Correlation of Insulin Resistance With COVID-19 Severity in Type 2 Diabetes Mellitus Patients

Priska Krinanta Ginting[a], Dharma Lindarto[a], Santi Syafril[a]

[a] gfriska@yahoo.com
[a]Department of Internal Medicine, Medical Faculty, University of North Sumatra, Haji Adam Malik General Hospital, Medan, 20136, Indonesia

Abstract

Insulin resistance (IR) may be a potential key factor for COVID-19 severity but in Indonesia itself, there is no data regarding relationship between insulin resistance and COVID-19 severity, especially those using HOMA IR examination. The aim of this research is to determine correlation between insulin resistance and COVID-19 severity in type 2 Diabetes Mellitus patients. This research was a cross-sectional analytic design with prospective data collection from medical records who were hospitalized in isolation room at Haji Adam Malik Hospital Medan from June 2021 – September 2021 on patients diagnosed with COVID-19 with comorbid diabetes mellitus who met inclusion and exclusion criteria. For analysis of insulin resistance based on HOMA-IR score with COVID-19 severity based on clinical manifestations (mild, moderate, severe, and critical), a chi square test was performed and assumed to be significant if p value <0.05. The majority of research subjects had HOMA-IR score >3.8 as many as 35 people, 21 people (60.0%) of whom were severe COVID-19 and 8 people (22.9%) were moderate COVID-19, 6 people (17.1%) were critical degrees COVID-19. The research subjects who had a HOMA-IR score <2.6 as many as 32 people, 24 people (75.0%) of whom were moderate COVID-19, 7 people (21.9%) were severe COVID-19 and 1 person (3.1%) were critical degree COVID-19. The research subjects who had a HOMA-IR score of 2.6-3.8 were 7 people, 4 people (57.1%) of whom were moderate COVID-19, 2 people (28.6%) were severe COVID-19 degrees and 1 person (14.3%) were critical degree COVID-19. There is a statistically significant correlation between HOMA-IR score and COVID-19 severity

Keywords: Insulin resistance; COVID-19; HOMA-IR; type 2 diabetes mellitus

1. Introduction

Four main demographic factors influence COVID-19 epidemiology, namely, advanced age (mean age of death—75 years); gender (male), immunocompromised, and underlying comorbidities such as cardiovascular disorders, diabetes mellitus, chronic respiratory disease and hypertension. Patients with a history of diabetes, hypertension, insulin resistance (IR), and respiratory distress have been reported to have decreased immune function leading to endothelial and ventilation disturbances. (De Lorenzo, Escobar and Tibiriçá, 2020;

Govender et al., 2021). Furthermore, hypercoagulation that occurs will put COVID-19 patients at greater risk of thrombosis, ischemia, and myocardial injury (Govender et al., 2021).

Insulin resistance (IR) is defined as a disturbance of glucose homeostasis involving decreased insulin sensitivity of muscle, adipose tissue, liver and other body tissues, despite normal or elevated blood concentrations. (Gierach, Gierach and Junik, 2014). IR is caused by reduced tissue sensitivity to insulin and refers to pancreas inability to secrete sufficient insulin for blood glucose regulation (Tam et al., 2012; Govender et al., 2021).

It is hypothesized that viral binding to ACE2 increases Ang II which have main role in synergism of IR and cardiovascular disease. Initially, ACE2 will regulate blood pressure by converting Ang II to Ang (1-7), therefore reduce IR, oxidative stress, and increase GLUT4 activity. However, in COVID-19 infection, ACE2 expression will decrease and result in excessive Ang II activity resulting in IR, oxidative stress, inflammation, hypertension, and cardiac dysfunction. In diabetic individuals, there is an increase inflammation, which induces IR and vice versa. As COVID-19 infection is characterized by an exaggerated inflammatory response, its coexistence with diabetes can lead to hyperinflammation and severe/fatal outcomes due to pre-existing inflammation. COVID-19, as a respiratory disease, also causes lung infiltrates among diabetic individuals thereby increasing patient's susceptibility to lung injury caused by IR. Thus, IR in diabetes mellitus itself will cause chronic inflammation and hyperinsulinemia which in turn leads to pulmonary dysfunction (Govender et al., 2021).

