Int J Med Rev 2023 March;10(1): 447-455

10.30491/IJMR.2022.267010.1174

INTERNATIONAL JOURNAL OF MEDICAL REVIEWS
Systematic Review

Hyperglycemia Induced by COVID-19 with and without Present Diabetes: A Systematic Review

Theodore Dharma Tedjamartono [1*], Gembong Satria Mahardhika [1], Haidar Zain [1]

[1] Emergency Hospital COVID-19, Wisma Atlet Kemayoran, Jakarta, Indonesia

*** Corresponding Author:** Theodore Dharma Tedjamartono, Emergency Hospital COVID-19, Wisma Atlet Kemayoran, Jakarta, Indonesia.

Received January 11, 2021; **Accepted** September 19, 2022; **Online Published** March 6, 2023

Abstract

COVID-19 is a major emerging disease that will affect any specific disease. However, a recent report suggests the occurrence of hyperglycemia without any present diabetes in COVID-19 patients. This study aimed to systematically review recent evidence on hyperglycemia in COVID-19 patients. Literature research was done using four search engines, consist of Google Scholar, PubMed, ScienceDirect, and ProQuest, and limited to English manuscripts only and published in the last 1 year. SARS-CoV-2 could damage the pancreas by causing the destruction of the β-cell structure that leads to impairment of glucose metabolism and worsen pre-existing diabetes or determine the appearance of hyperglycemia in non-diabetes. Inflammation also plays a major important role in hyperglycemia related to COVID-19. Hyperglycemia increased the vulnerability of the lung, by promoting and facilitating the entry of the SARS-CoV-2 into the host cells, and decreasing lung function. Moreover, the mortality and morbidity rate conceivable increased due to hyperglycemia. The presence of high glucose levels is linked with the progression of COVID-19 severity. Thus, the glucose level should be concerned, either in a patient with present diabetes or without any presence of diabetes. Examination and monitoring of glucose levels might be a useful tool to prevent the seriousness of COVID-19.

Keywords: Diabetes Mellitus, SARS-CoV-2, High Glucose Level, Pulmonary Infection

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic is not over and the solution has yet to be found. It is more than a health crisis, COVID-19 affected many aspects of life. To date, more than 1.000.000 deaths is caused by COVID-19.[1] Compared to other countries in South East Asia, Indonesia has higher mortality.[2] Several factors contribute to the severity and mortality of COVID-19. Comorbidities have been known to increase the severity of COVID-19 and diabetes is included.[3] It is also known that diabetic patients tend to have high blood glucose levels or hyperglycemia.[4] However, a recent report suggests the occurrence of hyperglycemia without any present diabetes in COVID-19 patients.[5-8] Some studies suggest hyperglycemic conditions could be a predictor of mortality in COVID-19 patients.[4,9-14] The systematic review was conducted to analyze the occurrence of hyperglycemia in COVID-19 patients with diabetes and without present diabetes.

Materials and Methods

Comprehensive literature searches were conducted using four electronic databases, PubMed, ProQuest, Science Direct, and Google Scholar. A limitation is set on literature searches using only published journals within the past year and English-language manuscripts. Boolean logic was used to combine search terms as seen in the following Table 1. Literature searches in each database were conducted to find journals that contain information about hyperglycemia-associated COVID-19. Full-text articles with various types of studies, case-control, cohort, time-series, systematic review, and meta-analysis containing hyperglycemia-associated COVID-19 were obtained.

Afterward, screening on journals abstract and title were done using inclusion criteria according to the following PICO, P: confirmed COVID-19 patients, I: diabetes and non-diabetes, C: not available, O: hyperglycemia. While the exclusion criteria were those journals contained a restricted discussion about diabetes as a comorbidity in COVID-19 patients without any further data about non-diabetes and those only discussed COVID-19 with or without diabetes, yet not associating hyperglycemia. Critical appraisals were conducted

using Oxford's Centre for Evidence-Based Medicine worksheets.[15] Available data about risk relatives and odds ratio from cross-sectional, cohort, and case-control studies were presented.

Table 1. Literature Search Strategy Using Boolean Logic

Database	Keywords	Results
PubMed	"COVID-19" or "sars-cov-2" and "hyperglycemia" and "diabetes"	101
ProQuest	"COVID-19" and "hyperglycemia" and "diabetes" and "without diabetes" or "non diabetes"	365
ScienceDirect	"COVID-19" or "sars-cov-2" and "diabetes" and "without diabetes" and "hyperglycemia"	172
Google Scholar	"COVID-19" and "hyperglycemia" and "diabetes" and "without diabetes" or "non diabetes"	66

Results

A total of 704 published papers about hyperglycemia in COVID-19 patients with diabetes or without present diabetes from four electronic databases were identified and 692 were excluded. Twelve articles were analyzed and discussed, the critical appraisals can be seen in Table 2 below. Each study compared high blood sugar levels or hyperglycemia in the diabetic patients group and non-diabetic patients group. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart can be seen in Figure 1.

