JAMA Internal Medicine | Original Investigation

Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities

The I-TECH Randomized Clinical Trial

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IMPORTANCE Ivermectin, an inexpensive and widely available antiparasitic drug, is prescribed to treat COVID-19. Evidence-based data to recommend either for or against the use of ivermectin are needed.

OBJECTIVE To determine the efficacy of ivermectin in preventing progression to severe disease among high-risk patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS The Ivermectin Treatment Efficacy in COVID-19 High-Risk Patients (I-TECH) study was an open-label randomized clinical trial conducted at 20 public hospitals and a COVID-19 quarantine center in Malaysia between May 31 and October 25, 2021. Within the first week of patients' symptom onset, the study enrolled patients 50 years and older with laboratory-confirmed COVID-19, comorbidities, and mild to moderate disease.

INTERVENTIONS Patients were randomized in a 1:1 ratio to receive either oral ivermectin, 0.4 mg/kg body weight daily for 5 days, plus standard of care (n = 241) or standard of care alone (n = 249). The standard of care consisted of symptomatic therapy and monitoring for signs of early deterioration based on clinical findings, laboratory test results, and chest imaging.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of patients who progressed to severe disease, defined as the hypoxic stage requiring supplemental oxygen to maintain pulse oximetry oxygen saturation of 95% or higher. Secondary outcomes of the trial included the rates of mechanical ventilation, intensive care unit admission, 28-day in-hospital mortality, and adverse events.

RESULTS Among 490 patients included in the primary analysis (mean [SD] age, 62.5 [8.7] years; 267 women [54.5%]), 52 of 241 patients (21.6%) in the ivermectin group and 43 of 249 patients (17.3%) in the control group progressed to severe disease (relative risk [RR], 1.25; 95% CI, 0.87-1.80; P = .25). For all prespecified secondary outcomes, there were no significant differences between groups. Mechanical ventilation occurred in 4 (1.7%) vs 10 (4.0%) (RR, 0.41; 95% CI, 0.13-1.30; P = .17), intensive care unit admission in 6 (2.4%) vs 8 (3.2%) (RR, 0.78; 95% CI, 0.27-2.20; P = .79), and 28-day in-hospital death in 3 (1.2%) vs 10 (4.0%) (RR, 0.31; 95% CI, 0.09-1.11; P = .09). The most common adverse event reported was diarrhea (14 [5.8%] in the ivermectin group and 4 [1.6%] in the control group).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial of high-risk patients with mild to moderate COVID-19, ivermectin treatment during early illness did not prevent progression to severe disease. The study findings do not support the use of ivermectin for patients with COVID-19.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04920942

JAMA Intern Med. doi:10.1001/jamainternmed.2022.0189
Published online February 18, 2022.

Visual Abstract
Related article
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Despite the success of COVID-19 vaccines and the implementation of nonpharmaceutical public health measures, there is an enormous global need for effective therapeutics for SARS-CoV-2 infection. At present, repurposed anti-inflammatory drugs (dexamethasone, tocilizumab, and sarilumab),[1-3] monoclonal antibodies,[4-6] and antivirals (remdesivir, molnupiravir, and nirmatrelvir/ritonavir)[7-9] have demonstrated treatment benefits at different stages of COVID-19.[10]

In Malaysia, about 95% of patients with COVID-19 present early with mild disease, and less than 5% progress to a hypoxic state requiring oxygen supplementation. Notably, patients 50 years and older with comorbidities are at high risk for severe disease.[11] Potentially, an antiviral therapy administered during the early viral replication phase could avert the deterioration. Although molnupiravir and nirmatrelvir/ritonavir have shown efficacy in the early treatment of COVID-19,[8,9] they can be too expensive for widespread use in resource-limited settings.

Ivermectin, an inexpensive, easy-to-administer, and widely available antiparasitic drug, has been used as an oral therapy for COVID-19. An in vitro study demonstrated inhibitory effects of ivermectin against SARS-CoV-2.[12] Although some early clinical studies suggested the potential efficacy of ivermectin in the treatment and prevention of COVID-19,[13,14] these studies had methodologic weaknesses.[15]

In 2021, 2 randomized clinical trials from Colombia[16] and Argentina[17] found no significant effect of ivermectin on symptom resolution and hospitalization rates for patients with COVID-19. A Cochrane meta-analysis[18] also found insufficient evidence to support the use of ivermectin for the treatment or prevention of COVID-19.

These findings notwithstanding, ivermectin is widely prescribed for COVID-19, contrary to the World Health Organization (WHO) recommendation to restrict use of the drug to clinical trials.[19] In the present randomized clinical trial, we studied the efficacy of ivermectin for preventing progression to severe disease among high-risk patients with COVID-19 in Malaysia.

Key Points

Question Does adding ivermectin, an inexpensive and widely available antiparasitic drug, to the standard of care reduce the risk of severe disease in patients with COVID-19 and comorbidities?

Findings In this open-label randomized clinical trial of high-risk patients with COVID-19 in Malaysia, a 5-day course of oral ivermectin administered during the first week of illness did not reduce the risk of developing severe disease compared with standard of care alone.

