**Supplementary Material**

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# **Precision Analysis**

The precision analysis was completed using the 5,000 computer simulations based on the generalized linear model (GLM).

*Observed data:*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Negative control | Positive control | HCQ alone | HCQ + anything |
| Sample size | 1321 | 327 | 179 | 359 |
| Mortality | 115 | 59 | 44 | 111 |
| Mortality rate | 0.09 | 0.18 | 0.25 | 0.31 |

Taking HCQ alone vs negative control as an example, we first generated 179 binary outcomes with the mortality rate of 0.25 for HCQ alone group and generated 1,321 binary outcomes with the mortality rate of 0.09 for the negative control group. Then, we performed the logistic regression analysis to estimate the odds ratio (OR) of HCQ alone vs negative control. Replicating the procedure 5,000 times, we obtained 5,000 ORs, ORs’ average and 95% confidence interval. Below are the simulation results.

Ratio of standard error (SE) of estimated OR to estimated OR [mean, 95% CI] is from logistic regression analysis based on 5,000 replications. SE of estimated OR is obtained using the Delta method, i.e., exp(beta.hat)\*se(beta.hat).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Negative control | Positive control | HCQ alone | HCQ + anything |
| Negative control |  |  |  |  |
| Positive control | 0.17 (0.16-0.19) |  |  |  |
| HCQ alone | 0.20 (0.19-0.21) | 0.23 (0.21-0.24) |  |  |
| HCQ + anything | 0.15 (0.14-0.16) | 0.18 (0.18-0.20) | 0.21 (0.20-0.22) |  |

# **Supplemental Table S1. Baseline demographic and clinical characteristics.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | All patients | Hydroxy-chloroquine | Azithromycin | Remdesivir | High-dose systemic cortico-steroids | Tocilizumab | Other COVID-19 treatmentse | No treatment |
| **Total** | 2186 (100) | 538 (25) | 485 (22) | 124 (6) | 109 (5) | 94 (4) | 90 (4) | 1321 (60) |
| **On clinical triala** | 134 (6) | 7 (1) | 2 (<1) | 86 (69) | 0 (0) | 5 (5) | 37 (41) | N/A |
| **Age** |  |  |  |  |  |  |  |  |
| Median, IQR | 67, 57-77 | 70, 61-79 | 69, 60-78 | 68, 58-76 | 69, 61-77 | 67.5, 61-77 | 69.5, 61-76 | 65, 54-76 |
| <65 | 956 (44) | 181 (34) | 183 (38) | 50 (40) | 41 (38) | 36 (38) | 30 (33) | 646 (49) |
| 65-74 | 559 (26) | 161 (30) | 133 (27) | 40 (32) | 32 (29) | 31 (33) | 34 (38) | 311 (24) |
| 75+ | 671 (31) | 196 (36) | 169 (35) | 34 (27) | 36 (33) | 27 (29) | 26 (29) | 364 (28) |
| **Sex** |  |  |  |  |  |  |  |  |
| Female | 1105 (51) | 241 (45) | 221 (46) | 54 (44) | 55 (50) | 43 (46) | 34 (38) | 706 (53) |
| Male | 1078 (49) | 297 (55) | 264 (54) | 70 (56) | 54 (50) | 51 (54) | 56 (62) | 612 (46) |
| Missing | 3 (<1) |  |  |  |  |  |  | 3 (<1) |
| **Race/ethnicity** |  |  |  |  |  |  |  |  |
| Non-Hispanic White | 1115 (51) | 247 (46) | 257 (53) | 65 (52) | 47 (43) | 44 (47) | 46 (51) | 693 (52) |
| Hispanic | 334 (15) | 76 (14) | 56 (12) | 25 (20) | 10 (9) | 9 (10) | 13 (14) | 217 (16) |
| Non-Hispanic Black | 476 (22) | 152 (28) | 126 (26) | 18 (15) | 37 (34) | 31 (33) | 23 (26) | 247 (19) |
| Other | 200 (9) | 56 (10) | 39 (8) | 8 (6) | 12 (11) | 7 (7) | 4 (4) | 120 (9) |
| Missing | 61 (3) | 7 (1) | 7 (1) | 8 (6) | 3 (3) | 3 (3) | 4 (4) | 44 (3) |
| **Region of patient residence** |  |  |  |  |  |  |  |  |
| US-Northeast | 1011 (46) | 289 (54) | 234 (48) | 58 (47) | 47 (43) | 53 (56) | 45 (50) | 574 (43) |
| US-Midwest | 597 (27) | 147 (27) | 143 (29) | 25 (20) | 42 (39) | 29 (31) | 27 (30) | 357 (27) |
| US-South | 275 (13) | 66 (12) | 74 (15) | 16 (13) | 11 (10) | 8 (9) | 10 (11) | 168 (13) |
| US-West | 303 (14) | 36 (7) | 34 (7) | 25 (20) | 9 (8) | 4 (4) | 8 (9) | 222 (17) |
| **Smoking Status** |  |  |  |  |  |  |  |  |
| Never | 1149 (53) | 246 (46) | 241 (50) | 64 (52) | 41 (38) | 42 (45) | 41 (46) | 731 (55) |
| Current or Former | 958 (44) | 275 (51) | 231 (48) | 53 (43) | 64 (59) | 46 (49) | 46 (51) | 541 (41) |
| Missing | 79 (4) | 17 (3) | 13 (3) | 7 (6) | 4 (4) | 6 (6) | 3 (3) | 49 (4) |
| **Comorbidities** |  |  |  |  |  |  |  |  |
| Obesity | 705 (32) | 183 (34) | 178 (37) | 48 (39) | 50 (46) | 48 (51) | 35 (39) | 394 (30) |
| Diabetes mellitus | 643 (29) | 209 (39) | 175 (36) | 39 (31) | 38 (35) | 35 (37) | 25 (28) | 338 (26) |
| Hypertension | 1258 (58) | 377 (70) | 320 (66) | 82 (66) | 68 (62) | 70 (74) | 63 (70) | 675 (51) |
| Pulmonary | 471 (22) | 147 (27) | 127 (26) | 36 (29) | 39 (36) | 25 (27) | 25 (28) | 239 (18) |
| Cardiovascular | 709 (32) | 198 (37) | 176 (36) | 44 (35) | 43 (39) | 38 (40) | 33 (37) | 396 (30) |
| Renal | 389 (18) | 135 (25) | 110 (23) | 11 (9) | 24 (22) | 17 (18) | 17 (19) | 198 (15) |
| **ECOG Performance Status** |  |  |  |  |  |  |  |  |
| 0 | 749 (34) | 133 (25) | 143 (29) | 44 (35) | 23 (21) | 22 (23) | 23 (26) | 515 (39) |
| 1 | 563 (26) | 175 (33) | 131 (27) | 30 (24) | 31 (28) | 30 (32) | 31 (34) | 311 (24) |
| 2+ | 352 (16) | 97 (18) | 61 (13) | 16 (13) | 21 (19) | 16 (17) | 12 (13) | 202 (15) |
| Unknown | 506 (23) | 127 (24) | 143 (29) | 34 (27) | 33 (30) | 26 (28) | 23 (26) | 284 (21) |
| Missing | 16 (1) | 6 (1) | 7 (1) |  | 1 (1) |  | 1 (1) | 9 (1) |
| **Malignancy typeb** |  |  |  |  |  |  |  |  |
| Solid tumors | 1781 (81) | 417 (78) | 390 (80) | 89 (72) | 85 (78) | 63 (67) | 60 (67) | 1107 (84) |
| Breast | 455 (21) | 94 (17) | 93 (19) | 15 (12) | 20 (18) | 13 (14) | 8 (9) | 297 (22) |
| Prostate | 368 (17) | 103 (19) | 87 (18) | 18 (15) | 17 (16) | 12 (13) | 17 (19) | 212 (16) |
| Gastrointestinal | 290 (13) | 67 (12) | 62 (13) | 17 (14) | 12 (11) | 12 (13) | 10 (11) | 186 (14) |
| Thoracic | 169 (8) | 54 (10) | 39 (8) | 9 (7) | 13 (12) | 11 (12) | 7 (8) | 90 (7) |
| Gynecologic | 143 (7) | 31 (6) | 31 (6) | 7 (6) | 7 (6) | 3 (3) | 5 (6) | 93 (7) |
| Solid tumors, NOS | 506 (23) | 105 (20) | 107 (22) | 30 (24) | 25 (23) | 19 (20) | 21 (23) | 320 (24) |
| Hematologic malignancies | 470 (22) | 141 (26) | 114 (24) | 38 (31) | 27 (25) | 36 (38) | 32 (36) | 251 (19) |
| Lymphoid neoplasms | 272 (12) | 82 (15) | 68 (14) | 23 (19) | 13 (12) | 19 (20) | 19 (21) | 146 (11) |
| Plasma cell disorders | 95 (4) | 34 (6) | 27 (6) | 10 (8) | 10 (9) | 11 (12) | 11 (12) | 42 (3) |
| Myeloid neoplasms | 98 (4) | 25 (5) | 19 (4) | 5 (4) | 5 (5) | 6 (6) | 2 (2) | 57 (4) |
| Hematologic malignancy, NOS | 12 (1) | 1 (<1) | 1 (<1) | 1 (1) | 0 (0) | 0 (0) | 1 (1) | 10 (1) |
| **Cancer Status** |  |  |  |  |  |  |  |  |
| Remission/NED | 1115 (51) | 258 (48) | 261 (54) | 61 (49) | 48 (44) | 36 (38) | 42 (47) | 682 (52) |
| Active, progressing | 239 (11) | 70 (13) | 52 (11) | 15 (12) | 21 (19) | 16 (17) | 8 (9) | 135 (10) |
| Active, stable/responding | 607 (28) | 149 (28) | 124 (26) | 36 (29) | 24 (22) | 31 (33) | 27 (30) | 375 (28) |
| Unknown | 214 (10) | 60 (11) | 47 (10) | 11 (9) | 16 (15) | 11 (12) | 13 (14) | 120 (9) |
| Missing | 11 (1) | 1 (<1) | 1 (<1) | 1 (1) |  |  |  | 9 (1) |
| **Active cancer treatmentc** |  |  |  |  |  |  |  |  |
| None | 1457 (67) | 359 (67) | 338 (70) | 77 (62) | 72 (66) | 56 (60) | 63 (70) | 866 (66) |
| Cytotoxic | 269 (12) | 69 (13) | 56 (12) | 19 (15) | 7 (6) | 8 (9) | 6 (7) | 165 (12) |
| Non-cytotoxic | 424 (19) | 102 (19) | 84 (17) | 24 (19) | 25 (23) | 28 (30) | 19 (21) | 268 (20) |
| Unknown | 36 (2) | 8 (1) | 7 (1) | 4 (3) | 5 (5) | 2 (2) | 2 (2) | 22 (2) |
| **Baseline COVID-19 severity** |  |  |  |  |  |  |  |  |
| Mild | 1037 (47) | 60 (11) | 121 (25) | 13 (10) | 22 (20) | 14 (15) | 10 (11) | 876 (66) |
| Moderate | 876 (40) | 356 (66) | 259 (53) | 70 (56) | 61 (56) | 47 (50) | 51 (57) | 360 (27) |
| Severe | 273 (12) | 122 (23) | 105 (22) | 41 (33) | 26 (24) | 33 (35) | 29 (32) | 85 (6) |
| **Concomitant medications** |  |  |  |  |  |  |  |  |
| Aspirin or other antiplatelet agents | 682 (31) | 191 (36) | 194 (40) | 52 (42) | 44 (40) | 37 (39) | 33 (37) | 364 (28) |
| Anticoagulation | 1087 (50) | 414 (77) | 353 (73) | 104 (84) | 91 (83) | 79 (84) | 76 (84) | 456 (35) |
| Statins | 927 (42) | 265 (49) | 244 (50) | 64 (52) | 59 (54) | 46 (49) | 39 (43) | 505 (38) |
| Low-dose steroidsd | 184 (8) | 55 (10) | 42 (9) | 22 (18) | 14 (13) | 12 (13) | 11 (12) | 94 (7) |

