# Supplemental Online Content

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

## Sensitivity Analysis

**eTable 1. Baseline Demographic and Clinical Characteristics of the Patients in Intention-to-Treat Population**

| Characteristics | No. (%) | | Difference (95% CI) |
|---|---|---|---|
| | Ivermectin (n = 247) | Control (n = 249) | |
| **Demographics** | | | |
| Age, mean (SD), y | 63.0 (8.9) | 62.0 (8.4) | 1.0 (-0.5 to 2.5)[a] |
| Sex | | | |
| Male | 113 (45.7) | 112 (45.0) | 0.77 (-7.99 to 9.53)[b] |
| Female | 134 (54.3) | 137 (55.0) | -0.77 (-9.53 to 7.99)[b] |
| Ethnicity | | | |
| Chinese | 38 (15.4) | 32 (12.9) | 2.53 (-3.59 to 8.66)[b] |
| Indian | 39 (15.8) | 30 (12.0) | 3.74 (-2.34 to 9.83)[b] |
| Malay | 157 (63.6) | 172 (69.1) | -5.51 (-13.82 to 2.79)[b] |
| Other[c] | 13 (5.3) | 15 (6.0) | -0.76 (-4.82 to 3.30)[b] |
| | | | |
| **Anthropometrics** | | | |
| Weight, mean (SD), kg | 68.0 (14.7) | 68.7 (14.6) | -0.7 (-3.2 to 1.9)[a] |
| BMI, mean (SD) | 26.8 (5.3) | 26.9 (5.4) | -0.1 (-1.0 to 0.9)[a] |
| | | | |

| | | | |
|---|---|---|---|
| **COVID-19 related history** | | | |
| COVID-19 vaccination | | | |
| Not vaccinated | 76 (30.8) | 84 (33.7) | -2.97 (-11.19 to 5.26)[b] |
| Received one dose of vaccine | 43 (17.4) | 35 (14.1) | 3.35 (-3.05 to 9.76)[b] |
| Completed two doses of vaccine | 128 (51.8) | 130 (52.2) | -0.39 (-9.18 to 8.41)[b] |
| Disease severity on enrollment (WHO scale 2-4) | | | |
| Mild | 85 (34.4) | 84 (33.7) | 0.68 (-7.66 to 9.02)[b] |
| Moderate | 162 (65.6) | 165 (66.3) | -0.68 (-9.02 to 7.66)[b] |
| Day of symptoms on enrollment, mean (SD) | 5.1 (1.3) | 5.1.(1.3) | 0 (-0.2 to 0.2)[a] |
| | | | |
| **Comorbidity** | | | |
| Hypertension | 184 (74.5) | 191 (76.7) | -2.21 (-9.77 to 5.34)[b] |
| Diabetes mellitus | 136 (55.1) | 131 (52.6) | 2.45 (-6.32 to 11.22)[b] |
| Dyslipidemia | 105 (42.5) | 82 (32.9) | 9.58 (1.09 to 18.07)[b] |
| Obesity | 57 (23.1) | 61 (24.5) | -1.42 (-8.91 to 6.07)[b] |
| Chronic disease | | | |
| Kidney | 28 (11.3) | 43 (17.3) | -5.93 (-12.07 to 0.20)[b] |
| Cardiac | 38 (15.4) | 20 (8.0) | 7.35 (1.73 to 12.98)[b] |
| Pulmonary | 17 (6.9) | 21 (8.4) | -1.55 (-6.23 to 3.13)[b] |
| Active smoker | 13 (5.3) | 7 (2.8) | 2.45 (-1.01 to 5.92)[b] |
| Cerebrovascular disease | 10 (4.0) | 9 (3.6) | 0.43 (-2.94 to 3.81)[b] |

