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Review

The effect of metformin on mortality and severity in COVID-19 patients with diabetes mellitus

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ABSTRACT

Aim: COVID-19 has spread globally with heavy impact on most countries and our therapeutic strategies in COVID-19 patients with diabetes are still limited. Recently, some new information was added to this field. We performed this updated *meta*-analysis to reveal the underlying effect of metformin on COVID-19 patients with diabetes.

Methods: We searched the PubMed, Embase and CNKI (China National Knowledge Infrastructure) databases for all articles. The odds ratio (OR) corresponding to the 95% confidence interval (95% CI) was used to assess the effect of metformin on COVID-19 patients with diabetes. The statistical heterogeneity among studies was assessed with the Q-test and I^2 statistics.

Results: We collected 17 studies including 20,719 COVID-19 patients with diabetes. Our results found that metformin was associated with significantly decreased mortality and severity in COVID-19 patients with diabetes (OR = 0.64, 95% CI = 0.51–0.79 for mortality, and OR = 0.81, 95% CI = 0.66–0.99 for severity).

Conclusions: Our *meta*-analysis indicated that following metformin treatment might benefit the patients with T2DM, both the mortality and severity. However, patients with severe COVID-19 should be monitored closely for the development of lactic acidosis, acidosis, and decreased kidney function.

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1. Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread throughout the world, afflicting more than 174.4 million people, resulting in more than 3.7 million deaths globally as of June 9, 2021, and with a mortality rate of about 2.1%. The epidemic of diabetes mellitus and its complications poses a major global health threat. The International Diabetes Federation (IDF) estimated that 1 in 11 adults had diabetes mellitus, the estimate is projected to rise to 642 million by 2040 globally [1]. The presence of diabetes mellitus, the individual degree of hyperglycaemia and the presence of typical complications of diabetes mellitus seem to be independently associated with COVID-19 severity and increased mortality [1,2]. Especially the hyperglycaemia might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes [2,3].

Glucose-lowering medications might have effects on COVID-19 pathogenesis, and these effects could have implications for the management of patients with diabetes mellitus and COVID-19 [3]. Dipeptidyl peptidase 4 (DPP4) and the renin–angiotensin–aldosterone system (RAAS) are linked genetically and are associated with the risk of SARS-CoV-2 infection and possibly severity of COVID-19[4]. Glucagon-like peptide 1 (GLP1) analogues are not recommended in severe COVID-19 patients, because they will take time to become effective [5]. Sodium–glucose cotransporter 2 (SGLT2) inhibitors might cause adverse effects such as osmotic diuresis and dehydration in patients with COVID-19 and so cannot be recommended [6].

Metformin is a widely used oral glucose-lowering drug and is recommended as a first-line drug in recent treatment guidelines of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [7]. The clinical science of the potential relationships between metformin and COVID-19 patients with diabetes mellitus has been widely studied. However, knowledge in this field is emerging rapidly, with numerous publications appearing frequently. In the present study, we carried out this *meta*-analysis to detect the overall effects of metformin on COVID-19 patients with diabetes. This study was reported in accordance with the PRISMA statement for reporting systematic reviews and *meta*-analysis [8].

2. Methods

2.1. Publication search and inclusion criteria

We searched the PubMed, Embase and CNKI (China National Knowledge Infrastructure) databases for all articles within a range of published years from 2019 to 2021 on the effect of metformin on COVID-19 patients with diabetes (last search was June 6, 2021). The following terms were used in this search: 'metformin', 'diabetes' and 'COVID-19'. In order to identify the relevant publications, the references cited in the research papers were also scanned. Combining searches resulted in 47 abstracts. In addition, eight studies were identified through review articles and *meta*-analysis, for a total of 55 studies were screened after duplicated records were removed. After screening the titles and abstracts, 24 were retrieved for more detailed evaluation (Fig. 1). We used the Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies and case-control studies based on three categories and eight items.

