Ivermectin

Section last reviewed and updated 10/10/2022

Last literature search conducted 8/31/2022

Recommendation 1: In hospitalized patients with COVID-19, the IDSA panel suggests against ivermectin. (Conditional recommendation††, Very low certainty of evidence)

Recommendation 2: In ambulatory persons with COVID-19, the IDSA panel recommends against ivermectin. (Strong recommendation, Moderate certainty of evidence)

††*The guideline panel concluded that the undesirable effects outweigh the desirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.*

Why is ivermectin considered for treatment?

Ivermectin is an anti-parasitic agent that is FDA-approved for onchocerciasis and strongyloidiasis and is used off-label for the treatment of many parasitic infections. Although it has *in vitro* activity against some viruses, including SARS-CoV-2, it has no proven therapeutic utility. *In vitro* activity against SARS-CoV-2 [1] requires concentrations considerably higher than those achieved in human plasma and lung tissue to reach the *in vitro* IC_{50} [2]. Ivermectin has been shown to have anti-inflammatory effects in *in vitro* and *in vivo* studies hence hypothesized to have a mechanism beyond its anti-viral effects in the treatment of COVID-19 [3, 4].

Since ivermectin is generally well tolerated, it was empirically evaluated in uncontrolled studies for COVID-19, alone and in combination with other off-label medications.

Summary of the evidence

Our search identified 28 studies in patients with COVID-19 with ages ranging between 8 and 86 years that reported on the outcomes of mortality, symptom resolution, viral clearance, and adverse events, and informed the evidence review for inpatient and outpatient therapy [5-

25]. Eligible studies compared treatment with ivermectin against a placebo or standard of care. Studies comparing ivermectin to a non-placebo, active comparison (i.e., a different agent considered a possible treatment for COVID-19 infection by clinicians) or that did not provide a comparison arm were not included in these analyses. Several studies did not meet eligibility for inclusion in this review. Three trials compared ivermectin to hydroxychloroquine (comparison to treatment with evidence of harm) [26-28]; two trials examined ivermectin as prophylactic treatment [29, 30]; and two trials did not provide study data in a peer-reviewed, published, or pre-print manuscript [28, 31].

The studies that informed the recommendations for hospitalized patients included 15 randomized control trials (RCTs) [5-9, 13-16, 24, 25, 32-35]. Sixteen RCTs [7, 8, 10-12, 17-23, 35-38] informed the recommendation for ambulatory persons. Each of them compared an active treatment arm of ivermectin to an inactive comparison (e.g., standard of care with or without placebo).

The evidence informing the recommendations for treating hospitalized and ambulatory persons with ivermectin reported on the use of a range of doses (100 mcg/kg/day to 400 mcg/kg/day) and durations (one day up to seven days). Among studies reporting on hospitalized patients, substantial heterogeneity was observed, introduced by one study (**Supplementary Figure s9c**) [5]. Ahmed 2020 treated patients with ivermectin for a duration of five days, rather than one day as used by the remaining studies. This may explain the heterogeneity between studies; however, excluding Ahmed 2020, any meaningful reduction in viral clearance was still not demonstrated by the summary estimate (**Supplementary Figure s9d**). Heterogeneity was not observed for other outcomes reported for hospitalized or ambulatory persons.

Among the RCTs, the risk of bias was high in two trials because of unsuccessful randomization into treatment and control groups. Hashim et al (2020) [8] inadequately randomized participants by allocating them to respective treatment arms on odd and even days, as well as assigning all critically ill patients to the ivermectin arm, and Podder et al (2020) [9] allocated participants based on odd or even registration numbers. In addition, across many RCTs, there were concerns due to lack of blinding of study personnel, which may lead to over-

or under-estimates of treatment effects, particularly for subjective outcomes (e.g., symptom resolution, adverse events).

Benefits

Hospitalized

The evidence from RCTs failed to demonstrate a meaningful effect on mortality or need for mechanical ventilation among persons with COVID-19 (risk ratio [RR]: 0.85; 95% confidence interval [CI]: 0.40, 1.84; moderate certainty of evidence [CoE] and RR: 0.45; 95% CI: 0.24, 0.86, low CoE, respectively). Persons receiving treatment with ivermectin rather than no ivermectin failed to demonstrate a beneficial or detrimental effect on symptom resolution or viral clearance at day seven (RR: 1.07; 95% CI: 0.69, 1.65; very low CoE and RR: 1.06; 95% CI: 0.74, 1.52; very low CoE, respectively).

Ambulatory

Treatment with ivermectin does not reduce mortality (RR: 0.86; 95% CI: 0.53, 1.40; high CoE). Treatment with ivermectin may reduce progression to severe disease; however, the evidence failed to demonstrate a beneficial or detrimental effect on symptoms (RR: 0.70; 95% CI: 0.44, 1.11; moderate CoE). Treatment with ivermectin failed to demonstrate a beneficial or detrimental effect on hospitalization or viral clearance at day seven (RR: 0.88; 95% CI: 0.71, 1.11, moderate CoE, and RR: 1.01; 95% CI: 0.78, 1.31; very low CoE, respectively). The evidence is very uncertain due to the inclusion of one study without appropriate randomization, but ivermectin may reduce the time to recovery among ambulatory persons with COVID-19 (mean difference: 2.99 days fewer; 95% CI: 4.76 to 1.22 days fewer; very low CoE). However, the ACTIV-6 trial did not show a reduction in time to recovery with a hazard ratio: 1.09 (0.98, 1.22) [23].

Harms

In doses typically used for the treatment of parasitic infections, ivermectin is well tolerated. We are unable to exclude the potential for serious adverse events in hospitalized patients and ambulatory persons with COVID-19 treated with ivermectin rather than no

ivermectin, (RR: 1.03; 95% CI: 0.32, 3.34; moderate CoE and RR: 0.81; 95% CI: 0.51, 1.30; moderate CoE, respectively).

Other considerations

The panel determined the certainty of evidence of treatment of ivermectin for hospitalized patients to be very low due to concerns with risk of bias (i.e., study limitations) and imprecision. However, the panel's decision for hospitalized patients was indirectly informed by the lack of benefit of ivermectin as seen in studies in ambulatory persons. The panel determined the certainty of evidence of treatment of ivermectin for ambulatory persons to be moderate due to concerns with imprecision. The guideline panel made a conditional recommendation against treatment of COVID-19 with ivermectin outside of the context of a clinical trial for both patients with COVID-19 hospitalized or in the outpatient setting.

Conclusions and research needs for this recommendation

The guideline panel suggests against ivermectin for the treatment of hospitalized patients with COVID-19. The guideline panel recommends against ivermectin for the treatment of outpatients with COVID-19.