Table 2. Critical Appraisal of the Studies Included in the Systematic Review

First author and year	Study sizeandsettings	Study design	Study period	Population	Outcomes	Hyperglycemia/diabetes status byoutcomes
Mamtani, 2020[5]	403 patientsadmitt edto John H StrogerChicago	Obervatio nalcohort	March 15,2020 to May 15, 2020	COVID-19 confirmed patients using PCR for RdRp and N genes	**Mortality** n=51(13%) **Admission to ICU** n=97 (24%) **Mechanical ventilation** n=56 (14%)	**Mortality** DM(-)HG(+) 20.5% DM(-)HG(-) 1.8% **Admissionto ICU** DM(+)HG(+) 32.4% DM(+) HG(-) 20.0% DM(-)HG(+) 43.4% DM(-)HG(-) 7.2% **Mechanical ventilation** DM(+)HG(+) 18.6% DM(+) HG(-) 10.0% DM(-)HG(+) 32.5% DM(-)HG(-) 0.6% DM = history of diabetes HG = blood glucose ≥7.78 mmol/L
Zhou, 2020[6]	80 patients in AnhuiProvinci al Hospital	Crosssecti onal	January 2020 to March 2020	COVID-19 patients	**Severe and critical cases** n=55 (68.75%)	**Severe and critical cases** Euglycemia 40% Hyperglycemia 28% Diabetes group 32%
Singh, 2020[7]	8 studies	Literaturer eview	2020	Hyperglyce mia with diabetes and without diabetes COVID-19 patients	Hyperglycemia without present diabetes in COVID-19 is associated with poorer outcome compared with diabetes	-
Sachdeva, 2020[8]	13 studies	A Pooled Analysis and Meta-Summary of Literature	August 2020 to September 2020	COVID-19 patients with and without diabetes	-	**Severe or critical case** OR; 1.837 (95% CI 1.368-2.465, p<0.001) **Mortality** OR 2.82 (95% CI 1.587-5.019), p<0.001)
Lee, 2020[9]	8 studies	Meta-analysis	2020	COVID-19 patient with available glycemic status	**Mortality Required ICU admission Ventilation Severe or critical COVID-19**	**Mortality** 5% in Non-diabetic with hyperglycemia 16% in Diabetic with hyperglycemia **Required ICU admission** 5% in Non-diabetic with hyperglycemia

						15% in Diabetic with hyperglycemia **Ventilation** 38% in Non-diabetic with hyperglycemia 16% in Diabetic with hyperglycemia **Severe or critical COVID-19** 75% in Non-diabetic with hyperglycemia 89% in Diabetic with hyperglycemia
Wu, 2020[10]	2,041 patientsfromtwomedicalcenters in Wuhan	Retrospectivecohort	December 26, 2019 to March 15, 2020	Hospitalized COVID-19 patients with available blood glucose data	**Critical condition** n=697 (29.2%)	**Critical condition** Normal initial glucose 33.7% Hyperglycemia initial glucose 66.3%
Zhu, 2020[11]	293 patientsfromfivehospitals in Wenzhou, China	Retrospectivecohort	January 17 toFebruary 22, 2020	COVID-19 adult patientswithout cancer, cachexiaorpre-existing diabetes	**Severe or critical case** n=76 (25.9%)	**Severe or critical case** FPG <7.05 mmol/L 32.8% FPG ≥7.05 mmol/L 67.2%
Yan Zhang, 2020[17]	166 patientsatTongji Hospital, Wuhan	Retrospectivecohort	February 8 to March 21, 2020	COVID-19 patients	**Mortality** n=24 (14.5%) **Composite outcomes** Mechanical ventilation, treated in ICU and death n=34 (20.5%)	**Mortality** 9.5% in No diabetes & FPG < 7.0 mmol/L 14.3% in No diabetes & FPG ≥ 7.0 mmol/L 21.3% in Diabetes & FPG ≥ 7.0 mmol/L **Composite outcomes** 10.7% in No diabetes & FPG < 7.0 mmol/L 38.1% in No diabetes & FPG ≥ 7.0 mmol/L 27.9% in Diabetes & FPG ≥ 7.0 mmol/L
Yang Zhang, 2020[12]	263 patientsatTongji Hospital Wuhan	Retrospectivecohort	February 4 to March 10, 2020	Laboratory-confirmed COVID-19 patients with available results of fasting plasma glucose (FPG) admission and not taking systemic corticosteroid treatment before taking blood sample of admission FPG	**Hyperglycemia** FPG ≥ 7.0 mmol/L n=128 (48.7%) **Acute respiratory distress syndrome** n=112 (42.6%) **Acute cardiac injury** n=73 (27.7%) **Shock** n=91 (34.6%) **Secondary infections** n=94 (35.7%) **Acute kidney injury** n=23 (8.7%) **28-day mortality** n=107 (40.7%)	**Hyperglycemia** 82.2% in diabetes 38.3% in non-diabetes **Acute respiratory distress syndrome** 58.0% in diabetes 40.8% in non-diabetes **Acute cardiac injury** 38.7% in diabetes 24.4% in non-diabetes **Shock** 40.3% in diabetes 32.8% in non-diabetes **Secondary infections** 43.5% in diabetes 33.3% in non-diabetes **Acute kidney injury** 16.1% in diabetes 6.5% in non-diabetes **28-day mortality:** 54.8% in diabetes 36.8% in non-diabetes
Liu, 2020[4]	255 patientsadmittedtoTongji Hospital, China	Retrospectivecohort	February 1 to February 24, 2020	COVID-19 patients by RT-PCR tests	**Required ICU** n=41 (16%)	**Required ICU** FPG >7.0 mmol/L 85.4% FPG ≤7.0 mmol/L 14.6%
Carrasco, 2020[13]	11,312 patients in 109 hospitals in	Retrospectivecohort	March 1 to May 31, 2020	Patients ≥18 years old admitted	**Mortality** n=2,289 (20.2%) **Mechanical**	**Mortality** 15.7% in Admission BG <140 mg/dl

