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Stress hyperglycemia is associated with disease severity in COVID-19

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) is a global pandemic that has affected millions of people worldwide. In this paper, we analyse the relationship between stress hyperglycaemia and disease severity in patients with COVID-19.

Material and methods: A total of 252 patients with COVID-19 were included in this study. The patients were divided into the following groups: COVID-19 with stress hyperglycaemia (SHG), COVID-19 with diabetes (DM), and COVID-19 with normal blood glucose (NG). The stress hyperglycaemia rate (SHR) was calculated using the fasting blood glucose (FBG)/glycated haemoglobin (HbA_{1c}) ratio. To further compare the disease characteristics of different SHRs, we divided the SHR into low SHR and high SHR according to the SHR median. Correlations between the severity of the disease and other factors were analysed after adjusting for sex and age. Multivariate analysis was performed using logistic regression to analyse the risk factors predicting the severity of COVID-19.

Results: Compared with the NG group, the SHG group had higher disease severity ($p < 0.001$); the SHG group had higher HbA_{1c}, FBG, SHR, blood urea nitrogen (BUN), interleukin 6 (IL-6), and neutrophil levels, while lymphocyte, CD3+ T cell, CD8+ T cell, CD4+ T cell, CD16+CD56 cell, and CD19+ cell counts were lower ($p < 0.05$). Compared with the NG group, the DM group had higher HbA_{1c}, blood glucose, BUN, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and neutrophils, while CD8+ T cell counts were lower ($p < 0.05$). Compared with the DM group, the SHG group had higher SHR and lower HbA_{1c}, CD3+ T cell, CD4+ T cell, CD16+CD56 cell, and T cell ratio levels ($p < 0.05$). Compared to the low SHR group, the high SHR group had patients with more severe COVID-19 ($p = 0.004$). Also, the high SHR group had higher age, HbA_{1c}, FBG, asparate aminotransferaze (AST), BUN, LDH, uric acid (UA), CRP, IL-6, and procalcitonin (PCT), while lymphocyte, CD3+ T cell, CD4+ T cell, CD8+ T cell, and CD19+ cell counts were lower ($p < 0.05$). Binary logistic regression analysis showed that SHR, gender, and lymphocyte count were risk factors for the severity of COVID-19.

Conclusion: Stress hyperglycaemia, as indicated by a higher SHR, is independently associated with the severity of COVID-19. **(Endokrynol Pol 2023; 74 (5): 528–535)**

Key words: *COVID-19; diabetes; severity of the disease; stress hyperglycaemia, stress hyperglycaemia rate; lymphocyte count*

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a different branch of the beta genus of coronaviruses similar to human severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [1]. SARS-CoV-2 is a COVID-19 pathogen [2]. Stress hyperglycaemia is an increase in blood glucose concentration in response to a stimulus to the body. Studies have shown that stress hyperglycaemia is closely associated with infection [3]. Viruses can cause stress hyperglycaemia by causing cytokine storms and acute inflammatory responses [4]. However, the impact of stress hyperglycaemia on disease treatment and prognosis is often neglected [5].

The relationship between diabetes mellitus and COVID-19 has been well reported. Our previous study showed that patients with COVID-19 combined with type 2 diabetes have more severe disease, in which glycaemia, lymphopaenia, and the inflammatory response play an important role [6]. Stress hyperglycaemia is defined as temporary elevation of blood glucose due to disturbance of substance and energy metabolism in stressful conditions such as major trauma, sepsis, or acute myocardial infarction [7]. Hyperglycaemia caused by coronavirus infection is associated with coronavirus binding to ACE2 receptors in islet cells, resulting in direct and indirect effects on islet cells [8]. However, there are few reports on whether there is an association between stress hyperglycaemia and COVID-19. Several previous studies have suggested that stress hyperglycaemia ratios, with adjustment factors for chronic hyperglycaemic states, may be more appropriate biomarkers for predicting poorer outcomes in certain critical illnesses with higher risk [9–11]. Moreover, previous

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studies on stress hyperglycaemia have mainly used the value of blood glucose as an indicator, while recent studies have found that the stress hyperglycaemia ratio (SHR) can better reflect the stress status of the organism compared with blood glucose [12]. A new index like SHR may be a more clinically meaningful parameter to identify COVID-19 patients at higher risk of adverse outcomes and thus be considered as a therapeutic target for intensive glucose monitoring and treatment. Therefore, we retrospectively analysed the relationship between stress hyperglycaemia and disease severity in COVID-19, using the SHR as a parameter of stress hyperglycaemia.

