



# Association Between Blood Glucose Profiles with Severity of Covid-19 and Type 2 Diabetes Mellitus Patients

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## ABSTRACT

**Background:** Individuals with diabetes mellitus (DM), hypertension, and severe obesity (BMI > 40 kg/m<sup>2</sup>) are more likely to be infected and are at a higher risk for complications and death from COVID-19. The purpose of the study was to evaluate the association between blood glucose profile with severity of Covid-19 and T2DM patients.

**Method:** The study was conducted from June 2021 – September 2021 in the isolation inpatient room of RSUP. H. Adam Malik Medan and the research samples were all new patients diagnosed with COVID-19 with T2DM comorbidity. The inclusion criteria were all patients aged ≥18 years, COVID-19 group: moderate, severe, and critical degrees, with comorbid T2DM. HOMA-IR was calculated based on fasting plasma insulin and fasting plasma glucose.

**Results:** There are significant differences in fasting insulin levels and insulin resistance (HOMA-IR) based on the severity of Covid-19 infection. There are significant differences in fasting plasma insulin and HOMA-IR between medium degree vs critical degree, and severe degree vs critical degree ( $p < 0.01$ ).

**Conclusion:** There is a significant association between Covid-19 severity with insulin resistance (HOMA-IR) in T2DM patients, but there isn't a significant association between Covid-19 severity with fasting plasma glucose, postprandial glucose, or HbA1c.

**Keywords:** Blood Glucose Profiles, Covid-19 and T2DM

## ABSTRAK

**Latar Belakang:** Individu dengan diabetes melitus (DM), hipertensi, dan obesitas yang berat (BMI > 40 kg/m<sup>2</sup>) lebih mungkin terinfeksi dan berisiko lebih tinggi mengalami komplikasi dan kematian akibat COVID-19. Tujuan dari penelitian ini adalah untuk mengevaluasi hubungan antara profil glukosa darah dengan keparahan pasien Covid-19 dengan DM tipe 2.

**Metode:** Penelitian dilakukan pada Juni 2021 – September 2021 di ruang isolasi rawat inap RSUP. H. Adam Malik Medan dan sampel penelitian semuanya adalah pasien baru yang didiagnosis dengan COVID-19 dengan komorbiditas T2DM. Kriteria inklusi adalah semua pasien berusia ≥18 tahun, kelompok COVID-19: derajat sedang, berat, dan kritis, dengan T2DM komorbid. HOMA-IR dihitung berdasarkan insulin plasma puasa dan glukosa plasma puasa.

**Hasil:** Ada perbedaan yang signifikan dalam kadar insulin puasa dan resistensi insulin (HOMA-IR) berdasarkan tingkat keparahan infeksi Covid-19. Terdapat perbedaan yang signifikan dalam insulin plasma puasa dan HOMA-IR antara derajat menengah vs derajat kritis, dan derajat berat vs derajat kritis ( $p < 0,01$ ).

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**Kesimpulan:** Ada hubungan yang signifikan antara keparahan Covid-19 dengan resistensi insulin puasa (HOMA-IR) pada pasien Covid-19 dan DM2, tetapi tidak ada hubungan yang signifikan antara keparahan Covid-19 dengan glukosa puasa, glukosa postprandial, atau HbA1c.

**Kata Kunci:** Profil Glukosa Darah, Covid-19 dan T2DM

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## 1 Introduction

Individuals with diabetes mellitus (DM), hypertension, and severe obesity (BMI > 40 kg/m<sup>2</sup>) are more likely to be infected [A3] and are at a higher risk for complications and death from COVID-19.[1,2] Interestingly, there was a similar increased risk for SARS and MERS in individuals with T2DM. Considering the high prevalence of cardiovascular disease (CVD), obesity, and hypertension in patients with DM, it is unknown whether DM independently contributes to this increased risk. However, plasma glucose levels and DM are independent predictors for mortality and morbidity in patients with SARS.[3] Potential mechanisms that may increase the susceptibility for COVID-19 in patients with DM include: 1) higher affinity cellular binding and efficient virus entry, 2) decreased viral clearance, 3) diminished T cell function, 4) increased susceptibility to hyperinflammation and cytokine storm syndrome, and 5) presence of CVD.[4] DM inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes. Impairments in adaptive immunity are characterized by an initial delay in the activation of Th1 cell-mediated immunity and a late hyperinflammatory response is often observed in patients with diabetes.[5] In an elegant study, Kulcsar et al.[6] examined the effects of DM in a humanized mouse model of MERS-CoV infection on a high-fat diet. Following MERS-CoV infection, the disease was more severe and prolonged in diabetic male mice and was characterized by alterations in CD4<sup>+</sup> T cell counts and abnormal cytokine responses (such as elevated IL17a). Consistent with this finding, in patients with COVID-19, peripheral counts of CD4<sup>+</sup> and CD8<sup>+</sup> T cells are low, but with a higher proportion of highly pro-inflammatory Th17 CD4<sup>+</sup> T cells, as well as elevated cytokine levels.[7] Thus, it is likely that patients with DM may have blunted anti-viral IFN responses, and the delayed activation of Th1/Th17 may contribute to accentuated inflammatory responses.

