Correlation between Diabetes Mellitus Comorbities with Severity of COVID-19 in Geriatric Patients: Retrospective Study

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Abstract: _Background: Diabetes mellitus (DM) is a risk factor for SARS-CoV-2 virus infection, as it increases disease severity and mortality, especially in elderly patients. The aim of this study is to assess the correlation between DM comorbidities with severity level of COVID-19 in geriatric patients._ _Method: This is a retrospective study which was held at Wangaya Hospital, Denpasar, from May to August 2021. The data taken from the medical record includes those from confirmed Covid-19 patients aged 60 and older. We exclude all patients under 60 years old._ _Result: 39 samples were obtained in this study. We found that there was no significant difference in severity of geriatric COVID-19 patients who had diabetes mellitus comorbities and those who had no diabetes mellitus as comorbities (p=0.267, CI 95; respectively)._ _Conclusion: There is no significant difference in severity in geriatric COVID-19 patients with diabetes mellitus comorbities. However, further researches with larger number of samples are needed to assess the correlation of diabetes mellitus comorbities with severity of Covid-19 disease in geriatric patients._

Keywords: Diabetes mellitus, DM, severity, COVID-19

1. Background

Coronavirus disease 2019 (COVID 19) is a disease that attacks the respiratory system caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV 2). COVID 19 was first discovered in Wuhan, Hubei province, China in December 2019.

COVID 19 was declared as a global pandemic by WHO in March 2020.[1]

Until February 22, 2022, there were 5,231,923 confirmed cases of COVID 19 in Indonesia, and 146,541 people died. Elderly aged 60 years or older who have confirmed COVID 19 are 11% of the total cases with 46.9% mortality rate. The number of confirmed cases of COVID 19 in Bali until February 21, 2022 was 149, 017 (2.8%) of the total cases.[2]

The most common symptoms of COVID-19 are respiratory symptoms such as shortness of breath, fever, cough, sore throat, and. In severe cases, acute respiratory distress syndrome (ARDS) and multiorgan failure can be found. This conditions also related to comorbidities that the patients may have such as, hypertension, diabetes melitus (DM), heart disease, and Chronic Obstructive Pulmonary Disease (COPD).[3-5]

Although the pathophysiological mechanism of COVID 19 is not fully understood, based on research and observations, it was found that DM is a risk factor for SARS-CoV-2 virus infection, as it increases disease severity and mortality, especially in elderly patients.[6-9] Predisposition that patients with DM have to develop severe cases of COVID-19 can be explained by the deregulation of the Renin- Angiotensin-Aldosterone System (RAAS), deterioration of the inflammatory response, hypercoagulable state,

physiological and structural lung abnormalities caused by hyperglycemia. Poor glucose control in patients with DM could promote glycosylation of angiotensin-converting enzyme 2 (ACE 2), the gateway for SARS- CoV-2 in the host.[10,11]

In Indonesia, from 6,112 available data of confirmed cases of COVID 19 until February 22, 2022, there is 36.7% of diabetes mellitus comorbities.[2]

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose due to defects of insulin secretion, insulin action, or both. DM definition in elderly is similar to the other people, which means fasting glycaemia ≥ 1.26 g/l (7.0 mmol/L) or glycemia after glucose loading (75 g) ≥ 2 g/l (11.11 mmol/L). People with postprandial or postloading glycemia between 1.40 and 1.99 g/l (7.78–11.06 mmol/L) suffer from a reduction in glucose tolerance.[12] Most people over than 60 years old suffer from type 2 DM due to insulin resistance and long life expectancy leading to a decrease in insulin secretion.[12-14]

Therefore, based on this background, this study aims to assess and evaluate the correlation between DM comorbities with severity of disease in geriatric COVID-19 patients at the Wangaya Regional General Hospital, one of marker referral hospital for COVID-19 in Bali Province since 2019.

2. Method

This is retrospective study design that was placed at Wangaya Regional General Hospital, Denpasar in January to February 2022. Data was obtained from patient's medical record and sample was taken from patient that hospitalized from May to August 2021. Inclusion criteria of this study

were confirmed COVID-19 patient (age range from 60 years and above) that hospitalized in Wangaya Regional General Hospital from May to August 2021. We exclude all patients under 60 years old.

