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ABOUT COVER

Editorial board member of World Journal of Diabetes, Dr. Luo-Hua Jiang is a biostatistician with a unique combination of expertise in biostatistics, epidemiology, and diabetes research. She obtained her MD degree from Peking University (China) and PhD in Biostatistics from the University of California Los Angeles (United States). She has led a series of investigations examining the relationship of diabetes with mental health and conducted multilevel analysis of the translational effects of lifestyle intervention to prevent diabetes among American Indians and Alaska Natives (AIs/ANs). She has also been funded by the National Institute of Diabetes and Digestive and Kidney Diseases to assess the comparative effectiveness of a diabetes case management intervention in AI/AN communities. She has authored and co-authored more than 80 publications. (L-Editor: Filipodia)

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ORIGINAL ARTICLE

Observational Study

Diabetic patients with COVID-19 need more attention and better glycemic control

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is a pandemic disease spreading all over the world and has aroused global concerns. The increasing mortality has revealed its severity. It is important to distinguish severe patients and provide appropriate treatment and care to prevent damages. Diabetes is reported to be a common comorbidity in COVID-19 patients and associated with higher mortality. We attempted to clarify the relationship between diabetes and COVID-19 patients' severity.

To determine the role of type 2 diabetes in COVID-19 patients.

METHODS

To study the relationship between diabetes and COVID-19, we retrospectively collected 61 patients' data from a tertiary medical center in Wuhan. All the patients were diagnosed with laboratory-confirmed COVID-19 and admitted to the center from February 13 to March 1, 2020. Patients' age, sex, laboratory tests, chest computed tomography findings, capillary blood glucose (BG), and treatments were collected and analyzed. Fisher exact test was used for categorical data. Univariate and multivariate logistic regressions were used to explore the relationship between clinical characteristics and patients' severity.

In the 61 patients, the comorbidity of type 2 diabetes, hypertension, and heart diseases were 24.6% (15 out of 61), 37.7% (23 out of 61), and 11.5% (7 out of 61), respectively. The diabetic group was related to more invasive treatments (P =0.02) and severe status (P = 0.003). In univariate logistic regression, histories of diabetes (OR = 7.13, P = 0.003), hypertension (OR = 3.41, P = 0.039), and hepatic dysfunction (OR = 7.69, P = 0.002) were predictors of patients' severity while heart revised according to the STROBE Statement – checklist of items.

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disease (OR = 4.21, P = 0.083) and large lung involvement (OR = 2.70, P = 0.093) also slightly exacerbated patients' conditions. In the multivariate analysis, diabetes (OR = 6.29, P = 0.016) and hepatic dysfunction (OR = 5.88, P = 0.018) were risk factors for severe patients. Diabetic patients showed elevated BG in 61.7% of preprandial tests and 33.3% of postprandial tests, revealing the limited control of glycemia in COVID-19 patients.

CONCLUSION

A history of type 2 diabetes is correlated with invasive treatments and severe status. Suboptimal glycemic control and hepatic dysfunction have negative effects on severity status and may lead to the exacerbation of COVID-19 patients.

Key Words: Diabetes; COVID-19; Comorbidity; Severity; Glycemic control; Hepatic dysfunction

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Core Tip: Type 2 diabetes is one of the most common comorbidities in coronavirus disease 2019 (COVID-19) patients. It is reported to be related to poorer prognosis in other infectious diseases. However, the role of diabetes in COVID-19, a newly pandemic disease, is not clearly investigated. We indicated that diabetes and hepatic dysfunction were risk factors for severe COVID-19 patients. Given that the blood glucose of patients with diabetes and COVID-19 is poorly controlled, glycemic management in COVID-19 patients needs to be optimized.

