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Metformin for covid-19: systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

OBJECTIVE To summarise the effects of metformin on covid-19 to inform a World Health Organization (WHO) clinical practice guideline.

DESIGN Systematic review and meta-analysis.

DATA SOURCES As part of a living systematic review and network meta-analysis of drug treatments for covid-19 (covid-19 LNMA), a search was performed of the WHO covid-19 database, six Chinese databases, and the Epistemonikos Foundation's Living Overview of the Evidence covid-19 Repository (covid-19 L-OVE).

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Randomised controlled trials that compared metformin with placebo in patients with acute covid-19 infection.

DATA SYNTHESIS Frequentist pairwise meta-analyses were performed using the restricted maximum likelihood random effects model. The effects of interventions on selected outcomes were summarised using risk ratios, risk difference, and mean difference when appropriate, along with their corresponding 95% confidence intervals (CIs). To estimate absolute effects, the control arm event rate was used as the baseline risk. The risk of bias of the included studies was assessed using a modification of the Cochrane risk of bias 2.0 tool and the certainty of evidence using the GRADE (grading of recommendations assessment, development and evaluation) approach, with the minimally important difference in effect as the threshold.

RESULTS Three randomised controlled trials of 1869 patients were included; one study provided long term follow-up on long covid. Metformin might have little or no impact on mortality (risk ratio 0.76, 95% CI 0.30 to 1.90; risk difference 3 fewer per 1000, 95% CI 8 fewer to 11 more; low certainty). The effects of metformin on admission to hospital because of covid-19 remain uncertain (risk ratio 0.74, 95% CI 0.28 to 1.95; risk difference 15 fewer per 1000, 95% CI 42 fewer to 55 more; very low certainty). Metformin results in little or no difference in adverse effects leading to discontinuation (risk difference 0.2 more per 1000, 95% CI 2.7 fewer to 3.1 more; high certainty). Metformin might decrease the development of long covid (risk ratio 0.6, 95% CI 0.4 to 0.9; risk difference 41 fewer per 1000, 95% CI 62 fewer to 10 fewer; low certainty). However, the effect is based on a single trial of 1126 patients, which has a high risk of bias owing to missing data, and nearly half of the participants were unvaccinated.

CONCLUSIONS Current evidence based on randomised trials suggests no significant effect of metformin on acute clinical outcomes in patients with non-severe covid-19. Metformin might reduce the incidence of long covid when used to treat patients with non-severe acute covid-19 infection, but this was suggested by low certainty evidence from a single trial.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mechanistic hypotheses and observational studies suggest that metformin might offer benefits for patients with covid-19
⇒ Recent randomised control trials have evaluated the effects of metformin on covid-19

WHAT THIS STUDY ADDS

⇒ This systematic review consolidates and critically appraises the existing evidence about the effects of metformin on covid-19, including long covid
⇒ Metformin appears to have little to no effect on mortality or adverse events leading to discontinuation and uncertain impact on admission to hospital; early administration of metformin in patients with non-severe acute covid-19 infection might reduce the risk of long covid, but this was suggested by low certainty evidence from a single trial

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ More randomised trials are necessary to provide definitive evidence about the effects of metformin on outcomes of patients with covid-19 infection, particularly long covid
⇒ The findings from this systematic review will inform the World Health Organization clinical practice guideline on metformin in patients with non-severe covid-19

Introduction

As a result of ongoing global efforts in medical treatment, vaccination, and public health measures, most patients with covid-19 experience only mild illness. However, some people, particularly those with underlying health conditions, could face complications requiring medical intervention. Additionally, people who have recovered from SARS-CoV-2 infection might experience prolonged effects on various organs and systems, collectively referred to as "long covid" or "post covid-19 condition."[1 2] This condition manifests as a multisystem disorder affecting the respiratory, cardiovascular, nervous, gastrointestinal, and musculoskeletal systems.[3] Studies have reported over 200 associated

symptoms, including pain, fatigue, cognitive impairment, and respiratory difficulties, with 66 of these symptoms sometimes persisting for longer than seven months.[4 5] Conservative estimates suggest that approximately 10% of patients with covid-19 will develop persistent long covid symptoms, with a major impact on individual health and socioeconomic dynamics.[4 5] Consequently, both acute and long term impacts of covid-19, including long covid, have emerged as a pressing global public health concern.[6]

