Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

RESEARCH QUESTION: Among COVID-19 patients, should metformin be used for treatment?

Review by: Anton G. Elepaño, MD; Christopher G. Manalo, MD, MSc (cand), Mario M. Panaligan, MD, Ivan N. Villespin, MD, Arnel Gerald Q. Jiao, MD, Marissa M. Alejandria, MD, MSc

RECOMMENDATION

Recommendation	Certainty of Evidence	Strength of Recommendation
We suggest against the use of metformin as treatment for COVID-19.	Low	Weak

Consensus Issues
No benefit on the critical outcomes of mortality and hospitalization were seen on the use of Metformin for COVID-19 hence the panel suggested against its use for treatment.

KEY FINDINGS

- Metformin did not improve mortality or hospitalization rates of patients with COVID-19 based on two randomized trials.
- A lower proportion of patients diagnosed with long COVID were seen among patients who were previously treated with metformin for acute COVID-19.
- The rates of serious adverse events were no different between patients receiving metformin and those on placebo.
- Overall certainty of evidence was low due to ascertainment of outcome of interest (for long COVID), inconsistency, and imprecision across different outcomes.

INTRODUCTION

Multiple observational studies have reported associations between pre-admission and in-hospital metformin use and improved COVID-19 outcomes among patients with diabetes [2,3], sparking interest in the potential of the drug as treatment for COVID-19. Beyond its antihyperglycemic properties, the benefits of using metformin in COVID-19 are attributed to its pleiotropic effects in regulating cytokine expression, dampening viral uptake, and mitigating pulmonary fibrotic sequelae [4]. This review was conducted to address the target question: “should metformin be used for COVID-19?”

REVIEW METHODS

A comprehensive literature search was conducted on 20 April 2023 across databases and registers, including Medline, Scopus, and ClinicalTrials.gov. The search strings included keywords such as “metformin”, “COVID-19”, and “post-acute sequelae of COVID-19”. The full search strategy is outlined in Appendix 2. No limitations were placed on the date or language of publication. We included studies that reported use of metformin among adult or pediatric patients with current or past COVID-19. Outcomes of interest included all-cause mortality, need for hospitalization, time to disease resolution, serious adverse events, and incidence of post-acute COVID-19 syndrome. Quality of included studies was appraised using the Cochrane risk of bias tool.

RESULTS

A total of three studies involving 1,869 patients were included in this review [5,6,7]. Patients enrolled were all adults, predominantly overweight or obese based on their body mass indices, and mostly non-diabetic. Metformin doses did not exceed 1,500 mg per day and were administered for ten to 14 days within seven days of symptom onset. Two studies looked at outcomes in non-hospitalized participants [5,6] while one study investigated clinical outcomes among patients admitted for COVID-19 [7]. Mortality and hospitalization rates were reported in the former two studies, while duration of hospitalization was reported in the latter. Only one study reported on the proportion of patients who developed long COVID on follow up [8].

Risk of bias is generally low for most domains except for attrition bias, wherein two studies [5,6] used multiple imputations and modified intention-to-treat analyses to account for low drug adherence and participants lost to follow-up. Attrition bias in the study of Reis [6] was also attributed to the platform trial design where some controls have been given a different treatment duration of placebo compared to metformin leading to disproportionately higher dropout rate in intervention group. Other potential sources of bias were detected but were deemed to be low risk for the two studies concerned. These include outcome measurement for long COVID in the study of Bramante [8] where self-reported diagnosis from a medical provider may be prone to recall bias. However, given that participant, provider, and outcome assessor blinding was preserved, risk of bias was rated to be low. The other potential issue was the non-simultaneous treatment with metformin and placebo which occurred because of the platform trial design of Reis [6]. Statistical adjustments were made to account for these temporal differences.

Efficacy outcomes

Mortality within 28 days of randomization was reported in two studies [5,6]. Pooled analysis of intention-to-treat analyses without imputations for missing data revealed that early treatment with metformin did not improve mortality rates among patients with symptomatic COVID-19 (RR 0.76; 95% CI, 0.30-1.89; I^2=0%; moderate certainty).

Similarly, in terms of decreasing the rate of hospitalization, data from two studies showed no benefit with use of metformin (RR 0.66; 95% CI, 0.30-1.45; I^2=68%)[5,6]. The substantial heterogeneity between the two studies can be explained by the differences in duration of follow up and reporting of the outcome (14 versus 28 days). Meanwhile, the third study, which enrolled hospitalized patients with COVID-19, showed a faster but statistically insignificant time to hospital discharge among patients given metformin (mean difference -1.00 days; 95% CI, -6.05 to 4.05) [7].

