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THE CORRELATION BETWEEN TYPE 2 DIABETES MELLITUS WITH BACTERIAL INFECTION IN COVID-19 PATIENTS ADMITTED TO INTENSIVE CARE UNIT AT CENTRAL GENERAL HOSPITAL PROF. DR. I.G.N.G. NGOERAH DENPASAR IN 2021-2022

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) has a detrimental impact on the immune system, resulting in a decrease in the body's immune response, making patients highly susceptible to bacterial infections. Patients with T2DM, especially those treated in the Intensive Care Unit (ICU) of a hospital, face an increased risk of infection. The emergence of COVID-19, which also infects T2DM patients, further diminishes the immune system's function in these patients. Consequently, individuals with both T2DM and COVID-19 are at a heightened risk of developing secondary infections, commonly referred to as Hospital-Acquired Infections.This research aims to explore the relationship between T2DM, assessed through blood sugar levels, and the occurrence of bacterial infections in COVID-19 patients treated in the ICU of Prof. Dr. I.G.N.G. Ngoerah Central Hospital from 2021 to 2022. The research design employed is quantitative analytical correlational study using a cross-sectional approach, with a sample size of 98 patients collected from the Medical Records and Hospital Management System of Prof. Dr. I.G.N.G. Ngoerah Central Hospital in Denpasar. This study found that there is a significant correlation between patient's infection profile with random blood glucose levels with an Odds Ratio (OR) of 1.15 (95% CI: 1.04 – 1.27; p = 0.013). Additionally, a significant relationship was observed between the severity of COVID-19 and bacterial infections in patients, with an Odds Ratio of 1.12 (95% CI: 1.01 – 1.26; p = 0.04).
Keywords : T2DM., ICU., Hospital-Acquired Infection

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is defined by hyperglycemia or a chronic and varied elevation in blood glucose levels.[1] This condition exerts an impact by disrupting the immune system, leading to a diminished immune system and making patients more susceptible to bacterial infections.[2]On March 2020, SARS-CoV-2 more commonly known as COVID-19 declared as a pandemic by the WHO. The demand for healthcare services significantly increased, especially for patients with comorbidities[3]

Patients with T2DM who are hospitalized, especially in the Intensive Care Unit (ICU), face an increased risk of infection. The emergence of COVID-19, which also infects T2DM patients, exacerbates insulin resistance in T2DM, leading to a further decline in the patient's immune system.[4,5] Therefore, patients with both T2DM and COVID-19 are highly susceptible to secondary infections, commonly referred to as Hospital-Acquired Infections.[6]In hospital settings, the risk of nosocomial infections is higher in the ICU compared to other departments within the hospital. The risk of nosocomial infections in the ICU is 5-10 times higher than in outpatient clinics or surgical rooms. Nosocomial infections are defined as those that develop 48 hours after admission to the hospital or within 48 hours of discharge. Patients in the ICU have a significantly higher risk of infection due to their increased immune vulnerability.[7] A multisite study in China revealed that 92.9% of COVID-19 patients with severe symptoms had co-infections. It is reported that a significant cause of these secondary co-infections is due to Healthcare Associated Infections (HAIs).[6] A systematic review study indicates that co-infection occurred in 3.5% of cases, with secondary infections present in 14.3% of COVID-19 patients. Bacteria are known to be the cause of infection in 6.9% of these cases.[8]

Additionally, the condition of COVID-19 patients worsens with various comorbidities, one of which is T2DM. Studies indicate that the presence of hyperglycemia in T2DM patients can increase mortality and result in a poor prognosis in the pathophysiology of COVID-19. Clinically, it is also stated that COVID-19 patients with T2DM experience a significant decline in immune response. Consequently, with a weakened immune system, bacterial co-infections can easily occur in COVID-19 patients with T2DM.[9]A study of 129 patients with comorbid Type 2 Diabetes Mellitus (T2DM) indicated that 64.2% of patients with T2DM and bacterial co-infections experienced mortality.[10] Co-infections were predominantly dominated by pathogenic respiratory bacteria such as K. pneumoniae (9.9%), S. pneumoniae (8.2%), and S. aureus (7.7%). The overall prevalence of co-infections (whether bacterial, viral, or fungal) in patients

was found to be 32%, with 32% of them having comorbidities.[11,12]

The importance of understanding the relationship between COVID-19 patients with T2DM treated in the Intensive Care Unit (ICU) and the potential co-infection by other bacteria compels the author to delve deeper into the association between the two. This research can subsequently serve as a scientific foundation for further research for COVID-19 patients with comorbidities.