Table 1. GRADE evidence profile, Recommendation 1

Question: Ivermectin compared to no ivermectin for patients hospitalized with COVID-19

Last reviewed and updated 10/10/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	no ivermectin	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 14 days to 28 days)												
11 [1-11]	randomized trials	not serious [a]	not serious [b]	not serious	serious [c]	none	66/1033 (6.4%)	53/937 (5.7%)	**RR 0.85** (0.40 to 1.84)	**8 fewer per 1,000** (from 34 fewer to 48 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation (follow-up: 28 days)												
3 [7,8,11]	randomized trials	serious [d]	not serious	not serious	very serious [c]	none	13/594 (2.2%)	28/583 (4.8%)	**RR 0.45** (0.24 to 0.86)	**26 fewer per 1,000** (from 37 fewer to 7 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Symptom resolution (follow-up: 7 days)												
1 [12]	randomized trials	serious [d]	not serious	not serious	very serious [c]	none	16/25 (64.0%)	15/25 (60.0%)	**RR 1.07** (0.69 to 1.65)	**42 more per 1,000** (from 186 fewer to 390 more)	⨁◯◯◯ VERY LOW	CRITICAL
Viral clearance at day 7 (RCT) (follow-up: range 7 days to 29 days)												
6 [4,5,8,10,13,14]	randomized trials	serious [e]	serious [f]	serious [g]	very serious [c]	none	77/202 (38.1%)	55/158 (34.8%)	**RR 1.06** (0.74 to 1.52)	**21 more per 1,000** (from 91 fewer to 181 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (follow-up: 28 days)												
6 [2,4,7,8,9,11]	randomized trials	not serious	not serious	not serious	serious [c]	none	38/734 (5.2%)	52/712 (7.3%)	**RR 1.03** (0.32 to 3.34)	**2 more per 1,000** (from 50 fewer to 171 more)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Hashim 2021 allocated patients based on odd/even days of recruitment.
b. Substantial heterogeneity observed (I2=68%) and introduced by Elshafie 2022 in which mortality events were reported at day 14 instead of 28 days.
c. The 95% CI cannot exclude no meaningful effect. Few events reported do not meet the optimal information size and suggest fragility of the estimate
d. Open label trial may lead to bias with measurement of subjective outcomes.
e. Podder 2020 assigns participants based on odd or even registration numbers, also, 20 patients were excluded following randomization without sensitivity analysis to explore imbalance across treatment arms.
f. Some heterogeneity observed (I2=53%). Possibly explained by the longer duration of treatment (5 days compared to 1 day) in Ahmed 2021.
g. Viral clearance is a surrogate for clinical improvement, such as hospitalization, need for ICU care and mechanical ventilation.

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Table 2. GRADE evidence profile, Recommendation 2

Question: Ivermectin compared to no ivermectin for ambulatory persons for management of COVID-19

Last reviewed and updated 10/10/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivermectin	no ivermectin	Relative (95% CI)	Absolute (95% CI)		
Mortality												
14 [1-14]	randomized trials	not serious [a]	not serious	not serious	not serious	none	29/3580 (0.8%)	37/3393 (1.1%)	**RR 0.86** (0.53 to 1.40)	**2 fewer per 1,000** (from 5 fewer to 4 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Progression to severe disease (assessed with: need for invasive ventilation)												
7 [1,2,4,5,7,8,12]	randomized trials	not serious	not serious	not serious	serious [b]	none	31/1505 (2.1%)	43/1375 (3.1%)	**RR 0.70** (0.44 to 1.11)	**9 fewer per 1,000** (from 18 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalization (follow-up: 28 days)												
7 [8,10-15]	randomized trials	not serious	not serious	not serious	serious [c]	none	134/2714 (4.9%)	141/2517 (5.6%)	**RR 0.88** (0.71 to 1.11)	**7 fewer per 1,000** (from 16 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Viral clearance at day 7 (RCT) (follow-up: range 6 days to 29 days)												
6 [2-4,8,13,15]	randomized trials	not serious	not serious	serious [d,e]	very serious [c]	none	178/574 (31.0%)	193/281 (68.7%)	**RR 1.01** (0.78 to 1.31)	**7 more per 1,000** (from 151 fewer to 213 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Time to recovery (assessed with: days)												
4 [1,5,6,12]	randomized trials	very serious [a,f]	serious [g]	not serious [h]	not serious	none	709	576	-	MD **2.99 days fewer** (4.76 fewer to 1.22 fewer)[i]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (respiratory failure, sepsis, multiorgan failure, etc.)												

7 [2,3,5,8,10,11,16]	randomized trials	not serious	not serious	not serious	serious [j]	none	31/1973 (1.6%)	40/1933 (2.1%)	**RR 0.81** (0.51 to 1.30)	**4 fewer per 1,000** (from 10 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Concerns with unmeasured and residual confounding. Hashim 2021 allocated patients based on odd/even days of recruitment.
b. The 95% CI cannot exclude no benefit from treatment.
c. The 95% CI includes the potential for both appreciable benefit as well as the potential for harm. Few events reported do not meet the optimal information size and suggest fragility of the estimate
d. Viral clearance is a surrogate for clinical improvement, such as hospitalization, need for ICU care and mechanical ventilation.
e. Ravikirti 2021 reported viral clearance at day 6.
f. Open label trial may lead to bias with measurement of subjective outcomes.
g. High heterogeneity I2=90% introduced by Hashim 2021.
h. Ivermectin was combined with doxycycline.
i. The binary endpoint of time to recovery from the ACTIV-6 trial could not be combined with pooled continuous analysis of days to recovery; however, did not show a reduction with a HR: 1.09 (0.98, 1.22).
j. The 95% CI cannot exclude the potential of increased SAEs in the treatment arm. Few events suggest fragility in the estimate.

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Supplementary Materials

Ivermectin

Table s1. Should ambulatory or hospitalized patients with COVID-19 receive ivermectin vs. no ivermectin?

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Abbas/ 2022 [1]	China/ China University of Medical Sciences hospitals	RCT	202 (99/103)	42	Mean: Intervention: 38.33 (6.84) Control: 37.33 (5.84)	Patients age 18-50 years old with COVID-19	Ivermectin 300 mcg/kg/day divided into 2 doses by mouth for 5 days	Placebo	None	All-cause mortality Time to complete symptom resolution Deterioration of WHO clinical status scale by 2 or more points Development of fever Escalation of care Adverse events	Unspecified
Abd-Elsalam/ 2021 [2]	Egypt/ 2 hospitals	RCT	164 (82/82)	50	Intervention: Mean of 42.4 (16)	Hospitalized mild-moderate disease (no definition given)	Ivermectin 12 mg by mouth every day for 3 days and SoC	SoC	Paracetamol, oseltamivir, hydrocortisone	Mortality at one month Length of hospital stay	None

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
					Control: Mean of 39.4 (16.9)					Progression to mechanical ventilation Safety	
ACTIV-6/ 2022 [3]	USA	RCT	1591 (817/774)	58.6	Median: 47.0 (39.0-56.0)	Patients ≥30 years old with confirmed SARS-CoV-2 infection within 10 days, and experiencing ≥2 symptoms of acute COVID-19 for ≤7 days from enrollment	Ivermectin 400 µg/kg for 3 days	Placebo	N/A	Time to sustained recovery Hospitalization pr death by day 28 COVID clinical progression scale on days 7, 14 and 28 Mortality Hospitalization, urgent care, or emergency department visit Adverse events	National Center for Advancing Translational Sciences
Ahmed/ 2020 [4]	Bangladesh	RCT	68: ivermectin alone vs. ivermectin plus doxycycline	54	Mean: 42	Hospitalized with a fever, cough, or sore throat	Ivermectin alone (12mg once daily for 5 days) Ivermectin plus doxycycline combination	Placebo	N/A	Length of hospitalization Incidence of hypoxia	Beximco Pharmaceutical Limited

