Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods

Time-dependent Propensity Score Matching

Since the timing of initial remdesivir administration was different and the remdesivir assignment was non-randomized, a time-dependent propensity score matching method was applied to undertake 1:1 propensity score matching for the treatment arm so that additional analyses could be performed on the matched patients. Propensity scores were calculated from a time-dependent Cox proportional hazards regression model using the time to the first receipt of remdesivir as the outcome, where the propensity score at a given hospitalization day is the hazard of exposure to remdesivir treatment at that day. The PH assumption was checked using the Schoenfeld residuals against the transformed time.1-2

Time-dependent covariates in records before the first remdesivir administration date (for treatment group patients) and records before right-censoring or last follow-up date (for control group patients) were used as predictors to obtain parameter estimates. Time-invariant (fixed) covariates included hospital admission race, age, sex, body mass index (BMI), Charlson comorbidity index (CCI), and code status (i.e. whether the patient had a “do not resuscitate” order). Time-dependent (varying) covariates included various clinical measures of disease severity, such as the ratio of measured oxygen saturation to fraction of inspired oxygen (SpO2/FiO2), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, temperature, respiratory rate, and supplemental oxygen device (O2 device). SpO2/FiO2 was selected since it can be calculated without obtaining an arterial blood gas (not available on all patients). Other time-dependent variables included key laboratory test results, such as C-reactive protein (CRP), absolute lymphocyte count (ALC), platelets count, white blood cell count (WBC), hemoglobin (HGB), albumin, alanine aminotransferase (ALT), estimated Glomerular Filtration Rate (eGFR), and D-dimer.

Beginning from day zero, a sequential 1:1 greedy matching without replacement was conducted. Patients were included in the matching process only if their admission dates were later than the earliest admission date (April 27, 2020) of patients in the remdesivir group. A patient who first received remdesivir at a given day t of hospitalization was matched with those who did not, based on their propensity scores (hazard components) at day t. In addition, a time constraint was imposed so that a patient in the remdesivir group with k days of treatment, was forced to match a patient in the control group who stayed at least k days (5 days maximum) in the hospital since the matched day. This constraint removed patients from the control group who were healthy enough to be discharged in one or two days.

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from the matched day as those patients were unlikely to receive remdesivir treatment at the matched day if they were close to discharge.

**Marginal Structural Cox Regression Model**

In sub-analyses considering the effects of combination drug use, comparisons of patients who used combination of corticosteroids and remdesivir (n=185) with patients who used remdesivir alone (n=158) were conducted. Since the sample sizes for two groups were similar, and patients’ exposure to corticosteroids was time-variant, instead of time-dependent propensity score matching, Marginal Structural Cox regression models were conducted to adjust for the non-randomized administration of corticosteroids, in the meantime, to analyze the effects of corticosteroids on outcomes of interests in patients who had exposure to remdesivir. The same set of time-dependent covariates and time-invariant variables as in the matching models from all remdesivir patients were included in the model. The Inverse Probability Treatment Weighting (IPTW) method was applied for parameter estimation.

**Outcome of Interest Analyses**

The primary outcome of interest was time to clinical improvement from the treatment start of remdesivir, defined as discharge alive from the hospital without worsening of their WHO disease severity score or at least a two-point decrease in the WHO severity score during hospitalization within 28 days or max follow-up after the first treatment of remdesivir. Failure of clinical improvement was censored at max follow-up day or 28 days, whichever came first. Death was also censored at 28 days. The secondary outcome was time to death from the first remdesivir treatment day. Patients who were discharged alive were censored at 28 days.

Cox proportional-hazards regression models were applied to estimate the association between remdesivir treatment and outcomes of interests. A set of demographics, clinical variables and laboratory test results were included in Cox regression models based on clinical interest and knowledge. Time-invariant variables included race, age, sex, body mass index (BMI), Charlson comorbidity index (CCI), and code. Time dependent covariates included SpO2/FiO2 ratio, SBP, DBP, CRP, ALC, respiratory rate, temperature, pulse, WBC, HGB, Albumin, ALT, eGFR, and D-dimer. The adjusted hazard ratio of remdesivir treatment was estimated from the Cox regression model after controlling these covariates.
Missing Data Imputations

For the laboratory results, missing values were imputed using the last observation carried forward if the last observation was within three days of the missing data, otherwise, using multiple imputation by chained equations (MICE) with predictive mean matching method.4