Meaning The study findings do not support the use of ivermectin for patients with COVID-19.

Methods

Trial Design and Patients

The Ivermectin Treatment Efficacy in COVID-19 High-Risk Patients (I-TECH) study was a multicenter, open-label, randomized clinical trial conducted at 20 government hospitals and a COVID-19 quarantine center in Malaysia between May 31 and October 25, 2021. The study was approved by the local Medical Research and Ethics Committee (NMRR-21-155-58433) and registered in ClinicalTrials.gov (NCT04920942). This trial was conducted in accordance with the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. All participants provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

In Malaysia, mandatory notification to public health authorities applies to all COVID-19 cases. Patients with mild to moderate disease at risk of disease progression are referred for hospitalization or admitted to a COVID-19 quarantine center to allow close monitoring for 10 or more days from symptom onset and timely intervention in the event of deterioration.

The study enrolled patients with reverse transcriptase-polymerase chain reaction (RT-PCR) test–confirmed or antigen test–confirmed COVID-19 who were 50 years or older with at least 1 comorbidity and presented with mild to moderate illness (Malaysian COVID-19 clinical severity stage 2 or 3; WHO clinical progression scale 2-4)[20,21] within 7 days from symptom onset. Patients were excluded if they were asymptomatic, required supplemental oxygen, or had pulse oximetry oxygen saturation (Spo_2) level less than 95% at rest. Other exclusion criteria were severe hepatic impairment (alanine transaminase level >10 times of upper normal limit), acute medical or surgical emergency, concomitant viral infection, pregnancy or breastfeeding, warfarin therapy, and history of taking ivermectin or any antiviral drugs with reported activity against COVID-19 (favipiravir, hydroxychloroquine, lopinavir, and remdesivir) within 7 days before enrollment. Eligibility criteria are detailed in the study protocol (Supplement 1). Study investigators collected information on ethnicity based on the patient's Malaysian identification card or passport (for non-Malaysian citizens).

All patients with COVID-19 were managed in accordance with the national COVID-19 Management Guidelines,[20] developed by a local expert panel based on consensus, WHO recommendations, and the US National Institutes of Health guidelines. High-risk patients were defined as those aged 50 years or older with comorbidity. Patients were staged according to clinical severity at presentation and disease progression: stage 1, asymptomatic; stage 2, symptomatic without evidence of pneumonia; stage 3, evidence of pneumonia without hypoxia; stage 4, pneumonia with hypoxia requiring oxygen supplementation; and stage 5, critically ill with multiorgan involvement. Stages 2 and 3 were classified as mild and moderate diseases (WHO scale 2-4), while stages 4 and 5 were referred to as severe diseases (WHO scale 5-9). The standard of care for patients with mild to moderate disease consisted of symptomatic therapy and monitoring for signs of early deterioration based on clinical findings, laboratory test results, and chest imaging.

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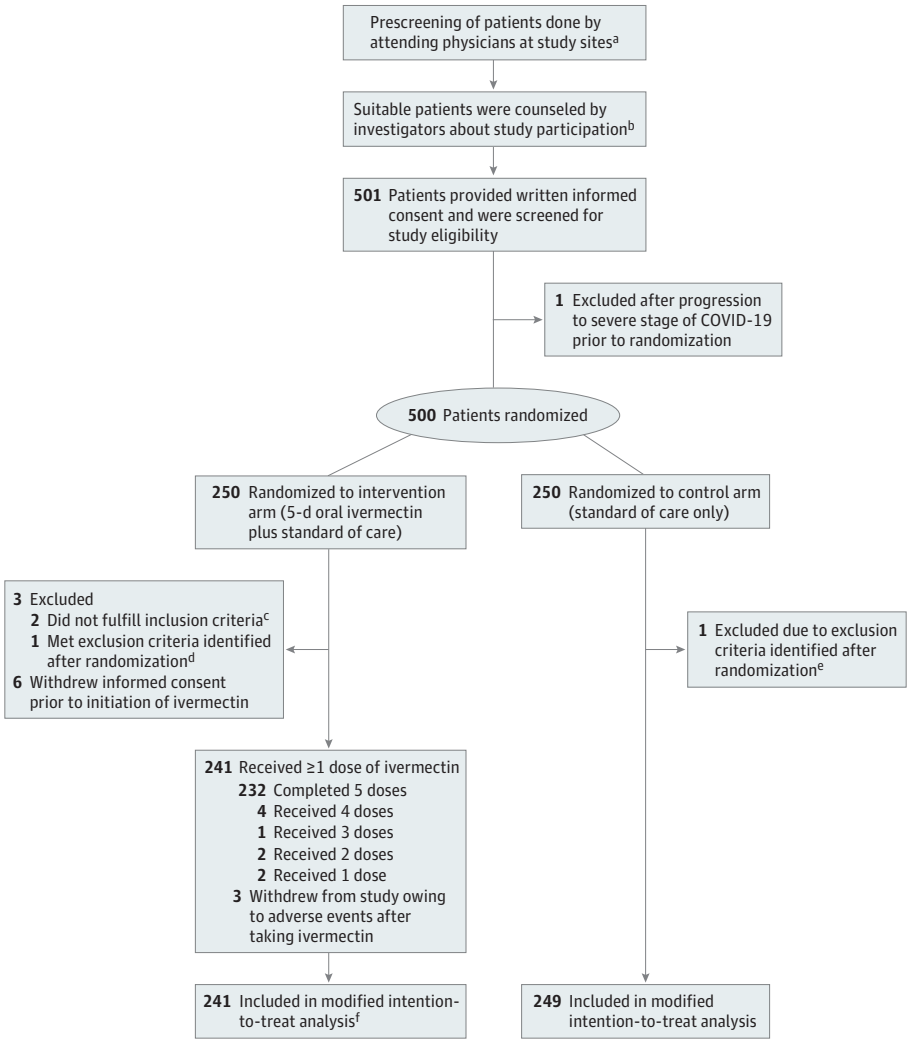
Figure. Screening, Enrollment, Randomization, and Treatment Assignment