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
			vs. placebo (22/23/23)				therapy (12mg ivermectin single dose plus doxycycline 200mg once, followed by 100mg twice daily for 4 days)			Time to virologic clearance Biomarker levels Adverse events	
Angkasekwinai/ 2022 [5]	Thailand/ Siriraj Hospital	RCT	1000 (500/500)	57.4	Mean (SD): 38.4 (12.1)	Suspected of having SARS-CoV-2 infection because of respiratory tract symptoms or because had a history of contact with a confirmed COVID-19 patient (also had documented positive or negative test for SARS-CoV-2 (RT-PCR) from a nasopharyngeal swab sample taken on the enrollment day)	Ivermectin 400-600 µg/kg/day	Placebo	None	Proportion of patients with positive RT-PCR within 14 days after enrollment among those with negative RT-PCR result at enrollment Proportion of patients with oxygen desaturation (oxygen saturation <96% or decreased from baseline ≥3% after exertion) Changes in the WHO 10-point clinical progression	Siriraj Foundation, Faculty of Medicine Siriaj Hospital, Mahidol University

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										score on Day 3, Day 7, and Day 14 Absence of all symptoms at Day 3, Day 7, and Day 14 Hospitalization within 14 days 28-day mortality Adverse effects	
Beltran Gonzalez/ 2021 [6]	Mexico/ Hospital Centenario Miguel Hidalgo	RCT	106 (33 hydroxychloroquine/ 36 ivermectin/ 37 placebo)	37.8	Mean: 53.8 (16.9)	COVID-19 pneumonia requiring hospitalization and recently established hypoxemic respiratory failure or acute worsening of pre-existing lung or heart disease, but not requiring mechanical ventilation	Ivermectin 12 mg (<80 kg) or 18 mg (>80 kg) by mouth once Hydroxychloroquine 400 mg by mouth every 12 hours on day 1, followed by 200 mg every 12 hours for 4 days Both groups in addition to SoC	SoC	Dexamethasone, pharmacologic thromboprophylaxis	In-hospital mortality Length of hospital stay Discharge without respiratory deterioration or death Time to respiratory deterioration or death	Aguascalientes State Health Institute

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Biber/ 2021 [7]	Israel/ hotels in 3 cities designated as isolation areas	RCT	89 (47/42)	21.6	Median: 35 (20-71)	Mild-moderate disease (non-hospitalized and not requiring oxygen)	Ivermectin 12 mg (40-69 kg) or 15 mg (≥ 70 kg) by mouth every day for 3 days	Placebo	None	Proportion with viral clearance at day 6 Culture viability days 2-6 Safety	None
Bramante/ 2022 [8]	United States/ 6 institutions	RCT	1431 (1431 metformin analysis/880 ivermectin analysis/721 fluvoxamine analysis)	56.0	Median: 46 (37-55)	SARS-CoV-2 infection within the past 3 days; and an onset of symptoms within 7 days before randomization	Ivermectin 390-470 µg/kg per day for 3 days Immediate release metformin with increase in dose over 6 days to 1500 mg/d for 14 days Fluvoxamine 50 mg BID for 14 days	Placebo	None	Severe COVID-19 through 14 days (composite of hypoxemia, emergency department visit, hospitalization, or death) Daily symptom severity Total symptom score Drug discontinuations	Parsemus Foundation Rainwater Charitable Foundation Fast Grants UnitedHealth Group Foundation
Bukhari/ 2021 [9]	Pakistan / Combined Military	RCT	86 (41/45)	15.1	Mean age: Intervention: 42.2 ± 12.0	Mild-moderate disease. Mild disease defined as clinical symptoms ,excluding dyspnea or	Ivermectin 12mg once plus standard of care	(1) SoC	Standard of care, which consisted of Vitamin C 500mg daily, Vitamin D3 50,000 units	Negative PCR test by day 3, 7 and 14 Adverse reactions	None

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
	Hospital Lahore				Comparator: 39.0 ± 12.6	gasping, with no imaging findings of pneumonia. Moderate disease defined as fever, respiratory symptoms, and imaging findings of pneumonia.			weekly, and paracetamol 500mg as needed.		
Buonfrate/ 2022 [10]	Italy/ 4 outpatient centers	RCT	87 (30 high-dose/28 low-dose/29 placebo)	41.9	Median: 47 (31-58)	Adult outpatients with newly diagnosed SARS-CoV-2 infection by RT-PCR not requiring supplemental oxygen or hospitalization	Ivermectin 1200 mcg/kg/day for 5 days OR Ivermectin 600 mcg/kg/day for 5 days	Placebo	Unspecified therapies related to COVID-19 treatment (61.3% overall)	Change in viral load at day 7 Severe adverse drug reactions Trend in quantitative viral load Proportion of patients with virologic clearance day 14 and 30 Hospitalizations COVID-19 severity score day 14 and 30	Italian Ministry of Health

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Chaccour/ 2021 [11]	Spain/ Clínica Universidad de Navarra	RCT	24 (12/12)	50%	Median (IQR) Ivermectin: 26 years (19-36) Placebo: 26 years (21-44)	RT-PCR positive for SARS-CoV-2 and non-severe symptoms compatible with COVID-19 and symptom onset <72 hours	Ivermectin 400 mcg/kg x one dose	Placebo (not matched)	Symptomatic treatments	Mortality Viral clearance at day 7 Progression to severe disease Viral load at days 4, 7, 14, and 21 Symptom resolution at days 4, 7, 14, and 21 Seroconversion day 21	ISGlobal and University of Navarra
Chachar / 2020 [12]	Pakistan /Fatima Memorial Hospital	RCT	50 (25/25)	38%	Mean: 41.84 (15.7)	Outpatients with positive RT-PCR	Ivermectin 12mg every 12 hours x 3 doses total	No ivermectin	Symptomatic treatment	Symptom improvement at day 7 Rate of heartburn	N/A
Elshafie 2022 [13]	Egypt	RCT	303 (104 ivermectin/87 HCQ/102 placebo)	47.5	Mean (SD): Patients receiving ivermectin: 59.84 (16.3)	Hospitalized moderate to severe COVID-19 patients	Ivermectin orally 36 mg dose on day 1, 3, 6	Placebo HCQ orally 400 mg loading dose on day 1, followed by a 200 mg	All patients who required supplemental oxygen received steroids in the form of dexamethas	Recovery (hospital discharge or improvement in clinical condition by 2 WHO ordinal scales)	None

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
					Patients receiving HCQ: 61.13 (18.8) Patients receiving placebo: 59.06 (16.7)			maintenance dose on day 2 until day 5	one 6 mg IV for 10 days or solumedrol 1– 2 mg/kg/day IV infusion in severe cases complicated with adult respiratory distress syndrome Antibiotics were given to cases clinically diagnosed with secondary bacterial infection based on radiological and laboratory findings Enoxaparin with prophylactic dose was	Mortality Adverse events	

