

EVALUATING the Effects of Metformin on Glycemic Control and Mortality Rates of Hospitalized COVID-19 Patients with Type 2 Diabetes Mellitus: A Systematic Review and META-ANALYSIS

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ABSTRACT

Patients with diabetes mellitus have become direct and incidental prey for COVID-19. The purpose of this study is to summarize multiple observational studies into a single report to show if metformin gives a statistically significant difference in the blood glucose levels and mortality rate of hospitalized COVID-19 patients with type 2 diabetes mellitus. The research performed a systematic search on PubMed, Google Scholar, ProQuest, Cochrane Library, Elsevier, Science Direct, Sage Journals, Springer Link, MDPI, and Wiley Library from 2020-2024. Participants, intervention, comparator, and outcome (PICO) analysis were employed in the study selection. The intervention group was the patients who received metformin during admission in the hospital, and the control group (comparator) was the non-metformin users. The outcomes measured were the blood glucose levels of the patients and the mortality. One hundred nine studies were initially reviewed, however, only six studies met the inclusion criteria and were included in systematic review and meta-analysis. All six studies utilized observational research design, five were retrospective, and one was a prospective cohort. Three studies showed statistically significant differences ($p < 0.05$) in blood glucose levels of the patients between metformin and non-metformin users. In fact, the blood glucose levels were lower in the non-metformin group. Three studies also reported a significant decrease in the mortality rate of the patients. The overall pooled result suggested that metformin may slightly lower the odds of mortality. There was no significant evidence of publication bias in the six studies included. In conclusion, metformin was not able to control and reduce the blood glucose levels of the patients. The mortality rate reduction effect of metformin was similar to non-metformin use.

KEYWORDS: *Pharmacy, blood glucose level, COVID-19 infection, meformin, Philippines*

INTRODUCTION

As the role of well-controlled blood glucose levels has been emphasized to be beneficial, the impact of the different glucose-lowering agents is yet to be established (Scheen, 2020). One of these agents is metformin, which remains the most commonly prescribed drug for type 2 diabetes mellitus (DM) due to its low cost, good safety profile, and broad spectrum of clinical benefits. It has been shown to reduce hepatic glucose production, though its mechanism of action is not yet fully understood (Rena et al., 2017). Aside from these, studies of this biguanide revealed that it also has an anti-inflammatory activity that may warrant its potential benefits in the prognosis of COVID-19 patients (Scheen, 2020).

Persons with diabetes can be direct and incidental prey of the coronavirus disease (COVID-19) pandemic. In the beginning, diabetes was identified as one of the susceptibility factors along with hypertension, obesity, smoking, and advanced age (Sacks et al., 2020). However, studies showed that the disease itself will not increase the likelihood of being infected, but if a person with diabetes gets infected, there will be a higher chance for the infection to worsen (Bouhanick et al., 2020).

Currently, data from community testing is limited; hence, most of the statistics of COVID-19-positive patients with diabetes come from hospitalized cohorts. A study in the United States showed that 10.9 percent of the total COVID-19 patients were diabetic, which was actually similar to the US population with diabetes. Of those patients, 24 percent were hospitalized but not admitted to an intensive care unit (ICU), and 32 percent accounted for ICU admissions (Hartmann-Boyce et al., 2020). In fact, the prevalence of COVID-19 patients in the ICU is two to three times higher, and the mortality rate is doubled compared to non-diabetic patients (Scheen et al., 2020).

In the Philippines, a study reported that among the first 100 cases, nine percent (9%) of the patients had diabetes as a comorbidity (Salva, et al., 2020). Due to the border restrictions and lockdowns implemented by the Philippine government during the COVID-19 pandemic, and the *covidization* of the healthcare system with additional financial instability, many of these diabetic patients were forced to manage their condition without professional guidance. This has resulted in a decrease in the daily medication intake of the patients, which may aggravate their condition when infected with the COVID-19 virus

(Malijan et al., 2024).

The CORONADO (Coronavirus SARS-CoV-2 and Diabetes Outcomes) study conducted in France on hospitalized COVID-19 patients with diabetes in March 2020 reported that previous glucose control has no impact on the severity of the condition of the patients; and, the plasma concentration at admission was significantly and positively associated with both the primary outcome and death by seventh day of hospitalization. However, this study failed to consider the management of diabetes and the quality of glucose control during hospitalization (Scheen et al., 2020).