The purpose of the study was to evaluate the association of Covid-19 severity with blood glucose profile in type 2 Diabetes Mellitus patients.

## 2 Method

The study was conducted from June 2021 – September 2021 in the isolated newly inpatient room of RSUP. H. Adam Malik Medan and the research samples were all patients diagnosed with COVID-19 with T2DM comorbidity. The inclusion criteria were all patients aged ≥18 years,

COVID-19 group: moderate, severe, and critical degrees, with comorbid T2DM. Moderate degree: clinical signs of pneumonia (fever, cough, tightness, rapid breathing) without signs of severe pneumonia including  $\text{SpO}_2 > 93\%$  with room air. Severe degree: (dyspnea,  $\text{RR} \geq 30$  times/min at rest, oxygen saturation averages  $\leq 93\%$ , and partial pressure of the oxygen artery ( $\text{PaO}_2$ ) / oxygen concentration ( $\text{FiO}_2$ )  $\leq 300$  mmHg). Critical degree: shock/ ARDS/MOD requiring mechanical ventilation and ICU monitoring. HOMA-IR: fasting plasma insulin (FPI) times fasting plasma glucose (FPG) divided by a constant of 22.5, i.e.  $\text{HOMA-IR} = (\text{FPI} \times \text{FPG})/22.5$  (mmol/L) (Antunes et al., 2016).[8]

### Statistical Analysis

Using SPSS the variables were expressed as means  $\pm$  standard deviation and normality test with Kolmogorov-Smirnov. A Kruskal-Wallis test is used to determine whether or not there is a statistically significant difference between the mean of three or more independent groups. This test is the nonparametric equivalent of the one-way ANOVA and is typically used when the normality assumption. Tukey test is a posthoc analysis, which means that it is used in conjunction with an ANOVA. Values were considered to be statistically significant when  $p < 0.05$ .

## 3 Result

There were 75 T2DM patients with Covid-19 consisting of moderate-degree: 36 patients, severe-degree: 31 patients, and critical-degree 8 patients. In table 1, there are significant differences in fasting insulin levels and insulin resistance (HOMA-IR) based on Covid-19 severity.

Table 1. Differences in Parameters of Blood Glucose Profile based on Covid-19 Severity Parameter

Parameter		Covid-19 Degree			p
		moderate, n=36	severity, n=31	critical, n=8	
Fasting Insulin	uIU/mL	6.3 $\pm$ 6.6	11.2 $\pm$ 8.4	24.5 $\pm$ 21.7	0.001*
FPG	mg/dl	220.4 $\pm$ 110.4	263.5 $\pm$ 109.5	238.0 $\pm$ 49.2	0.255
Homa-IR		3.3 $\pm$ 4.5	7.4 $\pm$ 6.2	14.5 $\pm$ 13.1	0.001*
PPG	mg/dl	296.3 $\pm$ 112.9	295.3 $\pm$ 99.2	241.4 $\pm$ 67.1	0.377
HbA1C	%	9.1 $\pm$ 1.8	9.5 $\pm$ 2.2	9.3 $\pm$ 2.1	0.756

FPG: fasting plasma glucose; PPG: postprandial glucose; HOMA-IR: homeostasis model assessment insulin resistance; \*:  $p < 0.01$

In table 2, there are significant differences in fasting plasma insulin and HOMA-IR between moderate degree vs critical degree, and severe degree vs critical degree.