| | | | |
|---|---|---|---|
| Malignant neoplasm | 5 (2.0) | 9 (3.6) | -1.59 (-4.50 to 1.32)[b] |
| Gout | 8 (3.2) | 5 (2.0) | 1.23 (-1.82 to 4.46)[b] |
| Thyroid disease | 5 (2.0) | 6 (2.4) | -0.39 (-2.98 to 2.21)[b] |
| Chronic disorder | | | |
| Neurological | 4 (1.6) | 4 (1.6) | 0.01 (-2.20 to 2.23)[b] |
| Liver | 3 (1.2) | 2 (0.8) | 0.41 (-1.35 to 2.17)[b] |
| Autoimmune disease | 2 (0.8) | 2 (0.8) | 0.01 (-1.57 to 1.58)[b] |
| Immunosuppressive therapy | 0 (0.0) | 1 (0.4) | -0.40 (-1.19 to 3.84)[b] |
| | | | |
| **Symptoms** | | | |
| Cough | 188 (76.1) | 195 (78.3) | -2.20 (-9.58 to 5.18)[b] |
| Fever | 116 (47.0) | 125 (50.2) | -3.24 (-12.03 to 5.56)[b] |
| Runny nose | 68 (27.5) | 82 (32.9) | -5.40 (-13.47 to 2.67)[b] |
| Sore throat | 31 (12.6) | 45 (18.1) | -5.52 (-11.84 to 0.80)[b] |
| Lethargy | 36 (14.6) | 31 (12.4) | 2.13 (-3.89 to 8.14)[b] |
| Anosmia | 31 (12.6) | 31 (12.4) | 0.10 (-5.72 to 5.92)[b] |
| Diarrhea | 29 (11.7) | 24 (9.6) | 2.10 (-3.33 to 7.54)[b] |
| Exertional dyspnea | 25 (10.1) | 27 (10.8) | -0.72 (-6.11 to 4.67)[b] |
| Headache | 22 (8.9) | 19 (7.6) | 1.28 (-3.57 to 6.12)[b] |
| Myalgia | 22 (8.9) | 14 (5.6) | 3.28 (-1.28 to 7.85)[b] |
| Ageusia | 22 (8.9) | 12 (4.8) | 4.09 (-0.35 to 8.53)[b] |

| | | | |
|---|---|---|---|
| Vomiting | 9 (3.6) | 12 (4.8) | -1.18 (-4.72 to 2.37)[b] |
| Anorexia | 7 (2.8) | 7 (2.8) | 0.02 (-2.89 to 2.94)[b] |
| Nausea | 6 (2.4) | 4 (1.6) | 0.82 (-1.65 to 3.30)[b] |
| | | | |
| **Imaging and laboratory parameters on enrollment** | | | |
| Presence of any COVID-19 lung changes (chest radiography) | 162 (65.6) | 165 (66.3) | -0.68 (-9.02 to 7.66)[b] |
| Absolute count, mean (SD), cells/ μL | | | |
| Lymphocyte | 1797 (793) | 1778 (775) | 20 (-119 to 158)[a] |
| Neutrophil | 4005 (1923) | 3859 (1835) | 145 (-186 to 477)[a] |
| Neutrophil to lymphocyte ratio, mean (SD) | 2.6 (1.7) | 2.6 (2.0) | 0 (-0.3 to 0.3)[a] |
| Creatinine, median (IQR), mg/dL | 0.98 (0.49) | 1.01 (0.64) | 0.02 (-0.12 to 0.03)[d] |
| Alanine transaminase, mean (SD), U/L | 30.3 (21.7) | 30.1 (22.0) | 0.2 (-3.7 to 4.1)[a] |
| C-reactive protein, mean (SD), mg/dL | 2.83 (3.66) | 2.79 (3.88) | 0.04 (-0.63 to 0.70)[a] |
| | | | |
| **Medications given within 7 days before enrollment** | | | |
| Antibiotics | 20 (8.1) | 7 (2.8) | 5.29 (1.31 to 9.26)[b] |
| Systemic anticoagulation | 20 (8.1) | 9 (3.6) | 4.48 (0.37 to 8.60)[b] |
| Corticosteroids | 2 (0.8) | 6 (2.4) | -1.60 (-3.81 to 0.61)[b] |
| Other antivirals (not for COVID-19) | 0 (0.0) | 1 (0.4) | -0.40 (-1.19 to 0.38)[b] |

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; WHO, World Health Organization.