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INTRODUCTION

In December 2019, a cluster of patients with pneumonia of unknown causes in Wuhan, China has aroused public attention. Since the diseases rapidly crossed the globe, the World Health Organization has announced it a pandemic disease, named coronavirus diseases 2019 (COVID-19) and the coronavirus that causes the public health events is called severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2). It has spread to at least 200 countries and more than 30000000 people were infected by September 25, 2020^[1]. The symptoms and signs of COVID-19 greatly varied from nonsymptomatic, mild cough, and fever to severe viral pneumonia^[2], and it has resulted in more than 970000 deaths worldwide. It is very essential to recognize patients' severity status and provide appropriate and adequate treatments. Diabetes has been reported as one of the most common comorbidities[3,4] and correlated with higher mortality in patients with COVID-19^[5]. In the descriptive reports of patients, the prevalence of diabetes in COVID-19 patients ranges from 6% to 11%[6], but there is very little literature focused on the situation of diabetic patients in the area of the first onset. The poor control of diabetes could be a factor of other complications and jeopardize recovery rates according to other infectious diseases including pandemic influenza A 2009 (H1N1), severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS)^[7,8]. However, there is limited evidence on the condition of glycemic control in diabetic patients with COVID-19 as well as the result that it may lead to. Under such a circumstance, we retrospectively inspected COVID-19 patients at our center. The data on patients' blood glucose (BG) were also collected. Our objective was to identify the potential relationship of diabetes with patients' severity and other clinical characteristics of COVID-19 patients. We also attempted to draw attention to the situation that glycemic control is not managed ideally during the treatment and this may bring risks for patients' prognosis.

MATERIALS AND METHODS

Study population

We retrospectively analyzed 61 consecutive patients from the Cancer Center of Wuhan Union Hospital, which was converted to a designated isolation medical center for COVID-19 patients. All the patients were diagnosed with laboratory-confirmed COVID-19 and admitted to the center from February 13 to March 1, 2020. All patients had their BG tested at least once. The BG monitoring frequencies and clinical managements for the diabetic patients varied according to their BG levels and physicians' advice. Patients' age, sex, and comorbidities were collected, and computed tomography (CT), laboratory examinations, and SARS-CoV-2 detection were conducted regularly to guide treatments. The patients mainly received oral, inhaled, and venous treatments though more intensive treatments could be taken when their conditions exacerbated.

Variables and outcomes

We collected the clinical information of the patients, including age, sex, histories of hypertension, heart disease, and type 2 diabetes, CT findings of patients' lungs at admission and during the treatment, laboratory tests, the treatments that they received, and severity evaluated by physicians. The diagnoses of hypertension, heart disease, and type 2 diabetes were recorded according to their diagnostic history. Lung involvement based on CT findings was evaluated and categorized as large to moderate if more than one lung segment was infiltrated and mild to none if less than a lung segment was infiltrated or no infiltration was shown. All patients were examined using CT scans more than once to monitor their progression. Thus, we could define their progression by comparing several CT scans. Patients received different treatments according to their severity. The laboratory tests that we mainly focused on were routine blood tests, biochemical markers indicating hepatic, renal, and heart functions, electrolytes balance, C reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Hepatic dysfunction in our work was defined when patients have elevated alanine aminotransferase, aspartate aminotransferase, or bilirubin in peripheral blood. Only oral or inhaled administration were marked as non-invasive treatments, while peripheral or central intravenous administration and tracheal intubation were marked as invasive treatments.

Patients' severity was the main outcome that we observed and patients were diagnosed as severe according to the Standard Diagnosis and Therapy Schema of COVID-19 of China (6th version)^[9] with one of the following manifestations: (1) Respiratory rate > 30 times per minute; (2) Peripheral oxygen saturation (SpO₂) < 93% at rest; (3) Partial arterial oxygen pressure (PaO₂)/fraction of inspiration oxygen (FiO₂) < 300 mmHg; and (4) Chest CT indicating more than 50% progression in 24 to 48 h. BG standard was set as 7.8 mmol/L (140.4 mg/dL) for preprandial BG and 10.0 mmol/L (180.0 mg/dL) for postprandial BG according to the suggestion from the American Association of Clinical Endocrinologists and American Diabetes Association^[10].

Statistical analysis

Clinical data are expressed as frequencies (%) and Fisher's exact test was used to compare the categorical data between diabetic and non-diabetic groups. The logistic regression was used to calculate odds ratios (ORs) of patients' severity status-related factors. Factors with P < 0.1 in univariate regression were included subsequently in multivariate regression and P < 0.05 was considered significant. All statistical analyses were conducted with R 3.6.0.

