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The paper:

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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Why was this study conducted?

Ivermectin, an inexpensive antiparasitic drug, is widely prescribed orally for COVID-19, contrary to the World Health Organization (WHO) recommendation to restrict the use of the drug in clinical trials (1). An in vitro study demonstrated the inhibitory effects of ivermectin against SARS-CoV-2(2). Some preliminary clinical studies suggest that ivermectin could be effective in the treatment and prevention of COVID-19 (3,4). In contrast, 2 randomized clinical trials from Colombia (4) and Argentina (6) found no significant effect of ivermectin on symptom resolution and hospitalization rates for patients with COVID-19. A Cochrane meta-analysis (7) also found insufficient evidence to support the use of ivermectin for the treatment or prevention of COVID-19. Accordingly, there was a need for better evidence to recommend either for or against the use of ivermectin. Thus, The Ivermectin Treatment Efficacy in COVID-19 High-Risk Patients (I-TECH) study was conducted to determine the efficacy of ivermectin in preventing progression to severe disease among high-risk patients with COVID-19 in Malaysia.

How was it done?

Trial designs and Patients

The Ivermectin Treatment Efficacy in COVID-19 High-Risk Patients (I-TECH) study was an open-label randomized clinical trial (RCT) conducted at 20 public hospitals and a COVID-19 quarantine center in Malaysia between May 31 and October 25, 2021. Within 7 days of patients' symptom onset, the study enrolled patients 50 years and older with laboratory-confirmed COVID-19, at least with 1 comorbidity, and mild to moderate clinical severity (stage 2-3 disease).

Primary and Secondary Outcomes

Primary Outcome Measure:

i. Number of patients who progressed to severe disease (hypoxic stage requiring supplemental oxygen to maintain oxygen saturation (SpO_2 95% or greater clinical stage 4 or 5).

Secondary Outcome Measure:

i. Time to progression to severe disease after enrollment.
ii. Number of patients who died in hospital within 28 days of study enrollment (28-day in-hospital all-cause mortality).
iii. Number of patients with complete resolution of symptoms by day 5 of enrollment.
iv. Changes in chest X-ray and laboratory investigations by day 5 of enrollment.
v. Number of patients admitted to ICU.
vi. Number of patients who required mechanical ventilation.
vii. Length of hospital stay in calendar days.

***Adverse events (AEs) and serious AEs (SAEs)** were evaluated and graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (8). The CTCAE terms are grouped by Medical Dictionary for Regulatory Activities (MedDRA) as Primary System Organ Class (SOC), the highest level of the MedDRA hierarchy. It is identified by the anatomical or physiological system, etiology, or purpose. Within each SOC, AEs are listed and accompanied by a description of severity (Grade). The CTCAE displays Grades 1 through 5 with unique clinical descriptions of the severity of each AE based on the general guidelines for reporting as such:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate Instrumental Activities of Daily Living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.).
- Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE.

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

Eligibility

Inclusion and exclusion criteria

Patients are eligible to be included in the study only if they fulfil ALL the following criteria:

1. RT-PCR or antigen test **confirmed COVID-19** cases
2. Aged **50 years and above**, with at least **one co-morbidity***
3. Within the first **7 days of illness (from symptom onset)**
4. Mild to moderate clinical severity (or stage 2 to 3 disease)

***Co-morbidities:**
Diabetes mellitus, hypertension, chronic kidney disease, chronic cardiac disease, chronic pulmonary disease, chronic liver disease, cerebral vascular disease, chronic neurological disorder, obesity (BMI ≥30kg/m2), dyslipidaemia, autoimmune disease, HIV, thyroid disease, malignancy, immunosuppressive therapy, and active smoker.

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 following Disease Staging from COVID-19 Management Guideline in Malaysia (9) in **Table 1** below. Stages 2 and 3 were classified as a mild and moderate diseases (WHO clinical progression scale 2-4) (10), while stages 4 and 5 were classified as severe diseases (WHO clinical progression scale 5-9) (10).

