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Meta-Analysis

The Effect of Metformin Use on Mortality of COVID-19 Patients with Diabetes Mellitus

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ABSTRACT

Background: COVID-19 is a disease caused by infection with the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). COVID-19 is still a worldwide threat because of its high morbidity and mortality. This is influenced by the occurrence of hypertension, obesity, age and diabetes mellitus. However, currently there is still controversy in the results of research regarding the use of metformin in COVID-19 with type 2 diabetes mellitus (type 2 DM). This study was aimed to analyze the effect of metformin in COVID-19 patients with diabetes mellitus on mortality rates.
Subjects and Method: This study was a systematic review and meta-analysis with the following PICO. P: COVID-19 patient with type-2 diabetes mellitus. I: administration of metformin therapy. C: therapy other than metformin and O: mortality. The articles used in this study were obtained from several databases, namely PubMed, Science Direct, Proquest, SpringerLink, Google Scholar and Scopus. The article search keywords were: "COVID-19" OR "coronavirus" AND "diabetes" AND "metformin" AND "mortality." Articles included are full-text English using a cohort study design from 2020 to 2021 and reporting the Odds Ratio in multivariate analysis. The selection of articles was carried out using the PRISMA flow chart. The articles were analyzed using the Review Manager 5.3 application.
Results: A total of 7 cohort studies involving 136,321 COVID-19 patients from the Americas (USA and Alabama United States), Europe (France and Spain), and Asia (China and South Korea) were selected for systematic review and meta-analysis. The data collected showed that COVID-19 patients with diabetes mellitus who were given metformin reduced the risk of death by 0.90 times higher compared to COVID-19 patients with diabetes mellitus who were not given metformin therapy (aOR= 0.90; CI 95%= 0.68 to 1.19; p=0.450).
Conclusion: Metformin can reduce the risk of death in COVID-19 patients with diabetes mellitus.

Keywords: Diabetes, COVID-19, SARS-CoV-2, metformin, mortality

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BACKGROUND

COVID-19, also known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is an acute respiratory infection disease caused by a coronavirus, which was first reported in December 2019 in Wuhan, China (Oduro-Mensah et al., 2020). The virus spread rapidly throughout the world and caused a pandemic with the total number of reported cases until January 19, 2022 reaching 399,600,607 people with a total death of 5,757,662

people (WHO, 2022). Based on existing reports, the clinical manifestations of COVID-19 vary widely. These clinical manifestations include fever, cough, cough with phlegm, headache, weakness, shortness of breath, anosmia, red eyes and diarrhea (Hu et al., 2021). The incubation period of the COVID-19 virus ranges from 1-14 days, the average symptom begins to appear on the fifth day, while the symptoms of shortness of breath and pneumonia can appear on the eighth day after clinical symptoms appear (Hu et al., 2021).

Clinical symptoms may vary in each individual due to the influence of comorbid factors. Most COVID-19 patients have comorbid diseases such as hypertension, cardiovascular disease, chronic liver disease and diabetes mellitus. Patients who have these comorbidities are more likely to experience worsening and death (Huang et al., 2020). Diabetes is a chronic disease characterized by abnormally high blood glucose levels due to impaired insulin action and/or insulin secretion. More than 425 million people have diabetes worldwide and projecttions show this number to increase to 629 million by 2045 (Cho, 2017). Studies have also shown that type 2 diabetes mellitus (T2DM) is a risk factor for more severe disease and is associated with increased mortality. People with diabetes are at greater risk for viral infection, adverse clinical outcomes, and death, as noted in previous coronavirus epidemics, namely the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Wargny et al., 2021).

