Fasting Plasma Glucose Level Independently Predicts the Mortality of Patients with Coronavirus Disease 2019 Infection: A Multicenter, Retrospective Cohort Study

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Background: Coronavirus disease 2019 (COVID-19) has become a global pandemic, which prompts a consensus for the necessity to seek risk factors for this critical disease. Risk factors affecting mortality of the disease remain elusive. Diabetes and hyperglycemia are known to negatively affect a host's antiviral immunity. We evaluated the relationship between a history of diabetes, fasting plasma glucose (FPG) levels and mortality among severely ill patients with COVID-19.

Methods: This was a retrospective cohort study that assessed 106 adult inpatients (aged ≥18 years) from two tertiary hospitals in Daegu, South Korea. The participants were transferred to tertiary hospitals because their medical condition required immediate intensive care. The demographic and laboratory data were compared between COVID-19 patients who survived and those who did not.

Results: Compared with the survivor group, age, and the proportions of diabetes, chronic lung disease and FPG were significantly higher in the deceased group. In the Cox proportional hazards regression model for survival analysis, FPG level and age were identified as significant predictors of mortality ($P<0.05$). The threshold values for predicting high mortality were age >68 years and FPG of 168 mg/dL, respectively. Among those without diabetes, high FPG remained a significant predictor of mortality ($P<0.04$).

Conclusion: High FPG levels significantly predicted mortality in COVID-19, regardless of a known history of diabetes. These results suggest intensive monitoring should be provided to COVID-19 patients who have a high FPG level.

Keywords: COVID-19; Diabetes mellitus; Coronavirus; Blood glucose; Mortality

INTRODUCTION

In the 3 months since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection followed by secondary pneumonia was first diagnosed in Wuhan, China, in December 2019, coronavirus disease 2019 (COVID-19) has spread to more than 200 countries [1-3]. The Republic of Korea was one of the countries that experienced the outbreak from February 2020, and the city of Daegu has accounted for over 60% of confirmed COVID-19 cases. More than 700 confirmed cases were reported daily in Daegu during the initial period of rapid spread [4], demonstrating the importance of early triage for severe COVID-19 patients. COVID-19 can extensively damage the respiratory system and lead to death. In addition, asymptomatic cases or those with mild symptoms can suddenly deteriorate and progress to fatality, so it is crucial to identify factors that can predict mortality early in the disease [4,5]. Knowing risk factors for mortality would also allow governments to elucidate more efficient strategies to decrease the mortality rate among COVID-19 patients.

Patients with diabetes are highly vulnerable to infectious diseases (particularly bacterial infections such as tuberculosis) due to a dysregulated immune system [6,7]. In addition to diabetes, hyperglycemia itself results in impaired immune function and increased susceptibility to infections [8], as shown in clinical studies. In-hospital hyperglycemia (including in patients without a history of diabetes) has been associated with an increased mortality rate [9,10]. A previous study reported that hyperglycemia as well as a known history of diabetes were independent predictors of mortality and morbidity in severe acute respiratory syndrome (SARS) [11]. Regarding COVID-19, there have been reports of epidemiological data suggesting that diabetes is linked to prognosis or mortality. However, little is known about the association between plasma glucose levels and mortality rate among patients with COVID-19.

We evaluated the relationship between a history of diabetes, fasting plasma glucose (FPG) levels, and mortality among patients with COVID-19.

METHODS

Study design and participants

This retrospective study involved two cohorts of inpatients with COVID-19 from Kyungpook National University Chilgok Hospital and Kyungpook National University Hospital in Daegu, Republic of Korea, from February 1 to April 10, 2020. These two university hospitals are the largest among the four designated explicitly for patients with severe COVID-19 transferred from other facilities or hospitals in Daegu. The diagnosis of COVID-19 was made with positive results by real-time reverse transcription polymerase chain reaction assay for SARS-CoV-2 in upper respiratory specimens (nasopharyngeal and oropharyngeal swab), with or without a lower respiratory specimen (sputum) [12]. Based on clinical judgments, patients who were transferred because their medical conditions required prompt intensive monitoring and care in the early stages of the outbreak were investigated.

This study was conducted in accordance with the tenets of the Declaration of Helsinki, and was reviewed and approved by the Institutional Review Board of Kyungpook National University Hospital (2020-04-015). The requirement for informed consent was waived by the Ethics Commission as described previously.

