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# Factors Affecting Outcome in Diabetic Patients with COVID-19: A Cross-sectional Study

Malik Chandra*, Andi Makbul Aman, Himawan Sanusi, Husaini Umar

*Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia*

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***Correspondence:** Malik Chandra, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. E-mail: malikchandra00@gmail.com
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**Abstract**

**BACKGROUND:** Type-2 diabetes mellitus (T2DM) is a chronic disease and often found as a comorbid in COVID-19. Poor glycemic control might play a role in worsening of clinical outcome in COVID-19 patients who lead to increase morbidity and mortality.

**AIM:** We conducted a study to evaluate relationship between T2DM with or without macrovascular and microvascular complications and cigarette smoking habit with COVID-19 outcomes.

**METHODS:** A cross-sectional study of hospitalized COVID-19 patients was conducted in Dr. Wahidin Sudirohusodo Hospital, Makassar from May 2020 to August 2020. COVID-19 status was obtained using real-time polymerase chain reaction for SARS-CoV-2, T2DM status was obtained using blood glucose or HbA1c, and other characteristic data were obtained. Mortality was the clinical outcome in our study.

**RESULTS:** One hundred and six subjects data were enrolled. Most subjects were male (n = 55; 51.9%), and 55–65 year-old (n = 40; 37.7%). Eighty subjects were survived (75.5%) and 26 subjects did not survive (24.5%). Onset of T2DM ≥ 5 years had a higher mortality rate compared to onset < 5 years (34.9% vs. 17.5%; p = 0.041). Other factors such as gender, age, nutritional status, hypertension, heart disease, smoking habit, and HbA1c did not show significant difference in terms of mortality.

**CONCLUSION:** COVID-19 patients with onset of T2DM for more than 5 years had a worse outcome compared to the onset of T2DM <5 years.

## Introduction

COVID-19 is an infectious disease caused by novel coronavirus or Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) and became pandemic in 2019. SARS-CoV-2 is known to destruct respiratory tract, lungs, and mostly causing pneumonia [1], [2], [3]. COVID-19 can progressively becoming an acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome (MODS) [4]. People with advanced age and comorbidities such as hypertension, cancer, cardiovascular diseases, diabetes mellitus and kidney diseases are at risk of severe COVID-19 case and higher mortality occurs [5].

Type-2 diabetes mellitus (T2DM) is a global chronic disease and can worsen the outcome of COVID-19 [6]. The presence of T2DM and higher plasma glucose concentration was found to be independent predictors for mortality and morbidity in SARS patients [7]. In two meta-analysis studies, the prevalence of T2DM appeared 8%−11% in COVID-19 cases, next to hypertension (17−21%) [8], [9] However, Onder *et al.* in Italy found a higher prevalence of T2DM in COVID-19 patients, which was 36% from 355 hospitalized COVID-19 patients [10]. A study in Indonesia by Karyono *et al.* found that T2DM was becoming the three most common comorbid found in COVID-19, in which T2DM appeared 33.6% in COVID-19 cases, next to hypertension [11].

Chronic inflammation, coagulation factor activation, immune dysregulation, and potential pancreas destruction by SARS-CoV-2 might be the pathomechanism between COVID-19 and T2DM [12]. Diabetic people are vulnerable to infection due to hyperglycemia, immune dysfunction, vascular complications, and other comorbidities such as hypertension, dyslipidemia, and cardiovascular diseases. Disease severity in COVID-19 patients is higher with T2DM being presented compared to COVID-19 without T2DM [13].

A retrospective and cohort study showed that cigarette smoking habit can worsen the outcome of COVID-19 patients. This phenomena might be due to declining of respiratory function that exacerbated by COVID-19 infections that manifested in respiratory system [14].

Based on condition and theory mentioned above, we conducted a study to evaluate relationship between T2DM with or without macrovascular and microvascular complications and cigarette smoking habit with COVID-19 outcomes.

## Methods

### *Study design*

This study is a cross-sectional study conducted in Dr. Wahidin Sudirohusodo Hospital, Makassar. Data were taken between April 2020 until the number of sample was fulfilled in August 2020.

### *Population*

Subjects were COVID-19 hospitalized patients in Dr. Wahidin Sudirohusodo Hospital, Makassar. Inclusion criteria for this study were adult (>20 year old) COVID-19 hospitalized patients with T2DM and agreed to participate in the study by signing informed consent. Exclusion criteria of this study were hyperglycemia without an established T2DM diagnosis and had pulmonary tuberculosis, advanced-stage malignancy and Acquired Immunodeficiency Syndrome. With an $\alpha$ risk of 0.05 and 80% power, the minimum required number of subjects was 94 subjects.

