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REVIEW

Ivermectin and outcomes from Covid-19 pneumonia: A systematic review and meta-analysis of randomized clinical trial studies

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Summary

Ivermectin is an FDA-approved drug for a parasitic disease that has broad antiviral activity. This study aims to analyse the efficacy of ivermectin in improving the Covid-19 outcomes. We systematically searched the PubMed, Europe PMC and ClinicalTrials.gov database using specific keywords related to our aims until 10th May 2021. All published randomized clinical trial studies on Covid-19 and ivermectin were retrieved. The quality of the study was assessed using Jadad scale assessment tool for clinical trial studies. Statistical analysis was done using Review Manager 5.4 software. A total of 19 studies with 2768 Covid-19 patients were included in this meta-analysis. This meta-analysis showed that ivermectin was associated with reduction in severity of Covid-19 (RR 0.43 [95% CI 0.23–0.81], $p = 0.008$), reduction of mortality (RR 0.31 [95% CI 0.15–0.62], $p = 0.001$), higher negative RT-PCR test results rate (RR 1.23 [95% CI 1.01–1.51], $p = 0.04$), shorter time to negative RT-PCR test results (mean difference [MD] −3.29 [95% CI −5.69, −0.89], $p = 0.007$), higher symptoms alleviations rate (RR 1.23 [95% CI 1.03–1.46], $p = 0.02$), shorter time to symptoms alleviations (MD −0.68 [95% CI −1.07, −0.29], $p = 0.0007$) and shorter time to hospital discharge (MD −2.66 [95% CI −4.49, −0.82], $p = 0.004$). Our study suggests that ivermectin may offer beneficial effects towards Covid-19 outcomes. More randomized clinical trial studies are still needed to confirm the results of our study.

KEYWORDS
covid-19, ivermectin, treatment

Abbreviations: CI, confidence intervals; Covid-19, coronavirus disease 2019; FDA, The United States Food and Drug Administration; FiO2, fractional concentration of oxygen inspired air; ICU, intensive care unit; IgE, immunoglobulin E; IgG1, immunoglobulin G1; IL-1, interleukin 1; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; LPS, lipopolysaccharide; NCP, nucleocapsid protein; NF-kB, nuclear factor-kappa B; PaO2, partial pressure of arterial oxygen; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, risk ratio; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS, severe acute respiratory syndrome; SARS-CoV-2, SARS-coronavirus-2; SD, standard deviations; TNF-α, tumour necrosis factor-α.

1 | INTRODUCTION

At the end of 2019, the first cases of a newly discovered acute respiratory illness, named coronavirus disease 2019 (Covid-19), were reported in Wuhan, China. As of 22 December 2020, a total of about 75.1 million cases and 1,680,794 deaths were identified across the world.[1] Covid-19 has various clinical manifestations, ranging from mild respiratory manifestations such as fever, cough, anosmia to severe or life-threatening conditions such as shock, respiratory distress, arrhythmia, sepsis, loss of consciousness.[2–5] Previous published meta-analysis studies have identified several comorbidities,[6–10] home medications[11,12] and laboratory values[13,14] which are associated with severe outcomes and the risk of dying from Covid-19. To reduce the severity and mortality rate of Covid-19, many attempts have been undertaken, including to discover the potential therapy. There were many therapeutic agents evaluated in clinical trials and suggested for Covid-19 therapy, such as remdesivir, dexamethasone, colchicine and tocilizumab.[15–17] These drugs may be beneficial for Covid-19 treatment because of their effects on the cytokine storm syndrome which may cause progression of the disease into more severe outcome.[18] Ivermectin is a drug that is used to manage parasitic infections with broad-spectrum effectivity and has been approved by The United States Food and Drug Administration (FDA). It has been long known for the treatment of onchocerciasis, strongyloidiasis, lymphatic filariasis and/or scabies.[19] Besides its potential as anti-parasitic agents, several articles have demonstrated the antiviral activity of ivermectin against various viruses.[20–22] Ivermectin has also been suggested to offer benefit in improving the outcomes from Covid-19 because of its action on prevention of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) proteins from entering the host cell nucleus in vitro.[23] Nonetheless, the evidence concerning the advantage of ivermectin, specifically in patients with SARS-CoV-2 infections, remains unclear. The objective of this meta-analysis is to explore the potential advantage of ivermectin to improve the outcomes of Covid-19 based on available randomized clinical trial studies.

2 | MATERIALS AND METHODS

2.1 | Eligibility criteria

The protocol of this study has been registered in PROSPERO (CRD42021230652). Included articles in this study are selected as potentially fulfilling the entry criteria: comply with the PICO framework (P: Population—Covid-19 patients; I: Intervention—ivermectin medications; C: Comparison or Control—a group of patients who did not receive ivermectin, only receive standard of care therapy or any other medications as control/placebo; O: Outcome—severe Covid-19, mortality, negative RT-PCR test results rate, time to negative RT-PCR test results, symptoms alleviations rate, time to symptoms alleviations and time to hospital discharge), randomized clinical trial articles were included, with the condition that the full-text paper was published. The exclusion criteria are any studies other than randomized clinical trials, studies reported other than in English language, studies focussing on the populations of young age (below 18 years old) and women during their pregnancy.

2.2 | Search strategy and study selection

The papers were searched systemically and obtained from PubMed, Europe PMC and ClinicalTrials.gov. Search terms used include 'ivermectin' OR 'stromectol' OR 'stromectal' OR 'sklice' OR 'ivomec' OR 'mectizan' AND 'SARS-CoV-2', OR 'coronavirus disease 2019' OR 'Covid-19' in a time range from 20th December 2019 until the present time (10th May 2021) with English-language restriction. The details regarding the search strategy used in this study are listed in Table 1. Studies evaluating the use of ivermectin therapy in patients with Covid-19, with a valid outcome of interest definition, were included in this study. Potential eligible articles searching was done by analysing the papers cited by authors of all identified studies. The search strategy was presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

2.3 | Data extraction and quality assessment

Two authors performed the data extraction process. An extraction form was developed to list the essential information about the study and its population characteristic, ivermectin dose, time to ivermectin administration, control group medications, the number of patients receiving ivermectin and the control group, also each outcome of Covid-19 patients' proportion.

