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Clinical analysis of risk factors for severe COVID-19 patients with type 2 diabetes

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A B S T R A C T
Aims: To describe characteristics of COVID-19 patients with type 2 diabetes and to analyze risk factors for severity.
Methods: Demographics, comorbidities, symptoms, laboratory findings, treatments and outcomes of COVID-19 patients with diabetes were collected and analyzed.
Results: Seventy-four COVID-19 patients with diabetes were included. Twenty-seven patients (36.5%) were severe and 10 patients (13.5%) died. Higher levels of blood glucose, serum amyloid A (SAA), C reactive protein and interleukin 6 were associated with severe patients compared to non-severe ones (P<0.05). Levels of albumin, cholesterol, high density lipoprotein, small and dense low density lipoprotein and CD4+ T lymphocyte counts in severe patients were lower than those in non-severe patients (P<0.05). Logistic regression analysis identified decreased CD4+ T lymphocyte counts (odds ratio [OR] = 0.988, 95% Confidence interval [95%CI] 0.979–0.997) and increased SAA levels (OR = 1.029, 95% CI 1.002–1.058) as risk factors for severity of COVID-19 with diabetes (P<0.05).
Conclusions: Type 2 diabetic patients were more susceptible to COVID-19 than overall population, which might be associated with hyperglycemia and dyslipidemia. Aggressive treatment should be suggested, especially when these patients had low CD4+ T lymphocyte counts and high SAA levels.

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1. Introduction
Coronavirus disease 2019 (COVID-19) is a newly recognized infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has been announced as a pandemic recently.1 The number of fatalities owing to COVID-19 is escalating. As of April 21, 2020, 2,397,217 patients were confirmed and 162,956 cases died globally.2 China has cumulative diagnosed 84,250 cases, among which 4642 died.2 Previous studies have described the general clinical characteristics and epidemiological findings of patients with COVID-19, and some of the clinical observations have shown that the condition of some patients deteriorates rapidly.3,4
Diabetic patients have a higher risk of infection and exhibit worse prognosis with multiple perturbations of innate immunity and metabolic disorders. Nowadays pneumonia due to different contributing pathogens has become an increasingly important cause of death in diabetes.5 Clinical characteristics of COVID-19 among diabetic population, especially severe cases, have generated considerable concern. In a retrospective cohort study from China,6 the overall case-fatality rate (CFR) of COVID-19 was 2.3% while CFR was significantly elevated among those with diabetes (7.3%). FeiZhou et al.7 reported that 31% of dead COVID-19 cases were preexisting diabetic patients. However, reports characterizing clinical features of COVID-19 patients with type 2 diabetes or clinical studies analyzing risk factors for severity of COVID-19 among diabetic populations are limited.
This study described clinical features of hospitalized COVID-19 patients with type 2 diabetes from Zhongnan Hospital of Wuhan University in Wuhan, China and specifically analyzed risk factors associated with COVID-19 severity among diabetic populations.

2. Materials and methods
2.1. Study design and participants
This single-center retrospective observational study was performed at Zhongnan Hospital of Wuhan University in Wuhan, China, which is a designated hospital for COVID-19. We analyzed 74 COVID-19 patients with type 2 diabetes who were either treated and discharged or died during hospitalization from January 3 to April 14, 2020. All patients were confirmed according to the diagnostic and treatment guideline for COVID-19 by Chinese National Health Committee (version 5).8 This study was approved by the institutional ethics board of Zhongnan Hospital of Wuhan University (No.2020042K).

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2.2. Data collection

The electronic medical records of these patients were reviewed by a trained team of physicians worked in Zhongnan Hospital of Wuhan University. Data collected included patients’ demographics, exposure history, comorbidities, diabetic medications, signs and symptoms, laboratory examinations, treatments (antibiotics, corticosteroid, respiratory supports, kidney replacement therapy and ECMO). Severity of COVID-19 and outcomes were also collected and analyzed. Severe COVID-19 was designated when patients had one of the following criteria: (a) respiratory distress with respiratory frequency ≥ 30/min; (b) pulse oximeter oxygen saturation ≤ 93% at rest; and (c) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO2/FiO2) ≤ 300 mm Hg.