[a] The study inclusion and exclusion criteria were made known to physicians at study sites to facilitate prescreening of patients.

[b] The number of patients counseled by study investigators was not collected.

[c] One patient had onset of COVID-19 symptoms 8 days prior to randomization, which exceeded the first 7 days of illness inclusion criterion. Another patient had a COVID-19 rapid test antigen positive result but polymerase chain reaction negative result. This was before a protocol amendment that included positive COVID-19 antigen test result as alternative inclusion criteria if polymerase chain reaction testing was not done or was negative.

[d] Patient was found to have acute coronary syndrome after randomization but before commencement of ivermectin therapy. Acute medical emergency was an exclusion criterion.

[e] Patient was diagnosed of dengue fever with NS-1 antigen positive. Concomitant viral infection was an exclusion criterion.

[f] In the intervention arm, only patients who received at least 1 dose of ivermectin were included in the modified intention-to-treat analysis.

Randomization and Data Collection

All study data were recorded in case report form and transcribed into the REDCap (Research Electronic Data Capture) platform.[22,23] Patients were randomized in a 1:1 ratio to either the intervention group receiving oral ivermectin (0.4 mg/kg body weight daily for 5 days) plus standard of care or the control group receiving the standard of care alone (**Figure**). The randomization was based on an investigator-blinded randomization list uploaded to REDCap, which allocated the patients via a central, computer-generated randomization scheme across all study sites during enrollment. The randomization list was generated independently using random permuted block sizes 2 to 6. The randomization was not stratified by site.

Intervention

The ivermectin dosage for each patient in the intervention arm was calculated to the nearest 6-mg or 12-mg whole tablets (dosing table in the study protocol, Supplement 1). The first dose of ivermectin was administered after randomization on day 1 of enrollment, followed by 4 doses on days 2 through 5. Patients were encouraged to take ivermectin with food or after meals to improve drug absorption. Storage, dispensary, and administration of ivermectin were handled by trained study investigators, pharmacists, and nurses.

Outcome Measures

The primary outcome was the proportion of patients who progressed to severe COVID-19, defined as the hypoxic stage requiring supplemental oxygen to maintain Spo_2 95% or greater (Malaysian COVID-19 clinical severity stages 4 or 5; WHO clinical progression scale 5-9). The Spo_2 was measured using a calibrated pulse oximeter per the clinical monitoring protocol.

Secondary outcomes were time of progression to severe disease, 28-day in-hospital all-cause mortality, mechanical ventilation rate, intensive care unit admission, and length of hospital stay after enrollment. Patients were also assessed on day 5 of enrollment for symptom resolution, changes in laboratory test results, and chest radiography findings. Adverse events (AEs) and serious AEs (SAEs) were evaluated and graded according to Common Terminology Criteria for Adverse Events,

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Table 1. Baseline Demographic and Clinical Characteristics of Patients in Primary Analysis Population