aFor all patients, this is the number of patients on any trial for treatment of COVID-19. For each specific exposure, this is the number of patients reported to be on a trial of that particular treatment.

bPercentages may add up to more than 100 because some patients had multiple malignancies.

cDefined as receipt of antineoplastic therapy within four (4) weeks of COVID-19 diagnosis.

dDefined as up to 20 mg/day in prednisone dose equivalents.

eIncludes patients enrolled in blinded randomized controlled trials e.g., of remdesivir.

\* Percentages are shown in parentheses; percentages may not add up to 100 due to rounding.

**Supplemental Table S2****: Distribution of matched and unmatched cohorts stratified by exposure of interest (EOI)**; percentages may not add up to 100 due to rounding. HCQ: hydroxychloroquine; PSM: Propensity score matching

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **HCQ with PSM, n (%)a** | **HCQ unmatched, n (%)** | **HCQ without severe cases, n (%)** | **HCQ, active cancer only, n (%)** | **Remdesivir, n (%)** | **High-dose sytemic corticosteroids, n (%)** |
| EOI alone | 179 (14) | 179 (8) | 151 (8) | 69 (8) | 57 (3) | 18 (1) |
| EOI + any other exposure | 359 (27) | 359 (16) | 265 (14) | 150 (18) | 67 (3) | 91 (4) |
| Negative controls | 544 (41) | 1321 (60) | 1236 (65) | 510 (60) | 1321 (60) | 1321 (60) |
| Positive controls | 240 (18) | 327 (15) | 261 (14) | 117 (14) | 741 (34) | 756 (35) |
| **Total** | **1322 (100)** | **2186 (100)** | **1913 (100)** | **846 (100)** | **2186 (100)** | **2186 (100)** |

aThis is a representative sample of one of the ten runs of the model; exact numbers of positive and negative controls fluctuate slightly across runs due to multiple data imputation.

# **Supplemental Table S3: Goodness of fit and variance inflation factors.**

|  |  |  |
| --- | --- | --- |
| **Model** | **C-statistic** | **Number of variables with VIF > 5** |
| Predictors of HCQ+AZ treatment | 0.72 | 0 |
| Predictors of remdesivir treatment | 0.70 | 0 |
| Predictors of any COVID-19 treatment | 0.75 | 0 |
| Predictors of mortality in HCQ-exposed patients, PSM | 0.79 | 0 |
| Predictors of mortality in HCQ-exposed patients, unmatched | 0.86 | 0 |
| Predictors of mortality in HCQ-exposed patients, without severe cases | 0.86 | 0 |
| Predictors of mortality in HCQ-exposed patients, active cancer only | 0.86 | 0 |
| Predictors of mortality in HCQ-exposed patients, remission/NED only | 0.88 | 0 |
| Predictors of mortality in remdesivir-exposed patients | 0.86 | 0 |
| Predictors of mortality in high-dose systemic corticosteroid-exposed patients | 0.86 | 0 |

# **Supplemental Table S4: Racial and ethnic characteristics of patients receiving remdesivir.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Non-Hispanic white** | **Non-Hispanic Black** | **Hispanic** | **Other** | **Missing** |
| On trial | 44 | 13 | 16 | 8 | 5 |
| Off trial1 | 21 | 5 | 9 | 0 | 3 |

1Includes compassionate use prior to May 1, 2020 and emergency use authorization (EUA) after May 1, 2020; limits of temporal resolution in the CCC19 registry do not allow for distinguishing between these two uses.

