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The effect of Metformin on improving survival among obese and diabetic patients affected with COVID-19: Findings of a Meta-analysis

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Abstract

Background: Diabetes Mellitus is one of the major non-communicable diseases among patients suffering from COVID-19, which increases the likelihood of hospital admission mortality. While Metformin has been found effective in reducing the mortality associated with COVID-19, there is a need to update the existing meta-analyses and quantitively synthesize the findings regarding the effect of Metformin in reducing mortality.

Methods: We undertook a meta-analysis of 21 studies after searching for epidemiological studies systematically in PubMed/Medline, EMBASE, and Science Direct. We used odds ratios and their respective 95% confidence interval (CI) for a binary outcome, which was mortality, to examine the effect of Metformin on mortality. Heterogeneity was assessed using the I2 statistic and Q-test statistics. We evaluated the publication bias using a funnel plot, which was further confirmed by eager test statistics. A p-value of < 0.05 was considered statistically significant.

Results: Overall, the findings revealed that Metformin reduced mortality by about 35%, and the results were statistically significant (OR= 0.66; 95% CI 0.62 to 0.69; $p<0.05$). This revealed that patients who took Metformin had improved survival by more than one-third than those who were not given Metformin. We found a relatively higher heterogeneity with an I2 value of 85.60% (Chi-squared = 138.85). The inverted funnel plot for the findings for the effect of Metformin on mortality was asymmetrical with test statistics for an eager test of -3.64 and a P-value of 0.002.

Conclusion: The present updated meta-analysis revealed a positive effect of Metformin in reducing mortality among diabetic patients suffering from COVID-19. However, before implementing Metformin at a larger scale, clinicians and endocrinologists need to assess the risks versus benefits associated with Metformin for diabetic patients of COVID-19. Also, future studies are warranted to investigate the effects of Metformin for non-diabetic patients.

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Keywords: Metformin; Mortality; COVID-19; Diabetes Mellitus; Meta-analysis.

1. Introduction

Since December 2019, the world has been in chaos due to the pandemic Corona Virus 2019 (COVID-19), which is also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). As a result, there are varying morbidity and mortality rates among all kinds of patients across the countries and regions(3, 4). Since then, the virus has spread over the world, infecting 4,806,299 individuals, and causing 318,599 fatalities as of the 20th of May 2020 (5). However, nothing is known about the SARS-CoV-2 pathophysiology. It is now well established that there is a strong relationship between the virus SARS-CoV-2 and an individual's immune system, resulting in a variety of clinical symptoms of the disease (6).

Diabetes mellitus (DM) is considered to be metabolic condition which caused by a deficiency of insulin production or insulin activity. Chronic hyperglycemia and abnormalities in carbohydrate, fat, and protein metabolism follow from insulin insufficiency (7). Diabetes mellitus is classified into various subtypes, the two most prevalent of which are type 1 (T1D) and type 2 (T2D) (8). Both Type 1 and Type 2 diabetes cause hyperglycemia, but the way this happens is different. T1D is usually caused by an autonomic dysfunction disease in which cells in the pancreas are damaged, resulting in less insulin production. On the other hand, T2D is caused by the body not being able to properly absorb insulin or insulin resistance. People with Type 2 diabetes make up more than 85%–95% of all diabetes cases (9). It has been shown that people with diabetes mellitus (DM) have a higher frequency of infection and more susceptible to infections compared to nondiabetic individuals (10).