Metformin is a widely used, cost effective, and safe antidiabetic treatment. Metformin could have anti-inflammatory properties, potentially reducing mortality rates and the development of prolonged covid-19 symptoms through various mechanisms.[7–10] Metformin elicits angiotensin converting enzyme 2 phosphorylation, impedes viral adhesion, hinders covid-19 cellular entry, and curtails the release of inflammatory mediators.[7–9] Furthermore, metformin attenuates dipeptidyl peptidase 4 activity, impeding viral entry and diminishing the expression of inflammatory markers.[10] Metformin has been proposed as an antiviral and a disease modifying drug to treat covid-19. Viral load analysis of specimens collected in the COVID-OUT trial showed that the mean SARS-CoV-2 viral load was reduced 3.6-fold with metformin compared with placebo (−0.56 $\log_{10}$ copies/mL, 95% confidence interval (CI) −1.05 to −0.06, P=0.027).[11]

Given the biological rationale for metformin use in covid-19, investigators have conducted several observational studies and randomised controlled trials (RCTs) with results summarised in systematic reviews; however, these reviews have limitations. Several reviews included low quality observational studies and did not incorporate data from recent randomised controlled trials.[12–19] One review of randomised controlled trials omitted a formal quantitative meta-analysis and did not adhere to current GRADE (grading of recommendations assessment, development and evaluations) guidance.[20] Initial randomised controlled trials assessing intervention effects on non-severe covid-19 did not address long covid, and the World Health Organization (WHO) guideline development group (GDG) responsible for WHO covid-19 guidelines did not identify long covid as a key outcome. Additionally, previous reviews did not consider the role of metformin in preventing and treating long covid.[20] When the metformin trial addressing long covid was published, the GDG added long covid as a key outcome for studies of treatment for non-severe covid-19. The GDG also commissioned this review to support their clinical guidelines on metformin in patients with non-severe covid-19, including long covid, a previously unaddressed outcome.[21]

Methods

This review is part of a living systematic review and network meta-analysis of drug treatments for covid-19 (covid-19 LNMA), with the fifth version published on 14 July 2022.[22] Although the covid-19 LNMA provided an evaluation of many therapeutic agents for covid-19, it did not address metformin. A protocol of our methodology for the covid-19 LNMA is available in the online supplemental material. Because evidence suggests different interventions are most effective at certain stages of the disease,[23] the authors of covid-19 LNMA are now in the process of publishing two separate articles addressing drug treatments for mild or moderate covid-19 (also known as non-severe covid-19) and drug treatments for severe covid-19 as the final iteration of this project. We report this review in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) checklist[24] (online supplemental file 2).

Search

Our full search strategy is given in a supplement to our drug treatment paper.[22] To summarise, we conducted daily searches until 22 August 2022 (then weekly until 17 February 2023) of the WHO covid-19 database, a comprehensive multilingual collection of global published and preprint literature on covid-19 (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov). Before its merger with the WHO covid-19 database on 9 October 2020, we searched the US Centres for Disease Control and Prevention's downloadable collection of covid-19 research publications.[25] A verified machine learning model helped to identify randomised trials.[26] Our search also encompassed six Chinese databases: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). We searched the Chinese databases from the conception of the databases to 20 February 2021. We also used the Norwegian Institute of Public Health systematic and living map on covid-19 evidence. Since 20 February 2023, our team performed weekly searches in the Living Overview of the Evidence covid-19 Repository (covid-19 L-OVE) in collaboration with Epistemonikos.[27] We linked preprint reports to future publications using trial registration numbers, authors, and other trial features.

Study selection

This review included reports of randomised controlled trials that compared metformin with placebo in patients with suspected, probable, or confirmed acute covid-19 infection, as defined by the study authors. Using systematic review

software, Covidence (www.covidence.org), pairs of reviewers worked independently to screen titles and abstracts of search records, followed by full texts of records identified as potentially eligible at the title and abstract screening stage. Reviewers resolved disagreements through consensus and, if necessary, adjudication with a third party reviewer.

Data collection and risk of bias assessment

After receiving training and undergoing calibration exercises, two reviewers independently gathered information from each eligible trial using a standardised and pilot tested form. This information included trial characteristics (such as trial registration, publication status, and study design), patient characteristics (such as country, age, sex, comorbidities, type of care, and severity of covid-19 symptoms), intervention characteristics, and outcomes of interest (such as the number of participants analysed and the number of participants who experienced an event). Reviewers resolved discrepancies through discussion and, when necessary, third party adjudication. We updated our data when a study preprint was published as a peer reviewed article.

