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The Effect of Diabetes Melitus and Blood Glucose on Patients Mortality with Severe COVID-19 Pneumonia Receiving Corticosteroids in RSUD Dr. Saiful Anwar Malang

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Abstract

Background: Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). WHO has recommended the use of systemic corticosteroid therapy in patients with severe and critical COVID-19 pneumonia. However, the use of systemic corticosteroids is also a major contributor to hyperglycemia which is a strong prognostic predictor of poor outcome in hospitalized patients with COVID-19. Furthermore, diabetes mellitus (DM) is one of the most widely reported comorbidities in COVID-19 patients which affects the risk of morbidity and mortality and systemic corticosteroids can aggravate hyperglycemia in patients with this comorbidity.

Objective: This study aims to determine the effect of DM and blood glucose on mortality in patients with severe COVID-19 pneumonia who received corticosteroids.

Methods: The design of this study was an observational retrospective which was conducted on the medical records of COVID-19 patients who received convalescent plasma therapy at RSUD Dr. Saiful Anwar Malang (RSSA). Of the 229 patients who received convalescent plasma therapy and had fairly complete data, there were 85 patients with severe COVID-19 pneumonia who received corticosteroids with blood glucose data for analysis.

Results: There were significant differences in mortality rates in DM and non-DM patients (OR 3.091; CI 1.232-7.756; p=0.015) with severe COVID-19 pneumonia who received corticosteroids. Analysis of blood glucose levels shows that the mean random blood glucose (RBG) and initial RBG levels were higher in patients with a death outcome compared to those who lived (mean RBG 176.07 ± 72.0 mg/dl VS 133.23 ± 56.38 mg /dl, p=0.02; initial RBG 198.40 ± 127.13 mg/dl VS 141.57 ± 73.28 mg/dl, p=0.022.

Conclusion: DM and blood glucose levels (mean RBG and initial RBG) affect mortality rates in patients with severe COVID-19 pneumonia who are given corticosteroids.

Keywords: COVID-19, diabetes mellitus, blood glucose, corticosteroids

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BACKGROUND

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] The SARS-CoV-2 virus infects the lungs through the respiratory tract by entering cells alveolar epithelium via the ACE2 receptor and activates the immune system. The immune

system activation produces pro-inflammatory factors and chemokines, which cause the translocation of leukocytes to areas of inflammation to eradicate the virus. However, when the viral load induces an increase in the pro-inflammatory cytokines and a cytokine storm. In severe COVID-19 patients, the SARS-CoV-2 virus can invade blood vessels, damage vascular endothelial cells, increase vascular permeability, cause cells and proteins to enter the alveoli, and accelerate alveolar endothelial cells, thereby worsening alveolar damage.[2] Clinical manifestations of COVID-19 patients for signs of asymptomatic, mild symptoms, pneumonia, severe pneumonia, ARDS, sepsis, and septic shock. About 80% of cases were classified as mild or moderate, 13.8% were severe, and 6.1% of patients identified as having critical conditions.[3]

The severity and pathophysiology of COVID-19 pneumonia are associated with hyperinflammation, therefore, therapy with immunosuppressant or immunomodulatory drugs, inflammatory cytokine antagonists, and nonsteroidal anti-inflammatory drugs (NSAIDs) may play a role in reducing the potential effects of the cytokine storm. Corticosteroids may be beneficial by suppressing inflammation-induced lung tissue damage by inhibiting lung inflammation in critically ill COVID-19 pneumonia patients.[4] Several randomized trial studies have demonstrated the benefit of systemic corticosteroid therapy in patients with COVID-19 pneumonia.[5,6] WHO has recommended systemic corticosteroid therapy in patients with severe and critical COVID-19 pneumonia.[7]