Meanwhile, other literature suggested that good inpatient glycemic control is thought to be very important in the comprehensive treatment of COVID-19. One of the largest retrospective cohort studies of in-hospital individuals revealed that well-controlled blood glucose levels are associated with a marked reduction of complications and deaths in COVID-19 patients with diabetes, highlighting the relevance and necessity of intensive blood glucose management (Zhu et al., 2020). For confirmed patients, it has become a challenge for clinicians to improve outcomes in the face of uncertainty regarding the level of glycemic control that should be maintained and any effects this might have on the benefits and risks of the overall treatment. A well-conducted systematic review, as well as meta-analysis, will help clinicians to stay abreast of contemporary evidence-based medicine as it uses a systematic method in summarizing evidence on question with a comprehensive plan of study (Tawfik, et al., 2019). Since multiple works of literature have been published about utilizing metformin for COVID-19 patients with type 2 DM, a systematic review and meta-analysis will be suitable to identify a single result for these vast growing interventional studies.

Review Question

For hospitalized COVID-19 patients with type 2 diabetes mellitus, does metformin reduce glycemic level and mortality rate compared with non-metformin use (control)?

METHODOLOGY

Research Design. This study employed systematic review and meta-analysis to verify the use of metformin in controlling blood glucose levels and reducing mortality rates of COVID-19 patients with type 2 diabetes mellitus.

The researcher utilized online research websites from the World Wide Web such as PubMed, Google Scholar, ProQuest, Cochrane Library, Elsevier, Science Direct, Sage Journals, Springer Link, MDPI, and Wiley Library, to gather specific studies containing the needed information.

Criteria for Inclusion and Exclusion. The researcher gathered studies that met the following criteria: research topic about the use of metformin use for hospitalized COVID-19 patients with type 2 diabetes mellitus; control group treatment includes non-metformin use; with data on blood glucose level of the patients and mortality rate; the design should be randomized and non-randomized controlled trial, retrospective observational studies, experimental or quasi-experimental, published or unpublished work with sufficient information; written in English, and the year of publication from 2020-2024. Exclusion criteria include the following: studies with COVID-19 patients with diabetes but non-hospitalized; studies that had abstract only or no full-text available; irrelevant studies that were purely observational or experimental without interventions and treatment outcomes; settings were in the community or outpatient or after-hospital discharge; systematic reviews and meta-analysis, and animal studies; duplicated studies in terms of publication status; and, cohort studies made without interventions.

Data Extraction. The studies included for systematic review and meta-analysis were metformin utilization to hospitalized COVID-19 patients with type 2 diabetes mellitus. The data that the researchers extracted include the title of the study, author, year of publication and place of study, publisher and link, design, the sample size of treatment and control groups, the outcome of the blood glucose level, and mortality rates, their mean scores, effect sizes, and the p-value.

Quality Assessment. Decisions to select retrieved studies for further assessment were based on eligibility criteria pre-determined by the researcher to minimize the inclusion of non-relevant articles. The Newcastle-Ottawa Scale was used to assess the risk of bias for the observation studies selected and retrieved.

Data Synthesis and Analysis. The study employed the Participants, Interventions, Comparison, and Outcomes (PICO) Analysis. The studies were tabulated first to see if they had valid electronic sources. Then, the studies were assessed to determine whether they fit within the criteria pre-determined by the

researcher. A flow diagram was used to present the process of selecting and excluding studies until all the criteria were checked and verified. The remaining studies after the assessment were tabulated again. The data included in the table were the data extracted from the remaining studies. Once the extraction and appraisal of individual studies were completed, a narrative synthesis was required.

The remaining studies were subjected to meta-analysis. The effect sizes reported as the odds ratio or hazard ratio were analyzed and used to generate the overall pooled effect of metformin on mortality rates of hospitalized COVID-19 patients with type 2 DM. Forest plot analysis was employed using the Comprehensive Meta-Analysis (CMA) Version 3.0. To determine the heterogeneity of the selected studies, the Q-test, I-square test, and tau-squared test were conducted. The presence of publication bias was determined using the funnel plot analysis and Egger's test.