Material and methods

Study design

In this retrospective, single-centre study, 252 patients were included with COVID-19, aged 17-97 years; 133 males and 119 females were treated at the General Hospital of Central Theatre Command from December 2019 to February 2020. Diagnostic criteria: The diagnostic criteria for stress hyperglycaemia were fasting blood glucose ≥ 7.78 mmol/L along with glycated haemoglobin (HbA_{1c}) < 6.5% [13, 14]. The diagnosis of COVID-19 was based on the pneumonia diagnosis protocol for novel coronavirus infection promulgated by the Health Care Commission of the People's Republic of China [15]. Severe COVID-19 was defined as patients who had one of the following criteria: (a) respiratory frequency ≥ 30/min; (b) oxygen saturation ≤ 93% at rest; and (c) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO_2/FiO_2) ≤ 300 mmHg. Critical COVID-19 was defined as follows: (1) respiratory failure requiring mechanical ventilation; (2) shock; and (3) other organ failure requiring Intensive Care Unit (ICU) monitoring and treatment. Inclusion criteria: (1) Chinese Han patients from the Wuhan area whose body mass index (BMI) was 18.5 to 28.0 kg/m^2 and (2) laboratory confirmation of COVID-19 by real-time polymerase chain reaction (PCR). The exclusion criteria were as follows: (1) missing data on clinical or laboratory characteristics; (2) type 1 diabetes and other types of diabetes and various acute complications of diabetes; (3) history of severe brain, kidney, or liver disease and congestive heart failure; or (4) chronic lung disease, including chronic obstructive pulmonary disease and asthma.

We defined patients with the common type of COVID-19 as the moderate subgroup, and we combined severe and critical patients into the severe subgroup, due to the small sample sizes. The population was divided into the following groups: COVID-19 combined with stress hyperglycaemia (SHG), COVID-19 combined with diabetes mellitus (DM), and COVID-19 combined with normal glycaemia (NG), and the results were followed up until 29 February 2020. The study was approved by the Ethics Committee of General Hospital of Central Theatre Command (2020033-1). Informed consent was waived by the Ethics Committee for emerging infectious diseases.

Clinical and biochemical analysis

We obtained information on patient history from their medical records and performed epidemiological and clinical analyses and laboratory data collection. Venous blood was collected from subjects after 8–12 h of overnight fasting. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (SCr), uric acid (UA), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were assessed using standard enzymatic methods. Lactate dehydrogenase (LDH), D-dimer, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and routine blood tests were assessed using standard laboratory techniques. T lymphocyte subsets were measured by a flow cytometry assay. Interleukin (IL)-6 and procalcitonin (PCT) were measured by enzyme-linked immunosorbent assay (ELISA). The estimated glomerular filtration rate (eGFR) was calculated as $175\times (SCr)^{-1.234}\times(Age)^{-0.179}\times$ (if female$\times$0.79), SCr: blood creatinine (mg/dL).

Assessment of stress hyperglycaemia

Peripheral blood was collected after 8–12 h of overnight fasting. FBG was measured by a glucose oxidase procedure, and HbA_{1c} was determined by high-performance liquid chromatography. To better estimate relative hyperglycaemia and to identify and quantify stress hyperglycaemia, the SHR was used as an indicator of stress hyperglycaemia. The SHR was defined as the index of the glucose/HbA_{1c} ratio, SHR = FPG (mmol/L)/HbA_{1c} (%), indicating a relative glycaemic increase after correcting for recent chronic average glycaemia [16]. To further compare the disease characteristics of different SHRs, we divided the SHRs into low SHRs and high SHRs according to the median SHR. The median SHR in this study population was 1.0; those above this value were included in the high-SHR group, and those below this value were included in the low-SHR group.