Metformin is one of the most widely used antidiabetic drugs in recent decades. In addition to its blood glucose lowering effect, metformin protects diabetics from cardiovascular disease, microvascular complications of diabetes and neoplasms. In addition, other potential underlying mechanisms explaining the beneficial impact of metformin in COVID-19 patients with diabetes have been explored, including its effect in reducing cytokine storm (Cameron et al., 2016). The use of metformin is the cornerstone of management in patients with type 2 diabetes mellitus due to it's therapeutic effect on glucose control and low cost, therefore, it is important to determine the outcome with its use in COVID-19 patients, which is also associated with lower COVID-19 patient mortality. However, the potential benefit of metformin in patients with COVID-19 remains uncertain. Therefore, the researchers undertook this systematic review and meta-analysis to explore the impact of metformin use on mortality of COVID-19 patients with diabetes mellitus and other important patient outcomes across different populations and studies.

SUBJECTS AND METHOD

1. Study Design

This study is a systematic review and meta-analysis. The articles used in this study are articles published from 2020 to 2021. The researchers conducted a comprehensive literature search from January 14 to January 27, 2022 in several databases including PubMed, Science Direct, Proquest, SpringerLink, Google Scholar and Scopus. The search strategy used the following specific keywords: "COVID-19" OR "coronavirus" AND "diabetes" AND "metformin" AND "mortality". After screening by identifying relevant abstracts, the researchers searched the reference list from retrieved articles to find additional potentially eligible studies.

2. Inclusion Criteria

Selected articles discussing the effect of metformin on COVID-19 patients with diabetes mellitus as a cause of death were

published in English. The study sample was patients who were confirmed positive for COVID-19. The final results of the study were reported using the Odds Ratio (OR). The inclusion criteria in this study were full text articles in English, observational studies (cohorts), multivariate analysis, COVID-19 patients with type 2 Diabetes Mellitus, hospitalized, aged >18 years old and <85 years old.

3. Exclusion Criteria

Exclusion criteria in this study were articles with RCTs, quasi-experiments, articles not published in English, pediatric patients and statistical results that did not report OR. The data was processed using the Review Manager (RevMan 5.3) by calculating the difference in results between variables (effect size) and providing an estimate of the combined effect and variation or heterogeneity of all studies.

4. Operational Definition of Variable

The search for articles was carried out by considering the eligibility criteria determined using the PICO model. P: COVID-19 patient with type-2 diabetes mellitus. I: administration of metformin therapy. C: therapy other than metformin and O: mortality.

Metformin is a biguanide used as first-line treatment of type 2 diabetes mellitus and is quite effective as monotherapy or in combination therapy with other glucose-lowering drugs (Baker et al., 2021). The instruments used are medical records and officer records regarding the chronic diagnosis of COVID-19 disease with diabetes mellitus. The measurement scale is categorical.

Type-2 Diabetes Mellitus is a heterogeneous metabolic disorder characterized by chronic hyperglycemia. The cause is a dominant insulin resistance with relative insulin deficiency to a secretory defect with insulin resistance (Kerner and Bruckel, 2014).

COVID-19 is a disease caused by infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 can cause respiratory system disorders, ranging from mild symptoms such as flu to lung infections, such as pneumonia.

COVID-19 patient deaths is the death status of a patient diagnosed with COVID-19 with type 2 diabetes mellitus. The tool used is a death certificate document with a diagnosis of COVID 19. The measurement scale is categorical.

5. Study Instrument

This study is guided by the PRISMA diagram and article quality assessment using the Critical Appraisal Skills Program (CASP, 2018).

6. Data Analysis

The data in this study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots were used to measure the relationship and heterogeneity of the data.

RESULTS

This meta-analysis process began with journal identification, namely searching for articles from several journal databases including PubMed, Science Direct, Proquest, SpringerLink, Google Scholar and Scopus with specified keywords. The next step was the review process of the article through the use of the PRISMA diagram (Figure 1). Research related to the death of COVID-19 patients in hospitals with diabetes mellitus who had received metformin therapy were 1,322 articles, from the initial search process by 2,052 articles. The next following step was to remove the same articles (removing duplicate articles) followed by a filtration process so that 23 articles are obtained that meet the requirements for further review. There were 7

articles that met the quality assessment to be included in the quantitative synthesis using meta-analysis.