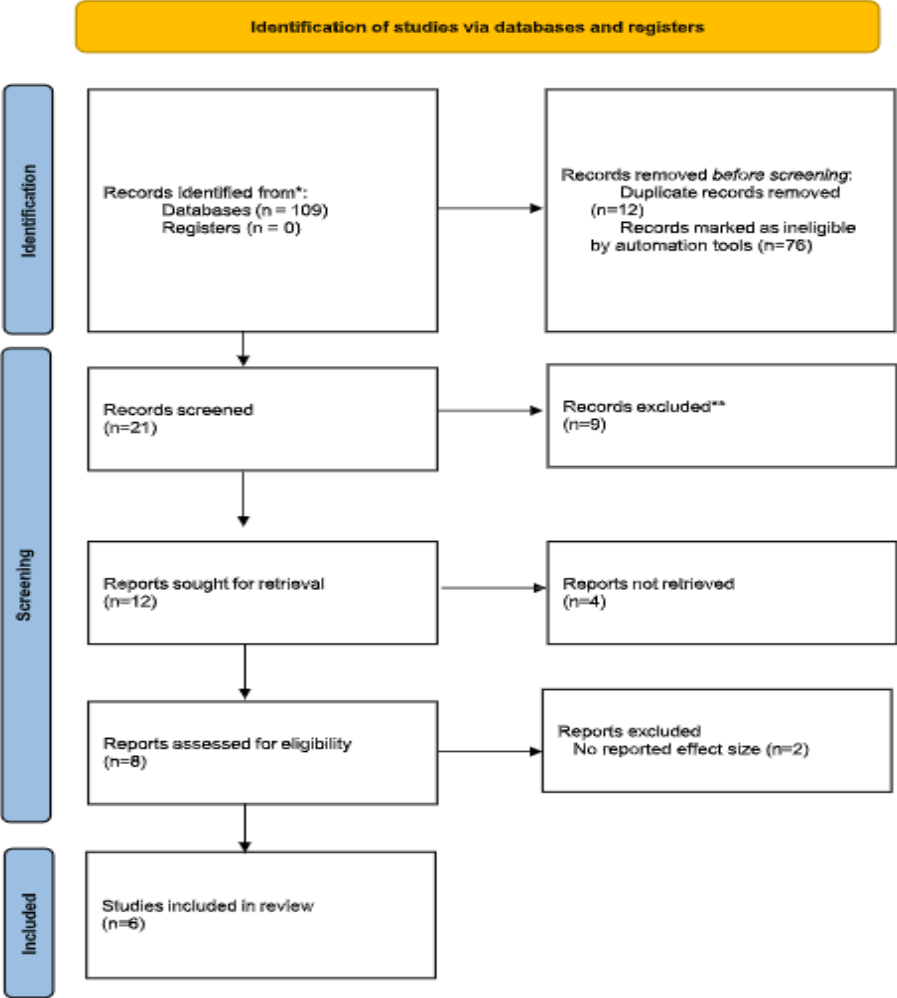
Ethical Considerations. The researcher applied for an Ethics Exemption from the REC. The University of the Immaculate Conception Research Ethics Committee (UIC-REC) assessed this to ensure that necessary elements (albeit exempt) met the required ethical features.

RESULTS AND DISCUSSION

Study Selection

After identifying the relevance of the titles and abstracts, 76 studies were excluded, as there were issues with the design being implemented in the current study. The excluded studies were considered irrelevant. Furthermore, twelve studies were also excluded as they were duplicates. Only 24 studies were left and underwent screening. Nine studies were removed due to insufficient information needed. Twelve remaining studies were sought for retrieval. Further screening of the remaining studies revealed that four studies did not have full articles or were only available as abstracts, and thus were also excluded from the review. The thorough stepwise identification, screening, and assessment processes narrowed the number of studies to eight from the initial 109 studies. These eight studies were subjected to quality assessment for eligibility. Two studies were further removed because the effect sizes needed for meta-analysis were not reported. The six studies left were finally included in the systematic review and meta-analysis.

Figure 1
PRISMA framework



Features of the Included Studies

Of the one hundred nine studies, only six studies met the set inclusion criteria and were included in the systematic review and meta-analysis. The

features of these six studies are presented in Table 1.

The studies included were conducted from 2020 to 2024. These timelines coincided with the outbreak of SARS-CoV-2, the virus causing COVID-19 infection. The World Health Organization (2023) characterized the outbreak of the viral infection as a pandemic in March 2020. Three years into the pandemic, the WHO Emergency Committee on COVID-19 recommended that, since the disease was well-established and ongoing, it no longer fit the definition of the Public Health Emergency of International Concern (PHEIC). The committee emphasized that the pandemic was not yet over, but the global emergency it caused was settled in 2023.