**Supplemental Table S5: Descriptive statistics for each variable of the matched data (N=1322)**. This table is from one of the ten model runs; absolute numbers change very slightly from run to run and are averaged in the model output. Absolute numbers are shown in parentheses.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Negative control**  **(N=544)** | **Positive control**  **(N=240)** | **HCQ alone**  **(N=179)** | **HCQ + any other exposure**  **(N=359)** |
| **Death** | 0.19 (101) | 0.22 (54) | 0.25 (44) | 0.31 (111) |
| **Age, median (IQR)** | 71 (60-81) | 70 (60-80) | 73 (64.5-81.5) | 69 (60.5-77) |
| **Sex** |  |  |  |  |
| Male | 0.50 (271) | 0.54 (129) | 0.53 (94) | 0.57 (203) |
| **Race** |  |  |  |  |
| Non-Hispanic White | 0.52 (285) | 0.53 (128) | 0.41 (74) | 0.49 (176) |
| Hispanic | 0.14 (74) | 0.13 (31) | 0.18 (32) | 0.13 (47) |
| Non-Hispanic Black | 0.25 (136) | 0.24 (57) | 0.26 (46) | 0.30 (106) |
| Other | 0.09 (49) | 0.10 (24) | 0.15 (27) | 0.08 (30) |
| **Region** |  |  |  |  |
| US Northeast | 0.49 (264) | 0.47 (112) | 0.63 (112) | 0.49 (177) |
| US Midwest | 0.27 (147) | 0.27 (64) | 0.21 (38) | 0.30 (109) |
| US South | 0.13 (73) | 0.13 (31) | 0.07 (12) | 0.15 (54) |
| US West | 0.11 (60) | 0.14 (33) | 0.09 (17) | 0.05 (19) |
| **Smoking** |  |  |  |  |
| Current or Former | 0.47 (257) | 0.49 (117) | 0.53 (95) | 0.53 (189) |
| **Obesity** | 0.29 (159) | 0.36 (87) | 0.27 (49) | 0.37 (134) |
| **Diabetes mellitus** | 0.33 (181) | 0.32 (76) | 0.38 (68) | 0.40 (142) |
| **Pulm. comorbidities** | 0.24 (129) | 0.25 (61) | 0.23 (41) | 0.30 (107) |
| **Card. comorbidities** | 0.41 (224) | 0.40 (97) | 0.37 (67) | 0.36 (131) |
| **Renal comorbidities** | 0.21 (113) | 0.20 (47) | 0.27 (48) | 0.24 (87) |
| **Hypertension** | 0.62 (340) | 0.68 (164) | 0.72 (129) | 0.69 (248) |
| **ECOG performance** |  |  |  |  |
| 0 | 0.26 (141) | 0.29 (69) | 0.22 (39) | 0.27 (96) |
| 1 | 0.25 (137) | 0.25 (61) | 0.33 (59) | 0.33 (119) |
| 2+ | 0.24 (131) | 0.18 (43) | 0.26 (47) | 0.14 (50) |
| Unknown | 0.25 (135) | 0.28 (67) | 0.19 (34) | 0.26 (94) |
| **Cancer status** |  |  |  |  |
| Remission/NED | 0.49 (266) | 0.50 (121) | 0.49 (87) | 0.48 (171) |
| Active, progressing | 0.13 (72) | 0.12 (29) | 0.12 (21) | 0.14 (49) |
| Active, stable/responding | 0.26 (144) | 0.26 (63) | 0.27 (48) | 0.28 (102) |
| Unknown | 0.11 (62) | 0.11 (27) | 0.13 (23) | 0.10 (37) |
| **Baseline COVID-19 severity** |  |  |  |  |
| Mild | 0.20 (109) | 0.08 (18) | 0.07 (13) | 0.13 (47) |
| Moderate | 0.64 (350) | 0.65 (157) | 0.77 (138) | 0.61 (218) |
| Severe | 0.16 (85) | 0.27 (65) | 0.16 (28) | 0.26 (94) |
| **Anticoagulants or antiplatelet agents** | 0.76 (414) | 0.87 (209) | 0.77 (137) | 0.87 (312) |

**Supplemental Table S6: Results of the logistic regression analysis with elastic-net and horeshoe regularization**. Elastic-net regularization was performed with a mixing parameter of 0.5; horseshoe regularization with 50% credible intervals. A standard deviation of 0.3 was used in the two-group matching.

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Multivariable AOR (95% CI)**  **Elastic-net** | **Multivariable AOR (95% CI)**  **Horseshoe** |
| **Treatment group** |  |  |
| Negative control | Reference | Reference |
| Positive control | 1.09 (0.72-1.65) | 1.11 (0.73-1.68) |
| HCQ alone | 1.19 (0.76-1.86) | 1.18 (0.75-1.84) |
| HCQ + any other exposure | 2.16 (1.52-3.09) | 2.20 (1.53-3.15) |
| **Age, per decade** | 1.31 (1.50-1.72) | 1.37 (1.57-1.81) |
| **Sex** |  |  |
| Female | Reference | Reference |
| Male | 1.22 (0.91-1.63) | 1.26 (0.94-1.69) |
| **Region** |  |  |
| US Northeast | Reference | Reference |
| US Midwest | 0.64 (0.45-0.91) | 0.65 (0.45-0.92) |
| US South | 0.68 (0.43-1.09) | 0.70 (0.44-1.11) |
| US West | 0.81 (0.47-1.41) | 0.80 (0.46-1.39) |
| **Smoking status** |  |  |
| Never | Reference | Reference |
| Current or Former | 1.18 (0.86-1.61) | 1.20 (0.88-1.63) |
| **Obesity** |  |  |
| Non-Obese | Reference | Reference |
| Obese |  | 1.32 (0.96-1.81) |
| **Renal comorbidities** |  |  |
| 0 | Reference | Reference |
| 1 | 1.17 (0.85-1.61) |  |
| **Hypertension** |  |  |
| 0 | Reference | Reference |
| 1 | 1.17 (0.84-1.62) |  |
| **ECOG performance status** |  |  |
| 0 | Reference | Reference |
| 1 | 1.51 (0.95-2.39) | 1.55 (0.98-2.45) |
| 2+ | 3.94 (2.48-6.27) | 4.07 (2.55-6.48) |
| Unknown | 2.04 (1.29-3.23) | 2.13 (1.34-3.38) |
| **Cancer status** |  |  |
| Remission/NED | Reference | Reference |
| Active, progressing | 2.55 (1.63-4.00) | 2.48 (1.58-3.90) |
| Active, stable/responding | 1.42 (0.98-2.06) | 1.42 (0.98-2.06) |
| Unknown | 1.46 (0.93-2.29) | 1.44 (0.91-2.27) |
| **Baseline COVID-19 severity** |  |  |
| Mild | Reference | Reference |
| Moderate | 2.16 (1.07-4.38) | 2.32 (1.14-4.74) |
| Severe | 7.75 (3.72-16.16) | 8.39 (3.99-17.62) |
| **Anticoagulants or antiplatelet agents** |  |  |
| Unexposed | Reference | Reference |
| Exposed |  | 0.72 (0.48-1.10) |

**Supplemental Table S7: Results of the horseshoe regularization analysis conditional on baseline COVID-19 severity with 50% credible intervals.** A standard deviation of 0.3 was used in the two-group matching.

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Multivariable AOR (95% CI)** | |
|  | **“Moderate”** | **“Moderate + Severe”** |
| **Treatment group** |  |  |
| Negative control | Reference | Reference |
| Positive control | **1.22 (0.71-2.11)** | **1.18 (0.77-1.81)** |
| HCQ alone | **1.26 (0.73-2.19)** | **1.01 (0.63-1.60)** |
| HCQ + any other exposure | **3.04 (1.91-4.86)** | **2.20 (1.51-3.19)** |
| **Age, per 10 years** | 1.36 (1.62-1.93) | 1.31 (1.50-1.73) |
| **Sex** |  |  |
| Female | Reference | Reference |
| Male | 1.17 (0.81-1.69) | 1.29 (0.95-1.74) |
| **Region** |  |  |
| US Northeast | Reference | Reference |
| US Midwest | 0.58 (0.37-0.92) | 0.63 (0.43-0.91) |
| US South | 0.71 (0.38-1.34) | 0.76 (0.47-1.22) |
| US West | 0.91 (0.42-1.97) | 0.98 (0.56-1.69) |
| **Obesity** |  |  |
| Non-Obese | Reference | Reference |
| Obese | 1.78 (1.18-2.69) | 1.47 (1.06-2.03) |
| **ECOG performance status** |  |  |
| 0 | Reference | Reference |
| 1 | 1.67 (0.87-3.23) | 1.29 (0.80-2.09) |
| 2+ | 5.07 (2.60-9.88) | 3.75 (2.32-6.05) |
| Unknown | 2.96 (1.51-5.78) | 1.86 (1.15-3.01) |
| **Cancer status** |  |  |
| Remission/NED | Reference | Reference |
| Active, progressing | 3.10 (1.79-5.35) | 2.21 (1.40-3.48) |
| Active, stable/responding | 1.80 (1.13-2.87) | 1.36 (0.92-2.00) |
| Unknown | 1.53 (0.82-2.87) | 1.52 (0.95-2.43) |
| **Anticoagulants or antiplatelet agents** |  |  |
| Unexposed |  | Reference |
| Exposed |  | 0.76 (0.49-1.17) |

**Supplemental Table S8: Results of mediation analysis.** Mediator: binary variable (Negative control + positive control vs. HCQ alone + HCQ plus other drugs). Independent variable: baseline COVID-19 severity (treated as a binary variable); Outcome: mortality. ACME: Average Causal Mediation Effects; ADE: Average Direct Effect

|  |  |
| --- | --- |
|  | **Estimate (95% CI)** |
| ACME (treated) | 0.0060 (-0.0003-0.02) |
| ADE (treated) | 0.1591 (0.1033-0.21) |
| Total Effect | 0.1612 (0.1082-0.21) |
| Prop. Mediated (treated) | 0.0369 (-0.0016-0.12) |