Insulin resistance (IR) may be a potential key factor of COVID-19 severity. An article published in Frontiers Public Health supports evidence of possible mechanism linking IR and COVID-19 severity via ACE 2 upregulation, a protein involved in viral entry. (Finucane and Davenport, 2020). In addition, research conducted by Ren et al. showed that insulin resistance, which is described by TyG index, was found to be high, especially in patients with more severe COVID-19 and those who died (Ren et al., 2020). In Indonesia itself, data regarding correlation between insulin resistance and COVID-19 severity haven't been found, especially those using HOMA IR examination. Therefore, researchers are interested in conducting research on this matter, to find out whether there is a correlation between insulin resistance and COVID-19 severity.

2. Material and methods

This research is cross sectional analytic study with prospective data collection from medical records. This research was conducted in June 2021 – September 2021 at isolation ward of Haji Adam Malik Hospital Medan. The research sample was patients diagnosed with COVID-19 with comorbid diabetes mellitus who met inclusion criteria namely male and female patients aged $\geq$ 18 years, moderate, severe, and critical COVID-19 groups, COVID-19 patients with comorbid diabetes mellitus type 2 and exclusion criteria were patients with history of asthma, COPD, autoimmune, malignancy, chemotherapy, severe liver and kidney disorders, immunocompromised patients such as HIV infection, ptients undergoing surgery, trauma, pregnancy, puerperium.

Researchers collected data in form of age, gender, COVID-19 severity, fasting blood sugar levels, and fasting insulin levels of COVID-19 inpatients at Haji Adam Malik Hospital Medan. The research results are processed and displayed in graphs and tables. Data that has been collected is processed and analyzed univariately, therefore analyzing research variables one by one to get an overview. Then to analyze correlation between independent and dependent variables followed by bivariate analysis, using chi square test. If chi square test conditions not met, Fisher Exact test will be used. The results were stated to be significant with p value <0.05. All data obtained will be analyzed using statistical software and displayed in frequency distribution table.

3. Results

This research was followed by 74 research subjects whose aim to determine correlation between insulin resistance and COVID-19 severity. Covid-19 patients with DM type 2 in this research were mostly male and in older age.

Table 1. Research Sample Characteristics

Characteristics	**n=74**
Gender, n(%)	
Male	42 (56,8)
Female	32 (43,2)
COVID-19 degree, n(%)	
Moderate	36 (48,6)
Severe	30 (40,5)
Critically Ill	8 (10,8)
Age, n(%)	
<20 years old	0 (0,00)
20 – 30 years old	0 (0,00)
31 – 40 years old	6 (8,10)
41 – 50 years old	7 (9,50)
51 – 60 years old	28 (37,5)
61 – 70 years old	23 (31,1)
>70 years old	10 (13,5)
HOMA-IR Score, n (%)	
< 2,6	32 (43,2)
2,6 – 3,8	7 (9,50)
>3,8	35 (47,3)
Insulin (IU/ml)	10,29 ± 11,187
Fasting Blood Glucose	240,18 ±106,87
Blood Glucose Post Prandial	290,23 ± 104,320
HbA1c	9,23 ± 1,990
GFR	70,31 ± 30,00
Haemoglobin	13,05 ± 1,879
Leucocyte	10253,51 ±5512,17
Trombocyte	291500 ± 130724,77
Neutrophil	77,22 ±12,032
Lymphocyte	14,51 ± 9,852
NLR	9,58 ± 9,392
Monocyte	7,52 ± 3,483

