***Research Letter***

**Patients with diabetes are at higher risk for severe illness from COVID-19**

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The World Health Organization recently declared the outbreak of severe acute respiratory syndrome coronavirus 2 disease (COVID-19) a global pandemic (1). It is known that people with diabetes have a higher overall risk of infection resulting from multiple perturbations of innate immunity (2).Presently, it remains uncertain whether people with diabetes are also at higher risk of infection and, especially, at greater severity of illness associated with COVID-19. A recent meta-analysis of 30 observational studies (most of which were preprint studies that have yet to be reviewed) showed that pre-existing diabetes is significantly associated with poorer in-hospital outcomes (3), but none of the included studies have examined whether the impact of diabetes on COVID-19 severity is independent of age, sex and metabolic comorbidities, such as obesity and hypertension. Therefore, in this retrospective study, we aimed to examine the association between diabetes and severity of COVID-19 illness (irrespective of metabolic comorbidities) among in-patients with confirmed COVID-19.

We studied a cohort of 339 middle-aged patients with COVID-19, who were consecutively hospitalized at four sites in Zhejiang Province (China) between January and February 2020. COVID-19 was diagnosed as a positive result by high-throughput sequencing or real-time reverse transcriptase-polymerase chain reaction assay of oropharyngeal swab specimens. Clinical and laboratory data were collected in all patients at hospital admission. The severity of COVID-19 was assessed during hospitalization and classified as mild, moderate, severe or critical, according to the COVID-19 management guidance (4). For the purposes of this analysis, we defined mild and moderate subtypes as ‘non severe COVID-19’, and severe and critically ill subtypes as ‘severe COVID-19’. Presence of diabetes was diagnosed as self-reported history of disease, a random plasma glucose level ≥11.1 mmol/L (≥200 mg/dL) and/or a hemoglobin A1c level ≥48 mmol/mol (HbA1c ≥6.5%), according to widely accepted diagnostic criteria. Fasting glucose measurements were not available in most of these infected patients. The study protocol was approved by the local ethics committees of the four hospitals. Informed consent was waived by the ethics committee due to both the emergent nature of COVID-19 and the anonymized retrospective nature of the analysis.

In our cohort of 339 patients with laboratory-confirmed COVID-19, 130 (38.4%) patients had obesity (defined as body mass index ≥25 kg/m2), 79 (23.3%) patients had established hypertension (defined as blood pressure ≥140/90 mmHg or specific drug treatment) and 59 (17.4%) patients had diabetes. As shown in **Table 1**, patients with diabetes were more likely to be older, obese and hypertensive and had higher values of neutrophil count, D-dimer, serum liver enzymes, as well as lower values of lymphocyte count, albumin and HDL-cholesterol compared with their counterparts without diabetes. As expected, they also had higher levels of random plasma glucose at admission and hemoglobin A1c (available only in a subset of patients). Notably, patients with diabetes had a remarkably greater severity of COVID-19 illness than their counterparts without diabetes.

When we explored the association between random plasma glucose levels and severity of COVID-19 illness (stratified also by history of diabetes), we found that the proportion of severe COVID-19 illness increased progressively (p<0.0001 by the chi-squared test) in relation to glucose abnormalities at admission: 7.1% in patients with random plasma glucose <5.6 mmol/L (n=127; mean±SD: 4.95±0.4 mmol/L), 20.3% in those with random plasma glucose 5.6-11 mmol/L (n=153; mean±SD: 7.03±1.3 mmol/L), 25.6% in those with previously known diabetes (n=39; mean±SD: 9.32±5.1 mmol/L), and 65.0% in those with random plasma glucose ≥11.1 mmol/L at hospital admission (n=20; mean±SD: 12.0±3.7 mmol/L), respectively.

In binary logistic regression analysis, the presence of diabetes was associated with an approximate 4-fold increased risk of having severe COVID-19 illness (unadjusted-odds ratio [OR] 3.83, 95% CI 2.06-7.13, p<0.0001). Notably, this association remained significant after adjustment for age, sex, obesity, hypertension and smoking (adjusted-OR 2.05, 95% CI 1.01-4.19, p<0.05). In this regression model, other variables that were independently associated with higher risk of severe COVID-19 illness were older age (adjusted-OR 1.05, 95%CI 1.02-1.08), male sex (adjusted-OR 2.01, 95%CI 1.05-4.0) and obesity (adjusted-OR 2.51, 95%CI 1.3-4.7).

Interestingly, during the revision process of our manuscript, it has been published a retrospective multicenter study from a cohort of nearly 7,300 cases of COVID-19 enrolled among 19 hospitals in Wuhan, Hubei Province (China) (5). This retrospective study confirmed that pre-existing diabetes (present in 952 of these patients) was significantly associated with adverse clinical outcomes, and that diabetic patients with better controlled blood glucose (glycemic variability between 3.9 to 10 mmol/L) had a lower mortality rate than those with poorly controlled blood glucose (glycemic variability >10 mmol/L) during hospitalization (5).

To date, the mechanisms underpinning the association between diabetes and increased risk of severe COVID-19 illness are poorly understood. It is conceivable that diabetes-induced abnormalities, such as the underlying metabolic changes, low-grade systemic inflammation and impaired innate cell-mediated immunity, may predispose these patients to infectious events of greater severity (2). Moreover, patients with diabetes may also have a higher angiotensin converting enzyme-2 (ACE2) expression, thereby facilitating viral uptake and increasing the risk of severe infection (6,7). However, further research is required to better understand the link between diabetes and the viral disease process.