2.3. Statistical analysis

Categorical variables are shown as frequency rates and percentages, and continuous variables were described using median (interquartile range [IQR]) values. The means for continuous variables were compared using independent group t-tests when the data were normally distributed; otherwise the Mann-Whitney test was used. Proportions for categorical variables were compared using the Chi-square test or Fisher’s exact test when data were limited. A 2-sided P < 0.05 was considered statistically significant. All statistical analyses were performed with the SPSS, version 22.0 (IBM Corp) for Windows.

3. Results

3.1. Clinical characteristics of COVID-19 patients with type 2 diabetes

A total of 74 confirmed COVID-19 patients with Type 2 diabetes were included in this study. Among these patients whose median age were 62 (interquartile range [IQR] 58–81) years, 36 (48.6%) were male and 38 (51.4%) were female. Most of the patients (71/74, 95.9%) infected COVID-19 in communities. Of the 74 patients, 55 (74.3%) had at least one coexisting chronic diseases besides diabetes, the three most common diseases were hypertension (47.3%), coronary heart disease (17.6%) and secondary pulmonary tuberculosis (16.2%). Symptoms of the patients on admission are shown in Table 1. The most common experienced symptom was fever (77.0%), followed by respiratory illness (70.3%, such as cough, chest tightness or dyspnea), gastrointestinal symptoms (28.4%, including nausea, diarrhea and abdominal pain) and fatigue (24.3%).

As shown in Table 1, among the 74 patients, 27 (36.5%) were severe cases and 10 patients (13.5%) died. Among the severe patients whose median age were 72 (58–81) years, 18 (66.7%) were male. Among the non-severe cases whose median age were 61 (54–67) years, 18 (38.3%) were male. Men with older age were more likely to exhibit severe COVID-19 conditions (P < 0.05). Twenty-two (81.5%) severe patients had pre-existing chronic diseases besides diabetes, compared to 33 (70.2%) in non-severe patients. The proportion of coronary heart disease in severe and non-severe group was 29.6% and 10.6% respectively (P < 0.05), indicating that type 2 diabetic patients with coronary heart disease are more prone to severe type of COVID-19. There were no significant differences in prevalences of hypertension between severe and non-severe ones (42.6% vs. 55.6%, P > 0.05). Overweight cases in total 74 patients were 58 (78.4%), without significant differences between severe and non-severe groups.