One study reported on the proportion of patients who were diagnosed with long COVID syndrome within 300 days of receiving either metformin or placebo for acute COVID-19 [8]. Significantly less patients in the metformin group received a diagnosis of long COVID from a medical provider (RR 0.59; 95% CI, 0.39-0.88). Interestingly, a priori subgroup analyses showed heterogeneous treatment effect favoring use of metformin among females, those younger than 45 years, those with BMI ≥30, and unvaccinated patients.

Safety outcomes

Data from three studies confirm the established safety of metformin at the doses used in the trials (1,000 to 1,500 mg daily). Reported serious adverse events were not in excess among patients who received metformin compared to those who received placebo (RR 1.11; 95% CI, 0.70-1.75) [6].

Table 1: Summary of findings

OUTCOMES	BASIS (No and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIIDENCE
All-cause mortality at 28 days	2 RCT (n=1,777)	RR 0.76	0.30 to 1.89	Inconclusive	Moderate
Hospitalization	2 RCT (n=1,773)	RR 0.66	0.30 to 1.45	Inconclusive	Moderate
Development of Long COVID within 300 days	1 RCT (n=1,125)	RR 0.59	0.39 to 0.88	Benefit	Low
Serious Adverse Events	3 RCT (n=1,869)	RR 1.13	0.67 to 1.93	Inconclusive	Low

Certainty of evidence

The overall certainty of evidence was low across the four outcomes reviewed. The outcomes on mortality, hospitalization, and serious adverse events were downgraded for imprecision given the wide confidence intervals of effects estimates. Reported outcome on the development of long COVID was downgraded twice for indirectness, since the outcome measure was self-reported diagnosis from a medical provider which only approximated the pre-specified outcome of interest, and for possible publication bias, given that the data is from a single preprint article. Finally, the safety outcome, which was the proportion of patients with serious adverse events was downgraded for imprecision and inconsistency due to unexplained heterogeneity in effect sizes.

RECOMMENDATIONS FROM OTHER GROUPS

Both World Health Organization and IDSA gave no recommendations regarding metformin in their respective COVID-19 guideline documents as of 25 April 2023 [9,10]. US CDC/NIH gives a recommendation against use of metformin which was last updated on December 1, 2022 [11]; The study of Bramante [8] which reported outcome on long COVID was posted on 24 December 2022.

ONGOING STUDIES AND RESEARCH GAPS

There are currently no ongoing randomized trials evaluating use of metformin among COVID-19 patients.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

The decision to recommend the use of metformin was based on a preprint of one study with low overall risk of bias. Despite the self-reported nature used in outcome determination, this method of data collection was unlikely to have affected the effect estimates given that blinding was preserved. Relying on physician diagnoses instead of employing a diagnostic criteria for long COVID was also deemed appropriate given the differences and the evolving definitions of long COVID during the time of the study.

Congruent with the trial methodology used in the relevant study [8], we specified that metformin must be given among adult patients who are overweight or obese and during the early symptomatic stage of COVID-19. The intended effect is limited to preventing the development of long COVID. This clinical outcome is deemed important, the benefit is substantial, and the established safety of metformin was reinforced in the trials.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=3/10)