This study's outcomes of interest are rate of negative RT-PCR test results, rate of symptoms alleviations, time to negative RT-PCR test results, time to symptoms alleviations, time to hospital discharge, severe Covid-19 and mortality. The rate of negative RT-PCR test results was described by the number of patients who were converted from positive to negative RT-PCR test results at the end of follow-up. The rate of symptoms alleviations was described by the number of patients who have symptoms improvement or who are symptoms-free at the end of follow-up. Time to negative RT-PCR test results was defined by the time needed for the conversion from positive RT-PCR to negative RT-PCR test results. Time to symptoms alleviations was defined by the time needed for the patients' symptoms to be disappeared. Time to hospital discharge was defined by the duration needed for patients to be discharged from the hospital. Severe Covid-19 manifestation was the one having either of the mentioned features at the time of, or after, admission: (1) respiratory distress ($\geq$30 breaths per min); (2) oxygen saturation at rest $\leq$93%; (3) ratio of the partial pressure of arterial oxygen (PaO2) to a fractional concentration of oxygen inspired air (FiO2) $\leq$300 mmHg; or (4) critical complication (respiratory failure, septic shock and or multiple

TABLE 1 Literature search strategy

Database	Keyword	Result
PubMed	('ivermectin'[MeSH Terms] OR 'ivermectin'[All Fields]) OR ('ivermectin'[MeSH Terms] OR 'ivermectin'[All Fields] OR 'stromectol'[All Fields]) OR stromectal[All Fields] OR sklice [All Fields] OR ('ivermectin'[MeSH Terms] OR 'ivermectin'[All Fields] OR 'ivomec'[All Fields]) OR ('ivermectin'[MeSH Terms] OR 'ivermectin'[All Fields] OR 'mectizan'[All Fields]) AND ('COVID-19'[All Fields] OR 'COVID-19'[MeSH Terms] OR 'COVID-19 Vaccines'[All Fields] OR 'COVID-19 Vaccines'[MeSH Terms] OR 'COVID-19 serotherapy'[All Fields] OR 'COVID-19 Nucleic Acid Testing'[All Fields] OR 'Covid-19 nucleic acid testing'[MeSH Terms] OR 'COVID-19 Serological Testing'[All Fields] OR 'Covid-19 serological testing'[MeSH Terms] OR 'COVID-19 Testing'[All Fields] OR 'Covid-19 testing'[MeSH Terms] OR 'SARS-CoV-2'[All Fields] OR 'sars-cov-2'[MeSH Terms] OR 'Severe Acute Respiratory Syndrome Coronavirus 2'[All Fields] OR 'NCOV'[All Fields] OR '2019 NCOV'[All Fields] OR (('coronavirus'[MeSH Terms] OR 'coronavirus'[All Fields] OR 'COV'[All Fields]) AND 2019/11/01[PubDate]: 3000/12/31 [PubDate]))	196
Europe PMC	'ivermectin' OR 'stromectol' OR 'stromectal' OR 'sklice' OR 'ivomec' OR 'mectizan' AND 'SARS-CoV-2', OR 'coronavirus disease 2019' OR 'Covid-19'	1350
ClinicalTrials.gov	'ivermectin' OR 'stromectol' OR 'stromectal' OR 'sklice' OR 'ivomec' OR 'mectizan' AND 'SARS-CoV-2', OR 'coronavirus disease 2019' OR 'Covid-19'	66

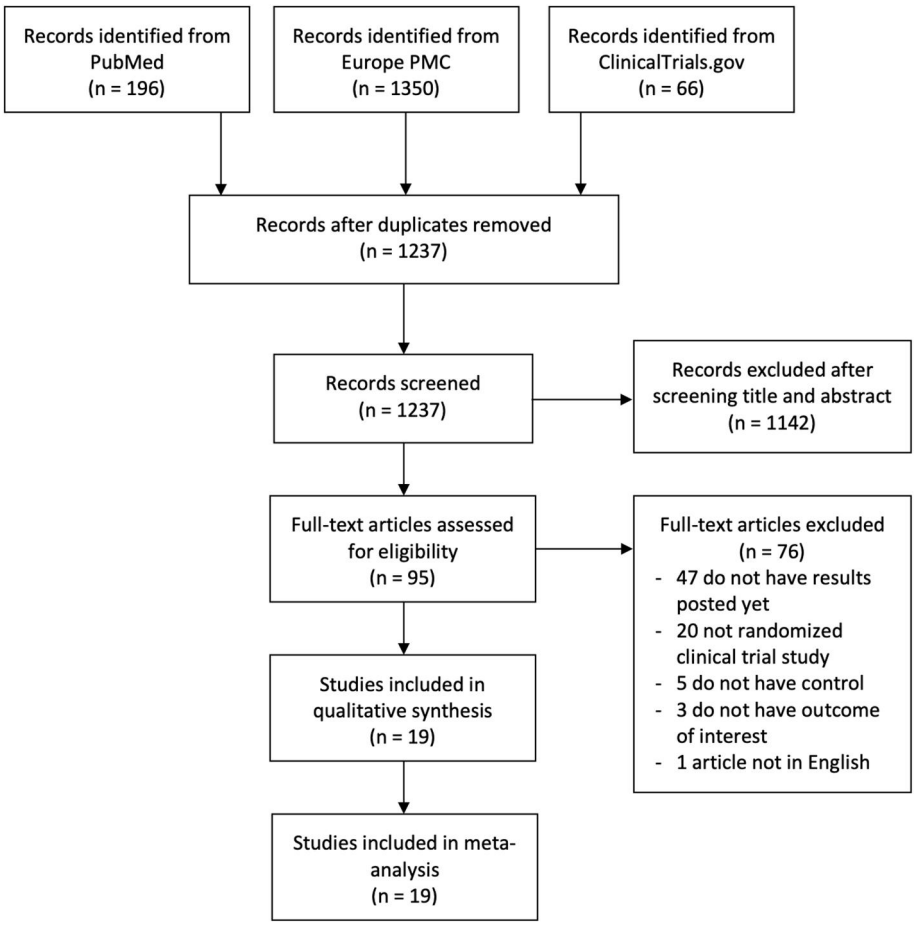

FIGURE 1 PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis

organ dysfunction/failure) or intensive care unit admission. The total of dead patients due to Covid-19 was described as the mortality outcome.