	Spain			with COVID-19 confirmed by RT-PCR	**ventilation** n=1,156 (10.2%) **ICU admission** n=935 (8.3%) **Composited endpoint** Death, mechanical ventilation, and/or ICU admission n=2,978 (26.3%)	33.0% in Admission BG 140 - 180 mg/dl 41.1% in Admission BG >180 mg/dl **Mechanical ventilation** 9.0% in Admission BG <140 mg/dl 14.3% in Admission BG 140 - 180 mg/dl 16.1% in Admission BG >180 mg/dl **ICU admission** 7.5% in Admission BG <140 mg/dl 10.6% in Admission BG 140 - 180 mg/dl 11.4% in Admission BG >180 mg/dl **Composited endpoint** 21.7% in Admission BG <140 mg/dl 40% in Admission BG 140 - 180 mg/dl 48.6% in Admission BG >180 mg/dl
Coppelli, 2020[14]	271 patientsadmitt edtotheUniver sity Hospital, Italy	Retrospect ivecohort	March 20 to April 30, 2020	COVID-19 patients with available blood glucose data	**In-hospital mortality** n=67 (24.7%) **Needformechani calventilation** n=46 (17.0%) **Admissionto ICU** n=80 (29.5%) **Acute respiratory distress syndrome** n=124 (45.8%)	**In-hospital mortality** 16.8%% in Normoglycemia 39.4% in Hyperglycemia 28.6% in Known diabetes **Need for mechanical ventilation** 11.4% in Normoglycemia 33.3% in Hyperglycemia 12.5% in Known diabetes **Admissionto ICU** 24.2% in Normoglycemia 45.4% in Hyperglycemia 25.0% in Known diabetes **Acute respiratory distress syndrome** 32.9% in Normoglycemia 59.1% in Hyperglycemia 64.3% in Known diabetes

Discussion

Hyperglycemia in COVID-19

COVID-19 is a highly contagious disease and has still become a major health problem. The mechanism of infection, therapies, and complications caused by COVID-19 is still being studied. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infected cell host through S Glycoprotein structure that binds Angiotensin Converting Enzyme 2 (ACE-2) receptor. Most of ACE-2 receptors are found in respiratory tract epithelium. Nevertheless, ACE-2 receptor also can be found in pancreas. SARS-CoV-2 may bind to ACE-2 receptor in the pancreas, thus impair the pancreas function resulting in high blood sugar.[6] Hyperglycemia is defined by random blood sugar level > 9.9 mmol/L or 178.2 mg/dl at least twice the tests or fasting blood sugar level > 6.9 mmol/Lor 124.2 mg/dl. Diabetes was defined by HbA1c level > 6.4% or has a past history of diabetes.[5,8,14,16] Hyperglycemia can occur in patients without prior diabetes. The non-diabetes group is defined by the absence of diabetes history or an HbA1c level < 6.5% and normal blood sugar level on discharge.[6,7,17] The prevalence of hyperglycemia in COVID-19 patients either with or without prior diabetes is high and should be studied further.[5]

Hyperglycemia in COVID-19 has several mechanisms. The major action can be divided into two subdivided. First, there was a direct mechanism via β cells impairment from the virus itself. Secondly, an indirect mechanism was found via the impact of pro-inflammatory cytokines, acute stress factors, or a

history of glucocorticoid therapy usage.[5] SARS-CoV-2 could damage pancreatic β cells by binding to ACE-2

