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BRIEF REPORT

Risk of Metformin in Patients With Type 2 Diabetes With COVID-19: A Preliminary Retrospective Report

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The current outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread across the world. No specific antiviral agents have been adequately evidenced for the treatment of coronavirus disease 2019 (COVID-19). Although metformin has been recommended as a host-directed therapy for COVID-19, there are some opposite views. The effects of metformin on the disease severity of patients with COVID-19 with diabetes during hospitalization remains unclear. This study aimed to determine the effect of metformin on disease severity. We enrolled 110 hospitalized patients with COVID-19 with diabetes prescribed either metformin or non-metformin hypoglycemic treatment for a case-control study. The primary outcome was the occurrence of life-threatening complications. There were no differences between the two groups in age, sex, comorbidities, and clinical severity at admission. Blood glucose and lactate dehydrogenase levels of the metformin group were higher than those of the non-metformin group at admission. Other laboratory parameters at admission and treatments after admission were not different between the two groups. Strikingly, the percentage of patients who experienced life-threatening complications was significantly higher in the metformin group (28.6% (16/56) vs. 7.4% (4/54), *P* = 0.004). Antidiabetic therapy with metformin was associated with a higher risk of disease progression in patients with COVID-19 with diabetes during hospitalization (adjusted odds ratio = 3.964, 95% confidence interval 1.034–15.194, *P* = 0.045). This retrospective analysis suggested a potential safety signal for metformin, the use of which was associated with a higher risk of severe COVID-19. We propose that metformin withdrawal in patients with COVID-19 be considered to prevent disease progression.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Diabetes is one of the most important comorbidities of coronavirus disease 2019 (COVID-19) associated with higher mortality. Metformin has been proposed to be a candidate for host-directed treatment for COVID-19. However, recent studies have argued that the risks of metformin in patients with COVID-19 and diabetes need to be considered.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We aimed to assess the association between metformin and life-threatening complications by conducting a comparison on patients with COVID-19 with diabetes between metformin users and nonusers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Among those patients with COVID-19 with diabetes, more severe cases were found in metformin users than in non-metformin cases (28.6% vs. 7.4%, *P* = 0.004). Antidiabetic therapy with metformin was associated with a higher risk of severe illness (adjusted odds ratio 3.964, 95% confidence interval 1.034–15.194).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study highlighted a potential safety signal for metformin, the use of which was associated with a higher risk of severe COVID-19. Thus, we propose that metformin withdrawal in patients with COVID-19 be considered to prevent disease progression.

The current outbreak of coronavirus disease 2019 (COVID-19) by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread quickly through human-to-human transmission,[1] and has been declared as "Public Health Emergency of International Concern" by the World Health Organization (WHO). As both SARS-CoV[2] and Middle East respiratory syndrome coronavirus (MERS-CoV),[3] the SARS-CoV-2 outbreak has caused a large number of human deaths

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in a short period. Up to May 16, 2020, the total number of fatalities is 302,059 of 4,425,485 confirmed cases in 212 countries with outbreaks around the world.[4] Oxygen therapy, nonspecific antivirals, and antibiotics are the mainstays of clinical management, but no antiviral agent is specifically effective against SARS-CoV-2.

Several studies have demonstrated that a higher proportion of intensive care unit (ICU) admission and more deaths in patients with COVID-19 with diabetes than those without diabetes.[5–8] As a first-line oral hypoglycemic agent for patients with type 2 diabetes with satisfying safety profile, metformin has been advised to be repurposed to COVID-19 treatment as a host-directed therapy.[9,10] However, several researchers recently summarized the current challenges for the prevention and management of patients with COVID-19 with diabetes, and indicated the importance of keeping an eye on the potential risk of metformin.[11,12] In addition, there is still no clinical evidence that metformin is a friend or foe for patients with diabetes with SARS-CoV-2 infection.

In this retrospective study, we aimed to identify the effect of metformin on the disease severity of patients with COVID-19 with diabetes during hospitalization.

METHODS

Participants and study design

Medical record data of confirmed patients with COVID-19 were collected in 40 hospitals in Hunan Province and five hospitals in Hubei Province from January 31, 2020, to March 20, 2020. Patient data were extracted from electronic medical records by clinical staff who had been treating patients with COVID-19. A total of 2,399 medical records were retrieved, and all personal information had already been de-identified. We used the followed inclusion criteria to determine the study cohort: (i) patients with COVID-19 diagnosed according to the interim guidance of the WHO, (ii) a history of diabetes, (iii) clear information on hypoglycemic medication, and (iv) complete documentation on the outcomes. The information regarding patients' age, sex, drug therapy, comorbidities, laboratory parameters, and COVID-19 severities was extracted from the medical records. The study was approved by the Institutional Ethics Board of Central South University, China. No consent from the patients was needed.