The other two authors assessing each included studies' quality independently, using the Jadad scale assessment.[24] The random allocation, allocation concealment, blindness and withdrawals and

TABLE 2 Characteristics of included studies

Study	Sample size	Design	Overall age mean ± SD	Outcome	Ivermectin dose	Patient category	Control	Ivermectin versus control *n* (%)
Ahmed S et al. 2020[27]	72	Double-blind randomized clinical trial	42 ± 15.8	- Time to negative PCR - Symptoms alleviations rate - Time to hospital discharge	12 mg, once daily for 5 days	Mild to severe patients	Placebo	24 (33.3%) versus 24 (33.3%)
Babalola OE et al. 2021[28]	62	Double-blind randomized clinical trial	44.1 ± 14.7	- Time to negative PCR	Divided into two groups: (1): 6 mg, twice a week for 2 weeks; (2): 12 mg, twice a week for 2 weeks	Mild to moderate patients	Lopinavir/ritonavir for 2 weeks	42 (67.7%) versus 20 (32.3%)
Bukhari KHS et al. 2021[29]	86	Open-label randomized clinical trial	40.3 ± 12	- Negative PCR rate	12 mg, single dose	Mild to moderate patients	Standard of care treatment (vitamin C 500 mg once daily, vitamin D3 200,000 IU once weekly, Paracetamol 500 mg)	41 (47.6%) versus 45 (52.4%)
Chachar AZK et al. 2020[30]	50	Open-label Randomized clinical trial	41.8 ± 15.6	- Symptoms alleviations rate	Total three doses: 12 mg at start, 12 mg after 12 h and 12 mg after 24 h	Mild patients	Symptomatic treatment only	25 (50%) versus 25 (50%)
Chowdhury ATMM et al. 2020[31]	116	Open-label Randomized clinical trial	33.9 ± 14.2	- Negative PCR rate - Symptoms alleviations rate - Time to negative PCR - Time to symptoms alleviations	200 μg/kg, once daily for 10 days	Mild to moderate patients	Hydroxychloroquine 400 mg on the first day then 200 mg BID for 9 days + Azithromycin 500 mg daily for 5 days	60 (51.7%) versus 56 (48.3%)
Elgazzar A et al. 2020[32]	400	Open-label Randomized clinical trial	56.7 ± 18.4	- Severity - Mortality - Negative PCR rate - Symptoms alleviations rate	400 μg/kg, once daily for 4 days	Mild to moderate and severe patients	Hydroxychloroquine 400 mg BID for the first day then 200 mg BID for 5 days	200 (50%) versus 200 (50%)

TABLE 2 (Continued)

Study	Sample size	Design	Overall age mean ± SD	Outcome	Ivermectin dose	Patient category	Control	Ivermectin versus control *n* (%)
				- Time to negative PCR - Time to hospital discharge				
Gonzalez JLB et al. 2021[33]	106	Double-blind randomized clinical trial	53.8 ± 16.9	- Mortality - Time to hospital discharge	12 mg, single dose in patients <80 kg and 18 mg, single dose in patients >80 kg	Severe patients	Calcium citrate as identical placebo	36 (33.9%) versus 37 (34.9%)
Hashim HA et al. 2020[34]	140	Open-label Randomized clinical trial	48.7 ± 8.6	- Severity - Mortality - Time to negative PCR - Time to hospital discharge	200 μg/kg, once daily for 2 days	Mild to moderate and severe-critical patients	Standard of care treatment (Azithromycin 250 mg/day for 5 days, vitamin C 1000 mg twice daily, zinc 75–125 mg/day, vitamin D3 5000 IU/day, acetaminophen 500 mg on need, dexamethasone 6 mg/day if needed, oxygen therapy if needed, and mechanical ventilation if needed)	70 (50%) versus 70 (50%)
Kishoria N et al. 2020[35]	32	Open-label randomized clinical trial	39.5 ± 15.4	- Negative PCR rate	12 mg, single dose	Mild to moderate patients	Hydroxychloroquine 400 mg BID + Paracetamol 500 mg as needed + Vitamin C 1 tablet BID	19 (59.3%) versus 13 (40.7%)
Lopez-Medina E et al. 2021[36]	398	Double-blind randomized clinical trial	37 ± 12.4	- Severity - Mortality - Symptoms alleviations rate - Time to symptoms alleviations	300 μg/kg/day for 5 days	Mild patients	Dextrose 5% as identical placebo	200 (50.2%) versus 198 (49.8%)
Mahmud R et al. 2020[37]	363	Double-blind randomized clinical trial	69.3 ± 9.6	- Severity - Mortality - Negative PCR rate - Symptoms alleviations rate	12 mg, once daily for 5 days	Mild to moderate patients	Standard of care treatment as an identical placebo (Paracetamol, vitamin D, oxygen if indicated, low molecular weight heparin, dexamethasone if indicated)	183 (50.4%) versus 180 (49.6%)
Mohan A et al. 2021[38]	125	Double-blind randomized	35.3 ± 10.5	- Severity		Mild to moderate patients	Identical placebo	80 (64%) versus 45

(Continues)

TABLE 2 (Continued)

Study	Sample size	Design	Overall age mean ± SD	Outcome	Ivermectin dose	Patient category	Control	Ivermectin versus control *n* (%)
		clinical trial		- Negative PCR rate - Time to negative PCR - Time to hospital discharge	Divided into two groups: (1): 12 mg, single dose; (2): 24 mg, single dose			(36%)
Niaee MS et al. 2020[39]	180	Double-blind randomized clinical trial	56 ± 16.2	- Mortality - Time to hospital discharge - Time to symptoms alleviations	Divided into several groups: (1): 200 μg/kg, single dose; (2): 200, 200 and 200 μg/kg in 1, 3 and 5 interval days; (3): 400 μg/kg, single dose; (4): 400, 200 and 200 μg/kg in 1, 3 and 5 interval days	Mild to severe patients	Standard of care treatment (Hydroxychloroquine 200 mg/kg, twice daily in an identical placebo)	120 (66.7%) versus 60 (33.3%)
Okumus N et al. 2021[40]	60	Open-label randomized clinical trial	62.2 ± 13	- Mortality - Negative PCR rate - Symptoms alleviations rate	200 mcg/kg/day for 5 days	Severe patients	Standard of care treatment (Hydroxychloroquine 2 × 400 mg loading dose followed by 2 × 200 mg for 5 days + favipiravir 2 × 1600 mg loading dose followed by 2 × 600 mg maintenance dose + azithromycin first day 500 mg followed by 4 days 250 mg/day) for a total of 5 days	30 (50%) versus 30 (50%)
Podder CS et al. 2020[41]	62	Open-label randomized clinical trial	39.1 ± 12	- Negative PCR rate - Time to symptoms alleviations	200 μg/kg, single dose	Mild to moderate patients	Standard of care treatment (Doxycycline 100 mg every 12 h for 7 days + symptomatic treatment)	32 (51.6%) versus 30 (48.4%)
Pott-Junior H et al. 2021[42]	31	Open-label randomized clinical trial	49.4 ± 14.6	- Severity - Negative PCR rate - Time to negative PCR	Divided into three groups: (1): 100 mcg/kg; (2): 200 mcg/kg; (3): 400 mcg/kg	Mild to severe patients	Standard of care treatment according to the latest recommendations on managing Covid-19	27 (87%) versus 4 (13%)
Ravikirti et al. 2021[43]	112	Double-blind randomized clinical trial	52.5 ± 14.7	- Severity - Mortality - Symptoms alleviations rate	12 mg, on days 1 and 2	Mild to moderate patients	Identical placebo tablets	55 (49.1%) versus 57 (50.9%)