MATERIALS AND METHODS

The design of this study employs a quantitative analytical correlational approach utilizing a cross-sectional method to investigate the relationship between Type 2 Diabetes Mellitus (T2DM), as indicated by random blood glucose levels, and the occurrence of bacterial infections in COVID-19 patients treated in the ICU of Prof. Dr. I.G.N.G Ngoerah Central Hospital during the years 2021-2022. Data for the study are sourced from secondary data available in the Medical Records Department of Prof. Dr. I.G.N.G. Ngoerah Central Hospital. The study sample consists of COVID-19 patients with T2DM admitted to the ICU of Prof. Dr. I.G.N.G. Ngoerah Central Hospital during 2021-2022 that meet the inclusion and exclusion criteria set for this research. In determining the sample size for this study, the Lemeshow Formula is utilized, yielding a minimum required sample size of 97 participants. The data were subsequently processed using Statistical Product and Service Solution (SPSS) version 26.0 software. Data analysis included univariate analysis based on variable types and bivariate analysis using hypothesis testing presented in chi-square tables to substantiate the research hypotheses. This study has obtained ethical clearance from with reference number 2060/UN 14.2.2.V11.14/LT/2023 issued by the Ethical Commission of the Faculty of Medicine, Udayana University and protocol number DP.04.03/XIV.2.2.2/48213/2023 from the Research and Education Unit of Prof. Dr. I.G.N.G. Ngoerah Teaching Hospital, valid until September 2024.

RESULT

The results of demographic and morbidity data based on univariate analysis are reported in Table 1-2. According to the table outlining the basic characteristics of patients involved in this study, several observations can be made regarding the analyzed variables, including gender, age, fasting blood glucose levels, HbA1c levels, duration of treatment in the ICU, severity of COVID-19, complications of diabetes mellitus, complications of COVID-19, comorbidities, and infection profile categorized into two groups: patients without nosocomial infections and patients with nosocomial infections.

Table 1. Result of Univariate Analysis of Demographic Data

Parameter	Frequency (N)	Percentage (%)
Gender		
Male	64	65.3
Female	34	34.7
Age (year) (Mean ± SD)	62.61 ± 11.36	
Random Blood Glucose Levels		
Normal	44	44.9
Abnormal	54	55.1
Mean (± SD) mg/dL	238.95 ± 124.13	
HbA1C		
Regulated	26	26.5
Unregulated	72	73.5
Mean (± SD) (%)	8.40 ± 2.02	

Based on gender, the majority of patients were found to be male, comprising 64 patients or 65.3%. The mean age of patients was 62.61 ± 11.36 years. The mean level of random blood glucose level in patients was 238.95 ± 124.13 mg/dL, with the majority of patients having abnormal blood glucose levels (55.1%). Meanwhile, based on HbA1c levels, the majority of patients had uncontrolled levels (73.5%), with an average level of 8.40 ± 2.02%. Regarding complications of diabetes mellitus, the majority of patients were those with complications, accounting for 50 individuals or 51%.

Table 2. Result of Univariate Analysis of Morbidity Data

Parameter	Frequency (N)	Percentage (%)
Duration of Stay in ICU		
< 7 days	42	42.9
≥7 days	56	57.1
Mean (± SD) days	7.99 ± 5.20	
Infeksi Profile		
Without Nosocomial Infection	91	92.9
With Nosocomial Infection	7	7.1
Severity of COVID-19		
Severe	45	45.9
Critical	53	54.1
Complication of Diabetes Mellitus		
Without Complication	48	49.0
With Complication	50	51.0
Complication of COVID-19		
Without Complication	8	8.2
With Complication	90	91.8
Comorbidities		
None	39	39.8
Hipertension	29	29.6
Heart Failure	5	5.1
Stroke	2	2.0
CAD	5	5.1
Arrhythmia	1	1.0
Hipertension and Hearth Failure	11	11.2
Hipertension and Stroke	2	2.0
Hipertension and COPD	1	1.0
Hipertension and CAD	3	3.1

Evaluated based on the patients' infection profiles, the majority of patients did not have nosocomial infections, totaling 91 individuals. Meanwhile, there were 7.1% of patients with nosocomial infections. Based on the severity of COVID-19, most patients were in critical condition, with 53 patients or 54.1%. Additionally, 91.8% of patients had complications related to COVID-19. In terms of the analysis of patient comorbidities, the most prevalent comorbidity among patients was hypertension, accounting for 29.6% of the total research sample.Bivariate analysis was used to find the relationships between variables included in this study and is presented in Tables 3-8.

