

Relationship Between Initial Glucose Levels And D-Dimer in Covid-19 Patients with Diabetes Mellitus at Dr. Soetomo General Hospital

Luthfiah Firdaus Maheswari¹, Soebagijo Adi Soelistijo², Aryati³

¹Medical Program, Faculty of Medicine, Airlangga University, Indonesia

² Department of Internal Medicine, Dr. Soetomo General Academic Hospital,
Faculty of Medicine Airlangga University

³Departemen of Clinical Pathology, Dr. Soetomo General Academic Hospital,
Faculty of Medicine Airlangga University

Corresponding Author: soebagijo.adi.s@fk.unair.ac.id

ABSTRACT

Background: The importance of people with diabetes mellitus controlling blood glucose levels when infected with COVID-19 is because there is experimental evidence that the effect of diabetes on COVID-19 facilitates the entry of the virus into cells and the inflammatory response occurs in infection. Coagulation disorders occur in COVID-19 patients with DM regardless of the degree of severity at admission. **Objective:** This study aims to determine the relationship between initial glucose levels and coagulation dysfunction in COVID-19 patients with diabetes mellitus at Dr. Soetomo General Hospital. **Method:** This research is an analytic observational study with a cross-sectional approach. Sampling used consecutive sampling technique with a correlation coefficient formula which resulted in a minimum number of subjects of 17 patients, then analyzed using the Spearman's Rho test. Demographic data for the study were obtained from the Medical Records of inpatients with COVID-19 infection with DM at Dr. Soetomo General Hospital for the 2021 period which meets the inclusion and exclusion criteria. **Results:** A total of 22 patients participated in this study, the dominant subjects were male (54.5%), aged 20-60 years (68.2%), had high glucose levels ≥ 200 mg/dL (86.4%) and moderate d-dimer levels of 500-2800 ng/mL (68.2%), while high ratios > 2800 ng/mL (31.8%) and with comorbid hypertension, malignancy, cardiovascular disease, and obesity (86.4%). The results of statistical analysis of initial glucose levels with coagulation dysfunction obtained a significance value (p) of 0.760 ($p > 0.05$). **Conclusion:** There is no significant relationship between initial glucose levels and d-dimer.

Keywords: COVID-19, Diabetes mellitus, Initial glucose level, D-dimer.

INTRODUCTION

Diabetes mellitus is a metabolic disorder that occurs in the pancreas which is characterized by increased blood sugar or hyperglycemia that occurs due to a decrease in the amount of insulin from the pancreas. Corona viruses are large positive single-stranded RNA viruses that can make the transition from animals to humans and infect humans and a variety of animals (Velevan & Meyer, 2020). COVID-19 is a disease caused by the coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome), including a highly contagious disease and currently affecting more than 200 countries around the world. According to Erenner (2020), more and more studies are showing that diabetes mellitus is an important risk factor that affects the clinical severity and infection of COVID-19. Diabetes mellitus is also associated with an increased risk of severe infection and higher mortality in patients with COVID-19 infection (Shang et al., 2020). COVID-19 will make blood glucose control difficult for people with DM, as a result diabetes appears to be a risk factor that can exacerbate serious clinical events caused by COVID-19 (Pal & Bhadada, 2020., Bouhanick et al., 2020). The relationship between diabetes mellitus and COVID-19

is based on the mechanism of chronic systemic inflammation, increased coagulation activity, impaired immune response, and potential damage to the pancreas by SARS-CoV-2 (Hussain et al., 2020). According to Erenur (2020) the increased risk of morbidity and mortality can be caused by changes in the expression of ACE2 receptors, dysregulation of the number and activity of immune cells, endothelial dysfunction,