TABLE 2 (Continued)

Study	Sample size	Design	Overall age mean ± SD	Outcome	Ivermectin dose	Patient category	Control	Ivermectin versus control n (%)
Shahbaznejad L et al. 2021[44]	69	Double-blind randomized clinical trial	47.6 ± 22.1	- Time to hospital discharge - Time to symptoms alleviations	200 μg/kg, single dose	Moderate to severe patients	Hydroxychloroquine and/or lopinavir/ritonavir according to national protocols of Iran	35 (50.7%) versus 34 (49.3%)
Shouman W et al. 2020[45]	304	Open-label randomized clinical trial	39.7 ± 14.9	- Symptoms alleviations rate - Time to symptoms alleviations	According to body weight: - 40–60 kg: 15 mg - 60–80 kg: 18 mg - >80 kg: 24 mg Given once daily at days 1 and 3	Asymptomatic patients	Only observations	203 (66.7%) versus 101 (33.3%)

drop-outs of each study were evaluated. Then, studies were scored from zero to seven. A study ranked as a high-quality study if the score was >4.[25]

2.4 | Statistical analysis

Review Manager 5.4 (Cochrane Collaboration) software was used to perform the meta-analysis. Mantel–Haenszel's formula was done to obtain risk ratios (RR) and its 95% confidence interval (CI), while Inverse Variance method was used to obtain mean difference (MD) and its standard deviations (SD). The heterogeneity was assessed by using the I^2 statistic with a value of <25%, 26%–50% and >50% were considered as low, moderate and high degrees of heterogeneity, respectively. The results were considered significant when the two-tailed p-value was ≤0.05. The formula by Wan X et al. was used for meta-analytical pooling, if the available data were in medians and interquartile ranges to be converted to mean and SD.[26] The qualitative risk of publication bias was assessed with Begg's funnel plot analysis.

3 | RESULTS

3.1 | Study selection and characteristics

In electronic databases, 1612 studies were found. A total of 1237 records remained following the elimination of duplicates. By screening the titles/abstracts and matching the inclusion and exclusion criteria, 1142 studies were removed. Among the 95 evaluated full-text articles for its eligibility, 47 articles were excluded due to unposted results (still recruiting or withdrawn), 20 articles because the study designs are not randomized clinical trial study (non-randomized clinical trial, cross-sectional, observational studies, case-series), 5 articles because of no control/comparison group in the studies, 3 articles because of they do not mention the criteria of our outcome of interest and 1 article because the article was not in English. At last, the meta-analysis included 19 randomized clinical trial studies[27–45] with a total of 2768 Covid-19 patients (Figure 1). Amongst them, 10 were open-label randomized clinical trial studies, while the rest nine studies were double-blind randomized clinical trial studies. Table 2 presents the characteristic of the studies.

3.2 | Quality of study assessment

Jadad scale assessments were used to assess clinical trial studies (Table 3). Seven out of 19 included studies were graded 'high quality', while the other 12 studies were graded 'moderate quality'. To sum up, all papers were decent to be further analysed using meta-analysis.

TABLE 3 Quality appraisal of studies included in the meta-analysis using Jadad scale assessment

Study	Random allocation	Concealment schemes	Blinding	Withdrawals and Drop-out	Total score	Interpretation
Ahmed S et al. 2020[27]	1	1	1	1	4	Moderate quality
Babalola OE et al. 2021[28]	1	1	1	1	4	Moderate quality
Bukhari KHS et al. 2021[29]	2	1	0	1	4	Moderate quality
Chachar AZK et al. 2020[30]	2	1	0	1	4	Moderate quality
Chowdhury ATMM et al. 2020[31]	2	1	0	1	4	Moderate quality
Elgazzar A et al. 2020[32]	1	1	0	1	3	Moderate quality
Gonzalez JLB et al. 2021[33]	1	1	2	1	5	High quality
Hashim HA et al. 2020[34]	0	1	1	1	3	Moderate quality
Kishoria N et al. 2020[35]	2	1	0	1	4	Moderate quality
Lopez-Medina E et al. 2021[36]	2	2	2	1	7	High quality
Mahmud R et al. 2020[37]	2	1	2	1	6	High quality
Mohan A et al. 2021[38]	2	1	2	1	6	High quality
Niaee MS et al. 2020[39]	2	2	2	1	7	High quality
Okumus N et al. 2021[40]	1	1	0	1	3	Moderate quality
Podder CS et al. 2020[41]	0	1	1	1	3	Moderate quality
Pott-Junior H et al. 2021[42]	2	2	0	1	5	High quality
Ravikirti et al. 2021[43]	2	2	1	1	6	High quality
Shahbaznejad L et al. 2021[44]	0	1	1	1	3	Moderate quality
Shouman W et al. 2020[45]	1	1	0	1	3	Moderate quality

Note: We used Jadad scale to assess the included studies. Points were determined as follows: (I) Random allocation: computer-generated random numbers, 2 points; not described, 1 point; inappropriate method, 0 point. (II) Allocation concealment: central randomization, sealed envelopes or similar, 2 points; not described, 1 point; inappropriate or unused, 0 point. (III) Blindness: identical placebo tablets or similar, 2 point; inadequate or not described, 1 point; inappropriate or no double blinding, 0 point. (IV) Withdrawals and drop-outs: numbers and reasons are described, 1 point; not described, 0 point. The Jadad scale score ranges from 1 to 7; higher score indicates better RCT quality. If a study had a modified Jadad score >4 points, it was considered to be of high quality; if the score was 3–4 points, it was moderate quality; and if the score was <3 points, it was low quality.

