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Evaluation of Insulin and Sulfonylurea Types on Severe Hypoglycemia Event Among Ambulatory Type 2 Diabetes Mellitus Patients. A Case-Control Hospital-Based Study in Bali

Made Krisna Adi Jaya[1,2], Fita Rahmawati[1], Nanang Munif Yasin[1] and Zullies Ikawati[1]*

[1]Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.
[2]Department of Pharmacy, Faculty of Maths and Science, Universitas Udayana, Bali, Indonesia.
*Corresponding Author E-mail: zullies_ikawati@ugm.ac.id

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The management of blood glucose levels in patients with type 2 diabetes mellitus (T2DM) often involves the use of effective diabetes medications, such as insulin and sulfonylurea (SU). Despite the potential, these drugs can potentially lead to hypoglycemia during treatment. Objective: Therefore, this study aims to determine the types of insulin and sulfonylureas that commonly cause hypoglycemia. Methods: Using a case-control study design, hospitalized occurrences of hypoglycemia were assessed while considering factors that influenced its incidence through Odds Ratio (OR) calculations at a confidence interval (CI) level of 95%. Results: The results showed that hypoglycemia occurred more often in patients who used insulin, SU, or both compared to non-users ($p<0.05$). In addition, a risk of 4.5 (CI95%: 1.580-12.817) times higher was found in patients taking insulin and SU compared to others. Conclusion: Ambulatory T2DM patients who use insulin or SU as DM therapy must be given special attention. Education related to the risk of hypoglycemia, how to use medication, and first aid in emergency conditions must be provided by health workers to outpatients with DM.

Keywords: Diabetes Mellitus; Hypoglycemia; Insulin; Medication Safety; Sulfonylurea.

Consuming glucose-lowering drugs can heighten the risk of hypoglycemia in individuals with type 2 diabetes mellitus (T2DM)[1]. This condition leads to symptoms related to autonomic or neuroglycopenic effects caused by low blood sugar levels (d" 70 mg/dl)[2]. Hypoglycemia may elevate mortality rates, induce hospital admittance, and lead to substantial medical expenses. Indonesia allocated a total cost of USD 23 million for treating hypoglycemic incidents incurred by their government during the year 2016, an amount that was exceedingly high[3,4].

Previous studies indicate that ambulatory T2DM patients in Indonesia are frequently prescribed insulin and sulfonylurea, which are covered by the Indonesian National Health Insurance (BPJS Kesehatan). These drugs have been shown to effectively regulate blood sugar levels[5,6], while also being cost-effective compared to other options[7,8]. However, hypoglycemia can occur when patients lack knowledge on how their correct use. Once educated on proper administration techniques, including initiation, consumption control, or regulation of dose intake

along with monitoring, there is no associated risk. A previous report revealed that many patients ignore the associated risk, which makes hypoglycemia occur [4,9,10].

In Bali Island, Indonesia, no reports have been conducted on how insulin and sulfonylurea frequently cause hypoglycemia in T2DM patients. Therefore, this study aims to determine the types of insulin and sulfonylureas that commonly cause hypoglycemia. The finding is significant for clinicians to assess the benefits and challenges in ambulatory patients who use T2DM treatment.

MATERIALS AND METHODS

Study Design, Setting, and Sample Size

A case-control design was used, and the procedures were conducted in Bali province at three government hospitals. The hospitals were in Badung district, Denpasar City, and Buleleng Regency. Observation of T2DM patients' demographic data and medical history was carried out. Furthermore, the presentation of results was based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for case-control design[11]. The case and control groups each contained 100 participants using the minimum sample calculation for the design used. The minimum number of patients who were analyzed was 200 participants.

Study Participants, Data Collection, Measurements, and Variables

The population of this study was all patients who were diagnosed with T2DM in three government hospitals in the province of Bali, Indonesia, with age criteria e"20 years, and those who carry diabetes medication such as biguanide drugs, sulfonylurea, TZDs, incretin mimetics, alpha-glucosidase inhibitors, SGLT2-inhibitors, or insulin. The sample was part of the population that met the inclusion criteria. Participants were included when their medical record data for the previous year was completed. In addition, the intended medical record consisted of a diagnosed individual with T2DM exhibiting primary identity data, age, gender, profile of DM drugs used, duration of DM, blood glucose profile, BMI, and comorbidities. Patients excluded from this study were those with hypoglycemia, which was not a result of medication, some records were not comprehensively reported, such as illegible, scattered, exchanged, and duplicated data.