We evaluated the eligible studies if all the following conditions were met: (1) evaluation on the effect of metformin on COVID-19 patients with diabetes; (2) inclusion of sufficient data or the data can be acquired from the manuscript or supplementary materials to calculate ORs and 95% CIs; and (3) the study was published in English.

2.2. Data extraction

Two authors (Kui Zhang and Wenxing Yang) independently reviewed and extracted the data needed. Disagreements were resolved through discussion among the authors to achieve a consensus. The following information was recorded for each study: first author, year of publication, region, outcome, number of metformin users, and number of patients (all of the data are shown in table 1).

2.3. Statistical analysis

The odds ratio (OR) corresponding to the 95% confidence interval (95% CI) was used to assess the effect of metformin on COVID-19 patients with diabetes. The statistical heterogeneity among studies was assessed with the Q-test and I^2 statistics [9]. If there was no obvious heterogeneity, the

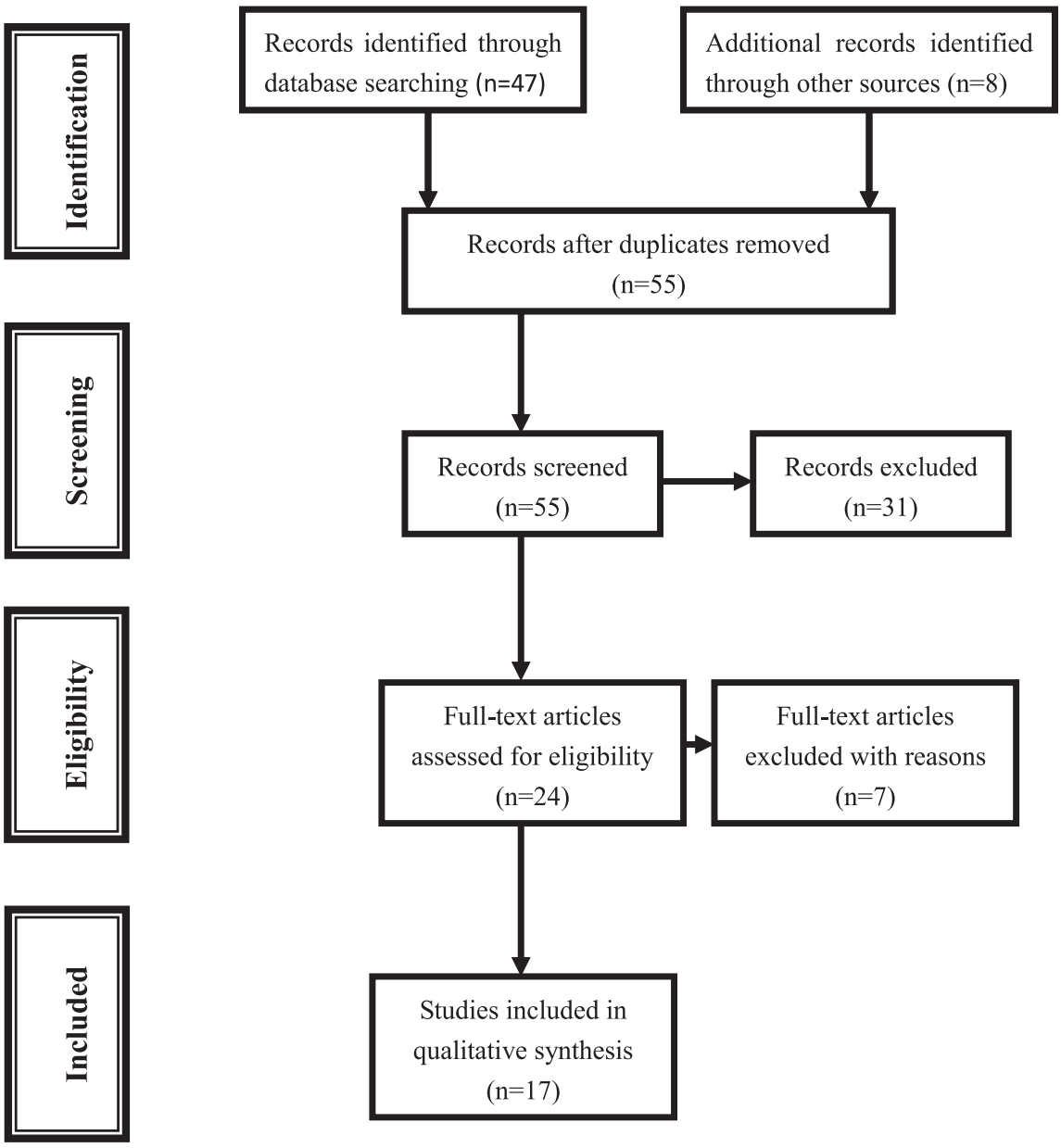

Fig. 1 – Flowchart for identification of studies.

fixed-effects model (the Mantel-Haenszel method) was used to estimate the summary OR [10]; otherwise, the random-effects model (the DerSimonian and Laird method) was used [11]. Finally, random effects models were used to calculate the overall OR estimates and 95% CIs to assess the effect of metformin on mortality and severity in COVID-19 patients with diabetes. To explore sources of heterogeneity across studies, we did logistic *meta*-regression analyses. We examined the following study characteristics: publication year, region, number of metformin users, and number of patients. Publication bias was evaluated with funnel plot and Begg's rank correlation method [12]. The statistical analyses were performed by STATA 12.0 software (Stata Corp., College Station, TX).

3. Results

3.1. *Characteristics of studies*

Out of a total of 55 titles and abstracts, 24 were retrieved for more detail evaluation. Of the seven excluded studies, two papers were reviews, three papers lacked enough data, and two papers were excluded with duplicated data [13,14] and the updated data were included. Finally, 17 studies met the inclusion criteria for this study, including 20,719 COVID-19 patients with diabetes. The details including first author, year of publication, region, outcome, number of metformin users, and number of patients in selected studies were listed in Table 1.

Table 1 – Characteristics of literatures included in the *meta*-analysis.