Measurements and outcomes

The primary outcomes were defined as the severities of COVID-19, which had been assessed by clinicians and were retrieved directly from the medical records. The severity of COVID-19 was classified according to the guidelines on *the Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus* issued by the National Health Commission of China. Based on the clinical information collected until March 20, 2020, patients with COVID-19 were divided into two categories as non-life-threatening and life-threatening complications. The life-threatening complications include acute respiratory distress syndrome, sepsis and septic shock, and those organ dysfunctions requiring admission to the ICU. Significantly, patients whoever had been admitted to the ICU were classified as the category of life-threatening complications.

Statistical analysis

Continuous variables were reported as median with interquartile range (IQR) and compared with the Mann–Whitney *U* test; categorical variables were expressed as number and percentage (%) and compared using Pearson χ^2 or Fisher's exact test. The adjusted odds ratio and its corresponding 95% confidence interval were calculated via a multivariable logistic regression analysis as the metformin group vs. the non-metformin group. Multivariable adjusted statistics, including age, sex, blood glucose, and lactate dehydrogenase (LDH) levels were performed. All data analyses were carried out using IBM SPSS Statistics (version 20.0).

RESULTS

Up to March 20, 2020, we retrieved a total of 2,399 medical records of COVID-19. Patients with diabetes, who were the focused subgroup in the present study, accounted for 5.1% (123/2,399) of this whole patient population. Thirteen patients (10.6%) were excluded due to a lack of documentation on the outcomes. A total of 110 hospitalized patients with COVID-19 with diabetes (median age 65 (IQR 58–74), 58.2% women), who received metformin or non-metformin hypoglycemic therapy, were enrolled for a case-control study (**Figure 1**). The subjects were divided into two groups:

1. The metformin group: 56 patients with confirmed COVID-19, who had a clear document on the outcome and were treated with metformin (median age 65 (IQR 56–72), 60.7% women).
2. The non-metformin group: 54 eligible patients received one or multiple antidiabetic drugs other than metformin (median age 71 (IQR 60–78), 55.6% women).

On admission, as shown in **Table 1**, no significant difference was found between the two groups in age ($P = 0.375$), sex ($P = 0.583$), and comorbidities ($P = 0.821$). There was also no difference in initial disease severity between metformin users and nonusers at admission ($P = 1.00$). Blood glucose and LDH levels on admission were higher in the metformin group (median blood glucose level 8.17 mmol/L (6.25–10.73), median LDH level 212.00 U/L (173.00–270.50)) than the non-metformin group (median blood glucose level 6.39 mmol/L (5.11–9.38), $P = 0.013$; median LDH level 178.50 U/L (158.75–233.25), $P = 0.024$; **Table 1**). However, no difference was found in blood creatinine ($P = 0.884$), aspartate aminotransferase ($P = 0.088$), alanine aminotransferase ($P = 0.279$), D-dimer ($P = 0.744$), and C-reactive protein ($P = 0.085$) levels between the two groups.

No significant difference was found between the two groups in antiviral therapy ($P = 0.188$), antibiotic therapy ($P = 0.605$), the use of corticosteroids ($P = 0.452$), Chinese traditional medicine ($P = 0.228$), and oxygen support ($P = 0.210$) after admission. Additionally, no case in the metformin group had metformin withdrawal.

Comparison between metformin cases and non-metformin treatment controls revealed a significant difference in disease severity of patients with COVID-19 while hospitalized ($\chi^2 = 12.7$, $P = 0.004$; **Table 1**). Only four patients

