Outcomes of Ivermectin in the treatment of COVID-19: a systematic review and meta-analysis

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Statement of financial support:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure statement: Authors declare that they have no conflict of interest.

Abstract

Background: To assess the outcomes of ivermectin in ambulatory and hospitalized patients with COVID-19.

Methods: Five databases and websites for preprints were searched until January 2021 for randomized controlled trials (RCTs) and retrospective cohorts assessing ivermectin versus control in ambulatory and hospitalized participants. The primary outcome was overall mortality. Secondary outcome was recovered patients. For meta-analysis, random-effects and inverse variance meta-analyses with logarithmic transformation were performed. ROBINS-I for cohort studies, and the Cochrane Risk of Bias 2.0 tool for trials were used. The strength of evidence was assessed using GRADE.

Results. After the selection, twelve studies (five retrospective cohort studies, six randomized clinical trials and one case series), were included. In total, 7412 participants were reported, the mean age was 47.5 (SD 9.5) years, and 4283 (58%) were male. Ivermectin was not associated with reduced mortality (logRR: 0.89, 95% CI 0.09 to 1.70, p = 0.04, I^2= 84.7%), or reduced patient recovery (logRR 5.52 , 95% CI -24.36 to 35.4, p = 0.51, I^2 = 92.6%). All studies had a high risk of bias, and showed a very low certainty of the evidence.

Conclusions: There insufficient certainty and quality of evidence to recommend the use of ivermectin to prevent or treat ambulatory or hospitalized patients with COVID-19.

Keywords: Ivermectin, Treatment, COVID-19, SARS-Cov-2

INTRODUCTION

Since the first reported case of severe respiratory syndrome coronavirus 2 (SARS-CoV-2), in December 2019 in Wuhan, China; cases of coronavirus disease (COVID-19) have increased exponentially, with more than 95 million infected people worldwide until January 18, 2021 (https://coronavirus.jhu.edu/map.html). This high volume of COVID-19 cases has led to several problems including an overburdened health system, and a worrisome shortage of healthcare personnel. In this setting, finding an effective therapy against SARS-CoV-2 has become an urgent need (1)

The current treatment of COVID-19 has been limited to general supportive care, because studies evaluating the efficacy of treatment in patients with COVID-19 have had several limitations and no treatment has demonstrated strong evidence for widespread recommendation (2).

Ivermectin is a semisynthetic anthelmintic agent that selectively binds to glutamate-gated chloride ion channels found in nerve and muscle cells of invertebrates (3). However, an antiviral activity in RNA and DNA viruses has also been reported (4).

Caly, et al. conducted an in vitro study, in which they inoculated the SARS-CoV-2 virus in Vero/hSLAM cells, and found that Ivermectin at a dose of 4 µM reduced the viral load after 48 hours. This finding encouraged the conduction of studies aimed to evaluate the clinical effectiveness of Ivermectin (5).

On the other hand, Virginia D. Schmith et al. developed a pharmacokinetic model, with transit absorption, first-order elimination and weight as covariates in the central volume of distribution and clearance. These authors used approved doses of 200 µg/kg (in 3 mg

increments); 120 mg MD and 60 mg three times weekly (every 72 hours) and concluded that the inhibitory concentration (IC_{50}) of ivermectin was not expected to inhibit SARS-CoV-2 in lung tissue even simulating with 10 times the approved dose in humans. Similar findings were reported by Caly et al (5, 6).

We conducted a systematic review and meta-analyses to evaluate the clinical efficacy of ivermectin for the treatment of COVID-19. This will provide clinicians with an overview of the scientific evidence on a potential treatment option, which will help in the clinical management of COVID-19 patients.

METHODS

Protocol

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (7).

Data sources

We searched PubMed, Scopus, Web of Science, Ovid-Medline, Embase, websites for preprints/preproofs ("Other sources"; https://www.medrxiv.org, https://preprints.scielo.org/index.php/scielo, https://www.biorxiv.org, https://arxiv.org), websites for protocols of clinical trials (https://clinicaltrials.gov). We performed a search strategy for each database. The complete search strategy is found in *Supplementary file*. We included all the original published studies (either as preprints or in scientific journals) of clinical trials, non-randomized studies of intervention, and retrospective cohorts, without language restrictions, from inception to January 21, 2020; that have included patients (ambulatory or hospitalized) with COVID-19, and have compared a group that received ivermectin with a group that did not; regardless of their study design. Systematic reviews, narrative reviews, conference proceedings, editorials, and letters to the editor without original data were excluded.