Guided by the corresponding WHO covid-19 GDG,[21] we concentrated on the following patient important outcomes: all cause mortality within 90 days, mechanical ventilation, admission to hospital, adverse effects leading to discontinuation, patients with long covid, duration of hospital stay, and time to symptom resolution. Long covid was not prespecified in the protocol of our covid-19 LNMA project, and therefore, it is a post hoc outcome in this review.

To assess the risk of bias, reviewers, after training and calibration exercises, used a modified version of the Cochrane tool to assess the risk of bias in randomised trials (RoB 2.0).[28] Reviewers rated trials as having a low risk of bias, probably low risk of bias, probably high risk of bias, or high risk of bias across the following domains: bias arising from the randomisation process, bias owing to deviations from the intended intervention, bias from missing outcome data, bias in outcome measurement, bias in the selection of reported results, and bias from competing risks. Reviewers resolved discrepancies by consensus and, when necessary, by third party adjudication. An online supplemental file includes our modified risk of bias tool.

Statistical analysis

We conducted frequentist pairwise meta-analyses with the random effects model using Stata (version 18). We used restricted maximum likelihood to estimate the between study variance in random effects models because it tends to perform better than other methods in meta-analyses with a small number of studies.[29 30] We summarised the effect of interventions on selected dichotomous outcomes using risk ratios and corresponding 95% confidence intervals. For outcomes where some trials reported no events in one or both arms, we meta-analysed the data using risk difference, applying a continuity correction of 0.5 to studies with no events.[31] We calculated and reported mean difference and corresponding 95% CIs for continuous outcomes. Study weights were generated using the inverse of the variance. The χ^2 test was used to assess statistical heterogeneity, and the I^2 statistic was used to assess inconsistency between studies.[26] When available, we used the intention-to-treat analysis population and events reported in primary studies in our meta-analyses. To calculate absolute effects, we used the control arm event rates as baseline risks. This baseline risk was determined by summing all events in the control arms and dividing this by the total population in the control arms of the included trials. We present the results for each outcome using a summary of findings table produced in MAGICapp (www.magicapp.org).

Certainty of evidence assessment

We assessed the certainty of evidence using the GRADE approach.[32] We made judgments of imprecision using the minimally important difference as a threshold and therefore rated certainty for each outcome in an important or unimportant effect.[33] The corresponding WHO GDG decided and agreed on the following minimally important differences to inform therapeutic recommendations for patients with non-severe covid-19: mortality—3 per 1000; mechanical ventilation—15 per 1000; admission to hospital—15 per 1000; adverse effects leading to discontinuation—15 per 1000; patients with long covid—20 per 1000; duration of hospital stay—1 day; time to symptom resolution—1 day.

Reviewers rated the certainty of outcome as high, moderate, low, or very low based on considerations of risk of bias, inconsistency, imprecision, indirectness, and publication bias. As fewer than 10 studies are included in the pooled estimate, we could not assess publication bias statistically. However, our search strategy included several databases, trial registries, and preprint repositories to capture published and unpublished studies, reducing the likelihood of missing relevant trials. Therefore, our approach reduces the risk of publication bias, but does not rule it out. We used standardised lay language to interpret and communicate the results, reflecting the level of certainty in the evidence.[34]

Patient and public involvement

Patients were part of the WHO guideline development group and were involved in the outcome selection and generation of WHO recommendations, and therefore, in the outcome selection for this systematic review. On publication, the findings of the review will be disseminated to relevant patients and the public.