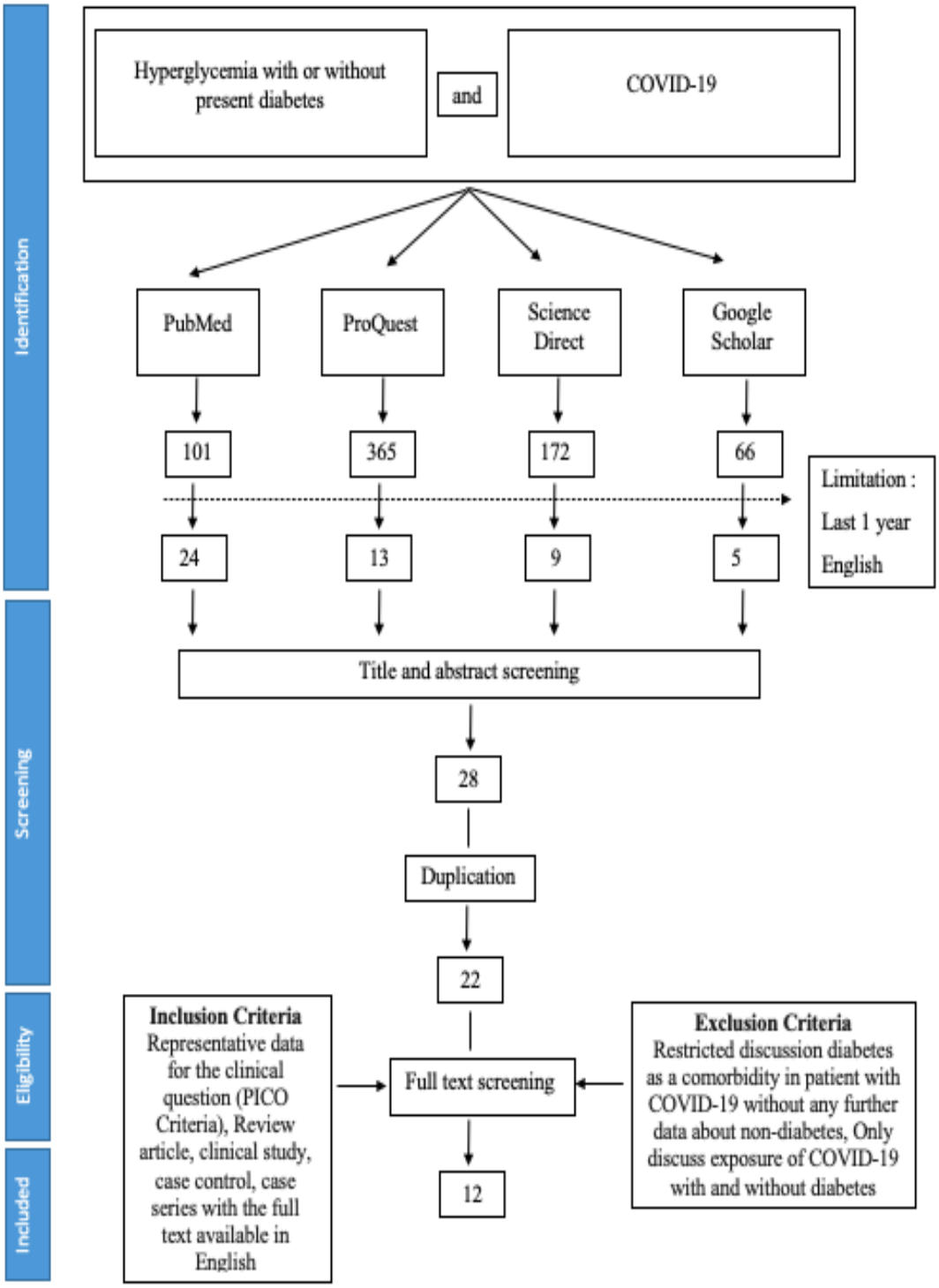

Figure 1. PRISMA Flowchart for Studies of Hyperglycemia Induced by COVID-19 with and without Present Diabetes.

receptor, hence insulin secretion is impaired. As a consequence, the blood sugar levels will increase and worsen the diabetes condition or induce hyperglycemia in patients without prior diabetes. This condition causes glycation of immunoglobulin, thus impair the antibodies function, weaken the immune systemsand elevation of HbA1c level. Furthermore, pancreatic beta cell impairment may worsen and insulin resistance occurs.[6] ACE-2 may also be glycosylated aberrantly,

enhancing cellular intrusion of SARS-CoV2 and increase the severity of the disease.[6,8,10,16,17]