SI conversion factors: To convert alanine transaminase to μkat/L, multiply by 0.0167; C-reactive protein to mg/L, multiply by 10; creatinine to μmol/L, multiply by 88.4; lymphocyte and neutrophil count to $\times 10^9$/L, multiply by 0.001.

[a] Mean difference (mean of ivermectin group minus mean of the control group) with 95% CI

[b] Absolute difference in proportion

[c] Other refers to Indigenous ethnic groups in Peninsular Malaysia, Sabah and Sarawak, individuals of mixed race, and foreigners residing in Malaysia.

[d] The 95% CI was estimated by bootstrap sampling for median difference by using confintr R package.

**eTable 2. Outcomes in Intention-to-Treat Population**

| Outcomes | No. (%) | | Absolute difference (95%CI) | Relative risk (95% CI) | *P-value* |
|---|---|---|---|---|---|
| | Ivermectin (n= 247) | Control (n = 249) | | | |
| **Primary outcome** | | | | | |
| Progression to severe disease (WHO scale 5-9) | 53 (21.5) | 43 (17.3) | 4.19 (-2.76 to 11.13)[a] | 1.24 (0.87 to 1.78) | .26 |
| **Secondary Outcomes** | | | | | |
| Time of progression to severe disease, mean (SD), d | 3.2 (2.4) | 2.9 (1.8) | 0.3 (-0.6 to 1.2)[b] | NA | .51 |
| Patients who had mechanical ventilation | 4 (1.6) | 10 (4.0) | -2.40 (-5.30 to 0.51)[a] | 0.40 (0.13 to 1.27) | .17 |
| Patients admitted to ICU | 6 (2.4) | 8 (3.2) | -0.78 (-3.70 to 2.13)[a] | 0.76 (0.27 to 2.15) | .79 |
| All-cause in-hospital mortality | 3 (1.2) | 10 (4.0) | -2.80 (-5.59 to 0.001)[a] | 0.30 (0.08 to 1.09) | .09 |
| Length of stay, mean (SD), d | 7.7 (4.4) | 7.3 (4.3) | 0.4 (-0.4 to 1.1)[b] | NA | .34 |

All outcomes were captured from randomization until discharge from study sites or day 28 of enrollment, whichever earlier.

Abbreviations: ICU, intensive care unit; NA, not applicable; WHO, World Health Organization.

[a] Absolute difference in proportion.

[b] Mean difference (mean of ivermectin group minus mean of control group) with 95% CI.

## Additional Primary Analysis

**eTable 3. Laboratory Findings at Baseline and on Day 5 of Enrollment in Primary Analysis Population**

| Laboratory values, mean (SD) | Ivermectin (n = 238[a]) | | | Control (n = 247[b]) | | | *P*-value[c] |
|---|---|---|---|---|---|---|---|
| | Baseline | Day 5 | Mean Difference (95% CI) | Baseline | Day 5 | Mean Difference (95% CI) | |
| Absolute lymphocyte count (cells/μL) | 1801 (793) | 1978 (923) | 176 (85 to 267) | 1780 (776) | 1970 (918) | 190 (109 to 271) | .82 |
| Absolute neutrophil count (cells/μL) | 3963 (1890) | 4550 (2568) | 588 (320 to 856) | 3852 (1826) | 4582 (2502) | 731 (443 to 1019) | .47 |
| Neutrophil-lymphocyte ratio | 2.6 (1.7) | 3.2 (3.5) | 0.6 (0.1 to 1.0) | 2.6 (2.1) | 3.1 (3.3) | 0.5 (0.1 to 0.9) | .82 |
| Creatinine (mg/dL) | 1.75 (2.74) | 1.72 (2.73) | -0.03 (-0.17 to 0.12) | 2.26 (3.52) | 2.23 (3.60) | -0.03 (-0.21 to 0.15) | .97 |
| Alanine transaminase (U/L) | 30.2 (21.8) | 31.3 (21.8) | 1.1 (-1.1 to 3.4) | 30.1 (22.0) | 32.8 (26.0) | 2.7 (0.2 to 5.3) | .36 |
| C-reactive protein (mg/dL) | 2.82 (3.68) | 3.16 (3.98) | 0.34 (-0.19 to 0.86) | 2.76 (3.87) | 3.65 (5.19) | 0.89 (0.22 to 1.56) | .20 |