Table 1. Clinical Severity in relation to Disease Staging from COVID-19 Management Guideline in Malaysia.

Clinical Severity	Disease Staging	Description
Asymptomatic	1	Asymptomatic
Mild	2	Symptomatic, No pneumonia
Moderate	3	Symptomatic, Pneumonia
Severe	4	Symptomatic, Pneumonia, Requiring supplemental oxygen
Severe	5	Critically ill

Exclusion Criteria

1) Asymptomatic stage 1 patient.
2) Patients with SpO_2 less than 95% at rest. (Unless it is an expected baseline SpO_2 due to pre-existing disease, e.g. COAD or pulmonary fibrosis).
3) Patients who need oxygen supplements.
4) Patients with concomitant bacterial, fungal, parasitic, or other viral infections before enrolment.
5) Patients with severe hepatic impairment (>Grade 3: ALT >10 times of upper normal limit).
6) Malabsorption syndrome or other clinically significant gastrointestinal diseases that may affect the absorption of the study drug (non-correctable vomiting, diarrhoea, ulcerative colitis, and others).
7) Pregnant or nursing women.
8) Female patients of reproductive age who cannot consent to contraceptive use of oral contraceptives, mechanical contraceptives such as intrauterine devices or barrier devices (pessaries, condoms), or a combination of these devices from the start of ivermectin administration to 7 days after the end of ivermectin administration.
9) Male patient who has a female partner of reproductive age and he cannot agree to use contraception from the start of ivermectin treatment till 7 days after treatment.
10) Patients receiving chemotherapy.
11) Patients who received interferon or drugs with reported antiviral activity against COVID-19 (favipiravir, hydroxychloroquine sulphate, chloroquine phosphate, lopinavir-ritonavir combination, remdesivir) in the past 7 days before enrolment.
12) Patients in whom this episode of infection is a recurrence or reinfection of COVID19.
13) Patients who have previously received ivermectin.

14) Patient receiving warfarin, or any medications known to interact with ivermectin.
15) Acute medical or surgical emergency (e.g., DKA/MI/stroke).
16) Other patients are judged ineligible by the principal investigator or sub-investigator.

Intervention and Control arm

- **Treatment group**: Ivermectin 0.4mg/kg/day for 5 days + standard-of-care
- **Control group**: Standard-of-care only.

- The ivermectin dosage for each patient in the intervention arm was calculated to the nearest 6-mg or 12-mg whole tablets. Details can be found in **Supplement 1** in the Supplemental Content of the paper.
- 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.

Study Schedules and Procedures

Timing of implementation / Item	Study period (Day 1 to maximum Day 28 of enrolment in hospital)			
	Day 1 (Enrollment before treatment initiation) (CRF 1)	Day 5 (Follow-up) (CRF 2)	Day of discharge* or in-hospital death (CRF 3)	Day of study event (clinical deterioration) (CRF 4)
Informed consent	●			
Patient characteristics ▪ *Patient's clinical history* ▪ *Anthropometric measurements*	●			
Clinical findings	● (a)	● (c)	●	● (c)
Clinical laboratory tests ▪ *CRP, full blood count, kidney and liver profiles, C-reactive protein levels*	● (a)	● (c)		● (c)
Chest X-Ray ▪ *Chest radiography*	●	●		●
Urine pregnancy test (b)	o			
Hospitalization	Mandatory hospitalization for at least the first 5 days of trial enrolment		(d)	
The adverse event assessment period	●	●	●	●

● : Required o : To be performed if necessary

a) Baseline blood tests are acceptable if done within 48 hours before enrolment. A baseline chest x-ray is acceptable if done within 48 hours before and 24 hours after enrolment.
b) A urine pregnancy test is needed for a female who is potentially pregnant.
c) Acceptable if done within 24 hours before and after.
d) Follow discharge criteria based on current national COVID-19 guidelines 17
*Discharge from the hospital or from the study at Day 28 (if still need to be in the hospital)

Screening, Enrolment and Randomization

Randomization was done based on 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**.** 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 enrolment. The randomization list was generated independently using random permuted block sizes 2 to 6. The randomization was not stratified by site. Figure 1 shows the screening, enrolment and randomization allocation followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