SARS-CoV-2 may affect the innate immune system by downregulating and shedding virus-induced ACE-2, thus stimulate abundant proinflammatory cytokines to release in hosts cell resulting in a cytokine storm.[5,8] Structural and functional damage in the endothelial cells occurs in this condition leading to impairment in insulin secretion and pancreatic beta cell causing hyperglycemia. Meta-analyses studies by Lee et al[9] and Sachdeva et al[8] showed that host immune response dysregulation which causes cytokine production impairment (e.g. IL-6) will induce or worsen insulin resistance and disrupt insulin secretion. Zhou et al[6] and Mamtani et al[5] in their studies showed that elevation of proinflammatory cytokines in circulation, such as CRP, IL-6, Interferon Gamma, and Tumor Necrosis Factor Alpha occurred in hyperglycemic patients either with diabetes or without diabetes. Sachdeva et al[8] found that IL-6 level decreased after the hyperglycemia was treated. Another finding in a study conducted by Zhou et al[6] shows a low level of CD3+ and CD4+/CD8+ ratio in hyperglycemic patients with and without prior diabetes indicated immune system impairment process. This led to a surge mechanism of activated-NK cells, proinflammatory cytokine production, reducing T-helper associated chemokine receptors, and disrupting T cell proliferation in the initial stage of infection, thus worsen the patient condition. Lee et al also stated that hyperglycemia in COVID-19 patients with diabetes was caused by inflammation and counterregulatory hormones.[9] A study by Wu et al shows that the infection process caused an inflammatory storm. Furthermore, insulin resistance can occur. Thus, infection also inducing stress mechanism and sympathetic stimulation.[10] These support the hypothesis of inflammatory factor over-expression induces hyperglycemia.

Another mechanism of high blood sugar level was related to stress-induced. Zhou et al[6] and Yan Zhang et al[17] in their studies showed that high cortisol levels induced by stress resulting in hyperglycemia by activating enzymes thatare involved in the gluconeo-genesis process in the liver and inhibiting glucose uptake in peripheral tissues, such as the skeletal muscle. Glucocorticoid therapy in severe or critical COVID-19 patients may induce hyperglycemia by a similar mechanism as stress-induced. However, glucocorticoid therapy is still used in many health facilities to manage inflammation in COVID-19 patients.

Hyperglycemia could disrupt the defensive capacity of airway epithelial. Furthermore, it will induce oxidative stress production. A high level of oxidative stress and the reduction of heparan sulfate induced by hyperglycemia may result in thrombosis.[9,12] Elevation of glucose concentration in the respiratory tract may result in local inflammation and worsen the patient condition. Hyperglycemia in a diabetic patient may impair pulmonary function by decreasing vital capacity and forced expiratory volume in one second (FEV1) due to microangiopathy development.[8,12] The immune system may also be harmed mainly innate immunity, hence the risk of being infected is increased in line hyperglycemia condition. Matrix metalloproteinases gene expression can be escalated in hyperglycemia condition resulting in more extensive spreading of the inflammation. In hypoxemic and hyperglycemic conditions, in order to obtain adenosine triphosphate (ATP), anaerobic glycolysis must occur. As a consequence, lactate and LDH levels will increase. High lactate and LDH level were associated with high mortality in COVID-19 patients.[8]

Mortality and Morbidity in Hyperglycemia Induced by COVID-19

Hyperglycemia was an independent risk factor to critical condition and death in many infectious diseases, such as SARS and COVID-19.[18] Dysregulation of the immune system associated with hyperglycemia may contribute to high infection susceptibility and disease severity.[19] CT scansofa patient with high fasting blood glucose showed more abnormalities rather than normoglycemic patients.[8] Length of stay (LOS) was found to be slightly longer in patients with blood sugar level > 180 mg/dl than in patients with blood sugar level 140-180 mg/dl and< 140 mg/dl, i.e. 12 days, 11.5 days, and 11.1 days, respectively (p<0.011).[13]

The mortality rate of COVID-19 patients with hyperglycemia was found to be high. A study by Carrasco et al[13] showed higher mortality rate in patient with blood sugar level on admission >180 mg/dl (41.1%) than patient with blood sugar level on admission 140-180 mg/dl (33.0%) and <140 mg/dl (15.71%). Yang et al reported that death within 28 days in COVID-19 patients was associated with a high level

of fasting blood sugar. There were 27.4% subjects with fasting blood sugar levels around 7.0-11.1 mmol/L and 21.3% subjects ≥ 11,1 mmol/L.[16] Moreover, the blood sugar level is also an independent factor of any inpatient death cause. This showed that there was a correlation between uncontrolled hyperglycemia with high mortality rate.[20]

A study by Zhang et al[12] showed that liver function impairment, elevation of LDH and IL-8 ratio were found more in COVID-19 patients with hyperglycemia without prior diabetes. Moreover, ahyperglycemic condition in non-diabetic patients may aggravate the symptom of COVID-19 by increasing proinflammatory cytokines, such as interferon alpha (IFN-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), monocyte chemo-attractant protein 1 (MCP1), interferon-γ-inducible protein 10 (IP-10), oxidative stresses, as well as disrupting inflammatory and anti-inflammatory cytokines balance.[16] As many as 20.6% of subjects with COVID-19, hyperglycemic conditions, and no diabetes history were having severe symptoms and high mortality rate as showed in a study by Mamtani et al,[5] while a study by Coppelli et al[14] was 24%and Zhou et al[6] was 27.5%.