Characteristic	No. (%)		Difference (95% CI)
	Ivermectin	Control	
No.	241	249	NA
Demographics			
Age, mean (SD), y	63.0 (8.9)	62.0 (8.4)	0.9 (−0.6 to 2.5)[a]
Sex			
Female	130 (53.9)	137 (55.0)	−1.08 (−9.90 to 7.74)[b]
Male	111 (46.1)	112 (45.0)	1.08 (−7.74 to 9.90)[b]
Ethnicity			
Chinese	37 (15.4)	32 (12.9)	2.50 (−3.66 to 8.67)[b]
Indian	38 (15.8)	30 (12.0)	3.72 (−2.41 to 9.84)[b]
Malay	153 (63.5)	172 (69.1)	−5.59 (−13.95 to 2.77)[b]
Other[c]	13 (5.4)	15 (6.0)	−0.63 (−4.74 to 3.48)[b]
Anthropometrics			
Weight, mean (SD), kg	68.0 (14.5)	68.7 (14.6)	−0.7 (−3.2 to 1.9)[a]
BMI, mean (SD)	26.8 (5.2)	26.9 (5.4)	−0.1 (−1.0 to 0.9)[a]
COVID-19–related history			
COVID-19 vaccination			
Not vaccinated	75 (31.1)	84 (33.7)	−2.61 (−10.90 to 5.67)[b]
Received 1 dose of vaccine	42 (17.4)	35 (14.1)	3.37 (−3.08 to 9.82)[b]
Completed 2 doses of vaccine	124 (51.5)	130 (52.2)	−0.76 (−9.61 to 8.09)[b]
Disease severity at enrollment (WHO scale 2-4)			
Mild	83 (34.4)	84 (33.7)	0.71 (−7.69 to 9.10)[b]
Moderate	158 (65.6)	165 (66.3)	−0.71 (−9.10 to 7.69)[b]
Day of symptoms at enrollment, mean (SD)	5.1 (1.3)	5.1 (1.3)	0 (−0.2 to 0.3)[a]
Comorbidity			
Hypertension	178 (73.9)	191 (76.7)	−2.85 (−10.49 to 4.79)[b]
Diabetes mellitus	131 (54.4)	131 (52.6)	1.75 (−7.09 to 10.58)[b]
Dyslipidemia	102 (42.3)	82 (32.9)	9.39 (0.85 to 17.94)[b]
Obesity	56 (23.2)	61 (24.5)	−1.26 (−8.81 to 6.29)[b]
Chronic disease			
Kidney	28 (11.6)	43 (17.3)	−5.65 (−11.85 to 0.55)[b]
Cardiac	37 (15.4)	20 (8.0)	7.32 (1.65 to 12.99)[b]
Pulmonary	17 (7.1)	21 (8.4)	−1.38 (−6.11 to 3.35)[b]
Active smoker	13 (5.4)	7 (2.8)	2.59 (−0.93 to 6.10)[b]
Cerebrovascular disease	10 (4.1)	9 (3.6)	0.53 (−2.89 to 3.96)[b]
Malignant neoplasm	5 (2.1)	9 (3.6)	−1.54 (−4.47 to 1.40)[b]
Gout	8 (3.3)	5 (2.0)	1.31 (−1.76 to 4.61)[b]
Thyroid disease	5 (2.1)	6 (2.4)	0.33 (−2.96 to 2.29)[b]
Chronic disorder			
Neurological	4 (1.7)	4 (1.6)	0.05 (−2.19 to 2.30)[b]
Liver	3 (1.2)	2 (0.8)	0.44 (−1.34 to 2.23)[b]
Autoimmune disease	2 (0.8)	2 (0.8)	0.02 (−1.57 to 1.62)[b]
Immunosuppressive therapy	0	1 (0.4)	−0.40 (−1.19 to 3.84)[b]
Symptom			
Cough	183 (75.9)	195 (78.3)	−2.38 (−9.82 to 5.06)[b]
Fever	112 (46.5)	125 (50.2)	−3.73 (−12.57 to 5.11)[b]
Runny nose	67 (27.8)	82 (32.9)	−5.13 (−13.26 to 3.00)[b]
Sore throat	30 (12.4)	45 (18.1)	−5.62 (−11.97 to 0.72)[b]
Lethargy	35 (14.5)	31 (12.4)	2.07 (−3.98 to 8.12)[b]
Anosmia	30 (12.4)	31 (12.4)	0 (−5.85 to 5.85)[b]
Diarrhea	28 (11.6)	24 (9.6)	−1.98 (−3.48 to 7.44)[b]
Exertional dyspnea	24 (10.0)	27 (10.8)	−0.88 (−6.29 to 4.52)[b]
Headache	22 (9.1)	19 (7.6)	1.50 (−3.41 to 6.41)[b]

(continued)

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Table 1. Baseline Demographic and Clinical Characteristics of Patients in Primary Analysis Population (continued)