Time to Clinical Improvement Using a 1-point Decrease in WHO severity score

We repeated the time to improvement analyses using a 1-point improvement in the WHO severity score and the results did not appreciably change. 239 (83.9%) remdesivir patients and 221 (77.5%) controls achieved clinical improvement before 28 days with a median time to clinical improvement of 4.0 days (IQR 3.0 – 7.0) and 5.0 days (IQR 3.0 – 9.0 days), respectively. In Cox proportional hazards models, remdesivir significantly shortened time to clinical improvement (aHR 1.28 [1.07; 1.55]). The results are sensitive to the requirement that controls be selected from among patients who remained hospitalized during the same period of treatment as their matched counterpart (up to 5 days). Although there is no qualitative change if the requirement is reduced to 4 days, the estimated aHR decreases to 1.07 [0.89;1.28] if the required period of hospitalization is lowered to 3 days or less. This is because 87 patients in the control group had their event (78 were discharged, and 9 achieved clinical improvement) within 4 days of matching compared to 26 patients (23 discharged and 3 improvement) in the treatment group.
**eFigure 1.** Exclusion Details under ACTT-1 Criteria

ACTT-1 Criteria: patients were excluded if age < 18 years, or pregnant, or PaO₂ ≥ 94% on room air, or either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 200, or estimated glomerular filtration rate (eGFR) < 30.
eFigure 2. Timing of Remdesivir and Corticosteroid Coadministration

eFigure 2 Legend. The time-course for co-administration of remdesivir and corticosteroids is shown for the 185 patients who received both corticosteroids and remdesivir. The majority of patients received 6mg of dexamethasone daily as utilized in the RECOVERY trial.
### Characteristics of Patients That Satisfied ACTT-1 Criteria, Before and After Propensity Score Matching

