

## Risk of Diabetic Retinopathy in Type 2 Diabetes Mellitus: Chest X-Ray Pattern and Lung Severity Score in COVID-19 Patients

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### Abstract

The aim of this study was to assess the potential benefits of caffeine intake in protecting against the development of Diabetic Retinopathy (DR) in subjects with type 2 diabetes. Furthermore, we tested the effect of topical administration of caffeine on the early stages of DR in an experimental model of DR. In the cross sectional study, a total of 144 subjects with DR and 147 individuals without DR were assessed. DR was assessed by an experienced ophthalmologist. A validated food frequency questionnaire was administered. In the experimental model, a total of 20 mice were included. One drop of caffeine was randomly administered directly onto the superior corneal surface twice daily for two weeks in each eye. Diabetes mellitus is a chronic hyperglycemic condition that can affect the body's immune response to SARS-CoV-2. This study aimed to determine the relationship between diabetes mellitus and lung severity in COVID-19 patients. The results of the BRIXIA score to assess lung severity found as many as 77 subjects had a score of 11-18 with 14 people with diabetes mellitus, five people with reactive hyperglycemia.

**Keywords:** COVID-19; Diabetes mellitus; X-ray chest; BRIXIA score; Hyperglycemia

### Introduction

Coronavirus disease 2019 is an infection caused by severe respiratory syndrome Coronavirus 2. The COVID-19 infection was declared a pandemic by the World Health Organization (WHO) because of its rapid spread from China to various countries around the world [1]. As of January 13, 2022, there were 315, 345, 967 confirmed cases of COVID-19 worldwide. In Indonesia, there were 4,268,890 confirmed cases with a death toll of 144,155 cases. Diabetes mellitus along with hypertension, cardiovascular disease, smoking, chronic obstructive pulmonary disease, malignancy and chronic kidney failure were the most common comorbidities in patients hospitalized with COVID-19 [2].

Diabetes mellitus is a chronic hyperglycemic condition that can affect the body's immune response to SARS-CoV-2. The condition of acute or reactive hyperglycemia can also affect the body's immune response, regardless of the condition of diabetes mellitus or not [3]. Data in Wuhan, China, found that as many as 51% of patients with COVID-19 came in a state of hyperglycemia. Diabetes mellitus is one of the factors that play a role in the outcome of patients with COVID-19. The presence of diabetes mellitus is associated with higher morbidity and mortality [4]. The relationship between diabetes mellitus and lung severity in COVID-19 patients has not been widely studied. A study by Iacobellis in Miami found that high blood glucose conditions at admission could be a predictor of lung severity, regardless of the previous history of diabetes mellitus. Therefore, this study aimed to determine the relationship between diabetes mellitus and lung severity in COVID-19 patients [5].

### Materials and Methods

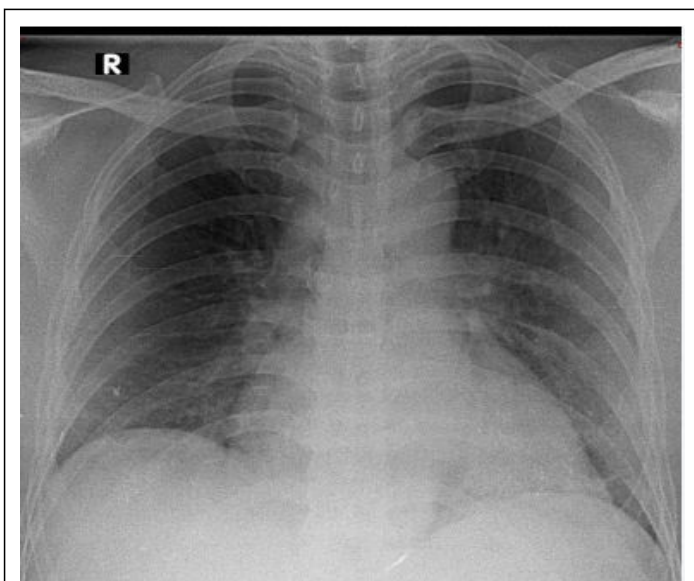
The research method used was analytic observational with a cross sectional design. The research data were taken based on medical records of patients with COVID-19 who were treated at Hasan Sadikin general hospital during the January-May 2021 period. Patients aged 18 years and over who were confirmed to have COVID-19 by polymerase chain reaction test were included in the study. All participants had performed conventional chest radiography with antero posterior projection using Philips medical system type SRO 33100 and reviewed by experienced thorax consultant radiologists. Chest radiography features findings were noted to the medical records. Patients were excluded if they had lung disease other than COVID-19 and incomplete medical record data (Figure 1) [6].