Outcomes

Primary outcome was overall mortality. Secondary outcome was recovered patients.

Study selection

Two authors (JJB, DCM) independently screened search results by title and abstract according to the inclusion and exclusion criteria, using a web program *Rayyan* (rayyan-

qcri.org). Also, two authors (JJB, DCM) independently assessed relevant studies and selected by full-text for the next phase of assessment. Discrepancies were consulted with another author (ACS), and a consensus was reached. The selection of articles in each stage of the review process was made using the Endnote X9 software.

Data extraction

Two authors (JJB, DCM) independently extracted the data using pre-piloted Excel spreadsheets. Again, discrepancies were consulted with another author (ACS). The data extracted from each study were: Author, year, country, type of study, number of patients with ivermectin treatment, treatment/comparison or control arm, characteristics and condition of the patient when the treatment was received, methods of assessment and confounding variables, outcomes, and absolute effect of ivermectin versus control. Regarding the outcome of recovered patients, this variable was evaluated according to the criteria considered by the authors of each included study.

Risk of bias assessment

Two investigators (JJB, DCM) independently assessed the risk of bias by using the ROBINS-I (Risk Of Bias In Non-Randomized Studies of Interventions) tool (8) for cohort studies and the Cochrane Risk of Bias 2.0 tool (9) for trials; disagreements were resolved by discussion with a third investigator (ACS).

Data synthesis and statistical analysis

We assessed the certainty of evidence using the GRADE methodology (10). When possible, we meta-analyzed results of RCTs and non-randomized studies that have used methods to control by possible confounders.

Random-effects models with Hartung-Knapp adjustment for random effects model, and the inverse variance method were used for all meta-analyses. Effects of ivermectin were described with log relative risks (LogRRs) with 95% confidence intervals (Log RR 95% CIs) for dichotomous outcomes in the observational studies that were assessed. Heterogeneity among studies was assessed using the I^2 statistic: 0–30% meant low, 30–60% moderate, and >60% high heterogeneity (11). Subgroup analysis by year (<60 years vs >60 years), condition (outpatient vs inpatient), and need of oxygen support (with vs without oxygen support) was proposed; however, due to the insufficient published evidence, these aspects were not evaluated. A sensitivity analysis was performed excluding those studies without adjustment for confounding. (12).

Ethical considerations

This is a systematic review of published and open information, in which no human subjects participated. No ethics committee approval was required.

Results

Selection of studies

The search yielded 532 results. After duplicates were excluded, 232 titles and abstracts were reviewed, 210 of these were excluded, and 22 scientific papers were evaluated in detail. Finally, 12 studies were included in the qualitative synthesis (13-24), and five studies were included in the quantitative synthesis (Figure 1). Most studies were pre-print studies and two studies (18, 22) were anticipated results of clinical trials protocols.

Characteristics of the studies included

Main characteristics of included studies are summarized in Table 1. Two studies were located in USA (21, 22) , two from South America (15, 23), one from Iraq (16), two from Spain, one from Iran, and four from Bangladesh (13, 17, 18, 20). Five retrospective cohort studies (14, 16, 17, 21, 23, 25), six clinical trials (13, 18-20, 22, 24), and one case series (15) were found. There were 7412 reported participants, the mean age was 47.5 (SD 9.1) years, and 4283 (58%) were male. The treatment was ivermectin (alone or with azithromycin, hydroxychloroquine, dexamethasone, enoxaparin, aspirin or dicloxacillin). Only one study reported no control group (15). Most patients were hospitalized and confirmed COVID-19 by RT-PCR, except for individuals included in one study evaluating asymptomatic families (22). Regarding methods of assessment and confounding variables, two studies analyzed the confounding variables by propensity score weighting and adjusted by age, sex, location, type of admission, comorbidities, antibiotics applied and other drugs (21, 23). One study assessed these variables by logistic and Cox regression adjusted by age, sex, comorbidities and use of other drugs (21). One study assessed the variables by Kaplan Meier survival curve, adjusted by age, gender, and severity (16). Finally, eight studies were not adjusted by confounding

variables because they only applied bivariate analysis (13-15, 17-20, 22). Different outcomes were evaluated by included studies, and most studies have assessed mortality and recovered patients as the primary outcome. Only four studies did not describe data regarding mortality and recovery in their analysis (14, 15, 22, 26).