Further, it has also been found that people suffering from non-communicable diseases such as chronic kidney disease, cardiovascular disease, cancers, diabetes mellitus, and obesity are at a higher risk of COVID-19 morbidity and mortality (3, 5, 6). For example, according to previous research, inflammation-related biomarkers and inflammation responses are somewhat higher among patients suffering from diabetes mellitus compared to non-diabetes(7). This implies that being diabetic is a potential risk factor that determines the prognosis and progression of COVID-19. Add more about non-communicable diseases with covid including diabetes

Diabetes Mellitus is one of the major non-communicable diseases among patients suffering from COVID-19, which increases the likelihood of admission to the intensive care units by 14 to 32%(8). The immunological explanations could be possibly due to decreased cluster of differentiations (CD-4) T-cells in diabetic patients infected with SARS-CoV-2, increased expression of inflammatory interleukin-6, or upregulation of angiotensin-converting enzyme-2 (9-11). Hence, the mortality rate from COVID-19 is

higher in patients with uncontrolled glucose levels. This suggests that medication that can reduce glucose levels and be prescribed safely among diabetic patients can be used to decrease the mortality associated with COVID-19 among diabetic patients(12). And Metformin is one of the most commonly prescribed medications to be used among diabetic patients(12). Besides the hypoglycemic activity, Metformin has anti-inflammatory properties through reduction of reactive oxygen species (ROS) (13). The mentioned mechanisms metformin advantages are extended to reduce the mortality associated with COVID-19.

Recently, a series of epidemiological studies have demonstrated the positive role of Metformin in decreasing mortality among COVID-19 patients(13, 14). These findings are further supported by the subsequent reviews and meta-analyses confirming the favorable effect of Metformin in decreasing mortality due to COVID-19(13, 15, 16). However, the existing meta-analyses have either included fewer studies or have missed the large observational cohort studies from various countries that are recently published in 2019(15, 16). Given this, there is a need to quantitatively analyze the data from recently published epidemiological studies examining the effect of Metformin in reducing mortality among diabetic patients admitted with COVID-19. Thus, we undertook this meta-analysis to quantitatively analyze the data on all studies that have been carried out since the inception of the pandemic assessing the role of Metformin in reducing mortality. This is crucial because it will facilitate evidence-based decisions to policymakers and clinicians to make evidence-based decisions to improve survival among diabetic patients affected with COVID-19.

2. Subjects and Methods

We undertook a meta-analysis to quantitatively summarize the existing data from epidemiological studies that assessed the role of Metformin in reducing mortality among diabetic patients admitted with COVID-19. We used updated Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines to undertake this meta-analysis(17).

2.1 Inclusion and Exclusion Criteria

The eligibility of a research article if an epidemiological study assessed the effect of Metformin in decreasing the mortality among diabetic or obese patients suffering from COVID-19, published in English through January 2022 across different regions of the world. Furthermore, only quantitative epidemiological studies were included, with qualitative studies and studies lacking full texts being excluded. All studies that were opinions, criticisms of previous research studies, or editorials were excluded. Furthermore, studies that looked at outcomes other than mortality were excluded because mortality was our primary focus.

2.2 Information sources and strategy to examine the appropriate research studies

A systematic search of research studies was initiated and finished in 2022. We searched databases like PubMed/Medline, EMBASE, and Science Direct. References of the selected articles were also screened according to the eligibility criteria for additional related publications. An independent search was undertaken to scan the results eligible studies, followed by retrieving full-text articles. We considered mortality or number of deaths among diabetic or obese COVID-19 patients as the main outcome of interest.

We identified a blend of Medical Subject Heading (MeSH) keywords and text words. The most prevalent search terms found in abstracts and titles comprised "metformin," "hypoglycemic agents," "role of metformin in COVI-19", "metformin and COVID-19", "effect of metformin in reducing mortality among diabetic and COVID-19", "metformin and deaths in COVID-19", "metformin and mortality rate in COVD-19". This was followed by merging these major concepts using combinations (AND, OR) appropriate to the aim of the meta-analysis. The keywords included "Metformin" OR "hypoglycemic agents" OR "Biguanides" OR AND "mortality in diabetic patients COVID-19" AND "diabetic" And "Obese" AND "COVID-19" AND "Death". In addition, to find more research articles, we used truncation (*) with the same root word. We used truncation to ensure that all possible search term variants were retrieved. To include eligible studies in the search, we also employed screens on the language (English) and the period of publication.