The last patient follow-up was completed on October 25, 2021. After randomization, 4 patients were excluded; 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

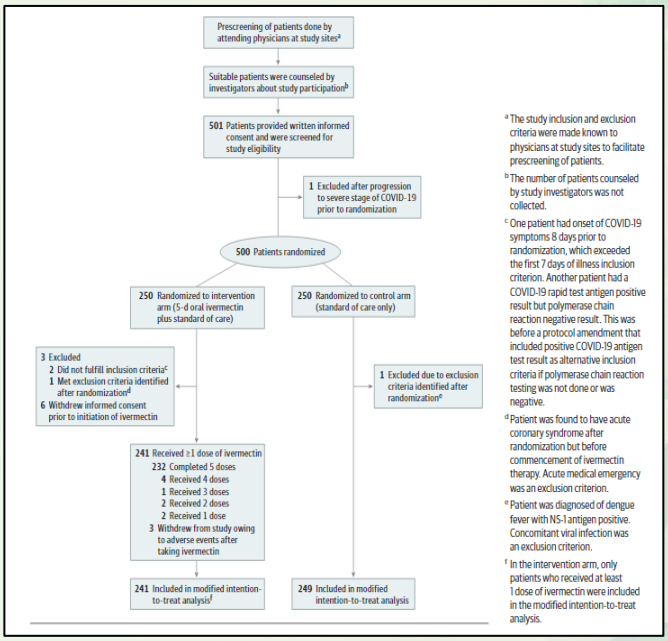

Figure 1. Screening, enrolment, randomization, and treatment assignment

RT-PCR test result, while 1 had acute coronary syndrome before ivermectin initiation. Before the initiation of intervention, 6 patients in the intervention arm withdrew consent.

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 1).

Sample size calculation

Using two proportion formula (Pocock's formula)

$$n = [(p_1 (1-p_1) + p_2 (1-p_2)] \times (Z_\alpha + Z_\beta)^2 / (p_1-p_2)^2$$

$$n = \frac{[0.175(1-0.175) + 0.087(1-0.087)] \times (0.84+0.05)^2}{(0.175-0.087)^2}$$

= 228 per arm

Where:

n = required sample size
α = level of statistical significance
1-β = power of study
$z\alpha$ = value of the standard normal distribution cutting off probability α in one tail for a one – sided alternative or α/2 in each tail for a two sided alternative
$z\beta$ = value of the standard normal distribution cutting off probability β

- Expected 17.5% progression to severe disease in control group
- Clinically important result: reduce by 50% (8.75%)
- To:
  - Correctly identify true effect of Ivermectin with 80% probability.
  - - Avoid false inferring an effect when there is really none with 95% probability ($p<0.05$)

A minimum of **456** subjects was needed for the study. Considering potential dropouts, a total of 500 patients (250 patients for each group) were recruited.

Data analysis

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 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 or Fisher exact test. The primary and categorical secondary outcome measures were estimated using relative risk (RR). The absolute difference in means of time on the progression to severe disease and lengths of hospitalization between the study groups were determined with a 95% CI. A mixed analysis of variance was used to determine whether the changes in 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.

Subgroup Analyses

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

What was the finding?

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 1). Drug compliance analysis showed that 232 patients (96.3%) in the intervention group completed 5 doses of ivermectin.

Table 1 in the original paper shows the Baseline Demographic and Clinical characteristics of Patients in the Primary Analysis Population. The mean (SD) age was 62.5 (8.7%) years. Both groups had a similar number of male and female patients with 130 women (53.9%) and 111 men (46.1%) in the Ivermectin group and 137 women (55.0%) and 112 (45.0%) in the control group., However number of the male and female patients in the same group was imbalanced with a total of 267 women (54.5%) and 223 men (45.5%). All major ethnic groups in Malaysia were well represented in the study population with Malay being the highest 372 (66.30%) in both groups. 254 patients (51.8%) were fully vaccinated with 2 doses of COVID-19 vaccines and the rest of the patients either received 1 dose of vaccine or were not vaccinated.