3.3 | Ivermectin and outcomes

3.3.1 | Severe Covid-19

Eight studies (n = 1638) reported on the severe Covid-19 outcome. Our pooled analysis showed that ivermectin administration was associated with reduction of severe Covid-19 outcome (RR 0.43 [95% CI 0.23–0.81], $p = 0.008$, $I^2 = 65\%$, random-effect modelling; Figure 2a).

3.3.2 | Mortality

Eight studies (n = 1726) reported on the mortality outcome. Our pooled analysis showed that ivermectin administration was associated with reduction of mortality from Covid-19 (RR 0.31 [95% CI 0.15–0.62], $p = 0.001$, $I^2 = 40\%$, random-effect modelling; Figure 2b).

3.3.3 | Negative RT-PCR test results rate

Nine studies (n = 1205) reported on the negative RT-PCR test results rate outcome. Our pooled analysis showed that ivermectin administration was associated with higher rate of negative Covid-19 RT-PCR test results (RR 1.23 [95% CI 1.01–1.51], $p = 0.04$, $I^2 = 91\%$, random-effect modelling; Figure 2c).

3.3.4 | Time to negative RT-PCR test results

Six studies (n = 782) reported on the time to negative RT-PCR test results outcome. Our pooled analysis showed that ivermectin administration was associated with shorter time to negative Covid-19 RT-PCR test results (MD −3.29 (95% CI −5.69, −0.89), $p = 0.007$, $I^2 = 96\%$, random-effect modelling; Figure 2d).

3.3.5 | Symptoms alleviations rate

Eight studies (n = 1535) reported on the symptoms alleviations rate outcome. Our pooled analysis showed that ivermectin administration was associated with higher rate of symptoms alleviations (RR 1.23 [95% CI 1.03–1.46), $p = 0.02$, $I^2 = 85\%$, random-effect modelling; Figure 2e).

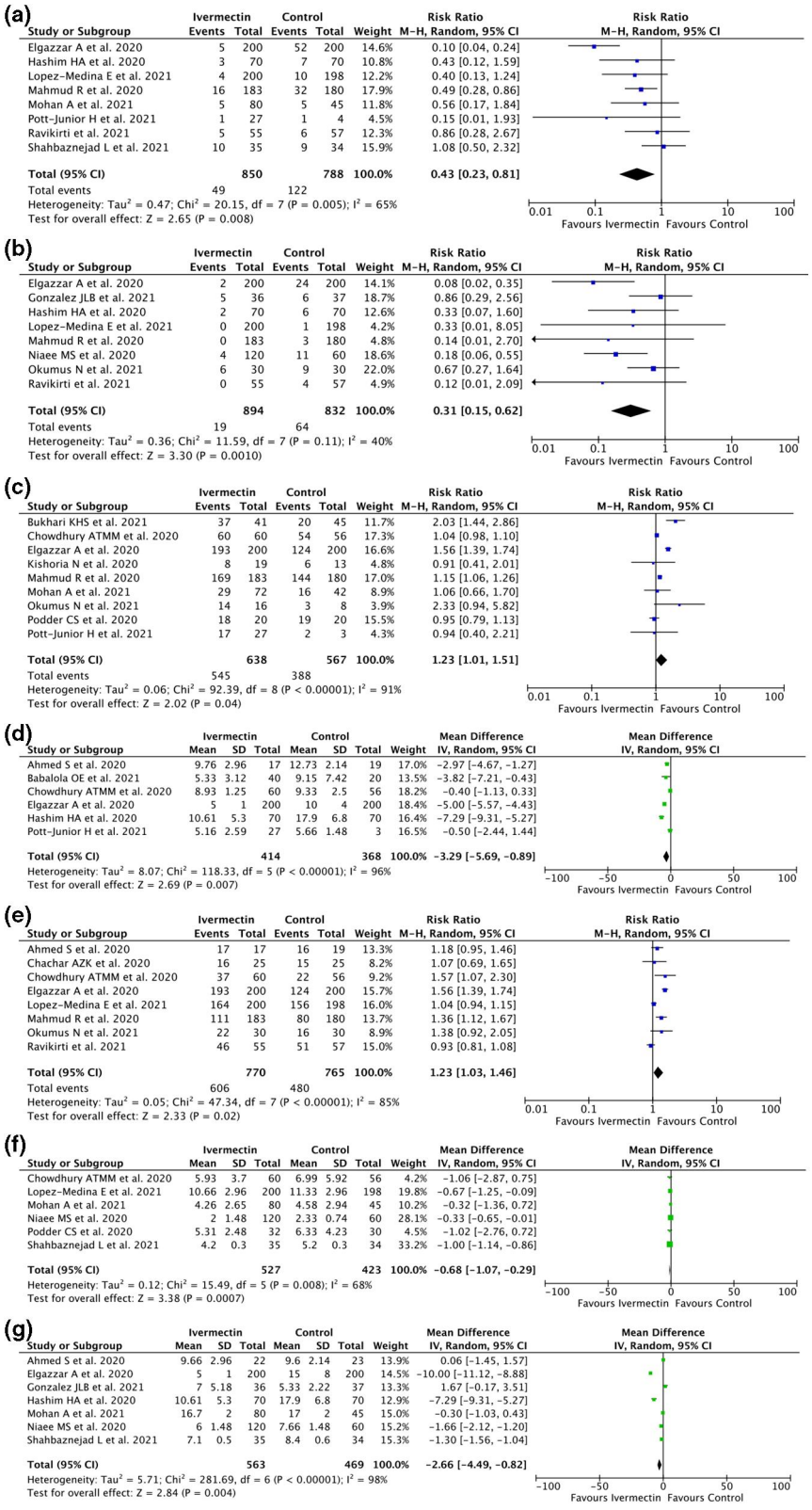

FIGURE 2 Forest plot that demonstrates the association of ivermectin administration with severe Covid-19 (a), mortality (b), negative RT-PCR test results rate (c), time to negative RT-PCR test results (d), symptoms alleviations rate (e), time to symptoms alleviations (f) and time to hospital discharge (g) outcomes