SI conversion factors: To convert alanine transaminase to μkat/L, multiply by 0.0167; C-reactive protein to mg/L, multiply by 10; creatinine to μmol/L, multiply by 88.4; lymphocyte and neutrophil count to $\times 10^9$/L, multiply by 0.001.

[a] Three patients withdrew from study before day 5 after taking at least one dose of ivermectin.

[b] Two patients died before follow-up on day 5.

[c] *P*-value showed statistical significance of interaction between time (baseline, day 5) and study groups (ivermectin, control).

**eTable 4. Incidence of COVID-19 related Complications in Primary Analysis Population**

| Complications | No. (%) | | *P-value* |
|---|---|---|---|
| | Ivermectin (n = 238[a]) | Control (n = 249) | |
| Any complications | 73 (30.7) | 70 (28.1) | .55 |
| Cytokine release syndrome | 28 (11.8) | 26 (10.4) | .56 |
| Pulmonary embolism | 5 (2.1) | 7 (2.8) | .77 |
| Organizing pneumonia | 13 (5.5) | 8 (3.2) | .27 |
| Bacterial infection | 26 (10.9) | 25 (10.0) | .77 |
| Fungal infection | 1 (0.4) | 2 (0.8) | >.99 |
| Other complications | 19 (8.0) | 12 (4.8) | .19 |

[a] Three patients withdrew from study before day 5 after taking at least one dose of ivermectin.

**eTable 5. Proportion of Patients with Highest Oxygen Requirement in Primary Analysis Population**

| Highest needs for oxygen therapy during study | No. (%) | | *P*-value |
|---|---|---|---|
| | Ivermectin (n = 241) | Control (n = 249) | |
| Room air | 189 (78.4) | 206 (82.7) | .07 |
| Nasal prong | 23 (9.5) | 18 (7.2) | |
| Simple face mask | 15 (6.2) | 4 (1.6) | |
| High-flow mask | 4 (1.7) | 6 (2.4) | |
| High-flow nasal cannula | 5 (2.1) | 4 (1.6) | |
| Non-invasive ventilation | 1 (0.4) | 1 (0.4) | |
| Mechanical ventilation | 4 (1.7) | 10 (4.0) | |

**eTable 6. Post-hoc Analyses on Clinical Outcomes by Vaccination Status in Primary Analysis Population**

| Outcomes | No. (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Ivermectin (n = 241) | | | | Control (n = 249) | | | |
| | Never Vaccinated (n = 75) | Vaccinated 1 Dose (n = 42) | Vaccinated 2 Doses (n = 124) | *P*-value | Never Vaccinated (n = 84) | Vaccinated 1 Dose (n = 35) | Vaccinated 2 Doses (n = 130) | *P*-value |
| Progression to Severe Disease (WHO scale 5-9) | 21 (28.0) | 9 (21.4) | 22 (17.7) | .23 | 22 (26.2) | 9 (25.7) | 12 (9.2) | <.01 |
| Death | 1 (1.3) | 0 (0) | 2 (1.6) | >.99 | 4 (4.8) | 1 (2.9) | 5 (3.8) | .91 |