2.3 Data abstraction

We imported all relevant research studies into the reference manager software (EndnoteTM) file, where every research study was evaluated, and we also used this software to screen titles for duplicates. Abstracts that did not explicitly address the study aim were not considered for full-text publication. In the end, we acquired and assessed the full-text articles of the leftover pertinent research papers. The articles that met the eligibility criteria were then abstracted and summarized using a standardized proforma. As a result, after eliminating repeats, screening titles, and abstracts, and removing papers that were outside the scope of this review as guided by inclusion criteria, we removed papers. Furthermore, the bibliography of the remaining studies was verified and examined to ensure that no valuable research articles were overlooked. The reviewers conducted the search for the articles independently, and their judgments and extracted summaries were compared to recognize and solve disagreements. Independent reviewers extracted study characteristics from eligible research articles using a standard data extraction sheet. Before beginning the data extraction process, the reviewers assessed the data extraction tables to ensure that the essential findings of the eligible studies were included. In addition, to describe the objects of the data extraction proforma, current research articles on the chosen topic were reviewed. Any disagreements

between the two reviewers were resolved through mutual agreement. The abstracted data included the study title, publication year, sample size or population, country or study setting, average age with age range, gender, and study participant characteristics.

2.4 Statistical Analysis

We used odds ratios and their respective 95% CI for a binary outcome, which was mortality, to examine the effect of Metformin on mortality. Since the outcome was dichotomous, percentages were used to compute ORs and their 95% CI. We carried out this meta-analysis using Open Meta[analyst] software. Heterogeneity was assessed using the I2 statistic and Q-test statistics(18). The cutoffs for I2 statistics were utilized to categorize the heterogeneity as very low (0 to 25%), low (25 to 50%), moderate (50 to 75%), and high (> 75%). An inverted variance statistical method and random-effect model were used for this meta-analysis because of the differences in studies either due to sample size, outcome assessment, and tools to measure the outcomes. This was also confirmed by a greater degree of heterogeneity using the I2 statistic and Q-test statistics. Finally, we used random-effects models to calculate the overall effect size and its respective 95% CI to evaluate the impact of Metformin in reducing mortality(19). Forest plots were generated to compute an individual as well as pooled effects of the intervention for the primary outcomes (mortality: Yes or NO) and to assess statistical heterogeneity. We also evaluated the publication bias visually using a funnel plot, which was further confirmed by eager test statistics. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1 Results of the search strategy

The selected articles were initially screened by titles, then by abstracts, and finally by full-text articles. Our preliminary search recognized 2356 citations in different databases, and after removing 1563 duplicates, 793 unique observational studies were screened for their titles and abstracts. This was followed by reviewing 88 full-text articles, and 64 were further excluded as these studies did not meet the eligibility criteria. Finally, we included 24 articles for qualitative synthesis, and 21 studies were incorporated in the quantitative synthesis as displayed in the PRISMA flow diagram for screening the studies (Figure 1).