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
									used in all patients unless there were indications for therapeutic dose		
George/ 2022 [14]	India/Christian Medical College	RCT	112 (38 ivermectin 12 mg/35 ivermectin 24 mg/39 SoC)	29	Median (range): Patients receiving ivermectin 12 mg: 38.5 (6-70) Patients receiving ivermectin 24 mg: 42.3 (4-73) Standard of care: 43.2 (3-77)	Patients with hematological disorders with positive rRT-PCR for SARS CoV-2 (asymptomatic, mild, or moderate COVID-19 illness as per the interim WHO definitions in May 2020)	Ivermectin 12mg x one dose Ivermectin 24 mg x one dose	SoC	None	Proportion of patients negative for SARS-CoV-2 RNA by rRT-PCR on day 7 post-treatment Viral load on days 3, 5 and 7 post treatment Proportion of patients with symptom progression as judged by the WHO ordinal scale Incidence of adverse events attributable to ivermectin	COVID grant from the Science and Engineering Board [SERB], Department of Science and Technology, Government of India

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										All-cause mortality at discharge from COVID ward	
Hashim/ 2020 [15]	Iraq/ Alkarkh and Alforat hospitals	RCT	140 (70/70)	48	Range: Total population: 16-86 Mean (SD): Patients receiving ivermectin/doxy: 50.1 (9.3) Patients not receiving ivermectin: 47.2 (7.8)	Mild, moderate, severe, or critical disease defined according to WHO guidelines	Ivermectin 200 mcg/kg daily for 2 days, with a possible 3rd dose 7 days after the first dose based on clinical improvement, plus doxycycline 100mg twice daily for 5-10 days, based on clinical improvement	(1) SoC	Standard of care, according to clinical status of the patients, which could include: acetaminophen as needed, Vitamin C, zinc, Vitamin D3, azithromycin, dexamethasone, oxygen therapy/mechanical ventilation if needed	Mortality Disease progression after 3 days Time to recovery	Baghdad-Alkarkh General Directorate of Health
Krolewiecki/ 2021 [16]	Argentina/ 4 hospitals	RCT	45 (30/15)	44	Intervention: Mean of 38.1 (11.7)	Hospitalized but not receiving intensive care	Ivermectin 600 mcg/kg by mouth every day for 5 days	SoC	None	Proportion with viral clearance at day 5	Grant from Agencia Nacional de Promoción de la Investigació

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
					Control: Mean of 42.3 (12.8)					Clinical evolution at day 7 and 30 Safety	n, Argentina
Lim/ 2022 [17]	Malaysia (20 hospitals, 1 quarantine center)	RCT	490 (241/249)	54.5	Mean: 62.5 (8.7)	Mild-moderate disease (at least 1 symptom but not on supplemental oxygen) within 7 days of laboratory-confirmed SARS-CoV-2 infection, considered high risk for progression (≥ 50 years old with ≥ 1 comorbidity)	Ivermectin 0.4 mg/kg/day for 5 days plus standard of care	Standard of care	Therapies considered standard of care per Malaysia guidelines (steroids, tocilizumab, convalescent plasma, anticoagulants)	28-day in-hospital all-cause mortality Proportion of patients progressing to severe COVID-19 Time of progression to severe disease Mechanical ventilation rate ICU admissions Length of hospitalization Adverse events	Institute for Clinical Research, Ministry of Health Malaysia
López-Medina/ 2021 [18]	Columbia/ Centro de Estudios en Infectol	RCT	398 (200/198)	58	Median (IQR): 37 (29-48)	Mild disease (Home or hospitalized but not receiving high-flow nasal oxygen or mechanical	Ivermectin 300 µg/kg/day for 5 days	Placebo	N/A	Mortality Time to symptom resolution	Grant from Centro de Estudios en Infectología Pediátrica

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
	ogía Pedíatrica					ventilation) within 5 days of illness onset				Clinical deterioration Hospitalization Oxygen supplementation Adverse events	
Mahmud/ 2021 [19]	Bangladesh/ Dhaka Medical College	RCT	400 (200/200)	41	Mean: 40	Mild-moderate disease (patients excluded if: >30 breaths/min, <90% SpO2 or requiring supplemental oxygenation, admitted to intensive care)	Ivermectin 12 mg by mouth every day for 5 days and doxycycline 100mg twice a day for 5 days in addition to SoC	SoC	Antihistamines, paracetamol, vitamins, low molecular weight heparin, remdesivir, "other antiviral drugs"	Mortality Disease progression Time to clinical recovery Proportion with positive test on day 14 Safety	None
Manomaipiboon / 2022 [20]	Thailand/ Vajira Hospital	RCT	72 (36/36)	62.5	Mean age: 48.57 (14.8)	Patients age 18-80 years with mild (cough, runny nose, anosmia, fever, or diarrhea, without dyspnea or tachycardia) or moderate (pneumonia	Ivermectin 12mg by mouth once daily for 5 days plus standard of care	SoC	Favipiravir, andrographolide, cetirizine	All-cause mortality Viral clearance on day 7 and 14 Length of hospitalization	Grant from Navamindradhiraj University

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						with oxygen saturation > 90%) COVID-19				Frequency of clinical worsening Mechanical ventilation Adverse events	
Mirahmadizadeh/ 2022 [21]	Iran/ 14 specialized COVID-19 outpatient treatment centres	RCT	393 (131 single dose ivermectin/131 double dose ivermectin/131 placebo)	45.8	Median (IQR): Single dose: 39.5 (16.5) Double dose: 39 (17) Placebo: 39.5 (17.5)	Mild symptomatic COVID- 19 confirmed by RT-PCR test, had symptom onset-to-visit interval of less than 48 h, were aged 18–80 years and had oxygen saturation levels of at least 93% in room air	Single dose ivermectin: 3 mg tablet x 4 tablets + placebo tablets x 4, at the second day Double dose ivermectin: 3 mg tablet x 4 tablets x 2 days	Placebo	None	Proportion of subjects who required hospitalization up to 28 days follow-up Proportion of subjects with resolution of symptoms, required machine ventilation or deceased, as well as time to resolution of symptoms Trend of change in severity scale Adverse events	Shiraz University of Medical Sciences

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Mohan/ 2021 [22]	India/ All India Institute of Medical Sciences	RCT	Ivermectin 24mg vs 12mg vs placebo: mITT population (40/40/45)	11.2	Mean: 35.3 (10.4)	Non-severe COVID-19 (SpO2 on room air > 90%, no hypotension, no mechanical ventilation)	Ivermectin elixir at a dose of 12mg or 24mg once	Placebo	Hospital standard protocol, which included some patients receiving hydroxychloroquine, favipiravir, remdesivir, dexamethasone, dalteparin, antibiotics	Reduction in viral load Conversion to negative PCR by day 5 Time to clinical resolution Clinical status on day 14 on WHO ordinal scale Hospital-free days on day 28 Adverse effects	Research grant from Department of Science and Technology, Government of India
Podder/ 2020 [23]	Bangladesh/ Debidwar Upazila Health Complex	RCT	62 (32/30)	29%	Mean (SD) Total enrolled population: 39.16 (12.07) Ivermectin: 38.41 (11.02) Control: 39.97 (13.24)	Positive RT-PCR with mild (no evidence of pneumonia and SpO_2 >93% on RA) to moderate COVID-19 (signs of pneumonia with SpO_2 >90%)	Ivermectin 200 mcg/kg on day 1	SOC	Symptomatic treatment with doxycycline 100 mg every 12 hours for 7 days	Viral clearance at day 10 Duration of symptoms Time to resolution of symptoms	None