### *Type 2 diabetes mellitus*

T2DM was diagnosed based on PERKENI 2019 diagnostic criteria. T2DM subject must have at least one of the following condition: (i) Fasting blood glucose ≥126 mg/dL (fasting is defined by absence of calorie intake for 8 h), (ii) 2-h post prandial glucose ≥200 mg/dL after oral glucose tolerance test with 75 g glucose, (iii) random blood glucose ≥200 mg/dL with classic symptoms, or (iv) HbA1c ≥6.5% using National Glycohaemoglobin Standardization Program standard [15].

### *COVID-19*

Confirmed case of COVID-19 was defined by the presence of SARS-CoV-2 virus in real-time polymerase chain reaction (RT-PCR). Samples were taken using nasopharyngeal or oropharyngeal swab.

### *Cigarette smoking*

Subjects with cigarette smoking were an active smoker within the past 6 months before study until the time of this study.

### *Statistic analysis*

Chi-square test was used to analyze the data, with level of significance determined by $p < 0.05$. Data and analysis were presented using narrative analysis, tables, and graphs.

### *Ethics approval*

Ethical approval for this study was obtained from Ethical Committee, Faculty of Medicine, Hasanuddin University (Approval Number: 258/UN4.6.5.31/PP36/2021).

## Results

Table 1 showed the descriptive study of our subjects. Mean age of our subjects was 55.2 ± 11.42 years old and mean onset of T2DM was 5.45 ± 5.83 years. Based on body mass index (BMI) by dividing body weight (kg) with square of body height (m), mean BMI was 23.26 ± 2.89 kg/m$^2$. Mean HbA1c was 9.25 ± 2.63%.

**Table 1: Descriptive statistic study of the variables**

| Variable | Minimum | Maximum | Mean ± SD |
|---|---|---|---|
| Age (years) | 30 | 84 | 55.21 ± 11.42 |
| BMI (kg/m$^2$) | 15.60 | 31.90 | 23.26 ± 2.89 |
| Onset of T2DM (years) | 1 | 32 | 5.45 ± 5.83 |
| HbA1c (%) | 5.20 | 18.40 | 9.25 ± 2.63 |

BMI: Body mass index, T2DM: Type-2 diabetes mellitus, SD: Standard deviation.

Table 2 showed variable distributions among subjects. Most subjects were male, non-obese, had hypertension, and no history of cigarette smoking. Most subjects were 55–65 year old (n = 40; 37.7%), and HbA1C > 6.5% (n = 94; 88.7%). Most subjects were survived throughout hospitalization (n = 80; 75.5%).

**Table 2: Variable distribution among subjects**

| Variable | n (%) |
|---|---|
| Gender | |
| Male | 55 (51.9) |
| Female | 51 (48.1) |
| Age (year old) | |
| < 45 | 21 (19.8) |
| 45–54 | 27 (25.5) |
| 55–65 | 40 (37.7) |
| > 65 | 18 (17.0) |
| Obesity | |
| Obese (BMI>30 kg/m$^2$) | 25 (23.6) |
| Nonobese (BMI≤30 kg/m$^2$) | 81 (76.4) |
| T2DM onset (years) | |
| ≥ 5 | 43 (40.6) |
| < 5 | 63 (59.4) |
| Hypertension | |
| Yes | 66 (62.3) |
| No | 40 (37.7) |
| Heart disease | |
| Yes | 20 (18.9) |
| No | 86 (81.1) |
| Cigarette smoking | |
| Yes | 18 (17.0) |
| No | 88 (83.0) |
| HbA1c | |
| > 6.5 | 94 (88.7) |
| ≤ 6.5 | 12 (11.3) |
| Outcome | |
| Death | 26 (24.5) |
| Survive | 80 (75.5) |

BMI: Body mass index, T2DM: Type-2 diabetes mellitus.

Table 3 showed that mortality rate was higher in male (29.1%), > 65 years old (33.3%), obese (28.0%), had hypertension (24.2%), active smoker (33.3%), and almost balanced in terms of heart disease and HbA1c level. However, these difference was not statistically significant ($p > 0.05$). T2DM onset showed