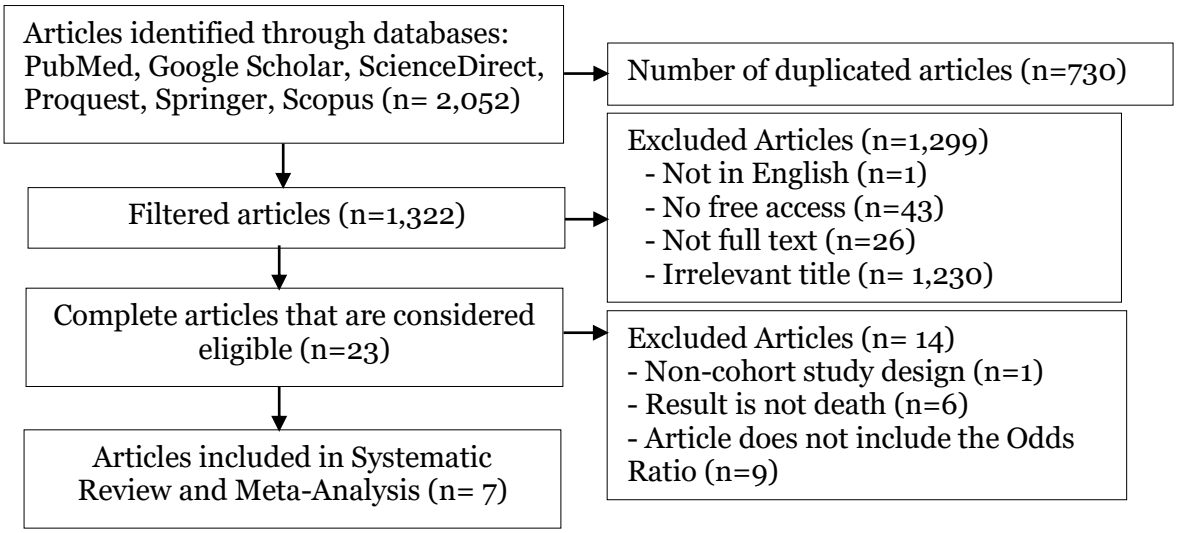

Figure 1. PRISMA flow Chart

Figure 2. Map of the study area of the effect of metformin use on COVID-19 patients with diabetes mellitus on mortality

It can be seen in Figure 2 that the research articles come from three continents, namely South America (USA and Alabama United States), Europe (France and Spain), and Asia (South Korea and China). In Table 1, the researchers conducted an assessment of the quality of the study using the Critical Appraisal Skills Program (CASP). Meanwhile, Table 2 described the description of the main studies included in the primary meta-analysis study which showed that 7 articles from observational studies (cohorts) provide evidence that the administration of metformin therapy in patients diagnosed with COVID-19 with diabetes mellitus who were hospitalized affected the patient's mortality rate.

Table 1. Assessment of study quality published by the Critical Appraisal Skills Program (CASP)

No	Indicators	Publication (Author and Year)						
		Luo et al. (2020)	Cariou et al. (2020)	Bramante et al. (2021)	Oh and Song (2020)	Lalau et al. (2020)	Crouse et al. (2020)	Perez-Belmonte et al. (2020)
1	Did the study address a clearly focused issue?	2	2	2	2	2	2	2
2	Was the cohort recruited in an acceptable way?	2	2	2	2	2	2	2
3	Was the exposure accurately measured to minimise bias?	2	2	2	2	2	2	2
4	Was the outcome accurately measured to minimise bias?	2	2	2	2	2	2	2
5	Have the authors identified all important confounding factors? Have they taken account of the confounding factors in the design and/or analysis?	0	2	2	2	2	2	2
6	Was the follow up of subjects complete enough? Was the follow up of subjects long enough?	0	2	0	2	0	0	2
7	What are the results of this study?	2	2	2	2	2	2	2
8	How precise are the results?	2	2	2	2	2	2	2
9	Do you believe the results?	2	2	2	2	2	2	2
10	Can the results be applied to the local population?	2	2	2	2	2	2	2
11	Do the results of this study fit with other available evidence?	2	2	2	2	2	2	2
12	What are the implications of this study for practice?	2	2	2	2	2	2	2
	Total	**20**	**24**	**22**	**24**	**22**	**22**	**24**