Table 1
Features of the Included Studies

Title	Authors: Year of Publication	Country	Study Design
1. Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis	Luo, P., Qui, L., Liu, Y., Liu, X., Zheng, J., Xue, H., Liu, W., Liu, D., Li, J. 2020	China	Retrospective
2. Association of metformin with mortality or ARDs in patients with COVID-19 and type 2 diabetes: a retrospective cohort study	Jiang, N., Chen, Z., Liu, L., Yin, X., Yang, H., Tan, X., Wang, J., Li, H., Tian, M., Lu, Z., Xiong, N., Gong, Y. 2021	China	Retrospective
3. The association of metformin treatment and COVID-19 outcomes according to metformin continuation during hospitalization	Al-salameh, A., Bennis, Y., Cariou, B., Lalau, J. 2021	France	Prospective Cohort
4. Is metformin use associated with a more favorable COVID-19 course in people with diabetes?	Silverii, G.A., Fumagalli, C., Rozzini, R., Milani, M., Mannucci, E., Marchionni, N. 2024	Italy	Retrospective
5. Insulin and metformin	Lewandowski, L.,Bronowicka-Szydelko, A., Rabczynski, M.,	Poland	Retrospective

administration: unravelling the multifaceted association with mortality across various clinical settings, considering type 2 diabetes mellitus and COVID-19	Bednarska-Chabowska, D., Adamiec-Mroczek, J., Doroszko, A., Trocha, M., Kujawa, K., Matera-Witkiewicz, A., Kuznik, E., Lubieniecki, P., Madziarski, M., Sokolowski, J.,		
6. Metformin is associated with a higher incidence of acidosis, but not mortality, in individuals with COVID 19 and pre-existing type 2 diabetes	Cheng, X., Liu, Y., Li, H., Zhang, X., Lei, F., Qin, J., Chen, Z., Deng, K., Lin, L., Chen, M., Song, X., Xia, M., Huang, X., Liu, W., Cai, K., Zhang, X., Zhou, X., Xia, J., Zhang, B., Guo, J., Zhu, L., Lu, Z., Yuan, Y., Wei, X., She, Z., Ji, Y., Li, H. F., Zhang, P., Wang, Y., Ma, X., Xu, Q., Yang, J., Ye, P., Mao, W., Huang,	China	Retrospective

Furthermore, three studies were conducted in various hospitals in China, and the other three were done in different countries in Europe, specifically in France, Italy, and Poland. More studies were conducted in China as COVID-19 originated in Wuhan City, China in early December 2019. Mohan and Nambiar (2020) highlighted that COVID-19 had spread widely in almost all countries worldwide after the outbreak in China and became a global public health crisis. In fact, over two million died from the disease in the European Region. On the other hand, five of the studies included were retrospective research designs, and one was a prospective cohort. In this case, clinical trials and other experimental study designs that fit the criteria of the study were currently not available.

Participants, Intervention, Comparator, and Outcomes (PICO) Analysis

Six studies were subjected to qualitative analysis. This study utilized the PICO analysis to review the six included studies.

Participants. The participants included in the selected studies were all confirmed COVID-19 patients with concomitant type 2 DM. They were admitted to various hospitals around the globe. The studies revealed the profiles or characteristics of the participants in terms of age, sex, and presence of comorbidities. Among them, five studies had participants with a median or mean age of 60 years old in above in both the intervention and control groups. The participants were either male or female for all six studies.

Table 2
Data for Participants, Interventions, Comparators, and Outcomes (PICO) Analysis

PARTICIPANTS/ PATIENTS	INTER VENTION	COMPA RATOR	OUTCOMES	
			(Intervention Group vs Control Group)	
			Blood Glucose Level (mmol/L)	Mortality/ Number of Deaths
1. Luo, P. et al. (2020) COVID-19 patients with type 2 diabetes mellitus hospitalized in Tongji Hospital, Wuhan, China	Metformin	Non-metformin	9.19 vs 7.36 (p=<0.01)	3 vs 22 (p = 0.01) OR=4.36
2. Jiang, N. et al. (2021) COVID-19 patients with diabetes mellitus hospitalized in different hospitals in Hubei Province, China	Metformin	Non-metformin	10.0 vs 9.3 (p=0.60)	14 vs 18 (p=0.08) HR = 0.54
3. Al-salameh, A. et al. (2021) COVID-19 patients with type 2 diabetes mellitus hospitalized in Amiens University Hospital, Amiens, France	Metformin	Non-metformin	8.3 vs 7.0 (p=0.01)	2 vs 13 (p=0.04) OR = 0.31
4. Silverii, G.A. et al. (2024) COVID-19 patients with type 2 diabetes mellitus hospitalized in two Italian tertiary hospitals (Poliambulanza Hospital and Careggi University Hospital)	Metformin	Non-metformin	N/A	Mortality 60 vs 99 (p=0.04) OR = 0.81
5. Lewandowski, L. et al. (2024) COVID-19 patients with type 2 diabetes mellitus hospitalized at the University and Temporary	Metformin	Non-metformin		14 vs 18 OR=0.72