Characteristic	No. (%)		Difference (95% CI)
	Ivermectin	Control	
Myalgia	22 (9.1)	14 (5.6)	3.51 (−1.12 to 8.13)[b]
Ageusia	21 (8.7)	12 (4.8)	3.89 (−0.55 to 8.34)[b]
Vomiting	9 (3.7)	12 (4.8)	−1.08 (−4.66 to 2.49)[b]
Anorexia	6 (2.5)	7 (2.8)	−0.32 (−3.17 to 2.52)[b]
Nausea	6 (2.5)	4 (1.6)	0.88 (−1.63 to 3.39)[b]
Imaging and laboratory parameters at enrollment			
Presence of any COVID-19 lung changes (chest radiography)	158 (65.6)	165 (66.3)	−0.70 (−9.10 to 7.69)[b]
Absolute count, mean (SD), cells/μL			
Lymphocyte	1803 (799)	1778 (775)	26 (−114 to 166)[a]
Neutrophil	3961 (1879)	3859 (1835)	103 (−227 to 432)[a]
Neutrophil to lymphocyte ratio, mean (SD)	2.6 (1.7)	2.6 (2.0)	0 (−0.4 to 0.3)[a]
Creatinine, median (IQR), mg/dL	0.97 (0.50)	1.01 (0.64)	−0.03 (−0.11 to 0.05)[d]
Alanine transaminase, mean (SD), U/L	30.3 (21.8)	30.1 (22.0)	0.3 (−3.6 to 4.2)[a]
C-reactive protein, mean (SD), mg/dL	2.81 (3.66)	2.79 (3.88)	0.02 (−0.65 to 0.69)[a]
Medications given within 7 d before enrollment			
Antibiotics	19 (7.9)	7 (2.8)	5.07 (1.10 to 9.05)[b]
Systemic anticoagulation	18 (7.5)	9 (3.6)	3.85 (−0.19 to 7.90)[b]
Corticosteroids	2 (0.8)	6 (2.4)	−1.58 (−3.80 to 0.64)[b]
Other antivirals (not for COVID-19)	0	1 (0.4)	−0.40 (−1.19 to 0.38)[b]
Concomitant medications given during study period			
No.	238[e]	249	NA
Corticosteroids	64 (26.9)	66 (26.5)	0.38 (−7.48 to 8.25)[b]
Antibiotics	55 (23.1)	54 (21.7)	1.42 (−5.99 to 8.83)[b]
Systemic anticoagulation	68 (28.6)	57 (22.9)	5.68 (−2.08 to 13.44)[b]
Baricitinib	4 (1.7)	7 (2.8)	−1.13 (−3.75 to 1.49)[b]
Tocilizumab	2 (0.8)	2 (0.8)	0.03 (−1.57 to 1.64)[b]
Other antivirals (not for COVID-19)	0	1 (0.4)	−0.40 (−1.18 to 0.38)[b]

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; NA, not applicable; 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.

[e] Three patients in the ivermectin group withdrew from the study after taking 1 or more doses of ivermectin, and data on these variables were not captured.

version 5.0.[24] All outcomes were captured from randomization until discharge from study sites or day 28 of enrollment, whichever was earlier.

Subgroup Analyses

Subgroup analyses were predetermined according to COVID-19 vaccination status, age, clinical staging, duration of illness at enrollment, and common comorbidities.

Procedures

Patients' clinical history, anthropometric measurements, blood samples for complete blood cell count, kidney and liver profiles, C-reactive protein levels, and chest radiography were obtained at baseline. Blood sampling and chest radiography were repeated on day 5 of enrollment. Study investigators followed up patients for all outcome assessments and AEs. All study-related AEs were reviewed by an independent Data and Safety Monitoring Board.

Sample Size Calculation

The sample size was calculated based on a superiority trial design and primary outcome measure. The expected rate of primary outcome was 17.5% in the control group, according to previous local data of high-risk patients who presented with mild to moderate disease.[11] A 50% reduction of primary outcome, or a 9% rate difference between intervention and control groups, was considered clinically important. This trial required 462 patients to be adequately powered. This sample size provided a level of significance at 5% with 80% power for 2-sided tests. Considering potential dropouts, a total of 500 patients (250 patients for each group) were recruited.

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Table 2. Outcomes in the Primary Analysis Population

Outcomes[a]	No. (%)		Absolute difference (95% CI)	Relative risk (95% CI)	*P* value
	Ivermectin	Control			
No.	241	249	NA	NA	NA
Primary outcome					
Progression to severe disease (WHO scale 5-9)	52 (21.6)	43 (17.3)	4.31 (−2.69 to 11.31)[b]	1.25 (0.87 to 1.80)	.25
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)[c]	NA	.51
Patients who had mechanical ventilation	4 (1.7)	10 (4.0)	−2.36 (−5.28 to 0.57)[b]	0.41 (0.13 to 1.30)	.17
Patients admitted to ICU	6 (2.5)	8 (3.2)	−0.72 (−3.67 to 2.22)[b]	0.78 (0.27 to 2.20)	.79
All-cause in-hospital mortality	3 (1.2)	10 (4.0)	−2.77 (−5.58 to 0.04)[b]	0.31 (0.09 to 1.11)	.09
Length of stay, mean (SD), d	7.7 (4.4)	7.3 (4.3)	0.4 (−0.4 to 1.3)[c]	NA	.38
Clinical outcome at day 5					
No.	238[d]	247[e]	NA	NA	NA
Complete symptom resolution	122 (51.3)	131 (53.0)	−1.78 (−10.70 to 7.12)[b]	0.97 (0.82 to 1.15)	.72
Normal chest radiography[f]	61 (25.6)	61 (24.9)	0.73 (−7.02 to 8.48)[b]	1.03 (0.76 to 1.40)	.92

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

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

[b] Absolute difference in proportion.

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

[d] Three patients withdrew from the study before day 5 after taking at least 1 dose of ivermectin.

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

[f] Two patients missed chest radiography on day 5 (n = 245 for control arm).

Statistical Analyses

Primary analyses were performed based on the modified intention-to-treat principle, whereby randomized patients in the intervention group who received at least 1 ivermectin dose and all patients in the control group would be followed and evaluated for efficacy and safety. In addition, sensitivity analyses were performed on all eligible randomized patients, including those in the intervention group who did not receive ivermectin (intention-to-treat population).

