Association of COVID-19 patient's condition with fasting blood glucose and body mass index: A retrospective study

Li-Gang Song[a], Su-Rong Bai[a], Deng-Hua Hui[b], Li-Ping Ding[a] and Lu Sun[c,*]
[a]*Department of Endocrinology, HuLun Buir People's Hospital, HuLun Buir, Inner Mongolia, China*
[b]*Department of Work Ability Appraisal, HuLun Buir Human Resources and Social Development, HuLun Buir, Inner Mongolia, China*
[c]*Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Abstract.
BACKGROUND: The COVID-19 pandemic broke out in 2019 and rapidly spread across the globe. Most of the severe and dead cases are middle-aged and elderly patients with chronic systemic diseases.
OBJECTIVE: This study aimed to assess the association between fasting blood glucose (FPG) and body mass index (BMI) levels in patients with coronavirus disease 2019 (COVID-19) under different conditions.
METHODS: Experimental-related information (age, gender, BMI, and FPG on the second day of admission) from 86 COVID-19 cases (47 males and 39 females) with an average age of (39 ± 17) years was collected in April and November 2020. These cases were divided into three groups according to the most severe classification of each case determined by the clinical early warning indicators of severe-critically illness, the degree of progression, and the treatment plan shown in the diagnosis and treatment plan of COVID-19 pneumonia. Statistical models were used to analyze the differences in the levels of FPG and BMI, age, and gender among the three groups.
RESULTS: 1. Experimental group: 21 patients with asymptomatic or and mild symptoms (group A), 45 patients with common non-progression (group B), and 20 patients with common progression and severe symptoms (group C). 2. The age differences among the three groups were statistically significant and elderly patients had a higher risk of severe disease ($t = 4.1404, 3.3933, 9.2123, P = 0.0001, 0.0012, 0.0000$). There was a higher proportion of females than males in the normal progression and severe disease cases ($\chi^2 = 5.512, P = 0.019$). 3. The level of FPG was significantly higher in group C than in group A ($t = 3.1655, P = 0.0030$) and B ($t = 2.0212, P = 0.0475$). The number of diabetes or IFG in group C was significantly higher than in group A ($\chi^2 = 5.979, P = 0.014$) and group B ($\chi^2 = 6.088, P = 0.014$). 4. BMI was significantly higher in group C than in groups A ($t = 3.8839, P = 0.0004$) and B ($t = 3.8188, P = 0.0003$). The number of overweight or obese patients in group C was significantly higher than in groups A ($\chi^2 = 8.838, P = 0.003$) and B ($\chi^2 = 10.794, P = 0.001$). 5. Patients' age, gender, and FPG were independent risk factors for COVID-19 disease progression ($\beta = 0.380, 0.191, 0.186; P = 0.000, 0.034, 0.045$).
CONCLUSION: The levels of FPG and BMI were significantly increased in the population with common progressive and severe COVID-19. FPG and age are independent risk factors for the progression of COVID-19.

Keywords: COVID-19, fasting plasma glucose, body mass index, diabetes

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*Corresponding author: Lu Sun, Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. E-mail: lsun@unc.edu.

1. Introduction

The new coronavirus disease broke out in 2019 and rapidly spread around the globe. The World Health Organization (WHO) defined the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as coronavirus disease 2019 (COVID-19) on 11 February 2020 [1]. As of April 16, 2022, there are 503,628,875 COVID-19 infected cases, 6,219,927 deaths, and 11.45 billion vaccinated cases that have been reported worldwide [2]. COVID-19 is the seventh type of coronavirus discovered so far that can infect humans. It belongs to the β genus coronavirus and is an enveloped single positive-stranded RNA virus [3]. COVID-19 unique FURIN cleavage site, papain-like protease (SCoV2-PLpro), ORF3b and nonstructural proteins, and dynamic conformational changes in the structure of spike protein during host cell fusion, which give it an edge in infectivity and virulence over previous coronavirus diseases [4].