| Characteristics                                      | All Remdesivir Patients Satisfied Criteria† (n = 306) | Matched Remdesivir (n=252) | Matched Control (n=252) | Absolute Standardized Differences |
|------------------------------------------------------|------------------------------------------------------|-----------------------------|-------------------------|----------------------------------|
| **Demographics:**                                    |                                                      |                             |                         |                                  |
| Male                                                  | 176 (57.5%)                                          | 147 (58.3%)                 | 144 (57.1%)             | 0.024                            |
| Race Black                                            | 105 (34.3%)                                          | 77 (30.6%)                  | 87 (34.5%)              | 0.085                            |
| Race Latinx                                           | 103 (33.7%)                                          | 88 (34.9%)                  | 80 (31.7%)              | 0.067                            |
| Race White                                            | 62 (20.3%)                                           | 56 (22.2%)                  | 55 (21.8%)              | 0.010                            |
| Race Others                                           | 36 (11.8%)                                           | 31 (12.3%)                  | 30 (11.9%)              | 0.012                            |
| Age, Median (IQR)                                     | 60.5 (10)                                            | 62 (10)                     | 61 (11.1)               | 0.039                            |
| BMI, Median (IQR)                                     | 31.1 (5.1)                                           | 30.1 (4.4)                  | 30 (4.6)                | 0.073                            |
| **DNR/DNI, no. (%):**                                 |                                                      |                             |                         |                                  |
|                                                      | 53 (17.3%)                                           | 49 (19.4%)                  | 61 (24.2%)              | 0.115                            |
| **O2 Devices, no. (%):**                              |                                                      |                             |                         |                                  |
| No Supplemental Oxygen                                | 11 (3.6%)                                            | 11 (4.4%)                   | 11 (4.4%)               | 0.000                            |
| Nasal Cannula or Face Mask                            | 193 (63.1%)                                          | 171 (67.9%)                 | 151 (59.9%)             | 0.166                            |
| High Flow Nasal Cannula                               | 54 (17.6%)                                           | 32 (12.7%)                  | 45 (17.9%)              | 0.144                            |
| Noninvasive Positive-Pressure Ventilation            | 4 (1.3%)                                             | 4 (1.6%)                    | 5 (2%)                  | 0.030                            |
| Mechanical Ventilator                                 | 44 (14.4%)                                           | 34 (13.5%)                  | 37 (14.7%)              | 0.034                            |
| **Vital Signs, Mean (SD):**                           |                                                      |                             |                         |                                  |
| Temperature (°Celsius)                                 | 37.9 (0.9)                                           | 37.8 (0.8)                  | 37.9 (0.9)              | 0.072                            |
| Pulse (beats per minute)                              | 96 (18.4)                                            | 96.1 (19.1)                 | 98.6 (18.3)             | 0.132                            |
| Systolic BP (mmHg)                                    | 105.6 (16.7)                                         | 106 (17)                    | 106.4 (17.4)            | 0.024                            |
| Diastolic BP (mmHg)                                   | 58.2 (10.5)                                          | 58.9 (10.6)                 | 58.2 (11.7)             | 0.064                            |
| SpO2/FiO2                                             | 334.4 (110.4)                                        | 345.4 (109.4)               | 336.7 (119.4)           | 0.076                            |
| **Laboratory Results, Mean (SD):**                    |                                                      |                             |                         |                                  |
| Estimated glomerular filtration rate (mL/min)         | 89.9 (27.2)                                          | 88 (25.9)                   | 87.1 (28.2)             | 0.032                            |
| C-reactive protein (mg/dL)                            | 11.7 (8.2)                                           | 11.8 (8.5)                  | 11.9 (10)               | 0.020                            |
| Absolute lymphocyte count (K cells/mm³)               | 236.7 (107.4)                                        | 235.9 (105.5)               | 224.5 (96.3)            | 0.113                            |
| Platelet count (K cells/mm³)                          | 8.2 (6.1)                                            | 8.1 (6.5)                   | 8.3 (4.6)               | 0.034                            |
| White blood cell count (K cells/mm³)                  | 12.2 (1.9)                                           | 12.2 (1.9)                  | 12.1 (2.2)              | 0.039                            |
| Hemoglobin (g/dL)                                     | 3.1 (0.6)                                            | 3.2 (0.6)                   | 3.2 (0.6)               | 0.035                            |
| Albumin (g/dL)                                        | 43.6 (31.8)                                          | 42 (30.8)                   | 40.7 (33.6)             | 0.040                            |
| Alanine aminotransferase (U/L)                        | 2.2 (4.5)                                            | 2.3 (4.7)                   | 2.1 (4.1)               | 0.033                            |
| D-dimer (mg/L FEU)                                    |                                                      |                             |                         |                                  |
| **Past Diagnoses, no. (%):**                          |                                                      |                             |                         |                                  |
| Hypertension                                          | 131 (42.8%)                                          | 110 (43.7%)                 | 96 (38.1%)              | 0.113                            |
| Coronary Artery Disease                               | 83 (27.1%)                                           | 75 (29.8%)                  | 79 (31.3%)              | 0.034                            |
| Congestive heart failure                              | 38 (12.4%)                                           | 32 (12.7%)                  | 43 (17.1%)              | 0.123                            |
| Chronic kidney disease                               | 17 (5.6%)                                            | 16 (6.3%)                   | 11 (4.4%)               | 0.088                            |
| Diabetes                                              | 96 (31.4%)                                           | 83 (32.9%)                  | 71 (28.2%)              | 0.104                            |
| Asthma                                                | 24 (7.8%)                                            | 19 (7.5%)                   | 22 (8.7%)               | 0.044                            |
| COPD/Chronic Lung Disease                             | 53 (17.3%)                                           | 43 (17.1%)                  | 36 (14.3%)              | 0.076                            |
| Cancer                                                | 20 (6.5%)                                            | 19 (7.5%)                   | 19 (7.5%)               | 0.000                            |
| Liver Disease                                         | 11 (3.6%)                                            | 11 (4.4%)                   | 12 (4.8%)               | 0.019                            |
| AIDS/HIV                                              | 3 (1%)                                               | 2 (0.8%)                    | 3 (1.2%)                | 0.040                            |
| Transplant                                            | 7 (2.3%)                                             | 7 (2.8%)                    | 3 (1.2%)                | 0.114                            |
| Charlson Comorbidity Index:                           |                                                      |                             |                         |                                  |
| =0                                                    | 128 (41.8%)                                          | 97 (38.5%)                  | 105 (41.7%)             | 0.065                            |
| 1-4                                                   | 172 (56.2%)                                          | 150 (59.5%)                 | 144 (57.1%)             | 0.048                            |
| >=5                                                   | 6 (2%)                                               | 5 (2%)                      | 3 (1.2%)                | 0.064                            |
| **Concomitant Medications, no. (%):**                  |                                                      |                             |                         |                                  |
| Hydroxychloroquine                                    | 1 (0.3%)                                             | 1 (0.4%)                    | 5 (2%)                  | 0.147                            |
| Azithromycin                                          | 137 (44.8%)                                          | 111 (44%)                   | 113 (44.8%)             | 0.016                            |
| Dexamethasone                                         | 143 (46.7%)                                          | 122 (48.4%)                 | 37 (14.7%)              | 0.779                            |
| Prednisone                                            | 22 (7.2%)                                            | 19 (7.5%)                   | 13 (5.2%)               | 0.098                            |
| Methylprednisolone                                    | 17 (5.6%)                                            | 14 (5.6%)                   | 23 (9.1%)               | 0.137                            |
| Hydrocortisone                                        | 9 (2.9%)                                             | 7 (2.8%)                    | 16 (6.3%)               | 0.172                            |
| Heparin                                               | 269 (87.9%)                                          | 220 (87.3%)                 | 214 (84.9%)             | 0.069                            |

