Therapeutic potential of ivermectin as add-on treatment in COVID 19: A systematic review and meta-analysis

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ABSTRACT -- The current management of COVID-19 is mostly limited to general supportive care and symptomatic treatment. Ivermectin is a broad-spectrum anti-parasitic drug used widely for the treatment of onchocerciasis and lymphatic filariasis. Apart from its anti-parasitic effect it also exhibits antiviral activity against a number of viruses both in vitro and in vivo. Hence, we conducted this systematic review and meta-analysis to assess the currently available data on the therapeutic potential of ivermectin for the treatment of COVID-19 as add on therapy. A total of 629 patients were included in the 4 studies and all were COVID-19 RT-PCR positive. Among them, 397 patients received ivermectin along with usual therapy. The random effect model showed the overall pooled OR to be 0.53 (95%CI: 0.29 to0.96) for the primary outcome (all-cause mortality) which was statistically significant (P=0.04). Similarly, the random effect model revealed that adding ivermectin led to significant clinical improvement compared to usual therapy (OR=1.98, 95% CI: 1.11 to 3.53, P=0.02). However, this should be inferred cautiously as the quality of evidence is very low. Currently, many clinical trials are on-going, and definitive evidence for repurposing this drug for COVID-19 patients will emerge only in the future.

INTRODUCTION:

Since the beginning of the outbreak in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a cause of global concern (1,2). Remdesivir, favipiravir, chloroquine, hydroxychloroquine, and azithromycin are some of the drugs commonly being used for the treatment of COVID-19 infection but with variable success (3-6). The current management is mostly limited to general supportive care and symptomatic treatment.

Recent reviews have discussed theeffectiveness of multiple classes of drugs including antimalarials, antivirals, antibiotics, corticosteroids and monoclonal antibodies in COVID-19 (7,8). However, the utility of ivermectin, a broad-spectrum anti-parasitic drug used widely for the treatment of onchocerciasis and lymphatic filariasis has largely been overlooked (9,10). Apart from its anti-parasitic effect it also exhibits antiviral activity against a number of viruses both *in vitro* and *in vivo* (11-13). The antiviral activity is purportedly due to the inhibition of importin (IMP) α/β Integrase which helps in the nuclear import and propagation of infection of RNA viruses (14,15). Based on this, researchers have proposed the use of ivermectin as an add on therapy for COVID-19 treatment (16). Few observational studies have been performed to evaluate the effectiveness of ivermectin in the treatment of COVID-19 and have shown favourable result (17-20). However, there is a wide disparity regarding the clinical benefit accrued from this drug. Hence, we conducted this systematic review and meta-analysis to assess the currently available data on the therapeutic potential of ivermectin for the treatment of COVID-19 as add on therapy. This review may provide clinicians an overview of contemporary scientific evidence regarding the therapeutic potential of ivermectin in the clinical management of COVID-19 patients.

MATERIALS AND METHODS:

Development and registration of protocol:

The protocol was written according to PRISMA-P guidelines. The prospective register of systematic

review (PROSPERO) registration number for the study is CRD42020207299.

Types of studies: All randomized controlled trials (RCTs) and observational studies reporting the use of ivermectin as an add-on therapy in COVID 19 patients in the English language were included. All the included articles reported all-cause mortality as an outcome measure. The study inclusion was not restricted by year of publication, site of study, dose of the drug, and the control arm.

Types of Participants: RT-PCR confirmed COVID-19 adult patients of both genders treated with ivermectin as an add-on therapy were included in the study.

Types of intervention: The intervention in all included studies was the administration of ivermectin in COVID 19 patients along with standard treatment protocol irrespective of the dose, timing, and frequency of administration of ivermectin.

Types of comparator: The comparison was between standard treatment protocol with and without ivermectin.

Outcome measures: Primary outcome were all-cause mortality and any death during the available period of follow up in the studies. Secondary outcomes were 1) time to discharge from the hospital, 2) time to viral clearance by RT-PCR, 3) clinical improvement assessed by the need for respiratory support.

