Elevated fasting blood glucose within the first week of hospitalization was associated with progression to severe illness of COVID-19 in patients with preexisting diabetes: A multicenter observational study

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Highlights
- Fasting blood glucose < 10 mmol/L was proposed as a target of glycemic control during the first week of hospitalization in patients with preexisting diabetes.
- Poor HbA1c levels prior to coronavirus disease 2019 (COVID-19) might not be associated with severity among patients with preexisting diabetes.
- Mean blood glucose seemed not to be associated with poor prognosis of COVID-19.

To the Editor:
Diabetes is one of the most common comorbidities in patients with coronavirus disease 2019 (COVID-19) and an established risk factor of poor prognosis and mortality.1-4 Clinical data has established the association between hyperglycemia and the poor prognosis of COVID-19 in patients with preexisting diabetes.5,6 However, data are still limited on the association of glycosylated hemoglobin (HbA1c) and the prognosis of COVID-19 and the optimal target of glycemic control, especially during the early stage of hospitalization.

Therefore, we conducted this study to investigate the association of HbA1c and the outcome of COVID-19 and determine the optimal glucose level during the early stage of their hospitalization among patients with preexisting diabetes, in a cohort of laboratory-confirmed COVID-19 patients in China.

1 METHODS

This was a multicenter observational study from “Construction of a bio-information platform for novel coronavirus pneumonia (COVID-19) patients follow-up in Anhui” (ChiCTR2000030331). Data of hospitalized,
### TABLE 1  Characteristics and laboratory findings on admission of the 702 COVID-19 patients

| Characteristics                                      | All patients | Patients with preexisting diabetes | Nondiabetic patients | P value |
|-----------------------------------------------------|--------------|-------------------------------------|----------------------|---------|
| N                                                    | 702          | 51                                  | 651                  |         |
| **Characteristics**                                  |              |                                     |                      |         |
| Age, years                                          | 42.49 ± 15.50| 58.40 ± 11.20                       | 41.25 ± 15.11        | 0.001   |
| 0-29, n(%)                                          | 157(22.36)   | 1(1.96)                             | 156(23.96)           | 0.001   |
| 30-50, n(%)                                         | 318(45.30)   | 11(21.57)                           | 307(47.16)           | 0.001   |
| ≥ 50, n (%)                                         | 227(32.34)   | 39(76.42)                           | 188(28.88)           | 0.001   |
| Male sex, n(%)                                      | 384(54.70)   | 35(68.63)                           | 349(53.61)           | 0.041   |
| **Body mass index, kg/m²**                          |              |                                     |                      | 0.391   |
| Male sex, n(%)                                      | 52(7.41)     | 3(5.88)                             | 49(7.53)             |         |
| Current smoking, n(%)                               |              |                                     |                      | 0.028   |
| Current smoker                                      |              |                                     |                      |         |
| Current smoker                                      | 52(7.41)     | 3(5.88)                             | 49(7.53)             |         |
| Former smoker                                       |              |                                     |                      |         |
| Former smoker                                       | 14(1.99)     | 4(7.84)                             | 10(1.54)             |         |
| Never smoked                                        | 636(90.60)   | 44(86.27)                           | 592(90.94)           |         |
| **Coexisting disorder, n(%)**                       |              |                                     |                      |         |
| Hypertension                                        | 83(11.82)    | 20(39.22)                           | 63(9.68)             | 0.001   |
| Cardiovascular disease                              | 18(2.56)     | 3(5.88)                             | 15(2.30)             | 0.136   |
| Chronic pulmonary disease                           | 11(1.57)     | 2(3.92)                             | 9(1.38)              | 0.188   |
| Chronic liver disease                               | 28(3.99)     | 4(7.84)                             | 24(3.69)             | 0.017   |
| Chronic renal disease                               | 5(0.71)      | 0                                   | 5(0.77)              | 1.000   |
| Autoimmune disease                                  | 5(0.71)      | 1(1.96)                             | 4(0.61)              | 0.315   |
| **Laboratory findings**                             |              |                                     |                      |         |
| **Fever**                                           | 545(77.64)   | 41(80.39)                           | 504(77.42)           | 0.752   |
| **Cough**                                           | 425(60.54)   | 35(68.63)                           | 390(59.91)           | 0.001   |
| **Sputum production**                               | 206(29.34)   | 15(29.41)                           | 191(29.14)           | 0.016   |
| **Fatigue**                                         | 112(15.95)   | 9(17.65)                            | 103(15.82)           | 0.309   |
| **Gastrointestinal symptoms**                       | 53(7.55)     | 8(15.69)                            | 45(6.91)             | 0.046   |
| **Severity, n(%)**                                  |              |                                     |                      | 0.001   |
| Mild                                                | 55(7.83)     | 0                                   | 55(8.45)             |         |
| Moderate                                            | 566(80.63)   | 28(54.90)                           | 538(82.64)           |         |
| Severe                                              | 81(11.54)    | 23(45.10)                           | 58(8.91)             |         |
| Admission to ICU, n(%)                              | 42(5.98)     | 16(31.37)                           | 26(3.99)             | 0.001   |
| Death, n(%)                                         | 1(0.14)      | 1(1.96)                             | 0(0.00)              |         |
| **Time from onset of symptom to hospital admission (days)** | 5.89 ± 4.61  | 7.39 ± 6.54                         | 5.77 ± 4.41          | 0.018   |
| **Time from onset of symptom to outcome (days)**    | 22.80 ± 7.47 | 26.57 ± 9.35                        | 22.51 ± 7.23         | 0.003   |
| **SpO2, %**                                         | 97.71 ± 1.84 | 96.61 ± 3.76                        | 97.80 ± 1.57         | 0.063   |
| **SBP, mm Hg**                                      | 126.94 ± 14.70| 131.37 ± 14.93                    | 126.59 ± 14.63       | 0.013   |
| **DBP, mm Hg**                                      | 81.28 ± 11.35| 81.53 ± 10.11                       | 81.26 ± 11.45        | 0.939   |