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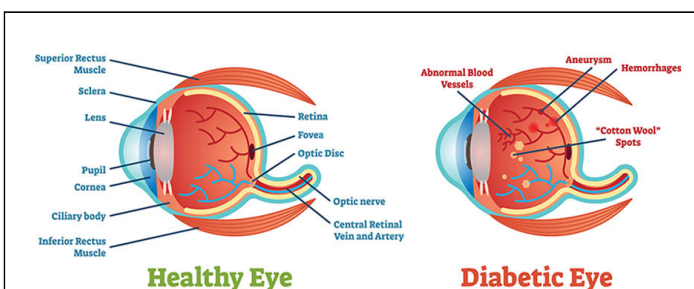


**Figure 1:** Correlation of Chest X-Ray Scores in SARS-CoV-2 Patients with the Clinical Severity.

Descriptive data in the form of age, gender, diabetes mellitus status and lung conditions are presented in tabular form. Pulmonary conditions consist of lung severity based on the BRIXIA score, the location of the infected lung, the predominance of the abnormal lung area and the presence of pleural effusion. The diagnosis of diabetes mellitus is made if the patient has HbA1c with a value of  $>6.5\%$  or has previously been diagnosed with diabetes mellitus.

## Results and Discussion

Pulmonary severity was assessed based on the BRIXIA score. The BRIXIA score determines lung involvement by dividing the lungs into six sections and each is assigned a score of 0, 1, 2 or 3 and the total obtained score is 0-18. The higher the score obtained, the more severe is the lung involved [7]. In this study, the majority of subjects (85.7%) had a BRIXIA score of 0-10, while the remaining subjects had more severe degrees (Figure 2).



**Figure 2:** Diabetic retinopathy.

In addition to the BRIXIA score, lung severity radiographs can also be assessed using the RALE score and percentage of opacity. These three assessments can be done in a short time. A higher value indicates a greater degree of lung severity and is associated with the risk of intensive care unit admission and death. In their study, Crooks and Card observed the severity of radiological features to predict the worsening and outcome of patients with COVID-19. In a study conducted in the UK during the February-July 2020 period, lung

radiographs were examined and assessed using the BRIXIA score, RALE, and percentage of opacity. The results showed 751 lung radiographs, patients with opacity  $>75\%$  had a median admission to the intensive care unit or death value within 1-2 days. In addition, the median survival value was found for the BRIXIA score category of 11-15 for 7.5 days and for the BRIXIA score category of 16-18 for 1.15 days. Using two scoring methods, namely the BRIXIA score and percentage of opacity, Balbi, et al. obtained similar results. In this study, it was stated that the use of the BRIXIA score can be used to predict mortality, while the percentage opacity score can be used to predict the need for ventilation assistance. A chest X-ray is a useful examination in assessing COVID-19 patients. Assessment of lung severity on X-rays needs to be integrated with other data such as patient history,  $\text{PaO}_2/\text{FiO}_2$  ratio and  $\text{SpO}_2$  values to predict mortality and the need for ventilation assistance when patients come to the emergency department.

Another study conducted by Maroldi, et al. also assessed the role of lung X-rays in predicting the outcome of patients with pneumonia due to COVID-19. In this study, a BRIXIA score of 0-18 was used to assess pulmonary involvement of a total of 953 patients who met the criteria; it was found that higher scores were found more in patients who died than in patients who recovered. In statistical analysis, it was found that the BRIXIA score has a strong correlation with disease severity and outcome. The BRIXIA score along with the prognostic model is recommended to be used in predicting outcomes in COVID-19 patients. Worse lung appearance was found more in male than female patients in the group of patients aged 50-79 years. This was found in a study by Borghesi, et al. in Italy who evaluated the relationship of chest X-ray score with the age and sex of patients with COVID-19. The highest chest X-ray score was found in men aged 50 years and older and women aged 80 years and older. These two groups are those with the highest risk for experiencing severe illness.