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia[8] and is one of the most frequently reported comorbidities in COVID-19 patients that determine their risk of morbidity and mortality.[9] The use of systemic corticosteroids are also a significant contributor to severe hyperglycemia. Corticosteroids potentially cause hyperglycemia through several mechanisms: suppression of insulin secretion increased gluconeogenesis, and decreased glucose uptake due to reduced insulin sensitivity.[10] Several studies have shown that hyperglycemia has been associated with poor mortality outcomes in hospitalized patients with infectious diseases.[11] Hyperglycemia in COVID-19 pneumonia alone is also a strong prognostic predictor of poor outcomes in hospitalized patients with COVID-19.[12]

METHOD AND ANALYSIS

Research Design

The study was an observational retrospective of the medical records of COVID-19 patients who received convalescent plasma therapy at Dr. Saiful Anwar Malang hospital (RSSA) collected from May 2021 to August 2021. There were 229 patients who participated in the study of convalescent plasma (CP) therapy that had comorbid data, the severity of COVID-19, and COVID-19 therapy. After applying the inclusion criteria, namely severe COVID-19 pneumonia[13] (respiratory rate > 30 x/minute, severe respiratory distress, or SpO2 < 93% on room air) and receiving corticosteroids during hospitalization, 85 patients had complete data of random blood glucose (RBG) during treatment (Figure 1). DM was defined as a history of DM or Hba1c levels > 6.5% during hospitalization. Mortality was defined by death for any cause during hospitalization.

Data Analysis

The data analysis was carried out using the bivariate chi-square test to determine the odd ratio. Statistical analysis in this study used IBM SPSS Statistics version 23 for Windows. All of these tests were considered significant if the p-value < 0.05.

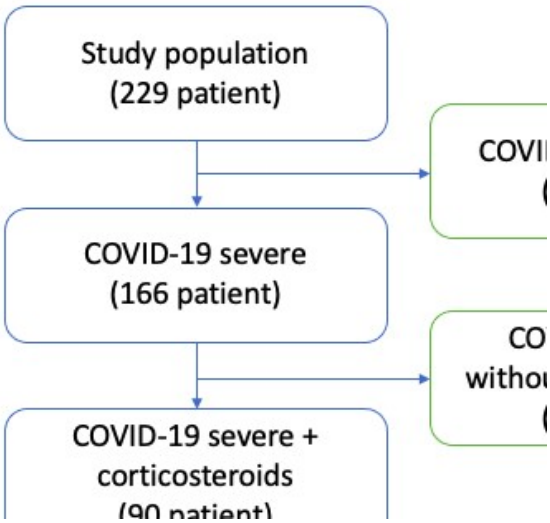

Figure 1. Collection of Research Subjects

FINDING AND DISCUSSION

Analysis based on DM vs. non-DM groups

The analysis was conducted on 85 severe COVID-19 patients who received corticosteroids at RSSA based on inclusion and exclusion criteria. In this study, there were 31 patients with DM and 54 non-DM patients. The characteristics of the study sample based on DM status showed in table 1. The mean age of the patients studied was 52.76 ± 12.23 years. The mean age in DM patients was 58.58 ± 10.01 years and 49.43 ± 12.22 years in non-DM patients. Statistically, a p-value of 0.002 ($p<0.05$) was obtained, proving a significant difference in the age of patients with DM and non-DM. The mean age of patients with DM was higher or older than that of non-DM patients.

Characteristic		Total	DM Classification (N=85)		p-value
			DM (n=31)	Non-DM (n=54)	
Sex (n%)	Male	52 (61.2%)	17 (54.8%)	35 (64.8%)	0.364
	Female	33 (38.8%)	14 (45.2%)	19 (35.2%)	
Age (mean±SD)		52.76 ± 12.23	58.58 ± 10.01	49.43 ± 12.22	0.002*
Hypertension (n%)	No	57(67.1%)	57 (67.1%)	22 (71%)	0.561
	Yes	28(32.9%)	28 (32.9%)	9 (29%)	
Heart failure (n%)	No	76(89.4%)	76 (89.4%)	28 (90.3%)	0.836
	Yes	9(10.6%)	9 (10.6%)	3 (9.7%)	
CKD (n%)	No	84(98.8%)	84 (98.8%)	31 (100%)	0.446
	Yes	1(1.2%)	1 (1.2%)	0 (0%)	
AKI (n%)	No	83(97.6%)	83 (97.6%)	30 (96.8%)	0.687
	Yes	2(2.4%)	2 (2.4%)	1 (3.2%)	
Obesity (%)	No	80(94.1%)	80 (94.1%)	29 (93.5%)	0.866
	Yes	5(5.9%)	5 (5.9%)	2 (6.5%)	