Assessment of risk of bias

Five RCT had high risk of bias due to missing outcome data (18-20, 22, 26). Four cohorts had serious risk of bias: Two studies were at serious risk of bias due to classification of interventions (16, 23), and two studies had critical risk of bias due to confounding (14, 17).

Primary and secondary outcomes of ivermectin in patients with COVID-19

In this analysis with four pre-print retrospective studies, and high risk of bias, ivermectin is not associated with reduced mortality (logRR 0.89, 95% CI 0.09 to 1.70, p = 0.04, I^2= 84.7%, Figure 2a). Additionally, ivermectin was not associated with reduced patient recovery (logRR 5.52 , 95% CI -24.36 to 35.4, p = 0.51, I^2 = 92.6%, Figure 2b).

Sensitivity analysis

No differences were found between the overall analysis and that proposed in the sensitivity analysis in terms of outcomes.

Certainty of evidence in included studies

For certainty of evidence and evaluation of study quality, the GRADE recommendation was used. Two outcomes were assessed: Mortality (3607 participants, 5 retrospective studies), and recovery (397 participants, 3 pre-print retrospective studies). Both showed a very low certainty of the evidence, based on study design, risk of bias, inconsistency, indirectness and imprecision (Table 2).

Discussion

Main results

We did not find a significantly reduction in the mortality and recovery of patients in the analyzed studies. It should be noted that the included studies are pre-print, so the information may vary and change the overall effect in our meta-analysis (although this trend may still be not significant).

Ivermectin has been widely used on the basis of having an antiviral effect against SARS-Cov-2 (27). In this regard, a study published in Australia showed in-vitro effectiveness of ivermectin in Vero-cells; however, its clinical application in humans is very doubtful (5). This study was rapidly adopted by clinical practice guidelines, recommending ivermectin for the treatment of patients hospitalized with COVID-19, especially in countries severely affected by the pandemic. For example, Peru, one of the countries hardest hit by the pandemic, included Ivermectin as a first-line treatment, even as prophylaxis (28).

The rationale to include this drug was based on its pharmacologic properties and application in other scenarios. Ivermectin belongs to the chemical group of avermectins, and is widely used in large animals for the treatment and control of parasitic infections, and to assist on the treatment of scabies and ticks. In humans, ivermectin has been used as a prophylactic drug in filariasis and as a therapeutic agent for scabies. It is a drug approved by the FDA and has shown to be safe in the recommended dosages (200 μg/kg) (29).

Despite the published theoretical information, there are not enough clinical trials to confirm the efficacy and safety of ivermectin for prophylaxis or treatment of patients with COVID-19.

A systematic review was performed by Padhy et al (30), and analyzed the effects of ivermectin in 629 patients with COVID-19 (4 observational studies were included). The ivermectin-treated group had 233 mild cases and 104 moderate to severe cases. All-cause

mortality was reduced in 2 out of the 3 included studies (OR 0.53, 95% CI 0.29-0.96). However, all these studies had a high risk of bias.

One of the limitations of the study conducted by Padhy et al. is that the overall effect of ivermectin on mortality was analyzed without considering the reported effect measure . Furthermore, the analysis was performed without transforming the individual effect (from OR to LogOR, for example), thus the OR reported was overestimated.

In another systematic review with networked meta-analysis, the effects of ivermectin on mortality were analyzed, and only two studies were included. The authors reported a very close statistical significance in terms of association of ivermectin with lower mortality (OR 0.15, 95% CI 0.04 to 0.57, p = 0.005); however, they pointed out that these data had very low certainty of evidence (31).

Despite the small amount of highly biased evidence that has been published supporting the efficacy of ivermectin, the specific human dose has not been established. Bray et al. evaluated in vitro whether an ivermectin concentration of 0.1 uM (instead of 5 uM) can inhibit SARS-Cov-2 (32). In clinical studies, the dose has ranged from 120 uM/kg to 200 uM/kg per dose in the intramuscular or oral form (33, 34). However, high doses for humans have not been approved (https://www.fda.gov/animal-veterinary/product-safety-information/faq-covid-19-and-ivermectin-intended-animals).

It is important to know that testing the efficacy of ivermectin in human clinical trials or observational study requires a previous evaluation in a dose-response trial, applying low dose (with less likelihood of pharmacological effect) and high dose relative to placebo. Given the lack of this type of studies, the ideal high dose of ivermectin has not been determined yet.