Eosinophil	0,44 ±0,889
Basophil	0,20 ± 0,170

3.1 Difference in Mean HOMA-IR Score Based on Severity of COVID-19 Patients with DM Type 2

HOMA-IR score for moderate COVID-19 patients was 3.36 ± 4.49, HOMA-IR score for severe COVID-19 patients was 7.49 ± 6.25, and HOMA-IR score for critically ill COVID-19 patients was 14 ,52 ± 13.14. Based on analysis results, it was found that there was a significant difference between HOMA-IR score and COVID-19 severity statistically with p value < 0.001. Based on post-hoc test, it was obtained that there was a statistically significant difference in mean HOMA-IR score at moderate degree compared to severe degree and moderate degree compared to critically ill patients with p value < 0.05, but there was no significant difference between severe degree compared to critically ill patients with p value > 0.05.

Table 2. Difference in Mean HOMA-IR Score Based on Severity of COVID-19 Patients with DM Type 2

	COVID-19 Severity			**P value[a]**
	Moderate	Severe	Critically ill	
HOMA-IR Score	3,36 ± 4,49	7,49 ± 6,25	14,52 ± 13,14	<0,001

[a] Kruskal–Wallis one-way analysis

Table 3. Post-Hoc Analysis of Differences in mean HOMA-IR scores based on severity of COVID-19 patients with DM Type 2

COVID-19 Severe	**P value[b]**
Moderate vs Severe	<0,001
Moderate vs Critically ill	0,001
Severe vs Critically ill	0,160

[b]Post-Hoc Mann Whitney Analysis

3.2 Correlation between HOMA-IR Score and Severity of COVID-19 patients with DM Type 2

Based on analysis results, there is a statistically significant correlation between HOMA-IR score and COVID-19 severity with p value < 0.001.

Table 4. Correlation between HOMA-IR Score and Severity of COVID-19 patients with DM Type 2

HOMA-IR Score	**COVID-19 Severity**			Total	**P value**
	Moderate	Severe	Critically Ill		
<2,6	24 (75,0)	7 (21,9)	1 (3,1)	32 (100,0)	<0,001
2,6 – 3,8	4 (57,1)	2 (28,6)	1 (14,3)	7 (100,0)	
>3,8	8 (22,9)	21(60,0)	6 (17,1)	35 (100,0)	
Total	36 (48,6)	30 (40,5)	8 (10,8)	74 100,0)	

3.3 Correlation between Age and Gender of Patients with Insulin Resistance and Severity of COVID-19 patients with DM Type 2

Based on analysis results, there was no statistically significant relationship between age and gender towards COVID-19 severity with p value of 0.642 and 0.281, respectively.

Table 5. Correlation between Age and Gender and Severity of COVID-19 patients with DM Type 2

Patient Characteristics	**COVID-19 severity [n(%)]** Moderate	Severe	Critically Ill	Total	**P value**
Age (years old)					0,642
31-40	3 (50,0)	1 (16,7)	2 (33,3)	6 (100,0)	
41-50	2 (28,6)	5 (71,4)	0 (0,00)	7 (100,0)	
51-60	13 (46,4)	14 (50,0)	1 (3,6)	28 (100,0)	
61-70	13 (56,5)	7 (30,4)	3 (13,0)	23 (100,0)	
>70	5 (50,0)	3 (30,0)	2 (20,0)	10 (100,0)	
Gender					0,281
Male	22 (52,4)	17 (40,5)	3 (7,1)	42 (100,0)	
Female	14 (43,8)	13 (40,6)	5 (15,6)	32 (100,0)	
Total	36 (48,6)	30 (40,5)	8 (10,8)	74 (100,0)	

4. Discussion

As an important comorbid metabolic disorder, diabetes characterized by hyperglycemia has been found to downregulate immune response and increase inflammation (Varikasuvu et al., 2021). DM inhibits neutrophil chemotaxis, phagocytosis, and killing intracellular microbes. Decreased adaptive immunity characterized by early delay of Th1 cell-mediated immune activation and delayed hyperinflammatory response is frequently observed in patients with diabetes. (Muhammad, 2020).