Note:
2: Yes; 1: Can't tell; 0: No

Table 2. Description of Main Studies Included in the Meta-Analysis Primary Study

Author, Year	Study Design	Country	Sample		Population	Intervention	Comparison	Outcome	aOR (95%CI)
			Total	Metformin Therapy					
Luo et al. (2020)	Retrospective	China	283	104	DM patient confirmed COVID-19	Metformin therapy or combination	Non-Metformin therapy	Healing and Death	4.36 (1.22 to 15.59)
Cariou et al. (2020)	Retrospective Cohort	France	1,521	1,317	COVID-19 patients with DM	Metformin therapy	Non-Metformin therapy	Tracheal Intubation and Death	0.80 (0.45 to 1.43)
Bramante et al. (2021)	Retrospective -Cohort	USA	6,256	2,333	Confirmed COVID-19 patients with diabetes mellitus and obesity aged 18 years old or older	Metformin therapy	Non-Metformin therapy	Death	0.79 (0.64 to 0.98)
Oh and Song (2020)	Retrospective Cohort	South Korea	122,040	7,204	COVID-19 Patients with Type-2 DM	Patients on oral metformin therapy for 90 consecutive days	Other Patients without Metformin Therapy	Death Death	1.26 (0.81 to 1.95)
Lalau et al. (2020)	Retrospective	France	2,951	1,496	COVID-19 patients with DM	Metformin therapy on admission to the hospital	Therapy without Metformin on admission to the hospital	Severity and Death	0.71 (0.54 to 0.94)
Crouse et al. (2020)	Retrospective	Alabama United State	604	194	COVID-19 patients with DM	Metformin Therapy Patients	Non-Metformin therapy	Death	0.38 (0.17 to 0.87)
Perez-Belmonte et al. (2020)	Retrospective Cohort	Spain	2,666	249	COVID-19 patients with DM aged 18 years old or older	Metformin therapy or combination	Non-Metformin therapy	Death	1.16 (0.78 to 1.72)

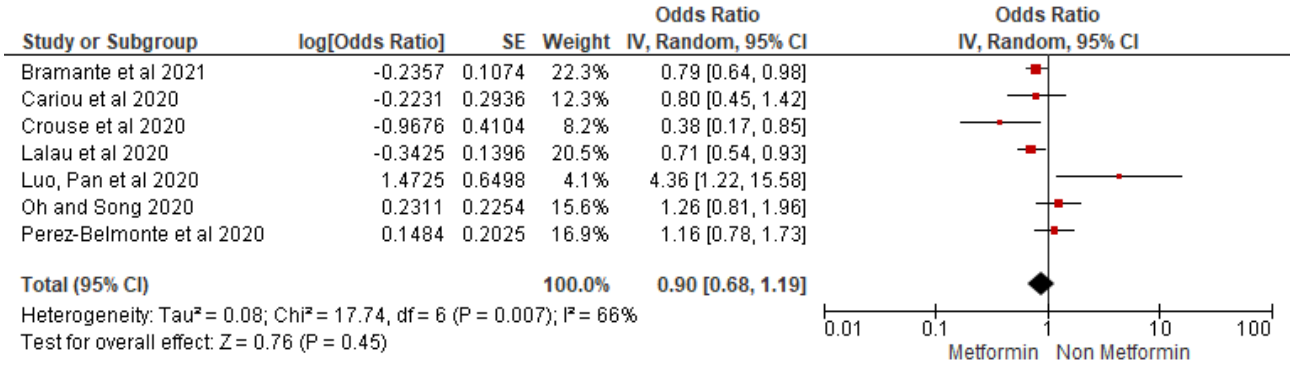

Figure 3. Forest Plot of the Effect of Metformin Use on COVID-19 Patients with Diabetes Mellitus on Mortality

Based on the results of the forest plot, the observational study (cohort) showed that the level of death of COVID-19 patients with diabetes mellitus who were given metformin reduced the risk of death by 0.90 times compared with COVID-19 patients with diabetes mellitus who were not treated with metformin (aOR= 0.90; 95% CI= 0.68 to 1.19), and the results were not statistically significant (p= 0.450). The heterogeneity data showed I^2= 66%, therefore, the distribution of data was declared heterogeneous (random effect model).

