Table S12.** Multivariable Risk of In-hospital mortality in COVID-19 patients with/without methylprednisolone *Model 1* included interaction of FiO2 and time to adjust for interaction between time and risk factors including methylprednisolone, nursing home, coronary artery disease, supplemental oxygen in mechanical ventilation form vs none, supplemental oxygen in non-mechanical ventilation form vs none, hydroxychloroquine, and azithromycin.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Category | HR (95% CI) | P-Value |
| **Methylprednisolone** | **Methylprednisolone vs None** | **0.40 (0.27, 0.59)** | **<.0001** |
| **Nursing home** | **Yes vs. No** | **3.08 (1.94, 4.89)** | **<.0001** |
| **Coronary Artery Disease** | **Yes vs. No** | **2.12 (1.38, 3.27)** | **0.0006** |
| **Supplemental Oxygen** | **Mechanical-Ventilation vs. None** | **2.87 (1.64, 5.02)** | **0.0002** |
| Supplemental Oxygen | Non-mechanical Ventilation vs. None | 1.11 (0.60, 2.05) | 0.7483 |
| Hydroxychloroquine | Yes vs. No | 0.67 (0.43,1.02) | 0.0644 |
| **Azithromycin** | **Yes vs. No** | **0.64 (0.44, 0.93)** | **0.0183** |

HR, Hazard Ratio; CI, confidence interval

Risk of in-hospital mortality by nonproportional hazard (NPH) Cox Regression model. Any p<0.05 was statistically significant.

**Table S13.** Multivariable Risk of In-hospital mortality in COVID-19 patients with HD, LD and No methylprednisolone. *Model 2* included interaction of FiO2 and time to adjust for interaction between time and risk factors including methylprednisolone dose {High Dose(HD),Low Dose (LD), None}, nursing home, coronary artery disease, supplemental oxygen in mechanical ventilation form vs none, supplemental oxygen in non-mechanical ventilation form vs none, hydroxychloroquine, and azithromycin.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Category | HR (95% CI) | P-Value |
| **Methylprednisolone Dose** | **HD Methylprednisolone vs. None** | **0.48 (0.30, 0.77)** | **0.0025** |
| **Methylprednisolone Dose** | **LD Methylprednisolone vs. None** | **0.35 (0.22, 0.53)** | **<.0001** |
| **Nursing home** | **Yes vs. No** | **2.95 (1.83, 4.76)** | **<.0001** |
| **Coronary Artery Disease** | **Yes vs. No** | **2.22 (1.44, 3.42)** | **0.0003** |
| **Supplemental Oxygen** | **Mechanical-Ventilation vs. None** | **2.77(1.58, 4.86)** | **0.0004** |
| Supplemental Oxygen | Non-mechanical Ventilation vs. None | 1.13 (0.61, 2.09) | 0.6992 |
| Hydroxychloroquine | Yes vs. No | 0.67 (0.44,1.02) | 0.0642 |
| **Azithromycin** | **Yes vs. No** | **0.66 (0.45, 0.95)** | **0.0262** |

HR, Hazard Ratio; CI, confidence interval. Risk of in-hospital mortality by nonproportional hazard (NPH) Cox Regression model. Any p<0.05 was statistically significant.

**Figure S17.** Boxplots of fraction of inspired oxygen (FiO2) reported on admission in COVID-19 patients who were not treated with methylprednisolone and COVID-19 patients who received methylprednisolone. In each boxplot, the horizontal line in the middle indicates the median, the bottom edge of the box is the 25th percentile and the top edge of the box is the 75th percentile of FiO2. The lower endpoints of the whiskers on each side of the box indicate the minimum and maximum value. The patients who did not receive methylprednisolone reported median FiO2 value of 28% (IQR: 21%- 36%) with a range of 20% to 100% from 368 of the 383 patients. The patients who received methylprednisolone reported median FiO2 value of 36% (IQR: 23% - 100%) with a range of 15% to 100% from 354 of the 380 patients. Analysis of FiO2 differences between matched patients indicated the median of 4.0% (IQR 0% to 35%) MP vs NMP was statistically significant (Wilcoxon signed rank test P<.0001).