Reference	Year	Region	Outcome	No. of metformin users	No. of patients	Adjustment for covariates
Jiang N[20]	2021	China	Mortality ARDS	100	328	age, gender, weight, FBG, severity of COVID-19, Charlson comorbidity index, CHD, metformin therapy prior to hospitalization, DDI, creatinine and site
Li W[22]	2021	China	Mortality	37	131	age, BMI, glucose, triglyceride, CRP, D-dimer, and steroid use
Bramante CT[18]	2021	USA	Mortality	2333	6256	age, sex, comorbidities, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, Charlson comorbidity index, and medications, and state
Lally MA[21]	2021	USA	Mortality	127	775	age, body mass index, hemoglobin A1c, estimated glomerular filtration rate, long stay (>90 days), and underlying psychoses
Cheng X[35]	2020	China	Mortality ARDS DIC Heart failure Acute kidney injury Acute heart injury	678	1213	age, gender, comorbidities, blood glucose, C-reactive protein, estimated glomerular filtration rate, alanine aminotransferase, and creatinine
Ghany R[19]	2021	USA	Mortality ARDS	392	1139	age, gender, Charlson score, diabetes, hypertension and ejection fraction
Luo P[40]	2020	China	Mortality	104	283	age, gender, underlying diseases, clinical severity
Oh TK[23]	2021	Korea	Mortality	480	2047	age, sex, underlying disability, Charlson Comorbidity Index
Li J[41]	2020	China	Mortality ventilation	37	131	age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers
Lalau J-D[36]	2020	France	Mortality IMV	1496	2449	sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs
Crouse A[42]	2020	USA	Mortality	76	239	age, race, sex, obesity and hypertension
Pérez-Belmonte LM[38]	2020	Spain	Mortality ICU admission mechanical ventilation in-hospital death	825	1488	age; gender; history of smoking, hypertension; dyslipidemia; chronic kidney disease; cerebrovascular disease; chronic obstructive pulmonary disease; atrial fibrillation; coronary artery disease; heart failure; obesity; dementia; Barthel Index score; and Charlson Comorbidity Index score
Wargny M[24]	2021	France	Mortality	1553	2794	sex, age, BMI, the patient's history, routine medication, symptoms on admission, biological features
Chen Y[34]	2020	China	Mortality Poor prognosis	43	120	age, albumin, creatinine, glucose, CRP, and usage of a specific medication
Goodall JW[39]	2020	UK	Mortality	210	981	age, sex, comorbidities and medication usage
Kim MK[37]	2020	Korea	Mortality severe disease	113	235	age, sex, and the presence of underlying diseases
Gao Y[44]	2020	China	Life threatening complications	56	110	age, gender, blood glucose and LDH levels

