Correlation between Fasting Blood Glucose Level at Admission and Mortality in COVID-19 Patients: A Retrospective Study

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Research Article

Keywords: COVID-19, fasting blood glucose, mortality, retrospective study, clinical characteristics

Posted Date: May 14th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-18484/v2>

Abstract

Background Coronavirus disease-19 (COVID-19) has spread rapidly, with a growing number of cases confirmed around the world. This study explores the relationship of fasting blood glucose (FBG) at admission with mortality.

Methods In this retrospective, single-center study, we analyzed the clinical characteristics of confirmed cases of COVID-19 in Wu Han from 29 January 2020 to 23 February 2020. Cox proportional hazard regression analysis was performed to evaluate the relationship between FBG and mortality.

Results A total of 107 patients were enrolled in our study. The average age was 59.49 ± 13.33 and the FBG at admission was 7.35 ± 3.13 mmol/L. There were 16 people died of COVID-19 with an average age 68.1 ± 9.5 and the FBG was 8.94 ± 4.76 mmol/L. Regression analysis showed that there were significant association between FBG and death (HR = 1.13, 95%CI: 1.02-1.24). After adjusting for covariables, the significance still exists. In addition, our result showed that FBG > 7.0 mmol/L or diabetic mellitus can significantly increase mortality after adjusting for the age and gender.

Conclusions This study suggests that FBG at admission is an effective and reliable indicator for disease prognosis in COVID-19 patients.

Background

Coronavirus disease 2019 (COVID-19) has spread rapidly worldwide (1-3). As a newly identified pathogen, there is no known pre-existing immunity in humans and symptoms are non-specific at early stage (mild respiratory symptoms and fever, 5-6 days after infection on an average) (4). Once exacerbating, patients developed acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis coagulation dysfunction and organ failure that are difficult to control (5,6). Most patients showed increased inflammation-related biomarkers such as C-reactive protein (CRP) and interleukin, while the pulmonary computed tomography (CT) revealed bilateral distribution of patchy shadows and ground glass opacity (7,8). There is no effective medicine or vaccine other than comprehensive clinical intervention.

Based on the epidemiologic characteristics observed, most patients with COVID-19 were 30 to 79 years of age and mortality increases with age (4,9). Although COVID-19 is aggressive, the majority of patients can recover shortly after appropriate clinical intervention, except that a small number of patients died. Patients aged over 60 years and those with underlying conditions such as hypertension, diabetes, cardiovascular disease are found with highest risk for severe disease and death (10). An outline of the most representative laboratory abnormalities found in patients with COVID-2019 infection is still lacking.

As a type of beta coronavirus, the genomic characterization and the epidemiological of this novel virus had been clearly elucidated (11). Although much has been learned in the past few weeks, crucial knowledge gap remains in clinical. The clinical investigation of risk factors especially the fasting blood-

glucose (FBG) with death is scarce. Therefore, this study retrospectively analyzed the FBG level on admission and disease progression of 107 patients with confirmed COVID-2019.

Methods

Patients

This was a retrospective study of the clinical characteristics of prospectively collected series of patients diagnosed with COVID-19 in West Branch of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology between January 2020 and 23 February 2020. All patients who were diagnosed as having COVID-19 pneumonia according to WHO interim guidance (Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, January 28, 2020). Those who received hormone therapy before admission were excluded from our study. The study was approved by the Ethics Committee of West Branch of Union hospital, Tongji Medical College, Huazhong University of Science and Technology and written informed consent was obtained from patients involved before enrolment when data were collected retrospectively.

Laboratory Assays

Fasting blood samples at admission were collected. The biochemical parameters comprising FBG, serum lipid profiles were examined in the Laboratory department of West Branch of Union hospital.

Throat swab specimens were collected at admission and the laboratory nucleic acid tests using real time polymerase chain reaction (RT-PCR) for COVID-19 RNA were conducted immediately in the Laboratory department of West Branch of Union hospital. In addition, all patients were given chest X-rays or chest CT to further identify the bilateral ground-glass opacity of infiltrates of lung.

Date Collected

Medical records including clinical, demographic, laboratory parameters, chest CT/X-ray, length of hospitalization and death time of enrolled patients were extracted using a standardized case report form. If information was not clear, we would consult with the doctor or other healthcare providers responsible for the treatment of the patient.