Statistical analysis

SPSS 25 statistical software was used for statistical analysis. Data were tested for normal distribution using the one-sample Kolmogorov-Smirnov test; normally distributed data are expressed as the mean ± standard deviation (SD). Nonnormally distributed data are expressed as the median (25^{th}–75^{th} quartile spacing), and categorical variables are expressed as the number of cases (percentage) [n (%)]. Pearson correlation analysis was used for normally distributed data, and Spearman correlation analysis was used for nonnormally distributed data. Multivariate logistic regression models were established based on the severity of the disease. All statistical analyses were performed using a two-sided test, and a P value < 0.05 was considered statistically significant.

Results

Clinical characteristics of subjects in the three groups

Table 1 shows the baseline characteristics of the three groups. Interestingly, when comparing the SHG group to the NG group, the former group had more severe COVID-19 cases. Patients in the SHG group also showed higher levels of HbA_{1c}, FBG, SHR, BUN, IL-6, and neutrophils, which are indicators of poor glycaemic control and increased inflammation. Moreover, the SHG group had lower counts of immune cells, such as lymphocytes, CD3+ T cells, CD8+ T cells, CD4+ T cells, CD16+CD56 cells, and CD19+ cells. However, there were no significant differences between the two groups in terms of age, gender, liver, and kidney function markers (ALT, AST, SCr, eGFR, UA), lipid profile (TC, TG, LDL-C, HDL-C), LDH, D-dimer, PCT, ESR, CRP, leucocyte count, and CD4+/CD8+ ratio.

Similarly, the DM group also had more severe COVID-19 cases. These patients exhibited higher levels of HbA_{1c}, FBG, BUN, LDH, ESR, CRP, and neutrophils, indicating poor glycaemic control and in-

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Table 1. *Clinical and biochemical characteristics in the three groups*