Our study has some limitations that should be mentioned, including the relatively modest sample size, the Asian ancestry of the patient cohort, and the lack of any detailed information on glucose-lowering medications, and type of diabetes (though it is reasonable that the vast majority of our diabetic cases were likely to be type 2). Thus, our results need to be further replicated in other Asian and non-Asian cohorts of COVID-19 patients

In conclusion, we found that in hospitalized middle-aged Chinese patients with laboratory-confirmed COVID-19, the presence of diabetes was strongly associated with an increased likelihood of having severe COVID-19 illness. We also observed a graded, positive relationship between random blood glucose levels at admission and severity of COVID-19 illness. Notably, the significant association between diabetes and risk of greater COVID-19 severity persisted even after adjustment for age, sex, smoking history and metabolic comorbidities. Our findings highlight the urgent need of a multidisciplinary team-based approach to the management of these patients.

**CONFLICT OF INTEREST STATEMENT:** nothing to declare.

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**Table 1.** Main clinical and biochemical characteristics of middle-aged Chinese patients with laboratory-confirmed COVID-19, stratified by diabetes status at hospital admission.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Without diabetes** | **With diabetes** | ***P* value** |
| *n* | 280 | 59 |  |
| Age (years) | 46.5 ± 15.7 | 57.0 ± 11.7 | **<0.0001** |
| Male sex (%) | 46.1 | 52.5 | 0.392 |
| BMI (kg/m2) | 23.8 ± 3.6 | 25.0 ± 4.3 | **0.034** |
| BMI ≥25 kg/m2 (%) | 35.0 | 54.2 | **0.008** |
| Current smokers (%) | 8.9 | 5.1 | 0.440 |
| Systolic blood pressure (mmHg) | 131 ± 16 | 135 ± 18 | 0.098 |
| Diastolic blood pressure (mmHg) | 81 ± 11 | 80 ± 10 | 0.640 |
| Hypertension (%) | 16.8 | 54.2 | **<0.0001** |
| White blood count (x 10\*9/L) | 4.78 (3.8-6.2) | 5.31 (4.3-7.1) | **0.028** |
| Neutrophil count (x 10\*9/L) | 3.02 (2.2-4.1) | 3.60 (2.8-5.1) | **<0.005** |
| Lymphocyte count (x 10\*9/L) | 1.20 (0.9-1.6) | 1.01 (0.6-1.3) | **<0.005** |
| Hemoglobin (g/L) | 133.1 ± 15 | 131.8 ± 18 | 0.559 |
| Platelet count (x 100,000/mmc) | 200 ± 71 | 216 ± 89 | 0.148 |
| Prothrombin time (sec) | 12.0 ± 1.5 | 12.5 ± 1.2 | 0.062 |
| Activated partial thromboplastin time (sec) | 32.1 ± 4.3 | 33.1 ± 4.9 | 0.172 |
| D-dimer (mg/L), n=200 | 0.18 (0.11-0.30) | 0.51 (0.2-0.8) | **<0.001** |
| C-reactive protein (mg/L) | 11.2 (2.5-31) | 14.1 (5-45) | 0.078 |
| Procalcitonin (ng/mL), n=190 | 0.06 (0.03-0.25) | 0.05 (0.04-0.11) | 0.819 |
| Albumin (g/L), n=231 | 41.5 (38.3-43.9) | 36.7 (31.6-42.1) | **<0.001** |
| Total bilirubin (µmol/L) | 10.8 (7.3-15.6) | 12.4 (9.0-16.7) | 0.162 |
| AST (IU/L) | 23 (19-32) | 29 (21-39) | **0.015** |
| ALT (IU/L) | 21 (14-31) | 24 (20-42) | **<0.005** |
| ALP (IU/L) | 57 (48-73) | 62 (50-82) | 0.205 |
| GGT (IU/L) | 23 (15-43) | 33 (24-51) | **<0.005** |
| Creatinine (µmol/L) | 65.2 ± 16.9 | 65.6 ± 17.2 | 0.897 |
| Random plasma glucose (mmol/L) | 6.11 ± 1.5 | 10.2 ± 4.8 | **<0.0001** |
| Hemoglobin A1c (mmol/mol), n=57 | 39.9 ± 2.3 | 60.1 ± 5.0 | **<0.0001** |
| Total cholesterol (mmol/L) | 3.98 ± 0.9 | 3.84 ± 0.8 | 0.261 |
| Triglycerides (mmol/L) | 1.22 (0.9-1.7) | 1.28 (1.1-1.9) | 0.106 |
| HDL-cholesterol (mmol/L) | 1.15 ± 0.3 | 1.01 ± 0.3 | **<0.005** |
| LDL-cholesterol (mmol/L) | 2.27 ± 0.8 | 2.11 ± 0.7 | 0.156 |
| Hospital stay (days) | 18 (13-24) | 19 (13-25) | 0.514 |
| Severity of COVID-19 illness |  |  | **<0.0001** |
| mild (%) | 5.0 | 3.4 |  |
| moderate (%) | 80.7 | 57.6 |  |
| severe (%) | 11.4 | 28.8 |  |
| critical (%) | 2.9 | 10.2 |  |

Sample size*, n*=339, except where indicated. Presence of diabetes was defined as prior history of diabetes (including current use of any glucose-lowering medication), a random plasma glucose level ≥11.1 mmol/L (≥200 mg/dL), and/or a hemoglobin A1c level ≥6.5% (≥48 mmol/mol).

Data are expressed as means ± SD, medians and IQRs (in parenthesis) or relative percentages. Differences between the two groups were tested by the chi-squared test or the Fisher’s exact test for categorical variables (as appropriate), the unpaired Student’s *t* test for normally distributed continuous variables, or the Mann-Whitney U test for non-normally distributed continuous variables, respectively.

*Abbreviations*: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.