Information source:

PubMed, EMBASE, the Cochrane Library, SCOPUS, and Web of Science were searched for articles on ivermectin as an add-on therapy in COVID 19 from inception till August 31, 2020. The reference lists of retrieved articles were checked for additional studies. For unpublished data, we checked the International Clinical Trials Registry Platform (ICTRP), which is a central database containing trial registration datasets provided by the different international trial registries including ClinicalTrials.gov.Pre-print servers medRxiv and bioRxiv were also searched for pre-print data.

Search strategy: A combination of subject terms and keywords were used and appropriate adjustments of vocabulary and grammar between different databases were done using PICO method. The search used both Medical Subject Headings (MeSH), as well as keyword variants of all relevant terms. A combination of keywords and Boolean operators like “Ivermectin” OR “Anthelminthic” AND “COVID-19” OR “Severe acute respiratory syndrome coronavirus 2" was used for designing the search algorithm.

Data extraction and management: The data were extracted and assessed for quality using the predesigned eligibility criteria following Cochrane Collaboration’s guidelines by 3 review authors (RRM, BRM, SD) independently. Any disagreement between them was resolved by the fourth author (BMP). A pre-designed data extraction format was used for the recording of data which included study design, basic information, treatment details, and outcome measures.

Assessment of risk of bias in included studies: Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) for observational studies was used to assess the risk of bias in the included studies.

Data analysis: Cochrane Program Review Manager 5.3 software was used for the Meta-analysis. For dichotomous values, odd’s ratio (OR) and 95% confidence interval was expressed in accordance with Cochrane Handbook for Systematic Reviews of Interventions. I^2 statistic was used to check heterogeneity among eligible studies. The random-effect model was used for data synthesis.

Assessment of publication bias: A funnel plot was used to assess the presence of publication bias.

Grade of evidence: GRADE profiler software (V 3.6.1) was used for quality assessment of the evidence.

RESULTS:

Description of studies: A total of 119 studies were found from all database searches. Out of those 91 were from PubMed and 28 from preprint server medRxiv. Search in clinicaltrials.gov resulted in 37 registered studies, among those 2 were completed studies with results. A total of 5 studies were selected for full-text review after screening and removal of duplicates. Other studies were excluded as those were letters to the editor, commentaries, and review articles. Finally, 4 observational studies were included for systematic review and meta-analysis, 3 with the control arm and 1 without control arm. One

of the studies evaluating the prophylactic effect of ivermectin for COVID-19 was excluded from the review. We did not find any published RCT evaluating the effect of ivermectin on COVID-19. Three of the included studies are not peer-reviewed as they were published in preprint server medRxiv.

A total of 629 patients were included in the 4 studies and all were RT-PCR positive. Among them, 397 patients received ivermectin along with usual therapy. Ivermectin treated group had 233 mild cases and 104 moderate to severe cases. Similarly, the usual treatment group had 121 mild and 57 moderate to severe cases. The study by Choudhury *et al* with 60 patients in the ivermectin group and 56 patients in the usual therapy group had not mentioned the severity of the disease. Most of the patients had one or more comorbidities like diabetes, hypertension, and bronchial asthma. The dose of ivermectin varied from 150 to 200 µg/kg body weight administered as a single dose. In the study by Rajtor *et al*, 13 patients also received the 2nd dose of ivermectin. The characteristics of studies included for systematic review and meta-analysis are depicted in Table 1.

Risk of bias in the included studies:

The risk of bias assessment of all studies included in the meta-analysis was carried out for the primary outcome (all-cause mortality) using the risk of bias in non-randomized studies - of interventions (ROBINS-I). The result of the risk of bias assessment of observational studies is depicted in table 2.

Effects of intervention:

The study by Bhattacharya *et al* did not have a control arm for comparison. Therefore, 3 studies were included for measuring the pooled effect of add on ivermectin to usual therapy on the primary and secondary outcomes. The forest plots for the pooled effect are depicted in Figure 1.

Primary outcome (all-cause mortality)

All-cause mortality was reportedly reduced in 2 of the 3 included studies. Test for heterogeneity for the pooled studies was not significant (Chi^2 =0.09, df=1, (P=0.77), I^2=0%) and the random effect model showed the overall pooled OR to be 0.53 (95%CI: 0.29 to 0.96). Sensitivity analysis was not carried out as the test of heterogeneity across the included studies was not significant. The overall result suggests that there was a statistically significant reduction in all-cause mortality with the additional use of ivermectin compared to usual therapy only (P=0.04).