Descriptive data were expressed as means and SDs unless otherwise stated. Categorical data were analyzed using the Fisher exact test. Continuous variables were tested using the *t*-test or Mann-Whitney *U* test. The primary and categorical secondary outcome measures were estimated using relative risk (RR). The absolute difference of means of time of progression to severe disease and lengths of hospitalization between the study groups were determined with a 95% CI. Mixed analysis of variance was used to determine whether the changes of laboratory investigations were the result of interactions between the study groups (between-patients factor) and times (within-patient factor), and $P < .05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp).

Interim analyses were conducted on the first 150 and 300 patients, with outcome data retrieved on July 13 and August 30, 2021, respectively. The overall level of significance was maintained at $P < .05$, calculated according to the O'Brien-Fleming stopping boundaries. Early stopping would be considered if $P < .003$ for efficacy data. The results were presented to the Data and Safety Monitoring Board, which recommended continuing the study given no signal for early termination.

Results

Between May 31 and October 9, 2021, 500 patients were enrolled and randomized. The last patient completed follow-up on October 25, 2021. Four patients were excluded after randomization. One patient in the control arm was diagnosed with dengue coinfection; in the intervention arm, 2 failed to meet inclusion criteria owing to symptom duration greater than 7 days and negative COVID-19 RT-PCR test result, while 1 had acute coronary syndrome before ivermectin initiation. In addition, 6 patients in the intervention arm withdrew consent before taking a dose of ivermectin. The modified intention-to-treat population for the primary analysis included 490 patients (98% of those enrolled), with 241 in the intervention group and 249 in the control group (Figure). Drug compliance analysis showed that 232 patients (96.3%) in the intervention group completed 5 doses of ivermectin.

Baseline demographics and characteristics of patients were well balanced between groups (**Table 1**). The mean (SD) age was 62.5 (8.7) years, with 267 women (54.5%); 254 patients (51.8%) were fully vaccinated with 2 doses of COVID-19 vaccines. All major ethnic groups in Malaysia were well represented in the study population. The majority had hypertension (369 [75.3%]), followed by diabetes mellitus (262 [53.5%]), dyslipidemia (184 [37.6%]), and obesity (117 [23.9%]).

The mean (SD) duration of symptoms at enrollment was 5.1 (1.3) days. The most common symptoms were cough (378 [77.1%]), fever (237 [48.4%]), and runny nose (149 [30.4%]). Approximately two-thirds of patients had moderate disease. The average baseline neutrophil-lymphocyte ratio and serum C-reactive protein level were similar between groups.

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Table 3. Subgroups Analyses for Patients With Severe Disease (WHO Scale 5-9) in Primary Analysis Population

Subgroup	Ivermectin	Control	Relative risk (95% CI)	*P* value	*P* value for interaction[a]
No.	52[b]	43[c]	NA	NA	NA
Ethnicity					
Chinese	8 (21.6)	5 (15.6)	1.38 (0.50-3.81)	.56	.87
Indian	4 (10.5)	1 (3.3)	3.16 (0.37-26.80)	.37	
Malay	36 (23.5)	33 (19.2)	1.23 (0.81-1.86)	.35	
Other[d]	4 (30.8)	4 (26.7)	1.15 (0.36-3.72)	>.99	
Sex					
Female	26 (20.3)	27 (19.7)	1.01 (0.63-1.64)	>.99	.21
Male	26 (23.4)	16 (14.3)	1.64 (0.93-2.88)	.09	
Age, y					
≤60	21 (20.0)	17 (14.3)	1.40 (0.78-2.51)	.29	.61
>60	31 (22.8)	26 (20.0)	1.14 (0.72-1.81)	.65	
COVID-19 vaccination					
Complete[e]	22 (17.7)	12 (9.2)	1.92 (0.99-3.71)	.06	.11
Partial or unvaccinated	30 (25.6)	31 (26.1)	0.98 (0.64-1.52)	>.99	
Disease severity at enrollment					
Mild	14 (16.9)	11 (13.1)	1.29 (0.62-2.67)	.52	.97
Moderate	38 (24.1)	32 (19.4)	1.24 (0.82-1.88)	.35	
Day of symptom at enrollment					
≤5 d	33 (23.4)	21 (14.4)	1.63 (0.99-2.67)	.07	.11
>5 d	19 (19.0)	22 (21.4)	0.89 (0.51-1.54)	.73	
Hypertension					
Yes	38 (21.3)	37 (19.4)	1.10 (0.74-1.65)	.70	.18
No	14 (22.2)	6 (10.3)	2.15 (0.88-5.22)	.09	
Diabetes mellitus					
Yes	31 (23.7)	26 (19.8)	1.19 (0.75-1.89)	.55	.81
No	21 (19.1)	17 (14.4)	1.33 (0.74-2.38)	.38	
Dyslipidemia					
Yes	25 (24.5)	14 (17.1)	1.44 (0.80-2.58)	.28	.50
No	27 (19.4)	29 (17.4)	1.12 (0.70-1.80)	.67	
BMI					
<30	32 (17.3)	31 (16.5)	1.05 (0.67-1.65)	.89	.13
≥30	20 (35.7)	12 (19.7)	1.82 (0.98-3.36)	.06	
Chronic disease					
Cardiac					
Yes	7 (18.9)	3 (15.0)	1.26 (0.37-4.35)	>.99	.99
No	45 (22.1)	40 (17.5)	1.26 (0.86-1.85)	.28	
Kidney					
Yes	8 (28.6)	6 (14.0)	2.05 (0.80-5.27)	.22	.27
No	44 (20.7)	37 (18.0)	1.15 (0.78-1.70)	.54	

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; NA, not applicable; WHO, World Health Organization.