† Data shown is from the day of remdesivir treatment initiation

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# Table 2. Characteristics of Remdesivir Patients Stratified by Corticosteroid Use

| Characteristics                                      | All Remdesivir Patients\(^\dagger\) | Rem Alone (n = 158) | Rem + Steroids (n = 184) | Absolute Standardized Differences |
|-------------------------------------------------------|--------------------------------------|---------------------|--------------------------|---------------------------------|
| Demographics:                                         |                                      |                     |                          |                                 |
| Male                                                  |                                      | 88 (55.7%)          | 101 (54.9%)              | 0.016                           |
| Race Black                                            |                                      | 55 (34.8%)          | 69 (37.5%)               | 0.056                           |
| Race Latinx                                           |                                      | 64 (40.5%)          | 50 (27.2%)               | 0.285                           |
| Race White                                            |                                      | 26 (16.5%)          | 40 (21.7%)               | 0.135                           |
| Race Others                                           |                                      | 13 (8.2%)           | 25 (13.6%)               | 0.173                           |
| Age, Median (IQR)                                     |                                      | 56 (12.2)           | 63 (10)                  | 0.249                           |
| BMI, Median (IQR)                                     |                                      | 31.5 (5.3)          | 30.1 (3.4)               | 0.178                           |
| DNR/DNI, no. (%)                                      |                                      | 18 (11.4%)          | 43 (23.4%)               | 0.320                           |
| O2 Devices, no. (%)                                   |                                      |                     |                          |                                 |
| No Supplemental Oxygen                                 |                                      | 7 (4.4%)            | 9 (4.9%)                 | 0.022                           |
| Nasal Cannula or Face Mask High Flow                  |                                      | 108 (68.4%)         | 102 (55.4%)              | 0.268                           |
| Nasal Cannula                                         |                                      | 21 (13.3%)          | 39 (21.2%)               | 0.210                           |
| Noninvasive Positive-Pressure Ventilation             |                                      | 1 (0.6%)            | 4 (2.2%)                 | 0.131                           |
| Mechanical Ventilator                                  |                                      | 21 (13.3%)          | 30 (16.3%)               | 0.085                           |
| Vital Signs, Mean (SD):                               |                                      |                     |                          |                                 |
| Temperature (°Celsius)                                 |                                      | 38 (0.8)            | 37.7 (0.9)               | 0.309                           |
| Pulse (beats per minute)                              |                                      | 99 (19.9)           | 94.2 (17.8)              | 0.254                           |
| Systolic BP (mmHg)                                    |                                      | 105.2 (15.9)        | 105.7 (17.7)             | 0.032                           |
| Diastolic BP (mmHg)                                   |                                      | 58.1 (9.3)          | 57.9 (11.4)              | 0.016                           |
| SpO2/FiO2                                            |                                      | 347.2 (108.4)       | 323.8 (110.1)            | 0.215                           |
| Laboratory Results, Mean (SD):                        |                                      |                     |                          |                                 |
| Estimated glomerular filtration rate (ml/min)         |                                      | 90.4 (31.9)         | 84.5 (30.1)              | 0.190                           |
| C-reactive protein (mg/dL)                            |                                      | 12 (7.8)            | 11.4 (8.9)               | 0.075                           |
| Absolute lymphocyte count (K cells/mm\(^3\))         |                                      | 1.2 (0.6)           | 1 (0.7)                  | 0.217                           |
| Platelet count (K cells/mm\(^3\))                    |                                      | 235.6 (108.6)       | 234.9 (102.6)            | 0.006                           |
| White blood cell count (K cells/mm\(^3\))            |                                      | 8 (7.7)             | 8.2 (4)                  | 0.037                           |
| Hemoglobin (g/dL)                                     |                                      | 12 (2)              | 12.1 (2)                 | 0.045                           |
| Albumin (g/dL)                                        |                                      | 3 (0.6)             | 3.2 (0.6)                | 0.324                           |
| Alanine aminotransferase (U/L)                        |                                      | 43.3 (34.9)         | 45.7 (39.1)              | 0.063                           |
| D-dimer (mg/L FEU)                                    |                                      | 2.7 (5.4)           | 1.9 (3.8)                | 0.177                           |
| Past Diagnoses, no. (%)                               |                                      |                     |                          |                                 |
| Hypertension                                          |                                      | 63 (39.9%)          | 89 (48.4%)               | 0.172                           |
| Coronary Artery Disease                               |                                      | 34 (21.5%)          | 58 (31.5%)               | 0.228                           |
| Congestive heart failure                              |                                      | 20 (12.7%)          | 25 (13.6%)               | 0.028                           |
| Chronic kidney disease                                |                                      | 10 (6.3%)           | 18 (9.8%)                | 0.127                           |
| Diabetes                                              |                                      | 53 (33.5%)          | 58 (31.5%)               | 0.043                           |
| Asthma                                                |                                      | 11 (7%)             | 18 (9.8%)                | 0.102                           |
| COPD/Chronic Lung Disease                             |                                      | 18 (11.4%)          | 41 (22.3%)               | 0.294                           |
| Cancer                                                |                                      | 12 (7.6%)           | 11 (6%)                  | 0.064                           |
| Liver Disease                                         |                                      | 5 (3.2%)            | 8 (4.3%)                 | 0.062                           |
| AIDS/HIV                                              |                                      | 0 (0%)              | 3 (1.6%)                 | 0.182                           |
| Transplant                                            |                                      | 2 (1.3%)            | 6 (3.3%)                 | 0.134                           |
| Charlson Comorbidity Index:                           |                                      |                     |                          |                                 |
| =0                                                    |                                      | 72 (45.6%)          | 70 (38%)                 | 0.153                           |
| 1-4                                                   |                                      | 81 (51.3%)          | 110 (59.8%)              | 0.172                           |
| >5                                                    |                                      | 5 (3.2%)            | 4 (2.2%)                 | 0.061                           |
| Concomitant Medications, no. (%):                     |                                      |                     |                          |                                 |
| Hydroxychloroquine                                    |                                      | 1 (0.6%)            | 2 (1.1%)                 | 0.049                           |
| Azithromycin                                          |                                      | 75 (47.5%)          | 78 (42.4%)               | 0.102                           |
| Dexamethasone                                         |                                      | N/A                 | 157 (85.3%)              | N/A                             |
| Prednisone                                            |                                      | N/A                 | 27 (14.7%)               | N/A                             |
| Methylprednisolone                                    |                                      | N/A                 | 20 (10.9%)               | N/A                             |
| Hydrocortisone                                        |                                      | N/A                 | 12 (6.5%)                | N/A                             |
| Heparin                                               |                                      | 140 (88.6%)         | 152 (82.6%)              | 0.172                           |