By December 22, 2020, COVID-19 cases affected all seven continents, and the number of confirmed cases and deaths is still increasing [5]. Based on a reported analysis of 72,314 cases in China, mild cases of COVID-19 are about 81%, whereas severe cases are 14% and critically-ill patients are 5%. The case fatality rate (CFR) is 2.6% [6]. The initial CFR of the European COVID-19 outbreak is between 4% and 4.5% [7]. A systematic review and meta-analysis including patients in 2020 showed that the overall estimated pooled case fatality rate for COVID-19 was 10.0%. Composite CRF is only 1.0% in the general population, compared with 29% in ICU inpatients and 15% in inpatients [8]. The current pandemic is severe and occurred with an increased number of confirmed and dead patients as well as more infectious COVID-19 mutant strains being discovered such as the Omicron [9] and Delta variant [10]. There are increasing omicron COVID-19 cases and this strain is much more infectious than other strains [11]. Given that COVID-19 has dramatically spread worldwide and limited research has investigated the impact of COVID-19 pneumonia on FPG and BMI levels, we aim to assess the association of FPG and BMI with COVID-19 patients under different conditions.

2. Materials and methods

2.1. Participants

Eighty-six COVID-19 patients treated by Hulunbuir People's Hospital in April 2020 (58 cases) and November 2020 (28 cases) were collected in this study. Approval was obtained from the Hulunbuir People's Hospital ethics committee. 47 were males (54.6%) and 39 were females (45.4%) with an average age of (39 ± 17) years. All cases met the diagnostic criteria of the new coronavirus pneumonia diagnosis and treatment prescription (trial version 8) [12].

2.2. Data collection and study design

Ninety-two patients were initially included in the study. The age, gender, body mass index (BMI), and fasting plasma glucose (FPG) levels on the second day of admission were collected from all 92 cases. The suspected cases must meet one of the following etiological or serological evidence: 1. Real-time fluorescent RT-PCR positive detection of novel coronavirus nucleic acid; 2. Virus gene sequencing is highly homologous to known novel coronaviruses; 3. The novel coronavirus-specific IgG antibody changes from negative to positive or the IgG antibody titer in the recovery phase is 4 or more times higher than in the acute phase [12]. Six patients were subsequently excluded due to the following exclusion

criteria: 4 patients tested COVID-19 negative for throat and nasal swabs and two patients were of Russian ethnicity instead of Chinese. Routine physical examinations and inquiries about family history and relevant information were collected followed by documenting the height and weight of all participants at admission. 3–5 ml of venous blood samples were collected (German Roche cobase 601) after an overnight fast lasting at least 8 hours from the patients in the early morning of the second day of admission. The serum samples free of hemolysis, lipemia, jaundice, and other influencing factors were tested for FPG levels according to the manufacturer's instructions (Roche). 86 cases were divided into three groups according to the new coronavirus diagnosis and treatment plan (8th Edition) [12].

2.3. Types of COVID-19 cases and diagnostic criteria for obesity and diabetes

According to the clinical classification based on the Guideline of Novel Coronavirus Pneumonia (8th Edition), the cases were divided into mild, ordinary, severe, and critical. (1) Mild type: mild clinical symptoms and no pneumonia imaging characteristics. (2) Ordinary type: any two of the clinical manifestations such as fever and/or respiratory symptoms, and pneumonia imaging characteristics. (3) Severe type: subjects meet any one of the followings: shortness of breath, RR $\geqslant$ 30 times/min; oxygen saturation $\leqslant$ 93% when inhaling air in the resting state; arterial partial pressure of oxygen (PaO2)/oxygen inhalation Concentration (FiO2) $\leqslant$ 300 mmHg (1 mmHg = 0.133 kPa), PaO2/FiO2 (in high altitude areas over 1000 meters above sea level) is calculated according to the formula: PaO2/FiO2 $\times$ [760/atmospheric pressure (mmHg)]; progressively worsened clinical symptoms, and lesions in lung imaging progressed significantly more than 50% within 24 to 48 hours. (4) Critical type: any one of the following conditions such as respiratory failure, requiring mechanical ventilation, and shock, combined with other organ failure requiring ICU monitoring and treatment [12].

Severe/critical early warning indicators were alerted to the deterioration of the disease: 1. Progressive aggravation of hypoxemia or respiratory distress; 2. Deterioration of tissue oxygenation indicators or progressive increase of lactate; 3. Peripheral Progressive decrease in blood lymphocyte count or progressive increase in peripheral blood inflammatory markers such as IL-6, CRP, and ferritin; 4. D-dimer and other coagulation-related indexes were significantly increased; 5. Chest imaging showed lung lesions progressed significantly [12].