The research results indicate that there is a significant difference between HOMA-IR score and COVID-19 severity statistically (p value < 0.001). In line with this, Finucane and Davenport in Ireland reported that COVID-19 severity is influenced by insulin resistance (Finucane and Davenport, 2020). However, how IR can affect COVID-19 degree itself and data regarding correlation between IR and COVID-19 are still very limited. In addition, any study using HOMA-IR to measure insulin resistance in COVID-19 patients. Govendar et al. stated that there is a hypothesis that virus binding to ACE2 increases Ang II which is main cause in synergy of IR and cardiovascular disease. Initially, ACE2 will regulate blood pressure by converting Ang II to Ang (1-7), therefore it will reduce IR, oxidative stress, and increase GLUT4 activity. However, in COVID-19 infection, ACE2 expression will decrease and result in excessive Ang II activity and stimulate IR, oxidative stress, inflammation, hypertension, and cardiac dysfunction. In obese and diabetic individuals, there is an increase in inflammation, which induces IR and vice versa. Since COVID-19 infection is characterized by an exaggerated inflammatory response, its coexistence with obesity and diabetes can lead to hyperinflammation and severe/fatal outcomes due to preexisting inflammation. COVID-19, as a respiratory disease, also causes lung infiltrates among diabetic and obese individuals thereby increasing patient's susceptibility to lung injury caused by IR. Thus, 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 (Govender et al., 2021).

Mukherjee et al. in United States reported an increase of insulin resistance in two days prior to clinical suspicion of ventilator-associated pneumonia (VAP) for critically ill patients based on glycemic control protocol. These changes occurred despite protocols achieve to maintain euglycemia. This suggests that insulin resistance markers can provide clinically useful information for initial diagnosis of VAP. Stress hyperglycemia is mediated by stress-induced IR and is promoted by increases stress hormones, pro-inflammatory cytokines, and oxidant stress after severe trauma. Stress-induced hyperglycemia induced by IR is associated with infection and death in critically ill patients. Hyperglycemia contributes directly to oxidative stress at cellular level and promotes activation of classical and acute-phase intracellular signaling pathways. Acute increases in blood glucose concentrations are highly pro-inflammatory and significantly alter neutrophil, endothelial, platelet, and antigen-presenting mitochondrial function, which is contributing to increased infectious morbidity and mortality in these patients. (Mukherjee et al., 2014).

Globally, an estimated 19.3% of people aged 65-99 years (135.6 million, 95% CI: 107.6-170.6 million) live with diabetes (Sinclair et al., 2020), whereas diabetes itself is known to be associated with increased risk of COVID-19 infection. In a meta-analysis of 8 studies in China to assess prevalence of comorbidities in 46,248 COVID-19patients, it was found that the mean age was 46 years (51.6%) in males, and diabetes mellitus was the second most common comorbidity, (8%) after hypertension (17%) and higher than cardiovascular (5%) and respiratory disease (2%) (Sinclair and Abdelhafiz, 2020; The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Older age is a risk factor for COVID-19 pneumonia mortality (Zhou et al., 2020) and ARDS occurences (Wu et al., 2020). Age-related impairments in immune system function may also be a contributing factor. The aging immune system is characterized by low levels of immunity and a state of chronic systemic inflammation or “InflammAgeing” which is characterized by increased inflammatory markers such as IL-6 and C-reactive protein and is associated with increased susceptibility to infection.

In addition, based on analysis results between age and COVID-19 severity as well as between gender and severity, there was no statistically significant correlation, with p values = 0.642 and p = 0.281, respectively. Contrary to this, Barek et al. in Bangladesh reported that males and elderly (age 50 years) were at higher risk for more severe COVID-19 (OR = 2.41, $p < 0.00001$; RR = 3.36 , $p = 0.0002$, respectively) (Barek, Aziz and Islam, 2020). Our finding results are not statistically significant may be due to the small samples number.