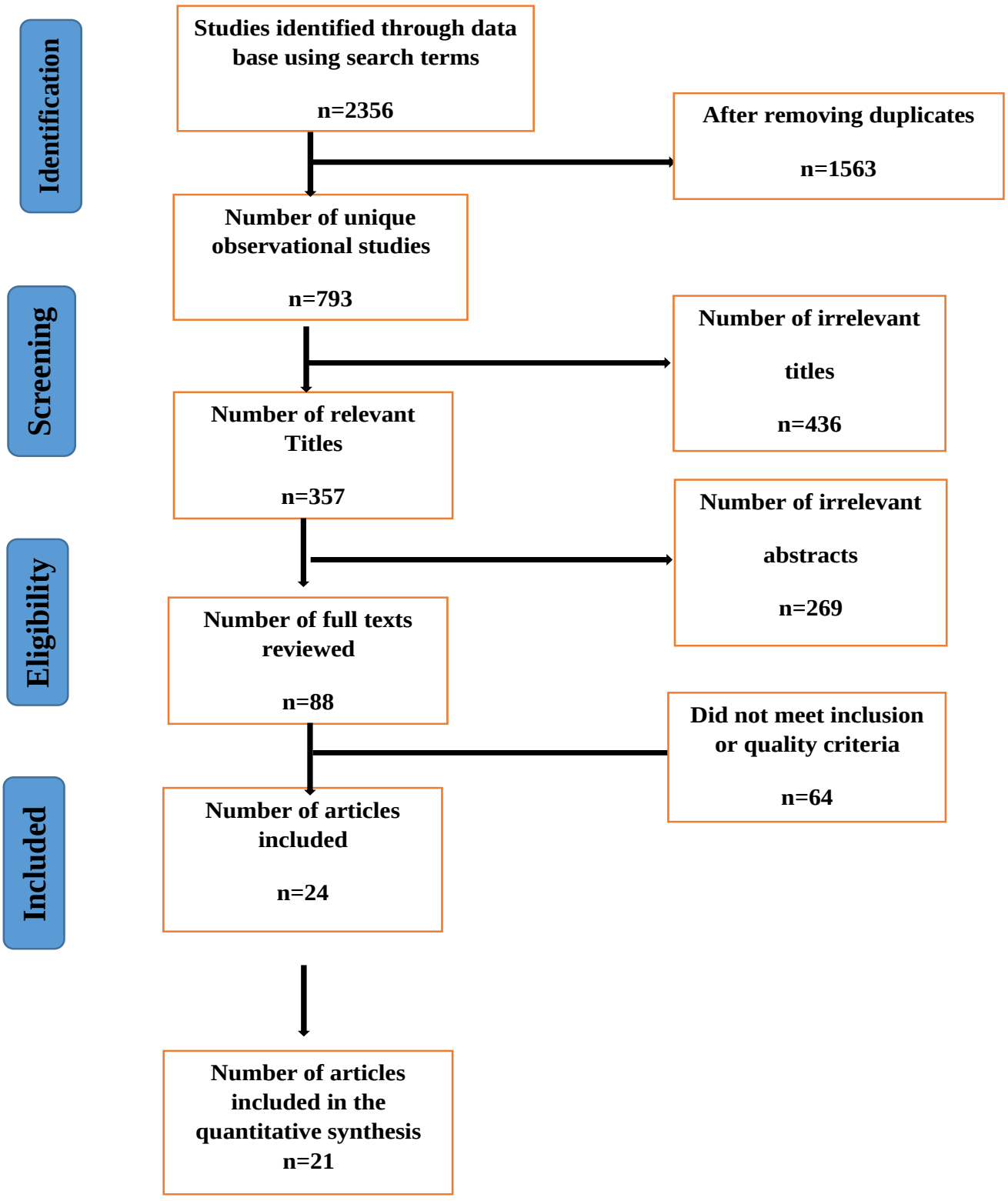

Figure (1) Flow chart summarizing the identification and selection of relevant papers

3.2 Characteristics of the eligible studies

With respect to the study design, all studies were observational epidemiological studies, i.e., either retrospective cohort one-center or multi-center studies or cross-sectional studies. However, almost more than 95% of the studies were retrospective cohort studies as shown in Table 1. The studies were conducted in countries such as the United States of America (USA) (n=5), United Kingdom (n=3), Turkey (n=1), Spain (n=1), Brazil (n=1), Ireland (n=1), Philippines (n=1), France (n=3), Korea (n=), and China (n=6). All studies were either conducted in 2021 or 2020. For example, eight studies were conducted recently in 2020, whereas the remaining studies (n=17) were conducted in 2021, as illustrated in Table 1. The overall sample size of all eligible research articles ranged between 131 to $2,851,465$ with an almost similar distribution by gender. On average, the study participants were between 51.8 years to 75.6 with varying proportions of males and females in the Metformin or no metformin group. While reviewing the studies, we found that most studies included participants who were either diabetic or obese and had been admitted to the hospital with COVID-19.