Table 2. Differential Blood Glucose Profile Between Groups

Parameter		Degree of Covid-19 severity		
		p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
Fasting Insulin	uIU/mL	0.110	0.001*	0.003*
Homa-IR		0.037	0.001*	0.020*

p<sup>1</sup>: moderate degree vs severe degree; p<sup>2</sup>: moderate degree vs critical degree; p<sup>3</sup>: severe degree vs critical degree. HOMA-IR: homeostasis model assessment insulin resistance; \*: p < 0.01

#### 4 Discussion

There is accumulating evidence that diabetes is closely correlated with increased risk of COVID-19, as well as poor outcomes.[9] However, it remains unclear regarding the effect of the severity of COVID-19 on glycemic parameters. Our analyses found that severe COVID-19 infection was significantly associated with increased blood glucose. Meanwhile, we investigated the correlation between severity and HbA1c. However, we did not provide adequate evidence that patients with severe COVID-19 were more likely to have higher HbA1c than those with mild COVID-19. Since viral infection and hyperglycemia adversely affect each other, this study highlights the need to effectively monitor blood glucose to improve prognosis in patients infected with COVID-19. Due to defects in innate immunity affecting phagocytosis, neutrophil chemotaxis, and cell-mediated immunity, individuals with diabetes are more likely to have an infection.[10] Numerous studies have been performed to focus on the association between diabetes and COVID-19. Based on the available data, patients with diabetes are more susceptible to COVID-19 than those without diabetes. However, it is worth noting that infection leads to profound alterations in whole-body metabolism.[11] Sustained inflammation affects systemic glucose homeostasis and contributes to hyperglycemia. Another study found that long-term innate immune activation could impair insulin secretion and action, and play an important role in the pathology of diabetes.[12]

Therefore, we speculated that there may be a strong relationship between the severity of COVID-19 and glycemic parameters, even in those without diabetes. In the present meta-analysis, they found that blood glucose was significantly higher in patients with severe COVID-19 than those with mild COVID-19 (WMD 2.21, 95% CI: 1.30–3.13,  $P < 0.001$ ,  $I^2 = 0\%$ ). A recent study by Zhang et al. reported that COVID-19 infection induced an increase in blood glucose, even among those not diagnosed with diabetes before admission. However, this study did not compare blood glucose between severe and mild COVID-19 patients. Notably, other studies have demonstrated that hyperglycemia is associated with poor prognoses, while better glycemic control is closely associated with improvement in clinical outcomes in COVID-19 patients.[13] Therefore, clinicians should pay more attention to the blood glucose status in patients with COVID-19.

Additionally, our study found that HbA1c was slightly higher in individuals with severe COVID-19 than those with moderate COVID-19, yet this difference did not reach significance ( $P = 0.52$ ). However, it is noteworthy that there were only two studies with a small sample size that explored the influence of severity of COVID-19 on HbA1c, which might affect the outcomes of interest. Moreover, HbA1c reflects the average blood glucose concentration over the past 2–3 months. Therefore, the effect of short-term viral infection on HbA1c levels may not be prominent. Nevertheless, additional research with large sample size is needed to verify our results.[14] Three studies reported blood glucose and HbA1c according to the severity of COVID-19 and were included in this meta-analysis. The combined results showed that severe COVID-19 was associated with higher blood glucose (WMD 2.21, 95% CI: 1.30–3.13,  $P < 0.001$ ). In addition, HbA1c was slightly higher in patients with severe COVID-19 than those with mild COVID-19, yet this difference did not reach significance (WMD 0.29, 95% CI: –0.59 to 1.16,  $P = 0.52$ ). [14]

In this study, the results indicate that there is a significant difference between the HOMA-IR score and COVID-19 severity statistically ( $p$ -value  $< 0.01$ ). (table 2) which is in line with Finucane and Davenport's study in Ireland.[15] However, how IR can affect the COVID-19 degree itself and data regarding the correlation between IR and COVID-19 are still very limited. IR in diabetes mellitus itself will cause chronic inflammation and hyperinsulinemia which in turn leads to pulmonary dysfunction. This shows that IR can be a key facilitator between diabetes mellitus and COVID-19.[16]

## 5 Conclusion

There is a significant association between Covid-19 severity with fasting insulin levels and insulin resistance (HOMA-IR) in T2DM patients, but there isn't a significant association between Covid-19 severity with plasma glucose, postprandial glucose, or HbA1c.

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