RESULTS

In total 61 patients diagnosed with COVID-19 were collected and analyzed with a mean age of 63.6 (standard deviation 10.78) years and 33 (54.1%) were male patients. As shown in Table 1, the number of patients with a history of type 2 diabetes, hypertension, and heart diseases was 15 (24.6%), 23 (37.7%), and 7 (11.5%), respectively. There were 22 cases (36.1%) having moderate to large lung involvement and 43 (70.5%) cases showing abnormal laboratory findings including hepatic dysfunction (42.6%) and elevated CRP (19.7%) and erythrocyte sedimentation rate (11.5%). Lung involvement was re-evaluated in several CT scans and 42 (68.9%) cases showed recovery during the treatments. However, the progression was not significantly related to the history of diabetes. In all patients, 28 (45.9%) cases received

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Table 1 Clinical characteristics in terms of diabetes in coronavirus disease 2019 patients (n = 61)

	Tatal	Diabetes				
	Total	No	Yes	P value		
Sample, n (%)	61 (100)	46 (75.4)	15 (24.6)			
Sex, n (%)						
Male	33 (54.1)	24 (52.2)	9 (60.0)	0.767		
Female	28 (45.9)	22 (47.8)	6 (40.0)			
Age [mean (SD)]	63.62 (10.78)	62.96 (10.71)	65.60 (11.11)	0.415		
Hypertension, n (%)						
No	38 (62.3)	32 (69.6)	6 (40.0)	0.065		
Yes	23 (37.7)	14 (30.4)	9 (60.0)			
Heart diseases, n (%)						
No	54 (88.5)	42 (91.3)	12 (80.0)	0.348		
Yes	7 (11.5)	4 (8.7)	3 (20.0)			
Lung involvement based on CT findings, n (%)						
Large-moderate	22 (36.1)	16 (34.8)	6 (40.0)	0.763		
Mild-none	39 (63.9)	30 (65.2)	9 (60.0)			
Lung involvement progression, n (%)						
Better	42 (68.9)	29 (63.0)	13 (86.7)	0.509		
Still	16 (26.2)	14 (30.5)	2 (13.3)			
Worse	3 (4.9)	3 (6.5)	0 (0.0)			
Laboratory findings, n (%) ¹						
Normal	18 (29.5)	13 (28.3)	5 (33.3)	0.751		
With abnormal value	43 (70.5)	33 (71.7)	10 (66.7)			
Treatments, n (%)						
Non-invasive	33 (54.1)	29 (63.0)	4 (53.3)	0.02		
Invasive	28 (45.9)	17 (27.0)	11 (46.7)			
Severity, n (%)						
Mild	44 (72.1)	38 (82.6)	6 (40.0)	0.003		
Severe	17 (27.9)	8 (17.4)	9 (60.0)			

¹Detailed laboratory findings are listed in Table 2. CT: Computed tomography.

invasive treatment and 17 (27.9%) were categorized as severe in the main outcome.

According to the clinical features of diabetic patients, we summarized that age, sex, lung involvement in CT scan, and laboratory tests were similar between these two groups. However, patients with diabetes were administered with significantly more invasive treatment including venous treatment (46.7% vs 27%, P = 0.02). This could be a result of the severity of their diseases. More severe patients could be seen in the diabetic group and the percent in our observation was 60% compared to 17.4% in nondiabetic patients (P = 0.003). Laboratory tests were used to monitor disease progression and recovery. Abnormal test values are shown in Table 2 and most of the tests did not display differences between patients divided by diabetes history. During the research, though, hepatic dysfunction was witnessed in most diabetic patients (9 out of 15, 60%) with respect to a minority in patients without diabetes (17 out of 46, 37%) even though the difference was not significant (P = 0.142).