Table 1 Characteristics of the studies that assessed the effect of metformin on mortality among diabetic patients with COVID-19 (n=24)

Study	Year	Country	Study Design	Sample size	Type of patients	Mean or Median Age (Years)	Gender (%)
Al-Salameh et al[20]	2021	France	Observational cohort study	433	COVID-19 diabetic patients	72	M=55 F= 45
Bramante et al[21]	2021	USA	Retrospective cohort study	6256	COVID-19 diabetic or obese patients	73	M=56.2 F= 43.8
Crouse et al[22]	2021	USA	Retrospective analysis	25,326	COVID-19 diabetic patients	NR	M=45 F= 55
Ghany et al[23]	2021	USA	Retrospective cohort study	1139	COVID-19 patients	70.9	M= 39 F= 61
Jiang et al[24]	2021	China	Multi-center retrospective study	328	COVID-19 diabetic patients	65	M= 44.6 F= 55.4
Khunti et al[25]	2021	UK	Nationwide observational cohort study	2,851,465	COVID-19 diabetic patients	67	M= 56 F= 44
Korkusuz et al[26]	2021	Turkey	Retrospective study	207	COVID-19 diabetic patients	59.6	M=60.4 F= 39.6
Lally et al[27]	2021	USA	Retrospective cohort study	775	COVID-19 patients	75.6	M= 97.3 F= 2.7
Li J et al[28]	2021	China	Retrospective cohort study	131	COVID-19 diabetic and pneumonia patients	66.8	M=56.5 F= 43.5
Ma et al[29]	2021	USA	Retrospective cohort study	1356	COVID-19 diabetic patients	NR	M=54-61 F= 39-46

Ong et al[30]	2021	Philippines	Cross-sectional	355	Diabetic patients	62.69	M=55.8 F=44.2
Saygili et al[31]	2021	Ireland	Retrospective cohort study	586	COVID-19 diabetic patients	66	M=50 F= 50
Tamura et al[32]	2021	Brazil	Retrospective study	1,170	COVID-19 diabetic patients	51.8	M=52.8 F= 47.2
Wang et al[32]	2021	UK	Cohort study	39829	COVID-19 diabetic patients	64.8	M= 61.9 F= 38.1
Wargny et al[33]	2021	France	Nationwide observational study	2,794	COVID-19 diabetic patients	69.7	M=63.7 F= 36.6
Oh et al[34]	2021	Korea	Population-based Retrospective cohort study	11,892	COVID-19 diabetic patients	NR	M=44.7 F= 55.3
Belmonte et al[35]	2020	Spain	Multi-center observational cohort study	2666	COVID-19 diabetic patients	74.9	M=62 F= 38
Chen Y et al[36]	2020	China	Retrospective study	904	COVID-19 diabetic patients	56	M=46.6 F= 53.4
Goodall et al[37]	2020	UK	Observational Retrospective study	981	COVID-19 patients	69	M=64.3 F= 35.7
Lalau et al[38]	2020	France	Nationwide observational study	2499	COVID-19 diabetic patients	70.9	M=64 F= 36
Li J et al[39]	2020	China	Retrospective cohort study	131	COVID-19 diabetic patients	66.8	M=43 F= 57
Luo et al [40]	2020	China	Retrospective analysis	283	COVID-19 diabetic patients	63	M=51 F= 49
Cheng et al[41]	2020	China	Retrospective study	1,213	COVID-19 diabetic patients	62	M=53.8 F= 46.2
Kim et al[42]	2020	Korea	Multi-center observational cohort study	235	COVID-19 patients	62	M=33-45 F= 55-67

3.3 Findings regarding the effect of Metformin in reducing the mortality

Quantitative synthesis and evaluation of heterogeneity

Figure 2 shows the forest plot for the pooled results for the effect of Metformin in reducing mortality or improving the survival among patients admitted with COVID-19.