Since the search period mentioned in our protocol registered on PROSPERO was from inception till August 31, 2020, data from the study by Hashim *et al* has not included in the primary meta-analysis as this trial was published in the preprint server in October 2020 (21). In this study, out of 140 COVID-19 patients, 70 were randomized to receive ivermectin plus standard treatment and the rest 70 received standard treatment only. In the ivermectin plus standard treatment arm, the mortality was 2 compared to 6 in the standard treatment only arm. As a secondary analysis, when this study was included, the test for heterogeneity for the pooled studies was not significant (Chi^2 =0.45, df=2, (P=0.80), I^2=0%) and pooled OR was 0.50 (95%CI: 0.29 to 0.88). This suggested that addition of ivermectin significantly reduced the mortality (P= 0.02).

Secondary outcomes:

Clinical improvement assessed by the need for respiratory support:

All the 3 studies included in the meta-analysis reported clinical improvement as assessed by the need for respiratory support until the available follow-up period. The test of heterogeneity was not significant (Chi^2=0.56, df=2, (P=0.76), I^2 =0%). The random effect model revealed that adding ivermectin led to significant clinical improvement compared to usual therapy (OR=1.95, 95% CI: 1.09 to 3.49, P=0.02).

Time to discharge from the hospital:

In the study by Gorial *et al*, the meantime of hospital stay was significantly lower in the ivermectin group than the non-ivermectin group (7.62± 2.75 versus 13.22± 5.90 days, p= 0.00005). But in other studies, there was no significant difference in time to discharge from the hospital between the 2 groups. As the exact data for time to discharge from the hospital within a specified time period was not available in all the studies, the data were not pooled for meta-analysis.

Time to viral clearance by RT-PCR:

The median time to viral clearance was lower in the ivermectin group (7 days) in the study by Gorial *et al*, which was statistically significant (p=0.001)

compared to the non-ivermectin group (12 days). But the study by Choudhury *et al* did not find any significant difference between the 2 groups. The other 2 studies by Rajter *et al* and Bhattacharya *et al* did not report about time to viral clearance.

Publication bias:

Although we created a Funnel plot for publication bias, it could not be assessed as there were only 2 studies where mortality was reported. However, due to the small sample size and large effect we expect that publication bias would be present.

Grade of evidence:

The evidence was assessed using GRADE profiler for all-cause mortality and clinical improvement. There were 54 lower deaths per 1000 population on the addition of ivermectin to usual therapy. Similarly, clinical improvement was achieved in 61 more cases per 1000 population when ivermectin was used as an add-on therapy. However, the grade of evidence was very low for both the outcomes. The detailed analysis of the summary of evidence is depicted in table 3.

DISCUSSION

In this systematic review and meta-analysis, we have synthesized the available evidence on the use of add on ivermectin in COVID-19 patients. We included 3 observational studies for estimating the pooled effect. It is important to note that at the time of analysis, 2 of the included studies were not peer-reviewed and were retrieved from the preprint server. However, one of these, the ICON study by Rajter *et al* has been recently published (18). To the best of our knowledge, this is the first systematic review and meta-analysis on the effectiveness of add-on ivermectin in COVID-19 patients. The pooled estimate suggested a statistically significant reduction in all-cause mortality when ivermectin was added to usual therapy with OR of 0.53 (P= 0.04). Even on secondary analysis after inclusion of the study by Hashim *et al*, the pooled OR did not change meaningfully and was 0.50 (P=0.02). Ivermectin has been hypothesized to exert its effect by inhibiting importin (IMP) α/β Integrase and thereby preventing the propagation of viruses. However, the exact mechanism is still not established.

The OR of 1.98 indicates significant clinical improvement as assessed by the need for respiratory support by using ivermectin as add-on therapy in the management of COVID-19 patients (p= 0.02). However, this should be inferred cautiously as the sample sizes of included studies were relatively small and showing large effect.

Most of the included studies involved mild to moderate cases that might have not required respiratory support. All the included studies were observational in nature and suffered from various biases inherent to such study design. The study by Gorial *et al* used a synthetic matched control group for comparison. Similarly, one of the included studies was a retrospective case-control study. All these factors, therefore, contribute to the overall very low quality of evidence. Additionally, the complication rate and mortality amongst patients with severe disease have been reported to be very high (22). In such patients the effectiveness of add on ivermectin has not yet been explored.