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laboratory-confirmed COVID-19 patients were obtained from 21 designated hospitals in 14 cities in Anhui, China, between 22 January to 16 April 2020. Epidemiological and clinical data of these patients were collected from medical records. Severe illness was defined according to the Chinese National guidelines. Fasting blood glucose (FBG) was measured at fasting status in the morning. Postprandial blood glucose (PBG) were measured 2 hours after a meal. This study was approved by the institutional review board of the First Affiliated Hospital of University of Science and Technology of China (2020-XG[H]-009). All patients who participated in the study had provided written informed consent.

2 | RESULTS

A total of 702 COVID-19 patients were included in this study. Among them, 51(7.26%) had preexisting diabetes, all of them had type 2 diabetes mellitus (T2D). Compared with patients without diabetes (Table 1), those with diabetes were more likely to progress to severe illness (45.10% vs 8.91%, relative risk [RR] 5.06, 95% confidence interval [CI] 3.43-7.48) and to be admitted to the intensive care unit (ICU) (31.37% vs 3.99%, RR 7.86, 95% CI 4.52-13.67).

To investigate the potential contribution of blood glucose to the progression of COVID-19, we divided the patients with diabetes, who were all nonsevere upon admission, into the severe group or the nonsevere group according to their final diagnosis. Two patients in the nonsevere group were excluded from analysis because of the unavailability of blood glucose data during hospitalization. Based on these findings, we established RR regression models and found that only mean FBG over the first week of admission ≥ 10 mmol/L was significantly associated with progression to severe illness.