BMI standard for adults was defined according to the Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 edition): less than 18.5 kg/m^2 is underweight, 18.5 kg/m^2 $\sim$ 23.9 kg/m^2 is normal weight, 24.0 kg/m^2 $\sim$ 27.9 kg/m^2 is overweight, and 28.0 kg/m^2 or more is obese [13].

1999 WHO diagnostic criteria for diabetes: diabetes symptoms (such as polyuria, polydipsia, and unexplained weight loss in type I diabetes patients); a random venous plasma glucose concentration $\geqslant$ 11.1 mmol/l or fasting blood glucose concentration $\geqslant$ 7.0 mmol/l or two-hour blood glucose concentration $\geqslant$ 11.1 mmol/l and 75 g of anhydrous glucose two hours later in oral glucose tolerance test (OGTT); Impaired Fasting Glucose (IFG) standard: 6.1 mmol/l $\leqslant$ FPG < 7.0 mmol/l [14].

2.4. Statistical analysis

Statistical analysis was carried out using SPSS 25.0 software and data was expressed as mean $\pm$ standard deviation (SD). Either *t*-test or chi-square test were used for comparisons between groups unless otherwise noted. Multivariate linear regression was used for correlation analysis. $p < 0.05$ was considered statistically significant.
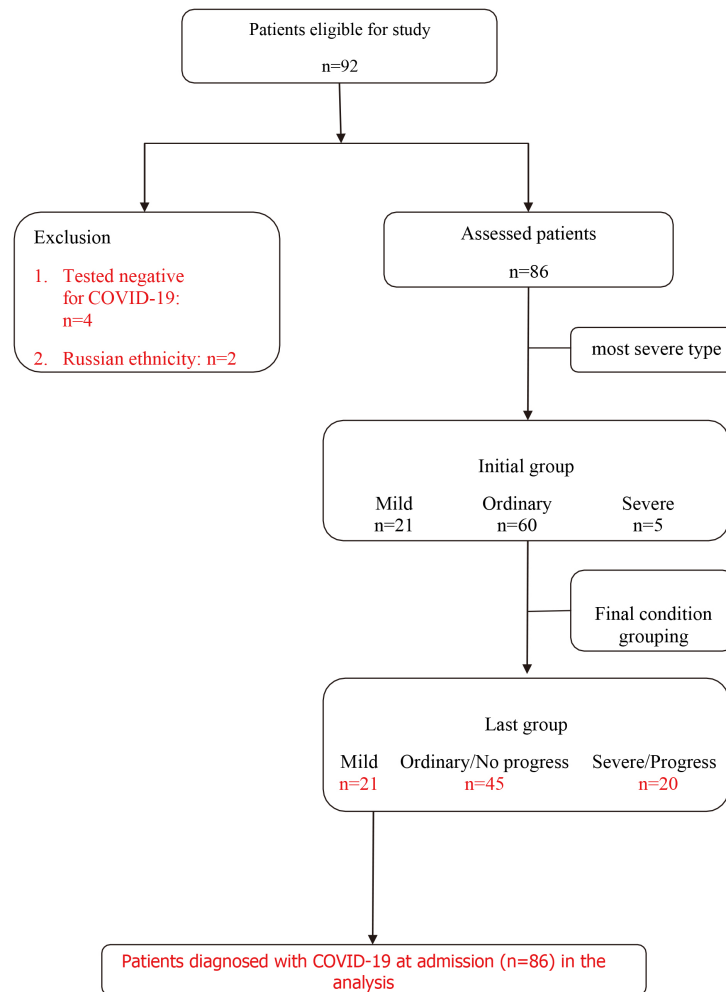
Fig. 1. Comparison of general clinical data of three groups of cases

3. Results

3.1. Classification and determination of cases

According to the most severe classification of each case determined by the Chinese expert group: 21 patients were asymptomatic and mild cases; 60 patients were ordinary cases, and five patients were severe cases. Twenty-one asymptomatic infections and mild patients were included in group A and five severe patients were included in group C. Fifteen out of those 60 ordinary cases had different degrees of severe/critical early warning indicators including progressive aggravation of hypoxemia or respiratory distress, deterioration of tissue oxygenation indicators or progressively increased of lactate, progressively decreased peripheral blood lymphocytes or progressively increased peripheral blood inflammatory markers (IL-6, CRP, ferritin), increased D-dimer and other coagulation function-related indexes, progression of pulmonary lesions showed in chest imaging [12]. Fifteen cases were finally classified as common progressive cases in group C (Fig. 1).