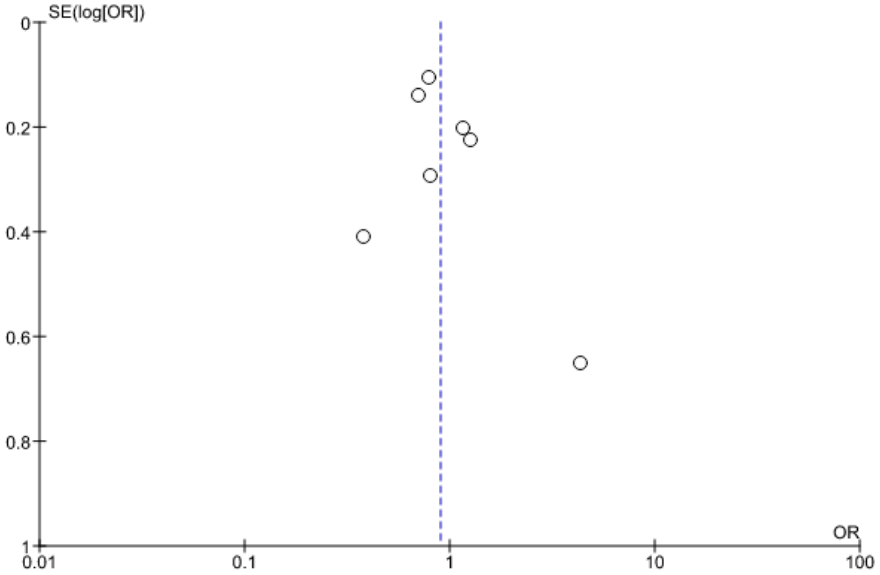

Figure 4. Funnel Plot Plot of the Effect of Metformin Use on COVID-19 Patients with Diabetes Mellitus on Mortality

The funnel plot results showed publication bias with an overestimated effect characterized by an asymmetric distribution between the right and left plots. There were three plots on the right, three plot on the left, and one plot touching the vertical line. The plot on the right side of the graph has a standard error (SE) between 0 and 0.8. The plot on the left side of the graph has a standard error (SE) between 0 and 0.6.

DISCUSSION

This study discussed metformin therapy in diabetes which was considered important because it was one of the risk factors that reduce mortality in COVID-19 patients. The use of metformin can reduce the mortality rate in COVID-19 patients with Type 2 Diabetes Mellitus. This is in line with the research of Lalau et al. (2020) which revealed a lower risk of death in diabetes mellitus patients who are hospitalized with COVID-19 (aOR= 0.71 95% CI= 0.54 to 0.94). Another finding from the retrospective cohort study of Bramante et al. (2021) in the USA which included 6,256 COVID-19 patients found that the use of metformin therapy was significantly associated with a reduction in mortality in women with obesity or type 2 diabetes mellitus (aOR=0.792 95% CI= 0.64 to 0.98).

Several studies have suggested that diabetes is an independent risk factor for death from COVID-19, this risk being reduced dramatically in patients taking metformin. Increasing the likelihood that metformin may provide a protective approach in this high-risk population (OR= 0.38 95% CI= 0.17 to 0.87) (Crouse et al., 2020).

Diabetes Mellitus is a disease that can cause morbidity and mortality. Patients with diabetes mellitus have a chronic inflammatory condition characterized by multiple metabolic and vascular disorders. Chronic inflammation, increased coagulation activity, impaired immune response, and potential direct pancreatic damage by SARS-CoV-2 may be one of the mechanisms underlying the association between diabetes and COVID-19 (Hasan et al., 2021).