100

MP Treatment

MP NMP

80

60

Fi O₂(%)

40

20

NMP MP

**Methylprednisolone Treatment**

**Figure S18**. Boxplots of fraction of inspired oxygen (FiO2) reported on admission in COVID-19 patients who were not treated with methylprednisolone (NMP) and COVID-19 patients who received LD methylprednisolone (LD MP) and HD methylprednisolone (HD MP). LD MP was defined as < 1.36 mg/kg/day and HD MP was defined as > 1.36 mg/kg/day. In each boxplot, the horizontal line in the middle indicates the median, the bottom edge of the box is the 25th percentile and the top edge of the box is the 75th percentile of FiO2. The lower endpoints of the whiskers on each side of the box indicate the minimum and maximum value. The patients who did not receive methylprednisolone reported median FiO2 value of 28% (IQR: 21%- 36%) with a range of 20% to 100% from 368 of the 383 patients. The patients who received LD MP reported median FiO2 value of 36% (IQR: 21% - 100%) with a range of 15% to 100% from 203 of the 380 patients. The patients who received HD MP reported median FiO2 value of 32% (IQR: 28%

- 80%) with a range of 21% to 100% from 151 of the 380 patients. Analysis of FiO2 differences between matched patients indicated the median of 4.0% (IQR 0% to 64%) LD MP vs NMP was statistically significant (Wilcoxon signed rank test P<.0001). Analysis of FiO2 differences between matched patients indicated the median of 7.0% (IQR 0% to 19%) HD MP vs NMP was statistically significant (Wilcoxon signed rank test P<.0001).

100

Dose HD MP NMP

LD MP

80

60

Fi O₂(%)

40

20

NMP LD MP HD MP

**Methylprednisolone Dose**

**Figure S19**. Boxplot of Total Dose/Absolute Body Weight/Day in hospitalized COVID-19 patients who received Methylprednisolone (N=380). In the box plot above, the horizontal line in the middle indicates the median, the bottom edge of the box is the 25th percentile and the top edge of the box is the 75th percentile of Total Dose/ABW/Day. The lower endpoints of the whiskers on each side of the box indicate the minimum and maximum value. The green dashed line at Total Dose/ABW/Day of 1.36 depicts the cut-off value that was determined by the Youden Index Method. The total dose/ABW/day in the all methylprednisolone treated patients had a median of 1.25 mg/kg/day (IQR: 0.93 – 1.72 mg/kg/day), range 0.27 – 7.98 mg/kg/day.The cut-off value of total dose/ABW/day of 1.36 mg/kg/day against the mortality event had an area under ROC curve of 56.8% (95% CI 51.7% to 62.0%), which is not very high. Further the cut-off value had a sensitivity of 51.8% and specificity of 62.0% in determining patients who are at higher risk for in-hospitality mortality than lower risk. Thus, while this cutoff value should not be used as a reference level since administration of methylprednisolone moderate-severe

COVID-19 was not employed as the main therapy in an clinically designed trial, but rescue therapy, it provides us with a measure of predictive capability that underpinned its prescription during new pandemic.

8

MP Dose

MP

6

**Total Dose/ABW/Day (mg/kg/day)**

4

2

0

MP

**All Methylprednisolone-treated Patients**

**Figure S20.** Boxplot of Total Dose/Absolute Body Weight/Day in hospitalized COVID-19 patients who received LD Methylprednisolone (N=216) and HD Methylprednisolone (N=164). In each boxplot, the horizontal line in the middle indicates the median, the bottom edge of the box is the 25th percentile and the top edge of the box is the 75th percentile of Total Dose/ABW/Day. The lower endpoints of the whiskers on each side of the box indicate the minimum and maximum value. The green dashed line at Total Dose/ABW/Day of 1.36 depicts the cut-off value that was determined by the Youden Index Method. The total dose/ABW/day in the LD methylprednisolone treated patients had a median of 0.98 mg/kg/day (IQR: 0.82 – 1.10 mg/kg/day), range 0.27 – 1.36 mg/kg/day. The total dose/ABW/day in the HD methylprednisolone treated patients had a median of 1.79 mg/kg/day (IQR: 1.55 – 2.14 mg/kg/day), range 1.37 – 7.98 mg/kg/day.