We included 21 studies to analyze the data for the effect of Metformin on reducing mortality as the remaining three studies did not have sufficient data to be incorporated in the analysis. Overall, it was found that Metformin reduced mortality by about 35%, and the results were statistically significant (OR= 0.66; 95% CI 0.62 to 0.69; $p<0.05$) (Fig. 2). This revealed that patients who took Metformin had improved survival by more than one-third than those who were not given Metformin. However, upon assessing the heterogeneity, we found a relatively higher heterogeneity with an I2 value of 85.60% (Chi-squared = 138.85), suggesting that there may be a range of factors explaining this heterogeneity.

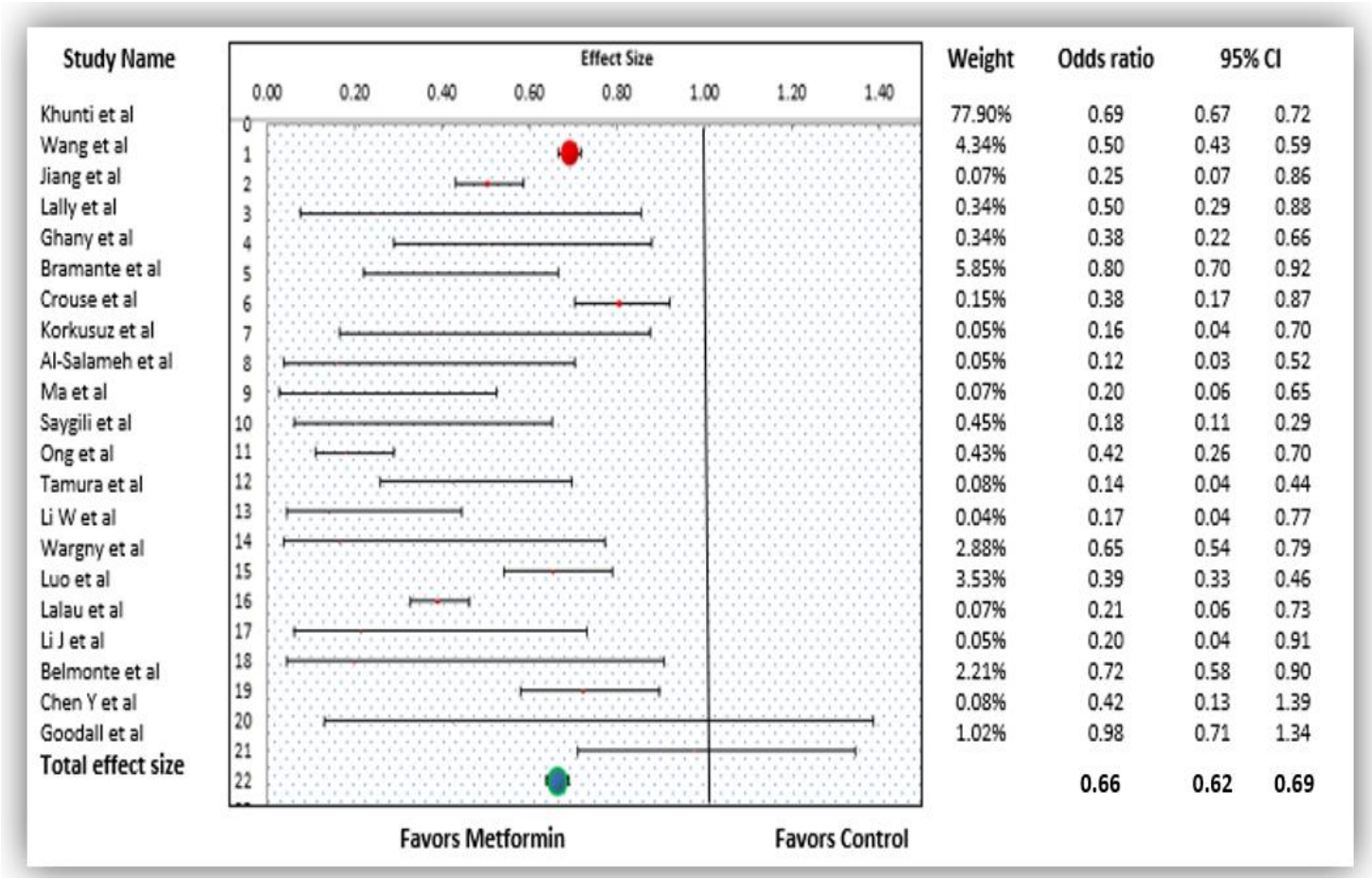

Figure (2) Forest plot showing the individual studies and overall effect of Metformin in reducing the mortality among COVID patients

3.4 Publication bias using funnel plot and eager test

We evaluated publication with the help of an inverted funnel plot and eager tests for the findings, as shown in figure 3. The inverted funnel plot for the results for the effect of Metformin on mortality revealed publication bias with test statistics for an eager test of -3.64 and a P-value of 0.002. A significant Eger's test indicated the presence of small-study effects. The asymmetrical funnel plot suggests the presence of systematic differences between the studies that are published and the studies that are not published.

