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LETTER TO THE EDITOR

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Minimized glycemic fluctuation decreases the risk of severe illness and death in patients with COVID-19

To the Editor,

The recent coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been spreading rapidly throughout the globe. Insights into how this viral disease affects the general population are thus urgently needed. Diabetes mellitus is a leading threat of morbidity and mortality globally. Infection of coronavirus in diabetic patients may trigger acute hyperglycemia due to increased secretion of hyperglycemic hormones and extensive application of glucocorticoids to patients with severe symptoms, and the potential pathogenicity of the coronavirus in the pancreas expressing angiotensin-converting enzyme 2.[1] Acute fluctuations of glucose have more deleterious effects on diabetes progression than sustained hyperglycemia. In this regard, the third metric of glucose control, known as glycemic variability, has been confirmed as a strong predictor of in-hospital mortality.[2] Glucose management of diabetic patients carrying COVID-19 poses challenges to physicians, including identifying blood glucose targets, judicious use of oral diabetes mellitus medications and insulin administration. However, information on epidemiological and glycemic control of diabetic patients, who have contracted this highly communicable disease, is still limited to date. Here, we performed a retrospective comparative study enrolling 800 COVID-19 patients (with or without diabetes), who were discharged or died between February 1st and March 30th, 2020. These patients were enrolled from two government-designated hospitals for COVID-19 patients in Wuhan, China. We analyzed the risk of severe clinical outcomes (death, intensive care unit [ICU] administration, invasive mechanical ventilation, severe, or critical symptoms) among these patients after being infected with SARS-CoV-2 and investigated the short-term impact of glycemic control on COVID-19 patients. The definition of "severe/critical symptom" was done following the 5th edition 2019 Novel Coronavirus Disease (COVID-19) Diagnostic criteria. This study was approved by the institutional ethics board of Renmin Hospital of Wuhan University (No. WDRY2020-K062). The study obtained the patients' verbal consent.

Our COVID-19 patient population composed 101 patients with diabetes (12.6%) and 699 without diabetes (87.4%). Patients with diabetes tend to be older in age (median, 66; interquartile range [IQR], 61–71) when compared to those without diabetes (median, 57; IQR, 42–68). Additionally, patients with diabetes suffer more frequently from hypertension (58.4% vs. 23.0%, $p < .01$) and chronic cardiac disease (9.9% vs. 5.2%, $p < .01$), but exhibit no significant differences in sex and other comorbidities.

COVID-19 patients with diabetes demonstrate a higher death rate (15.6% vs. 5.7%, $p < .01$) and a greater frequency of ICU admission (19.7% vs. 6.0%, $p < .01$) when compared to those without diabetes. Furthermore, patients with diabetes show a stronger tendency to develop one or more severe clinical symptoms (45.1% vs. 16.2%, $p < .01$). The association between diabetes and severe clinical outcomes was assessed using multivariate logistic regression models. Model 1 was adjusted for age and sex; Model 2 included the Model 1 covariates and other comorbidities including hypertension, chronic pulmonary disease, chronic cardiac disease, cerebrovascular disease, renal insufficiency, and hypohepatia.

The adjusted odds ratio (aOR) in Table 1 reveals that diabetes increases the risk of severe outcomes to approx. A total of 2.74 times after unbiased adjustment of age/sex and other comorbidities. The cumulative incidence curves (Figure 1) show that the COVID-19 patients with diabetes deteriorate more rapidly than those without diabetes (hazard ratio, 3.13; 95% CI, 1.85–5.27; $p < .01$).

We next calculated the standard deviation (Glu_{SD}), average blood glucose (Glu_{Ave}), and maximal blood glucose (Glu_{Max}) of COVID-19 patients with diabetes during hospitalization. Using multivariate logistic regression analysis, we observed that Glu_{SD}, a parameter commonly used to describe variability of blood glucose, is significantly associated with severe outcomes in diabetic COVID-19 patients (aOR, 4.13; 95% CI, 1.82–9.33; $p < .01$) during hospitalization. We also have found a positive correlation between Glu_{Max} and Glu_{Ave} with severe outcomes. Moreover, our data show that blood glucose on admission (Glu_{Adm}) is positively linked to patients' severe clinical outcomes (Model 2, aOR, 1.38; 95% CI, 1.16–1.65; $p < .01$). Remarkably, the area under the ROC curve in the predictive model is 0.76 ($p < .01$), which will subsequently provide essential information on these patients to physicians for further prognosis on admission. In our research, there were a total of 16 testing for four outcomes and four covariates (Glu_{Adm}, Glu_{Ave}, Glu_{SD}, and Glu_{Max}). Bonferroni correction was implemented to adjust the multiple comparisons, and the adjusted p values of GluAdm, GluSD, and GluMax of diabetic patients with COVID-19 still showed significance (Table 1).