Diabetes is a common comorbid disease in COVID-19 patients and linked to severity of the symptom. Chronic inflammation and dysfunction of immune system may happen progressively in diabetic patients showed by the presence of abnormal T cell, hence cytokine storm occurs faster.[12] Immune paralysis, or the inability of the immune response to recover despite clearance of pathogens by antimicrobials taking a major part in COVID-19 patients with diabetes and associated with high mortality rate.[17] Another study showed that deaths in hospital caused by COVID-19 were found to be higher in patient with diabetes than in patient without any comorbidities.[21] Mortality rate in COVID-19 patients with diabetes caused by hyper-glycemic condition was 21.3%, higher than control group which was only 9.5%.[12] Hyperglycemia in diabetes also linked to higher chance for patients to acquire acute respiratory distress syndrome (ARDS) (58%), acute cardiac injury events (38.7%), shock (40.3%), secondary infection (43.5%), and acute kidney injury (AKI) (16.1%) than patients without diabetes (p<0.05).[20]

Patient with new-onset hyperglycemia, such as stress hyperglycemia and undiagnosed diabetes, had higher mortality rate in hospital than patient with history of diabetes or normoglycemia as shown in a study by Cakir et al.[22] This condition is linked to more gluconeogenesis and less glycogenolysis caused by the increase of counterregulatory hormone secretion. An autopsy of COVID-19 patient found Langerhans cell degeneration supports the statement.[20] Acute hyper-glycemia occured in 22% of confirmed COVID-19 patients in hospital and 18.9% of them have been diagnosed with diabetes.[20] Another study showed 50% confirmed COVID-19 patients had hyperglycemia and only 7% of them had diabetes history.[23]

Hyperglycemia may worsen the severity of COVID-19 and cause critical condition in patients.[24] Study by Zhang et al[17] showed significant increment of patient risk having worse condition, for example mechanical ventilation usage, intensive care unit (ICU) admission, and death in group of patients with COVID-19 and hyperglycemia without history of diabetes (fasting blood sugar level ≥7.0 mmol/L, yet HbA1c level <6.5%) than in group of normoglycemic patients (OR 5.47; confidence interval 95% (CI), 1.51-19.82; p = 0.010). Hyperglycemia increase the mortality risk in COVID-19 patients three times greater than normo-glycemic patient (OR 2.822, 95% CI = 1.587-5.019, p<0.001).[16] Sardu et al[25] also showed 71% relative increase of mortality in group of patient with severe COVID-19 and hyperglycemia on admission (new-onset hyperglycemia without history of diabetes; plasma blood sugar level >7.77 mmol/L or 140 mg/dl) than in group of normoglycemic or non-diabetes patient, within 18 days. Thus, insulin therapy in hyperglycemic patient has been proved to decrease the severity of COVID-19 than no insulin therapy.

Yang et al[16] reported significant raise of emerging complication during 28 days of hospital stays (OR 2.61; 95% CI = 1.64-4.41) in group of patients with COVID-19 and hyperglycemia without diabetes (blood sugar level 6.1-6.9 mmol/L) compared to normoglycemic patients. Meanwhile, Li et al[23] showed increment of death caused by COVID-19 in a group of hyperglycemic patients without diabetes (fasting blood sugar level 5.6-6.9 mmol/L or HbA1c level 5.7 – 6.4%) compared to normoglycemic patients (fasting blood sugar level <5.6 mmol/L and HbA1c <5.7%) (HR 3.29; 95% CI=0.65-16.6). Coppelli et al[14] stated that mortality was found to be significantly higher in a group of COVID-19 patients with hyperglycemia and no diabetes history (defined as no history of diabetes and blood sugar level

≥7.78 mmol/L on admission) compared to group of normoglycemic patients (blood glucose level <7.78 mmol/L on admission) (39.4% vs 16.8%, respectively; HR 2.20; 95% CI = 1.27-3.81; p = 0.005) on 17 days observation.