# **Supplemental Table S9: Additional covariates from the mortality models**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **HCQ with PSM, AOR (95% CI)** | **HCQ, AOR (95% CI)a** | **HCQ without severe cases, AOR (95% CI)a** | **Remdesivir, AOR (95% CI)a** | **High-dose sytemic corticosteroids, AOR (95% CI)a** |
| **Ageb** | 1.60 (1.38-1.86) | 1.56 (1.36-1.80) | 1.58 (1.34-1.87) | 1.52 (1.32-1.74) | 1.53 (1.34-1.76) |
| **Sex** |  |  |  |  |  |
| Female | Ref | Ref | Ref | Ref | Ref |
| Male | 1.24 (0.92-1.67) | 1.26 (0.94-1.67) | 1.17 (0.83-1.64) | 1.3 (0.98-1.73) | 1.3 (0.97-1.72) |
| **Race/ethnicity** |  |  |  |  |  |
| Non-Hispanic white | Ref | Ref | Ref | Ref | Ref |
| Hispanic | 1.39 (0.85-2.27) | 1.29 (0.82-2.02) | 1.29 (0.75-2.21) | 1.29 (0.82-2.02) | 1.25 (0.8-1.96) |
| Non-Hispanic Black | 1.22 (0.85-1.76) | 1.22 (0.86-1.74) | 1.18 (0.77-1.80) | 1.2 (0.85-1.71) | 1.21 (0.85-1.72) |
| Other | 1.00 (0.59-1.69) | 1.13 (0.69-1.87) | 1.08 (0.58-2.02) | 1.06 (0.64-1.76) | 1.08 (0.66-1.78) |
| **Region of patient residence** |  |  |  |  |  |
| US-Northeast | Ref | Ref | Ref | Ref | Ref |
| US-Midwest | 0.65 (0.44-0.95) | 0.65 (0.46-0.93) | 0.64 (0.42-0.97) | 0.68 (0.48-0.96) | 0.65 (0.46-0.93) |
| US-South | 0.71 (0.43-1.15) | 0.72 (0.45-1.15) | 0.74 (0.41-1.33) | 0.75 (0.47-1.2) | 0.74 (0.47-1.18) |
| US-West | 0.88 (0.51-1.53) | 0.94 (0.6-1.49) | 1.02 (0.58-1.79) | 0.94 (0.59-1.49) | 0.89 (0.56-1.41) |
| **Smoking status** |  |  |  |  |  |
| Never smoker | Ref | Ref | Ref | Ref | Ref |
| Current or former smoker | 1.21 (0.89-1.66) | 1.23 (0.91-1.66) | 1.2 (0.84-1.71) | 1.22 (0.9-1.64) | 1.19 (0.89-1.61) |
| **Obesity** |  |  |  |  |  |
| Not obese | Ref | Ref | Ref | Ref | Ref |
| Obese | 1.31 (0.95-1.81) | 1.23 (0.9-1.68) | 1.39 (0.95-2.02) | 1.25 (0.91-1.71) | 1.23 (0.9-1.69) |
| **Diabetes mellitus** |  |  |  |  |  |
| Not present | Ref | Ref | Ref | Ref | Ref |
| Present | 0.99 (0.73-1.35) | 1.04 (0.77-1.4) | 1.11 (0.78-1.59) | 1.05 (0.78-1.42) | 1.07 (0.79-1.44) |
| **Pulmonary comorbidities** |  |  |  |  |  |
| Not present | Ref | Ref | Ref | Ref | Ref |
| Present | 0.95 (0.68-1.34) | 0.94 (0.68-1.31) | 0.88 (0.59-1.31) | 0.97 (0.7-1.34) | 0.94 (0.68-1.31) |
| **Cardiovascular comorbidities** |  |  |  |  |  |
| Not present | Ref | Ref | Ref | Ref | Ref |
| Present | 1.09 (0.79-1.51) | 1.05 (0.77-1.42) | 1.08 (0.75-1.57) | 1.03 (0.76-1.4) | 1.03 (0.76-1.39) |
| **Renal comorbidities** |  |  |  |  |  |
| Not present | Ref | Ref | Ref | Ref | Ref |
| Present | 1.18 (0.85-1.65) | 1.19 (0.86-1.64) | 1.18 (0.81-1.72) | 1.15 (0.83-1.59) | 1.2 (0.87-1.66) |
| **Hypertension** |  |  |  |  |  |
| Not present | Ref | Ref | Ref | Ref | Ref |
| Present | 1.17 (0.83-1.65) | 1.16 (0.84-1.61) | 1.08 (0.73-1.59) | 1.15 (0.83-1.59) | 1.17 (0.84-1.61) |
| **ECOG performance status** |  |  |  |  |  |
| 0 | Ref | Ref | Ref | Ref | Ref |
| 1 | 1.48 (0.92-2.38) | 1.57 (1-2.46) | 1.57 (0.88-2.82) | 1.61 (1.02-2.53) | 1.61 (1.02-2.53) |
| 2+ | 3.99 (2.48-6.42) | 4.2 (2.67-6.62) | 4.82 (2.68-8.66) | 4.05 (2.56-6.39) | 4.07 (2.57-6.43) |
| Unknown | 2.09 (1.29-3.38) | 2.06 (1.3-3.26) | 2.5 (1.38-4.54) | 2.14 (1.36-3.38) | 2.09 (1.32-3.31) |
| **Cancer status** |  |  |  |  |  |
| Remission/NED | Ref | Ref | Ref | Ref | Ref |
| Active, progressing | 2.55 (1.60-4.06) | 2.69 (1.75-4.13) | 3.06 (1.86-5.05) | 2.72 (1.77-4.17) | 2.63 (1.71-4.03) |
| Active, stable or responding | 1.43 (0.99-2.06) | 1.45 (1.02-2.06) | 1.75 (1.15-2.66) | 1.47 (1.04-2.08) | 1.48 (1.04-2.09) |
| Unknown | 1.43 (0.90-2.28) | 1.64 (1.05-2.57) | 1.87 (1.08-3.25) | 1.53 (0.98-2.41) | 1.54 (0.98-2.42) |
| **Baseline COVID-19 severity** |  |  |  |  |  |
| Mild | Ref | Ref | Ref | Ref | Ref |
| Moderate | 2.11 (1.03-4.32) | 5.04 (3.12-8.13) | 4.13 (2.54-6.72) | 5.05 (3.14-8.12) | 5.11 (3.17-8.24) |
| Severe | 7.78 (3.63-16.68) | 17.38 (10.32-29.26) | N/A | 18.79 (11.18-31.58) | 18.25 (10.85-30.7) |
| **Aspirin/APA/Anticoagulation** |  |  |  |  |  |
| Absent | Ref | Ref | Ref | Ref | Ref |
| Present | 0.67 (0.43-1.02) | 0.84 (0.58-1.22) | 1.15 (0.73-1.8) | 0.89 (0.61-1.3) | 0.85 (0.58-1.23) |

aUnmatched controls

bRisk per decade

**Supplementary Table S10: Data elements in the CCC19 data collection form.** These variables are current as of June 29th, 2020 and do not include free text response elements. Note that the survey contains extensive branching logic; not every patient will have every one of these elements completed. ABNL: abnormal (outside normal reference range); ATC: Anatomical Therapeutic Classification; HI: above normal reference range; LO: below normal reference range; N: No; NA: not applicable; NAACCR: North American Association of Central Cancer Registries; NCIT: National Cancer Institute Thesaurus; OMOP: Observational Medical Outcomes Partnership Data Model; PHIN VADS: Public Health Information Network Vocabulary Access and Distribution System; SNOMED-CT: Systematized Nomenclature of Medicine, Clinical Terms; UNK: Unknown; WNL: within normal limits; Y: Yes