	Normal range	Total	Non-diabetes	Stress hyperglycaemia	Diabetes	p-value
Male/Female	NA	133 (52.8)/119 (47.2)	82 (50.6)/80 (49.4)	24 (50)/24 (50)	27 (64.3)/15 (35.7)	0.261
Age [y]	NA	55 (40,66)	50 (36,63.3)	57 (45,66.8)	64.5 (57.8,72)*†	< 0.001
Liver and renal function						
ALT [U/L]	9–50	23 (16,36)	22 (14,36)	25 (17,37)	22.5 (17.8,33.5)	0.744
AST [U/L]	15–40	29 (23,42)	28.5 (23,42)	29 (24.3,45.8)	29.5 (21.5,40.3)	0.946
BUN [mmol/L]	2.5–6.3	4 (3.5,5.1)	3.8 (3.2,5)	4.5 (3.8,5.4) *	4.3 (3.7,6) *	0.005
SCr [μmol/L]	45–110	62 (52,76)	62.5 (50.8,78)	60.5 (51,73)	65 (55.8,75.3)	0.55
eGFR [mL/min/1.73 m^2]	> 90	121.6 ± 32.1	121.1 ± 30.8	125.1 ± 31.1	119.4 ± 38.2	0.668
HbA_{1c} (%)		5.9 (5.6,6.2)	5.8 (5.6,6.1)	6 (5.9,6.2)*	8.8 (7.7,10)*†	< 0.001
FBG [mol/L]	3.6–6.11	5.9 (5.4,7.8)	5.6 (5.2,6)	8.5 (7.9,9.2)*	10.1 (6.2,12.8)*	< 0.001
SHR	NA	1 (0.9,1.2)	0.97 (0.90,1.05)	1.4 (1.31,1.54)*	1.07 (0.80,1.25)†	< 0.001
UA [μmol/L]	140–400	240 (193.8,304)	240 (195.5,315.3)	213 (178,285.8)	253 (234,313.8)	0.054
LDH [U/L]	109–225	220 (184.3,275)	214 (177.5,266)	221 (186.5,300.5)	237 (212,288) *	0.029
Blood lipids						
TC [mmol/L]	3.10–5.69	3.9 ± 1	3.9 ± 0.9	3.8 ± 0.8	4.1 ± 1.3	0.542
TG [mmol/L]	0.41–1.88	1.2 (0.8,1.7)	1.2 (0.8,1.7)	1 (0.8,1.5)	1.4 (0.,1.9)	0.121
HDL-C [mmol/L]	1.16-1.82	1.1 (0.9,1.2)	1.1 (0.9,1.3)	1.1 (0.9,1.2)	1 (0.9,1.2)	0.537
LDL-C [mmol/L]	2.10-3.10	2.2 ± 0.6	2.2 ± 0.5	2.1 ± 0.6	2.2 ± 0.8	0.881
Inflammatory biomarkers						
ESR [mm/h]	≤ 15	25 (13,45)	22 (12,43)	30 (14.5,46.3)	35 (19.5,69)*	0.029
CRP [mg/L]	0-8	10.4 (4.2,26.8)	7.9 (3.7,18.4)	11.8 (4.9,37.3)	14.9 (8.9,57.5)*	0.004
IL-6 [pg/mL]	0.0-7.0	18 (7.5,33.2)	15.7 (5.7,30.1)	26 (10.5,55.6)*	22.7 (6.1,46.6)	0.022
PCT [ug/L]	0.00-0.50	0.05 (0.03,0.08)	0.05 (0.03,0.07)	0.06 (0.04,0.11)	0.06 (0.04,0.1)	0.045
D-dimer [ug/L]		145 (86,289.5)	135.5 (81.3,265)	146 (102.5,386.5)	173.5 (88,413.5)	0.445
Blood cell count						
Leucocytes [10^9/L]	3.5–9.5	4.9 (3.9,6.1)	4.7 (3.8,5.9)	5.1 (3.8,6.7)	5.2 (4.3,6.4)	0.148
Neutrophils [10^9/L]	1.8–6.3	3.1 (2.4,4.2)	2.9 (2.3,3.9)	3.7 (2.4,5.3)*	3.5 (2.7,4.6)*	0.006
Lymphocytes [10^9/L]	1.1–3.2	1.1 (0.8,1.5)	1.2 (0.9,1.6)	0.9 (0.6,1.3)*	1.1 (0.8,1.4)	< 0.001
Lymphocyte subsets						
CD3+ T cells/μL	955–2860	697 (432.5,1061.5)	803 (557.5,1136.3)	306 (216,527)*	598.5 (396,1033)†	< 0.001
CD8+ T cells/μL	320–1250	245 (144,362.5)	285 (173.8,414)	118 (78,229)*	190 (119.5,275.8)*	< 0.001
CD4+ T cells/μL	550–1440	363 (232.5,567)	425 (306.5,634.5)	153 (99,262)*	313 (197.5,474.8)†	< 0.001
CD16+CD56 cells/μL	150–1100	158 (97.5,244.5)	157 (105.3,246)	101 (62,218)*	214 (118.5,294.3)†	0.015
CD19+ cells/μL	90–560	138 (87,207)	149 (98.5,217.8)	98 (53,153)*	156 (82.5,190.3)	0.011
CD4+/CD8+ ratio	0.71–2.78	1.6 (1.1,2.2)	1.6 (1.2,2.2)	1.2 (0.8,2.1)	1.8 (1.3,2.8)†	0.029
Clinical classification (moderate/severe)	NA	206 (81.7)/46 (18.3)	140 (86.4)/22 (13.6)	35 (72.9)/13 (27.1)*	31 (73.8)/11 (26.2)*	0.036