COVID-19 Hospital organized by the University Medical Hospital, Wroclaw, Poland				
6. Cheng, X. et al. (2020) COVID-19 patients with diabetes mellitus hospitalized in 16 hospitals in Hubei Province, China	Metformin	Non-metformin	9.0 vs 8.3 (p<0.01)	HR= 1.65

Intervention group – received metformin alone or in combination with other antidiabetic drugs
Control group – non-metformin/ received other antidiabetic drugs except metformin
OR – odds ratio
HR – hazard ratio
N/A – not applicable/ not reported

Furthermore, four studies revealed no significant differences ($p>0.05$) were found between all the identified comorbidities or coexisting diseases among the participants. These notable comorbidities include hypertension, cardiovascular diseases, malignancies or cancer, respiratory diseases, obesity, liver and renal diseases. However, two studies reported statistical differences ($p<0.05$) between the following comorbidities present in the participants: cardiovascular diseases and renal diseases. In all these two studies, the control groups had a higher number of cases of the aforementioned comorbidities compared to the intervention groups.

According to Chatterjee et al. (2023), SARS-CoV-2, the virus that causes COVID-19, can infect people of all ages and sexes. However, infected patients with coexisting diseases were found to be more susceptible to COVID-19 infection. The presence of comorbid conditions, such as age and concomitant illnesses, has been considered a significant predictor for the severity of the infection. Among the comorbid conditions, age was found to be the highest factor in the COVID-19 condition. The elderly are more sensitive to immune responses, and studies revealed that there was an increase in the mortality of COVID-19 patients with age-related disease conditions such as diabetes mellitus, cardiovascular diseases, and cancer.

Intervention. All studies reviewed utilized metformin as the drug received by the intervention group. The patients in this group were given metformin alone or in combination with other antidiabetic drugs throughout their hospital stay. One study considered the preadmission use of metformin as long

as the therapy continued during hospitalization. Only three studies provided the doses of metformin given to the patients. Two studies provided the median doses, 1.0 grams per day and the other one 1326 milligrams, respectively. The remaining study revealed that the patients received an initial dose of 500 milligrams per day of metformin during admission.

This drug is a Food and Drug Administration (FDA) approved agent for the management of type 2 DM. It is considered the first-line drug for patients newly diagnosed with type 2 DM and is prescribed either alone or in combination with other antidiabetic drugs. It is a biguanide drug that acts by decreasing glucose production in the liver. It can lower both basal and postprandial blood glucose levels, and at the same time, it has the potential to induce weight loss. Furthermore, metformin is considered an euglycemic agent, which means it can lower the blood glucose level of the patient, but it does not cause hypoglycemia. Aside from this advantage over other antidiabetic drugs, studies showed that it may have cardioprotective effects (Corcoran and Jacobs, 2023).

Comparator. Among the six studies, the comparator was non-metformin use. This means that the patients did receive other antidiabetic drugs during hospitalization, but not metformin. These drugs include other types of antidiabetic agents such as insulin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, and SGLT2 inhibitors. These drugs lower blood glucose levels with a different mechanism of action compared to metformin. These antidiabetic agents were given alone or in combination with other agents in different classes.

Outcome. Table 2 presents the outcomes of the studies measured and compared after the participants received the intervention. Outcomes included were the blood glucose level of the participants and mortality or the number of deaths.

Among the six studies, only four reported the median blood glucose levels in millimoles per liter (mmol/L) of the participants. In these four studies, three reported significant differences ($p < 0.05$), while the other one found no significant difference ($p < 0.05$) in the blood glucose levels of the participants between the intervention and control groups. However, all these studies reported higher levels of blood glucose in the intervention group compared to the control group.

The World Health Organization (2024), in its published Indicator Metadata Registry List, stated that the normal fasting blood glucose levels are between 3.9 mmol/L and 5.6 mmol/L. If the values are between 5.6-6.9 mmol/L, lifestyle modifications, and glycemia monitoring should be recommended to the patients. However, if the fasting blood glucose level is 7 mmol/L or higher on two separate tests, diabetes is diagnosed.

All studies reported that the blood glucose levels of the participants in both the intervention and control groups were not lower than 7 mmol/L. These outcomes suggest that there was no difference in the effect of metformin and non-metformin use in the glycemic control of the patients. The blood glucose levels of the participants were not generally managed to normal levels. Riaz et al. (2021) identified factors related to uncontrolled fasting blood sugar among type 2 diabetic patients. This may include older age, male gender, illiteracy, longer duration of disease, and presence of comorbid conditions such as hypertension, smoking, and obesity.