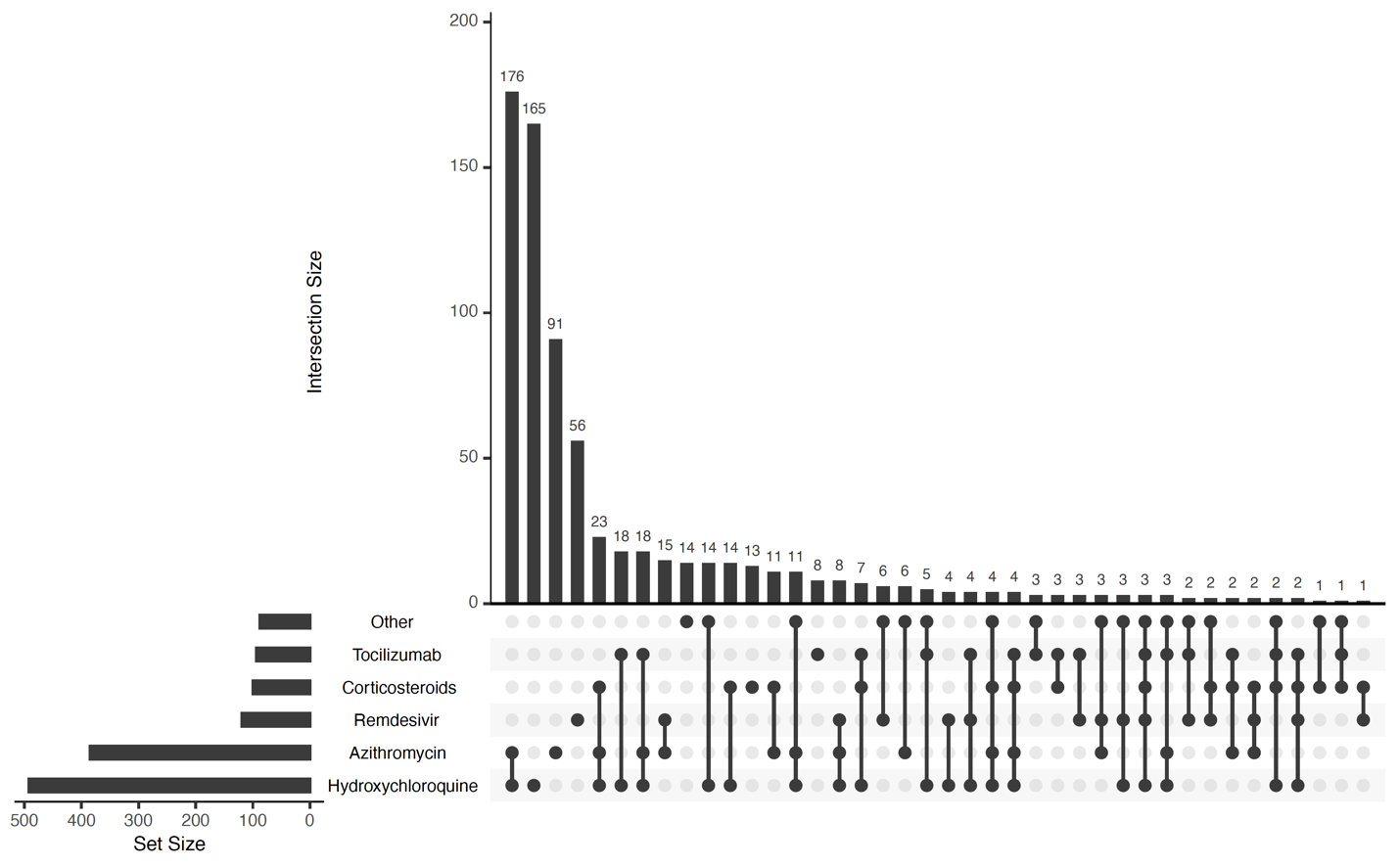
| Variable Name | Description | Value Set or Terminology | Category |
| --- | --- | --- | --- |
| aspirin\_dose |  | SNOMED-CT | Baseline clinical details |
| bcg\_vax | History of BCG vaccine? | Y/N/UNK | Baseline clinical details |
| bl\_anticoag\_reason | Why anticoag at baseline? | SNOMED-CT | Baseline clinical details |
| bl\_anticoag\_type | Anticoag at baseline? | ATC | Baseline clinical details |
| blood\_type | ABO blood type | Direct coding + UNK | Baseline clinical details |
| blood\_type\_rh | Rh blood type | Direct coding + UNK | Baseline clinical details |
| bmi |  | Numeric, kg/m2 | Baseline clinical details |
| comorbid\_no | number of comorbidities | Integer + UNK | Baseline clinical details |
| concomitant\_meds |  | ATC | Baseline clinical details |
| ecog\_status |  | Direct coding + UNK | Baseline clinical details |
| gcsf | G-CSF within 2 weeks of diagnosis? | Y/N/UNK | Baseline clinical details |
| height |  | Numeric, units not specified | Baseline clinical details |
| influenza\_vax | Seasonal flu vaccine? | Y/N/UNK | Baseline clinical details |
| o2\_requirement |  | Y/N/UNK | Baseline clinical details |
| recent\_surgery |  | Y/N/UNK | Baseline clinical details |
| significant\_comorbidities |  | SNOMED-CT | Baseline clinical details |
| smoking\_product |  | SNOMED-CT | Baseline clinical details |
| smoking\_status |  | Custom | Baseline clinical details |
| steroid\_specific\_2 | Steroid dosing | Custom | Baseline clinical details |
| surgery\_timing |  | Custom | Baseline clinical details |
| weight |  | Numeric, units not specified | Baseline clinical details |
| adt | Has patient had ADT? | Y/N/UNK | Cancer details |
| bcg\_intraves\_ever |  | Y/N/UNK | Cancer details |
| cancer\_status |  | Custom | Cancer details |
| cancer\_timing |  | Custom | Cancer details |
| cancer\_type |  | NCIT | Cancer details |
| cancer\_type\_2 | 2nd maligancy type (if applicable) | NCIT | Cancer details |
| clinical\_trial |  | Y/N/UNK | Cancer details |
| gleason | Gleason score | NAACCR | Cancer details |
| gleason\_source |  | NAACCR | Cancer details |
| hospice |  | Y/N/UNK | Cancer details |
| hx\_treatment | Timing of cancer treatment | Custom | Cancer details |
| intravesicular\_bcg |  | Y/N/UNK | Cancer details |
| irae\_past |  | Y/N/UNK | Cancer details |
| mets\_sites | Sites of metastatic cancer | NAACCR | Cancer details |
| mets\_yn | Metastatic at COVID-19 diagnosis? | Y/N/UNK | Cancer details |
| multiple\_ca |  | Y/N/UNK | Cancer details |
| on\_treatment | On recent cancer treatment | Y/N/UNK | Cancer details |
| orchiectomy | Has patient had bilateral orchiectomy? | Y/N/UNK | Cancer details |
| other\_irae |  | Y/N/UNK | Cancer details |
| pneumonitis | Concurrent irAE pneumonitis? | Custom | Cancer details |
| prior\_tx | prior lung-toxic therapy? | HemOnc | Cancer details |
| prostate\_tx | Prostate cancer therapy | RxNorm | Cancer details |
| radiotherapy |  | Y/N/UNK | Cancer details |
| recent\_treatment | Most recent anti-cancer treatment | Custom | Cancer details |
| stage |  | NAACCR | Cancer details |
| transplant\_cellular\_therapy | | Custom | Cancer details |
| transplant\_cellular\_timing | | Custom | Cancer details |
| treatment\_context |  | HemOnc | Cancer details |
| treatment\_intent |  | Custom | Cancer details |
| treatment\_modality |  | HemOnc | Cancer details |
| what\_immunotherapy |  | HemOnc | Cancer details |
| berlin\_2 | Berlin criteria if ARDS | Direct coding + UNK | COVID-19 details |
| berlin\_yn | Berlin criteria collected? | Y/N/UNK | COVID-19 details |
| c19\_anticoag\_reason | Purpose of anticoagulation | Custom | COVID-19 details |
| c19\_anticoag\_type | Type of anticoagulant used | ATC | COVID-19 details |
| c19\_aspirin\_dose |  | SNOMED-CT | COVID-19 details |
| c19\_bleeding |  | SNOMED-CT-modified | COVID-19 details |
| c19\_complications\_card |  | SNOMED-CT | COVID-19 details |
| c19\_complications\_gi |  | SNOMED-CT | COVID-19 details |
| c19\_complications\_other |  | SNOMED-CT | COVID-19 details |
| c19\_complications\_pulm |  | SNOMED-CT | COVID-19 details |
| c19\_complications\_systemic | | SNOMED-CT | COVID-19 details |
| c19\_workup\_why | Reason for COVID-19 workup | Custom | COVID-19 details |
| c19\_workup\_why\_2 | Reason for COVID-19 workup | Custom | COVID-19 details |
| coinfection |  | SNOMED-CT | COVID-19 details |
| coinfection\_yn |  | Y/N/UNK | COVID-19 details |
| complications\_severity |  | Custom | COVID-19 details |
| covid\_19\_diagnosis |  | Custom | COVID-19 details |
| covid\_19\_dx\_interval | Time since COVID-19 diagnosis | Custom | COVID-19 details |
| covid\_19\_treatment |  | ATC/HemOnc/OMOP/RxNorm | COVID-19 details |
| covid\_19\_treatment\_trial |  | Y/N/UNK | COVID-19 details |
| covid\_19\_trial\_tx | Treatment(s) on trial | ATC/HemOnc/OMOP/RxNorm | COVID-19 details |
| covid\_19\_tx\_interleukin | Anti-interleukin treatments | ATC | COVID-19 details |
| covid\_19\_tx\_tnf | TNF-alpha treatments | ATC | COVID-19 details |
| current\_status | ADT status | Custom | COVID-19 details |
| current\_status\_clinical | Clinical status | Custom | COVID-19 details |
| current\_status\_retro | Clinical status | Custom | COVID-19 details |
| current\_status\_v2 | Clinical status | Custom | COVID-19 details |
| days\_to\_death |  | Integer | COVID-19 details |
| dx\_year | year of COVID-19 diagnosis | Integer | COVID-19 details |
| hosp\_los | floor LOS | Integer, days | COVID-19 details |
| hosp\_los\_2 | floor LOS if transferred to ICU | Integer, days | COVID-19 details |
| hosp\_status |  | Custom | COVID-19 details |
| icu\_los |  | Integer, days | COVID-19 details |
| labs | Timepoint when labs were drawn | Custom | COVID-19 details |
| mortality |  | Y/N/NA/UNK | COVID-19 details |
| neg\_test | was initial COVID-19 test negative | Y/N/UNK | COVID-19 details |
| o2\_policy | Policy on intubation? | Y/N/UNK | COVID-19 details |
| o2\_requirement\_c19 |  | Y/N/UNK | COVID-19 details |
| prbc | PRBC transfusions given? | Y/N/UNK | COVID-19 details |
| resp\_failure\_tx |  | Custom | COVID-19 details |
| sepsis\_pressors | Pressors for sepsis or HoTN? | Y/N/UNK | COVID-19 details |
| severity\_of\_covid\_19 |  | Custom | COVID-19 details |
| steroid\_specific | Steroid dosing | Custom | COVID-19 details |