Statistical Analysis

Data were presented as Means (SD) or medians (25th percentile-75th percentile) and proportions were calculated for population characteristics. Cox proportional hazard regression analysis was performed to evaluate the relationship between FBG and death. In addition, we adjusted for age, gender, body mass index (BMI), systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol in the multivariable model. FBG and death rate were estimated using the Kaplan-Meier method. Survival differences between groups were compared using the log-rank test. All

statistical tests were 2-sided with the significant level set at 0.05. Statistical analyzes were performed using Empower Stats (<http://www.empowerstats.com>) and the R software, version 3.3.1 (<http://www.R-project.org/>).

Results

Demographics, baseline and clinical characteristics of patients

A total of 107 patients were included in this study. The average age were 59.49 ± 13.33 year and the pneumonia severity index (PSI) was 64.97 ± 38.68 . The FBG at admission was 7.35 ± 3.13 mmol/L. Of them 54 were male with an average age 58.2 ± 13.0 year and 53 were female with an average 60.6 ± 13.7 . The pneumonia severity index (PSI) for male was 70.9 ± 40.2 and 59.1 ± 34.7 for female. There were 16 patients (10 male; 6 female) died of COVID-19 with an average age 68.1 ± 9.5 year. The PSI was 105.0 ± 22.7 and the glucose was 8.94 ± 4.76 mmol/L. Of the death case, three patients with diabetes mellitus (DM), 5 patients with hypertension, 2 patients with coronary heart disease and one patient was both with hypertension and coronary heart disease.

Association of FBG and Death

Associations of FBG level at admission with death are presented in table 2. We found that there were significant association between FBG and death (HR = 1.13, 95%CI: 1.02-1.24). Once adjust for covariables such as age, gender, blood pressure and serum lipid, the significance still exists (model 1: HR = 1.13, 95%CI: 1.03-1.25, $p = 0.015$ and model 2: HR = 1.33, 95%CI: 1.02-1.73, $p = 0.037$). To further explore the influence of FBG to death, 7.0 mmol/L was used as a cutoff value to evaluate the relationship (Figure 1). Regression analysis results showed that FBG > 7.0 or DM can significantly increase mortality after adjusting for the age and gender (HR = 2.86, 95%CI: 1.04-7.78, $p = 0.043$) (Table 3).

Kaplan-meier survival analysis was used to compare the variation trend of survival rate between the FBG < 7.0 and FBG ≥ 7.0 mmol/L during hospitalization. The results showed that compared with patients with FBG under 7.0 at admission, there was a significant decline of the cumulative survival rate in those with FBG over 7.0 ($p = 0.043$) (Figure 2).

Discussion

An outbreak of COVID-19 has become a global health concern. Although, the epidemiological and clinical characteristics of patients were well documented, understanding of the clinical spectrum of COVID-19 infection is still limited. As a human-to-human transmission disease, a majority of patients have a favorable prognosis, however, there was still with 3.8% crude fatality ratio (CRF) especially in those over 80 years of age (10,12). Thus, explore risk factors related to the prognosis would be helpful. In this study, we systematically investigated the effect of FBG on mortality. Our results showed that the death risk was associated with the FBG level at admission, which was not reported elsewhere.

Although epidemiology and the genome had been well elucidated, much remain unknown. The risk factors which influence death are still not clear and until now, there is no specific drug for the treatment of patients with COVID-19 (13). According to WHO guideline, symptoms of COVID-19 are non-specific and the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. The typical signs and symptoms include: fever, dry cough, fatigue, sputum production, shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhea, and hemoptysis and conjunctival congestion (5,6,14). These symptoms of mild illness in the early stage of COVID-19 infection may be indistinguishable clinically from many other common infectious diseases. However, in our study, we had observed that the FBG level were also increased (> 6.1 mmol/L) when excluded those with diabetes history. Normal human physiology is dependent on a tight control of the FBG levels. Zhang *et al.* had revealed that 57/64 diseases showed with increased FBG (15). Li *et al.* had reported that patients with $\text{FBG} \geq 7.0$ mmol/L was one of predictors of all-cause mortality in dilated cardiomyopathy patients (16). Thus, we believe increased FBG may play an important role in COVID-19 patients' prognosis.