Several studies have shown that cardiovascular disease and diabetes mellitus are common diseases among COVID-19 patients treated in the ICU (Lim et al, 2021). According to KOMINFO JATIM (2020) put forward by dr. Kohar as the head of the COVID-19 taskforce tracing team in East Java, from patients who died from COVID-19 infection, 18 percent, a total of 22 patients died with the most comorbid or comorbid diseases, such as diabetes mellitus, heart disease, hypertension, DHF, obesity, bronchitis, to asthma. Data from the Surabaya Health Office (2020) shows that the most cases of death in patients who were confirmed positive for COVID-19 in Surabaya were diabetes mellitus, with 251 cases identified. People with diabetes mellitus generally have impaired innate and adaptive immune responses, characterized by a state of low-grade chronic arousal, which can cause sudden systemic metabolic changes, characterized by higher levels of leptin (proinflammatory adipokines) and lower levels of adiponectin (anti-inflammatory adipokines). Of the 70,000 cases of people infected with COVID-19, the Chinese Center for Disease Control and Prevention reported that an increase in mortality in individuals with diabetes increased from 2.3% in the general population to 7.3% in people with diabetes mellitus (Abu Farha et al, 2020). Coagulation disorders and acute inflammation occur in almost all cases of COVID-19 with diabetes mellitus (Minuljo et al., 2020). according to the Chinese Center for Disease Control and Prevention reported that the increase in mortality in individuals with diabetes, increased from 2.3% in the general population to 7.3% in people with diabetes mellitus (Abu Farha et al, 2020). Coagulation disorders and acute inflammation occur in almost all cases of COVID-19 with diabetes mellitus (Minuljo et al., 2020). according to the Chinese Center for Disease Control and Prevention reported that the increase in mortality in individuals with diabetes, increased from 2.3% in the general population to 7.3% in people with diabetes mellitus (Abu Farha et al, 2020). Coagulation disorders and acute inflammation occur in almost all cases of COVID-19 with diabetes mellitus (Minuljo et al., 2020).

The increase in diabetes mellitus sufferers to control blood glucose levels when infected with COVID-19 is because there is experimental evidence that the effect of diabetes on COVID-19 facilitates the entry of the virus into cells and the inflammatory response to infection (Singh et al., 2020). In patients with COVID-19 who are in critical condition, it is caused by an increase in inflammatory parameters such as d-dimer levels and prolonged coagulation (Romadhon, et al., 2022). According to Minuljo et al. (2020) that coagulation disorders occur in COVID-19 patients with DM regardless of the degree of severity of symptoms upon admission. The average d-dimer level in the patient group with COVID-19 at Dr. Kariadi who died appeared to be much higher than living patients (Minuljo et al., 2020).

Based on the description of the analysis above, it is necessary to conduct research on the relationship between initial glucose levels and coagulation dysfunction in COVID-19 patients by analyzing data on patients with COVID-19 and diabetes mellitus at Dr. Soetomo General Hospital Surabaya.

MATERIALS & METHODS

Type and Design of Research

The type of research design used is analytic observational. Analytical observational is a survey or research that explores how and why this health phenomenon occurs. Then analyze the dynamics of the correlation between phenomena or between risk factors and effect factors (Natoatmodjo, 2012).

This study used a survey research design with a cross-sectional approach, in which each subject was only observed once and measurements were taken together (Natoatmodjo, 2012). This study used secondary data in the form of medical records at Dr. Soetomo General Hospital.

Population and Research Sample

Research Population

The population studied in this study were inpatients with diabetes mellitus with COVID-19 infection at Dr. Soetomo General Hospital period 2021..

Research Sample

The sample is the object under study and is considered to represent the entire population (Notoatmojo, 2012). The sample of this study was data on inpatients with COVID-19 infection with several criteria, namely adult patients who had a history of DM and had comorbidities such as hypertension, malignancies, heart disease, and obesity at Dr. Soetomo General Hospital.

Research Technique

In this study the sampling technique used consecutive sampling technique, namely the samples taken were all observed subjects and met the sample selection criteria which were then included in the sample until the required sample size was met (Sastroasmoro and Ismael, 2008). In this study, sample data was collected by selecting the RM of inpatient DM patients who were infected with COVID-19 at Dr. Soetomo General Hospital for the 2021 period which fits the inclusion criteria in the study.