The number of diabetic COVID-19 patients having high fasting blood sugar was found to be greater than non-diabetic patient, 82.3% versus 38.3%. This study also showed that diabetes patients had blood sugar levels in the range of 8.49-19.09 mmol/L, while patients without diabetes in the range of 5.67-7.95 mmol/L. Another parameter was used to compare COVID-19 patient with diabetes and without diabetes, for example differential white blood cell count, D-dimer level, albumin level, inflammatory markers (hsCRP, procalcitonin, ferritin, IL-2R, IL-6, and TNF-α). In patients with diabetes, absolute neutrophil count was higher compared to lymphocyte count, D-dimer and inflammatory markers level increased, and albumin level was lower than patients without diabetes.[23]

Hyperglycemia also can be found in COVID-19 patients during the hospital stay, even in patients without history of diabetes.[10] Hyperglycemia in non-diabetic patients may worsen the prognosis of COVID-19. The median of blood sugar level was observed to be high in patients whose condition was critical. (OR 2.39; 95% CI = 1.41-4.07, p = 0.001).[13] Compared to hyperglycemic patients with diabetes, hyperglycemic patients without diabetes history had significantly higher mortality rate. In a study by Bode et al[24] showed that mortality rate was found to be very high in non-diabetic patients with uncontrolled hyperglycemia (41.7%) compared to diabetic patients (14.8%) (p<0.001). This finding is supported by study from Carrasco et al that showed mortality rate in non-diabetic COVID-19 patients with blood sugar level >180 mg/dl on admission was 43.3%.[13]

A study by Zhang et al[12] evaluated the association between hyperglycemia in confirmed COVID-19 patients with diabetes and without diabetes. The study divided subjects to three group: control group or first group (patients had no diabetes history and the fasting blood glucose level was <126 mg/dl), secondary hyperglycemia or second group (patients had no diabetes history and the HbA1c level <6.5%, but the fasting blood glucose level was ≥126 mg/dl), and diabetes group or third group (patients had diabetes history, the HbA1c level ≥6.5%, and the fasting blood sugar level was ≥126 mg/dl). Mortality rate of second and third group were significantly higher than the first group (21.3%, 14.3%, dan 9.5%, repectively; p<0.05). After the confounding factors were controlled, the odd ratio between the second group and third group versus first group were 5.47 (95% CI = 1.56-19.82) and 2.61 (95% CI = 0.86-7.88), respectively. This data showed that hyperglycemia is associated with bad prognosis and high mortality rate in COVID-19 patients.

It has been mentioned that hyperglycemia in COVID-19 leads to a more severe prognosis (intensivecare unit care necessity, mechanical ventilation usage, and hemo dynamic instability) and a higher mortality rate either patients have diabetes or not. In otherwords, blood glucose level can be used as a predictor for COVID-19 patients outcome.[12,13] Hyperglycemia also has been used as an independent factor to predict these verity of viral infection, such as influenza A (H1N1) in 2009, MERS-CoV, and SARS-CoV.[18,26,27] Based on Mamtani et al[5] study, random blood glucose level ≥10 mmol/L in more than two tests or fasting blood glucose level ≥7 mmol/L in COVID-19 patients lead to a worse prognosis. While another study by Liu et al[4] showed more severe COVID-19 conditions were found in patients with fasting blood glucose levels ≥ 6.50 mmol/L. For every 2 mmol/L or 36 mg/dl the fasting blood glucose rises, the outcome will be more severe.[28]

Blood sugar levels may fluctuate at different times. A study by Yang et al [16] showed that sample collection time affects the level of blood sugar. Blood glucose level test on admission could predict the mortality rate in COVID-19 patients, higher blood glucose level resulting in higher mortality risks. The controlled blood glucose levels in hyperglycemic COVID-19 patients either with or without a history of diabetes showed a decrease in mortality and severity. We recommend that every healthcare facility test blood glucose levels periodically for COVID-19 patients on admission and during the hospital stay. The earlier it is detected, the earlier patients are treated. As a consequence, a better outcome in COVID-19 patients.

Conclusion

Hyperglycemia is associated with COVID-19 either in diabetic or non-diabetic patients and it increases the severity in both conditions. Therefore, blood sugar level could predict the outcome of COVID-19 patient.