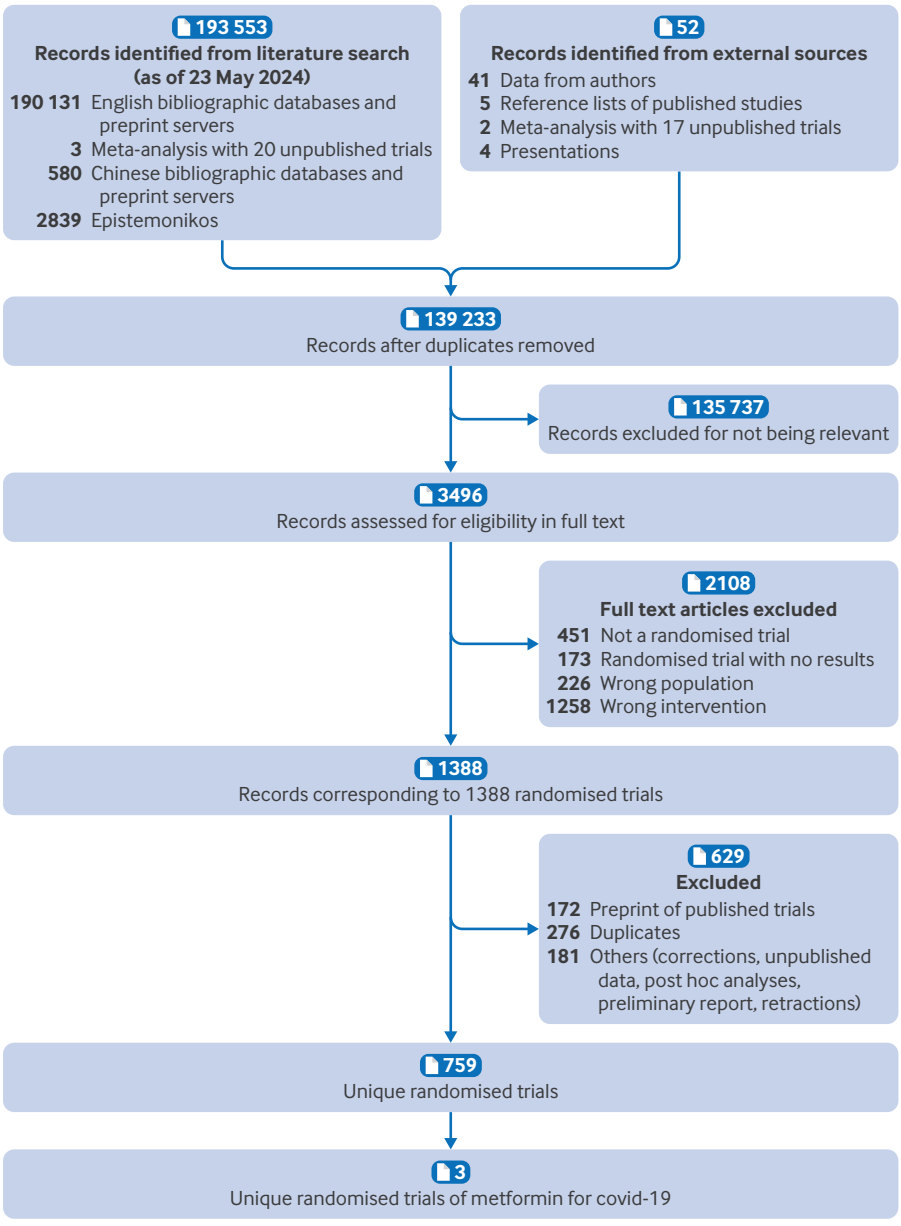

Figure 1 | PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of selected studies

Results

Study characteristics

As of 23 May 2024, we identified 139 233 records after removing duplicates, and we assessed 3496 full texts for our living systematic review and network meta-analysis. Ultimately, we identified 759 eligible unique randomised controlled trials, including three trials focused on the effects of metformin for covid-19 that enrolled 1869 patients (figure 1)[35–37]; one study had a long term follow-up on long covid.[38] These three trials were conducted in Brazil, Mexico, and the United States. The mean age of participants ranged from 46 to 52 years. The TOGETHER trial[35] and COVID-OUT trial[36] enrolled patients with non-severe covid-19 who were not admitted to hospital, and Ventura-López and colleagues recruited a mixed population admitted to hospital with only 20 participants.[37] Table 1 presents the characteristics of the included studies.

Risk of bias in included studies

For mortality, mechanical ventilation, admission to hospital, adverse effects leading to discontinuation, and duration of hospital stay, all studies had a low risk of bias across all domains, including bias from the randomisation process, bias owing to deviations from the intended intervention, missing data, measurement of the outcome, bias in the selection of the reported results, and bias because of competing risks. In the COVID-OUT trial,[36] for long covid, the risk of bias from missing data was likely high owing to 14.9% missing outcome data (1126 of 1323 participants