Inclusion and Exclusion

a. Inclusion criteria

1. Willing to become a research subject by signing an informed consent sheet
2. 60-70 years old
3. Is a person with hypertension
4. Have good hearing and are able to speak Indonesian

b. Exclusion criteria

1. Have a history of severe head trauma
2. Have a history of or are suffering from brain tumors
3. Have a history of or are suffering from CNS infections and/or HIV/AIDS, such as neurocysticercosis (NCC) and HIV-Associated Neurocognitive Disorder (HAND)
4. Have metabolic and hormonal disorders, such as DM, hypoglycemia, and Cushing's syndrome
5. Have been diagnosed with another neurodegenerative disease
6. Have been diagnosed with a mental disorder or psychological problem
7. Taking drugs that affect cognitive function, such as psychotropic substances (codeine, pethidine/meperidine) and glucocorticoids

Sample Size

The sample size in this study was calculated using the correlation coefficient analysis formula (Dahlan, 2011):

$$n = \left\{ \frac{Z\alpha + Z\beta}{0,5 \ln \left[\frac{(1+r)}{(1-r)} \right]} \right\}^2 + 3$$

$$= \left\{ \frac{1,96+1,28}{0,5 \ln [(1+0,64)/(1-0,64)]} \right\}^2 + 3$$

$$= 17$$

Where:

- n = sample size
 $Z\alpha$ = Normal default value based on $\alpha = 0.05 \rightarrow Z\alpha = 1.96$
 $Z\beta$ = Normal default value based on $\beta = 0.15 \rightarrow Z\beta = 1.28$
r = Estimated correlation coefficient

Based on the calculation of the sample size from the correlation analysis formula above, it produces a minimum sample size of 17 samples.

RESULTS

Research Overview

This research was conducted from December 2022 to March 2023 starting from licensing to data collection. Data collection was carried out by taking secondary data in the form of medical records of patients with COVID-19 with diabetes mellitus at Dr. Soetomo General Hospital in 2021. The number of medical records that have been taken is 22 medical records. All research data were analyzed using the IBM SPSS version 26 application.

Characteristics of Research Subjects

The characteristics of the study subjects included gender, patient age, initial glucose levels, d-dimer levels, and comorbidities experienced by the patients. Univariate analysis was performed using frequency analysis on IBM SPSS version 26.

Gender of COVID-19 sufferers with DM at Dr. Soetomo General Hospital as Frequency Distribution

Table 1 Gender of COVID-19 sufferers with DM at Dr. Soetomo General Hospital as Frequency

Gender	Distribution	
	Frequency	Percentage(%)
Woman	10	45.5%
Man	12	54.5%
Total	22	100%

Age of COVID-19 Sufferers with DM at Dr. Soetomo General Hospital as Frequency Distribution

Table 2 Age of COVID-19 Sufferers with DM at Dr. Soetomo General Hospital as Frequency

Age	Distribution	
	Frequency	Percentage(%)
20-60	15	68,2
>60	7	31.8
Total	22	100

Initial Glucose Levels of COVID-19 Patients with DM at Dr. Soetomo General Hospital as Frequency Distribution

Table 3 Initial Glucose Levels of COVID-19 Patients with DM at Dr. Soetomo General Hospital as Frequency Distribution

Initial Glucose Levels	Frequency	Percentage(%)
≤200 mg/dL	3	13,6
≥200 mg/dL	19	86.4
Total	22	100

D-Dimer Levels of COVID-19 Patients with DM at Dr. Soetomo General Hospital as Frequency Distribution

Table 4 D-Dimer Levels of COVID-19 Patients with DM at Dr. Soetomo General Hospital as Frequency Distribution

D-Dimer levels	Frequency	Percentage(%)
Low <500 ng/mL	0	0
Medium 500-2800ng/mL	15	68,2
High >2800 ng/mL	7	31.8
Total	22	100

Comorbidities of COVID-19 Patients with DM at Dr. Soetomo General Hospital as Frequency Distribution

Table 5 Comorbidities of COVID-19 Patients with DM at Dr. Soetomo General Hospital as Frequency Distribution

Comorbidity	Frequency	Percentage(%)
No Comorbid	3	13,6
With Comorbid (Hypertension, malignancy, cardiovascular disease, and obesity)	19	86.4
Total	22	100

Relationship Between Initial Glucose Levels and D-dimer in COVID-19 Patients with Diabetes Mellitus at Dr. Soetomo General Hospital

Initial Glucose Level Normality Test

Table 6 Initial Glucose Level Normality Test

<i>Shapiro Wilk</i>				
Initial Glucose Levels		Statistics	df	Sig.
	≤200 mg/dL	0.896	4	0.413
	≥200 mg/dL	0.904	18	0.66

In the Shapiro Wilk normality test table above, the results of a significance value (p) of ≤200 mg/dL were 0.413 and ≥200 mg/dL were 0.66 which means greater than 0.05. It can be interpreted that the normality test on initial glucose levels can be said to be a normal distribution.