Mortality or the number of deaths of the patients in each group, was also measured and compared. The number of deaths, p-values, and effect sizes or measures were presented in the included studies. Five studies specified the number of deaths per group. These studies reported that all the control groups, or the non-metformin group, had a higher number of deaths compared to the intervention group or the metformin group. Detailed comparison between the intervention and control group was highlighted by the computed p-values. Among the six studies, only four revealed the p-values. Three studies reported that the difference in the number of deaths between the intervention and control groups was statistically significant ($p < 0.05$).

In terms of effect sizes or measures, the odds ratio (OR) or hazard ratio (HR) was reported. Four studies computed the odds ratio, wherein three studies had OR values of less than one, and the remaining study was more than one. An OR value of less than one means that there are lower odds of the event in the exposed or experimental group. The findings suggested that mortality was more likely lower in the patients who received metformin than those who received other antidiabetic agents. All reported odds ratios were computed with a 95 percent confidence interval (CI). The odds ratio measures the association between exposure and outcome in case-control and cross-sectional studies. According to Tenny & Hoffman (2023), it represents the odds of an outcome that will occur with a particular exposure, compared to the odds of the outcome in

the absence of that exposure.

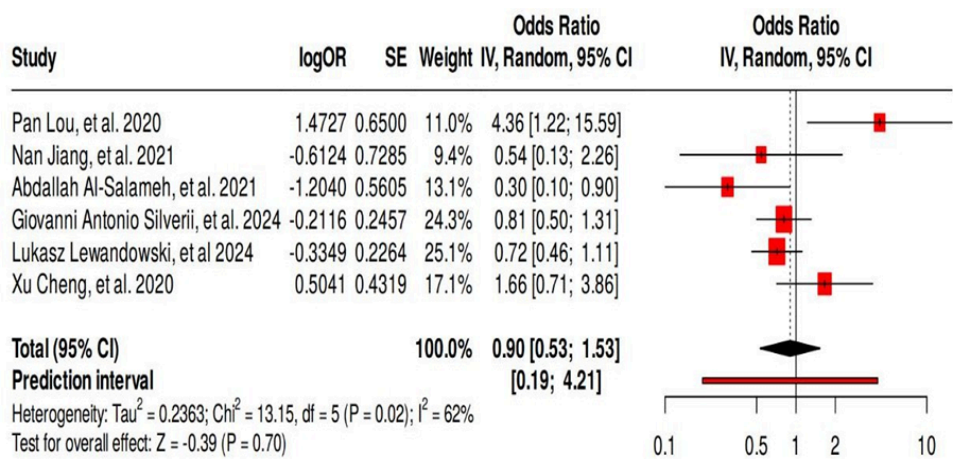
Meanwhile, two studies reported the hazard ratios between the intervention and control groups. One of the studies has an HR value of less than one, and the other study has an HR value of more than one. These findings suggested that the risk of mortality was higher in the intervention group in one of the studies, and lower in another study. The National Cancer Institute (n.d.) expressed that the hazard ratio measures how often a particular event or outcome occurs in one group compared to another group over time. A hazard ratio of less than one is interpreted as a lower risk or hazard in the exposed or experimental group.

Meta-Analysis

Six studies were eligible for meta-analysis. Only the outcomes on mortality were subjected to meta-analysis using the odds ratio or hazard ratio. The blood glucose levels of the participants were not analyzed in the meta-analysis due to insufficient data, specifically on the standard mean differences (SMD). The results of the meta-analysis are presented in a forest plot, wherein the effect sizes and their respective 95% confidence interval are shown in Figure 2. Homogeneity and publication bias were also analyzed.

Figure 2 presents the forest plot for the effect sizes or measures of the mortality outcome between the intervention group (metformin) and the control group (non-metformin). The first column in the figure is the six studies with the names of the authors included in the meta-analysis. Column 4 shows the weight of each study. Study 5 (Lewandowski, et al., 2024) had the highest weight percentage, 25.1%, while study 2 (Jiang, et al., 2021) got the lowest percentage, 9.4%. These numerical values were assigned to individual studies according to their contribution to the pooled estimate.

Figure 2
Forest Plot for the Effect Sizes Between the Intervention and Control Groups of the Observational Studies



This means that the results of Study 5 contributed the most to the overall effect size, and Study 2 least contributed to it. The study weights are also indicated by the box sizes. The larger the box, the more weight is assigned to the study. According to Chang, et al. (2022), the weight is closely associated with the sample size of the study. However, this is unlikely the reason for the assigned weights of the included studies as study 6 (Cheng et. al, 2020) had the greatest number of participants in both the intervention and control groups and, study 3 (Al-Salameh, et al., 2021) had the least number of participants.