| symptoms |  | SNOMED-CT | COVID-19 details |
| symptoms\_none\_why | Why tested? | Y/N/UNK | COVID-19 details |
| timing\_of\_report | Real-time or retrospective? | Custom | COVID-19 details |
| worst\_complications\_severity | Retrospective worst complications | Custom | COVID-19 details |
| worst\_status\_clinical | Retrospective worst clinical status | Custom | COVID-19 details |
| age | age in decades | Custom | Demographics |
| age\_exact |  | Integer | Demographics |
| city | city of healthcare delivery | N/A (free text) | Demographics |
| country\_of\_patient\_residen | | Custom | Demographics |
| ethnicity |  | PHIN VADS | Demographics |
| facility | facility of healthcare delivery | N/A (free text) | Demographics |
| gender |  | Custom | Demographics |
| hcw | health care worker | Y/N/UNK | Demographics |
| insurance | Insurance type | Custom | Demographics |
| race |  | PHIN VADS | Demographics |
| state\_of\_patient\_residence | | Direct coding (US abbreviations) | Demographics |
| berlin\_fu | Berlin criteria if ARDS | Direct coding + UNK | Follow-up details |
| berlin\_yn\_fu | Berlin criteria collected? | Y/N/UNK | Follow-up details |
| c19\_addl\_treatment |  | Y/N/UNK | Follow-up details |
| c19\_anticoag\_reason\_fu | Purpose of anticoagulation | Custom | Follow-up details |
| c19\_anticoag\_type\_fu | Type of anticoagulant used | ATC | Follow-up details |
| c19\_aspirin\_dose\_fu |  | SNOMED-CT | Follow-up details |
| c19\_bleeding\_fu |  | SNOMED-CT-modified | Follow-up details |
| c19\_complications\_card\_fu | | SNOMED-CT | Follow-up details |
| c19\_complications\_gi\_fu |  | SNOMED-CT | Follow-up details |
| c19\_complications\_other\_fu | | SNOMED-CT | Follow-up details |
| c19\_complications\_pulm\_fu | | SNOMED-CT | Follow-up details |
| c19\_complications\_systemic\_fu | | SNOMED-CT | Follow-up details |
| cancer\_status\_fu |  | Custom | Follow-up details |
| cancer\_tx\_fu | Was treatment modified d/t COVID-19? | Y/N/UNK | Follow-up details |
| complications\_severity\_fu | | Custom | Follow-up details |
| covid\_19\_status\_fu |  | Custom | Follow-up details |
| covid\_19\_treatment\_fu |  | ATC/HemOnc/OMOP/RxNorm | Follow-up details |
| covid\_19\_treatment\_trial\_fu | | Y/N/UNK | Follow-up details |
| covid\_19\_trial\_tx\_fu |  | ATC/HemOnc/OMOP/RxNorm | Follow-up details |
| covid\_19\_tx\_interleukin\_fu | | ATC | Follow-up details |
| covid\_19\_tx\_tnf\_fu | x+[@[Variable / Field Name]] | ATC | Follow-up details |
| current\_status\_clinical\_fu | | Custom | Follow-up details |
| current\_status\_fu |  | Custom | Follow-up details |
| days\_to\_death\_fu |  | Integer | Follow-up details |
| fu\_weeks |  | Numeric, weeks | Follow-up details |
| hosp\_los\_fu |  | Integer, days | Follow-up details |
| hosp\_los\_fu\_2 |  | Integer, days | Follow-up details |
| hosp\_status\_fu |  | Y/N/UNK | Follow-up details |
| hospice\_fu |  | Y/N/UNK | Follow-up details |
| hotn\_pressors\_fu |  | Y/N/UNK | Follow-up details |
| icu\_los\_fu |  | Integer, days | Follow-up details |
| o2\_requirement\_fu |  | Y/N/UNK | Follow-up details |
| resp\_failure\_tx\_fu |  | Custom | Follow-up details |
| steroid\_specific\_fu | Steroid dosing | Custom | Follow-up details |
| timing\_of\_report\_weeks |  | Numeric, weeks | Follow-up details |
| who\_ordinal\_scale | WHO Ordinal Scale for Clinical Improvement | Custom | Follow-up details |
| worst\_complications\_severity\_fu | | Custom | Follow-up details |
| aec | absolute eosinophil count | Numeric, per uL | Laboratory values |
| aec\_range |  | LO/WNL/HI/UNK | Laboratory values |
| alc | absolute lymphocyte count | Numeric, per uL | Laboratory values |
| alc\_range |  | LO/WNL/HI/UNK | Laboratory values |
| alt |  | NL/ABNL/UNK | Laboratory values |
| alt\_numeric |  | Numeric, units/L | Laboratory values |
| anc | absolute neutrophil count | Numeric, per uL | Laboratory values |
| anc\_range |  | LO/WNL/HI/UNK | Laboratory values |
| aptt | activated partial thromboplastin time | NL/ABNL/UNK | Laboratory values |
| aptt\_numeric |  | Numeric, s | Laboratory values |
| ast |  | NL/ABNL/UNK | Laboratory values |
| ast\_numeric |  | Numeric, units/L | Laboratory values |
| bnp |  | NL/ABNL/UNK | Laboratory values |
| bnp\_numeric |  | Numeric, pg/mL | Laboratory values |
| creat | creatinine | NL/ABNL/UNK | Laboratory values |
| creat\_numeric |  | Numeric, mg/dL | Laboratory values |
| crp | C-reactive protein | NL/ABNL/UNK | Laboratory values |
| crp\_numeric |  | Numeric, specify units | Laboratory values |
| ddimer |  | NL/ABNL/UNK | Laboratory values |
| ddimer\_numeric |  | Numeric, specify units | Laboratory values |
| fibrinogen |  | NL/ABNL/UNK | Laboratory values |
| fibrinogen\_numeric |  | Numeric, mg/dL | Laboratory values |
| hgb | hemoglobin | Numeric, g/dL | Laboratory values |
| hgb\_range |  | LO/WNL/HI/UNK | Laboratory values |
| hiv\_cd4 | CD4+ T-cell count | Numeric | Laboratory values |
| hiv\_vl | HIV viral load | Numeric | Laboratory values |
| hs\_trop | high-sensitivity troponin | NL/ABNL/UNK | Laboratory values |
| hs\_trop\_numeric |  | Numeric, pg/mL | Laboratory values |
| il6 |  | NL/ABNL/UNK | Laboratory values |
| il6\_numeric |  | Numeric, pg/mL | Laboratory values |
| ldh | lactate dehydrogenase | NL/ABNL/UNK | Laboratory values |
| ldh\_numeric |  | Numeric, specify units | Laboratory values |
| other\_lab |  | NL/ABNL/UNK | Laboratory values |
| plt | platelets | Numeric, per 10^3/uL | Laboratory values |
| plt\_range |  | LO/WNL/HI/UNK | Laboratory values |
| pt | prothrombin time | NL/ABNL/UNK | Laboratory values |
| pt\_numeric |  | Numeric, s | Laboratory values |
| tbili | total bilirubin | NL/ABNL/UNK | Laboratory values |
| tbili\_numeric |  | N/A (free text) | Laboratory values |
| tni | troponin I | NL/ABNL/UNK | Laboratory values |
| tni\_numeric |  | Numeric, ng/mL | Laboratory values |
| wbc\_numeric |  | Numeric, per 10^9/L | Laboratory values |
| wbc\_range |  | LO/WNL/HI/UNK | Laboratory values |
| ccc19 |  | Y/N | Metadata |
| ccc19\_institution |  | Integer | Metadata |
| patient\_id | CCC19 institution non-PHI ID | Integer | Metadata |
| record\_id |  | Integer | Metadata |
| practice\_setting |  | Custom | Respondent details |
| role | primary managing hem/onc? | Y/N | Respondent details |
| role\_2 | expand if role = N | Custom | Respondent details |