Data collection

Epidemiologic, demographic, clinical, laboratory, and outcome data were investigated from the electronic medical records. All participants underwent laboratory tests within 48 hours of admission. With fasting for at least 8 hours, blood samples were drawn from the antecubital vein into vacuum tubes and subsequently analyzed at central, certified laboratories in Kyungpook University Hospital and Kyungpook University Chilgok Hospital. FPG concentrations were measured using an AU 5800 analyzer (Beckman Coulter Inc., Brea, CA, USA). Glycated hemoglobin (HbA1c) assays were performed using the HLC-723G7 high-performance liquid chromatography system (Tosoh, Tokyo, Japan). HbA1c measurements were standardized to the reference method used in the Diabetes Control and Complications Trial and according to the National Glycohemoglobin Standardization Program.

All data were extracted independently by two physicians (J.M.H. and D.P.) using a standardized data collection form. Discrepancies were resolved through discussions with a third investigator (M.C.C.).

Classifying risk factors

Based on previous studies of the risk factors for COVID-19 and the classification system announced by the Korea Centers for Disease Control and Prevention [13], the presence of underlying chronic medical conditions such as diabetes, chronic kidney disease (CKD), chronic lung disease, cardiovascular disease, carcinoma, dyslipidemia, and hypertension were investigated. Diabetes was defined according to any of the following criteria:

(1) a previous diagnosis made by a doctor, (2) subjects taking oral hypoglycemic agents or injections, or (3) a history of any abnormal plasma glucose levels based on the diagnostic criteria for type 2 diabetes put forth by the Korean Diabetes Association [14]. CKD was defined according to the Kidney Disease Improving Global Guidelines (KDIGO) for CKD [15]. Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, interstitial lung disease, idiopathic pulmonary fibrosis, or bronchiectasis.

All underlying chronic medical conditions such as hypertension, diabetes, chronic lung disease, and dyslipidemia were confirmed by a physician (J.S.M.).

Statistical analysis

All data are expressed as mean±standard deviation or percentage, as appropriate. Differences in parametric and non-parametric demographic data between COVID-19 survivors and non-survivors were assessed using an independent *t* test, Mann-Whitney *U* test, or chi-square test, as appropriate. For survival analysis, the Cox proportional hazards regression model was used. In non-diabetes patients with COVID-19, the Cox proportional hazards regression model was also used for survival analysis. Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive accuracy of age and FPG level for mortality among patients with COVID-19. Survival analyses were performed using the Kaplan-Meier method and differences in patient survival periods were determined using the log-rank test with respect to the FPG level. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics comparison between the survivor group and the non-survivor group among COVID-19 patients

Table 1 demonstrates the baseline characteristics of all COVID-19 participants and comparisons between the survivor and non-survivor groups. As of April 11, 2020, a total of 106 patients with severe COVID-19 were investigated. The mean age was 67.6±15.3 years and the sex ratio was 54:52 (male:female). Hypertension was the most common comorbidity, in 55.7% ($n=59$) of the patients, followed by diabetes ($n=42$, 39.6%) and CKD ($n=17$, 16.0%). During the study period, 30 patients died, so the mortality rate of this study was 28.3%.

Compared to the survivor group, mean age, FPG, and white

blood cell (WBC) count levels at admission were significantly higher in the non-survivor group. Regarding comorbidities, the non-survivor group showed a higher proportion of diabetes and chronic lung disease. However, there were no significant differ-

Table 1. Clinical Characteristics of Study Subjects

Variable	Total	Survivor	Non-survivor	*P* value
Total no.	106	76 (71.7)	30 (28.3)	
Age, yr	67.6±15.3	65.1±16.3	75.5±9.3	<0.001[a]
Sex				
Male	54 (50.1)	35 (46.1)	19 (63)	0.109
Female	52 (49.9)	41 (53.9)	11 (37)	
FPG, mg/dL	157±73.1	139.4±64.0	196.4±77.2	<0.001[a]
White blood count, ×10⁹/L	7.2±3.4	6.6±2.8	8.8±4.2	0.010[a]
Plasma creatinine, μmol/L	1.9±2.8	2.0±3.1	1.6±1.9	0.361
Medication				
ARB	13 (14.8)	8 (11.9)	5 (23.8)	0.181
NSAID	5 (4.7)	3 (3.9)	2 (6.7)	0.552
Comorbidities				
Hypertension	59 (55.7)	39 (51.3)	20 (66.7)	0.152
Diabetes mellitus	42 (39.6)	25 (32.9)	17 (56.7)	0.024[a]
Chronic kidney disease	17 (16.0)	14 (18.4)	3 (10.0)	0.287
Dyslipidemia	13 (12.3)	8 (10.5)	8 (16.7)	0.385
Chronic lung disease	7 (6.6)	2 (2.6)	5 (16.7)	0.009[a]
Malignancy	9 (8.5)	5 (6.6)	4 (13.3)	0.261
Cardiovascular disease	12 (11.3)	6 (7.9)	6 (20)	0.076
Stroke	6 (5.7)	3 (3.9)	3 (10)	0.224
Hospitalization type				
General ward	80 (75.5)	59 (77.6)	21 (70)	0.411
ICU	26 (24.5)	17 (22.4)	9 (30)	
Types of intensive care				
Mechanical ventilator	27 (25.5)	19 (25.0)	8 (26.7)	0.859
ECMO	4 (3.8)	2 (2.6)	2 (6.7)	0.326