In COVID-19 patients, there was an increase in levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and C-reactive protein, as well as an increase in coagulation activity characterized by higher d-dimer concentrations. Whereas in patients with type 2 diabetes, in addition to the inflammatory process, it is also characterrized by an imbalance between coagulation and fibrinolysis, with increased levels of clotting factors and inhibition of the fibrinolytic system. Insulin resistance and Type 2 diabetes are associated with endothelial dysfunction, and increased platelet aggregation. This disorder supports the development of a hypercoagulable pro-thrombotic state. (ACE2) has been identified as one of the main receptors for SARS-CoV and SARS-CoV-2. ACE2 is a receptor present in the respiratory tract and pancreas (Hasan et al., 2021). When SARS-CoV-2 binds to the ACE2 receptor, it will inhibit the normal function of ACE so that tissue damage can occur, especially the pancreas (Hoffmann et al., 2020).

Metformin is a widely used oral glucose-lowering drug and is recommended as a first-line drug based on the recommendations of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Yang et al., 2020). Metformin activates adenosine monophosphate protein kinase (AMPK), which ultimately increases mitochondrial metabolism and autophagy and reduces levels of inflammatory factors (Poly et al., 2021). More specifically, metformin is reported as one of the drugs that targets the human host factor of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via the mTOR pathway. In addition, metformin exerts direct and indirect immunosuppressive effects as illustrated by its ability to reduce the secretion of pro-inflammatory cytokines by macrophages, regardless of diabetic status. Of particular interest is the activity of metformin on mitochondrial ROS/Ca2+.

Activated Ca2+ channel/IL-6 cascade can reduce the proinflammatory/ prothrombotic properties of aggressive COVID-19. Finally, metformin is able to fix fibrosis in various lung conditions by facilitating myofibroblast deactivation and apoptosis and accelerates fibrosis resolution by inducing transdifferentiation of myofibroblasts into lipofibroblasts (Lalau et al., 2020). Considering all these effects, metformin may be a good drug candidate to reduce the severity of COVID-19.

In a meta-analysis taken from seven research articles that have been conducted by Bramante et al., 2021; Cariou et al., 2020; Lalau et al., 2020; Pérez-Belmonte et al., 2020; Oh and Song, 2020; Crouse et al., 2020; and Luo et al., 2020, most of the studies evaluated have shown that the use of metformin in the treatment regimen of COVID-19 patients with type 2 diabetes mellitus is beneficial. COVID-19 is associated with poor prognosis and increased mortality in patients with diabetes mellitus. In addition, the management of diabetes mellitus in patients suffering from COVID-19 is a major clinical challenge. Most of the studies evaluated in the current systematic review demonstrated a beneficial effect of metformin in the treatment of COVID-19 patients with diabetes mellitus. Metformin as a host-directed therapeutic agent can modulate immune mechanisms and therefore may prevent the development of acute respiratory distress syndrome (ARDS). Since there are several metabolic similarities between COVID-19 and Diabetes Mellitus such as hyperglycemia, oxidative stress, and pro-inflammatory cytokines, it is not reasonable to expect metformin to have effects such as decreasing levels of the inflammatory cytokines IL-6 and TNFalpha as well as increasing IL-1 (Zumla et al., 2020).

Metformin induces the formation of M2 and T-regulatory macrophages and CD8 memory T cells which in turn minimizes the inflammatory reaction. However, some studies suggest against using this drug in COVID-19 treatment protocols. However, in patients with heart failure, respiratory distress, sepsis or renal impairment, metformin should be discontinued because of the risk of lactic acidosis (Singh and Singh, 2020).

AUTHOR CONTRIBUTION

Dini Hapsari and Dwi Trisnawati Zainal as the main researchers who designed the study, collected articles from electronic journal databases and analyzed the data.

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This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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