Effect Size, Confidence Intervals, and the Null Effect Vertical Line. In this figure, the x-axis represents the effect sizes being compared among the six included studies. Specifically, the individual study effect sizes, with their confidence intervals, were expressed as odds ratios since the measured outcomes were considered binary or dichotomous variables. The outcome measured in the studies included in the meta-analysis was the mortality or the number of deaths for each group. Each line in the forest plot represents a study.

Among the six studies, only study 3 (Al-Salameh et. al., 2021), OR = 0.30 (CI: 0.10-0.90), did not cross the vertical line, which means the difference between the mortality in the intervention and control group was significant.

Additionally, the effect size ($OR < 1$) favored the intervention, which means that the intervention group had lower odds of mortality in this study. However, study 1 (Lou et al., 2020) showed a potentially harmful effect ($OR = 4.36$, $CI: 1.22-15.59$). Though the difference was not statistically significant as the confidence interval crossed the vertical line, the OR value implied that the odds of mortality in the intervention group were four times higher than the control group. Nevertheless, most of the confidence intervals of the six studies were wide and crossed the vertical line in the forest plot. This indicates concern about the precision of the data, and no statistically significant effects were observed.

Pooled Effect. The diamond below the effect sizes and confidence intervals of each study represents the overall pooled effect. The width of the diamond shows the confidence interval for the overall effect. The result presented in the forest plot revealed a pooled odds ratio of 0.90 with a 95% confidence interval from 0.53-1.53, $p = 0.70$. The pooled odds ratio indicates a probability of a 10% reduction in the odds of mortality in the intervention group (metformin) compared to the control group (non-metformin). Metformin may reduce mortality in COVID-19 patients with type 2 DM; however, the confidence interval crossed the vertical line or the line of 'no effect,' and the p-value was more than 0.05, suggesting that the effect was not statistically significant or reliable.

These results are contrary to the study conducted by Lalau et al. (2020), which concluded that metformin use appeared to be associated with a lower risk of death ($OR = 0.838$) in patients with diabetes hospitalized for COVID-19. In addition, Parveen et al (2023) reported that the meta-analysis of their study suggested a 37% lower risk of mortality in patients receiving metformin.

Heterogeneity. Heterogeneity reflects the variation in the results of the study that may be associated with population, intervention, comparator, outcome measure, risk of bias, study method, health systems, and other factors affecting the individual study included in a meta-analysis (Chang et. al., 2022). The results of the homogeneity tests are as follows:

Q-test. The Cochran's Q computation result was 13.15 ($df = 5$), with $p\text{-value} = 0.02$. This indicates that there is a significant heterogeneity among the included studies and that they did not evaluate the same effect size, with respect to the overall pooled effect size. This also suggests that the variability in the effect sizes is unlikely due to chance alone but due to relevant factors. Fletcher

(2007) ascertained that aside from clinical differences, other reasons for heterogeneity could include methodological issues such as problems with randomization, the use of absolute rather than relative measures of risk, and publication bias.

I² test. The test revealed that the collection of studies has established an I^2 of 62%, which is interpreted as substantial heterogeneity. This suggests that the differences in study outcomes are most likely due to more than chance alone and that 62% of the total variation was due to true differences between studies, rather than sampling error. Fletcher (2007) also highlighted that individual studies in a systematic review may seem to measure similar outcomes, but they may have results that are not consistent with each other. There are studies that may show a benefit while others show harm, or it is just that the studies are inconsistent in the size of benefit or harm.

Tau². The Tau2 generated using the online software application was 0.2363 which indicates a moderate degree of variability in the true effect sizes across the six studies. This represents the variance of true effect size between the studies and is used in random-effects models to properly weigh the studies. Higgins et al. (2022) stated that currently, there is no fixed cut-off for this test, however, larger values mean more variability.