Our study has some limitations that are worthy to mention. First, regarding heterogeneity, we found that five out of the eight studies were done in inpatients, two studies focused on outpatients only, and one study focused on both outpatients and inpatients. Similarly, we have found differences between treatment arms, for example, five studies reported the use of ivermectin by itself compared to the standard of care, and the remaining studies used ivermectin in combination with other drugs (dexamethasone, hydroxychloroquine, azithromycin). Although the outcome in hospitalized patients was overall mortality or recovery time, in outpatients the outcome was appearance of symptoms of Covid-19, except in one study (Carvallo) that measured disease severity and mortality. As observed, there is clinical heterogeneity that makes it difficult to combine the estimates in a pooled estimate.

It is possible that the methodological heterogeneity and biases found in this systematic review and meta-analysis provided results inconsistent with reality. For this reason, it was proposed to meta-analyze the outcomes separately, assuming for each of them the model of random effects, and thus having greater precision in the effect. In spite of having statistical heterogeneity, the analysis of biases performed on the selected studies and the measurement of the size of the effect according to the outcome made a very close approximation to the reality.

Finally, the LogRR and confidence intervals for mortality and recovery were found to be non-significant, and by applying GRADE, we determined the certainty of the evidence for this estimated effect: The true effect is likely to be substantially different from the estimated effect.

This systematic review and meta-analysis concludes that more randomized clinical trials need to be included in a meta-analysis, with fewer biases to approximate more to the real measurable effect. At the moment, there is no evidence that the use of ivermectin changes the clinical outcome of inpatients or outpatients.

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Figure legends

Figure 1. PRISMA flowchart for included studies

Figure 2. Forest plot for primary and secondary outcomes (a: Mortality; b: Recovered)

Table 1. Characteristics of studies included

Author	Year	Country	Type of Study	Nº of patients with Ivermectin treatment/total patients	Treatment/Comparison or control arm	Characteristics and condition of patients when received treatment	Methods of assessment and confounding variables	Outcomes	Absolute Effect of Ivermectin Versus Control (95% CI) (Mortality or Recovery)	Certainty of the evidence
Soto et al	2020	Peru	Retrospective cohort/NRSI (pre-print)	203/5683	IVM, IVM+AZT / SC	Hospitalized patients confirmed SARS-CoV-2 infection by RT-qPCR, and clinical manifestations compatible with non-life-threatening disease at admission	Propensity score weighting: Age, sex, healthcare centre location, month, Charlson's index at hospital admission, comorbidities registered in the first 48 hours, emergency care before admission, antibiotics used in the first 48 hours, ACEI/angiotensin-II receptor antagonists use, and pneumonia diagnosis in the first 48 hours.	In-hospital and overall mortality and worsening of the disease	Mortality: 47/203 vs 401/2630. RD 7% (1% to 13%)	Low
Gorial et al	2020	Iraq	Retrospective cohort/NRSI (pre-print)	16/87	IVM / Control not specified	Mild to moderate hospitalized patients with COVID-19 by RT-PCR	Kaplan Meier survival curve analysis: Age, gender, severity, clinical features	Recovered patients, time of cure, and safety outcomes	Mortality: 0/16 vs 2/71. RD -3% (-6% to 1%) Recovery: 16/16 vs 69/71. RD -3% (-6% to 1%)	Low

Khan et al	2020	Bangladesh	Retrospective cohort/NRSI (pre-print)	115/248	IVM/SC	Hospitalized patients confirmed SARS-CoV-2 infection	Bivariate analysis only: No counfounding adjusted	Viral clearance, lenght of hospitalization, recovered, mortality	Mortality: 1/115 vs 9/133. RD -5% (-10% to -1%) Recovery: 114/115 vs 124/133. RD 5% (1% to 10%)	Low
Camprubi et al	2020	Spain	Retrospective cohort/NRSI	13/26	IVM/Control group	Hospitalized patients confirmed SARS-CoV-2 infection	Bivariate analysis only: No counfounding adjusted	Severe adverse events	No data	Insufficient
Rajter et al	2020	USA	Retrospective cohort/NRSI	98/196	IVM/Control group	Hospitalized patients confirmed SARS-CoV-2 infection	Propensity score weighting: age, sex, pulmonary condition, hypertension, HIV status, severe pulmonary presentation, and exposure to corticosteroids, hydroxychloroquine, or azithromycin.	Mortality, extubation rates, length of hospital stay	Mortality: 13/85 vs 24/74. RD -17% (-30 to -4%)	Low
Carvallo et al	2020	Argentina	Case series (pre-print)	167/167	IVM+DXM+ENX+AAS / No comparison	Patients with positive RT-PCR diagnosis pf COVID-19	Bivariate analysis only: No counfounding adjusted	Severity of disease, mortality	No data	Insufficient
Podder et al	2020	Bangladesh	Randomized clinical trial	32/62	IVM + SC/SC	Outpatient at a semi-rural settings with COVID-19	Bivariate analysis only: No counfounding control	Recovered patients	Recovery time: 10.09±3.24 vs 11.50±5.32	Low