Test for Normality of D-dimer Levels

Table 7 Test for Normality of D-dimer Levels

<i>Shapiro Wilk</i>				
D-dimer levels		Statistics	df	Sig.
	Low <500 ng/mL	0	0	0.00
	Medium 500-2800ng/mL	0.840	15	0.013
	High >2800 ng/mL	0.779	7	0.025

In the Shapiro Wilk normality test table above, the distribution results are not normal because the significance value (p) is 0.00, which means less than 0.05.

Spearman's Rho Correlation Test on Initial Glucose Levels and D-dimer Levels

In this study, the results of the normality test on initial glucose levels were normal distribution, while there were d-dimer levels, the results of the distribution were not normal. If one of the normality tests results in an abnormal distribution, then a bivariate analysis of the Spearman's Rho correlation test is performed.

The bivariate analysis carried out in this study was to look for a relationship between initial glucose levels and d-dimer in COVID-19 sufferers and DM.

Table 8 Relationship of Initial Glucose Levels with D-dimer

		Initial Glucose Levels	D-Dimer levels
Spearman's rho	Correlation Coefficient	1000	0.069

Initial Glucose Levels	Sig. (2-tailed)		0.760
	N	22	22
D-Dimer levels	Correlation Coefficient	0.069	1000
	Sig. (2-tailed)	0.760	
	N	22	22

*Correlation is significant at the 0.05 level (2-tailed)

The table above describes the relationship between initial glucose levels and d-dimer levels in COVID-19 patients with DM as assessed using a bivariate statistical test with Spearman's Rho. The statistical test results with Spearman's Rho give a p-value of 0.760. This value is more than 0.05 which indicates that there is no correlation between initial glucose levels and d-dimer levels in patients with COVID-19 and DM. Meanwhile, the Spearman correlation coefficient was 0.069 which showed a positive correlation, which meant that the initial glucose levels and d-dimer levels had a unidirectional relationship.

Measurement Results on Initial Glucose and D-dimer Levels in COVID-19 Patients with DM at Dr. Soetomo General Hospital

Table 9 Mean Value at Initial Glucose Level and Median at D-dimer Level

Variable	Means	Median
Initial Glucose Levels	311,32	278.50
D-Dimer levels	2412.59	1120

General Characteristics of the Research Sample

The data in this study were taken from secondary data in the form of medical records of inpatients with COVID-19 with diabetes mellitus at Dr. Soetomo General Hospital Surabaya. Secondary data was collected from 22 medical records that met the inclusion and exclusion criteria used in this study, from a minimum sample size of 17 subjects. Then the data was processed using IBM SPSS version 26. The number of samples used was different from the study by Shang, et al. (2021) in China using 584 subjects. The number of samples may vary based on the type of research being conducted, as well as the length of time the research takes. This research has met the minimum amount required based on the points above.

Based on the results of the univariate analysis of this study, the sexes that were more numerous were male (54.5%), namely 12 patients, while the rest were female patients, namely 10 patients (45.5%). This is in line with previous studies regarding the characteristics of COVID-19 which do not infect specifically by gender, but in cases of COVID-10 men have a higher tendency (Guan, et al., 2019).

In this study, it was found that there were 15 patients (68.2%) aged 20-60 years, while 7 patients (31.8%) were elderly patients >60 years. According to Guan, et al. (2019), stated that the characteristics of COVID-19 and DM can infect all age groups, but in this study the median results were obtained from the age of those infected around 20-60 years which includes adults.