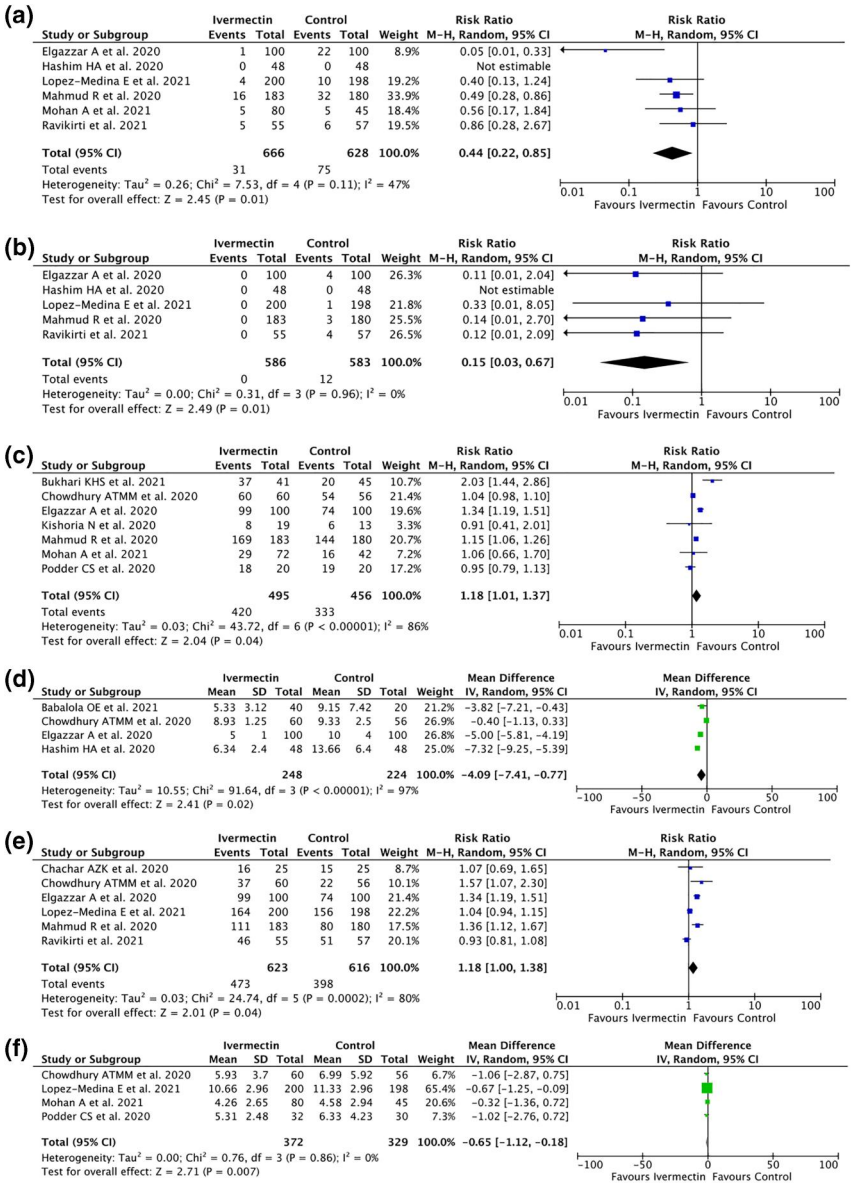

FIGURE 3 Subgroup analysis in mild to moderate patients that demonstrates the association of ivermectin administration with severe Covid-19 (a), mortality (b), negative RT-PCR test results rate (c), time to negative RT-PCR test results (d), symptoms alleviations rate (e) and time to symptoms alleviations (f) outcomes

3.3.6 | Time to symptoms alleviations

Six studies (n = 950) reported on the time to symptoms alleviations outcome. Our pooled analysis showed that ivermectin administration was associated with shorter time to symptoms alleviations (MD −0.68 (95% CI −1.07, −0.29), p = 0.0007, I^2 = 68%, random-effect modelling; Figure 2f).

3.3.7 | Time to hospital discharge

Seven studies (n = 1,032) reported on the time to hospital discharge outcome. Our pooled analysis showed that ivermectin administration was associated with shorter time to hospital discharge (MD −2.66 (95% CI −4.49, −0.82), p = 0.004, I^2 = 98%, random-effect modelling; Figure 2g).

3.4 | Subgroup analysis

Subgroup analysis revealed that ivermectin administration in mild to moderate patients showed a lower RR, therefore was associated with lower severity (n = 1294; RR 0.44 [95% CI 0.22–0.85], p = 0.01, I^2 = 47%, random-effect modelling; Figure 3a) and mortality (n = 1169; RR 0.15 [95% CI 0.03–0.67], p = 0.01, I^2 = 0%, random-effect modelling; Figure 3b) outcomes when compared with severity (n = 313; RR 0.41 [95% CI 0.10–1.59], p = 0.20, I^2 = 83%, random-effect modelling; Figure 4a) and mortality (n = 377; RR 0.41 [95% CI 0.16–1.04], p = 0.06, I^2 = 58%, random-effect modelling) outcomes (Figure 4b) in severe patients.

On the other side, subgroup analysis also revealed that ivermectin administration in severe patients showed a higher RR and higher MD in terms of negative RT-PCR test results rate (n = 224; RR 1.90 [95% CI 1.56–2.31], p < 0.00001, I^2 = 0%, random-effect