Shouman	2020	USA	Randomized clinical trial (protocol registered)	203/304	IVM/Control group	Asymptomatic Family Close Contact for Patient With COVID-19	Bivariate analysis only: No counfounding adjusted	Development of Symptoms, development of COVID-19	No data	Insufficient
Mahmud	2020	Bangladesh	Randomized clinical trial(protocol registered)	183/363	IVM+DXC/Placebo	Hospitalized patients confirmed SARS-CoV-2 infection	Bivariate analysis only: No counfounding adjusted	Early Clinical Improvement, Late Clinical Recovery, mortality	Mortality: 0/183 vs 3/180. RD -2% (-3% to -0.2%) Recovery: 42/183 vs 67/180. RD -14% (-23 to -4%)	Low
Shakhsi et al	2020	Iran	Randomized clinical trial(pre-print)	120/180	IVM (4 arms) / Hydroxychrloroquine - Placebo	Hospitalized patients with confirmed mild to severe SARS-CoV-2 infection	Bivariate analysis only: No counfounding adjusted	Mortality	Mortality: 0/183 vs 3/180. RD -15% (-25% to -4%)	Insufficient
Chaccour et al	2020	Spain	Randomized clinical trial	Dic-24	IVM/Placebo	Patients with non-severe COVID-19 and no risk factor	Bivariate analysis only: No counfounding adjusted	Proportion of patients with SARS-CoV-2 at day 7 post-treatment, viral load at days 4, 7, 14 and 21 post treatment.	No data	Insufficient
Ahmed et al	2020	Bangladesh	Randomized clinical trial	24/72	IVM, IVM+DXC/Placebo	Hospitalized patients confirmed SARS-CoV-2 infection	Bivariate analysis only: No counfounding adjusted	Virological clearance, remission or fever, clinical worsening, all-cause mortality	No data	Insufficient

Table 2. Summary of certainty evidence

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with [Standar care]	Risk difference with [Ivermectin]
Mortality assessed with: RR	3607 (5 observational studies)	⨁◯◯◯ VERY LOW	**RR 0.70** (0.31 to 2.28)	154 per 1,000	**46 fewer per 1,000** (106 fewer to 197 more)
Recovery assessed with: RR	397 (3 observational studies)	⨁◯◯◯ VERY LOW	**RR 1.37** (0.61 to 3.07)	857 per 1,000	**317 more per 1,000** (334 fewer to 1,773 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

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

Identification

Screening

Elegibility

Inclusion

Records identified through database searching (n=532)

Additional records identified through other sources (n=0)

Duplicates removed (n = 330)

Records screened (n =232)

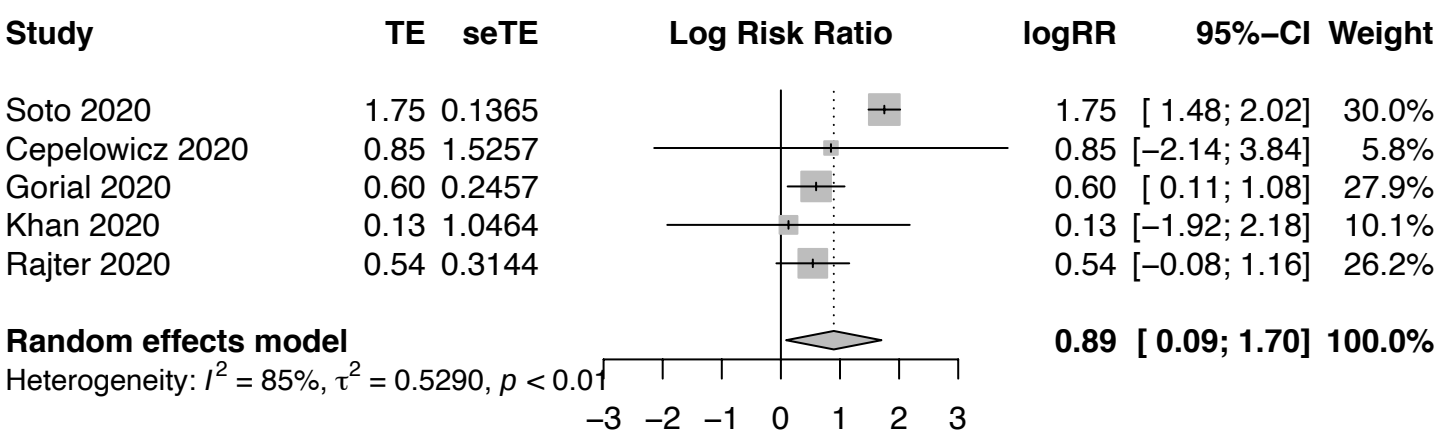
Records excluded (n = 210)