Table 1
Comparison of general clinical data of three groups of cases ($x \pm s$)

Different types of COVID-19	Cases	Age	Male/female	Height (cm)	Weight (kg)
Group A	21	24 ± 11	14/07	168 ± 7	63 ± 9
Group B	45	40 ± 16	25/20	167 ± 8	63 ± 9
Group C	20	53 ± 9	06/14	157 ± 24	70 ± 12

Group A: asymptomatic infection and mild group; group B: common type without progression group; group C: common type progressive and severe group.

Table 2
Comparison of FPG levels in three groups of cases ($x \pm s$)

Group	Normal blood sugar	Diabetes or IFG	FPG (mmol/l)
Group A	21	0	4.80 ± 0.44
Group B	43	2	5.11 ± 0.76
t	0.963^a		1.7341
P	0.327		0.0877
Group B	43	2	5.11 ± 0.76
Group C	15	5	5.57 ± 1.02
t	6.088^a		2.0212
P	0.014		0.0475
Group A	21	0	4.80 ± 0.44
Group C	15	5	5.57 ± 1.02
t	5.979^a		3.1655
P	0.014		0.0030

Group A: asymptomatic infection and mild group; Group B: normal type without progression group; C group: normal type progressive and severe group; IFG: impaired fasting blood glucose regulation; ^{a}: χ^2.

3.2. Comparison of general clinical data of three groups of cases

Age was compared among the three groups and the differences were statistically significant ($t = 4.1404$, 3.3933, 9.2123, $P = 0.0001$, 0.0012, 0.0000). The average age of the normal progressive and severe groups was greater than the normal non-progressive group. The average age of the non-progressive group was greater than the asymptomatic infection and mild group. In the chi-square test for the comparison of the two sample rates, the proportion of females in group C was higher than in group A ($\chi^2 = 5.512$, $P = 0.019$). However, there was no statistical difference between group B and group C nor between group A and group B ($P > 0.05$) (Table 1).

3.3. Comparison of FPG levels in three groups of cases

The FPG level in group C was higher than in groups A ($t = 3.1655$, $P = 0.0030$) and B ($t = 2.0212$, $P = 0.0475$). There was a difference in FPG between group A and group B but no statistical significance ($t = 1.7341$, $P = 0.0877$). The number of diabetes or IFG in group C was significantly higher than that in group A ($\chi^2 = 5.979$, $P = 0.014$) and group B ($\chi^2 = 6.088$, $P = 0.014$) (Table 2).

3.4. Comparison of BMI levels of three groups of patients

The BMI in group C was significantly higher than in groups A ($t = 3.8839$, $P = 0.0004$) and B ($t = 3.8188$, $P = 0.0003$). No significant difference in BMI was observed between groups A and B ($t = 1.0764$, $P = 0.2858$). The overweight or obese patients in group C were higher than in groups A ($\chi^2 = 8.838$, $P = 0.003$) and B ($\chi^2 = 10.794$, $P = 0.001$) (Table 3).

Table 3
Comparison of BMI levels of three groups of patients ($x \pm s$)

Group	Normal weight	Overweight or obese	BMI (kg/m^2)
Group A	15	6	21.72 ± 2.61
Group B	31	14	22.50 ± 2.80
T	0.044[a]		1.0764
P	0.834		0.2858
Group B	31	14	22.50 ± 2.80
Group C	5	15	25.79 ± 3.99
t	10.794[a]		3.8188
P	0.001		0.0003
A	15	6	21.72 ± 2.61
C	5	15	25.79 ± 3.99
t	8.838[a]		3.8839
P	0.003		0.0004

Group A: asymptomatic infection and mild group; group B: common type without progression group; C group: common type progressive and severe group; [a]: χ^2.

Table 4
Multivariate linear regression models affecting COVID-19

IV	B	SE	β	t	P
Age	0.020	0.005	0.380	3.713	0.000
Gender	0.264	0.122	0.191	2.156	0.034
FPG	0.157	0.077	0.186	2.035	0.045
BMI	0.037	0.020	0.182	1.850	0.068

β: standardized regression coefficient; IV: independent variable; B: unstandardized regression coefficient.