Egger test

t-test	-3.64
p-value	0.002

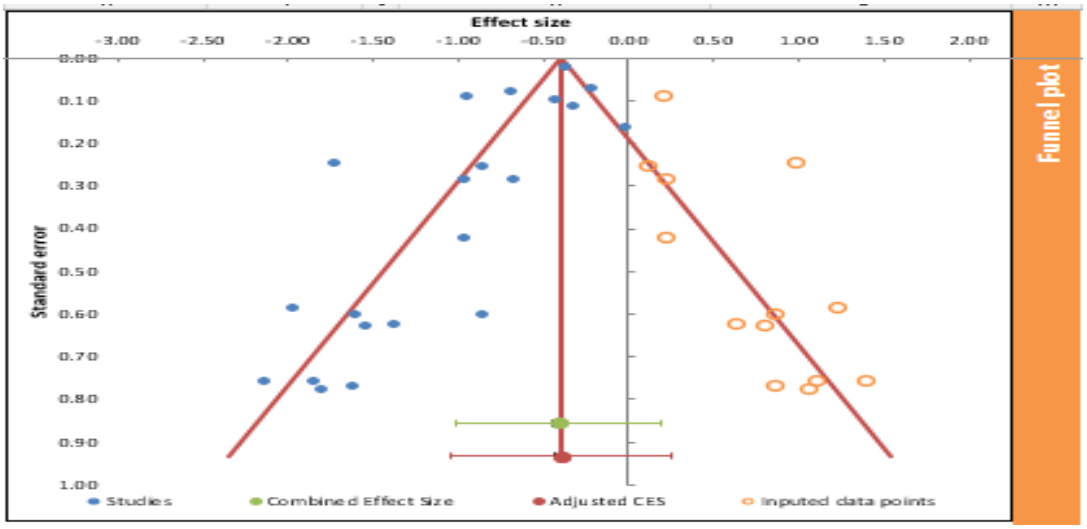

Figure (3) Funnel plot visually representing the publication bias and Eager test

4. Discussion

The COVID-19 pandemic has affected the world severely, and the effects are even more drastic for diabetic patients. Diabetes is usually associated with adverse outcomes among COVID-19 patients, and this is further supplemented by a higher body mass index. Since diabetic patients are usually obese, which increases their susceptibility to getting infected by COVID-19 easily and also experiences complications more than non-diabetic and non-obese patients. This has encouraged researchers and physicians to find out ways to reduce such adverse outcomes, such as mortality. Metformin could be a potential drug that can reduce mortality among COVID-19 patients owing to its anti-inflammatory and hypoglycemic properties. Thus, in the existing pandemic crisis with changing variants of the COVID-19 virus, Metformin could be a promising therapy and a potential agent to reduce the complications, and subsequent mortality rates among diabetic patients admitted with COVID-19.