Although add-on ivermectin was associated with a significant reduction in all-cause mortality and clinical improvement it did not translate into early discharge from the hospital or viral clearance. Only the study by Gorial et *al* reported a significant decrease in a hospital stay and viral clearance. This might have been due to differences in the management protocol followed in different countries.

In a recent study whose data has been made publicly available on www.clinical trials.gov , [NCT04422561] prophylactic use of ivermectin has reduced the development of COVID-19 symptoms during 14 days follow up period (7.4% in ivermectin group compared to 58.4% in the control group). This drug has traditionally been used in the mass prophylaxis programs of filariasis, onchocerciasis and is generally safe and well-tolerated. In all the studies included in this review, the safety profile of ivermectin was reported to be favourable.

STRENGTH AND LIMITATIONS:

This is the first meta-analysis on the effectiveness of ivermectin as an add-on therapy in COVID-19 using a comprehensive search strategy and assessing the strength of evidence using GRADE profiler. Limitations include small observational studies with confounders and possible publication bias thus providing very low-quality evidence.

Table 1: Characteristics of included studies

Study, Year, Country	Patient characteristics		Primary outcome, All-cause mortality		Secondary outcome						Additional comment
					Time to discharge		Clinical improvement		Viral clearance		
	IVM	No IVM	IVM	No IVM	IVM	No IVM	IVM	No IVM	IVM	No IVM	
Gorial *et al*, 2020, Iraq (17), [From preprint server]	n= 16; age, 44.9±10.6; male/female, 11/5; 9 mild,7 moderate	n= 71; age- 45.2± 18.5; Male/Female, 52/19; 40 Mild, 31Moderate	0	2	Mean, 7.62± 2.75	Mean- 13.22± 5.90	16	69	Median- 7 (95% CI 6-11)	Median- 12 (95% CI 10-15)	Matched control study; exclusion- severe covid-19; follow up, 23 days, IVM dose- 200µg/ kg, single dose; received hydroxychloroquine, azithromycin
Rajter *et al*, 2020, USA (18)	n= 173; age- 60.2± 17.6; male/female, 89/84; mild,124; moderate to severe, 49	n= 107; age- 58.6± 18.5; Male/Female, 64/43, mild, 81; moderate to severe, 26	26	27	Median (IQR), 7 (4-13)	Median (IQR), 7 (4-10)	147	80	Not reported	Not reported	Retrospective study; follow up, 7 to 64 days; 200 µg/ kg IVM, single dose; 13 received 2nd dose of IVM. also received hydroxychloroquine azithromycin
Chowdhury *et al*, 2020, Bangladesh (19)	n= 60; male/female, 43/17; asymptomatic, 11; symptomatic,49	n=56; male/female, 47/9; asymptomatic,14; symptomatic,42	0	0	Mean- 8.9 days	Mean- 9.33 days	60	54	Mean- 5.93 days	Mean- 7 days	Comparative observational study; IVM dose- 200 µg/ kg, single dose; IVM group also received doxycycline; non IVM treatment group received hydroxychloroquine, azithromycin
Bhattacharya *et al*, 2020, India (20)	n=148; mean age- 57.57male/female, 72/76; mild,100; moderate to severe, 48	No comparator	2		Average- 12 days		146				Retrospective case series; IVM dose- 200 µg/ kg, single dose. Also received n-acetylcysteine and atorvastatin

IVM- Ivermectin, IQR- Inter quartile range, µg/kg- Microgram/ kilogram body weight.