| Table 1 |
| --- |
| Demographics and clinical characteristics of 74 COVID-19 patients with type 2 diabetes. |
| All patients (n = 74) | Non-severe patients (n = 47) | Severe patients (n = 27) | P value |
| --- | --- | --- | --- |
| Age, years | 62(56–72) | 61(54–67) | 72(58–81) | 0.012 |
| Sex | | | | |
| Male | 36(48.6%) | 18(38.3%) | 18(66.7%) | 0.019 |
| Female | 38(51.4%) | 29(61.7%) | 9(33.3%) | 0.961 |
| BMI, kg/m² | 24.54 | 24.66 | 24.54 | |
| (22.27–27.55) | (21.72–27.69) | (22.64–26.99) | |
| <BML < 18.5 | 0 | 0 | 0 | 0.495 |
| BMI ≥ 23 | 16(21.6%) | 9(19.1%) | 7(25.9%) | 0.256 |
| Exposure history | | | | |
| Hospital infections | 71(95.9%) | 47(100%) | 24(88.9%) | 0.012 |
| Community infections | 3(4.1%) | 0 | 3(11.1%) | 0.112 |
| Comorbiditiy | 55(74.3%) | 33(70.2%) | 22(81.5%) | 0.285 |
| Hypertension | 35(47.3%) | 20(42.6%) | 15(55.6%) | 0.281 |
| Coronary heart disease | 13(17.6%) | 5(10.6%) | 8(29.6%) | 0.042 |
| Stroke | 2(2.7%) | 0 | 2(7.4%) | 0.042 |
| Secondary pulmonary tuberculosis | 12(16.2%) | 6(12.8%) | 6(22.2%) | 0.295 |
| Tumor | 7(9.5%) | 5(10.6%) | 2(7.4%) | 0.642 |
| Cholelithiasis | 10(13.5%) | 4(8.5%) | 6(22.2%) | 0.104 |
| Symptoms during hospitalization | | | | |
| Fever | 57(77.0%) | 34(72.3%) | 23(85.2%) | 0.206 |
| Respiratory symptoms | 52(70.3%) | 29(61.7%) | 23(85.2%) | 0.033 |
| Gastrointestinal symptoms | 21(28.4%) | 10(21.3%) | 11(40.7%) | 0.074 |
| Fatigue | 18(24.3%) | 12(25.5%) | 6(22.2%) | 0.749 |
| Headache | 4(5.4%) | 3(6.4%) | 1(3.7%) | 0.614 |
| Treatments | | | | |
| Antibiotics therapy | 59(79.7%) | 32(68.1%) | 27(100%) | 0.01 |
| Mechanical ventilation | 11(14.9%) | 0 | 11(40.7%) | <0.01 |
| ECMO | 2(2.7%) | 0 | 2(7.4%) | 0.042 |
| CRRT | 3(4.1%) | 0 | 3(11.1%) | 0.012 |
| Glucocorticoid therapy | 33(44.6%) | 17(36.2%) | 15(55.6%) | 0.015 |
| Antibiotics therapy | 59(79.7%) | 32(68.1%) | 27(100%) | 0.01 |
| Anti-fungal therapy | 9(12.2%) | 2(4.1%) | 7(25.9%) | <0.01 |
| Prognosis | | | | |
| Recovery | 54(73.0%) | 43(91.5%) | 11(40.7%) | <0.01 |
| Dead | 10(13.5%) | 0 | 10(37.0%) | <0.01 |
| In hospital | 10(13.5%) | 4(8.5%) | 6(22.2%) | 0.156 |
| Diabetic management | | | | |
| Insulin injection | 43(58.1%) | 24(51.1%) | 19(70.4%) | 0.105 |
| Metformin | 25(33.8%) | 21(44.7%) | 4(14.8%) | <0.01 |
| α-Glucosidase inhibitors | 37(50.7%) | 23(48.9%) | 14(51.9%) | 0.809 |
| Others | 20(27.0%) | 12(25.5%) | 8(29.6%) | 0.702 |

**Abbreviations:** ECMO Extracorporeal Membrane Oxygenation, CRRT Continuous Renal Replacement Therapy.

Data are n (%), n/N (%) and median (IQR).

P < 0.05 was considered statistically significant between severe and non-severe subgroups.

3.2. Laboratory findings and risk factors for severity

Significantly higher levels of fasting blood glucose (FBG), serum amyloid A (SAA), C-reactive protein (CRP), interleukin 6 (IL-6), absolute numbers of neutrophils, alanine aminotransferase, aspartate aminotransferase, creatinine, serum cystatin C, eGFR (estimating glomerular filtration rate calculating from CKD-EPI cystatin and creatinine 2012 equation), β2-microglobulin, creatine kinase isoenzyme (CK-MB), high sensitive troponin I (hsTnl), lactate dehydrogenase and D-dimer were associated with severe patients compared to non-severe ones (P < 0.05). In the other hand, levels of albumin, cholesterol, high density lipoprotein (HDL), small and dense low density lipoprotein (sd-LDL), CD4+ T lymphocyte counts and absolute numbers of lymphocytes in
severe patients were noticeably lower than levels in non-severe cases \( (P < 0.05) \). Furthermore, severe patients showed higher percentages of positive protein, glucose and ketone in routine urine analysis than non-severe ones \( (P < 0.05) \). In addition, levels of hemoglobin, platelet count, glycated hemoglobin (HbA1c), triglyceride, low density lipoprotein (LDL), free fatty acid (FFA), uric acid, creatinine, cytokine, erythrocyte sedimentation rate, NK cell count, CD8+ T lymphocyte count, ACE, serum antibodies for SARS-CoV-2 didn’t show any significant differences between the two groups \( (P > 0.05) \). Duration of infectious virus replication (defined as conversion from positive to negative swabs) was also similar between severe and non-severe patients \( (P > 0.05) \) (Table 2).