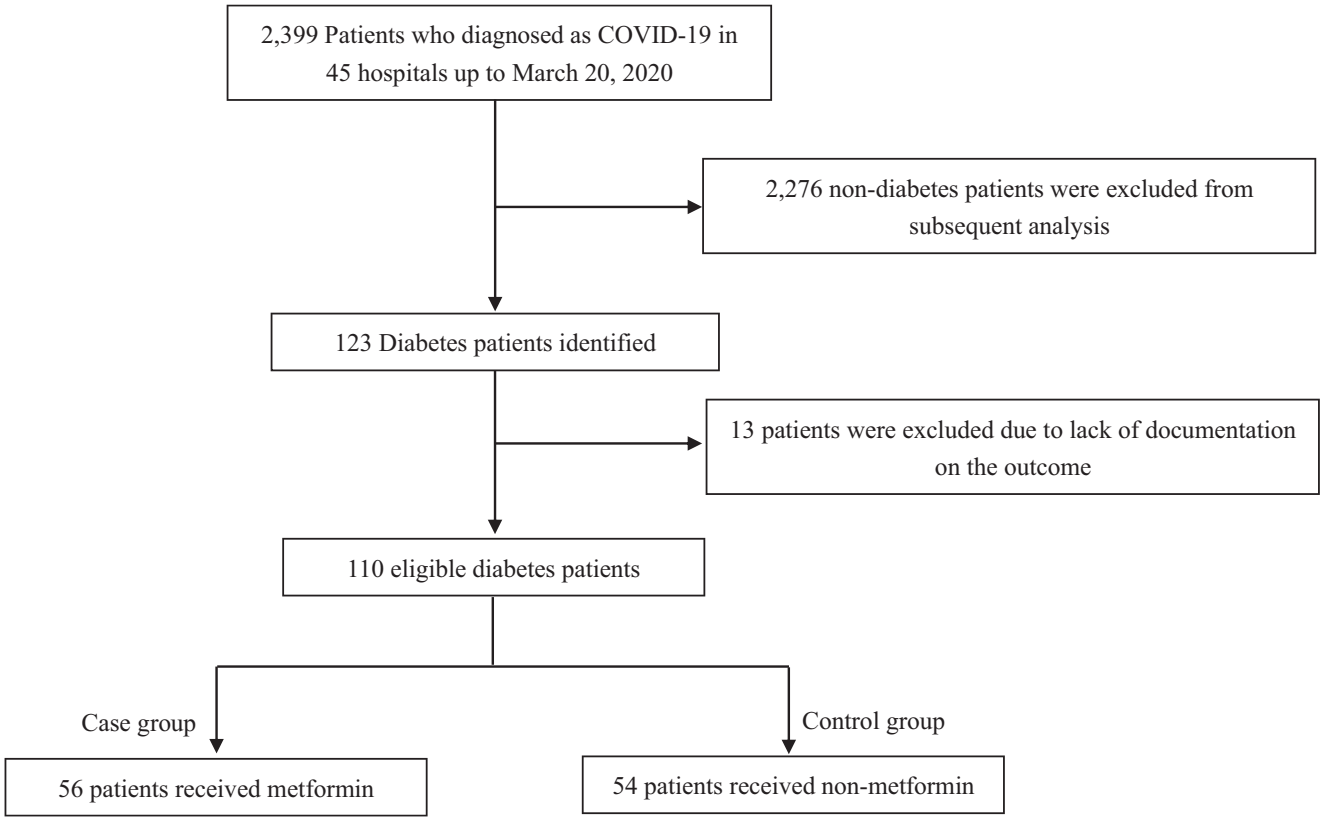

Figure 1 Enrollment and analysis of patients. COVID-19, coronavirus disease 2019.

(7.4%) treated with non-metformin had been admitted to the ICU due to life-threatening complications, compared with 16 patients (28.6%) of metformin users (P = 0.004; **Table 1**). Of 56 metformin users, 15 patients (26.8%) had developed to life-threatening complications during hospitalization. After adjusting for age, sex, blood glucose, and LDH levels, the risk of life-threatening complications was higher in patients treated with metformin (adjusted odds ratio: 3.964, 95% confidence interval 1.034–15.194, P = 0.045).

DISCUSSION

It is apparent that individuals with diabetes increase the risk of SARS-CoV-2 infection and can worsen the outcomes of COVID-19.[13] However, little is known about the effect of metformin, a commonly prescribed medication for type 2 diabetes, on the development of COVID-19 severity. In this retrospective study, we evaluated the impact of metformin on the disease severity of patients with diabetes who are infected with SARS-COV-2. The data showed that among those patients with COVID-19 with diabetic complications, compared with patients with non-metformin treatment, metformin users have a higher proportion of severe disease during hospitalization. Increasing odds of severe disease during hospitalization were associated with the use of metformin.

