Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis

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Abstract. Metformin was proposed to be a candidate for host-directed therapy for COVID-19. However, its efficacy remains to be validated. In this study, we compared the outcome of metformin users and nonusers in hospitalized COVID-19 patients with diabetes. Hospitalized diabetic patients with confirmed COVID-19 in the Tongji Hospital of Wuhan, China, from January 27, 2020 to March 24, 2020, were grouped into metformin and no-metformin groups according to the diabetic medications used. The demographics, characteristics, laboratory parameters, treatments, and clinical outcome in these patients were retrospectively assessed. A total of 283 patients (104 in the metformin and 179 in the no-metformin group) were included in this study. There were no significant differences between the two groups in gender, age, underlying diseases, clinical severity, and oxygen-support category at admission. The fasting blood glucose level of the metformin group was higher than that of the no-metformin group at admission and was under effective control in both groups after admission. Other laboratory parameters at admission and treatments after admission were not different between the two groups. The length of hospital stay did not differ between the two groups (21.0 days for metformin versus 19.5 days for no metformin, \(P = 0.74\)). However, in-hospital mortality was significantly lower in the metformin group (3/104 (2.9%) versus 22/179 (12.3%), \(P = 0.01\)). Antidiabetic treatment with metformin was associated with decreased mortality compared with diabetics not receiving metformin. This retrospective analysis suggests that metformin may offer benefits in patients with COVID-19 and that further study is indicated.

INTRODUCTION

SARS-CoV-2 can cause exaggerated and aberrant non-effective host immune responses that are associated with acute respiratory distress syndrome.1 In these critically ill patients infected with COVID-19, the cytokine storms mediated by overproduction of pro-inflammatory cytokines have been observed in a large population.2 The exaggerated immune responses lead to long-term lung damage and fibrosis, causing functional disability, reduced quality of life, and even death.3 For these reasons, host-directed therapies were proposed to be a promising treatment for COVID-19.

The goal of host-directed therapies is to modulate immune mechanisms that relieve exaggerated inflammation to reduce lung tissue damage.4 Metformin, a most commonly used medication for type 2 diabetes, was proposed to be a candidate for host-directed therapy for COVID-19 to reduce mortality.5 However, its efficacy remains to be validated.

In this retrospective observational study, we aimed to identify the role of metformin as a host-directed therapy in COVID-19 by comparing the outcome of metformin users and nonusers in these COVID-19 patients with diabetic complications.

METHODS

Study design and participants. For this retrospective study, we recruited the diabetic patients with confirmed COVID-19 discharged or died from January 27, 2020 to March 24, 2020, at Tongji Hospital in Wuhan, China. All patients were anonymous. The study was approved by the Ethical Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB20200338).

The diagnosis procedures of COVID-19 were referred to the Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus issued by the National Health Commission of China. Briefly, epidemiological history or clinical symptoms are needed. Exposure history referred to any form of body contact with confirmed cases within 14 days. Clinical features include symptoms like fever, computed tomography (CT) images with signs like patchy ground-glass opacities, and laboratory examination showing decrease in both leukocytes and lymphocytes. One with exposure history can be considered as a suspected patient if any two of the clinical features show up, but only when an exposure-free patient represents all three clinical features can he/she be suspected. The suspected patients with a positive result of any nuclear acid test or IgM–IgG test will be confirmed with COVID-19. Patients with body temperature returns to normal for more than 3 days, respiratory symptoms and lung imaging improved significantly, and two consecutive negative for nuclear acid test can be discharged.

The clinical severity of patients was graded as mildly ill (clinical symptoms were mild, and no signs of pneumonia were found on CT), moderately ill (clinical features include symptoms like fever and respiratory symptoms, and CT images with signs of pneumonia), seriously ill (respiratory rate: \(\geq 30\) breaths/minutes; resting oxygen saturation: \(\leq 93\%\); or \(\text{PaO}_2/\text{FiO}_2\) ratio: \(\leq 300\) mmHg), and critically ill (respiratory failure and mechanical ventilation, shock or intensive care required) according to the Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus issued by the National Health Commission of China.

The exclusion criteria of this retrospective analysis were hospital stay or medication course less than 3 days, age \(\geq 85\) years, and lack of information about laboratory parameters at admission. A retrospective review of the characteristics of these patients was performed through the electronic medical record system, and the medications, laboratory parameters,
Comparison of clinical characteristics of patients between the metformin group and no-metformin group