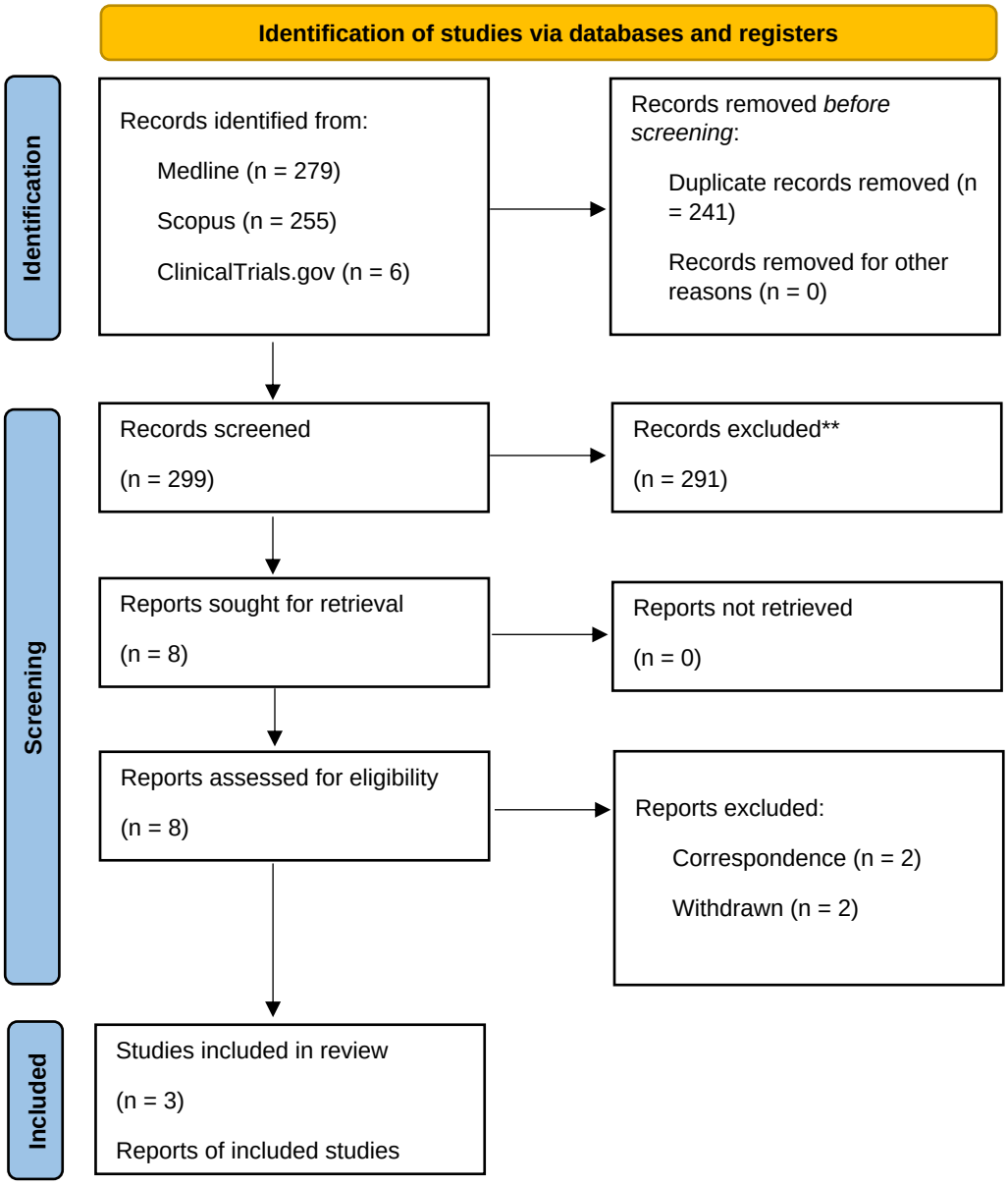
FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (3)					Based on a meta-analysis published this year, the estimated prevalence of long COVID is 45% among COVID-19 survivors. No pharmacologic treatment for long COVID is currently recommended in both local and international guidelines.
Benefits	Large	Moderate (3)	Small	Uncertain	Trivial		The risk of being diagnosed with long COVID was 0.56 times less among patients who received metformin for their acute COVID-19 symptoms compared to those who were given placebo (RR 0.56; 95% CI, 0.36-0.87).
Harm	Large	Moderate	Small (2)	Uncertain	Trivial (1)		The trials included confirm the established safety of metformin having no excess serious adverse events compared to placebo (RR 1.13; 95% CI, 0.66-1.93).
Certainty of Evidence	High	Moderate (2)	Low (1)	Very low			The overall certainty of evidence was moderate. Mortality was downgraded for imprecision given the low event rates and wide confidence intervals of effects estimates. Development of long COVID was downgraded for indirectness since the outcome measure was self-reported diagnosis of long COVID by a medical provider. Serious adverse events was downgraded for inconsistency given that the unexplained heterogeneity in effect sizes.
Balance of effects	Favors treatment (1)	Probably favors treatment (2)	Does not favor treatment	Favors no treatment			The significant benefit of using metformin to reduce the risk of developing long COVID is weighed against its ignorable harms.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability	Possibly NO important uncertainty or variability (2)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate cost (2)	Negligible cost (1)	Moderate savings	Large savings	The drug price reference index (ceiling price) is ₱7.58 for a 500mg metformin tablet. For the prevention of long COVID, the trial methodology specified using 36 tablets for a 14-day regimen. This totals to a price range of ₱14.04 to ₱272.88 for the total duration of treatment.
Certainty of evidence of	No included studies (2)	Very low	Low	Moderate (1)	High		