Most of both groups had hypertension (369 [75.3%]), followed by diabetes mellitus (262 [53.5%]), dyslipidemia (184 [37.6%]), and obesity (117 [23.9%]). There was an imbalanced number of patients in the intervention versus control group for chronic diseases; Kidney with 28 subjects (11.6%) versus 43 subjects (17.3%) and Cardiac with 37 subjects (15.4%) versus 20 subjects (8.0%), active smoker with 13 subjects (5.4%) versus 7 subjects (2.8%), and malignant neoplasm with 5 subjects (2.1%) versus 9 subjects (3.6%). 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 a moderate disease. There were no significant differences in the concomitant medications prescribed for both groups.

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 (Table 2).

Table 2. Outcomes in Primary Analysis Population

Table 2. Outcomes in the Primary Analysis Population

Outcomes[a]	No. (%) Ivermectin	No. (%) Control	Absolute difference (95% CI)	Relative risk (95% CI)	*P* value
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).

Subgroup Analyses

Subgroup analyses for patients with severe diseases were unremarkable (Table 3 in the original paper). Among fully vaccinated patients, 22 (17.7%) in the ivermectin group and 12 (9.2%) in the control group developed the 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 control 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 in the original paper). 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 a 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. Most 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.

How much can we take out from this research/paper?

The I-TECH randomised controlled trial (RCT) is an exemplary effort of the Malaysian clinicians and scientists in responding to the issue of Ivermectin as a treatment option for COVID-19. It was amicably completed and reported. This proves to be a good model of scientific response to clinical problems where necessary collaboration and administrative support garnered efficiently to realise the clinical trial.

Based on the post-publication comments on JAMA website and on a myriad of social media platforms, it is possible that the report could be clearer and more comprehensively reported. Some of the approaches used in the conduct of the trials were not usual and considered to be of advanced techniques such as mixed analysis of variance. Others could be misconstrued and confused for other things without specification such as open-label, superiority approach in the sample size determination, modified intention-to-treat analysis, and posthoc analysis. A sufficient and detailed description of these methods would all be helpful to readers.

There are 2 major issues and a few minor issues to be mindful of when appraising this paper. The first is the open-label RCT by design. This may be argued that the primary outcome of progress to severe disease is hard to be biased by any personal preference for being an objective outcome on maintaining SpO_2 at 95% with supplemental oxygen. However, the decision when this happens could be subjective especially when the SpO_2 was hovering around 95% either with patient effort in breathing with or without encouragement, etc. The point is for a RCT to be clear of this kind of doubt/query of performance and detection biases, it would require a double-blind placebo-controlled trial. Nevertheless, it is to bear in mind also that this 'additional' would increase the cost and complexity of the trial especially in the situation where a relatively urgent answer is needed about the efficacy of Ivermectin for COVID-19. The second is the sample size determination that estimated the treatment effect to be 9% absolute different in the proportion of progress to severe disease, but this primary outcome was observed to be at just 4.3%. Revisiting the sample size determination with this rate different would require about 3000 participants in total presuming this is treatment effect holds to the end. Minor issues include lacking sensitivity analyses to examine the consistency of the results by controlling for some of the variables that were imbalanced at baseline. The writing of the report is infused with the flavour of the investigator's prejudice against the studied drug, and less openness to allow the data to speak and be received by the authors. There are inconsistent patterns of the inefficacy of Ivermectin that can be observed in both the primary and secondary outcomes in both groups, even the types of oxygen required to maintain SpO_2. Unfortunately, the conclusions were too much of unwarranted certainty.

The invaluable lessons from I-TECH study re-emphasise meticulous research planning of no compromised measures (double blind in drug trial where outcome measures could be subjected to personal judgments), a more generous sample size estimation or adopting adaptive design [11] in the situation of real uncertainty, sensitivity analyses as the extra miles in statistical analyses, careful interpretation [12] and complete description of methods and reporting would allow the results to go a longer way.

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