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Ravikirti / 2021 [24]	India/ All India Institute of Medical Sciences	RCT	112 (55/57)	27.7	Mean age: 52.5 ± 14.7	Mild-moderate disease. Mild defined as having no evidence of breathlessness or hypoxia. Moderate defined as breathlessness and/or hypoxia (90-95% SpO_2 on room air), respiratory rate >23, no features of severe disease.	Ivermectin 12mg daily for 2 days	Placebo	Hydroxychloroquine, corticosteroids, enoxaparin, antibiotics, remdesivir, convalescent plasma, tocilizumab	In-hospital mortality PCR positivity rate at day 6 Symptom resolution Discharge by day 10 Admission for ICU Mechanical ventilation	All India Institute of Medical Sciences
Reis/ 2022 [25]	Brazil/ 12 public health clinics	RCT	1358 (679/679)	58.2	Median: 49 (38-57)	Adult outpatients not requiring hospitalization with laboratory-confirmed SARS- CoV-2 infection within 7 days with ≥1 risk factor for progression	Ivermectin 400 mcg/kg/day for 3 days plus standard of care	Standard of care	None specified	All-cause mortality Hospitalization or ED visit by day 28 due to COVID-19 SARS-CoV-2 viral clearance Length of hospitalization	FastGrants Rainwater Charitable Foundation

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Mechanical ventilation Health-related quality of life Adverse reactions	
Rezai/ 2022 [26]	Iran/ 6 trial sites	RCT	891 (447/444)	35.7	Mean (SD): 53.79 (15.3)	Patients with positive diagnostic by RT-PCR assay for SARS-CoV-2 using a nasopharyngeal swab ≤ 4 days prior to screening or positive rapid COVID-19 test, without evidence of viral pneumonia or hypoxia	Ivermectin 0.4 mg/kg x 3 days	Placebo	None	Time to resolution of symptoms Time to recovery including complete recovery and relative recovery Progression (needing hospitalization) Negative RT-PCR result at 5 days ICU admission Drug-induced adverse events Death	

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Vallejos/ 2021 [27]	Argentina	RCT	501 (250/251)	47	Intervention: Mean of 42.6 (15.3) Control: Mean of 42.4 (15.8)	RT-PCR positive and non-hospitalized and not requiring home oxygen	Ivermectin weight-based dosing at 12 mg, 18 mg, or 24 mg every day for 2 days, plus SoC	SoC	Supplements including zinc and vitamin c	Mortality All-cause hospitalization Mechanical ventilation Proportion with viral clearance at day 12 Adverse events	None

Figure s1a. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among hospitalized patients (from RCTs)

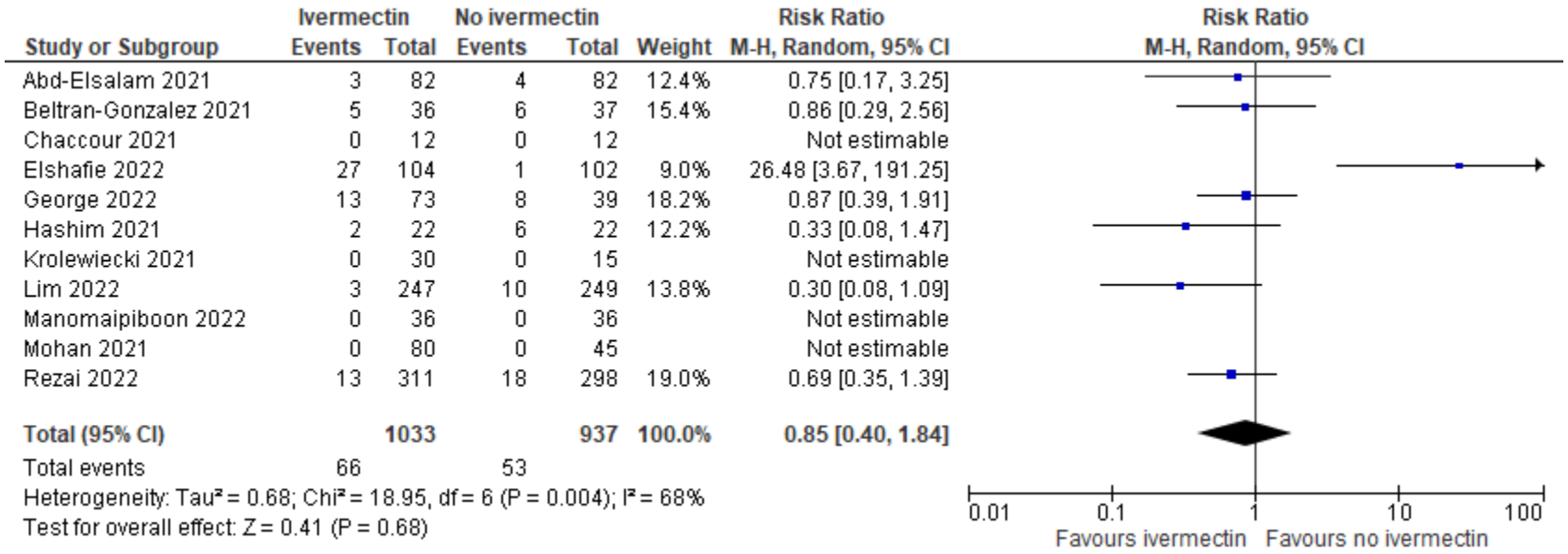

Figure s1b. Forest plot for the outcome of need for mechanical ventilation for ivermectin vs. no ivermectin among hospitalized patients

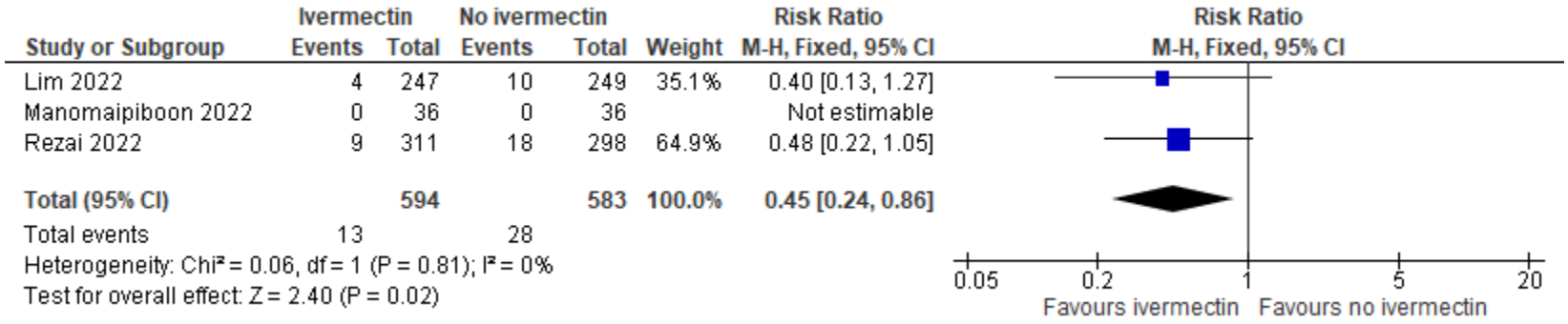

Figure s1c. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (all studies)