### 3.3. Risk factors for severity of COVID-19 patients with diabetes

Logistic regression analysis identified decreased CD4+ T lymphocyte counts \( (\text{odds ratio [OR]} = 0.988, 95\% \text{CI} 0.979–0.997) \) and increased SAA levels \( (\text{OR} = 1.029, 95\% \text{CI} 1.002–1.058) \) at

| Table 2: Laboratory results of COVID-19 patients with type 2 diabetes. |
|---------------------------------------------------------------|
| **Non-severe patients (n = 47)**                               |
| **Severe patients (n = 27)**                                   |
| **P value**                                                   |
| **Complete blood cell count, \( \times 10^9 \)/L**               |
| Leukocytes                                                  5.66(4.74–7.67)  |
| Neutrophils                                                 3.53(2.89–6.21)  |
| Lymphocytes                                                 1.12(0.70–1.71)   |
| Eosinophils                                                  0.06(0.03–0.10)   |
| Hemoglobin, g/L                                              122(114–132)      |
| Platelet count, \( \times 10^9 \)/L                          186(148–255)       |
| **Diabetic indexes**                                         |
| HbA1c, \( \% \) (mmol/mol)                                    |
| Blood glucose, mmol/L                                       8.7(7.72)–10.2(88) |
| **Blood lipids**                                             |
| Triglyceride, mmol/L                                         1.26(0.93–2.19)   |
| Cholesterol, mmol/L                                          4.21(3.64–4.97)   |
| HDL, mmol/L                                                  1.03(0.86–1.25)   |
| LDL, mmol/L                                                  2.60(1.97–3.25)   |
| sd-LDL, mmol/L                                               0.90(0.55–1.22)   |
| FFA, \( \mu \)mol/L                                          122.4(474.6–4282.2) |
| **Liver and renal function**                                 |
| Albumin, g/L                                                 35.0(31.2–39.9)   |
| Alanine aminotransferase, U/L                                30(15–49)         |
| Aspartate aminotransferase, U/L                              26(17–43)         |
| Creatinine, \( \mu \)mol/L                                   60.2(49.5–76.3)   |
| Cystatin C, mg/L                                             0.98(0.80–1.25)   |
| eGFR, ml/min/1.73m²                                          88.00(68.00–105.00) |
| Uric acid, \( \mu \)mol/L                                    154(294–600)      |
| T2-microglobulin, \( \mu \)g/L                               890(1837–6185)    |
| **Cardiac biomarkers**                                       |
| CK, U/L                                                     65(44–137)        |
| CK-MB fraction, U/L                                          10(8–14)         |
| Lactate dehydrogenase, U/L                                   196(159–272)      |
| hsTnl, pg/mL                                                 5.7(2.2–22.7)     |
| **Inflammatory biomarkers**                                  |
| Procalcitonin, ng/ml                                         0.05(0.05–0.24)   |
| CRP, \( \mu \)g/L                                            15.0(3.8–56.3)    |
| ESR, \( \mu \)m/h                                             26(15–50)         |
| IgG, kU/L                                                   39.6(23.7–150.2)  |
| IL-6, pg/ml                                                  11.7(3.56–57.17)  |
| SAA, mg/L                                                   31.16(808–106.02) |
| SOD, kU/L                                                   74.0(160.3–224.9) |
| CTq, mg/L                                                   123.9(185.3–313.7) |
| **Liver function**                                           |
| Albumin, g/L                                                 38.5(34.6–41.1)   |
| Alanine aminotransferase, U/L                                30(15–49)         |
| Aspartate aminotransferase, U/L                              26(17–43)         |
| Creatinine, \( \mu \)mol/L                                   60.2(49.5–76.3)   |
| Cystatin C, mg/L                                             0.98(0.80–1.25)   |
| eGFR, ml/min/1.73m²                                          88.00(68.00–105.00) |
| Uric acid, \( \mu \)mol/L                                    154(294–600)      |
| T2-microglobulin, \( \mu \)g/L                               890(1837–6185)    |
| **Cardiac biomarkers**                                       |
| CK, U/L                                                     65(44–137)        |
| CK-MB fraction, U/L                                          10(8–14)         |
| Lactate dehydrogenase, U/L                                   196(159–272)      |
| hsTnl, pg/mL                                                 5.7(2.2–22.7)     |
| **Inflammatory biomarkers**                                  |
| Procalcitonin, ng/ml                                         0.05(0.05–0.24)   |
| CRP, \( \mu \)g/L                                            15.0(3.8–56.3)    |
| ESR, \( \mu \)m/h                                             26(15–50)         |
| IgG, kU/L                                                   39.6(23.7–150.2)  |
| IL-6, pg/ml                                                  11.7(3.56–57.17)  |
| SAA, mg/L                                                   31.16(808–106.02) |
| SOD, kU/L                                                   74.0(160.3–224.9) |
| CTq, mg/L                                                   123.9(185.3–313.7) |
| **Liver function**                                           |
| Albumin, g/L                                                 38.5(34.6–41.1)   |
| Alanine aminotransferase, U/L                                30(15–49)         |
| Aspartate aminotransferase, U/L                              26(17–43)         |
| Creatinine, \( \mu \)mol/L                                   60.2(49.5–76.3)   |
| Cystatin C, mg/L                                             0.98(0.80–1.25)   |
| eGFR, ml/min/1.73m²                                          88.00(68.00–105.00) |
| Uric acid, \( \mu \)mol/L                                    154(294–600)      |
| T2-microglobulin, \( \mu \)g/L                               890(1837–6185)    |