### TABLE 1 (Continued)

| All patients | Patients with preexisting diabetes | Nondiabetic patients | P value |
|--------------|-----------------------------------|----------------------|---------|
| Hemoglobin, g/L | 135.06 ± 17.94 | 136.86 ± 16.33 | 134.92 ± 18.07 | 0.555 |
| Platelet count, × 10^9/L | 187.90 ± 73.96 | 175.88 ± 71.35 | 188.85 ± 74.13 | 0.209 |
| PT, s | 13.15 ± 2.58 | 13.05 ± 2.01 | 13.16 ± 2.62 | 0.935 |
| APTT, s | 34.40 ± 9.77 | 34.29 ± 7.60 | 34.41 ± 9.95 | 0.877 |
| ALT, U/L, median (IQR) | 25.30(15.00,38.00) | 23.70(16.00,30.30) | 26.00(15.00,38.05) | 0.413 |
| AST, U/L, median (IQR) | 25.00(20.00,34.00) | 24.00(20.13,33.50) | 25.00(20.00,34.00) | 0.843 |
| Total bilirubin, μmol/L | 14.22 ± 8.98 | 16.67 ± 9.40 | 14.02 ± 8.93 | 0.023 |
| Creatinine, μmol/L | 64.54 ± 18.24 | 66.05 ± 18.12 | 64.42 ± 18.27 | 0.633 |
| BUN, mmol/L | 4.14 ± 2.05 | 4.76 ± 1.81 | 4.09 ± 2.06 | 0.001 |
| Blood glucose, mmol/L | 6.28 ± 2.20 | 10.11 ± 4.29 | 5.90 ± 1.41 | 0.001 |
| Procalcitonin, ng/mL, median (IQR) | 0.06(0.03,0.11) | 0.10(0.02,0.18) | 0.05(0.03,0.10) | 0.094 |
| C reactive protein, mg/L, median (IQR) | 10.51(2.50,30.10) | 33.75(13.35,77.30) | 9.60(2.10,27.90) | 0.001 |
| CK, U/L, median (IQR) | 59.20(42.00,87.75) | 68.00(48.00,80.70) | 59.00(42.00,88.00) | 0.328 |
| CK-MB, U/L, median (IQR) | 9.00(3.16,13.00) | 9.05(4.00,16.70) | 9.00(3.00,13.00) | 0.272 |
| IL-6, pg/ml, median (IQR) | 16.80(5.23,31.05) | 32.95(22.59,56.97) | 13.30(4.93,25.63) | 0.001 |
| Urine protein (+ or ++), n(%) | 53/368(14.40) | 3/22(13.64) | 50/346(14.45) | 0.204 |
| Abnormalities on chest CT, n(%) | 647/702(92.17) | 51/51(100.00) | 596/651(91.55) | 0.026 |

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatinine kinase; CK-MB, creatinine kinase-MB; DBP, diastolic blood pressure; ICU, intensive care unit; IL-6, interleukin 6; IQR, interquartile range; PT, prothrombin time; SBP, systolic blood pressure; SpO2, saturation of oxygen.

aThe data in this section represented the highest severity level assessed of a patient during hospitalization.
found that FBG ≥10 mmol/L could serve as an upper limit of FBG control for COVID-19 patients with diabetes. That might be caused by inflammatory responses following the viral infection, which was also observed in previous studies.\textsuperscript{5} Also, hyperglycemia during early admission may directly accelerate the damage or promotes the life cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), so as to propel progression to severe illness.\textsuperscript{8} But mean blood glucose seemed not to be associated with poor prognosis. A possible reason may be different food administering pattern between patients of different severity.

Besides, HbA1c upon admission represents the glycemic status prior to SARS-CoV-2 infection. A previous report of 132 COVID-19 patients indicated that HbA1c was associated with systemic inflammation, hypercoagulability, and poor prognosis, but these results are not adjusted for known risk factors of age, sex, or body mass index.\textsuperscript{9} But in a multicenter study in France, association between HbA1c and the outcome of tracheal intubation for mechanical ventilation and/or death within 7 days of admission was not observed among COVID-19 patients with diabetes.\textsuperscript{10} In our study, we added the evidence that glycemic control prior to the infection was not associated with increased risk of progression of COVID-19.

Collectively, hyperglycemia prior to the infection of SARS-CoV-2 might not play a significant role, but special attention should be paid to diabetic patients with suboptimal glucose control (≤10.0 mmol/L) during the early stage of hospitalization, especially within the first week.

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**DISCLOSURE**

None declared.

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