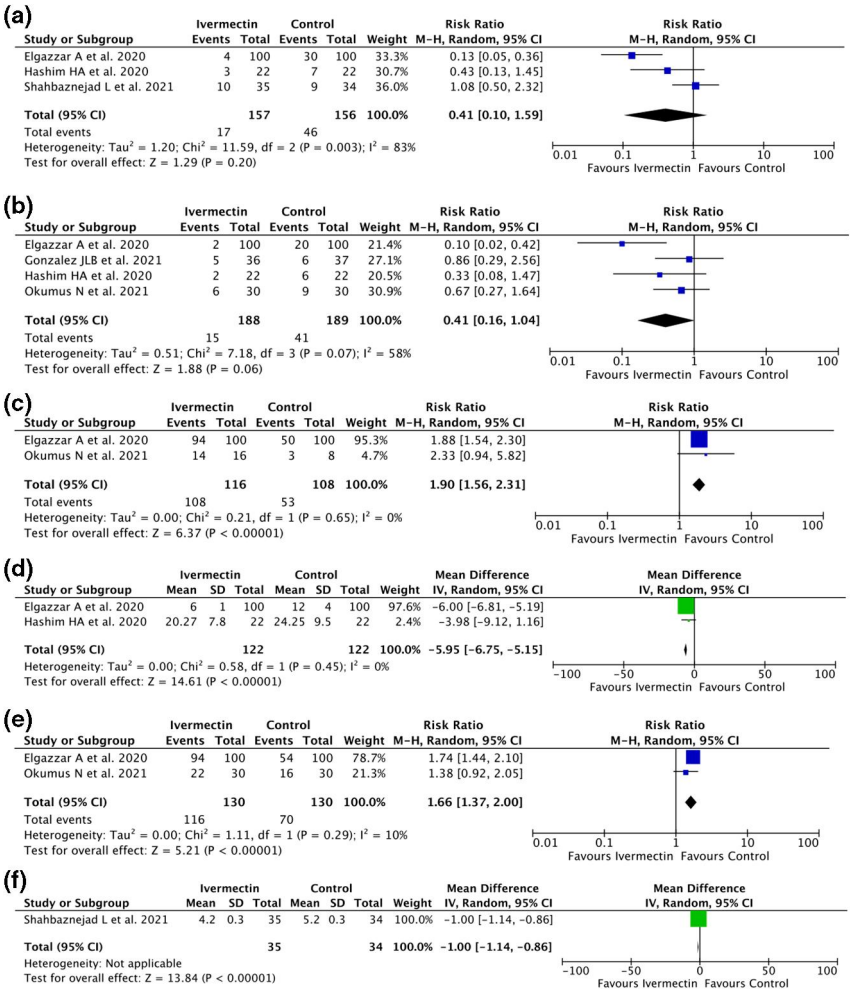

FIGURE 4 Subgroup analysis in severe patients that demonstrates the association of ivermectin administration with severe Covid-19 (a), mortality (b), negative RT-PCR test results rate (c), time to negative RT-PCR test results (d), symptoms alleviations rate (e) and time to symptoms alleviations (f) outcomes

modelling; Figure 4c), time to negative RT-PCR test results (n = 244; MD −5.95 (95% CI −6.75, −5.15), p < 0.00001, I^2 = 0%, random-effect modelling; Figure 4d), symptoms alleviations rate (n = 260; RR 1.66 [95% CI 1.37–2.00], p < 0.0001, I^2 = 10%, random-effect modelling; Figure 4e) and time to symptoms alleviations (n = 69; MD −1.00 [95% CI −1.14, −0.86), p < 0.00001, I^2 = 0%, random-effect modelling; Figure 4f) when compared with those outcomes in mild to moderate patients (negative RT-PCR test results rate, n = 951 [RR 1.18 (95% CI 1.01–1.37), p = 0.04, I^2 = 86%, random-effect modelling; Figure 3c], time to negative RT-PCR test results, [n = 472; MD −4.09 (95% CI −7.41, −0.77), p = 0.02, I^2 = 97%, random-effect modelling; Figure 3d], symptoms alleviations rate [n = 1239; RR 1.18 (95% CI 1.00–1.38), p = 0.04, I^2 = 80%, random-effect modelling; Figure 3e] and time to symptoms alleviations [n = 701; MD −0.65 (95% CI −1.12, −0.18), p = 0.007, I^2 = 0%, random-effect modelling; Figure 3f]).

3.5 | Publication bias

Funnel plot analysis showed a relatively symmetrical inverted-plot for the negative RT-PCR test results rate (Figure 5c), time to negative RT-PCR test results (Figure 5d), symptoms alleviations rate (Figure 5e), time to symptoms alleviations (Figure 5f) and time to hospital discharge (Figure 5g), showing no indication of publication bias. Funnel plot analysis showed an asymmetrical inverted-plot for the severe Covid-19 (Figure 5a) and mortality outcome (Figure 5b), showing some indication of publication bias. However, because the number of included studies in each outcomes are fewer than 10 studies, the funnel plots and statistical tests for detecting publication bias are not much reliable when compared with whenever there are more than 10 included studies in each outcomes.[46,47]

4 | DISCUSSION

According to our pooled analysis, ivermectin was discovered to have an association with a higher negative RT-PCR test results rate, shorter time to negative RT-PCR test results, higher symptoms alleviations rate, shorter time to symptoms alleviations, shorter time to hospital discharge and reduction in the severity and mortality from Covid-19. Our subgroup analysis also showed that the benefits of ivermectin therapy in reducing the severity and mortality outcomes from Covid-19 were more prominent when administered into mild to