The results of this study obtained initial glucose levels in COVID-19 patients with DM ≤ 200 mg/dL in 3 patients (13.6%), while 19 patients (86.4%) had initial glucose levels ≥ 200 mg/dL. This research is in accordance with the research conducted by Cozzi et al. (2020), that the degree of severity of COVID-19 is significantly higher in patients with diabetes than non-diabetics. Blood glucose levels and diabetes mellitus are predictors of the morbidity and mortality of people with COVID-19 (Erlina et al., 2020).

In COVID-19 patients there was damage to the vascular endothelium due to the invasion of the SARS-CoV-2 virus which resulted in hemostatic disorders in the form of coagulopathy and the average

COVID-19 patient experienced an increase in d-dimer levels. According to Yoa, et al. (2020), that the d-dimer level has a relationship with the severity of the disease and as a prognostic marker used in patients being treated for COVID-19. The above research has similarities with this study, which obtained the results of COVID-19 sufferers with DM with d-dimer levels <500 as many (4.5%) as 1 patient, while patients with d-dimer levels >500 as many as 21 patients or 95, 5%.

Comorbid or co-morbidities are aspects that influence the severity of many diseases. Comorbidities in patients with COVID-19 with diabetes mellitus are hypertension, malignancy, cardiovascular disease, and obesity are risk factors that cause patient severity (Jing et al., 2020). In this study, the results were (86.4%) 19 patients with comorbidities and as many as (13.6%) 3 patients without comorbidities. According to Mudatsir et al. (2021) stated that several co-morbidities, including chronic respiratory disease, cardiovascular disease, and hypertension were observed more frequently among patients with severe COVID-19 than those with mild ones. In this study, the measurement results of the mean initial glucose level were 311.32 and the median value of d-dimer levels was 1120 from a total of 22 samples.

Relationship Between Initial Glucose Levels and D-Dimer

In this study, the Shapiro Wilk normality test was carried out on initial glucose levels and d-dimer levels. The normality test on initial glucose levels results in a normal distribution with a sig value. 0.413 in patients with baseline glucose levels ≤ 200 mg/dL and sig 0.066 in patients with baseline glucose levels ≥ 200 mg/dL ($p > 0.05$). From these results it can be interpreted that the initial glucose levels in COVID-19 patients with DM have a normal distribution. While the normality test at moderate ratio d-dimer levels of 500-2800 ng/mL yielded 0.013 ($p < 0.05$) and high ratios > 2800 ng/mL yielded 0.025 ($p < 0.05$) which means the distribution is not normal. If in the Shapiro Wilk normality test on the variables obtained normal and not normal distribution, then Spearman's Rho correlation test is performed.

Based on the results of the Spearman's Rho correlation test, it was found that there was no significant relationship between initial glucose levels and d-dimer (p value = 0.760 (> 0.05)). Meanwhile, the Spearman correlation coefficient was 0.069 which showed a positive correlation, which meant that the initial glucose levels and d-dimer levels had a unidirectional relationship. Overall, it can be concluded that there is no significant relationship between initial glucose levels and d-dimer in COVID-19 patients with diabetes mellitus at Dr. Soetomo General Hospital.

The results of this study are in line with research conducted by Lucky A. (2021) with 20 subjects which stated that the results of bivariate analysis showed initial glucose levels with d-dimer levels obtained $p = 0.734$ (> 0.05) and the correlation value was 0.081, which means it can be concluded that there is no correlation between initial glucose levels and d-dimer levels in COVID-19 patients with DM. This is inversely proportional to the research by Rostami & Hassan (2020) that underlying diseases such as diabetes can trigger an increase in d-dimer levels in people with COVID-19.

Research Limitations

1. There is a high difference in d-dimer levels in diabetes mellitus patients with COVID-19 and non-COVID-19.
2. The types of COVID-19 in the 2021 period varied, whereas the medical record data did not mention the type of COVID-19 the patient had.
3. There is no information on the time of measurement of initial blood glucose levels and d-dimer.
4. There are confounding factors such as comorbidities in patients, making it difficult to identify the effect of comorbidities such as hypertension, malignancy, cardiovascular disease and obesity on the severity of COVID-19 patients with diabetes mellitus.