ALT — alanine aminotransferase; AST — aspartate aminotransferase; BUN — blood urea nitrogen; SCr — serum creatinine; eGFR — estimated glomerular filtration rate; UA — uric acid; TC — total cholesterol; TG — triglycerides; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; LDH — lactate dehydrogenase; ESR — erythrocyte sedimentation rate; CRP — C-reactive protein; IL-6 — interleukin 6; tumour necrosis factor alpha (TNF-α); PCT — procalcitonin. Data are n (%), n/N (%) and median (IQR). *$p < 0.05$ compared with the normal blood glucose (NG) group; †$p < 0.05$ compared with the stress hyperglycaemia (SHG) group

creased inflammation. The only immune cell count that was significantly lower in the DM group was the CD8+ T cell count. There were no significant differences between the DM and NG groups in terms of gender, blood pressure (SHR), liver and kidney function markers (ALT, AST, SCr, eGFR, UA), lipid profile (TC, TG, LDL-C, HDL-C), IL-6, D-dimer, PCT, leucocyte, lymphocyte, CD3+ T cell, CD4+ T cell,

CD16+CD56 cell, and CD19+ cell levels, as well as CD4+/CD8+ ratio.

Lastly, when comparing the SHG group to the DM group, the stress hyperglycaemia group had a higher SHR, while HbA_{1c}, CD3+ T cell, CD4+ T cell, CD16+CD56 cell, and CD4+/CD8+ levels were lower. No significant differences were observed between the two groups in terms of gender, blood glucose (FBG), liver and kidney function markers (ALT, AST, BUN, SCr, eGFR, UA), lipid profile (TC, TG, LDL-C, HDL-C), LDH, ESR, CRP, IL-6, D-dimer, PCT, leucocyte, neutrophil, lymphocyte, CD8+ T cell, and CD19+ cell levels.

Clinical characteristics of the subjects divided by SHR median

Table 2 shows the comparison of characteristics by median SHR. Compared to the low SHR group, the high SHR group had patients with more severe COVID-19. This group had had higher age, HbA_{1c}, FBG, AST, BUN, LDH, UA, CRP, IL-6, and PCT values and lower lymphocyte, CD3+ T cell, CD4+ T cell, CD8+ T cell, and CD19+ cell counts. Whereas, gender, ALT, SCr, eGFR, TC, TG, LDL-C, HDL-C, D-dimer, leucocyte, neutrophil, CD16+CD56 cell, and CD4+/CD8+ ratio levels did not differ between the two groups.

The correlations between disease severity and other variables

To explore the relationship between disease severity and other variables, correlation analyses were performed. Controlling for age and gender, severity of the disease was associated with BUN ($r = 0.206$, $p < 0.001$), FBG ($r = 0.202$, $p = 0.001$), SHR ($r = 0.297$, $p = 0.001$), LDH ($r = 0.215$, $p = 0.001$), LDL-C

Table 2. *Comparison of the characteristics of the subjects divided by stress hyperglycaemia rate (SHR) median*