[a] *P* values were obtained from an interaction term between the treatment groups and the prognostic factor for severe disease in a logistic regression analysis.

[b] Total number of patients from the ivermectin group included in the analyses was 52 of 241.

[c] Total number of patients from the control group included in the analyses was 43 of 249.

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

[e] Received 2 doses of COVID-19 vaccines.

There were no significant differences in the concomitant medications prescribed for both groups. In sensitivity analyses, baseline characteristics were similar in the intention-to-treat population (eTable 1 in Supplement 2).

Primary Outcome

Among the 490 patients, 95 (19.4%) progressed to severe disease during the study period; 52 of 241 (21.6%) received ivermectin plus standard of care, and 43 of 249 (17.3%) received standard of care alone (RR, 1.25; 95% CI, 0.87-1.80; *P* = .25) (**Table 2**). Similar results were observed in the intention-to-treat population in the sensitivity analyses (eTable 2 in Supplement 2).

Secondary Outcomes

There were no significant differences between ivermectin and control groups for all the prespecified secondary outcomes

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Table 4. Summary of Adverse Events (AEs) and Serious AEs (SAEs) in the Primary Analysis Population

AE	No.		
	Total	Ivermectin	Control
No.	490	241	249
Patients who had ≥1 AE/SAE, No. (%)	44 (9.0)	33 (13.7)	11 (4.4)
Total nonserious AE	50	38	12
Diarrhea	18	14	4
Acute kidney injury	4	3	1
Acidosis	3	2	1
Alanine aminotransferase increased	2	2	0
Dizziness	2	2	0
Hypertension	2	1	1
Hyperglycemia	2	1	1
Hypoglycemia	1	1	0
Headache	1	1	0
Abdominal pain	1	1	0
Nausea	1	1	0
Constipation	1	1	0
Fever	1	1	0
Epistaxis	1	0	1
Conjunctivitis	1	1	0
Urticaria	1	1	0
Rash, maculopapular	1	0	1
Myalgia	1	1	0
Noncardiac chest pain	1	1	0
Palpitation	1	1	0
Sinus tachycardia	1	1	0
Muscle weakness, upper limb	1	0	1
Vascular access complication[a]	1	1	0
Fall	1	0	1
Total SAE	5	4	1
Myocardial infarction	2	2	0
Arterial injury[b]	1	0	1
Anemia[c]	1	1	0
Hypotension[d]	1	1	0
Severity by CTCAE grading			
1	30	23	7
2	11	8	3
3	8	6	2
4	6	5	1

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

[a] Bleeding from brachiocephalic fistula after hemodialysis.

[b] Inferior epigastric arterial bleeding.

[c] Severe anemia precipitating an acute coronary syndrome.

[d] Hypovolemic shock due to severe diarrhea.

(Table 2). Among patients who progressed to severe disease, the time from study enrollment to the onset of deterioration was similar across ivermectin and control groups (mean [SD], 3.2 [2.4] days vs 2.9 [1.8] days; mean difference, 0.3; 95% CI, −0.6 to 1.2; *P* = .51). Mechanical ventilation occurred in 4 patients (1.7%) in the ivermectin group vs 10 (4.0%) in the control group (RR, 0.41; 95% CI, 0.13 to 1.30; *P* = .17) and intensive care unit admission in 6 (2.5%) vs 8 (3.2%) (RR, 0.78; 95% CI, 0.27 to 2.20; *P* = .79). The 28-day in-hospital mortality rate was similar for the ivermectin and control groups (3 [1.2%] vs 10 [4.0%]; RR, 0.31; 95% CI, 0.09 to 1.11; *P* = .09), as was the length of hospital stay after enrollment (mean [SD], 7.7 [4.4] days vs 7.3 [4.3] days; mean difference, 0.4; 95% CI, −0.4 to 1.3; *P* = .38).

By day 5 of enrollment, the proportion of patients who achieved complete symptom resolution was comparable between both groups (RR, 0.97; 95% CI, 0.82-1.15; *P* = .72). Findings of chest radiography without pneumonic changes or with resolution by day 5 were also similar (RR, 1.03; 95% CI, 0.76-1.40; *P* = .92). No marked variation was noted in blood parameters (eTable 3 in Supplement 2). There was no significant difference in the incidence of disease complications and highest oxygen requirement (eTables 4 and 5 in Supplement 2).