Table 1 | Characteristics of trials included in systematic review

Characteristics	TOGETHER trial	DMMETCOV19-2 trial	COVID-OUT trial
Author, year	Reis et al, 2022[35]	Ventura-López et al, 2022[37]	Bramante et al, 2022[36]; Bramante et al, 2023 (long term follow-up)[38]
Trial registration	NCT04727424	NCT04625985, RNEC: 203 301 410 A0085	NCT04510194
Study status	Phase 3: completed, terminated early	Phase 2b: completed	Phase 3: completed
Country	Brazil	Mexico	USA
Mean age (years)	52	49.55	46
Median (interquartile range) body mass index	≥30 (44.98)§	28.54 (24.83-31.0)	30 (27-34)
Male	42.82	85	43.99
Pregnant	0	0	3.4
Smoking	5.98	Not reported	Not reported
Respiratory condition	1.2 (chronic pulmonary disease), 8.13 (asthma)	10	Not reported
Cardiovascular disease	3.35 (chronic cardiac disease)	Not reported	26.68*
Diabetes	14.59	20	1.97
Hypertension	39.95	20	Not reported
Inpatient	0	100	0
Oxygen saturation	Not reported	92	>93
Vaccinated	0	Not reported	52.15
Severity of covid-19	Mild or moderate	Mixed	Mild or moderate
Severity justification	Outpatient trial including adults with symptoms	Patients with radiographic evidence of pulmonary infiltrates admitted to hospital	Adults with covid-19 symptoms for <7 days not admitted to hospital
Intervention	Metformin *v* placebo	Metformin *v* placebo	Metformin *v* placebo†
Intervention description	Metformin 750 mg twice daily for 10 days	Metformin glycinate 620 mg twice a day for 14 days	Metformin 500 mg on day 1, 500 mg twice daily on days 2-5, then 500 mg in the morning and 1000 mg in the evening up to day 14
Randomised	Metformin 215 *v* placebo 203	Metformin 10 *v* placebo 10	Metformin 718 *v* placebo 713
Patient enrolment period	15 January 2021 to 3 April 2021	July 2020 to March 2021	30 December 2020 to 28 January 2022
Inclusion criteria	Participants aged ≥18 years with an acute clinical condition consistent with covid-19, symptoms for ≤7 days, a positive antigen test, and at least one high risk criterion‡, or age ≥50 years	Participants aged >18 years, positive PCR test ≤4 days before randomisation, admitted to hospital, and radiographic evidence of pulmonary infiltrates	Participants aged 30-85 years with overweight or obesity who had covid-19 symptoms for <7 days and positive PCR or antigen test within 3 days before enrolment

Data are percentages unless stated otherwise.

*Hypertension, hyperlipidemia, coronary artery disease, previous myocardial infarction, heart failure, pacemaker placement, arrhythmias, or pulmonary hypertension.

†Factorial design: some patients in metformin and placebo group received ivermectin and fluvoxamine. However, there was no treatment interaction on outcomes.

‡Diabetes mellitus, hypertension requiring drug treatment, cardiovascular diseases, symptomatic lung disease or being treated, symptomatic asthma requiring treatment, smoking, obesity (body mass index >30), transplant patients, patients with stage IV chronic kidney disease or receiving dialysis, patients who were immunosuppressed or having corticosteroid treatment or immunosuppressive therapy, patients with cancer in past five years or currently having cancer treatment.

§Median not available; 44.98% of participants had body mass index ≥30.

PCR, polymerase chain reaction.

consented to participate in long term follow-up). Bias because of measurement of the outcome and bias in the selection of the reported results were probably low (figure 2). The online supplemental material provides details of the risk of bias assessment.

Effects of intervention

Mortality

Two randomised controlled trials including 1615 patients with maximum follow-up of 28 days reported mortality.[35 36] The pooled estimate suggests that metformin might result in little or no difference in mortality (risk ratio 0.76, 95% CI 0.30 to 1.90; risk difference 3 fewer per 1000, 95% CI 8 fewer to 11 more; low certainty). The certainty of the evidence was low owing to very serious imprecision (table 2 and online supplemental figure S1).

Mechanical ventilation

Based on data from 1197 participants in one randomised controlled trial with a follow-up time of 28 days,[36] metformin has little or no impact on mechanical ventilation (risk difference 3 fewer per