IMV, tracheal intubation for mechanical ventilation; severe disease, the necessity for the use of a high-flow nasal cannula, mechanical ventilation, CRRT, or ECMO, or admission to an ICU; CRP, C-reactive protein; BMI, body mass index.

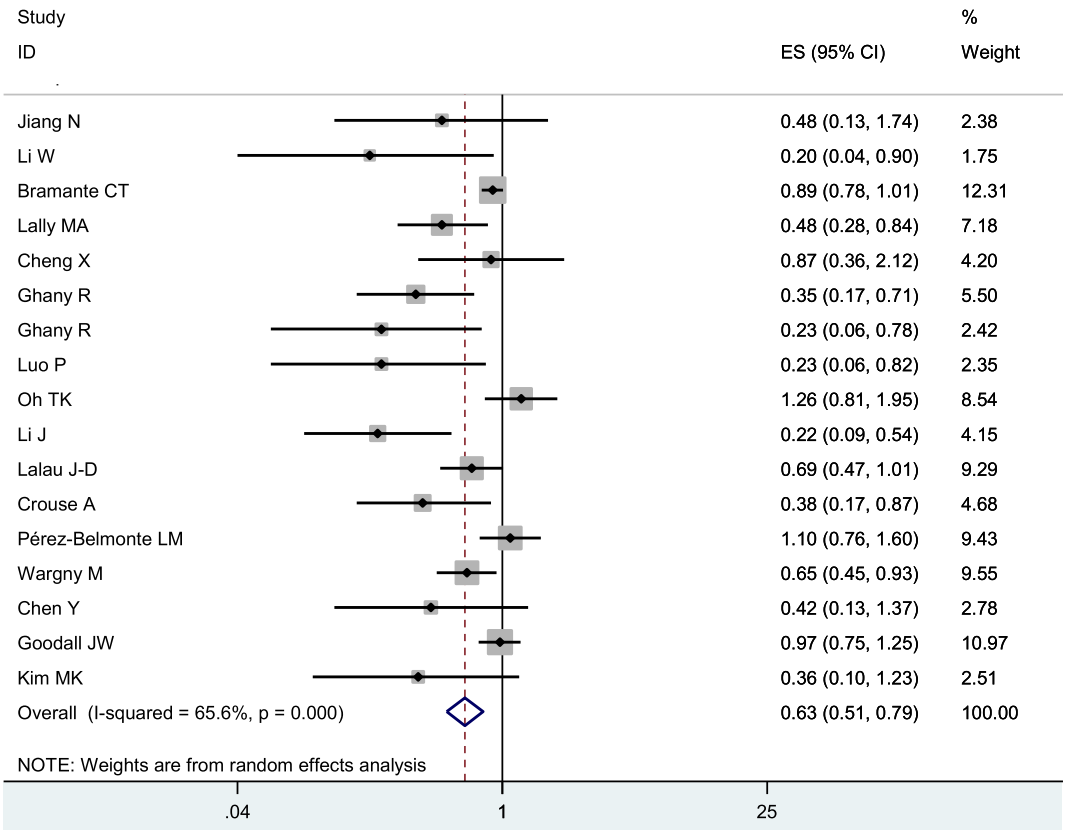

Fig. 2 – Forest plot of mortality following metformin treatment in COVID-19 patients with diabetes.