Table 3. Correlation Between Random Blood Glucose Levels in Type 2 Diabetes Mellitus with Bacterial Infection in COVID-19 Patients

Random Blood Sugar	Infection Profile				OR (CI95%)	p
	Without Infection		With Infection			
	n	%	n	%		
Normal	44	44.9	0	0.0	1.15 (1.04 – 1.27)	0.013
Abnormal	47	48.0	7	7.1		
Total	91	92.9	7	7.1		

The analysis results related to diabetes mellitus reveal a significant correlation between the patient's infection profile and the random blood glucose levels, with an Odds Ratio (OR) of 1.15 (95% CI: 1.04 – 1.27; p = 0.013).

Table 4. Correlation Between HbA1C in Type 2 Diabetes Mellitus with Bacterial Infection in COVID-19 Patients

HbA1C	Infection Profile				OR (CI95%)	p
	Without Infection		With Infection			
	n	%	n	%		
Regulated	22	22.4	4	4.1	0.88 (0.74 – 1.05)	0.08
Unregulated	69	70.4	3	3.1		
Total	91	92.9	7	7.1		

The analysis results related to diabetes mellitus using HbA1c levels reveal that there is no significant correlation between the infection profile and the HbA1c levels of patients, with an Odds Ratio (OR) of 0.88 (95% CI: 0.74 – 1.05; p = 0.08).

Table 5. Correlation Between Length of Stay Hubungan Lama Perawatan in ICU with Bacterial Infection in COVID-19 Patients

ICU	Infection Profile				OR (CI95%)	p
	Without Infection		With Infection			
	n	%	n	%		
< 7 days	41	41.8	1	1.0	1.09 (0.98 – 1.21)	0.115
≥ 7 days	50	51.0	6	6.1		
Total	91	92.9	7	7.1		

Based on the duration of stay, no significant correlation was found with the infection profile, with an Odds Ratio (OR) of 1.09 (95% CI: 0.98 – 1.21; p = 0.115).

Table 6. Correlation Between T2DM Complication with Bacterial Infection in COVID-19 Patients

T2DM Complication	Infection Profile				OR (CI95%)	p
	Without Infection		With Infection			
	n	%	n	%		
With Complication	45	45.9	3	3.1	1.02 (0.91 – 1.14)	0.523
Without Complication	46	46.9	4	4.1		
Total	91	92.9	7	7.1		

Non-significant results were also found in the analysis of the association between the infection profile and comorbidities related to diabetes mellitus, with an Odds Ratio (OR) of 1.02 (95% CI: 0.91 – 1.14; p = 0.523).

Table 7. Correlation Between COVID-19 Severity with Bacterial Infection in COVID-19 Patients

Severity	Infection Profile				OR (CI95%)	p
	Without Infection		With Infection			
	n	%	n	%		
Severe	50	51	1	1.0	1.12 (1.01 – 1.26)	0.04
Critical	41	41.8	6	6.1		
Total	91	92.9	7	7.1		

Based on the correlation between nosocomial infection and COVID-19, there are several analysis parameters that can be reported. The data analysis results show a significant relationship between COVID-19 severity and bacterial infection in patients, with an Odds Ratio of 1.12 (95% CI: 1.01 – 1.26; p = 0.04).

Table 8. Correlation Between COVID-19 Complication with Bacterial Infection in COVID-19 Patients

COVID-19 Complication	Infection Profile				OR (CI95%)	p
	Without Infection		With Infection			
	n	%	n	%		
With Complication	8	8.2	0	0.0	1.08 (0.92 – 1.02)	0.540
Without Complication	83	84.7	7	7.1		
Total	91	92.9	7	7.1		

Based on correlation between COVID-19 complications and bacterial infection in patients, no significant association was found with an Odds Ratio of 1.08 (95% CI: 0.92 – 1.02; p = 0.540).

DISSCUSSION

Discussion regarding the research on the association between Type 2 Diabetes Mellitus (T2DM) and bacterial coinfection in COVID-19 patients has been reported in previous studies. This research reports a significant relationship between blood glucose levels and bacterial nosocomial infections, as well as a relationship between the severity of COVID-19 and bacterial infections. These conditions have been described in earlier research by He et al. (2020), who evaluated nosocomial infections in COVID-19 patients in Wuhan, China. The analysis results indicated several comorbidity predictors closely related to nosocomial infection occurrences in patients, including hypertension, cardiovascular diseases, diabetes, kidney problems, and others. Specifically, regarding diabetes mellitus, the study reported that diabetes mellitus is a dependent variable for nosocomial infection, with an Odds Ratio of 3.06 (95% CI, 1.41–7.22; p = 0.037).[13]

Patients that diagnosed with both COVID-19 and Type 2 Diabetes Mellitus (T2DM), as discussed earlier, are at risk of a poor prognosis with a high probability of complications. Dysregulation and weakened immunity, coupled with chronic inflammation, can lead patients into a chaotic metabolic state. Various studies have indicated that hyperglycemia in T2DM patients poses a significant risk of COVID-19 infection. This is further exacerbated by the decreased body immunity, providing an opportunity for coinfection.[14]