In univariate logistic regression in Table 3, histories of diabetes (OR = 7.13, 95%CI: 2.03-27.32, P = 0.003) and hypertension (OR = 3.41, 95%CI: 1.08-11.35, P = 0.039), and emerging hepatic dysfunction (OR = 7.69, 95%CI: 2.27-33.33, P = 0.002) were correlated

Table 2 Laboratory findings in patients diagnosed with or without diabetes (n = 61)

		Total	Diabetes		- <i>P</i> value
		Total	No	Yes	- P value
Sample, n (%)		61 (100)	46 (75.4)	15 (24.6)	
Routine blood parameters, n (%)					
	Normal	54 (88.5)	42 (91.3)	12 (80.0)	0.399
	Hemoglobin	1 (1.6)	0 (0.0)	1 (6.7)	
	Neutrophil%	3 (4.9)	2 (4.3)	1 (6.7)	
	Lymphocytes count	3 (4.9)	2 (4.3)	1 (6.7)	
	Platelets count	2 (3.3)	2 (4.3)	0 (0.0)	
CRP, n (%)					
	Normal	49 (80.3)	37 (80.4)	12 (80.0)	1
	Abnormal	12 (19.7)	9 (19.6)	3 (20.0)	
ESR, n (%)					
	Normal	54 (88.5)	39 (84.8)	15 (100.0)	0.178
	Abnormal	7 (11.5)	7 (15.2)	0 (0.0)	
Hepatic dysfunct	tion, n (%)				
	No	35 (57.4)	29 (63.0)	6 (40.0)	
	Yes	26 (42.6)	17 (37.0)	9 (60.0)	0.142
	ALT or AST (%)				
	Normal	43 (70.5)	34 (73.9)	9 (60.0)	0.34
	Abnormal	18 (29.5)	12 (26.1)	6 (40.0)	
	Bilirubin (%)				
	Normal	53 (86.9)	39 (84.8)	14 (93.3)	0.666
	Abnormal	8 (13.1)	7 (15.2)	1 (6.7)	
	Albumin (%)				
	Normal	57 (93.4)	45 (97.8)	12 (80.0)	0.043
	Abnormal	4 (6.6)	1 (2.2)	3 (20.0)	
Other (%)					
	Normal	57 (93.4)	43 (93.4)	14 (93.3)	0.687
	Abnormal	4 (6.6)	3 (6.6)	1 (6.7)	

The normal ranges of WBC, hemoglobin, neutrophil%, lymphocytes count, and platelets count are 3.5-9.5 × 109 cells/L, 120-160 g/L, 43-76, 0.8-4.0 × 109 cells/L, and 125-325 × 109 cells/L, respectively. The normal ranges of aspartate aminotransferase, alanine aminotransferase, C reactive protein, erythrocyte sedimentation rate, bilirubin, and albumin were defined as 8-40 U/L, 5-35 U/L, 0-5.0 mg/L, 0-18 mm/h, 3.4-17.1 µmol/L, and 35-55 g/L, respectively. CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

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with patients' severity while age, sex, heart diseases, and lung involvement had limited effects. The multivariate analysis revealed that diabetes (OR = 6.29, 95%CI: 1.48-31.34, P = 0.016) and hepatic dysfunction (OR = 5.88, 95%CI: 1.45-33.33, P = 0.018) could be independent risk factors for severe disease status. The limited sample size in our study may bring some deviations.

Capillary BG was tested in 15 patients pre- and post-prandially and in total 614 tests were recorded (Table 4). Preprandial tests of 51 in 133 (38.4%) were abnormal compared to 312 in 481 (64.9%) postprandial tests, indicating the defect of glycemia control during the treatment of COVID-19, especially postprandial BG.

Table 3 Logistic regression of multiple variables on patients' severity (n = 61)							
	Univariat	Univariate analysis			Multivariate analysis		
	ORs	95%CI	P value	ORs	95%CI	P value	
Age (> 65 $vs \le 65$)	1.29	(0.39, 4.67)	0.686				
Sex (female vs male)	1.48	(0.48, 4.65)	0.494				
Diabetes	7.13	(2.03, 27.32)	0.003	6.29	(1.48, 31.34)	0.016	
Hypertension	3.41	(1.08, 11.35)	0.039	1.63	(0.38, 6.87)	0.504	
Heart diseases	4.21	(0.83, 23.79)	0.083	2.94	(0.42, 21.78)	0.271	
Hepatic dysfunction	7.69	(2.27, 33.33)	0.002	5.88	(1.45, 33.33)	0.018	
Mild-nonelung involvement	0.37	(0.11, 1.18)	0.093	0.41	(0.09, 1.78)	0.239	

Only variables with *P* < 0.1 in univariate logistic regression were analyzed in multivariate analysis. OR: Odds ratio; 95%CI: Two tailed 95% confident interval.