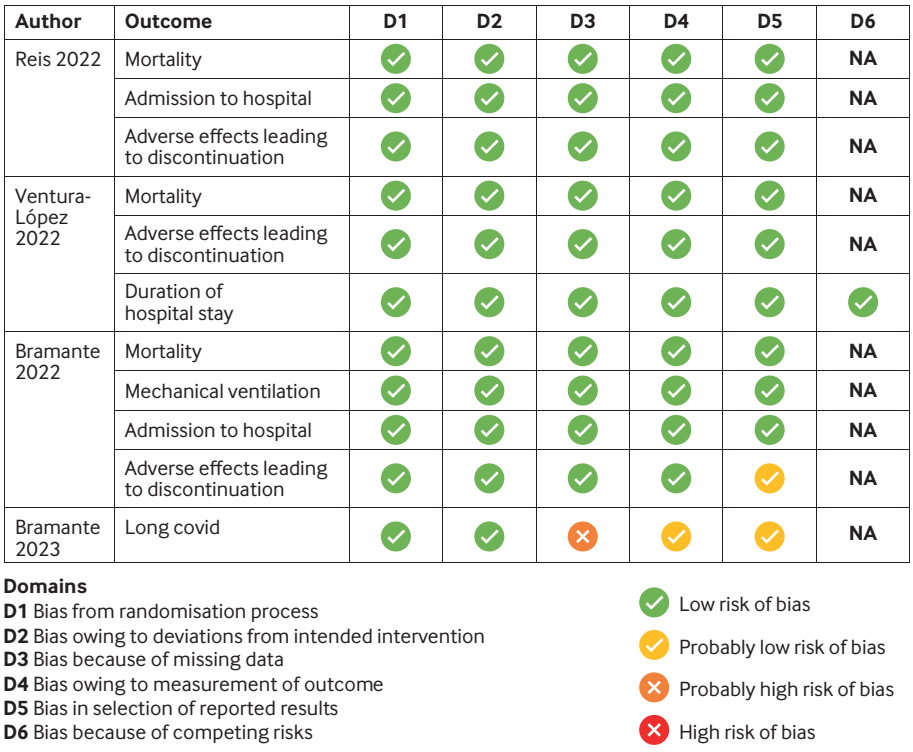

Figure 2 | Risk of bias assessment for each outcome among randomised trials of metformin for covid-19. NA, not applicable

1000, 95% CI 9 fewer to 2.3 more; high certainty (table 2; and online supplemental figure S2).

Admission to hospital

Two studies reported on admission to hospital within 28 days and included 1615 patients.[35 36] The evidence is uncertain regarding the effect of metformin on admission to hospital because of covid-19 (risk ratio 0.74, 95% CI 0.28 to 1.95; risk difference 15 fewer per 1000, 95% CI 42 fewer to 55 more; very low certainty). The certainty of the evidence was very low because of serious inconsistency and very serious imprecision (table 2 and online supplemental figure S3).

Adverse effects leading to discontinuation

Based on data from 1761 participants in all three included studies,[35–37] metformin has little or no impact on adverse effects leading to discontinuation (risk difference 0.2 more per 1000, 95% CI 2.7 fewer to 3.1 more; high certainty; table 2 and online supplemental figure S4).

Long covid

Data from one randomised controlled trial that followed 1126 patients for 300 days provided evidence that metformin might decrease incidence of long covid (risk ratio 0.6, 95% CI 0.4 to 0.9; risk difference 41 fewer per 1000, 95% CI 62 fewer to 10 fewer; low certainty). The certainty of the evidence was low owing to the serious risk of bias and serious imprecision (table 2 and online supplemental figure S5).

Duration of hospital stay

Ventura-López and colleagues reported on the duration of hospital stay, with 20 patients in one randomised controlled trial.[37] The effects of metformin on the duration of hospital stay because of covid-19 remain uncertain (mean difference 1 fewer, 95% CI 6.05 fewer to 4.05 more; very low certainty). The certainty of the evidence was very low because of extremely serious imprecision (table 2 and online supplemental figure S6). Studies did not report any data on time to symptom resolution.

Discussion

Principal findings

In this systematic review and meta-analysis, we summarised the effects of metformin on patients with non-severe acute covid-19 infection. Metformin might have little or no impact on mortality, and little or no difference was shown for mechanical ventilation. Similarly, the effects of metformin on admission to hospital and duration of hospital stay remain uncertain, and it has little or no impact on adverse effects leading to treatment discontinuation.

The findings suggest that metformin might decrease post-covid-19 conditions; the certainty of the evidence was low. The COVID-OUT trial was the only eligible trial that reported on long covid.[38] The authors evaluated the effects of metformin on long covid based on participant reported receipt of