CONCLUSION

Based on the research objectives and results, these conclusions are as follows.

1. COVID-19 sufferer with DM at Dr. Soetomo General Hospital was found to be the most susceptible to adults aged 20-60 years in 15 patients (68.2%) and the least in older adults > 60 years in 7 patients (31.8%).
2. Initial glucose levels of COVID-19 patients with DM at Dr. Soetomo General Hospital ≤ 200 mg/dL in 3 patients (13.6%), and as many as 19 patients (86.4%) had initial glucose levels ≥ 200 mg/dL.
3. d-dimer levels of COVID-19 with DM at Dr. Soetomo General Hospital with d-dimer levels moderate ratio 500-2800 ng/mL 15 patients (68.2%), while patients with high d-dimer ratio >2800 ng/mL were 7 patients or 31.8%.
4. Initial glucose levels in COVID-19 sufferers with DM at Dr. Soetomo General Hospital has no significant relationship with d-dimer levels.
5. COVID-19 sufferer with DM at Dr. Soetomo General Hospital with comorbidities, such as hypertension, malignancy, cardiovascular disease, and obesity was found mostly (86.4%) in 19 patients, while there were (13.6%) 3 patients without comorbidities.

REFERENCES

- Abu-Farha, M., Al-Mulla, F., Thanaraj, TA, et al. (2020). Impact of Diabetes in Patients Diagnosed With COVID-19. *Frontiers in immunology*, 11, 576818.
- Bouhanick, B., Cracowski, JL, Faillie, JL, et al. (2020). Diabetes and COVID-19. *Therapy*, 75(4), 327–333.
- Cozzi D, Albanesi M., Cavigli E., Moroni C., et al., (2020). Chest X-ray in new Coronavirus Disease 2019 (COVID-19) infection: finding and correlation with clinical outcome. *La radiology medica*. 2020 Aug;125:730-7
- Dahlan, MS (2011). *Statistics for Medicine and Health*, 5th edition. ed. Salemba Medica, Jakarta
- Erener S. (2020). Diabetes, infection risk and COVID-19. *Molecular metabolism*, 39, 101044.
- Erlina B., Agus DS., Sally AN., et al (2020). Covid-19 Management Protocol. PDPI, PERKI, PAPDI, PERD ATIN. IDAI. 2020;2-3
- Hussain, A., Bhowmik, B., and do Vale Moreira, NC (2020). COVID-19 and diabetes: Knowledge in progress. *Diabetes research and clinical practice*, 162, 108142.
- Lim, S., Bae, JH, Kwon, HS, & Nauck, MA (2021). COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nature reviews. Endocrinology*, 17(1), 11–30.
- Mudatsir M, Fajar JK, Wulandari L, Soegiarto G, Ilmawan M, Purnamasari Y, et al. (2021) Predictors of COVID-19 severity: a systematic review and meta-analysis. 2021;9:1–26.
- Notoatmodjo. (2012). *Health Research Methods*. Jakarta: Rineka Cipta
- Pal R and Bhadada SK. (2020). COVID-19 and non-communicable diseases. *Postgrad Med J*. 2020 Jul;96(1137):429-430. doi: 10.1136/postgradmedj-2020-137742. Epub 2020 Mar 30. PMID: 32234837.
- Shang, J., Wang, Q., Zhang, H., et al.. (2021). The Relationship Between Diabetes Mellitus and Covid-19 Prognosis: A Retrospective Cohort Study in Wuhan, China. *The American Journal of Medicine*, 134(1), e6–e14. <https://doi.org/10.1016/j.amjmed.2020.05.033>.
- Singh AK, R. Gupta, A. Misra, and A. Ghosh. (2020). "Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations,". *Diabetes & Metabolic Syndrome*, vol. 14, no. 4, pp. 303-310.
- Velavan, TP, and Meyer, CG (2020). The COVID-19 epidemic. *Tropical medicine & international health : TM & IH*, 25(3), 278–280.
- Yao Y, Cao J, Wang Q, ShiQ, Liu K, Luo Z, et al. (2020). D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case. control study. *J Intensive Care* 2020;8:49.