**Table 3: Association between risk factors with outcome**

| Variable | Outcome | | Total | p |
|---|---|---|---|---|
| | Death (n = 26) | Survive (n = 80) | | |
| Gender | | | | |
| Male | 16 (29.1) | 39 (70.9) | 55 (100.0) | 0.257 |
| Female | 10 (19.6) | 41 (80.4) | 51 (100.0) | |
| Age group (year old) | | | | |
| <45 | 2 (9.5) | 19 (90.5) | 21 (100.0) | 0.317 |
| 45–54 | 7 (25.9) | 20 (74.1) | 27 (100.0) | |
| 55–65 | 11 (27.5) | 29 (72.5) | 40 (100.0) | |
| > 65 | 6 (33.3) | 12 (66.7) | 18 (100.0) | |
| T2DM onset (years) | | | | |
| ≥ 5 | 15 (34.9) | 28 (65.1) | 43 (100.0) | 0.041 |
| < 5 | 11 (17.5) | 52 (82.5) | 63 (100.0) | |
| Nutritional status | | | | |
| Obese (BMI>30 kg/m$^2$) | 7 (28.0) | 18 (72.0) | 25 (100.0) | 0.644 |
| Nonobese (BMI≤30 kg/m$^2$) | 19 (23.5) | 62 (76.5) | 81 (100.0) | |
| Hypertension | | | | |
| Yes | 16 (24.2) | 50 (75.8) | 66 (100.0) | 0.930 |
| No | 10 (25.0) | 30 (75.0) | 40 (100.0) | |
| Heart disease | | | | |
| Yes | 5 (25.0) | 15 (75.0) | 20 (100.0) | 0.957 |
| No | 21 (24.4) | 65 (75.6) | 86 (100.0) | |
| Active smoker | | | | |
| Yes | 6 (33.3) | 12 (66.7) | 18 (100.0) | 0.341 |
| No | 20 (22.7) | 68 (77.3) | 88 (100.0) | |
| HbA1c | | | | |
| > 6.5 | 23 (23.7) | 71 (76.3) | 94 (100.0) | 0.968 |
| ≤ 6.5 | 3 (30.8) | 9 (69.2) | 12 (100.0) | |

BMI: Body mass index, T2DM: Type-2 diabetes mellitus.

to be associated with mortality rate. Most dead subjects had T2DM onset ≥ 5 years (34.9%).

## Discussion

The baseline characteristics of our study were similar to Suhendra *et al.* findings, in which dominated by male (52%), 50–59 years old (22%), and non-obese (99.2%). Mortality rate on their study was 29%. The relative risk for death in male, 50–59 years old and T2DM were 1.5, 4, and 2.8, respectively [16].

In terms of T2DM onset, a study in Wuhan, China, showed that COVID-19 patients with T2DM were at a higher risk for complications and mortality. In terms of complications (ARDS, acute kidney injury, shock, and secondary infection), COVID-19 with T2DM patients was significantly higher than non-T2DM COVID-19 patients. Moreover, death rate in T2DM COVID-19 patients was higher compared to non-T2DM (20.3% vs. 10.5%, p = 0.017) [17].

The onset of T2DM more than 5 years significantly increased mortality in our study (34.9%). A cohort study in Scotland found a higher mortality rate and risk for severe case in COVID-19 patients with Type-1 and Type-2 diabetes mellitus with mean diabetes mellitus onset of 13.5 years for severe case. Another study in China showed that T2DM onset more than 2 years increased mortality rate. Poor glycemic control was a contributing factor to these findings [18], [19].

Other factors such as gender, age, hypertension, HbA1c, obesity, and smoking habit did not show any significant difference in terms of mortality rate in subjects with COVID-19 and T2DM. Our findings were in line with a study in the Philippines that BMI, hypertension and cardiovascular diseases did not increase mortality rate and length of stay in hospital. T2DM was contributing to higher risk for moderate and severe case [20]. Another supporting study was conducted in German, which active smoking, overweight and obesity did not associate with severity and mortality rate in COVID-19 [21]. However, a retrospective study in Wuhan showed that COVID-19 death was dominated by male, mean age of 64 years old and HbA1c > 9% [17]. Similar to the study mentioned, a retrospective study in America also showed that COVID-19 death was dominated by male, mean age of 65 years old, and HbA1c > 8.5% [22].

Our study had several limitations. Some intrinsic (e.g., comorbidities, T2DM treatment, glycemic control, and nutritional status) and extrinsic factors (e.g., nosocomial infection and treatment during hospitalization) which could affect outcome was not evaluated. Further study should be conducted regarding to insulin use, adherence to T2DM therapy, and medication history before COVID-19 onset. Changes in the guideline of COVID-19 therapy that have been revised 3 times in Indonesia can be used as a comparison of the outcomes of each change in guidelines to assess the success of therapy.

## Conclusion

The onset of T2DM for more than 5 years was associated with higher hospitalized COVID-19 mortality rate. Other risk factors such as male, 55 – 65 years old and HbA1c > 6.5% was found to be higher in COVID-19 patients who died during hospitalization.

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