**Supplementary Table S11: Derived variables.** In order to conduct the analysis, transformations were necessary to create derived variables. Raw variable names are shown in italics and are described in Supplementary Table S1. Rules are applied in order.

|  |  |
| --- | --- |
| Derived variable name | Description |
| Age | 1. If *age\_exact* exists, keep 2. If *age\_exact* does not exist and *age* equals “Older than 90” 🡪 90 3. If *age\_exact* does not exist and *age* equals “18-29”, “30-39”, “40-49”, “50-59”, “60-69”, “70-79”, or “80-89” 🡪 take the midpoint of the age interval as the age |
| Sex | 1. If *gender* equals female, keep 2. If *gender* equals male, keep 3. If *gender* equals other or prefer not to say 🡪 missing |
| Race/ethnicity | 1. If *race* has white checked AND *ethnicity* equals NOT Hispanic or Latino OR unknown/not reported 🡪 White non-Hispanic 2. If *race* has black or African American checked AND *ethnicity* equals NOT Hispanic or Latino OR unknown/not reported 🡪 Black non-Hispanic 3. Any other *race* choice is assigned 🡪 Other/Unknown 4. If *ethnicity* equals Hispanic or Latino 🡪 Hispanic |
| Region of patient residence | 1. If *state\_of\_patient\_residence* equals ME, NH, VT, MA, RI, CT, PA, NY, or NJ 🡪 US-Northeast 2. If *state\_of\_patient\_residence* equals WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, or IA 🡪 US-Midwest 3. If *state\_of\_patient\_residence* equals DE, MD, DC, VA, WV, NC, SC, GA, FL, TN, KY, MS, AL, OK, TX, LA, or AR 🡪 US-South 4. If *state\_of\_patient\_residence* equals ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, or HI 🡪 US-West |
| Smoking status | 1. If *smoking\_status* equals never smoker, keep 2. If *smoking\_status* equals current smoker or “former smoker, NOS” OR “former smoker, quit less than 1 year ago” OR “former smoker, quit between 1 and 5 years ago” OR “former smoker, quit between 6 and 10 years ago” OR “former smoker, quit more than 10 years ago” 🡪 current or former smoker 3. If *smoking\_status* equals unknown 🡪 missing |
| Obesity | 1. If *significant\_comorbidities* has obesity OR morbid obesity checked 🡪 Obese 2. If *significant\_comorbidities* does not have either obesity or morbid obesity checked AND has at least one other choice checked 🡪 Not obese 3. If *bmi* has a value that is greater than or equal to 30 kg/m2 🡪 Obese 4. If *height* and *weight* have values and *bmi* is missing, calculate BMI. If calculated BMI has a value that is greater than or equal to 30 kg/m2 🡪 Obese 5. If *significant\_comorbidities* does not have any choices checked and *height*, *weight*, and *bmi* are missing 🡪 Missing |
| Diabetes mellitus | 1. If *significant\_comorbidities* has diabetes mellitus checked 🡪 Present 2. If *significant\_comorbidities* does not have diabetes mellitus checked 🡪 Absent 3. If *significant\_comorbidities* does not have any choices except for “Unknown” checked 🡪 Unknown 4. If *significant\_comorbidities* does not have any choices checked 🡪 Missing |
| Hypertension | 1. If *significant\_comorbidities* has hypertension checked 🡪 Present 2. If *significant\_comorbidities* does not have hypertension checked 🡪 Absent 3. If *significant\_comorbidities* does not have any choices except for “Unknown” checked 🡪 Unknown 4. If *significant\_comorbidities* does not have any choices checked 🡪 Missing |
| Pulmonary comorbidities | 1. If *significant\_comorbidities* has ANY of the following checked: “13645005”, “19829001”, “195967001”, “84004001”, or “427046006” 🡪 Present 2. If *significant\_comorbidities* does not have any of #1 checked 🡪 Absent 3. If *significant\_comorbidities* does not have any choices except for “Unknown” checked 🡪 Unknown 4. If *significant\_comorbidities* does not have any choices checked 🡪 Missing |
| Cardiovascular comorbidities | 1. If *significant\_comorbidities* has ANY of the following checked: “53741008”, “56265001”, “42343007”, “698247007”, “49436004”, “400047006”, “275526006” 🡪 Present 2. If *significant\_comorbidities* does not have any of #1 checked 🡪 Absent 3. If *significant\_comorbidities* does not have any choices except for “Unknown” checked 🡪 Unknown 4. If *significant\_comorbidities* does not have any choices checked 🡪 Missing |
| Renal comorbidities | 1. If *significant\_comorbidities* has ANY of the following checked: “90708001”, “723190009”, “46177005”, “236435004” 🡪 Present 2. If *significant\_comorbidities* does not have any of #1 checked 🡪 Absent 3. If *significant\_comorbidities* does not have any choices except for “Unknown” checked 🡪 Unknown 4. If *significant\_comorbidities* does not have any choices checked 🡪 Missing |
| Cancer status | 1. If *cancer\_status* equals “remission/NED”, keep 2. If *cancer\_status* equals “active disease, responding to treatment” OR “active disease, stable” 🡪 present, stable or responding to treatment 3. If *cancer\_status* equals “active disease, progressing”, keep 4. If *cancer\_status* equals “unknown”, keep |
| ECOG performance status | 1. If *ecog\_status* equals 0, keep 2. If *ecog\_status* equals 1, keep 3. If *ecog\_status* equals 2, 3, or 4 🡪 2+ 4. If *ecog\_status* equals unknown, keep |
| Baseline severity of COVID-19 | 1. If *severity\_of\_covid\_19\_v2* equals 1 (Mild – no hospitalization required) 🡪 Mild 2. If *severity\_of\_covid\_19\_v2* equals 2 (Moderate – hospitalization indicated) 🡪 Moderate 3. If *severity\_of\_covid\_19\_v2* equals 3 (Severe – ICU admission indicated) 🡪 Severe |
| Anticoagulation, aspirin, or other anti-platelet agent exposure (ever/never) | 1. If *concomitant\_meds* OR *covid\_19\_treatment* OR *covid\_19\_treatment\_fu* have ANY of the following checked: “B01A”, “N02BA”, or “B01AC” 🡪 Yes 2. If *concomitant\_meds* AND *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* have NONE of the following checked: “B01A”, “N02BA”, or “B01AC” 🡪 No 3. If *concomitant\_meds* AND *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices except for “Unknown” checked 🡪 Unknown 4. If *concomitant\_meds* AND *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices checked 🡪 Missing |
| Hydroxychloroquine for treatment of COVID-19 | 1. Assign all exposures as Missing 2. If *covid\_19\_treatment* OR *covid\_19\_treatment\_fu* OR *covid\_19\_trial\_tx* OR *covid\_19\_trial\_tx\_fu* have hydroxychloroquine checked 🡪 Yes 3. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* have hydroxychloroquine unchecked and exposure is Missing 🡪 No 4. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices except for “Unknown” checked and exposure is No or Missing 🡪 Unknown 5. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices checked and exposure is No 🡪 Missing |
| Azithromycin for treatment of COVID-19 | 1. Assign all exposures as Missing 2. If *covid\_19\_treatment* OR *covid\_19\_treatment\_fu* OR *covid\_19\_trial\_tx* OR *covid\_19\_trial\_tx\_fu* have azithromycin checked 🡪 Yes 3. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* have azithromycin unchecked and exposure is Missing 🡪 No 4. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices except for “Unknown” checked and exposure is No or Missing 🡪 Unknown 5. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices checked and exposure is No 🡪 Missing |
| Remdesivir for treatment of COVID-19 | 1. Assign all exposures as Missing 2. If *covid\_19\_treatment* OR *covid\_19\_treatment\_fu* OR *covid\_19\_trial\_tx* OR *covid\_19\_trial\_tx\_fu* have remdesivir checked 🡪 Yes 3. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* have remdesivir unchecked and exposure is Missing 🡪 No 4. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices except for “Unknown” checked and exposure is No or Missing 🡪 Unknown 5. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices checked and exposure is No 🡪 Missing |
| Tocilizumab for treatment of COVID-19 | 1. Assign all exposures as Missing 2. If *covid\_19\_treatment* OR *covid\_19\_treatment\_fu* OR *covid\_19\_trial\_tx* OR *covid\_19\_trial\_tx\_fu* have tocilizumab checked 🡪 Yes 3. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* have tocilizumab unchecked and exposure is Missing 🡪 No 4. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices except for “Unknown” checked and exposure is No or Missing 🡪 Unknown 5. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices checked and exposure is No 🡪 Missing |
| High-dose systemic corticosteroids for treatment of COVID-19 | 1. Assign all exposures as Missing 2. If *steroid\_specific* OR *steroid\_specific\_fu* have 2 (More than 20 mg/day but less than 1 mg/kg/day) OR 3 (Equal to or greater than 1 mg/kg/day) checked 🡪 Yes 3. If *covid\_19\_treatment* OR *covid\_19\_treatment\_fu* have systemic corticosteroids checked AND *steroid\_specific* OR *steroid\_specific\_fu* have 1a (10 mg/day or below [low dose]) OR 1b (More than 10 mg/day up to 20 mg/day) checked AND exposure is Missing 🡪 No 4. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* have systemic corticosteroids unchecked AND exposure is Missing 🡪 No 5. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices except for “Unknown” checked AND exposure is No OR Missing 🡪 Unknown 6. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices checked and exposure is No 🡪 Missing |
| Other treatments for COVID-19 | 1. Assign all exposures as Missing 2. If *covid\_19\_treatment* OR *covid\_19\_treatment\_fu* have any of the following checked: “RXCUI-2393”, “ATC-J05AE08”, “ATC-J05AR10”, “L04AA37”, “ATC-L04AC”, “ATC-L04AB”, or “B05AX03” 🡪 Yes 3. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* have all of the above unchecked and exposure is Missing 🡪 No 4. If *covid\_19\_trial\_tx* OR *covid\_19\_trial\_tx\_fu* have anything checked other than hydroxychloroquine, azithromycin, remdesivir, tocilizumab, systemic corticosteroids, or unknown 🡪 Yes 5. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices except for “Unknown” checked and exposure is No or Missing 🡪 Unknown 6. If *covid\_19\_treatment* AND *covid\_19\_treatment\_fu* do not have any choices checked and exposure is No 🡪 Missing |
| Death | 1. If *current\_status\_retro* equals “Died” or *current\_status\_v2* equals “Died” or *current\_status* equals “None – patient is deceased” 🡪 Yes 2. If *current\_status\_retro* NOT equals “Died” AND *current\_status\_v2* NOT equals “Died” AND *current\_status* NOT equals “None – patient is deceased” 🡪 No 3. If *covid\_19\_status\_fu* equals “Died” or *current\_status\_fu* equals “None – patient is deceased” or *fu\_reason* equals “Death” 🡪 Yes 4. If none of the above are met 🡪 Unknown |
| Death within 30 days | 1. If *Death (derived)* equals Yes and calculated time to death based on interval from diagnosis to timing of most recent report is less than or equal to 30 days 🡪 Yes 2. If *Death (derived)* equals Yes and *mortality* is set to 0 (patient was not alive 30 days after diagnosis) 🡪 Yes 3. If *Death (derived)* equals Yes and a follow-up form is present with *fu\_weeks* equals “Approximately 30 days after COVID-19 diagnosis” AND the *fu\_reason* equal to “Death” OR *covid\_19\_status\_fu* equals “Died” OR *current\_status\_fu* equals “None – patient is deceased” 🡪 Yes 4. If *Death (derived)* equals Yes and a follow-up form is present with *fu\_weeks* equals “All other time intervals” AND timing\_of\_report\_weeks is less than or equal to four AND the *fu\_reason* equal to “Death” OR *covid\_19\_status\_fu* equals “Died” OR *current\_status\_fu* equals “None – patient is deceased” 🡪 Yes 5. If *Death (derived)* equals Yes and days to death is present and is less than or equal to 30 days 🡪 Yes 6. If *Death (derived)* equals Yes and days to death is present and is greater than 30 days 🡪 No |