Table 4 Summary of capillary blood glucose in diabetic patients (n = 61)					
Tests, n	Time	Tests, n	Status	Tests, n (%)	
614	Preprandial	133	Normal	82 (61.7)	
			Abnormal	51 (38.3)	
	Postprandial	481	Normal	160 (33.3)	
			Abnormal	312 (66.7)	

DISCUSSION

In recent retrospective studies concerning comorbidities of COVID-19, diabetes was thought to be one of the most common comorbidities[11,12] in COVID-19 patients. Our research showed that the incidence of type 2 diabetes was 24.6% in COVID-19 patients, which was much higher than the average incidence as reported in a cohort including 1099 patients as 16.7% [11]. The reason for the higher morbidity could come from the limited sample size. Besides, our center as an equipped hospital with advanced life support may have received more severe patients (27.9%) as well as other patients with complications. In past studies, type 2 diabetes is a risk factor for multiple pulmonary diseases including pneumonia, asthma, and chronic obstructive pulmonary disease^[13]. Diabetic patients also have an increased mortality of influenza pneumonia as reported in H1N1 infection^[14].

Other than morbidity, diabetes was also reported to be related to patients' severity and death[15,16] in COVID-19 patients. In earlier statistics from Chinese Center for Disease Control and Prevention, the case-fatality rate for diabetes was 7.3% whereas the overall case-fatality rate was 2.3% (1023 deaths among 44672 confirmed cases). In our analysis, diabetes was a risk factor for patients' severity (OR = 6.29, 95%CI: 1.48-31.34, P = 0.016). A study collected 29900 cases admitted with pneumonia in Denmark and showed increased mortality of type 2 diabetes[17]. Viral pneumonia caused by influenza and MERS also indicated the effects of diabetes on patients' mortality or severity[18,19].

The potential reason why diabetes increases the risk of pulmonary diseases is that diabetes has long-term mechanical, physiological effects on the lungs as well as immune abnormality[20]. Reduced lung volume and airflow limitation could be a chronic complication of type 2 diabetes^[21]. Forced expiratory volume in 1 s and forced vital capacity declined in diabetic patients in longitudinal cohorts[22,23]. In diabetic patients, inadequate glucose control impaired lung function and systematic inflammation compared to patients in good control of glycosylated hemoglobin^[24].

Diabetes might also play a detrimental part in immune responses that are important during the process of defecting viruses. Infection with SARS-CoV-2 activated innate and adaptive immune responses but the overwhelming response could bring organ injury and systemic inflammatory responses^[25]. Investigations into the injury mechanisms in multiple organs indicated that most of the severe cases demonstrated lower lymphocyte counts and elevated levels of infection-related biomarkers and inflammatory cytokines^[26]. Elevated interleukin (IL)-6 and IL-10 were detected in severe patients than in mild patients^[27]. Infectious status activated stress reaction and increased secretion of hyperglycemic hormones, resulting in elevated BG and diabetic complications^[15]. In turn, enhanced glucose levels in the blood could bring alterations to immune response^[28], which influenced the prognosis of COVID-19 patients and elevated the severe proportion as we reported. A review summarized the effect of acute hyperglycemia on the innate system and found reduced neutrophil activity and increased concentrations of proinflammatory cytokines including tumor necrosis factor-alpha and IL-6^[29]. Hyperglycemia also increased the susceptibility to other infections and patients' deterioration[30]. Therefore, glycemic control is necessary not only for diabetic patients with COVID-19 but also for those who had acute hyperglycemia.

