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

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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.

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.
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
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 age, BMI, glucose, triglyceride, CRP, D-dimer, and steroid use age, sex, comorbidities, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, Charlson comorbidity index, and medications, and state age, body mass index, hemoglobin A1c, estimated glomerular filtration rate, long stay (>90 days), and underlying psychoses age, gender, comorbidities, blood glucose, C-reactive protein, estimated glomerular filtration rate, alanine aminotransferase, and creatinine |
| Li W[22]      | 2021 | China  | Mortality ARDS        | 37                     | 131            | age, BMI, glucose, triglyceride, CRP, D-dimer, and steroid use age, sex, comorbidities, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, Charlson comorbidity index, and medications, and state age, body mass index, hemoglobin A1c, estimated glomerular filtration rate, long stay (>90 days), and underlying psychoses age, gender, comorbidities, blood glucose, C-reactive protein, estimated glomerular filtration rate, alanine aminotransferase, and creatinine |
| Li J[21]      | 2021 | USA    | Mortality ARDS        | 2333                   | 6256           | age, BMI, glucose, triglyceride, CRP, D-dimer, and steroid use age, sex, comorbidities, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, Charlson comorbidity index, and medications, and state age, body mass index, hemoglobin A1c, estimated glomerular filtration rate, long stay (>90 days), and underlying psychoses age, gender, comorbidities, blood glucose, C-reactive protein, estimated glomerular filtration rate, alanine aminotransferase, and creatinine |
| Cheng X[35]   | 2020 | China  | Mortality ARDS        | 127                    | 775            | age, BMI, glucose, triglyceride, CRP, D-dimer, and steroid use age, sex, comorbidities, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, Charlson comorbidity index, and medications, and state age, body mass index, hemoglobin A1c, estimated glomerular filtration rate, long stay (>90 days), and underlying psychoses 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 age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs |
| Luo P[40]     | 2020 | China  | Mortality ARDS        | 104                    | 283            | age, gender, Charlson score, diabetes, hypertension and ejection fraction age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs |
| Oh TK[23]     | 2021 | Korea  | Mortality ARDS        | 480                    | 2047           | age, gender, Charlson score, diabetes, hypertension and ejection fraction age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs |
| Li J[41]      | 2020 | China  | Mortality ARDS        | 37                     | 131            | age, gender, Charlson score, diabetes, hypertension and ejection fraction age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs |
| Lalau J-D[36] | 2020 | France | Mortality ARDS        | 1496                   | 2449           | age, gender, Charlson score, diabetes, hypertension and ejection fraction age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers 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 ARDS        | 76                     | 239            | age, gender, Charlson score, diabetes, hypertension and ejection fraction age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs |
| Pérez-Belmonte LM[38] | 2020 | Spain  | Mortality ARDS        | 825                    | 1488           | age, gender, Charlson score, diabetes, hypertension and ejection fraction age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs |
| Wargny M[24]  | 2021 | France | Mortality ARDS        | 1553                   | 2794           | age, gender, Charlson score, diabetes, hypertension and ejection fraction age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs |
| Chen Y[34]    | 2020 | China  | Mortality ARDS        | 43                     | 120            | age, gender, Charlson score, diabetes, hypertension and ejection fraction age, gender, underlying diseases, clinical severity age, sex, underlying disability, Charlson Comorbidity Index age, body weight, BMI, oxygen desaturation, glucose, triglyceride, CRP, and D-dimers sex, age, BMI, arterial hypertension, history of disease, active cancer, treated obstructive sleep apnoea, use of any of anti-diabetes drugs |
| Goodall JW[39] | 2020 | UK     | Mortality ARDS        | 210                    | 981            | age, sex, comorbidities and medication usage age, sex, and the presence of underlying diseases age, sex, comorbidities and medication usage age, sex, and the presence of underlying diseases age, sex, comorbidities and medication usage age, sex, and the presence of underlying diseases age, sex, comorbidities and medication usage age, sex, and the presence of underlying diseases |
| Kim MK[37]    | 2020 | Korea  | Mortality ARDS        | 113                    | 235            | age, sex, comorbidities and medication usage age, sex, and the presence of underlying diseases age, sex, comorbidities and medication usage age, sex, and the presence of underlying diseases age, sex, comorbidities and medication usage age, sex, and the presence of underlying diseases age, sex, comorbidities and medication usage 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 age, gender, blood glucose and LDH levels age, gender, blood glucose and LDH levels age, gender, blood glucose and LDH levels age, gender, blood glucose and LDH levels age, gender, blood glucose and LDH levels 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.
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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