3.5. Multivariate linear regression analysis on the impact of COVID-19 conditions

The previously mentioned classification of COVID-19 patients was used as the dependent variable. Age, gender, BMI, and FPG were used as independent variables. Multivariate linear regression analysis showed that age ($\beta = 0.380$, $P = 0.000$), gender ($\beta = 0.191$, $P = 0.034$), and FPG ($\beta = 0.186$, $P = 0.045$) were independent risk factors for disease progression in patients with COVID-19 (Table 4).

4. Discussion

In the 21st century, there have been three deadly global pandemics related to coronaviruses with high infectivity and high mortality: SARS, Middle East respiratory syndrome (MERS) and COVID-19 [15]. A study of 115 patients diagnosed with SARS in Hong Kong showed that the coexistence of diabetes was independently associated with death [16]. Among the 32 MERS-CoV-infected patients in Saudi Arabia, those who had diabetes or more severe systemic diseases had higher mortality rates [17]. A group of scholars proposed that type 2 diabetes and BMI are independent risk factors for severe COVID-19 [18]. Preventing and effectively managing COVID-19 requires basic and clinical investigations, public health management, and clinical interventions [19]. According to the report from the International Diabetes Federation (IDF), 537 million adults (20–79 years old) will have diabetes in 2021 worldwide and 6.7 million adults will die from diabetes and its complications [20]. The management of blood sugar in diabetic patients is very important for the progress of COVID-19 under the current pandemic [21].

Previous COVID-19 data shows that the main risk factors in determining the severity of COVID-19 include age, gender, type 2 diabetes, obesity, smoking, and hypertension [22–24]. A meta-analysis showed that patients with diabetes had a higher COVID-19 infection rate and risk of developing to severe disease [25]. People with cardiovascular disease and diabetes have a higher chance of developing severe COVID-19 [26]. Diabetes is one of the most prevalent chronic diseases in the world and is closely associated with poor prognosis in COVID-19 [27]. Related studies have shown that diabetes increases mortality in patients with COVID-19 [28], and patients with diabetes who are infected by COVID-19 have a 2.95-fold higher risk of death compared with COVID-19 patients without diabetes [29]. Diabetes is associated with an increased risk of multiple infections such as viral infections [30]. The possible mechanism of diabetes-induced exacerbation of COVID-19 is the increased expression of the novel coronavirus angiotensin-converting enzyme 2 (ACE2) receptor in the lungs and other tissues of patients with type 2 diabetes [31], which is associated with chronic inflammation, insulin resistance, aggravated inflammatory responses and dysfunction of alveolar-capillary diffusion [32]. COVID-19 leads to insulin resistance and even direct damage to β-cell pancreatic function, leading to new-onset diabetes and a bidirectional relationship between viral infection and disturbance of glucose metabolism [33–35]. Elevated FPG leads to increased mortality and predicts a worse prognosis in hospitalized patients with COVID-19 [36,37]. Several steps can be taken to manage the impact of COVID-19 on people with diabetes, such as comprehensive guidelines, prioritizing vaccinations, and the use of telehealth services [38,39]. In this study, we found that FPG levels of patients in the severe and common progression group of COVID-19 were significantly higher than the asymptomatic infection group or the mild group or the common un-progressive group. We chose FPG on the second day of admission as the indicator in our study because the inflammatory response of newly diagnosed COVID-19 patients admitted to the hospital has little effect on FPG and can reflect the patient's normal FPG level. Therefore, patients with diabetes and elevated FPG should pay attention to the control of blood sugar.

Obesity is a serious public health problem with approximately 2 billion people are overweight [40,41]. The obesity rate was 6.2% in China, 27.8% in the UK, 19.9% in Italy, 3.9% in India, 4.7% in South Korea, and 22.1% in Brazil according to a WHO report in 2016 [42]. Obesity is associated with different systemic diseases such as hypertension, angina pectoris, diabetes, and arthritis [43]. Overweight and obesity are the fifth highest risk of death in the world [44]. The COVID-19 pandemic has a dramatic impact on human health leading to changes in lifestyle through social distancing and home isolation accompanied by social and economic consequences [45,46]. A meta-analysis showed that mortality, acute respiratory distress syndrome (ARDS), invasive mechanical ventilation (IMV), and increased visceral fat appears to be associated with severe adverse COVID-19 [47,48]. The risk of COVID-19 exacerbation and death increases linearly with increased BMI [49]. Obesity may affect COVID-19 outcomes through multiple potential mechanisms [50]. Early detection and aggressive treatment of obesity and COVID-19 patients are imperative [51]. Clinicians should recognize that individuals with more severe obesity have higher risk of exacerbated COVID-19 [52]. Our data suggest that BMI levels of patients with severe and common progression groups are significantly higher than asymptomatic infection and mild and common non-progressive groups, which may ultimately affect the prognosis of COVID-19. In this study, three patients who met the Chinese obesity diagnostic criteria had a BMI > 28.0 kg/m^2 in group C, so early targeted intervention should be performed for obese patients with COVID-19.