Table 2 | Summary of effects of metformin on patients with covid-19

Outcome	Study results and measurements	Absolute effect estimates		Certainty of evidence	Summary
		Placebo	Metformin		
Mortality	Risk ratio 0.76 (95% CI 0.30 to 1.90) based on data from 1615 participants in two studies (metformin 8/811 *v* placebo 10/804), follow-up 28 days	12 per 1000	9 per 1000	Low, owing to very serious imprecision*	Metformin might have little or no impact on mortality
		Difference: 3 fewer per 1000 (95% CI 8 fewer to 11 more)			
Mechanical ventilation	Risk difference†: 0.33 (95% CI −0.90 to 0.23) based on data from 1197 participants in one study (metformin 0/596 *v* placebo 2/601), follow-up 28 days	3 per 1000	0 per 1000	High	Metformin has little or no impact on mechanical ventilation
		Difference: 3 fewer per 1000 (95% CI 9 fewer to 2.3 more)			
Admission to hospital	Risk ratio 0.74 (95% CI 0.28 to 1.95) based on data from 1615 participants in two studies (metformin 42/811 *v* placebo 47/804), follow-up 28 days	58 per 1000	43 per 1000	Very low, owing to serious inconsistency and very serious imprecision‡	Uncertain whether metformin decreases admission to hospital
		Difference: 15 fewer per 1000 (95% CI 42 fewer to 55 more)			
Adverse effects leading to discontinuation	Risk difference†: 0.02 (95% CI −0.27 to 0.31) based on data from 1761 participants in three studies (metformin 1/888 *v* placebo 0/873), follow-up 14 days	0 per 1000	0.2 per 1000	High	Metformin has little or no impact on adverse effects leading to discontinuation
		Difference: 0.2 more per 1000 (95% CI 2.7 fewer to 3.1 more)			
Long covid	Risk ratio 0.6 (95% CI 0.4 to 0.9) based on data from 1126 participants in one study (metformin 35/564 *v* placebo 58/562), follow-up 300 days	103 per 1000	62 per 1000	Low, owing to serious risk of bias and serious imprecision§	Metformin might decrease incidence of long covid
		Difference: 41 fewer per 1000 (95% CI 62 fewer to 10 fewer)			
Duration of hospital stay	Lower better, based on data from 20 participants in one study (metformin 10 *v* placebo 10), follow-up 14 days	9.8 days (mean)	8.8 days (mean)	Very low, owing to extremely serious imprecision¶	Uncertain whether metformin decreases the duration of hospital stay
		Difference: mean difference 1.00 fewer (95% CI 6.05 fewer to 4.05 more)			

Certainty of evidence was assessed using GRADE (grading of recommendations assessment, development and evaluation) approach as high, moderate, low, and very low.

*Imprecision: very serious. Confidence intervals include important benefits and harms.

†Risk differences are converted to percentages.

‡Inconsistency: serious. Point estimates vary widely, and magnitude of statistical heterogeneity was high, with I^2=76.7%; confidence intervals do not overlap. Imprecision: very serious. Wide confidence intervals include important benefits and harms.

§Risk of bias: serious. High risk of bias mainly because of loss to follow-up. Imprecision: serious. Confidence intervals include no important effect but no harm (minimally important difference 20/1000).

¶Imprecision: extremely serious. Only data from one study, with a low number of patients and confidence intervals include important benefits and harms.

CI, confidence interval.

a diagonosis of long covid from a medical provider. Analysis of data with 1126 participants revealed that outpatient treatment with metformin reduced long covid incidence by 40%, with an absolute risk reduction of 41 per 1000 compared with placebo after 300 days of follow-up.

Strengths and limitations

The strengths of this review include our comprehensive search, duplicate assessment of eligibility, risk of bias, and data extraction. We evaluated the certainty of evidence with the formal application of the GRADE approach, using the minimally important differences chosen by the WHO GDG as thresholds.

The review had potential limitations. The studies included a limited range of patients in terms of presentation and severity. We identified only three relevant studies with a very limited total sample size. The effects of metformin on mechanical ventilation, length of hospital stay, and long covid were based on a single trial. We could not analyse the time to symptom resolution because studies did not report any data. Only one study included long term follow-up, and there is a high risk of bias owing to missing data for long covid. Although the study was blinded, the reliance on participant reported diagnoses of long covid by a medical provider, without a unified diagnostic criterion, could lead to misclassification. The generalisability of the findings is limited because almost half of the participants were non-vaccinated. Moreover, WHO commissioned this review when the appearance of the trial alerted the WHO GDG to the potential importance of long covid as a key outcome of trials primarily focused on the immediate consequences of covid-19 treatment. The apparent effect of metformin on long covid could have influenced the decision to commission the review, and might contribute to lower certainty in the existence of this effect.