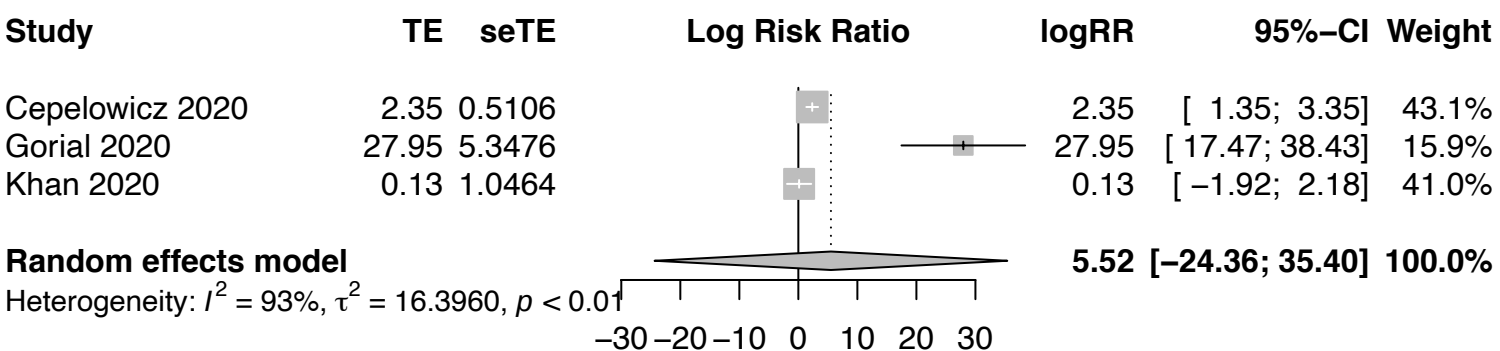
Full-text articles assessed for elegibility (n = 22)

Full-text articles excluded (n = 10)
Letters: 9
Wrong outcomes: 1

Studies included in qualitative synthesis (n = 12)

Studies included in quantitative synthesis (n = 5)


Study
TE
seTE
Log Risk Ratio
logRR
95%−CI
Weight
Soto 2020 1.75 0.1365 1.75 [1.48; 2.02] 30.0%
Cepelowicz 2020 0.85 1.5257 0.85 [−2.14; 3.84] 5.8%
Gorial 2020 0.60 0.2457 0.60 [0.11; 1.08] 27.9%
Khan 2020 0.13 1.0464 0.13 [−1.92; 2.18] 10.1%
Rajter 2020 0.54 0.3144 0.54 [−0.08; 1.16] 26.2%
Random effects model 0.89 [0.09; 1.70] 100.0%
Heterogeneity: I^2 = 85%, τ^2 = 0.5290, p < 0.01
−3 −2 −1 0 1 2 3


Study
TE
seTE
Log Risk Ratio
logRR
95%−CI
Weight
Cepelowicz 2020
2.35
0.5106
2.35
[1.35; 3.35]
43.1%
Gorial 2020
27.95
5.3476
27.95
[17.47; 38.43]
15.9%
Khan 2020
0.13
1.0464
0.13
[−1.92; 2.18]
41.0%
Random effects model
5.52
[−24.36; 35.40]
100.0%
Heterogeneity: I^2 = 93%, τ^2 = 16.3960, p < 0.01
−30
−20
−10
0
10
20
30