As a central regulator of energy homeostasis, AMP-activated protein kinase (AMPK) also played a key role in a multitude of benefits of metformin. Zhang *et al*.[14] reported the potential role of AMPK in the regulation of angiotensin-converting enzyme 2 (ACE2) expression and stability. The authors confirmed that the expression of ACE2 was upregulated by increased phosphorylation of ACE2 Ser680 with the treatment of metformin in human umbilical vein endothelial cells, human pulmonary artery endothelial cells, and lung endothelial cells. Meanwhile, the stability of ACE2 was improved due to the elevated phosphorylation of Ser680 residue, via hampering the ubiquitination-associated degradation. As far as known, ACE2 represents the cell entry receptor for SARS-CoV-2.[15] In the present study, we hypothesized that metformin might cause a theoretical increase in the availability of ACE2 in the respiratory tract mediated by AMPK–phospho-ACE2 axis, which promoted SARS-CoV-2 infection and aggravated the disease of COVID-19. Furthermore, patients with COVID-19 have a high risk of kidney injury during illness,[16] which may induce lactic acidosis under metformin treatment and aggravate the disease.[11,12]

In our study, both blood glucose and LDH levels of patients in the metformin group were higher than those in the non-metformin group at admission. Elevated blood glucose has been reported to correlate with higher levels of proinflammatory cytokines following viral infection,[17] which contribute to the worsening of COVID-19.[18] In addition, poor glycemic control (> 10.0 mmol/L) was associated with worsening outcomes in patients with diabetes and COVID-19,[8] but it was under well-controlled in both groups of our study. Increased LDH level has also been found associated with a higher risk of mortality and disease progression in

Table 1 Comparison between metformin users and non-metformin users of diabetes

		Metformin	Non-metformin	*P* value[b]
All	110	56	54	
Age[a]				0.375
< 50		8/54 (14.8%)	5 (9.3%)	
≥ 50		46/54 (85.2%)	49 (90.7%)	
Sex				0.583
Female		34 (60.7%)	30 (55.6%)	
Male		22 (39.3%)	24 (44.4%)	
COVID-19 severity				0.004
Non-life-threatening		40 (71.4%)	50 (92.6%)	
Life-threatening complications		16 (28.6%)	4 (7.4%)	
Initial disease severity				1.000
Non-life-threatening		55 (98.2%)	54 (100%)	
Life-threatening complications		1 (1.8%)	0	
Comorbidities				0.821
Hypertension		21 (37.5%)	13 (24.1%)	
Hyperlipidemia		10 (17.9%)	5 (9.3%)	
Others		6 (10.7%)	5 (9.3%)	
Treatment[a]				
Antiviral therapy		28/31 (90.3%)	36/36 (100%)	0.188
Antibiotic therapy		20/31 (64.5%)	21/36 (58.3%)	0.605
Use of corticosteroid		15/31 (48.4%)	10/36 (27.8%)	0.452
Chinese traditional medicine		12/31 (38.7%)	9/36 (25.0%)	0.228
Oxygen support[a]		16/31 (51.6%)	24/36 (66.7%)	0.210
Baseline characteristics[a] median (IQR)				
Glucose, mmol/L		8.17 (6.25–10.73)	6.39 (5.11–9.38)	0.013
Creatinine, μmol/L		67.20 (55.20–89.88)	70.41 (52.65–86.23)	0.884
Aspartate aminotransferase, U/L		25.30 (17.18–34.45)	19.20 (16.35–31.02)	0.088
Alanine aminotransferase, U/L		23.25 (14.40–33.88)	19.10 (12.30–28.85)	0.279
Lactate dehydrogenase, U/L		212.00 (173.00–270.50)	178.50 (158.75–233.25)	0.024
D-dimer, mg/L		0.84 (0.41–1.45)	0.85 (0.41–1.13)	0.744
C-reactive protein, mg/L		22.80 (5.43–80.83)	7.9 (3.23–28.83)	0.085

Data are median (IQR), *n* (%), or *n*/*N* (%), where *N* is the total number of patients with available data.
COVID-19, coronavirus disease 2019; IQR, interquartile range.
[a]Information was only available for a proportion of patients.
[b]*P* values comparing between metformin and non-metformin were from χ^2 test, Fisher's exact test, or Mann–Whitney *U* test.

patients with COVID-19.[19,20] There was no difference in the clinical characteristics and other laboratory parameters in metformin and non-metformin cases at admission. These suggest that the conditions of the two groups were comparable. Moreover, our results showed that metformin users were more likely to develop life-threatening complications during hospitalization.

Admittedly, the present study had convincing findings and shortcomings. To the current knowledge, our study provided the first clinical evidence for the influence of metformin on patients with COVID-19 with diabetes. However, our sample sizes were relatively small, only 110 patients with diabetes were involved in our study. Our study was also limited as some patients were not discharged who had been classified according to the most severe assessment during their hospitalization.

In conclusion, our preliminary report suggested that the metformin usage may be associated with a higher risk of severe COVID-19 in patients with diabetes. Due to the widespread use of metformin, formal proof based on clinical trials in different ethnic and geographic populations is needed to better understand the association between metformin and complications of COVID-19.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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Conflict of Interest. All other authors declared no competing interests for this work.

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