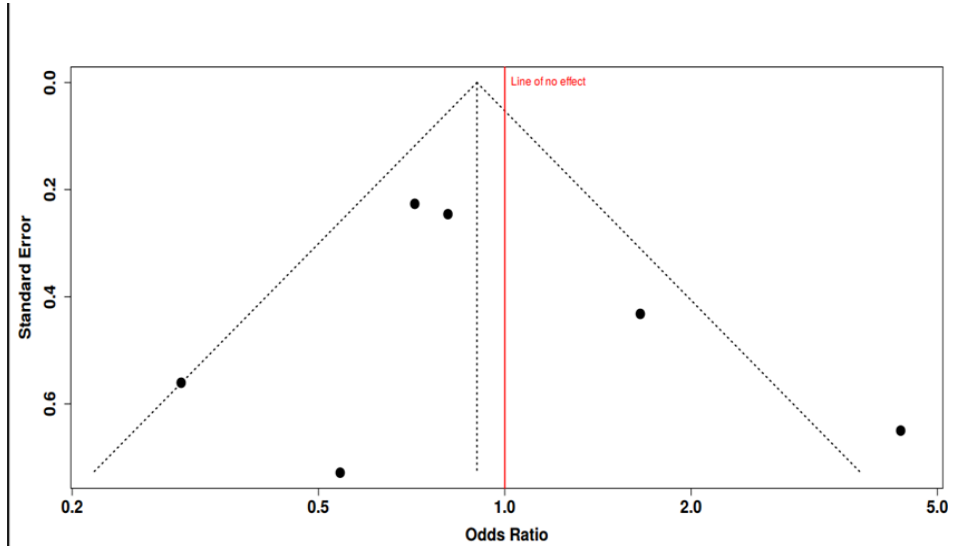
Prediction Interval. At 95% confidence interval, the prediction interval of the six included studies was between 0.19 to 4.21. This indicates a wide variation in the expected effects of future studies. According to Spineli et al. (2020), some future studies might show benefits, and others might show harm in this wide range of prediction interval.

Overall, uncertainty and inconsistency were high in the pooled evidence. If a new study is added to the meta-analysis, uncertainty would be expected in the effect summary.

Funnel Plot and Publication Bias. Figure 3 shows the funnel plot for the six studies included in the meta-analysis. The plot displays the study effect sizes in odds ratios on the x-axis and the standard error on the y-axis. The line of no effect ($OR = 1$) is shown in the center. Visual inspection of the funnel plot suggests that the distribution of studies appears asymmetrical. More studies were clustered on the left side, and there is a visible gap on the opposite side of the funnel, especially at the bottom, where small studies should appear. This implies

that there is the presence of publication bias or small-study effects. It appears that smaller studies with negative results may not have been published or included in the meta-analysis, which may lead to an overestimation of the overall effect. To strengthen the interpretation of the funnel plot, Egger’s test was conducted.

Figure 3
Funnel Plot



Egger’s Test. Egger’s test result showed a p-value of 0.647. This means the Egger’s test does not support the presence of funnel plot asymmetry. This further suggests that there is no strong evidence of a publication bias, and even though the funnel plot may appear asymmetrical visually, it is not statistically meaningful or significant. Aside from that, there was only one outlier result presented. The results might be skewed due to the missing or unpublished studies; however, there is no sign of such bias, and the results are likely considered reliable.

Table 3
Egger's Test

Bias Assessment	Test Statistic	95% Confidence Interval	p-value	Interpretation
Egger's Test	0.83	-2.48 to 4.15	0.647	No significant publication bias

According to Lau et al. (2006), the asymmetry of the funnel plot does not all the time accurately predict publication bias. Funnel plots examine whether small studies affect the overall pooled effect than larger studies. Hence, asymmetry in the funnel plot may result not from a systematic under-reporting of negative studies but from the indispensable difference between studies with little precision and greater precision that may have emerged from the immanent between-study heterogeneity. Variations in the quality of the studies can affect the shape of the funnel plot, sometimes, with smaller or lower quality studies presenting more benefit of treatment.

In conclusion, a qualitative systematic review of the selected studies suggested that metformin was not able to control or reduce back to normal the blood glucose levels of the patients. The control group, which did not receive metformin during admission, had generally lower blood sugar levels than those who received metformin. In terms of mortality, metformin showed a lower number of deaths compared to non-metformin use. Most of the studies reported that the odds and risk of mortality were substantially lower when the patients were given metformin during hospitalization. On the other hand, the findings of the meta-analysis revealed that the current evidence does not support a statistically significant mortality benefit of metformin to hospitalized COVID-19 patients with type 2 diabetes mellitus. Although there was a small probability of a reduction in mortality of the patients who received metformin, as shown in the pooled effect size in the meta-analysis, the effects were statistically not significant, as the studies included in the analysis yielded inconsistent results.

However, results should be interpreted cautiously as the pooled effect may be misleading because of the presence of moderate heterogeneity and uncertainty in the effect direction. The inconsistencies may be attributed to the differences in the study design, patient populations, interventions, or other

methodological factors. Due to the presence of heterogeneity between the studies, the random effects model was used in this study, as this allows unconditional inferences or generalizations to be made beyond the individual studies included in the meta-analysis. Nevertheless, there was no strong evidence of a publication bias, which contributed to the increase in confidence in the validity of the pooled estimate despite its non-significance. There was only one outlier reported that may have affected the symmetry of the funnel plot however, further statistical testing suggested no significant publication bias on the studies included in the analysis.

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