required resources								No cost-effectiveness studies were found.
Cost effectiveness	No included studies (1)		Probably / Favors the comparison		Probably favors the intervention (2)	Favors the intervention	Does not favor either the intervention or the comparison	No cost-effectiveness studies were found, but the low cost of a full course of metformin (₱14-273) may be easily offset considering the indirect costs which a diagnosis of long COVID may entail.
Equity	Uncertain	Varies (1)	Reduced		Probably reduced	Probably no impact	Probably increased (2)	Increased
Acceptability	Varies		No	Probably no	Yes (1)	Probably yes (2)		**For the use: 3 (weak)** Against the use: 0 **No additional considerations or comments**
Feasibility	Varies		No	Probably no	Yes (2)	Probably yes (1)		

Appendix 2: Search Yield and Results

Database or Register	Search String	Records
Medline	("Metformin"[Mesh] OR metformin OR Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage) AND ("COVID-19"[Mesh] OR COVID OR COVID-19 OR "Post-Acute COVID-19 Syndrome"[Mesh] OR "Long COVID" OR "Long COVID-19" OR “Long haul COVID” OR “Long haul COVID-19” OR Post-COVID OR "Post-COVID-19" OR "Post-Acute Sequelae")	279
Scopus	TITLE-ABS (Metformin OR Dimethylbiguanidine OR Dimethylguanylguanidine OR Glucophage) AND TITLE-ABS (COVID OR COVID19 OR COVID-19 OR “SARS-CoV-2 Infection” OR “Post-Acute COVID-19 Syndrome” OR "Long COVID" OR "Long COVID-19" OR “Long haul COVID” OR “Long haul COVID-19” OR Post-COVID OR "Post-COVID-19" OR "Post-Acute Sequelae")	255
ClinicalTrials.gov	Metformin | COVID-19	6

Appendix 3: PRISMA Flow Diagram

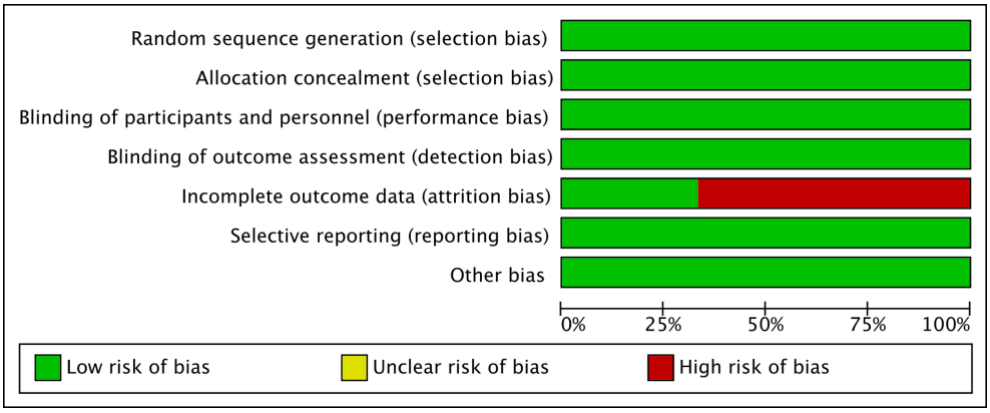


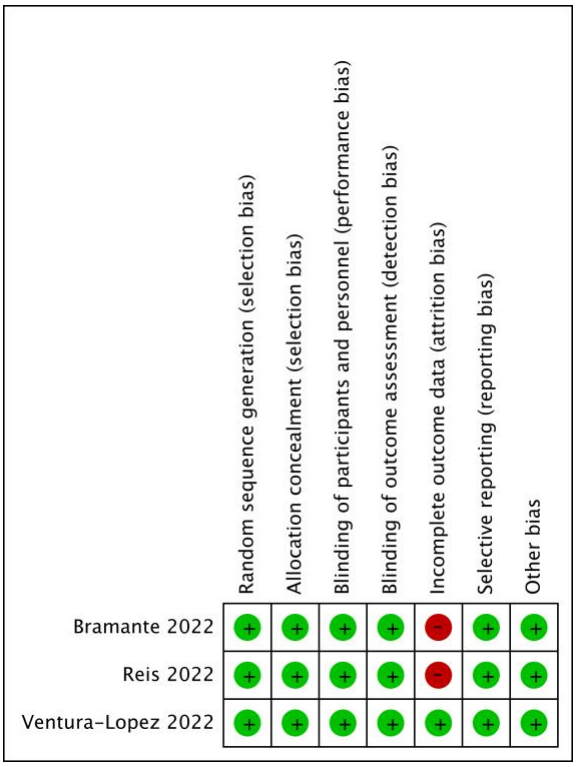
Appendix 4: Characteristics of Included Studies