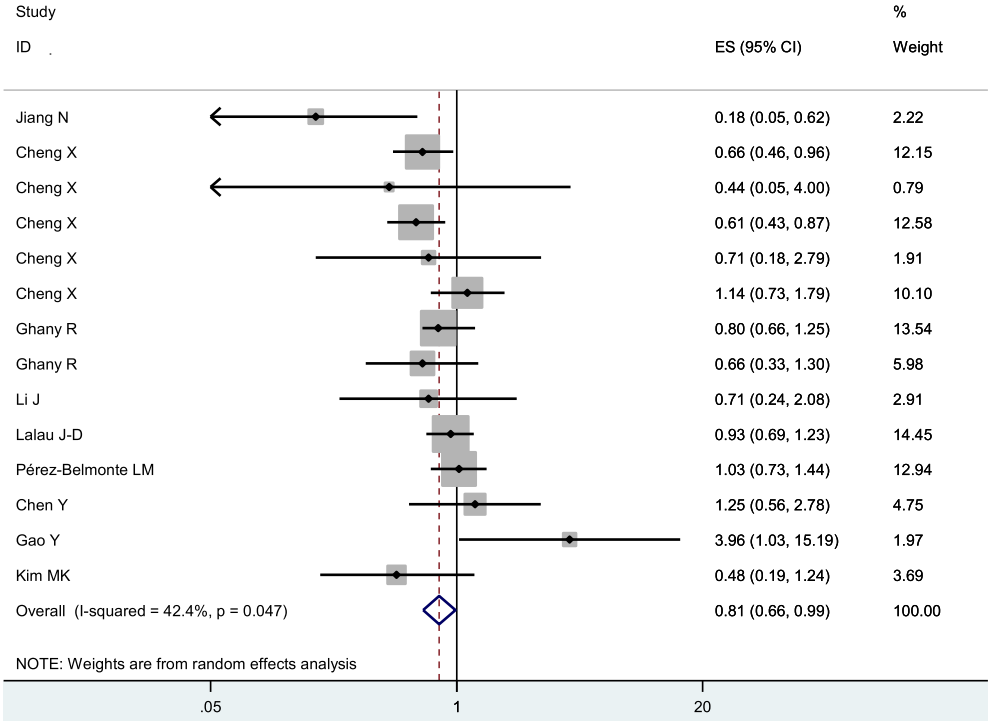

Fig. 3 – Forest plot of severity following metformin treatment in COVID-19 patients with diabetes.

3.2. *Quantitative synthesis*

Overall, metformin was associated with significantly decreased mortality and severity in COVID-19 patients with diabetes (OR = 0.64, 95% CI = 0.51–0.79 for mortality, and OR = 0.81, 95% CI = 0.66–0.99 for severity, shown in Fig. 2 and Fig. 3)

3.3. *Evaluation of heterogeneity*

There was heterogeneity among studies in comparisons ($P_{heterogeneity} < 0.001$, $I^2 = 65.6$ %, $Tau^2 = 0.0996$ for mortality, and $P_{heterogeneity} = 0.047$, $I^2 = 42.2$ %, $Tau^2 = 0.0493$ for severity). Logistic *meta*-regression analyses found no possible factors that may substantially influence the initial heterogeneity.

3.4. *Sensitivity analysis*

The influence of a single study on the overall *meta*-analysis estimate was investigated by omitting one study at a time, and the omission of any study made no significant difference, indicating that our results were statistically reliable.