Until now, data and research regarding correlation of insulin resistance to COVID-19 severity is still very limited, especially by using HOMA-IR score as an IR parameter. Our research is the first research to address this relationship. Meanwhile, Ren et al. in China used TyG index to measure insulin resistance in COVID-19 patients, and has shown that TyG index is associated with severity and morbidity of COVID-19 patients. (Ren et al., 2020)

5. Conclusion

There is a statistically significant correlation between HOMA-IR score and COVID-19 severity.

Acknowledgements

None to acknowledge

References

Barek, M. A., Aziz, M. A. and Islam, M. S. (2020) ‘Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: A meta-analysis with 55 studies and 10014 cases’, Heliyon, 6(12), pp. 1–24. doi: 10.1016/j.heliyon.2020.e05684.

De Lorenzo, A., Escobar, S. and Tibiriçá, E. (2020) ‘Systemic endothelial dysfunction: A common pathway for COVID-19, cardiovascular and metabolic diseases’, Nutrition, Metabolism and Cardiovascular Diseases, 30(8), pp. 1401–1402. doi: 10.1016/j.numecd.2020.05.007.

Finucane, F. M. and Davenport, C. (2020) ‘Coronavirus and Obesity: Could Insulin Resistance Mediate the Severity of Covid-19

Infection?', Frontiers in Public Health, 8(May), pp. 1–5. doi: 10.3389/fpubh.2020.00184

Gierach, M., Gierach, J. and Junik, R. (2014) 'Insulin resistance and thyroid disorders', Endokrynologia Polska, 65(1), pp. 70–76. doi: 10.5603/EP.2014.0010.

Govender, N. et al. (2021) 'Insulin resistance in COVID-19 and diabetes', Primary Care Diabetes, 15(4), pp. 629–634. doi: 10.1016/j.pcd.2021.04.004.

Muhammad, I. D. (2020) 'Mekanisme Potensial Peningkatan Derajat Keparahan Infeksi COVID-19 – Diabetes Mellitus', Wellness and Healthy Magazine, 3(1), pp. 309–313. Available at: https://wellnes.journalpress.id/wellnes.

Mukherjee, K. et al. (2014) 'Insulin resistance increases before ventilator-associated pneumonia in euglycemic trauma patients', Surgical Infections, 15(6), pp. 713–720. doi: 10.1089/sur.2013.164.

Ren, H. et al. (2020) 'Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19', Cardiovascular Diabetology, 19(1), pp. 1–8. doi: 10.1186/s12933-020-01035-2

Sinclair, A. et al. (2020) 'Diabetes and global ageing among 65–99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9th edition', Diabetes Research and Clinical Practice, 162, p. 108078. doi: 10.1016/j.diabres.2020.108078.

Sinclair, A. J. and Abdelhafiz, A. H. (2020) 'Age, frailty and diabetes – triple jeopardy for vulnerability to COVID-19 infection', EClinicalMedicine, 22, pp. 8–9. doi: 10.1016/j.eclinm.2020.100343.

Tam, C. S. et al. (2012) 'Defining Insulin Resistance From Hyperinsulinemic-Euglycemic Clamps', Diabetes Care, 35(7), pp. 1605–1610. doi: 10.2337/dc11-2339.

Varikasuvu, S. R. et al. (2021) 'Diabetes and COVID-19: A pooled analysis related to disease severity and mortality', Primary Care Diabetes, 15(1), pp. 24–27. doi: 10.1016/j.pcd.2020.08.015.

Wu, C. et al. (2020) 'Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China', JAMA Internal Medicine, 180(7), p. 934. doi: 10.1001/jamainternmed.2020.0994.

Zhou, F. et al. (2020) 'Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study', The Lancet, 395(10229), pp. 1054–1062. doi: 10.1016/S0140-6736(20)30566-3.