In terms of comorbidities suffered by patients, hypertension was most common with 28 (32.9%) patients. There were no significant differences in the comorbid characteristics of patients with severe COVID-19 pneumonia who received corticosteroids.

The comparison of the mean RBG levels in the DM group compared to those in the non-DM group can be seen in Figure 2. It was shown that the mean RBG level in the DM group was 202.64 ± 70.17 mg/dl, and in the non-DM group it was 125.12 ± 46.54 mg/dl. The mean RBG of the DM group was significantly higher than that of the non-DM group in patients with severe COVID-19 pneumonia who received corticosteroids.

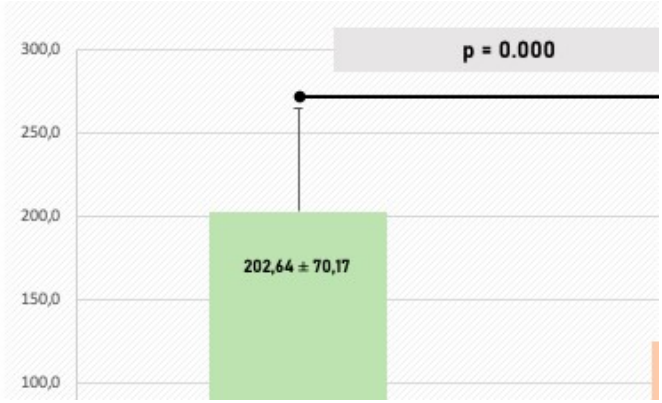

Figure 2. Comparison of the mean levels of RBG in the DM VS non-DM group.

Outcome Analysis

Based on outcome of 85 patients, 45 (52.9%) patients survived, meanwhile 40 (47.1%) patient did not. Analysis of sample characteristic data was carried out using Chi-Square and Mann-Whitney test. DM variable on patient outcomes had a p-value of 0.015 ($p < 0.05$), which indicates that in this study, patient with DM was more likely to have increased mortality (OR 3.09, 95% CI 1.232-7.756).

Characteristic	Total (N=85)	Outcomes		OR (95% CI)	p-value
		Alive (n=45)	Dead (n=40)		
DM					
Without	54 (63.5%)	34 (75.6%)	20 (50.0%)	3.091 (1.232-7.756)	0.015*
With	31 (36.5%)	11 (24.4%)	20 (50.0%)		
Sex					
Male	52 (61.2%)	29 (64.4%)	23 (57.5%)	0.746 (0.311-1.791)	0.512
Female	33 (38.8%)	16 (35.6%)	17 (42.5%)		
Age (mean ± SD)	52.76 ± 12.23	50.47 ± 12.13	55.35 ± 11.97		0.069
Hypertension					
Without	57 (67.1%)	22 (48.9%)	35 (87.5%)	0.137 (0.045-0.412)	0.000*
With	28 (32.9%)	23 (51.1%)	5 (12.5%)		
Heart Failure					
Without	76 (89.4%)	38 (84.4%)	38 (95.0%)	0.286 (0.56-1.465)	0.114
With	9 (10.6%)	7 (15.6%)	2 (5.0%)		
CKD					
Without	84 (98.8%)	44 (97.8%)	40 (100.0%)	-	0.343
With	1 (1.2%)	1 (2.2%)	0 (0.0%)		
AKI					
Without	83 (97.6%)	45 (100.0%)	38 (95.0%)	-	0.129
With	2 (2.4%)	0 (0.0%)	2 (5.0%)		
Obesity					
Without	80 (94.1%)	41 (91.1%)	39 (97.5%)	0.263 (0.028-2.456)	0.211
With	5 (5.9%)	4 (8.9%)	1 (2.5%)		