It is noteworthy that most patients were not with diabetes mellitus, but their FBG level at admission were still high. Before admitted, they had only treated according to syndrome using lopinavir, ritonavir or arbidol. Without considerate psychological factors, we think increased FBG should raise even more attention in the treatment of COVID-19.

This finding of our study is also consistent with published article. In our study, the average age of death cases was older than those recovered patients, which was in accordance with Chen *et al.* and (4,9). In addition, we had observed a greater number of men than women in the 107 cases of COVID-19 infection.

Although our results might be helpful in COVID-19 prognosis, the results should be considered as preliminary ones and further research is necessary. Some limitations could not be ignored. First of all, due to the limited number of patients, our conclusions need to be further verified by larger samples and multi-center data. And there was only 16 persons died of COVID-19. Secondly, we did not get a dynamic FBG level during the treatment to complete elucidating the important role of blood glucose in the progress of COVID-19. Thirdly, there were not a long-time follow-up to observe whether those with increased FBG patients developed to diabetes or other metabolic disease when they recovery from COVID-19.

Conclusion

In conclusion, our study suggests that FBG at admission is an effective and reliable indicator for disease prognosis in COVID-19 patients. Increased FBG should be given more attention in the treatment of COVID-19.

Abbreviations

COVID-19: Coronavirus disease-19; FBG : Fasting blood glucose; PSI: Pneumonia severity index; ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; CT: Computed tomography;

Declarations

Acknowledgments

We thank the authors of the primary studies for their timely and helpful responses to our information requests.

Authors' Contributions

BZ and XKF designed the study and wrote the first draft. CGJ and XKF guided the methodology, YFZ and JY were responsible for statistics. FW and LS helped in data collection. FHX, LMZ, ZGZ and ZRT critically reviewed, discussed, and modified the manuscript. All authors read and approved the final manuscript for publication.

Funding

This research was funded by Beijing Municipal Administration of Hospitals (grant number ZYLY201827).

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of West Branch of Union hospital, Tongji Medical College, Huazhong University of Science and Technology and written informed consent was obtained from patients involved before enrolment when data were collected retrospectively.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Xu B, Kraemer MUG, Open C-DCG. Open access epidemiological data from the COVID-19 outbreak. *Lancet Infect Dis*. 2020.
2. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med*. 2020;382:929-36.

3. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares Global Emergency: A review of the 2019 Novel Coronavirus (COVID-19). *Int J Surg*. 2020.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-13.
5. Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, et al. Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study. *Clin Infect Dis*. 2020.
6. WHO. Coronavirus disease (COVID-19) outbreak. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>.
7. Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L, et al. Chest CT Findings in Patients with Corona Virus Disease 2019 and its Relationship with Clinical Features. *Invest Radiol*. 2020.
8. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia. *Radiology*. 2020:200370.
9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020.
10. Novel Coronavirus Pneumonia Emergency Response Epidemiology T. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41:145-51.
11. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565-74.
12. Ralph R, Lew J, Zeng T, Francis M, Xue B, Roux M, et al. 2019-nCoV (Wuhan virus), a novel Coronavirus: human-to-human transmission, travel-related cases, and vaccine readiness. *J Infect Dev Ctries*. 2020;14:3-17.
13. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends*. 2020.
14. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*. 2020;368:m606.
15. Zhang Q, Zhao G, Yang N, Zhang L. Fasting blood glucose levels in patients with different types of diseases. *Prog Mol Biol Transl Sci*. 2019;162:277-92.
16. Li X, Jiang R, Kong H, Shu Y, Li Q, Hua W. Fasting blood glucose at admission and survival in patients with dilated cardiomyopathy: a single-center cohort study. *Exp Clin Endocrinol Diabetes*. 2014;122:457-62.

Tables

Table 1 Baseline characteristics of the study participants by sex.