\(^\dagger\) Data shown is from the day of Remdesivir treatment initiation

Rem denotes Remdesivir. Steroids denotes Corticosteroids (dexamethasone, prednisone, prednisolone, methylprednisolone or hydrocortisone)
**eTable 3. Adverse Events**

|                          | Matched Remdesivir (n = 285) | Matched Control (n = 285) |
|--------------------------|-------------------------------|----------------------------|
| **Before Matched Day or Drug Day, no. (%):** |                               |                            |
| ALT or AST > 200 IU      | 5 (1.8%)                      | 7 (2.6%)                   |
| bilirubin > 2 mg/dL      | 3 (1.1%)                      | 4 (1.4%)                   |
| eGFR < 30 ml/min         | 3 (1.1%)                      | 4 (1.4%)                   |
| **On/After Matched Day or Drug Day, no. (%):** |                               |                            |
| ALT or AST > 200 IU      | 29 (10.2%)                    | 29 (10.2%)                 |
| bilirubin > 2 mg/dL      | 10 (3.5%)                     | 17 (6.0%)                  |
| eGFR < 30 ml/min         | 27 (9.5%)                     | 58 (20.4%)                 |
| **Anytime in hospital, no. (%):** |                               |                            |
| ALT or AST > 200 IU      | 32 (11.2%)                    | 36 (12.6%)                 |
| bilirubin > 2 mg/dL      | 11 (3.9%)                     | 18 (6.3%)                  |
| eGFR < 30 ml/min         | 31 (10.9%)                    | 71 (24.9%)                 |

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