NB: *p-value < 0.05 shows the significance
*CKD and AKI do not have OR because one of the groups does not have a comparison group

Table 2. Outcome analysis based on patient characteristics

Hypertension variable to the patient's outcome has a p-value of 0.000 ($p<0.05$) with odds ratio 0.137 (95% CI 0.045-0.412). In this study, patient with hypertension was more likely to survived compared to those who did not have hypertension.

Meanwhile, for other variables such as gender, age, heart failure, CKD, AKI, and obesity, the p-value was more than 0.05 ($p>0.05$), so it could be concluded that there was no significant difference between the patients outcomes. The odds ratio was not interpreted because there is no significant difference between the independent and dependent variables. The outcome analysis based on the patient characteristics is presented in table 2.

Based on the analysis of the mean RBG level on the outcome, it was shown that the mean value of RBG levels of the non-surviving group was 176.07 ± 72 mg/dl, and of those who survived was 133.23 ± 56.38 mg/dl. The mean RBG of the non-surviving group was significantly higher than that of the surviving group ($p=0.002$) (figure 3).

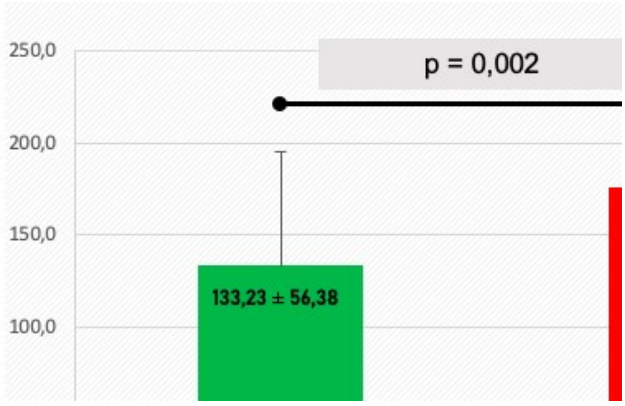

Figure 3. Comparison of the Mean RBG Levels of COVID-19 Patients by Outcome

Based on the analysis of the initial RBG levels against the outcome, it was shown that the initial RBG level of patients who died was 198.40 ± 127.13 and in the surviving group was 141.57 ± 73.28. The initial RBG level in the group of patients with a death outcome was significantly higher than in the group of patients who survive ($p=0,022$) (figure 4).

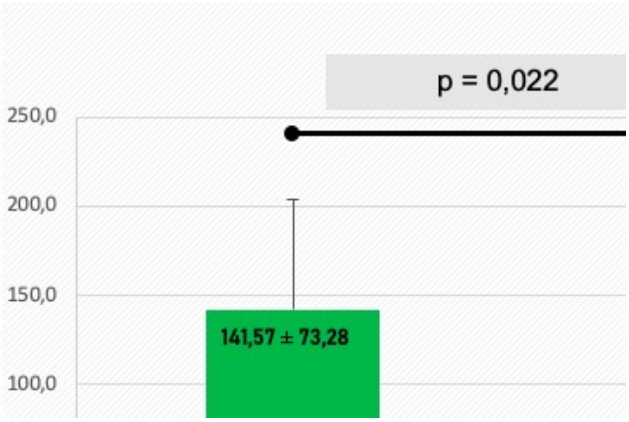

Figure 4. Comparison of Initial RBG Levels for COVID-19 Patients based on the Outcomes

Result of comorbid DM on outcomes

The data analysis results on mortality showed a significant difference in mortality rates in DM and non-DM patients with severe COVID-19 pneumonia who received corticosteroids (OR 3.091; CI 1.232-7.756; p=0.015). These results were consistent with other studies showing that comorbid DM was associated with an increased risk of death in COVID-19. However, in this study all participant are given corticosteroids as a treatment for severe COVID-19 pneumonia.