It has been reported that lowering the blood glucose concentration may improve the critical symptoms of COVID-19 patients with diabetes.[3] However, blood glucose concentrations in COVID-19 patients with diabetes often undergo substantial fluctuation due to extensive application of glucocorticoids and the potential damage of SARS-CoV-2 to pancreas, which may invite

TABLE 1 Disease characteristics by outcomes in COVID-19 patients with diabetes

	Severe outcomes in patients with diabetes compared to without diabetes		Association between glycemic control and severity in diabetes patients		
	Model 1*	Model 2†		Model 1*	Model 2†
ICU administration	3.04 (1.69–5.45, $p < .01$)++	2.47 (1.29–4.74, $p < .01$)+	Glu_{Adm}	1.38 (1.17–1.63, $p < .01$)++	1.38 (1.16–1.65, $p < .01$)++
Severe or critical symptom	3.55 (2.24–5.62, $p < .01$)++	2.74 (1.67–4.51, $p < .01$)++	Glu_{Ave}	1.47 (1.13–1.92, $p < .01$)+	1.45 (1.09–1.92, $p < .01$)+
Invasive mechanical ventilation	1.63 (0.62–4.27, $p < .05$)+	1.19 (0.39–3.64, $p < .05$)+	Glu_{SD}	4.53 (2.09–9.84, $p < .01$)++	4.13 (1.82–9.33, $p < .01$)++
Death	2.81 (1.45–5.43, $p < .01$)++	1.86 (0.87–3.95, $p < .01$)+	Glu_{Max}	1.33 (1.14–1.56, $p < .01$)++	1.31 (1.12–1.54, $p < .01$)++

Note: Data are aOR (95% CI, *p* value). aOR estimated by logistic regression.

*Model 1: the results were adjusted for age and sex.

†Model 2: the results were adjusted for age, sex, other comorbidities including hypertension, chronic pulmonary disease, chronic cardiac disease, cerebrovascular disease, renal insufficiency, and hypohepatia.

+Significant *p* value estimated by logistic regression.

++Significant adjusted *p* value after Bonferroni correction.

FIGURE 1 Cumulative incidence curves of severe events among COVID-19 patients with diabetes and without diabetes. The clinical definition of severe/critical symptoms follows the 5th edition of 2019 COVID-19 Diagnostic criteria published by the National Health Commission in China, including septic shock, acute respiratory distress syndrome, acute kidney injury, disseminated intravascular coagulation, rhabdomyolysis

more adverse effects than sustained hyperglycemia.[4] In these patients, the Glu_{SD} is therefore a significant predictor of severe outcomes during hospitalization and its predictive ability is greater than that of Glu_{Adm}, Glu_{Max}, and Glu_{Ave}. In our research, some results showed a significant *p* value ($p < .05$ or $p < .01$) with the confidence intervals cover 1 (Table 1), which may be related to the relatively small population involved in this study. Further studies with a larger sample size may improve the significance of the study. Our findings suggest that minimizing glycemic fluctuation should be an important dimension of glycemic control for COVID-19 patients with diabetes. It might not be necessary to keep pursuing lower glucose levels with the attendant risk of hypoglycemia or with a protocol requiring frequent and accurate glucose measurements, however, it is necessary to avoid large glucose fluctuation in these patients during hospitalization.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Miao Liu and Zhongyuan Xia designed the study and contributed to data interpretation. Mengyuan Dai and Yan Leng contributed to data collection. Ning-Yi Shao, Ming Chen, and Yang Wu compiled and analyzed the data. Yan Leng wrote the manuscript. Miao Liu and Zhongyuan Xia reviewed and edited the manuscript. All authors reviewed the manuscript and edited it for intellectual content and gave final approval for this version to be published.

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