Study ID/ Study Design	Population	Intervention/Comparator	Outcome
Bramante 2022 Randomized factorial trial	Setting: outpatients in six institutions in the United States Inclusion: 30 to 85 years of age, laboratory-confirmed COVID-19 diagnosis, within 7 days of symptom onset, a body-mass index associated with overweight or obesity Enrollment period: May 2021 to January 2022 Allocated to intervention: 718 Allocated to control: 713 Participant characteristics: median age of 46; sex: 56% female; race: 82% white, 4% asian, 6% other; comorbidities: 2% with diabetes, 27% with cardiovascular disease, 49% with BMI ≥30, median BMI 30; 52% fully or partially-vaccinated	Intervention: intermediate release metformin given orally with dose titration as follows: 500 mg on day 1, 1000 mg on days 2-5, 1500 mg on days 6-14 Co-intervention (2x3 factorial design): fluvoxamine, ivermectin Comparator: placebo	Bramante 2022a: • Composite of all-cause mortality, hospitalization, emergency room visits, and hypoxemia within 14 days of randomization • All-cause mortality within 28 days of randomization (presented in Supplementary appendix) • Daily symptom severity • Adverse events Bramante 2022b: Development of long COVID (defined as participant-reported receipt of a long Covid diagnosis from a medical provider) until 300 days from randomization
Reis 2022 Randomized platform trial	Setting: outpatients in ten participating cities in Brazil Inclusion: at least 18 years of age, laboratory confirmed COVID-19, within 7 days of symptom onset, high-risk for developing severe COVID-19 Enrollment period: January 2021 to April 2021 Allocated to intervention: 215 Allocated to control: 203 Participant characteristics: median age of 52; sex: 57% female; race: 91% mixed race, 2% white, 1% unknown; comorbidities: 15% with diabetes, 40% with hypertension, 3% with chronic cardiac disease, 45% with BMI ≥30; 0% vaccinated	Metformin 750 mg given orally twice daily for 10 days Other interventions (platform trial): hydroxychloroquine, lopinavir/ritonavir, fluvoxamine, ivermectin Comparator: placebo	• Composite of hospitalizations and emergency room visits within 28 days of randomization • All-cause mortality within 28 days of randomization • Time to clinical improvement • Adverse events
Ventura-Lopez 2022 Randomized phase 2b trial	Setting: hospitalized patients in one institution in Mexico Inclusion: at least 18 years of age, laboratory confirmed COVID-19 within 4 days of randomization, hospitalized and with radiographic evidence of pulmonary infiltrates Enrollment period: July 2020 to March 2021	Metformin glycinate 620 mg given orally twice daily for 14 days Comparator: placebo	• Duration of hospitalization • Need for supplemental oxygen • Adverse events

	Allocated to intervention: 10 Allocated to control: 10 Participant characteristics: median age of 47; sex: 15% female; race unspecified; comorbidities: 20% with diabetes, 20% with hypertension, median BMI of 29; 0% vaccinated		

Appendix 5. Risk of Bias Assessment





Appendix 6. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	metformin	placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality at 28 days												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	8/897 (0.9%)	10/880 (1.1%)	**RR 0.76** (0.30 to 1.89)	**3 fewer per 1,000** (from 8 fewer to 10 more)	⨁⨁⨁◯ Moderate	CRITICAL
Hospitalization												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	34/890 (3.8%)	48/883 (5.4%)	**RR 0.66** (0.30 to 1.45)	**18 fewer per 1,000** (from 38 fewer to 24 more)	⨁⨁⨁◯ Moderate	CRITICAL
Development of long COVID within 300 days of follow-up												
1	randomised trials	not serious	not serious	serious[c]	not serious	publication bias strongly suspected[d]	35/564 (6.2%)	59/561 (10.5%)	**RR 0.59** (0.39 to 0.88)	**43 fewer per 1,000** (from 64 fewer to 13 fewer)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events												
3	randomised trials	not serious	serious[e]	not serious	serious[b]	none	34/943 (3.6%)	29/926 (3.1%)	**RR 1.13** (0.67 to 1.93)	**4 more per 1,000** (from 10 fewer to 29 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. There are low event rates and wide confidence intervals.
b. There are wide confidence intervals.
c. A self-reported diagnosis of long COVID-19 only indirectly measured the pre-specified outcome of interest, which was the proportion of patients who developed the syndrome.
d. Only one preprint article was considered.
e. There is unexplained heterogeneity in effect sizes.