Severity of COVID-19 was categorized into 2 categories, mild-moderate and severe-critically ill. Determination severity level of COVID-19 based on the following criteria[4] :

Table 1: Severity Criteria of COVID-19 Patient

Mild	Moderate	Severe	Critical
>95% oxygen saturation in room air.	≥93% oxygen saturation in room air	<93% oxygen saturation in room air	<93% oxygen saturation in room air
Without clinical signs of pneumonia (fever, cough, dyspnea, tachypnea)	With clinical signs of pneumonia (fever, cough, dyspnea, tachypnea) without severe pneumonia signs, or confirmed from Chest X-ray results.	With clinical signs of pneumonia and 1 of these below: Respiratory rate >30/minutes, or Severe respiratory distress.	ARDS, Sepsis, Septic shock, or need mechanical ventilation/ vasopress or to support life.

Statistical analysis was generated with SPSS 25.0. Data were expressed as median with standard deviation. Data will be done with Shapiro-Wilk distribution test. If normally distributed, t-test dependent was used to analyse data. If data is not normally distribution, association analysis will be processed by *chi-square* association if there is no low expected count data. If there is low expected count data, the analyze will be done by *fisher-exact* test.

3. Result

We present summary characteristics to obtain the association. We found no significant difference between DM of the study population in Table 2. Total subjects of 39 that hospitalized in May 2021 to August 2021 was in this study. Median of subjects were 67.5 years ± 8.5 years, with 25 subjects (62.5%) were male and 14 subjects (37.5%) were female. There is 20 (51.2%) subjects had DM comorbities and 19 (48.7%) subjects had no DM comorbities. Severity level of COVID-19 was categorized into 2 categories, 24 subjects (60.0%) had mild- moderate and 16 subjects (40.0%) had severe-critically ill.

Table 2: Baseline Characteristic of COVID-19 Patient

Characteristic	N
Age, n Median	67.5 ± 8.5
Gender, n (%) Male Female	25 (62.5) 14 (37.5)
DM comorbities (%) With DM Non – DM	20 (51.2) 19 (48.7)
Severity of disease Mild-moderate Severe-critically ill	24 (60.0) 16 (40.0)

Data were analysed with Saphiro- Wilk test to obtain normality of data. Data of this study were not normally distributed p = 0.000 (p>0.05, CI 95%). In association with severity, data were tested with *chi square* test comorbities and patient's severity of Covid- 19 (p=0.267, p < 0.05, CI 95%). Results can be seen in Table 3.

Table 3: Data Analysis of DM comorbities with severity of COVID-19

Variable	Correlation coefficient	p value
Severity of disease	0.267	p < 0.05

4. Discussion

The current study included 39 cases admitted to the Wangaya Regional General Hospital with a diagnosis of COVID-19 from May to August 2021. Cases were managed in the hospital-based on available resources and guidelines.

This study found that DM comorbities on hospital admitted patients was insignificantly associated with severity level of COVID-19. This result could be affected by low sample counts in single center, other comorbities (such as hypertension, cardiovascular disease, cerebrovascular disease, etc), differences of blood sugar control profile in COVID-19 patients before admissions, and physicians strategies to improve hyperglicemic conditions of diabetes.

The presence of DM and the individual's level of hyperglycemia appear to be independently associated with Covid-19 severity and increased mortality. In addition, complications of DM (cerebrovascular disease, heart failure, and chronic kidney disease) increase the mortality of COVID- 19.[8-11]

Infection with SARS-COV-2 increase blood levels of inflammatory mediators and toxic metabolites. Modulation of natural killer cell activity (increased or decreased) and IFN$^\gamma$ production may increase interstitial and/or vascular permeability for pro- inflammations products. In addition, SARS- COV-2 infection leads to increased production of reactive oxygen species (ROS). These effects lead to pulmonary fibrosis, acute lung damage and impaired acute respiratory distress syndrome. ROS production and viral activation of the renin- angiotensin-aldosterone system (RAAS) causes insulin resistance, hyperglycemia and vascular endothelial damage, all of which contribute to cardiovascular, thromboembolic and disseminated intravascular coagulation (DIC).[10,11,15,17]