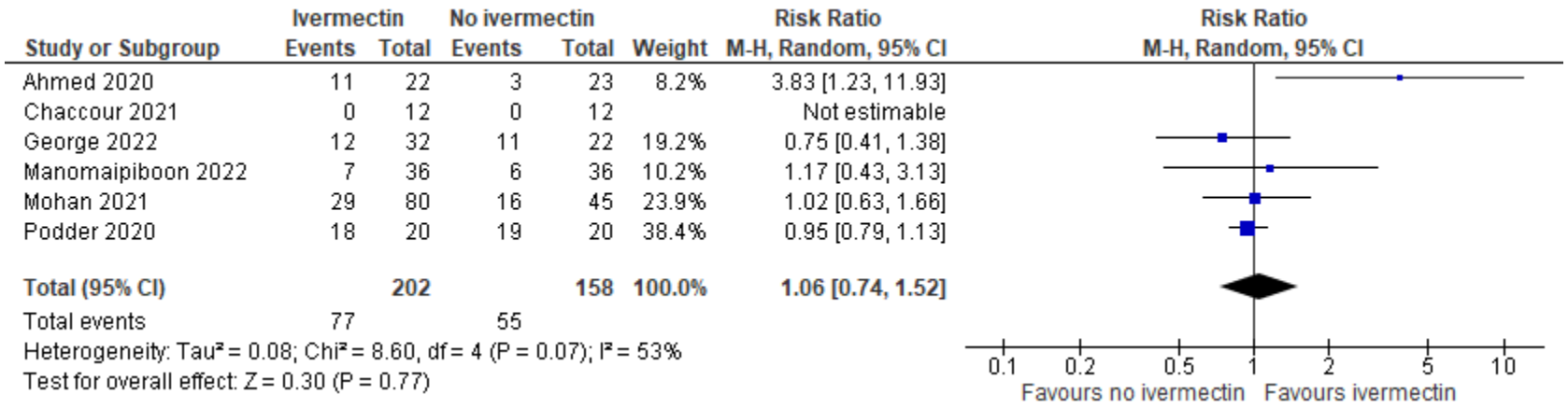

Figure s1d. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among hospitalized patients (without Ahmed 2020)

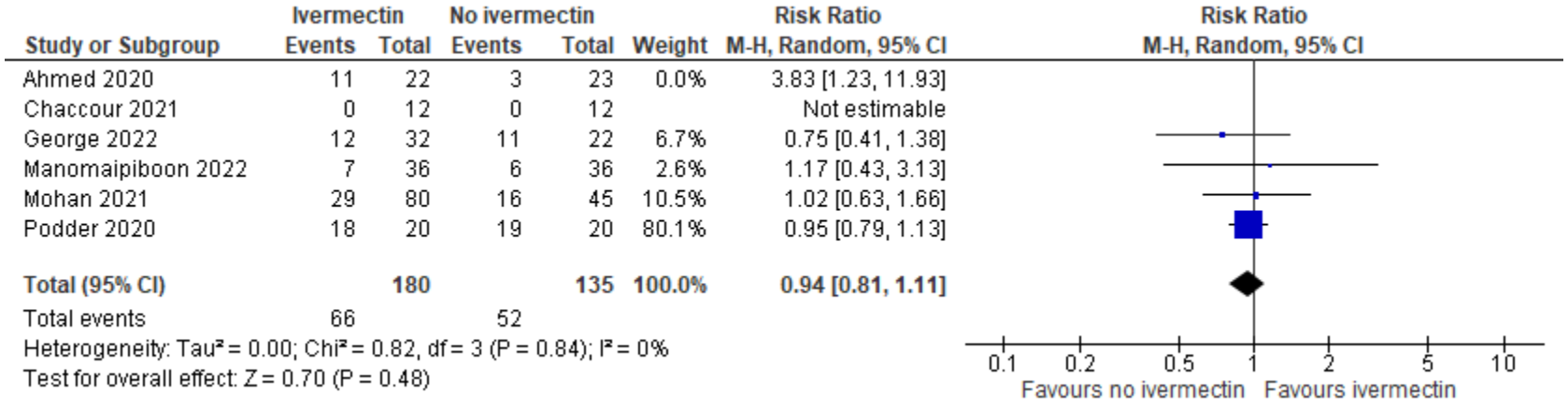

Figure s1e. Forest plot for the outcome of serious adverse events for ivermectin vs. no ivermectin among hospitalized patients

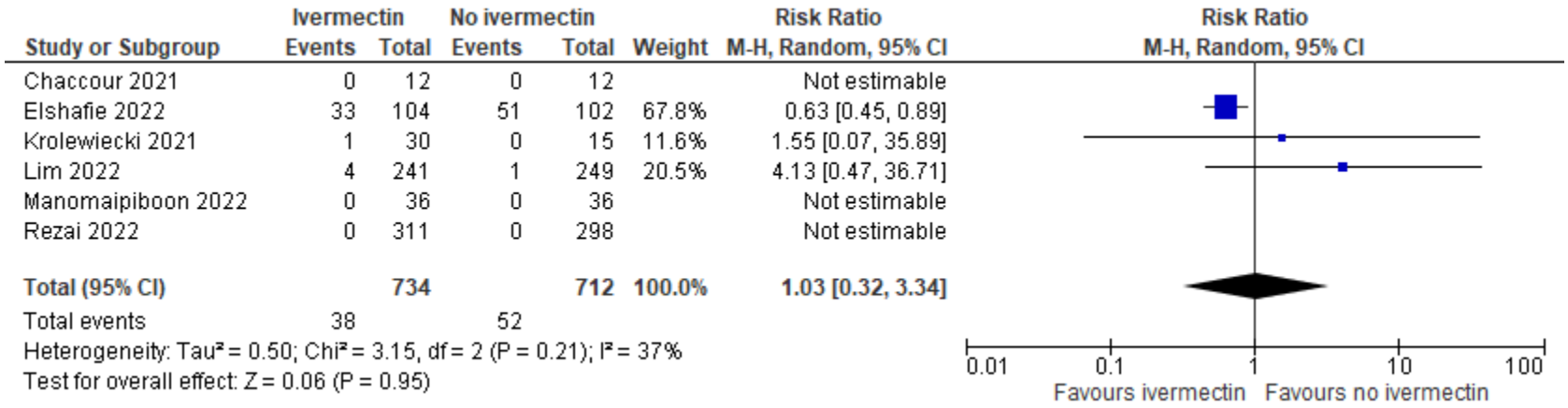

Figure s1f. Forest plot for the outcome of mortality for ivermectin vs. no ivermectin among ambulatory patients