A meta-analysis by Gupta showed that comorbid DM was associated with a significantly increased risk of death in patients hospitalized with COVID-19.[14] COVID-19 infection in DM, including dysregulation of the immune response and thromboembolic complications due to glucotoxicity, oxidative stress, and endothelial damage due to inflammation.[15]

In our analysis, there were no significant differences in other comorbidities (hypertension, heart failure, CKD, AKI, and obesity) between the DM and non-DM groups, so this difference in mortality could be associated with the presence or absence of DM comorbidities. Another possible explanation for the difference in mortality in the 2 groups is that there is a significant age difference (p=0.002) between the DM group (58.58 ± 10.01 years) and the non-DM group (49.43 ± 12.22 years). A meta-analysis states that patients over 50 years of age with SARS-CoV-2 infection were associated with a 15.4-fold significantly increased risk of death compared with patients <50 years of age.[16] However, DM is a disease associated with old age, so the relationship between comorbid DM and old age as mortality risk factors for COVID-19 is still unknown.

The result of the RBG analysis on outcomes

The results showed a significant difference in the mean RBG of patients with severe COVID-19 pneumonia who were given corticosteroids with DM compared to non-DM. The mean level of RBG in the DM group was 202.64 ± 70.17 mg/dl, and in the non-DM group it was 125.12 ± 46.54 mg/dl. This difference may be due to both groups underlying comorbid DM and corticosteroid administration, which can cause impaired glucose metabolism.

When analyzed for outcomes, there was a significant difference in the mean RBG levels in patients with COVID-19 pneumonia who were given corticosteroids who died compared to those who lived in either DM or non-DM patients. The mean RBG level of COVID-19 patients with comorbid DM and non-DM who died was 176.07 ± 72 mg/dl and in the surviving group was 133.23 ± 56.38 mg/dl. These results are consistent with the findings of other studies showing that hyperglycemia is associated with an increase in the severity of COVID-19 in both DM and non-DM patients.[17] A meta-analysis study by Yang showed that hyperglycemia on hospital admission in COVID-19 patients strongly predicted mortality and complications. Inflammatory cytokine and immune system dysfunction caused by hyperglycemia may play a role in poor outcomes and death in COVID-19 patients.[18] The results of our analysis also showed similar findings, namely that there were significantly higher initial RBG levels in COVID-19 patients who were given corticosteroids who died (198.4 ± 127.13 mg/dl) compared to surviving group (141.57). ± 73.28 mg/dl; p=0,022) in both DM and non-DM patient.

CONCLUSION

This study was conducted to determine the effect of DM and blood glucose on mortality in patients with severe COVID-19 pneumonia who received corticosteroids. We found that DM and blood glucose levels influence mortality rates in patients with severe COVID-19 pneumonia receiving corticosteroids. There was a significantly higher mortality rate in DM patients than in non-DM patients with severe COVID-19 pneumonia who were given corticosteroids. We also found that the mean GDS and initial GDS levels were significantly higher in patients that died compared to those who survived severe COVID-19 pneumonia receiving corticosteroids, regardless of DM status.

This study has several limitations, namely that several confounding variables such as duration of diabetes, history of medication taken, markers of the immune response, and causes of mortality were not assessed. In addition, this study did not match groups of independent variables. In this study, there was also no data on the SARS-CoV-2 variant that caused COVID-19 pneumonia in patients, which could also be a confounding factor. The study design is also an observational retrospective, which may lead to bias. Further study is needed to explain the effects of COVID-19 pharmacological treatment related to glucose metabolism in patient with DM with more data variables and a prospective study design.

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