COVID-19 patients with T2DM are estimated to have a 14% to 32% higher risk of falling into critical conditions. The majority of patients in the ICU are those with comorbidities of the metabolic system, with T2DM being one of them. This double diagnosis indicates a percentage of 22.2% in the ICU compared to 5.9% of T2DM patients outside the ICU. The death rate is also reported to be seven to eight times higher in T2DM patients.[14] A study shows the occurrence of coinfections in COVID-19 patients with chronic diseases (hypertension, T2DM, chronic heart disease, chronic lung disease, etc.) dominated by respiratory pathogenic bacteria with some also lead to bacteremia.[7]

Regarding comorbidities, other complications experienced by patients, and their connection to diabetes mellitus, COVID-19, and nosocomial infections, previous research by Mohammadnejad et al. (2021) has been reported. This study, conducted in Tehran, evaluated the comorbidities of COVID-19 patients. The research reports that out of 289 COVID-19 patients, 221 had comorbidities, and 141 of those with comorbidities tested positive for nosocomial infection. This figure is higher compared to patients without comorbidities who experienced nosocomial infection, numbering 22 patients.[15]

Certainly, this correlate with the decreased immunity induced by occurring comorbidities, one of which is caused by diabetes mellitus. The presence of hyperglycemia in T2DM patients can risen mortality and increase bad prognosis in the pathophysiology of COVID-19. Various complications from the interaction of these two diseases can arise at any time, including heart disease, heart failure, and chronic kidney disease.[16] Clinically, it is also stated that COVID-19 patients with T2DM experience a significant decrease in immune response, causing the lung's survival against bacterial infections to weaken. As a result, with a weakened immune system, bacterial coinfection can easily occur in COVID-19 patients with T2DM. A study on 129 comorbid T2DM patients showed a Case Fatality Rate (CFR) of 35.8%. This result increased compared to non-DM patients with a CFR of 10%. In the same sample, it was found that 64.2% of T2DM patients with bacterial coinfection died, with the majority of coinfections by K. pneumonia and A. Baumannii.[10]

This decrease in immunity is related to the severity of the disease, which was also significant in this study. This is similar with previous research by Asmarawati et al. (2021), who evaluated bacterial coinfection in COVID-19 patients with mild, severe, and critical conditions in Surabaya, Indonesia. The study showed an increase in the duration of hospitalization between patients with bacterial infection and non-bacterial infection (<0.05). The study reported the average duration of hospitalization in patients without bacterial infection was 13.31 + 7.12, while in patients with bacterial infection, the average duration of hospitalization was 17.6 + 6.62 days. In addition, the severity of COVID-19 is closely related to the duration of hospitalization, where the average duration of hospitalization in patients with mild, severe, and critical COVID-19 is 12.97 + 6.7, 15.61 + 7.1, and 16.89 + 9.4 days, respectively (p = 0.03).[17]

The worsening of clinical manifestations in patients is associated with several other factors. Comorbidities, including diabetes mellitus, are closely related to the clinical outcomes and severity levels of COVID-19.[18] Moreover, complications from COVID-19 are also closely related to the duration of hospitalization, severity, and clinical outcomes of patients. Previous research by Hasabo et al. (2021) showed several

COVID-19 complications related to patients' clinical outcomes and predictors of patient mortality. The study indicated symptoms such as shortness of breath as a specific predictor of patient mortality, with an Odds Ratio of 3.39 (95% CI: 1.35-8.54; p = 0.01). In addition, other COVID-19 complications that also have an impact include sepsis (OR: 15.07; p <0.001), acidosis (32.7; p < 0.001), respiratory failure (OR: 44.75; p < 0.001), and ARDS (OR: 6.53; p = 0.002). The results of these complications were also found in severe and critical COVID-19 patients in this study.[19,20]

CONCLUSIONS AND SUGGESSTION

From the study and discussion above, several conclusions can be drawn. Significant relationship can be found between Type 2 Diabetes Mellitus (T2DM), as indicated by random blood glucose levels, and the occurrence of bacterial infections. Additionally, the severity of COVID-19 is correlated with bacterial infections in COVID-19 patients treated at the ICU of Prof. Dr. I G.N.G. Ngoerah Regional General Hospital in 2021-2022.Furthermore, the author suggests conducting further research with a cohort design that can follow up and determine patient outcomes based on their infection status over a specific duration. Additionally, it is necessary to perform multivariate analysis to exclude confounding variables in this study to reduce bias.

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