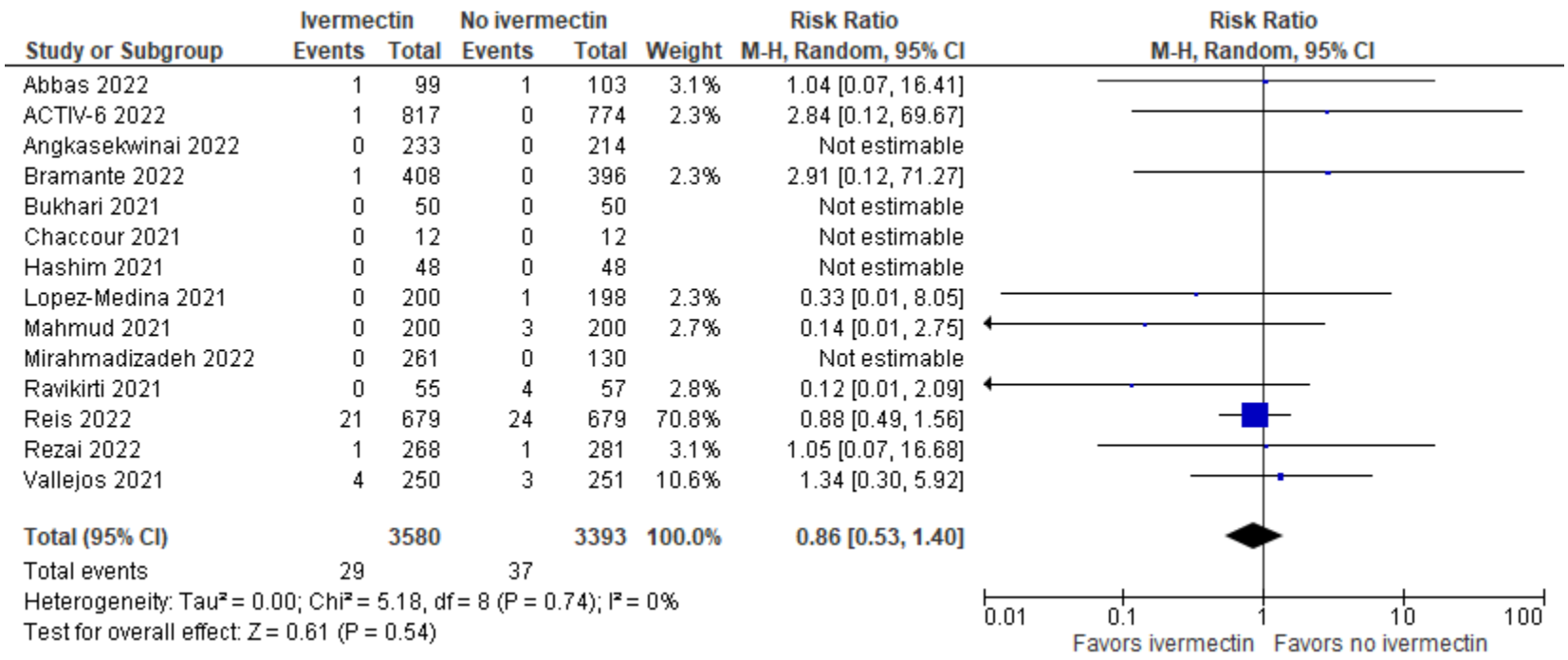

Figure s1g. Forest plot for the outcome of progression to severe disease for ivermectin vs. no ivermectin among ambulatory patients

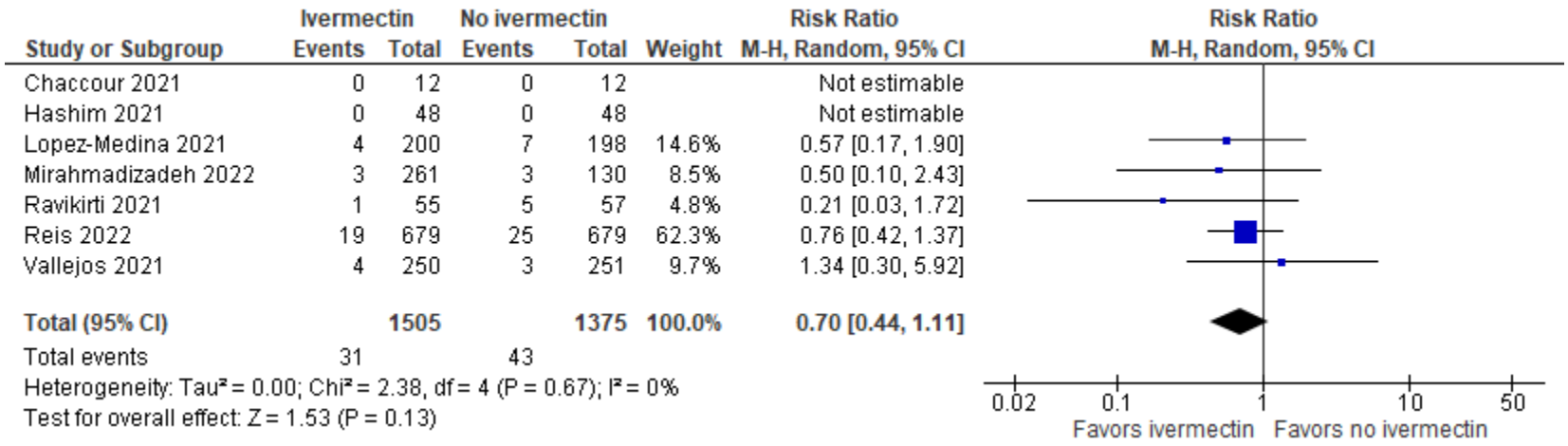

Figure s1h. Forest plot for the outcome of viral clearance at seven days for ivermectin vs. no ivermectin among ambulatory patients

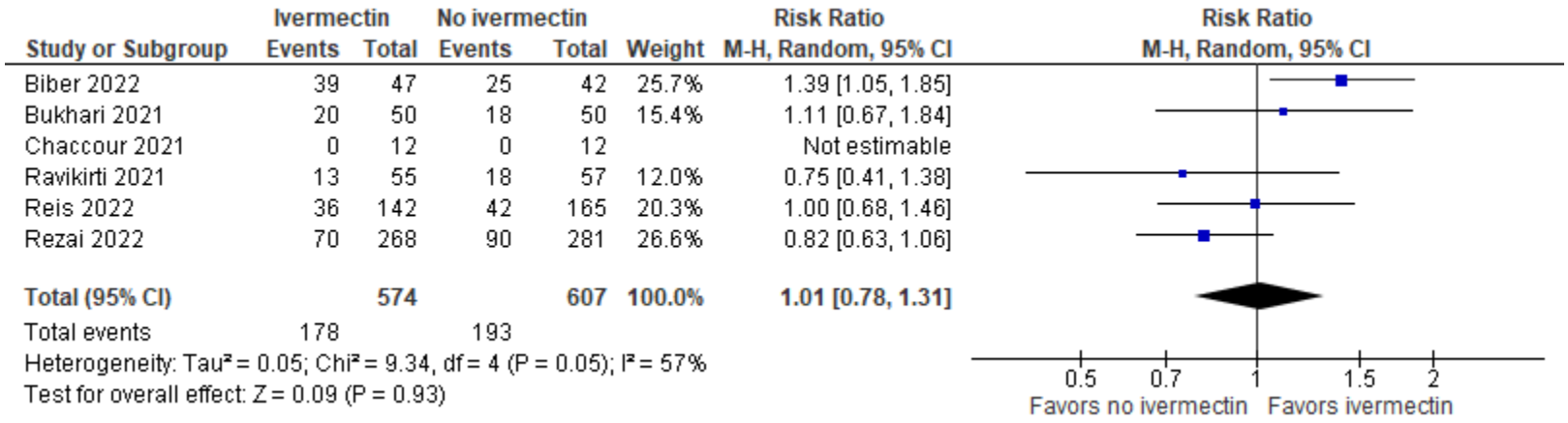

Figure s1i. Forest plot for the outcome of time to recovery for ivermectin vs. no ivermectin among ambulatory patients