8

MP Dose

HD MP LD MP

TotalDoseByABWByDay

6

**Total Dose/ABW/Day (mg/kg/day)**

4

2

0

LD MP

**Methylprednisolone Dose**

HD MP

**Table S14.** Level of Oxygen Support with Treatment (Methylprednisolone and Anticoagulation)

|  |  |
| --- | --- |
|  | **MP + Anticoagulant (n=754)** |
| **Oxygen Support** | **Total (n=754)** | **NMP, NAc (n=106)** | **NMP, PAc (n=214)** | **NMP, TAc (n=58)** | **MP, NAc (n=24)** | **MP, PAc (n=178)** | **MP, TAc (n=174)** |
| **None** | 256 | 4441.51 | 8740.65 | 2441.38 | 1250.00 | 6033.71 | 2916.67 |
| **Non-Invasive Oxygen Support** | 282 | 5450.94 | 10850.47 | 2034.48 | 937.50 | 6938.76 | 2212.64 |
| **Invasive Mechanical- Ventilation** | 216 | 87.55 | 198.88 | 1424.14 | 312.50 | 4927.53 | 12370.69 |

**Abbreviations:** NAc = No anticoagulation; Pac = Prophylactic anticoagulation; Tac = Therapeutic anticoagulation

**Table S15.** Level of Oxygen Support and No methylprednisolone and Prophylactic anticoagulation.

Out of 214 hospitalized patients, 42(19.6%) in the NMP+ PAc arm. The difference in in-hospital mortality between the levels of supplemental oxygen: None (16.1%) vs Non-invasive oxygen support (10.2%) vs invasive mechanical ventilation (89.5%%), was significant (p<0.0001)

|  |
| --- |
| **No methylprednisolone + Prophylactic Anticoagulant (n=214)** |
|  | **Level of Oxygen Support** |
| **Expired** | **None (n=87)** | **Non-invasive oxygen****support****(n=108)** | **Invasive Mechanical-Ventilation (n=19)** | **P-value** |
| **Alive** | 73 | 97 | 2 |  |
|  | 83.91 | 89.81 | 10.53 |  |
| **Expired** | 14 | 11 | 17 | <.0001 |
|  | 16.09 | 10.19 | 89.47 |  |

**Table S16.** Level of Oxygen Support for No Methylprednisolone and Therapeutic Anticoagulation.

26 of 58 (44.8%) in the NMP+ Therapeutic Anticoagulant group. The difference in in-hospital mortality between the levels of supplemental oxygen: None (25.0%) vs non invasive oxygen support (45.0%) vs mechanical ventilation (78.6%) was significant(p=0.0059)

|  |  |
| --- | --- |
|  | **No Methylprednisolone and Therapeutic Anticoagulation****(N=58)** |
|  | **Level of Oxygen Support** |
| **Expired** | **None (N=24)** | **Non Invasive Oxygen Support****(N=20)** | **Invasive****Mechanical-Ventilation (N=14)** | **P-value** |
| **Alive** | 18 | 11 | 3 |  |
|  | 75.00 | 55.00 | 21.43 |  |
| **Expired** | 6 | 9 | 11 | 0.0059 |
|  | 25.00 | 45.00 | 78.57 |  |

**Table S17.** Level of Oxygen Support and Methylprednisolone and Prophylactic Anticoagulation.

46 of 178(25.8%) in the MP+ Prophylactic Anticoagulant group. The difference in in-hospital mortality between the levels of supplemental oxygen: None (16.7%) vs non invasive oxygen support(8.7%) vs invasive mechanical ventilation (61.2%) was significant(p<0.0001)

|  |
| --- |
| **Methylprednisolone + Prophylactic Anticoagulant (n=178)** |
|  | **Supplemental Oxygen** |
| **Expired** | **None (n=60)** | **Non-invasive oxygen support (n=69)** | **Invasive Mechanical****Ventilation****(n=49)** | **P-value** |
| **Alive** | 50 | 63 | 19 |  |
|  | 83.33 | 91.30 | 38.78 | <.0001 |
| **Expired** | 10 | 6 | 30 |  |
|  | 16.67 | 8.70 | 61.22 |  |

**Table S18.** Level of Oxygen Support and Methylprednisolone and Therapeutic Anticoagulation

90 of the 174 (51.7%) who were treated with MP + therapeutic anticoagulants expired during the COVID-19 hospitalization. The difference in in-hospital mortality between the levels of supplemental oxygen: None (16.7%) vs. Non-mechanical ventilation (8.7%) vs. mechanical ventilation (61.2%) was significant (P<0.0001)

|  |
| --- |
| **Methylprednisolone + Therapeutic Anticoagulant(n=174)** |
|  | **Supplemental Oxygen** |
| **Expired** | **None (n=29)** | **Non invasive oxygen support (n=22)** | **Invasive****Mechanical-Ventilation (n=123)** | **P-value** |
| **Alive** | 22 | 18 | 44 |  |
|  | 75.86 | 81.82 | 35.77 | <.0001 |
| **Expired** | 7 | 4 | 79 |  |
|  | 24.14 | 18.18 | 64.23 |  |