The findings of the current meta-analysis suggest that Metformin improves the survival among COVID-19 patients by about 65% and can be used to reduce the rates of deaths among diabetic patients suffering from COVID-19. The findings of this meta-analysis are similar to previously conducted series of reviews and meta-analyses findings of a on various outcomes including mortality. Also, the research has demonstrated that metformin use before the confirmation of COVID-19 can be beneficial to diabetic patients (22). However, it is noteworthy to mention that all meta-analyses have been performed on observational studies, which are not free from issue of unmeasured confounding. This warrants for more interventional studies in future before making any definitive conclusions about the role of Metformin in

improving the survival among diabetic patients suffering from COVID-19 patients.

The possible explanations for these consistent findings of the effect of metformin could be attributed to its anti-inflammatory role potentially via 1- reduction of the oxidative damage (43, 44); 2- minimize the neutrophils' extracellular traps among diabetic patients infected with COVID-19 (43, 44); 3- decreasing the release of cytokines, mainly interleukin-6 (13); 4- decrease the formation of thrombosis reduce glycemia which reduces the release of inflammatory markers (13). The COVID-19 virus leads to vascular endothelial glycocalyx damage, which is a further potential life-threatening complication causes subsequent mortality (45). These damages are prevented by metformin because it restores the glycocalyx and protects the cardiovascular system (46, 47). As a result of these properties, metformin can play a role in reducing the cytokines storm, thereby reducing the inflammation and subsequent mortality (48).

4.1 Strengths and Limitations

This is the large meta-analysis of its kind that provides valuable evidence regarding the effect of Metformin in improving survival among diabetic patients with COVID-19. Secondly, we updated the existing meta-analyses by including more studies from 2021, which could not be incorporated in the previously conducted meta-analyses. Third, this meta-analysis included a relatively more significant number of studies when compared to the previously undertaken meta-analysis that included less than 20 studies. However, one limitation of this meta-analysis was that all the included studies were not intervention studies; therefore, there is a threat to the internal validity of the original studies. Besides, these studies were primarily retrospective in nature, which undoubtedly warrants conducting more prospective studies. Second, the likelihood of publication bias was high, as indicated by asymmetrical funnel plots and significant eager tests, which implies that studies with negative findings or small sample sizes may not have been published. Third, studies primarily did not consider the dosage of metformin, thus there is a need to analyze the data in future to see the dose-response relationship between metformin and mortality. Besides, most of the studies were from high-income countries; therefore, we may not be able to make any firm conclusions about generalizing the results to low-income countries. Despite these limitations, we hope that this updated and large meta-analysis can provide useful insights to both physicians and policymakers to make evidence-based decisions for diabetic patients affected with COVID-19.

5. Conclusion

The present updated meta-analysis revealed a positive effect of Metformin in reducing mortality among diabetic patients suffering from COVID-19. However, the presence of confounding, small-study effects, and possible publication bias indicate publishing and conducting randomized controlled trials to confirm the findings from existing literature on observational studies. Therefore, before implementing

Metformin at a larger scale, clinicians and endocrinologists need to assess the risks versus benefits associated with Metformin for diabetic patients of COVID-19. Also, future studies are warranted to investigate the effects of Metformin for non-diabetic patients as well.

6. Declarations

6.1 Abbreviations

SARS-CoV-2 = Severe Acute respiratory syndrome coronavirus 2

T2D = Type 2 Diabetes

DM = Diabetes Mellitus

6.2 Conflict of Interest Statement

The authors have no conflict of interests to declare.

6.3 Funding Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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