Values are expressed as mean±standard deviation or number (%). *P* values were calculated by independent *t* test or chi-square test as appropriate.
FPG, fasting plasma glucose; ARB, angiotensin II receptor blocker; NSAID, non-steroid anti-inflammatory drug; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.
[a]Significant difference noted compared between two groups (*P*<0.05).

ences in the rates of hypertension, dyslipidemia, CKD, and stroke between the non-survivor and survivor groups. With regard to prior medication use such as angiotensin II receptor blockers or non-steroid anti-inflammatory drugs, similar proportions were observed.

About a quarter of the patients were admitted to the intensive care unit (24.5%) and required invasive mechanical ventilation (25.5%). Four patients were treated with extracorporeal membrane oxygenation. The proportion of patients who required advanced life support was no different between the two groups. All hospitalized patients underwent anti-viral treatment with either two tablets of lopinavir/ritonavir (200/50 mg) (Kaletra, AbbVie Inc., North Chicago, IL, USA) alone or a combination of two tablets of lopinavir/ritonavir (200/50 mg) and hydroxychloroquine sulfate 400 mg (Oxiklorin, Myungmoon Pharm Co. Ltd., Seoul, Korea).

Analysis of clinical factors affecting mortality in patients with COVID-19 infection
We analyzed which clinical factors were associated with the death of COVID-19 patients. Age and FPG significantly predicted mortality in the Cox proportional hazard model (hazard ratio

[HR] and 95% confidential intervals [CIs] were 1.058, 1.02 to 1.106; 1.015, 1.008 to 1.021, respectively), whereas WBC and a known history of chronic lung disease or diabetes did not (Table 2). To determine a mortality risk factor in non-diabetic patients, we extracted the diabetic patients ($n=42$) and explored the effects of age, FPG, WBC, and chronic lung disease on the deaths of the remaining COVID-19 patients (Table 3). The FPG level at admission, even in patients without a prior history of diabetes, remained a significant predictor for the death of COVID-19 patients (HR, 1.012; 95% CI, 1.001 to 1.024; $P=0.038$).

Among COVID-19 patients, the area under the ROC (AUROC) curve of FPG for predicting mortality was 0.759 (95% CI, 0.660 to 0.841; $P<0.0001$) (Supplemental Fig. S1). The optimal cut-off value assessed using the maximum Youden's index (J) was 168 mg/dL (sensitivity 66.67%, specificity 84.62%). The AUROC curve of age for predicting mortality was 0.702 (95% CI, 0.605 to 0.787; $P=0.0001$), and the optimal cut-off value was 72 years (sensitivity 73.33%, specificity 63.16%). Given the cut-off value, Fig. 1 showed the event-free (no death) rates between the two groups of COVID-19 patients who were divided by the cut-off FPG value of 168 mg/dL on admission.

Table 2. Risk Factors Associated with Mortality in Patients with Coronavirus Disease 2019 Using Cox Proportional Hazard Model

Parameter	Beta coefficient	SE	HR (95% CI)	*P* value
Age	0.057	0.023	1.058 (1.012–1.106)	0.013[a]
Chronic lung disease	0.523	0.507	1.688 (0.625–4.559)	0.302
WBC	0.043	0.051	1.044 (0.945–1.153)	0.399
DM	0.149	0.422	1.160 (0.508–2.652)	0.724
FPG	0.014	0.003	1.015 (1.008–1.021)	0.000[a]

P values by cox proportional hazard model.
SE, standard error; HR, hazard ratio; CI, confidence interval; WBC, white blood cell; DM, diabetes mellitus; FPG, fasting plasma glucose.
[a]Statistically significant with *P*<0.05.