Appendix 7. Pooled Efficacy and Safety Outcomes

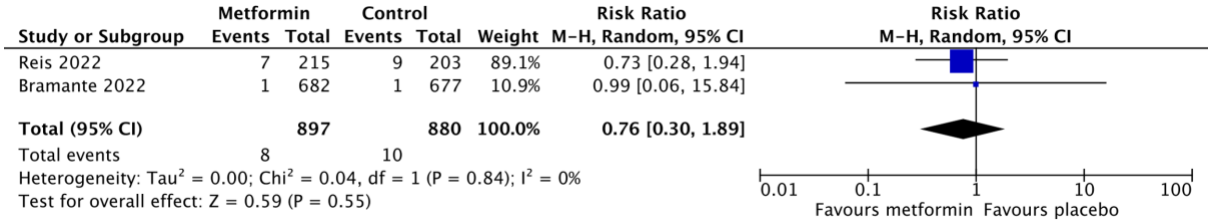


Figure 1. Effect of metformin on overall mortality at 28 days.

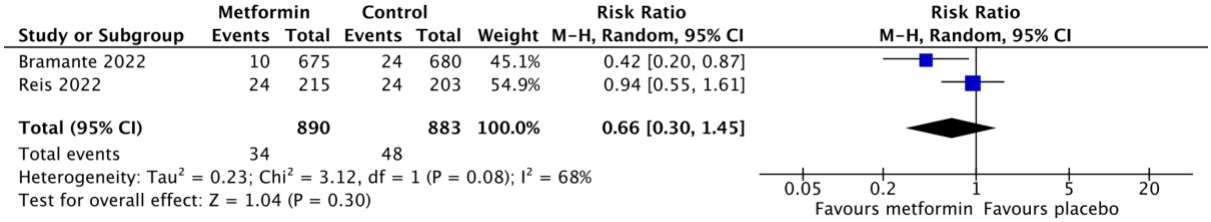


Figure 2. Effect of metformin on proportion of hospitalization.

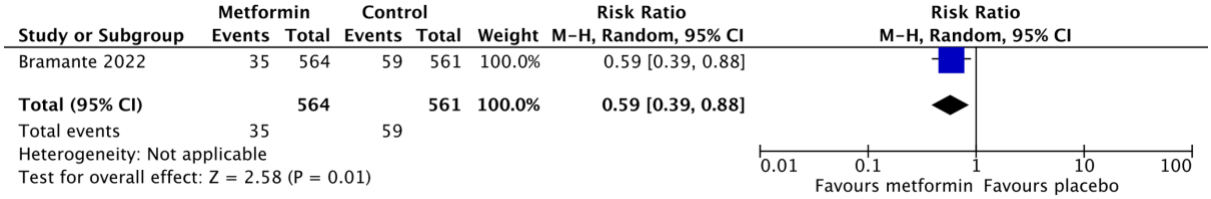


Figure 3. Effect of metformin on developing long COVID.

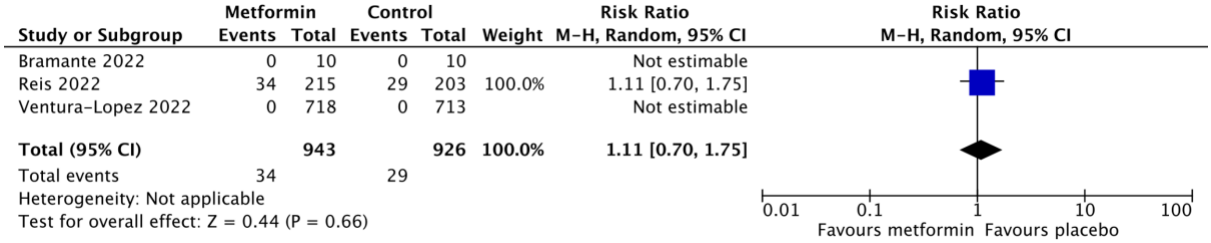


Figure 4. Effect of metformin on the proportion of serious adverse events reported.