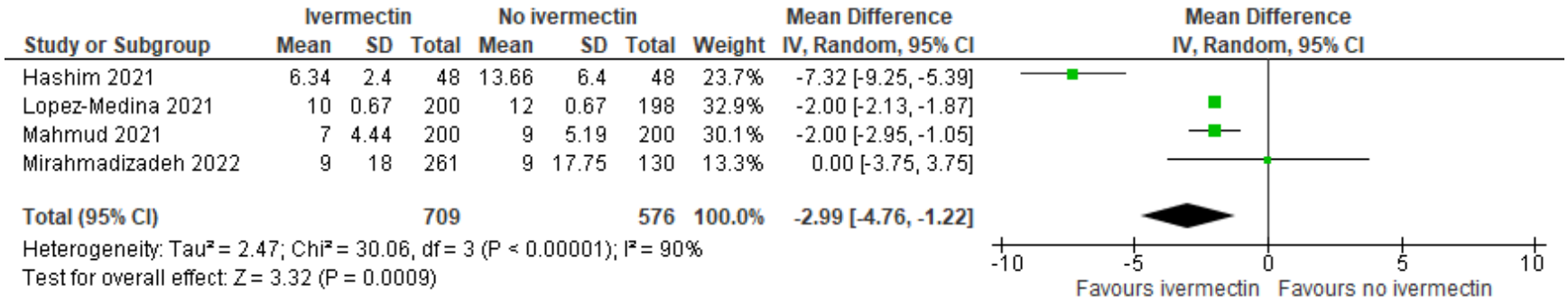

Figure s1j. Forest plot for the outcome of hospitalization for ivermectin vs. no ivermectin among ambulatory patients

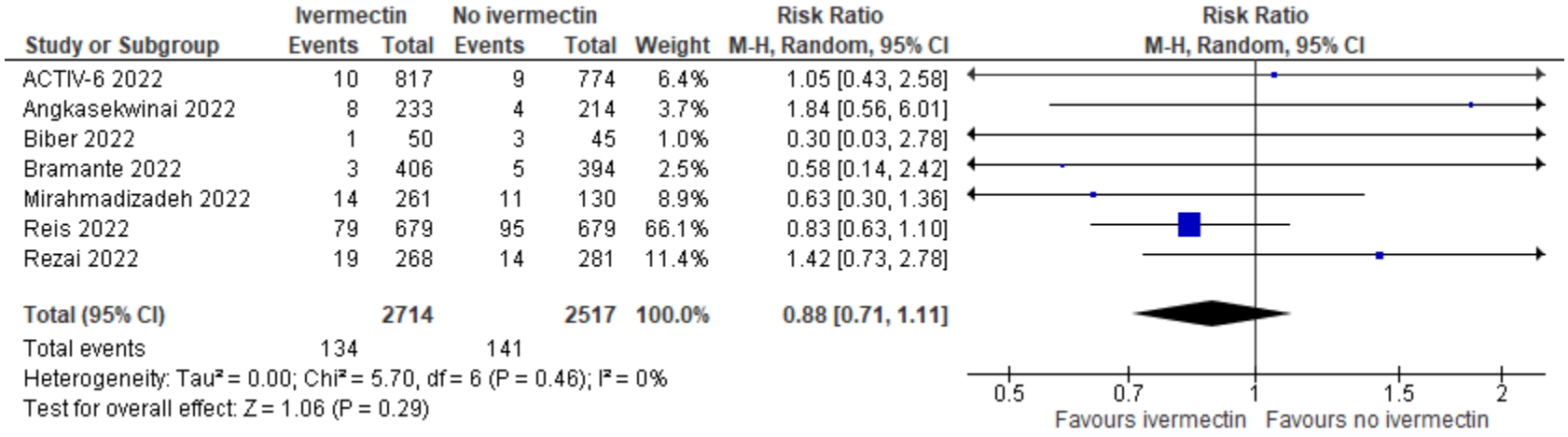

Figure s1k. Forest plot for the outcome of serious adverse events for ivermectin vs. no ivermectin among ambulatory patients

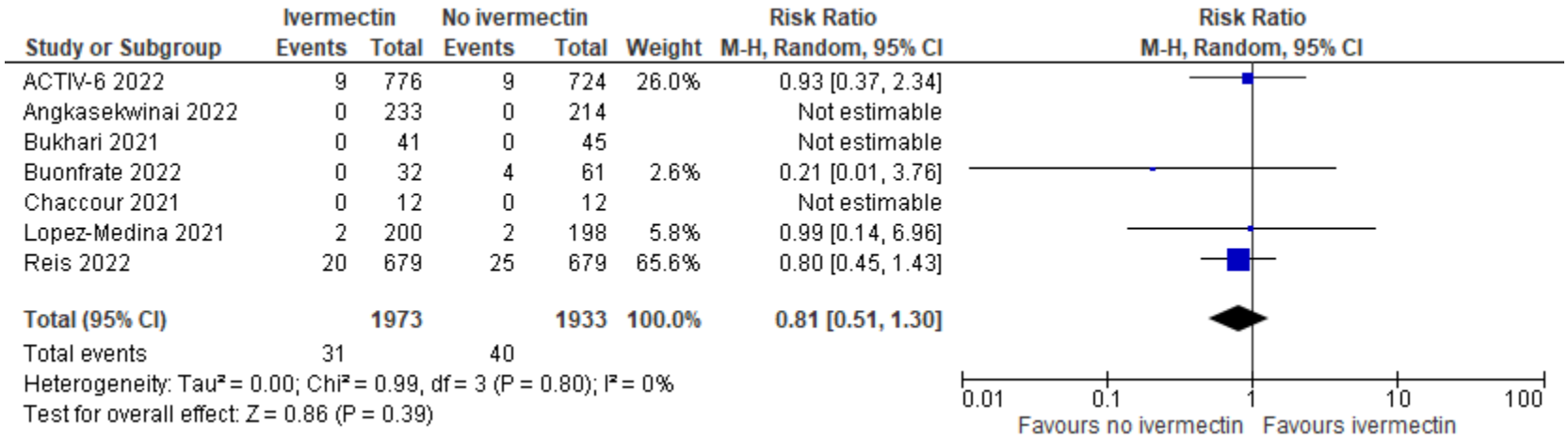

Table s2. Risk of bias for randomized controlled studies (ivermectin vs. no ivermectin)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Abbas 2022 [1]							
Abd-Elsalam 2021 [2]							
ACTIV-6 2022 [3]							
Ahmed 2020 [4]							
Angkasekwinai 2022 [5]							
Beltran Gonzalez 2022 [6]							
Biber 2021 [7]							
Bramante 2022 [8]							
Bukhari 2021 [9]							
Buonfrate 2022 [10]							
Chaccour 2021 [11]							
Chachar 2020 [12]							
Elshafie 2022 [13]							
George 2022 [14]							
Hashim 2020 [15]							
Krolewiecki 2021 [16]							
Lim 2022 [17]							
López-Medina 2021 [18]							

Mahmud 2021 [19]							
Manomaipiboon 2022 [20]							
Mirahmadizadeh 2022 [21]							
Mohan 2021 [22]							
Podder 2020 [23]							
Ravikirti 2021 [24]							
Reis 2022 [25]							
Rezai 2022 [26]							
Vallejos 2021 [27]							

Low	High	Unclear

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