Insulin, as a regulator for glucose metabolism, also improves patients' outcomes by suppressing excessive inflammation and enhancement of macrophage function[28]. Therefore, insulin should be introduced early in diabetic patients, especially when their BG is dysregulated. In our observation, we recorded the patients' BG and found that it was not appropriately managed. A total of 614 capillary BG tests were performed for 15 diabetic patients in this observational study, among which 59.1% (363/614) of the tests were considered non-ideal. As recorded, most of the patients were mainly treated with oral antidiabetic drugs and the surveillance of their BG was not sufficient, indicating the lack of effective glucose management in COVID-19 patients. The treatment could be ameliorated using insulin combined with oral administration[31,32]. Shortage of professionals, diet, and exercise, potential anxiety[33], and organ damages owing to viral infection[34,35] may also be reasons for the failure in BG management during the COVID-19 pandemic. Since glycemic control is critical for patients' outcomes, clinicians should make more efforts in monitoring and improving patients' BG stability. Even though it could be very difficult for the overloaded hospitals to maintain the BG in an ideal range, limited glycemic control will still have an improvement in patient outcomes from the experience of critically ill patients^[30].

Other than diabetes, hepatic dysfunction was witnessed in 14%-53% of COVID-19 patients[36]. In our research, hepatic dysfunction was an independent predictor of the severity of patients in Wuhan in February 2019. There is also other literature reporting that hepatic dysfunction was a risk factor related to mechanical ventilation[87], intensive care unit admission[98], and in-hospital death[99]. As shown in our work, the most common abnormalities were elevated alanine aminotransferase, aspartate aminotransferase, or total bilirubin^[40,41]. Gamma-glutamyl transferase increase was also seen in COVID-19 patients[40,41]. With the investigation into the mechanisms, researchers found that angiotensin converting enzyme 2 (ACE2), as a potential receptor for COVID-19 in the lung, is also expressed in the liver and may lead to the binding of SARV-CoV-2 with liver cells and cause liver damage^[36]. Moreover, the use of lopinavir/ritonavir was also reported to be related to liver injury[38,40], which reminded us of the importance to monitor liver functions in patients administrated with antiviral drugs. Even though the attention to hepatic dysfunction has arisen nowadays, further studies into the interaction of liver injury, diabetes, and COVID-19 are still needed.

Our present study has some limitations. First of all, the sample size of our work is quite small and only 61 patients were included. Some features of COVID-19 patients were not shown in our study such as lymphocytopenia and increased lactate dehydrogenase and D-dimer[11]. The relatively small size to some extent limited the application of our findings to other studies. Second, restricted to our working status, we were not able to record detailed information including patients' length of hospitalization, glycated hemoglobin, and follow-up. These led to limited findings on the specific and elaborate relationship between BG levels in diabetic patients and prognosis or treatment costs. Last but not least, the overload of patients and shortage of medical caregivers restrained the standard treatments and adequate care to all patients, thereby negatively affecting glycemic control and patient outcomes^[42]. As in Jiangsu Province of China, with advanced medical care and sufficient medical resources, critical care-dominated treatment patterns were summarized as the core of low mortality (0/641). The main steps include early recognition and early intervention^[43], which are probably not feasible in practice in Wuhan or other cities that are suffering from similar conditions.

CONCLUSION

In this study, we demonstrated the features of diabetic patients with COVID-19 in our center and gave some evidence of the relationship of diabetes and hepatic dysfunction with patients' severity. Although the relationship between diabetes and poor outcomes in COVID-19 needs more clinical and pathophysiological studies to confirm and explain, we appeal on the optimized strategies for diabetes patients with COVID-

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) is a pandemic disease that results in more than one million deaths. Diabetes is one of the most common comorbidities in COVID-19 patients and possibly increases mortality in patients.

Research motivation

Diabetic patients tend to develop into severe status, leading to poor prognosis. The importance of glycemic control needs to be emphasized.

Research objectives

We attempted to clarify the relationship between diabetes and patients' severity at the beginning of the pandemic.

Research methods

The clinical characteristics of 61 consecutive patients diagnosed with COVID-19 were collected. The logistic regression was used to calculate ORs of patients' severity statusrelated factors.

Research results

Diabetes (OR = 6.29, P = 0.016) and hepatic dysfunction (OR = 5.88, P = 0.018) were independent risk factors for severe disease status in COVID-19 patients in multivariate logistic regression. Poor control of blood glucose (BG) can be seen in diabetic patients.

Research conclusions

In this article, we give evidence on the relationship of diabetes and hepatic dysfunction with patients' severity in COVID-19 patients. Based on the fact that patients' BG was not well-managed, we appeal to the optimized strategies for diabetes patients with COVID-19.

Research perspectives

Attention should be paid to BG management.

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