Abbreviations: HbA1c: glycated hemoglobin, HDL: high density lipoprotein, LDL: low density lipoprotein, sd-LDL: small and dense low density lipoprotein, FFA: free fatty acid, eGFR: estimating glomerular filtration rate, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IgG: immunoglobulin G, IL-6: interleukin 6, SOD: superoxide dismutase, CTq: complement 1q, SAA: serum amyloid A, CK: creatine kinase, CK-MB: creatine kinase isoenzyme, hsTnl: high sensitive troponin I.

Data are n (%), n/N (%), and median (IQR).

\( P < 0.05 \) was considered statistically significant between severe and non-severe subgroups.
admission as risk factors for severity of COVID-19 with type 2 diabetes (P < 0.05) (Table 3).

4. Discussion

In this single center, retrospective study of 74 COVID-19 patients with type 2 diabetes, 36.5% (27/74) were severe cases and the mortality rate was 13.5% (10/74). Patients with elder age and male sex were more prone to develop into severe type of COVID-19 (median age 72 (58–81) years, 66.7% male). As statistics shown in previous report, 99 cases of COVID-19 admitted in Jinyintan Hospital in Wuhan were predominately men (68.0%) with a median age of 55.5 years, 23% intensive care unit (ICU) care requirement, and a 11% mortality rate. In another report, 138 COVID-19 case series characterized an ICU admission rate of 26% (36/138) with a mortality of 4.3%(6/138). As compared to their results, our study, which focused on COVID-19 patients with type 2 diabetes, showed a higher tendency of ICU admission and even death than overall populations infected with COVID-19. However, whether hyperglycemia and dyslipidemia in type 2 diabetes take roles in promoting exacerbation of COVID-19 is still unclear.

Although two groups shared similar levels of HbA1c, level of FBG in severe patients was 9.67 (7.72–12.88) mmol/L, noticeably higher than that in non-severe cases (7.35 [5.91–10.65] mmol/L, P = 0.044). Besides, positive rates of glucose and ketone in urine tests were significantly higher in severe group, compared with non-severe one (90.5% vs 47.6%, P = 0.01), suggesting acute hyperglycemia might be associated with COVID-19 deterioration. Despite that our study failed to confirm hyperglycemia as a risk factor in leading to severe infections, a multicentered study of 7337 cases in Wuhan announced that well-controlled blood glucose (BG, glycemic variability within 3.9–10.0 mmol/L) was associated with markedly lower mortality than that in individuals with poorly controlled BG.

With lower levels of albumin, cholesterol, HDL and sd-LDL (P < 0.05), severe patients were suffering more from hypoalbuminemia and dislipidemia than non-severe ones. Although significant differences were not found in levels of triglyceride, LDL or FFA, downtrends were observed between two groups (P > 0.05). Previous studies demonstrated that specific nutrients such as amino acids, lipids might affect immune system by playing essential roles in immune cell triggering, interaction, differentiation and functional expression. Besides, nutritional deficiencies of energy or protein were significant risk factors associated with the gut dysbacteriosis which increased infection susceptibility and inflammation cascades. On the contrary, over consumption of inflammation in the host would give rise to worse nutritional status. The causal relationship between nutritional status and severity of infection was still controversial. But timely identification and correction of malnutrition might help to improve outcomes of COVID-19 with diabetes.