	Low SHR	High SHR	p-values
Male/Female	59 (47.2)/66 (52.8)	73 (57.9)/53 (42.1)	0.089
Age [y]	51 (36.5,65)	57.5 (46.5,67)	0.013
Liver and renal function			
ALT [U/L]	22 (15,35.5)	24.5 (16.8,36.3)	0.23
AST [U/L]	27 (22,41.5)	31 (25,42.5)	0.047
BUN [mmol/L]	3.9 (3.4,4.7)	4.4 (3.5,5.7)	0.02
SCr [μmol/L]	61 (51,76.5)	63.5 (52.8,76)	0.466
eGFR [mL/min/1.73 m^2]	122.5 ± 30.3	120.6 ± 34	0.644
HbA_{1c} (%)	6.1 (5.8,6.1)	6.4 (5.8,7.9)	0.014
FBG [mol/L]	5.4 (5.1,5.8)	7.2 (6,9.4)	< 0.001
UA [μmol/L]	250 (210,320)	231 (181.3,291)	0.011
LDH [U/L]	211 (178.5,261.5)	234.5 (190.8,294)	0.007
Blood lipids			
TC [mmol/L]	3.9 ± 1	3.9 ± 0.9	0.748
TG [mmol/L]	1.3 (0.9,1.8)	1.1 (0.8,1.6)	0.172
HDL-C [mmol/L]	1.1 (0.9,1.3)	1.1 (0.9,1.2)	0.62
LDL-C [mmol/L]	2.1 ± 0.5	2.2 ± 0.6	0.303
Inflammatory biomarkers			
ESR [mm/h]	22 (11,42)	30 (13.8,50.3)	0.051
CRP [mg/L]	7 (3.7,18.4)	13.8 (5.8,35.2)	0.002
IL-6 [pg/mL]	13.2 (4.7,26.3)	25.8 (9.9,38.1)	< 0.001
PCT [ug/L]	0.05 (0.03,0.07)	0.06 (0.04,0.1)	0.002
D-dimer [ug/L]	123.5 (81.3,258.5)	156.5 (90,339)	0.111
Blood cell count			
Leucocytes [10^9/L]	4.8 (3.9,6)	4.9 (3.9,6.2)	0.457
Neutrophils [10^9/L]	3 (2.3,3.9)	3.3 (2.5,4.6)	0.053
Lymphocytes [10^9/L]	1.2 (0.9,1.6)	1 (0.7,1.4)	0.001

Table 2. *Comparison of the characteristics of the subjects divided by stress hyperglycaemia rate (SHR) median*

	Low SHR	High SHR	p-values
Lymphocyte subsets			
CD3+ T cells/μL	905 (604,1220)	538 (341,791.5)	< 0.001
CD8+ T cells/μL	294 (186,409)	180 (114.5,280.5)	< 0.001
CD4+ T cells/μL	474 (309,711)	288 (171,398)	< 0.001
CD16+CD56 cells/μL	158 (103,242)	159 (88,254)	0.729
CD19+ cells/μL	150 (101,225)	124 (65,184)	0.012
CD4+/CD8+ ratio	1.6 (1.2,2.2)	1.5 (1.1,2.3)	0.474
Clinical classification (moderate/severe)	111 (88.8)/14 (11.2)	94 (74.6)/32 (25.4)	0.004

ALT — alanine aminotransferase; AST — aspartate aminotransferase; BUN — blood urea nitrogen; SCr — serum creatinine; eGFR — estimated glomerular filtration rate; UA — uric acid; TC — total cholesterol; TG — triglyceride; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; LDH — lactate dehydrogenase; ESR — erythrocyte sedimentation rate; CRP — C-reactive protein; IL-6 — interleukin 6; TNF-α — tumour necrosis factor alpha; PCT — procalcitonin. Data are n (%), n/N (%), and median (IQR).

Table 3. *Binary logistic regression analysis with the clinical classification as the dependent variable*

	B	S.E.	Wals	Sig.	Exp (B)	95% CI
Gender (male)	1.244	0.535	5.397	0.02	3.469	1.215–9.909
Lymphocytes	–1.789	0.608	8.644	0.003	0.167	0.051–0.551
SHR	0.294	0.096	9.292	0.002	1.341	1.11–1.62

SHR — stress hyperglycaemia rate; S.E. — standard error; CI — confidence interval. A p-value < 0.05 was considered to indicate a significant difference

(r = -0.154, p = 0.026), CRP (r = 0.258, p < 0.001), IL-6 (r = 0.232, p < 0.001), D-dimer (r = 0.18, p = 0.006), neutrophil count (r = 0.129, p = 0.042), lymphocyte count (r = -0.219, p < 0.001), CD3+ T cell (r = -0.198, p = 0.008), CD4+ T cell (r = –0.215, p = 0.004), and CD19+ cells (r = –0.209, p = 0.005). However, severity of the disease was not found to be associated with HBA_{1c}, ALT, AST, Scr, eGFR, UA, TC, TG, HDL-C, ESR, PCT, leukocyte count, CD8+ T cell, CD16+ CD56 cells, and CD4+/CD8+.