| Characteristic                  | Metformin group (n = 104) | No-metformin group (n = 179) | P-value |
|--------------------------------|---------------------------|-------------------------------|---------|
| Age (years)                    | 63.0 (55.8–68.3)          | 65.0 (57.5–71.0)              | 0.06    |
| Male gender, n (%)             | 53 (51.0)                 | 103 (57.5)                    | 0.29    |
| Underlying disease, n (%)      |                           |                               |         |
| Hypertension                   | 62 (59.6)                 | 102 (57.0)                    | 0.67    |
| Coronary heart disease         | 11 (10.6)                 | 32 (17.9)                     | 0.10    |
| Malignancies                   | 1 (1.0)                   | 6 (3.4)                       | 0.40    |
| Chronic nephrosis              | 1 (1.0)                   | 3 (1.7)                       | 1.00    |
| Chronic obstructive pulmonary disease | 0 (0.0) | 6 (3.4) | 0.09 |
| Clinical severity, n (%)       |                           |                               |         |
| Moderately ill                 | 27 (26.0)                 | 39 (21.8)                     |         |
| Seriously ill                  | 75 (72.1)                 | 132 (73.7)                    |         |
| Critically ill                 | 2 (1.9)                   | 8 (4.5)                       |         |
| Oxygen-support category, n (%) |                           |                               | 0.43    |
| Ambient air                    | 27 (26.0)                 | 39 (21.8)                     |         |
| Noninvasive oxygen support    | 76 (73.1)                 | 135 (75.4)                    |         |
| Invasive ventilation           | 1 (1.0)                   | 5 (2.8)                       |         |

Data are expressed as median (IQR). P-values denoted the comparison between the metformin group and no-metformin group.

RESULTS

Two hundred eighty-three diabetic patients infected with COVID-19 were enrolled into this study. One hundred four patients (metformin group) received metformin alone or with other medications for at least 3 days. The remaining 179 patients (no-metformin group) received one or multiple antidiabetic drugs other than metformin. Clinical characteristics at the time of admission are shown in Table 1. Fifty-three (51.0%) and 103 (57.5%) of the metformin group and no-metformin group participants were males (P = 0.28), and the age in the two groups was 63.0 (55.8–68.3) and 65.0 (57.5–71.0) years (P = 0.06), respectively. No significant difference was found between the two groups in underlying diseases including hypertension (P = 0.67), coronary heart disease (P = 0.10), malignancies (P = 0.40), chronic nephrosis (P = 1.00), and chronic obstructive pulmonary disease (P = 0.09). There is also no difference in any grade of clinical severity and category of oxygen support between metformin group and no-metformin group at admission (P = 0.40 and P = 0.43).

On admission, as shown in Table 2, there was no difference in the white blood count (P = 0.55), lymphocyte count (P = 0.13), monocyte count (P = 0.55), neutrophil count (P = 0.50), eosinophil count (P = 0.31), basophil count (P = 0.86), platelet count (P = 0.05), alanine aminotransferase levels (P = 0.672), aspartate aminotransferase levels (P = 0.39), gamma-glutamyltransferase levels (P = 0.91), serum creatinine levels (P = 0.36), blood urea levels (P = 0.38), and C-reactive protein levels (P = 0.78) between two groups. However, the fasting blood glucose level of the metformin group was higher that of the no-metformin group at admission (P < 0.01).

All patients received antiviral, appropriate supportive therapies and strict glucose control after admission. As shown in Table 3, there was no difference in the use of insulins (P = 0.20), glucosidase inhibitors (P = 0.31), insulin secretory drugs (P = 0.12), dipeptidyl peptidase-4 inhibitors (P = 0.65), and insulin-sensitizing agents (P = 0.33) between two groups. The use of antiviral including arbidol (P = 0.45), lopinavir–ritonavir (P = 0.11), chloroquine/hydroxychloroquine (P = 0.62), ribavirin...
Multivariate analysis showed that the use of metformin (therapy) was also not different between the two groups. The use of statins, another promising agent for host-directed and Chinese traditional medicine (no-metformin group) decreased compared with the mortality of 12.3% (22/179) in the metformin group was markedly decreased compared with the mortality of 2.9% (3/104) in the no-metformin group. Moreover, our results showed that the in-hospital mortality of metformin users was lower than that of nonusers in COVID-19 patients with diabetes. However, there was no difference in hospital stays between two groups. This suggests that the condition was comparable between the two groups after admission. It was under effective control in both metformin group and no-metformin group at admission, it was under effective control in both groups. There was no difference of the clinical characteristics, other laboratory parameters, and concurrent medications in metformin users and nonusers at admission. These suggest that the condition was comparable between the two groups. Moreover, our results showed that the in-hospital mortality of metformin users was lower than that of nonusers in COVID-19 patients with diabetes. However, there was no difference in hospital stays between two groups. This is most probably because the primary goal of host-directed therapies is to modulate immune mechanisms that diminish excess inflammation to prevent the transition from the very first symptoms to acute respiratory distress syndrome (a life-threatening lung condition) in COVID-19 patients. However, effects of host-directed therapies on SARS-CoV-2 are likely very limited. Therefore, treating with metformin is very limited.
expected to have little impact on viral clearance or length of hospital stay when discharge is premised on negative viral nucleic acid tests. Metformin’s glucose-lowering effect is achieved by enhancing the activity of existing insulin and reducing hepatic glucose production. For this reason, it is well tolerated and does not usually cause hypoglycemia in diabetic or non-diabetic patients. Moreover, metformin has a low risk of lactic acidosis in patients with altered liver or kidney function. Therefore, metformin therapy is ideally suited for repurposing as host-directed therapies for COVID-19 patients whether they have diabetes or not.

In conclusion, this retrospective study suggests that metformin may contribute to reduce the mortality due to COVID-19 and justifies the implementation of a randomized clinical study in hospitalized nondiabetic patients with COVID-19.

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