Decreased CD4+ T lymphocyte counts and elevated IL-6, SAA, CRP levels were observed in this study (P < 0.05). Furthermore, decreased CD4+ T lymphocyte counts (OR = 0.988, 95%CI 0.979–0.997) and increased SAA levels (OR = 1.029, 95%CI 1.002–1.058) at admission were confirmed to be independent risk factors of severity in COVID-19 patients with type 2 diabetes (P < 0.05) by a logistic regression analysis.

| Item                           | β     | S.E.  | Wald | df  | P value | OR       | 95% CI     |
|--------------------------------|-------|-------|------|-----|---------|----------|------------|
| SAA                            | 0.029 | 0.014 | 4.289| 1   | 0.038   | 1.029    | 1.002–1.058|
| CD4+ lymphocyte count           | −0.012| 0.004 | 7.311| 1   | 0.007   | 0.988    | 0.979–0.997|

Abbreviations: SAA serum amyloid A.

CD4+ T cells were playing key roles in the proper development of numerous cellular and humoral immune responses when infections occurred. In diabetic patients, constant hyperglycemia impaired glucose utilization in CD4+ T cells by decreasing sensitivity of insulin receptors. Simultaneously, CD4+ T cells' differentiation and activation were also aggrieved by dyslipidemia, due to insufficient bioenergetic and biosynthetic supply under infections. SARS-CoV-2 invasion activated T cell-mediated immunity, which resulted in increasing production of inflammatory cytokines (for example, IL-6). SAA and CRP were both acute-phase proteins in response to inflammatory cytokines after infections. High levels of IL-6, SAA and CRP might associate with “cytokine storm” and the severity of inflammation. So whether hyperglycemia or dyslipidemia played roles in deterioration of COVID-19 by affecting CD4+ T cells or inflammatory proteins remained to be clarified. Aggressive treatment should be suggested when these patients have lower CD4+ T lymphocyte counts or higher SAA levels.

Consistent with other reports, higher levels of neutrophil counts, alanine aminotransferase, aspartate aminotransferase, creatinine, serum cystatin C, eGFR, j2-microglobulin, CK-MB, hsTnI and lower levels of lymphocyte counts in severe patients reflected more secondary infections and impaired functions of liver, kidney or heart. In this study, overweight or hypertension did not show any significant role in predicting severe and non-severe COVID-19 patients. In a previous study, Simonnet et al. reported that obesity and high BMI were positively correlated with disease severity and need for invasive mechanical ventilation. Hypertension had also been confirmed to be the most common comorbidity of COVID-19 in some studies. However, due to lower prevalence of obesity in China and limited sample size in this series, similar conclusion could not be reached.

5. Limitations

This study has several limitations. First, only 74 patients with confirmed COVID-19 and diabetes in one hospital were included, and a larger multi-center study is required to verify our conclusions. Second, as a retrospective study, some other specific information such as serum glycated albumin, postprandial glucose levels and the use of ACE inhibitors were not presented in the study because the data were incomplete owing to the limited conditions in the isolation ward and the urgency of confronting the COVID-19 pandemic. Long-term observation and larger studies of COVID-19 in diabetic populations are needed.

6. Conclusion

In summary, the present study showed that diabetic patients had a higher incidence to develop more severe conditions compared with overall population when infected with SARS-CoV-2. Severe cases of COVID-19 patients with diabetes were predominantly elder men. Hyperglycemia and dyslipidemia might be associated with susceptibility to virus and impairment of immunity. Aggressive treatment, such as better blood glucose management and nutrient supply, should be suggested in COVID-19 patients with diabetes, especially when these patients had lower CD4+ T lymphocyte counts and higher SAA levels.

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Author contributions

Qianhui Zhang, Yanhong Wei and Min Chen collected and analyzed the data, and prepared the manuscript. Xiaoqi Chen designed the study...
and reviewed the manuscript. Xiaoqi Chen is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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