In the study by Guan, et al., on the clinical characteristics of COVID-19 patients in China, it was reported that ground glass opacity was the most common finding in Computed Tomography (CT) chest radiographs. In 157 of 877 patients (17.9%) no chest radiographic abnormalities were found. This is somewhat different from the results of this study which found consolidation as the most abundant pattern, followed by ground glass opacity, which was close to the number. Patients without abnormalities on chest radiographs were reported in a higher number of 33.6% than in Guan, et al., of 17.9%. The main difference in the two studies is the use of radiographic modalities where Guan, et al used a CT scan while this study used a chest X-ray.

Diabetes mellitus is one of the factors that play a role in the outcome of patients with COVID-19. Pazoki, et al., investigated the mortality risk and severity of COVID-19 patients with diabetes mellitus. The results were obtained from 574 patients treated with COVID-19; 135 of the 176 patients with diabetes mellitus had severe conditions with a higher mortality rate of 30.7% than the non-diabetic patients with a mortality rate of 12.6%. Patients with diabetes mellitus who present with conditions of lower oxygen saturation, higher body temperature and higher blood urea levels are more prone to develop severe COVID-19 and have a poorer prognosis. In this study, the radiological features of the patient were not explained. However, 38.6% of patients with diabetes mellitus had Acute Respiratory Distress Syndrome (ARDS) and 19.3% of them required invasive ventilation. A meta-analysis by Kumar, et al. stated that diabetes mellitus in COVID-19 patients was associated with a two fold increase in mortality and severity of symptoms. In this study, several

confounding factors for the risk of diabetes mellitus include old age, hypertension, the presence of cardiovascular disease and obesity that occur together with diabetes mellitus suffered by the patient.

The condition of hyperglycemia, whether in patients diagnosed with diabetes mellitus or not, is thought to be associated with a more severe COVID-19 condition. This was stated by Iacobellis, et al., who conducted an analysis of hyperglycemic conditions related to radiological predictors of patients with COVID-19. Acute hyperglycemia conditions can cause an inflammatory process and abnormal immune response. These contribute to the worsening and progression of the radiological features of ARDS in COVID-19 patients. Adequate management of hyperglycemia can contribute to the outcome of patients with COVID-19, whether or not they have diabetes mellitus. In this study, it was found that diabetes mellitus was associated with a more severe degree of lung severity in patients aged  $\geq 60$  years. According to Dessie, et al., old age is one of the factors that increase the risk of fatal outcomes. In addition, other factors are acute kidney failure, chronic obstructive pulmonary disease, hypertension, cardiovascular disease, diabetes mellitus, obesity and cancer.

The relationship of lung severity with diabetes mellitus was previously reported in patients with tuberculosis infection. In their study, Barreda, et al., stated that patients with hyperglycemia had a more severe radiographic presentation and a number of pulmonary tuberculosis lesions [8]. It was found that patients with hyperglycemia had more cavities, alveolar infiltrates and fibrosis than normoglycemic patients. The underlying mechanism is associated with a state of leukocyte hyperstimulation due to tuberculosis and hyperglycemia causing the process of 'premature aging' of the lungs. The condition of acute hyperglycemia commonly suffered in patients with sepsis or trauma causes an increase in the inflammatory process; this is reported to exacerbate the damage suffered in patients with Acute Lung Injury (ALI). Wu et al., found that, in ALI with hyperglycemia, severe lung injury occurred along with pulmonary edema, alveolar protein leakage and lung inflammation. This was not observed in the ALI model without hyperglycemia. The pulmonary injury occurs along with increased proinflammatory cytokines, infiltration of neutrophils and alveolar macrophages and expression of pulmonary Sodium Potassium Chloride Co-transporter 1 (NKCC1).

This study is the first study conducted in Indonesia to analyze the relationship between diabetes mellitus and lung severity in COVID-19 patients. Limitations in this study are the presence of confounding

factors such as hypertension, obesity and cardiovascular disorders which were not taken into account. Therefore, further studies are needed with more complete data and larger sample size to ascertain the relationship between diabetes mellitus and hyperglycemia with lung severity.

## Conclusion

There is a significant relationship between diabetes mellitus and lung severity in COVID-19 patients aged  $\geq 60$  years with bilateral lung involvement without pathognomonic pattern and BRIXIA score over 11. Chest X-rays have various advantages, such as: Faster to do, minimal cost and more availability in the emergency room compared to thorax CT scan. It also can be concluded that DM is not the only aggravating factors of the lung severity from this study. A geriatric category is needed in addition to comorbidities to obtain a severe degree.

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