Blood sugar level tests, especially fasting blood sugar levels and random blood sugar levels can be used to detect hyperglycemia as an indicator for COVID-19 severity. Monitoring on blood sugar level should be done periodically on COVID-19 patients despite the symptoms are absent or not severe. Early detection of hyperglycemia leads clinicians to the early and right management for the patients. As a result, the mortality rate due to COVID-19 decreases. We suggest periodic blood sugar tests as screening for hyperglycemia in hospitalized COVID-19 patients since COVID-19 can induce hyperglycemia in both diabetic patients and non-diabetic patients.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. 2020. Available from: https://covid19.who.int
2. Briefing AS, Shira D. COVID-19 Vaccine Roll Outs in ASEAN & Asia–Live Updates by Country. Retrieved on May. 2021. Available from: https://www.aseanbriefing.com
3. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet. 2020;396(10247):320-32. doi:10.1016/S0140-6736(20)31305-2
4. Liu SP, Zhang Q, Wang W, Zhang M, Liu C, Xiao X, et al. Hyperglycemia is a strong predictor of poor prognosis in COVID-19. Diabetes Res Clin Pract. 2020;167:108338. doi:10.1016/j.diabres.2020.108338
5. Mamtani M, Athavale AM, Abraham M, Vernik J, Amarah AR, Ruiz JP, et al. Association of hyperglycaemia with hospital mortality in nondiabetic COVID-19 patients: A cohort study. Diabetes Metab. 2021;47(3):101254. doi:10.1016/j.diabet.2021.101254
6. Zhou W, Ye S, Wang W, Li S, Hu Q. Clinical features of COVID-19 patients with diabetes and secondary hyperglycemia. J Diabetes Res. 2020;2020:3918723. doi:10.1155/2020/3918723
7. Singh AK, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract. 2020;167:108382. doi:10.1016/j.diabres.2020.108382
8. Sachdeva S, Desai R, Gupta U, Prakash A, Jain A, Aggarwal A. Admission hyperglycemia in non-diabetics predicts mortality and disease severity in COVID-19: a pooled analysis and meta-summary of literature. SN Compr Clin Med. 2020;2:2161-6. doi:10.1007/s42399-020-00575-8
9. Lee MH, Wong C, Ng CH, Yuen DC, Lim AY, Khoo CM. Effects of hyperglycaemia on complications of COVID-19: a meta-analysis of observational studies. Diabetes Obes Metab. 2021;23(1):287-9. doi:10.1111/dom.14184
10. Wu J, Huang J, Zhu G, Wang Q, Lv Q, Huang Y, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Res Care. 2020;8(1):e001476. doi:10.1136/bmjdrc-2020-001476
11. Zhu B, Jin S, Wu L, Hu C, Wang Z, Bu L, et al. J-shaped association between fasting blood glucose levels and COVID-19 severity in patients without diabetes. Diabetes Res Clin Pract. 2020;168:108381. doi:10.1016/j.diabres.2020.108381
12. Zhang Y, Li H, Zhang J, Cao Y, Zhao X, Yu N, et al. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: a single-centre, retrospective, observational study in Wuhan. Diabetes Obes Metab. 2020;22(8):1443-54. doi:10.1111/dom.14086
13. Carrasco-Sánchez FJ, Lypez-Carmona MD, Martínez-Marcos FJ, Pérez-Belmonte LM, Hidalgo-Jiménez A, Buonaiuto V, et al. Admission hyperglycaemia as a predictor of mortality in patients hospitalized with COVID-19 regardless of diabetes status: data from the Spanish SEMI-COVID-19 Registry. Ann Med. 2021;53(1):103-16. doi:10.1080/07853890.2020.1836566
14. Coppelli A, Giannarelli R, Aragona M, Penno G, Falcone M, Tiseo G, et al. Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: the Pisa COVID-19 study. Diabetes Care. 2020;43(10):2345-8. doi:10.2337/dc20-1380
15. Van der Looven R, Pitt M. Response to the "letter to editor": Critical appraisal of systematic review. Muscle Nerve. 2020;62(4):E72-3. doi:10.1002/mus.27012
16. Yang P, Wang N, Wang J, Luo A, Gao F, Tu Y. Admission fasting plasma glucose is an independent risk factor for 28-day mortality in patients with COVID-19. J Med Virol. 2021;93(4):2168-76. doi:10.1002/jmv.26608
17. Zhang Y, Cui Y, Shen M, Zhang J, Liu B, Dai M, et al. Association of diabetes mellitus with disease severity and prognosis in COVID-19: a retrospective cohort study. Diabetes Res Clin Pract. 2020;165:108227. doi:10.1016/j.diabres.2020.108227
18. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med. 2006;23(6):623-8. doi:10.1111/j.1464-5491.2006.01861.x
19. Hodgson K, Morris J, Bridson T, Govan B, Rush C, Ketheesan N. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. Immunology. 2015;144(2):171-85. doi:10.1111/imm.12394
20. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81. doi:10.1016/S2213-2600(20)30079-5
21. Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. Diabetes Care. 2020;43(7):1382-91. doi:10.2337/dc20-0598
22. Cakir M, Altunbas H, Karayalcin U. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2003;88(3):1402-5. doi:10.1210/jc.2002-021718
23. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-8. doi:10.1016/j.jaci.2020.04.006
24. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol. 2020;14(4):813-21. doi:10.1177/1932296820924469
25. Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control?. Diabetes Care. 2020;43(7):1408-15. doi:10.2337/dc20-0723
26. Banik GR, Alqahtani AS, Booy R, Rashid H. Risk factors for severity and mortality in patients with MERS-CoV: analysis of publicly available data from Saudi Arabia. Virol. Sin. 2016;31(1):81-4. doi:10.1007/s12250-015-3679-z
27. Schoen K, Horvat N, Guerreiro NF, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infect Dis. 2019;19(1):964. doi:10.1186/s12879-019-4592-0
28. Fadini GP, Morieri ML, Boscari F, Fioretto P, Maran A, Busetto L, et al. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. Diabetes Res Clin Pract. 2020;168:108374. doi:10.1016/j.diabres.2020.108374