Factors predicting the severity of COVID-19

Here, we are interested in the factors that predict the severity of COVID-19. After correcting for sex, age, BUN, FBG, SHR, LDH, LDL-C, CRP, IL-6, D-dimer, neutrophil count, and lymphocyte count, a binary logistic regression analysis was performed, and the results showed that SHR, sex, and lymphocyte count were influencing factors for the severity of COVID-19 (Tab. 3).

Discussion

Patients with COVID-19 often suffer from chronic diseases, mainly cardiovascular and cerebrovascular diseases and diabetes mellitus. Our group analysed the clinical characteristics of patients with stress hyperglycaemia who had COVID-19 and the differences between the different disease severities. Our findings showed the following: 1. Patients with abnormal blood glucose had a higher rate of severe disease than those with normal blood glucose, and they were more likely to have decreased lymphocytes; 2. Stress hyperglycaemia increases disease severity compared with normal blood glucose, and the higher the SHR level is, the more severe the disease. Compared with normal blood glucose, stress hyperglycaemia was more likely to have elevated inflammatory cytokines (such as IL-6), while diabetes was more likely to have elevated ESR, CRP, and LDH levels; 4. Stress hyperglycaemia had elevated SHR (but not blood glucose) and lower T lymphocyte subsets compared with diabetes; 5. Men are more likely to progress to the severe type, and the lymphocyte count and SHR can predict the severity of the disease.

Stress hyperglycaemia is more likely to occur after COVID-19 infection. As with other acute infections, severe COVID-19 is often accompanied by an inflammatory storm with elevated levels of proinflammatory cytokines, such as IL-6 and tumour necrosis factor alpha (TNF-α), which can subsequently lead to the development of insulin resistance and stress hyperglycaemia [17]. This is consistent with our finding of elevated inflammatory factors in the presence of stress hyperglycaemia. It has been reported that SARS-CoV-2 infection

seems to be associated with the development of acute pancreatitis [18]. This suggests that viral infection can lead to disruption of β-cell function and consequently the development of stress hyperglycaemia.

In contrast, stress hyperglycaemia also increases the risk of infection and the severity of the disease. Zhang et al. [19] showed that FBG at admission accurately predicted 30-day adverse outcomes in patients with COVID-19 infection, regardless of the presence of diabetes. It has also been suggested that blood glucose levels should be considered a "vital sign" when assessing patients hospitalized with COVID-19 infection [20]. Our study confirmed that, in the SHG group, the lymphocyte, CD3+ T cell, CD8+ T cell, CD4+ T cell, CD16+CD56 cell, CD19+ cell, and CD4+/CD8+ ratio levels were lower than those in the other two groups. Possible reasons for this include the following: (1) Stressors promote the release of catecholamines and cortisol compared to diabetes. On the one hand, catecholamines negatively regulate immune cell activity, while on the other hand, elevated cortisol levels due to stress can also induce chronic immunosuppression [3]; (2) High levels of systemic glucose increase glucose concentrations in respiratory epithelial secretions, thereby disrupting the innate and humoral immune responses [21]; (3) Elevated blood glucose also increases susceptibility to viral infections [22]. The reason for this may be related to a reduction in mitochondrial DNA function that leads to downstream lymphocyte dysfunction, thus increasing susceptibility to infection [23].