Subgroup Analyses

Subgroup analyses for patients with severe disease were unremarkable (**Table 3**). Among fully vaccinated patients, 22 (17.7%) in the ivermectin group and 12 (9.2%) in the control group developed severe disease (RR, 1.92; 95% CI, 0.99-3.71; *P* = .06). Post hoc analyses on clinical outcomes by vaccination status showed that fully vaccinated patients in the con-

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trol group had a significantly lower rate of severe disease (P = .002; supporting data in eTable 6 in Supplement 2).

Adverse Events

A total of 55 AEs occurred in 44 patients (9.0%) (**Table 4**). Among them, 33 were from the ivermectin group, with diarrhea being the most common AE (14 [5.8%]). Five events were classified as SAEs, with 4 in the ivermectin group (2 patients had myocardial infarction, 1 had severe anemia, and 1 developed hypovolemic shock secondary to severe diarrhea), and 1 in the control group had inferior epigastric arterial bleeding. Six patients discontinued ivermectin, and 3 withdrew from the study owing to AEs. The majority of AEs were grade 1 and resolved within the study period.

Among the 13 deaths, severe COVID-19 pneumonia was the principal direct cause (9 deaths [69.2%]). Four patients in the control group died from nosocomial sepsis. None of the deaths were attributed to ivermectin treatment.

Discussion

In this randomized clinical trial of early ivermectin treatment for adults with mild to moderate COVID-19 and comorbidities, we found no evidence that ivermectin was efficacious in reducing the risk of severe disease. Our findings are consistent with the results of the IVERCOR-COVID19 trial,[17] which found that ivermectin was ineffective in reducing the risk of hospitalization.

Prior randomized clinical trials of ivermectin treatment for patients with COVID-19 and with 400 or more patients enrolled focused on outpatients.[16,17] In contrast, the patients in our trial were hospitalized, which permitted the observed administration of ivermectin with a high adherence rate. Furthermore, we used clearly defined criteria for ascertaining progression to severe disease.

Before the trial started, the case fatality rate in Malaysia from COVID-19 was about 1%,[25] a rate too low for mortality to be the primary end point in our study. Even in a high-risk cohort, there were 13 deaths (2.7%). A recent meta-analysis of 8 randomized clinical trials of ivermectin to treat SARS-CoV-2 infection, involving 1848 patients with 71 deaths (3.8%), showed that treatment with the drug had no significant effect on survival.[26]

The pharmacokinetics of ivermectin for treating COVID-19 has been a contentious issue. The plasma inhibitory concentrations of ivermectin for SARS-CoV-2 are high; thus, establishing an effective ivermectin dose regimen without causing toxic effects in patients is difficult.[27,28] The dose regimens that produced favorable results against COVID-19 ranged from a 0.2-mg/kg single dose to 0.6 mg/kg/d for 5 days[29-32]; a concentration-dependent antiviral effect was demonstrated by Krolewiecki et al.[29] Pharmacokinetic studies have suggested that a single dose of up to 120 mg of ivermectin can be safe and well tolerated.[33] Considering the peak of SARS-CoV-2 viral load during the first week of illness and its prolongation in severe disease,[34] our trial used an ivermectin dose of 0.4 mg/kg of body weight daily for 5 days. The notably higher incidence of AEs in the ivermectin group raises concerns about the use of this drug outside of trial settings and without medical supervision.

Limitations

Our study has limitations. First, the open-label trial design might contribute to the underreporting of adverse events in the control group while overestimating the drug effects of ivermectin. Second, our study was not designed to assess the effects of ivermectin on mortality from COVID-19. Finally, the generalizability of our findings may be limited by the older study population, although younger and healthier individuals with low risk of severe disease are less likely to benefit from specific COVID-19 treatments.

Conclusions

In this randomized clinical trial of high-risk patients with mild to moderate COVID-19, ivermectin treatment during early illness did not prevent progression to severe disease. The study findings do not support the use of ivermectin for patients with COVID-19.

ARTICLE INFORMATION

Accepted for Publication: January 22, 2022.

Published Online: February 18, 2022. doi:10.1001/jamainternmed.2022.0189

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Conflict of Interest Disclosures: None reported.

The I-TECH Study Group: Members of the I-TECH Study Group are listed in Supplement 3.

Data Sharing Statement: See Supplement 4.

Additional Contributions: The authors thank all the investigators at the 21 study sites and the Institute for Clinical Research, Ministry of Health Malaysia, for their immense contribution and support. In addition, we are grateful for the participation of the patients enrolled in this study. We also thank the members of the independent Data and Safety Monitoring Board, namely Petrick Periyasamy, MMed, National University Medical Centre, Malaysia; Lai Hui Pang, BPharm, Institute for Clinical Research, Malaysia; Mohamad Adam Bujang, PhD, Institute for Clinical Research, Malaysia; Wei Hong Lai, PhD, Institute for Clinical Research, Malaysia; and Nurakmal Baharum, BSc, Institute for Clinical Research, Malaysia. They did not receive compensation for their contribution to this study. We also thank Noor Hisham Abdullah, M Surg, Director-General of Health Malaysia, for his permission to publish this study.

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