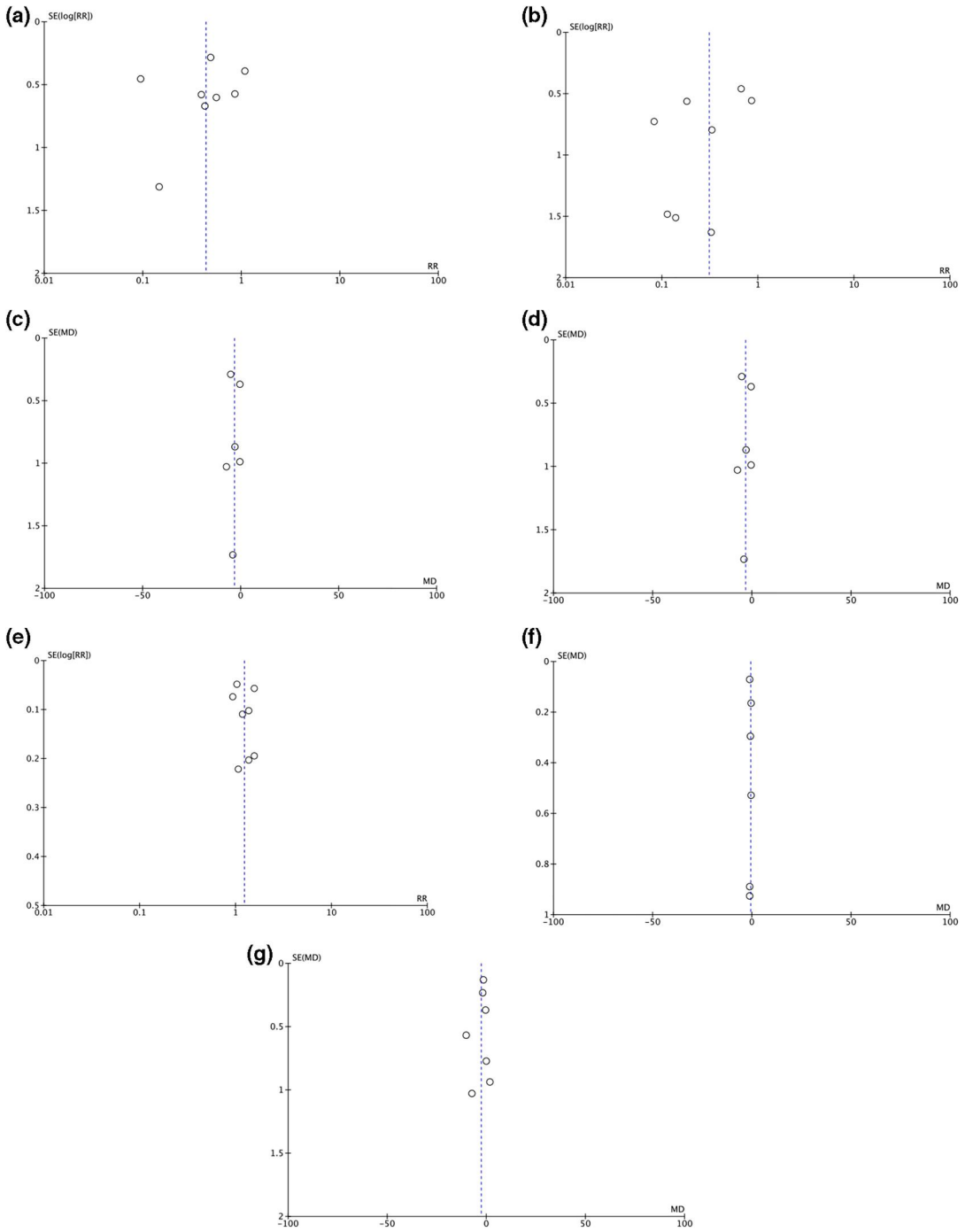

FIGURE 5 Funnel plot analysis for the association of ivermectin administration with severe Covid-19 (a), mortality (b), negative RT-PCR test results rate (c), time to negative RT-PCR test results (d), symptoms alleviations rate (e), time to symptoms alleviations (f), and time to hospital discharge (g) outcomes

moderate patients, compared with in severe patients. On the other side, the benefits of ivermectin therapy in increasing negative RT-PCR test results rate, shortening time to negative RT-PCR test results, increasing symptoms alleviations rate and shortening time to symptoms alleviations were more apparent in severe patients when compared with in mild to moderate patients.

A few arguments might explain these findings. The sequestration of the SARS-CoV-2 viral nucleocapsid protein (NCP) into the host nucleus through the nuclear-pore-complex is a vital step in viral pathogenesis and defence against host immune response.[48] Ivermectin can selectively inhibit the host importin α/β transporter protein which decreases translocation (shuttling) of SARS-CoV-2 NCP from the cytoplasm to the nucleus, alteration of NCP distribution will lead to viral propagation disruption and survival.[23] The in vitro study by Caly et al.[23] has proved that giving ivermectin in one dose was able to reduce the viral RNA load by 99.98% at 48 h and

replication of an Australian isolate of SARS-CoV-2 in Vero/hSLAM cells by 5000-folds. Therefore, it has potent effects in altering disease progression and spread. These in vitro findings were further supported with the results from a double-blind, placebo-controlled, randomized clinical trial study, showing that patients who received ivermectin 400 μg/kg single dose have a lower median viral load at Day 4 (161,000 vs. 493,500 copies/ml) and Day 7 post-treatment (1018 vs. 23,550 copies/ml). The differences were found, rising from a threefold decrease on the fourth day to about 18-fold lower on the seventh day when compared with placebo.[49] Second, the pathophysiologic process which underlies severe Covid-19 involves hyperinflammatory response and accumulation of cytokines, called a cytokine storm. A meta-analysis study has demonstrated that severe Covid-19 patients tend to produce higher cytokine levels such as interleukin-6 (IL-6), IL-8, IL-10 and tumour necrosis factor-α (TNF-α), in comparison to non-severe cases.[50] On the other side, an anti-inflammatory effect was also demonstrated in ivermectin, both in vivo and in vitro studies. Ivermectin can reduce the IL-1, IL-6, TNF-α production and suppressing lipopolysaccharide-induced nuclear factor-kappa B translocation.[51] The suppression of mucus due to hypersecretion in the respiratory tract, the reduction of immune cell recruitment, and a decrease in the production of cytokines and immunoglobulin E/immunoglobulin G1 in bronchoalveolar lavage of experimental mice, were found as a consequence of 2 mg/kg of ivermectin administration.[52] These findings suggest that ivermectin has an anti-inflammatory effect on the lung tissue, besides at the systemic level, which might help to reduce the severity and prevent mortality from Covid-19.

This study has several limitations. First, significant heterogeneities were found on most of the outcomes of interests included in this study. This was probably caused by the difference in the given ivermectin doses and the medications used as a standard of care or placebo. Second, the total number of patients included in this study was relatively small because at this time, ivermectin is still considered as new repurposed drug for Covid-19 where early trials still show conflicting results and there is still no meta-analysis study to support its efficacy, therefore it may be difficult to collect the participants and receiving their consent to participate in the trials. Third, we include some pre-print studies to minimize the risk of publication bias; however, the authors have made exhaustive efforts to ensure that only sound studies were included, and we expect that most of those studies currently available in pre-print form will eventually be published and that we will identify them through ongoing electronic literature surveillances. We hope that this study can give further insight into the management of Covid-19 patients.

5 | CONCLUSION

Our meta-analysis of randomized clinical trial studies indicates that ivermectin administration had an association with favourable outcomes of Covid-19, compromising of higher rate of negative RT-PCR test results, shorter time to negative RT-PCR test results, higher rate of symptoms alleviations, shorter time to symptoms alleviations, shorter time to hospital discharge, reduction in the severity and mortality rate from Covid-19. This study suggests that ivermectin may be the potential therapeutic agents for the managements of Covid-19 to give better outcomes for the patients. However, more randomized clinical trial studies are still necessary and encouraged to be done for confirming the results of our study. Finally, ivermectin should be considered as an essential drug for future Covid-19 therapy models.

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CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Conceptualization, methodology, formal analysis, data curation, writing-original draft, visualization, writing-review and editing: Timotius Ivan Hariyanto. Conceptualization, methodology, formal analysis, data curation, writing-original draft, writing-review and editing: Devina Adella Halim. Conceptualization, validation, supervision, writing-review and editing: Jane Rosalind. Conceptualization, validation, supervision, writing-review and editing: Catherine Gunawan. Conceptualization, validation, supervision, writing-review and editing: Andree Kurniawan.

DATA AVAILABILITY STATEMENT

Data analysed in this study were a re-analysis of existing data, which are openly available at locations cited in the reference section.

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