In the SARS study, it was found that the virus can enter the islets of Langerhaans via combination to angotensin converting enzyme 2 (ACE2), damages pancreatic cells and causes acute hyperglycemia conditions. ACE2 is expressed in various tissues and organs of the human body. Significant inhibition of ACE2/Ang1-7/Mas signaling pathway and increased activity of the ACE/AngII/AT1R pathway occurs after SARS-COV-2 binds to ACE2 in vivo. ACE2 is also a SARS-COV-2 receptor. Critically ill occurs through imbalance renin-angiotensin system (RAS) and increased levels of inflammatory factors.[10,11,15]

DM inhibits neutrophil chemotaxis, phagocytosis, and killing process of intracellular microorganism. Decreased adaptive immunity characterized by a delay in early activation of Th1 cell-mediated and delayed hyperinflammatory responses are frequently observed in patients with DM. In study examining the effects of DM in a mouse model of MERS-COV infection on a high-fat diet, the disease is more severe and prolonged in diabetic male rats and characterized by changes in CD4+ and abnormal cytokine response (such as increased IL17a). consistent with this finding, in patients with Covid-19, low peripheral T cell counts, but with a higher proportion of proinflammatory T cells, as well as elevated levels of cytokines. Thus, it is likely that patients with DM may have blunted IFN antiviral responses, and delayed Th1/Th17 activation may contribute to accentuate the inflammatory response.[15-16]

COVID-19 infection exacerbates DM stress by releasing glucocoticoids and cathecolamines into the circulation. This worsens glycemic control and improves formation of glycation end products in many organs and worsen the prognosis. Policy implemented in many countries in an effort to flatten the COVID-19 curve. Impact of the policy is limitation the access of many diabetic patients to diet, exercise, medication,and routine hospital checks.[4,10,11]

Leon-Abarca JA.et al. was investigate patients with DM had a 21.8% higher prevalence of COVID-19 and an additional 120.2% higher prevalence of COVID-19 pneumonia. The adjusted prevalence was also higher for these outcomes as well as for hospitalization, intubation and ICU admission. COVID-19 and pneumonia patients with DM had a 97.0% and 19.4% higher CFR, respectively. With increasing altitudes, the probability of being a confirmed COVID-19 case and the development of pneumonia decreased along CFR for patients with and without DM. However, COVID-19 patients with DM were more likely to require intubation when residing at high altitude. The study suggests that patients with DM have a higher probability of being a confirmed COVID-19 case and developing pneumonia. Higher altitude had a protective relationship against SARS-CoV-2 infection; however, it may be associated with more severe cases inpatients with and without DM.[18]

Clinical spectrum of COVID-19 is heterogeneous, ranging from mild flu-like symptoms to acute respiratory distress syndrome, multiple organ failure and death. Older age, diabetes and other comorbidities are reported as significant predictors of morbidity and mortality. Chronic inflammation, increased coagulation activity, immune response impairment, and potential direct pancreatic damage by SARS-CoV-2 might be among the underlying mechanisms of the association between diabetes and COVID-19. No conclusive evidence exists to support the discontinuation of angiotensin- converting enzyme inhibitors (ACEI), angiotensin receptor blockers or thiazolidinediones because of COVID-19 in people with diabetes. Caution should be taken to potential hypoglycemic events with the use of chloroquine in these subjects. Patient tailored therapeutic strategies, rigorous glucose monitoring and careful consideration of drug interactions might reduce adverse outcomes. No definite conclusions can be made based on current limited evidence. Further research regarding this relationship and its clinical managementis warranted.[8-11,16,17]

5. Conclusion

COVID-19 have become pandemic all around the world and have high mortality. Early isolation, diagnosis, and management might collectively contribute to a better control of the disease and outcome. Diabetes and other comorbidities are significant predictors of morbidity and mortality in patients with COVID-19. In this study, we found there is no association between DM comorbities with severity level of COVID-19in 39 subjects. This result differs from other studies, that most of studies shows there are association between diabetes and severity of COVID-19 patients. Future research is urgently needed to provide a better understanding regarding potential differences in genetic predispositions across populations, underlying pathophysiological mechanisms of the association between COVID-19 and diabetes, and its clinical management.

6. Conflict of Interest

There is no conflict of interest in this study.

7. Author Contribution Statement

A.G conceptualized and wrote thepaper; C.A.A.B and Y.O collected the data, W.W.S.P and N.M.D.Y revised the text; andall approved the final manuscript.

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