Table 2: Risk of bias assessment in included studies (ROBINS I)

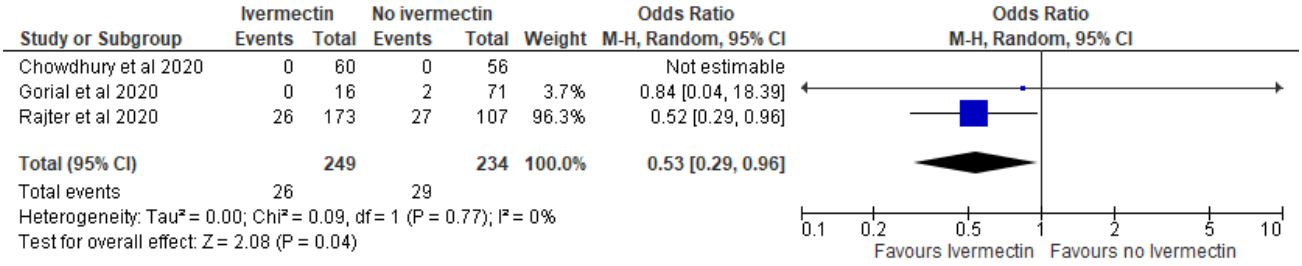
Study	D1	D2	D3	D4	D5	D6	D7	Overall
Chowdhury *et al,* 2020								
Gorial *et al*, 2020								
Rajter *et al*, 2020								

Domains:
D1: Bias due to confounding
D2: Bias in selection of participants into the study
D3: Bias in classification of intervention
D4: Bias due to deviation from intended intervention
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of reported outcome

Low:
Moderate:
Serious:
Critical:
No inference:

Figure 1: Forest plots of effectiveness of add-on ivermectin therapy

a. All-cause mortality



b. Clinical improvement

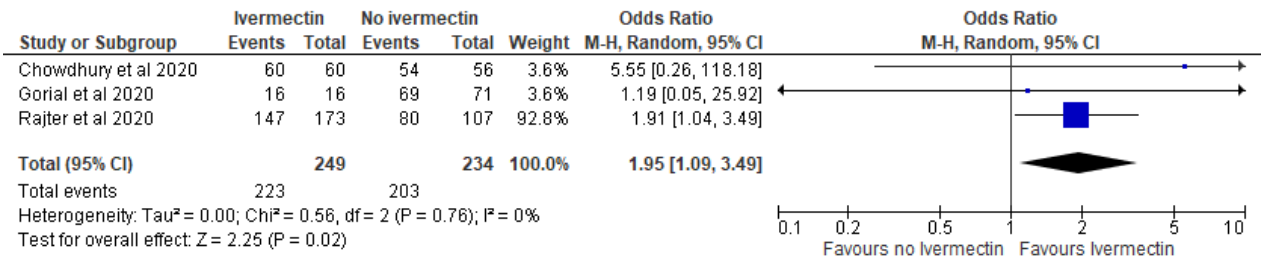


Table III: Grade of evidence for included studies

Ivermectin for COVID-19, Bibliography: Meta-analysis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence(GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Ivermectin (95% CI)
All-cause mortality	483 (3 studies)	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5] due to risk of bias, inconsistency, indirectness, publication bias, large effect	OR 0.53 (0.29 to 0.97)	Study population 125 per 1000 moderate effect	54 fewer per 1000 (from 3 fewer to 85 fewer)
Secondary outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects,	
				Risk with control	Risk difference with Ivermectin (95% CI)
Clinical improvement	483 (3 studies)	⊕⊖⊖⊖ VERY LOW[1,2,3,4,5] due to risk of bias, inconsistency, indirectness, publication bias, large effect	OR 1.98 (1.11 to 3.53)	Study population 868 per 1000 moderate effect	61 more per 1000 (from 12 more to 91 more)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and it CI). CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estim effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and ma change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.

[1] Bias due to confounding: [2] Due to study types,[3] Due to retrospective study, [4] Due to small number of studies' [5] due to less numb study and small sample size

CONCLUSION

Ivermectin is an established drug with a long history of clinical use and with minimal safety concern. Recent observational studies have reported the effectiveness of this drug as add-on therapy in patients with COVID-19. Our meta-analysis also supports this finding and suggests the modest utility of ivermectin in reducing all-cause mortality and improving clinical outcomes. Currently, many clinical trials are on-going, and definitive evidence for repurposing this drug for COVID-19 patients will emerge only in the future.

AUTHOR CONTRIBUTION: The concept was developed by RRM and BMP. BRM, SD, and RRM carried out the search, data extraction, and quality assessment. Any disagreement was resolved by BMP. Statistical analysis and inference was done by BMP and BRM. The manuscript was written by RRM, BRM, BMP, and SD. All authors approved the final version for publication.

CONFLICTS OF INTEREST: There are no conflicts of interest.

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