Comparison with other studies

Our findings suggest that metformin might result in little or no reduction in mortality, which contrasts with results from some observational studies suggesting

a substantial reduction in mortality.[12–19 39] There are a few possible explanations for the differences found between results from randomised controlled trials and those from observational studies. Patients in observational studies were admitted to hospital and received long term metformin treatment for diabetes, which was not the case for the trials. Therefore, the variation could be attributed to differences in non-severe versus severe disease or dose dependency—prolonged use of metformin might offer greater benefits than short term administration. Alternatively, biases inherent in observational studies could be responsible for the differences. Our own data and meta-analysis of observational studies suggest that metformin does not reduce the incidence of mechanical ventilation. A meta-analysis of two observational studies did not identify a statistically significant association between metformin and intubation.[15] Similar results were reported in a retrospective observational study.[40]

Results for hospital admission were inconsistent among the eligible randomised controlled trials in our systematic review, which failed to find a benefit for metformin in the pooled estimate. The eligible TOGETHER trial did not find any clinical benefit of metformin compared with placebo in ambulatory patients with covid-19; no reduction was reported in the need for retention in an emergency setting or hospital admission because of worsening covid-19.[35] However, the COVID-OUT trial found that metformin resulted in a 58% reduction in hospital admissions over 28 days because of covid-19 (hazard ratio 0.42, 95% CI 0.18 to 0.95).[36] The results from observational studies were inconsistent[41]; however, the pooled estimate from a meta-analysis showed only a borderline significant reduction in hospital admission with metformin (odds ratio 0.73, 95% CI 0.53 to 1.00).[15] Similar to the findings from our systematic review, a meta-analysis of four observational studies with 1646 patients did not find any significant difference in hospital stay (mean difference 1.07, 95% CI −0.55 to 2.69).[12]

Metformin's anti-inflammatory capabilities and function in modifying the immune response could explain the reported reduction in long covid. Bramante and colleagues underlined the anti-inflammatory capabilities of metformin, which might contribute to its long term covid-19 efficacy.[38] Studies have shown that metformin lowers inflammatory mediator release and limits viral adherence, potentially decreasing the prolonged inflammatory state associated with covid-19.[39] However, understanding the hypothetical mechanisms involved in long covid is challenging because the underlying processes of the condition are not well understood. Several potential disease modifying mechanisms of action have been proposed, each with varying degrees of plausibility. There is no direct in vitro or in vivo preclinical evidence supporting a specific mechanism of action for long covid. The indirect evidence available for various mechanisms varies in quality, particularly concerning the concentrations used (physiological *v* supraphysiological) and the sophistication of the methodologies applied.[42–44] A retrospective study based on electronic health records assessed the risk of post-acute sequelae of SARS-CoV-2 infection by comparing 5596 prevalent users of metformin with 1451 prevalent users of sulfonylureas or dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. The effects of metformin on the risk of post-acute sequelae of SARS-CoV-2 infection at three month follow-up (risk ratio 0.86, 95% CI 0.56 to 1.32; risk difference 14 fewer per 1000, 95% CI 45 fewer to 33 more; very low certainty) or at six month follow-up (0.81, 0.55 to 1.20; 20 fewer per 1000, 46 fewer to 21 more; very low certainty) were uncertain.[45]

Implications for practice and research

The findings from this systematic review and meta-analysis will inform the WHO clinical practice guideline on metformin in patients with non-severe covid-19.[21] Because the only finding suggesting a beneficial effect of metformin is the reduction in long covid, and that finding is informed by low certainty evidence from a single trial, more randomised trials are needed to provide definitive evidence. Future randomised controlled trials should aim to include larger and more diverse populations to ensure broader applicability of findings. Studies should prioritise enrolling patients admitted to hospital and those who have been vaccinated because these groups are underrepresented in existing randomised controlled trials. Establishing a consistent diagnostic approach and a standardised definition for long covid would strengthen outcome assessment and comparability across studies. Additional research into the mechanisms through which metformin might affect viral dynamics and inflammatory responses could further clarify its role in long covid and as an adjunct treatment in covid-19. Future research addressing these gaps might provide more substantial evidence to guide clinical practice and optimise the use of metformin in managing patients with covid-19.

Conclusions

Low certainty evidence suggests that metformin might have little or no impact on mortality when used to treat patients with non-severe acute covid-19 infection. The effects of metformin on admission to hospital remain uncertain, and it shows little or no difference in adverse effects leading to discontinuation. Metformin might reduce incidence of long covid when used to treat patients with non-severe acute covid-19 infection, but this was suggested by low certainty evidence from a single trial. Further research is required to establish the impact of metformin on long covid.

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