Table 3. Risk Factors Associated with Mortality Coronavirus Disease 2019 Patients without a History of Diabetes Using Cox Proportional Hazard Model

Parameter	Beta coefficient	SE	HR (95% CI)	*P* value
Age	0.016	0.031	1.016 (0.956–1.079)	0.616
Chronic lung disease	1.039	1.035	2.827 (0.372–21.499)	0.315
WBC	0.063	0.120	1.065 (0.841–1.349)	0.588
FPG	0.012	0.006	1.012 (1.001–1.024)	0.038[a]

P values by cox proportional hazard model.
SE, standard error; HR, hazard ratio; CI, confidence interval; WBC, white blood cell; FPG, fasting plasma glucose.
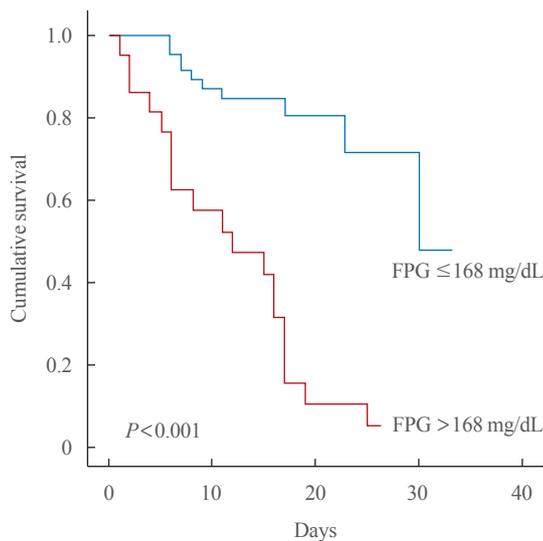[a]Statistically significant with *P*<0.05.

Fig. 1. Cumulative survival of patients with coronavirus disease 2019 according to the fasting plasma glucose (FPG) level (≤168 mg/dL vs. >168 mg/dL).

DISCUSSION

In this study, we evaluated risk factors for mortality among patients with COVID-19 who were admitted with severe symptoms to two tertiary hospitals in Daegu. The deceased group showed higher FPG and proportion of a known history of diabetes compared to the survivor group. Given that severe COVID-19 patients required intensive treatment, we found that FPG independently predicted mortality among patients with COVID-19, regardless of diabetes. Notably, although pre-existing diabetes was twice as prevalent among non-survivors, the multivariate logistic analysis revealed that, unlike FPG, the presence of pre-existing diabetes *per se* did not reflect higher mortality.

A hyperglycemic milieu increases susceptibility to all kinds of infection, due to impaired T cell response, neutrophil function, and humoral immunity [16]. Certain microorganisms (*Staphylococcus pneumoniae* and influenza virus) are well-known to be associated with increased mortality and morbidity among patients with diabetes [17]. More specifically, how hyperglycemia contributes to higher mortality in corona virus infection (including COVID-19) has been investigated. Angiotensin-converting enzyme 2 (ACE2) seems to be the primary receptor for COVID-19 entry via direct interaction of a viral spike [18]. The degree of glycosylation affects the binding affinity of both the ACE2 and viral spike, and it is plausible to assume that hyperglycemia can enhance the affinity of the viral spike and the receptor and thereby the subsequent viral immune response.

An elegant study has revealed that in those who were infected with SARS-CoV [19], significant elevations in FPG, serum creatinine, and lactate dehydrogenase were critical predictors for death. In the same study, compared with non-SARS pneumonia, SARS patients had significantly elevated FPG on day 0 and day 2 after admission, suggesting that hyperglycemia is a pathogen-specific phenomenon rather than merely a result of systemic inflammatory response. Importantly, their hyperglycemia was significantly improved at discharge, suggesting this elevation is temporary and probably correlates with disease course. Because ACE2 immunostaining was found in lung, kidney, heart, and islets of the pancreas, and that FPG, serum creatinine, and lactate dehydrogenase reflect mortality, it is highly likely that SARS as well as COVID-19 infection induces transient inflammation in islets and thereby promotes transient hyperglycemia. Indeed, our study consistently found that mean FPG levels were higher in the non-survivor group and an increase in FPG concentration by 1 mg/dL increased the mortality risk by 1.5%.