3.5. *Publication bias*

The Begg's test was performed to evaluate the publication bias of selected literatures. No evidence of publication bias in our study was observed ($P = 0.064$ for mortality and $P = 0.827$ for severity).

4. Discussion

COVID-19 has spread globally with heavy impact on most countries and our therapeutic strategies in COVID-19 patients with diabetes are still limited. Diabetes was associated with poorer outcomes in COVID-19 patients [3,15]. Previous *meta*-analysis indicated that metformin consumption was associated with lower mortality in COVID-19 patients among diabetic populations [16,17]. However, whether to continue or withdraw metformin therapy in COVID-19 patients with diabetes remains contentious. Knowledge in this field is emerging rapidly, with numerous publications appearing frequently. Recently, some new information was added to this field [18–24], so we performed this updated *meta*-analysis to reveal the underlying effect of metformin on COVID-19 patients with diabetes.

Metformin can promote lifespan [25] and facilitates health [26,27] through mitohormesis [28] and lysosomal pathway [25] to coordinate mTORC1 and AMPK [29] via host-microbe- metformin -nutrient interactions [30,31]. Metformin has been reported to have anti-inflammation properties and reduced oxidative damage [32]. Metformin's ability to reduce neutrophil counts and to reduce neutrophil extracellular traps have also been proposed as potential mechanisms for its beneficial use in patients with diabetes and COVID-19[33]. In previous clinical researches, some studies found that metformin use was not significantly associated with lower mortality in COVID-19 patients with diabetes [18,20,23,34–39]. However, others found that patients using metformin after admission were significantly more likely to survive than those who did not use [19,21,22,24,40–42]. Significantly, Oh TK et al found that metformin therapy might have potential benefits for the prevention of COVID-19 in Korean population [23]. Bramante CT et al revealed that metformin was associated with decreased mortality in women with obesity or type 2 diabetes who were admitted to hospital for COVID-19, but not in men [18], and they contributed the results to different cytokine responses to COVID-19 between genders. Most strikingly, research revealed that metformin use prior to the diagnosis of COVID-19 have more potential benefits in subjects with diabetes [42]. Our results with accumulated data indicated that metformin was associated with significantly decreased mortality in COVID-19 patients with diabetes.

Acute respiratory distress syndrome (ARDS) is one of the most common complications in patients with COVID-19. It is of great significance to prevent the incidence of ARDS for improving the outcome of patients [43]. The effect of metformin on the incidence of ARDS was controversial [19,20]. Significantly, metformin use was significantly associated with reduced heart failure and inflammation [35]. However, some researches did not find any significant results of metformin use on clinical severity of the disease [37], and adverse outcomes [38]. Another study found that antidiabetic therapy with metformin was associated with a higher risk of disease progression in COVID-19 patients with diabetes during hospitalization [44], and the reason was that blood glucose and lactate dehydrogenase (LDH) levels of the metformin group were higher than those of the non-metformin group at admission [44]. Our results with accumulated data indicated that metformin was associated with significantly decreased severity in COVID-19 patients with diabetes.

A few limitations of our study should be considered. Although we did not observe significant publication bias, publication bias is possible in any *meta*-analysis. Moreover, there was heterogeneity among studies in overall comparisons. Although we performed logistic *meta*-regression analyses and stratified analysis to explore sources of heterogeneity across studies, we still found no possible factors that may substantially influence the initial heterogeneity, and the heterogeneity may potentially affect the results.

In conclusion, our *meta*-analysis indicated that following metformin treatment in COVID-19 patients with diabetes might decrease the mortality and severity. However, metformin use was significantly associated with a higher incidence of acidosis, particularly in cases with severe COVID19 [35]. Thus, patients with severe COVID-19 should be monitored closely for the development of lactic acidosis, acidosis, and decreased kidney function.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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