Compared with normal blood glucose, stress hyperglycaemia was more likely to have elevated inflammatory cytokines (such as IL-6), while diabetes was more likely to have elevated ESR, CRP, and LDH levels. IL-6 is more sensitive than CRP to better respond to the onset of the inflammatory response. IL-6 has been used clinically to measure the severity of community-acquired pneumonia [24]. Using a glucose clamp test, Esposito et al. found that elevated blood glucose caused increased IL-6 concentrations and that the elevation was greater and lasted longer in patients with reduced glucose tolerance [25]. This might be related to the low level of inflammation in diabetes [26]. Some related in vitro studies have also found that the ability of peritoneal macrophages in mice with type 2 diabetes or peripheral blood mononuclear cells in diabetic patients to secrete inflammatory factors (e.g. TNF-α and IL-18) after ILPS stimulation was significantly reduced compared to normal inflammatory cells [27]. While CRP is a nonspecific marker in the acute phase of the systemic inflammatory response synthesized by liver cells when the body is subjected to inflammatory stimuli, such as microbial invasion or tissue damage, the elevation of CRP occurs after the induction of the inflammatory initiating factor IL-6. As a result, the inflammatory response to stress hyperglycaemia is more intense compared with that of diabetes, and as the presence of chronic inflammation in diabetes (instead of CRP levels) increases, IL-6 is rapidly released by inflammatory cells, while hepatocytes take longer to produce CRP [28].

Unlike the pathogenesis of type 2 diabetes, stress hyperglycaemia occurs due to highly complex interactions between counterregulatory hormones (e.g. catecholamines, growth hormone, cortisol, and cytokines). The immune system changes induced by stress hyperglycaemia are incidental events and should be different from those caused by chronic hyperglycaemia [29]. Basic studies have found that the adaptation of rats with type 2 diabetes to chronic inflammatory disease makes them more resistant to acute inflammatory stimuli and that the vicious cycle of hyperglycaemia and inflammatory factors caused by it is not as strong as stress hyperglycaemia [30]. Therefore, we should pay more attention to the effects of stress hyperglycaemia on organisms in patients with COVID-19.

For the predictors of stress hyperglycaemia in this study, our results show that SHR, but not FBG or HbA_{1c}, predicts the severity of COVID-19. Our study also found that the high-SHR group had patients with more severe COVID-19 than in the low-SHR group, suggesting that relative hyperglycaemia as defined by the SHR is independently associated with critical illness, whereas absolute hyperglycaemia is not associated with absolute illness [12]. The SHR rather than blood glucose or HbA_{1c} predicted the severity of COVID-19 and that relative hyperglycaemia was a better biomarker of critical illness than absolute hyperglycaemia. Similarly, BMI is better than body weight at predicting health [31]. Corsino et al. showed that 60% of newly admitted hyperglycaemic patients were identified as diabetic after one year, and newly crowned patients may be more likely to develop diabetes [32]. Therefore, follow-up is recommended for hyperglycaemic patients after infection with COVID-19 [33]. In addition, consistent with the findings of Haitao [34], our study showed that men were more likely to develop COVID-19 than women, suggesting that there are differences between sexes in COVID-19. Possible reasons for this are a combination of behavioural/lifestyle risk factors, comorbidity prevalence, aging, and underlying biological sex differences.

This study has several limitations. First, this is a retrospective cross-sectional study with a relatively small number of cases at present, and some prospective and randomized clinical trials are needed to investigate the causal relationship between higher blood glucose

and COVID-19. Second, this study included only people from the Chinese population, which suggests that it is uncertain whether our findings can be generalized to subjects of other races.

Conclusion

Our findings suggest that patients with COVID-19 with stress hyperglycaemia are more likely to progress to severe disease and produce inflammatory factor storms; elevated SHR is an important clinical feature of severe COVID-19. This may offer fresh insights and evidence for the clinical treatment of COVID-19 patients with stress-induced hyperglycaemia. Firstly, early detection and regular monitoring of blood glucose levels in patients with COVID-19 can help identify those at higher risk of serious disease, for timely intervention and better patient care. Secondly, it can better establish optimal glycaemic control strategies and assess the long-term risk of diabetes or other metabolic complications in COVID-19 patients with stress hyperglycaemia.

Author contributions

Y.Y.C. were responsible for data acquisition and interpretation. G.D.X. and J.X.Z. designed the study and drafted the article. Y.Y.C. and L.Y. contributed to the conception and design of the study and analysis of data. All authors contributed to its revision and approved the manuscript for submission. G.D.X. is the guarantor and, as such, is responsible for final approval of the version to be published.

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Disclosure summary

The authors have nothing to disclose.

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