There are still insufficient epidemiologic data to determine whether diabetes triggers the mortality of COVID-19 patients; however, we can refer to the experience regarding SARS in 2003 [11]. A retrospective analysis demonstrated that the mortality rate was significantly higher among patients with diabetes and the risk of death was three times higher compared to those without diabetes. Regarding COVID-19 mortality, the proportion of diabetes has been reported to vary from 9.7% to 22.4% in China [20-22]. This variation might result from the differences in disease severity and the volume of participants in each study. Korea Centers for Disease Control and Prevention reported that there were 66 deaths among 7,755 confirmed cases as of March 13, 2020. Among the deceased patients, 36.5% had diabetes, which was somewhat higher than that reported in previous studies [13]. In our study, the proportion of diabetes patients among those who died was 56.7%, higher than that reported in any previous study.

Nevertheless, although the proportion of diabetic patients was significantly higher in the deceased group, and twice as high as that among survivors (Table 1), we failed to observe a critical contribution of diabetes in the mortality of severe COVID-19 infected patients by multivariate logistic analysis (Table 2). In addition, in most studies of COVID-19, cardiovascular disease, which was identified as a risk factor for the severe outcome, was not significant in our study [23]. The discrepancy of importance of pre-existing diabetes in the mortality of COVID-19 probably relates to the distinct characteristics of the enrolled patients in this study. Because there were more than 6,000 cases

within 2 months during the major outbreak in Daegu, the majority without traditional high risk factors were admitted to therapeutic living centers [4]. Considering that the mortality of COVID-19 in South Korea is around 2%, whereas in our study mortality was as high as 28.3%, these patients were clearly critically ill. In addition, the prevalence rate of diabetes among those aged >65 is 30.4% in South Korea [24], whereas its prevalence in the deceased group was as high as 53.3%. Therefore, it is very likely that if all COVID-19 patients who enrolled were re-analyzed, pre-existing diabetes might have arisen as another independent predictor of mortality. What we can learn from these data is that patients with diabetes are susceptible to COVID-19 infection, requiring active preventive strategies and intensive monitoring.

Surprisingly, FPG levels of severe COVID-19 patients without an antecedent diagnosis of diabetes were rather high in our study, and FPG was revealed as an independent risk factor for mortality. Similar to our study, the FPG levels among SARS patients were observed to be significantly higher in the deceased group than in the survivor group, regardless of diabetes, and hyperglycemia, defined as an FPG level ≥7.0 mmol/L, increased the risk of death 3.3 times [11]. Interestingly, HbA1c level was not significantly different between the survivor and non-survivor group (data was not snown). Hyperglycemia is commonly observed among critically ill patients at hospital admission, even in patients without a prior diagnosis of diabetes mellitus [10,25], and it is estimated to affect 40% of hospitalized patients [26]. Stress conditions induce excessive secretion of counter-regulatory hormones such as glucocorticoids, glucagon, and catecholamines and these contribute to poor immune response and inflammatory changes as well as hyperglycemia [27]. It appears that these connections are responsible for the mortality of non-diabetic patients.

Our study is limited to representing the COVID-19 epidemic in Korea. The outbreak of Daegu city was characterized by an explosive increase in COVID-19 patients over a short two to three week period, and the number of new confirmed cases had reached over 700 by February 29, 2020. Authorities began operating supportive facilities ('therapeutic living centers') for asymptomatic to mild cases and prioritized general or tertiary hospital admission for severe cases to avoid shortages in medical resources. Thus, selective bias cannot be ruled out because clinically categorized 'severe' patients requiring intensive monitoring were included in this study. However, experts have warned that severe clinical outcomes may begin with mild symptoms for around 1 week, which suddenly deteriorate until

they require intensive care. This underscores the importance of the initial screening of COVID-19 patients for the efficient distribution of medical resources. To the best of our knowledge, ours is the first study suggesting FPG as a simple predictor for COVID-19 mortality. Simple surrogates for assessing severity would be helpful to healthcare professionals for rapid clinical judgments in the COVID-19 pandemic era.

In conclusion, high FPG levels (particularly >168 mg/dL) independently predicted the mortality of COVID-19 infected patients and were a significant risk factor for death even after adjusting for other risk factors, and even in patients without diabetes. Therefore, healthcare professionals who take care of COVID-19 patients should closely monitor blood glucose levels and provide intensive monitoring to those with high FPG.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: M.C.C., J.M.H., J.H.J., D.P., J.S.M. Acquisition, analysis, or interpretation of data: M.C.C., J.M.H., J.H.J., S.G.K., D.P., J.S.M. Drafting the work or revising: M.C.C, J.H.J., J.S.M. Final approval of the manuscript: M.C.C., J.M.H., J.H.J., S.G.K., D.P., J.S.M.

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