Variables	Stratified by sex		
	Male	Female	<i>P value</i>
N.	54	53	
Age, y	58.2 ± 13.0	60.6 ± 13.7	0.201
SBP, mmHg	24.6 ± 3.2	23.1 ± 2.8	0.055
DBP, mmHg	134.4 ± 18.2	128.5 ± 17.4	0.103
BMI, kg/m ²	83.1 ± 10.4	77.9 ± 11.7	0.012
PSI	70.9 ± 42.0	59.1 ± 34.7	0.036
CURB.65			0.663
0	20 (37.0)	22 (41.5)	
1	19 (35.2)	15 (28.3)	
2	11 (20.4)	14 (26.4)	
3	4 (7.4)	2 (3.8)	
DM			0.556
0	46 (85.2)	48 (90.6)	
1	8 (14.8)	5 (9.4)	
CHD			0.526
0	50 (92.6)	47 (88.7)	
1	4 (7.4)	6 (11.3)	
Hypertensive			0.304-
0	37 (68.5)	41 (77.4)	
1	17 (31.5)	12 (22.6)	
Laboratory results			
Fasting blood glucose, mmol/L [†]	6.4 (5.7-7.6)	5.9 (5.4-6.8)	0.156
Total cholesterol, mmol/L [†]	4.0 (3.5-4.4)	4.2 (3.8-4.8)	0.041
Triglycerides, mmol/L [†]	1.2 (1.0-1.9)	1.4 (1.1-1.7)	0.575
HDL cholesterol, mmol/L [†]	0.9 (0.8-1.0)	1.0 (0.8-1.2)	0.033
LDL cholesterol, mmol/L [†]	2.2 (1.8-2.7)	2.4 (2.0-2.9)	0.215

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein

* For continuous variables, values are presented as mean ± SD.

[†] Values are presented as median (IQR)

Table 2 Baseline characteristics of the study participants by death.

Variables	Stratified by Death		
	Non-Death	Death	<i>P value</i>
No.	91	16	
Age, y	57.9 ± 13.4	68.1 ± 9.5	0.003
Female, n (%)	47 (51.6)	6 (37.5)	0.417
SBP, mmHg	131.6 ± 17.9	130.6 ± 19.1	0.863
DBP, mmHg	81.3 ± 11.3	76.1 ± 10.8	0.190
BMI, kg/m ²	23.9 ± 3.1	23.7 ± 2.6	0.700
PSI	58.0 ± 36.9	105.0 ± 22.7	< 0.001
Fasting blood glucose, mmol/L [†]	5.9 (5.4-7.3)	7.0 (6.4-8.2)	0.003
Total cholesterol, mmol/L [†]	4.2 (3.7-4.6)	3.8 (3.3-4.2)	0.134
Triglycerides, mmol/L [†]	1.3 (1.0-1.8)	1.3 (1.1-1.9)	0.906
HDL cholesterol, mmol/L [†]	0.9 (0.8-1.2)	0.8 (0.6-1.0)	0.046
CURB.65			
0	41 (45.1)	1 (6.2)	
1	32 (35.2)	2 (12.5)	
2	16 (17.6)	9 (56.2)	
3	2 (2.2)	4 (25.0)	

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein;

* For continuous variables, values are presented as mean ± SD.

[†] Values are presented as median (IQR)

Table 3 The association between fasting blood glucose and death.

Fasting blood glucose, mmol/LN	Case (%)	Crude model	Adjusted model 1*		Adjusted model 2 [†]	
		HR (95CI)	HR (95CI)	<i>P value</i>	HR (95CI)	<i>P value</i>
Continuous	107 16 (15.0)	1.13 (1.02, 1.24)	1.13 (1.03, 1.25)	0.015	1.33 (1.02, 1.73)	0.037
	71 7 (9.9)	<i>Ref</i>	<i>Ref</i>		<i>Ref</i>	<i>Ref</i>
	36 9 (25.0)	2.65 (0.99, 7.12)	2.86 (1.04, 7.78)	0.043	3.53 (0.59, 21.15)	0.1667

* Model 1 adjusted for age, sex.

[†] Model 2 adjusted for age, sex, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, triglycerides, HDL cholesterol.

Figures

Figure 1

Smooth curves between fasting blood glucose and death. (A) Adjusted for age, sex; (B) Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, triglycerides, HDL.

Figure 2

The survival rate of patients with COVID-19 between the FBG < 7.0 and FBG ≥ 7.0 mmol/L during hospitalization.