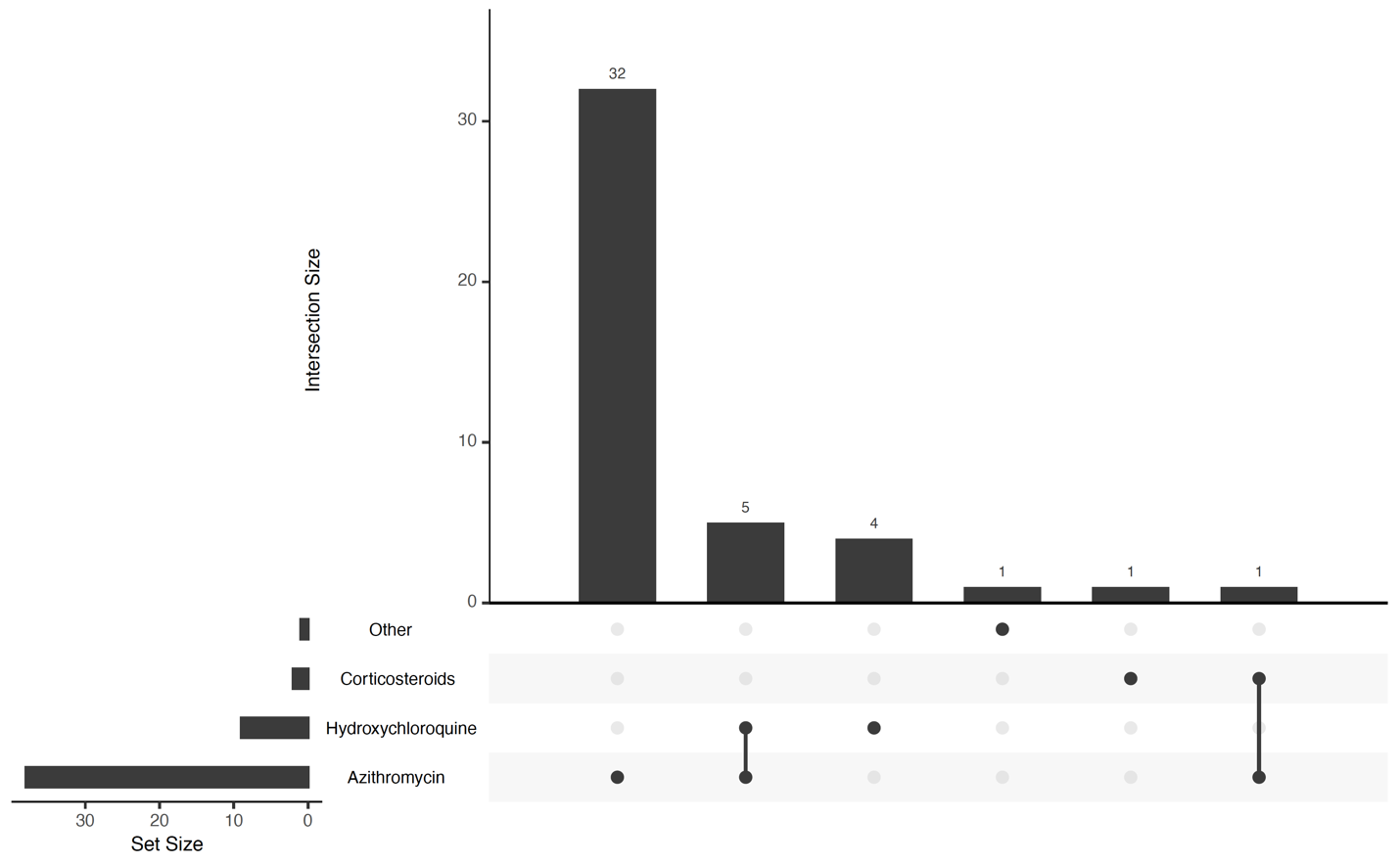
# **Supplemental Figure S1: UpSet plot of treatment exposures in hospitalized patients.**

This includes n=1243 (57%) patients known to be hospitalized at some point during their COVID-19 illness.



# **Supplemental Figure S2: UpSet plot of treatment exposures in never-hospitalized patients.**

This includes n=569 (26%) patients known not to be hospitalized during the course of their COVID-19 illness (up until the time of last reporting). It does not include n=24 (1%) patients with unknown hospitalization status, or n=350 (16%) patients with missing hospitalization status.



**Supplemental Figure S3: Propensity score matching results**. Distributions of propensity scores of HCQ alone, HCQ plus anything, Negative control, and Positive control before (left) and after (right) matching using the nearest-neighbor method with a 1:2 ratio and 0.3 standard deviation.

A close up of a map

Description automatically generatedA picture containing text, map

Description automatically generated

**Supplemental Figure S4: Determination of standard deviation for propensity score matching**. Loss of events (mortality) and maximum mean difference of propensity scores between the four treatment groups, which are obtained from two-group propensity score matching using the nearest-neighbor method with a 1:2 ratio (treated units: control units) and different multipliers of standard deviation.

A picture containing large

Description automatically generated