An earlier study of 79,394 confirmed COVID-19 patients (aged 30–59 years) clearly showed that older patients have a higher probability of more severe disease [53]. Patients over the age of 59 were 5.1 (4.2–6.1) times more likely to die after developing symptoms [54,55]. The above studies are consistent with our findings that the age of the patients in the severe and common progression group of COVID-19

was significantly higher than that in the asymptomatic infection group. The elderly people needed more attention from society during the COVID-19 pandemic and vaccination is essential for the COVID-19 prevention. Regarding the effect of gender on the condition of COVID-19, most studies show that men have a higher risk of infection, severe disease, and mortality than females [22,24]. Elderly males and coexisting with COVID-19 can lead to acute lung injury due to increased expression of ACE2 [56], and estrogen can participate in the regulation of the renin-angiotensin-aldosterone system (RAAS) including ACE2 [57]. Another study showed that nurses have a higher frequency of hospital visits made themselves more susceptible to infection [58]. Females with high FPG levels and low eGFR, age < 70 years, were significantly associated with the risk of severe COVID-19 [59]. Our findings suggest that females significantly outnumbered than men in critically-ill patients. Therefore, it is recommended that health care workers should increase their vigilance, and prioritize the detection and treatment of patients with higher BMI and other systemic diseases (diabetes and hypertension), and elderly COVID-19 pneumonia patients [60].

This study demonstrates the impact of different conditions of COVID-19 on FPG and BMI levels. However, some limitations exist in this study: the retrospective data prevented us from assessing longitudinal changes and correlation analyses of biochemical and clinical parameters during the disease progression; the relatively limited number of patients. Therefore, larger-scale studies in the future may help to elucidate better the action of FPG and BMI on the impact of COVID-19. FPG and BMI might even serve as predictors of COVID-19 progression [61,62]. Even though our study assessed the association of COVID-19 with BMI that is one of the measurements of obesity and is widely recognized as a predictor of chronic diseases [63,64], it should be noted that the definition of overweight and obesity in China differs from that in the United States and Europe [65]. Therefore, it is necessary to consider the potential impact of this difference when applying the conclusions of this study to others. In addition, COVID-19 leads to a significant increased glycated hemoglobin, fasting blood glucose, and BMI levels in patients with type 2 diabetes [66]. It is documented that random blood glucose and BMI on admission are associated with mortality in patients with COVID-19 [67], and hyperglycemia is an independent predictor of high inflammation levels and severe COVID-19 [68]. Some studies suggest that COVID-19 patients with FPG $\geqslant 6.1$ mmol/l should receive timely intervention regardless of their history of diabetes [69]. It is recommended to promote effective blood glucose management strategies in patients with type 2 diabetes [70]. With the advancement of science and technology, we can use the expert diagnosis system and telemedicine system to classify the COVID-19 condition in the future [71,72]. Such solutions are particularly useful for the implementation in rural and remote communities as well as for the elderly or patients with disability [72]. The application of AI algorithms in these areas will show great potential for the accurate classification of respiratory diseases.

5. Conclusion

In our retrospective study, FPG and BMI were significantly increased in the severe and common disease progression group. Also, patients' age in the severe and common disease progression group was significantly higher than that in the other two groups. FPG and age are independent risk factors for COVID-19 disease progression and it is speculated that FPG, BMI, and advanced age are predictors of COVID-19.

Author contributions

LGS and SRB conceived the study and collected patients; LGS conducted the experiments; LGS and

DHH analyzed the data; LGS, DHH and LS wrote the manuscript; LS and LPD revised the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors have no conflicts of interest to report.

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Data availability

All data generated and analyzed during this study are included in this article.

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