The hospital medical database was initially sorted by ICD-10 codes E11 and E16.2 to obtain patients' record numbers and were taken sequentially according to their database from January 2022 to May 2024 for review. The case-control study commenced with the determination of patients' results in the form of history, and there was no history of hospitalization hypoglycemia. The operational definition of hospitalized hypoglycemia was a patient who comes with signs and symptoms of hypoglycemia characterized by blood sugar levels <54 mg/dL. Medical personnel treated this condition with 10% Dextrose fluid. This outcome was further observed retrospectively as a medication predictor that had the potential to cause outcomes, specifically in the insulin and sulfonylurea medication groups. T2DM patient's medication variables were analyzed as exposure were the use of basal-bolus, basal, bolus, mixed, sulfonylurea (glimepiride, glibenclamide, glikazide, gliquidone), and a combination use of insulin and sulfonylurea.

The review process was conducted by eight reviewers, who held open meetings to discuss the results. An evaluation phase was carried out until an agreement was reached when there were differences of opinion. Furthermore, for medical records that underwent the review stage and agreed to be utilized in the analysis, patients were contacted by telephone to obtain approval for their inclusion. The data was finally analyzed to observe when patients had obtained consent by signing the consent form, which was sent and signed digitally.

Potential Sources of Bias

Potential bias was the type of insulin and sulfonylurea used by T2DM patients as well as patients' compliance with their disease control. This bias was controlled by setting inclusion criteria in the form of patients who only had regular check-ups at the multicenter study site from the previous year. Meanwhile, bias in the type of insulin and sulfonylurea used by patients was overcome by conducting a multivariate analysis to assess the interacting variables of the type of insulin and sulfonylurea in obtaining more detailed results as the strongest predictor of causing hypoglycemia.

Statistical Analysis

Data analysis was conducted descriptively

and analytically. Descriptive data showed the demographic characteristics of all participants observed. Analytical data was to assess the risk of hypoglycemia in patients using insulin, sulfonylurea, and combinations of insulin and sulfonylurea in the case and control groups. Data analysis was assisted with the IBM SPSS 21 version. In addition, the primary data were analyzed using chi-square analysis with odds ratio (OR) parameters, and 95% confidence intervals were used in the initial analysis. When data was found with a p-value d"0.25, the variables continued to be analyzed with multivariate logistic regression. Final statistical analyses were two-tailed, and a p-value of <0.05 was considered statistically significant.

Ethical Consideration

This report was part of a larger study in which the data collection process was conducted from January 2022 to May 2024. The Faculty of Medicine, Udayana University, Bali, ethics commission approved this study with an ethical clearance number 1165/UN.14.2.2.VII.14/LT/2024. Ethical clearance was obtained from the multicenter hospitals, namely Denpasar City Hospital, Badung Regency Hospital, and Buleleng Regency Hospital, with ethical clearance number 052/EA/KEPK.RSBM.DISKES/2024, B/475/UN14.6/PT.01.04/2024, and 019/EC/KEPK-RSB/V/2023 respectively. Consent was obtained from participants using an approved and locally translated digital consent form. Patients were informed about the details of the study, including the general overview, purpose, risks, and benefits. Confidentiality was maintained throughout all stages. This study was conducted following the Declaration of Helsinki.

RESULTS

The Flow of Study Subjects and Data Selection

During the study period, 1231 patients were identified in the database. After the screening process, a total of 260 patients were eligible to be participants (Figure 1). Some medical record data was found to be incomplete or scattered because the multicenter site had not fully implemented digital health records. The medical record data reviewed was paper-based hardcopy data.

Some patients were recorded to be suffering from hypoglycemia not due to diabetes medication but due to certain medical conditions such as decompensated cirrhosis, delirium, schizophrenia, non-hemodialysis CKD, complex heart disease, etc. Consequently, it must be excluded from the criteria. A total of 138 patient data in the case group and 122 patient data were successfully included in the analysis until the final stage following the study criteria.

Demographic Characteristics of Study Subjects

The T2DM patients involved in this study were distributed proportionally between men and women. In addition, their age was more distributed in the age group >46 years. Patients who had diabetes for more than five years with typical comorbidities in the form of macrovascular and microvascular complications were more dominant. The detailed demographic characteristics are shown in Table 1.

Approximately 60% of the total patients involved were consumers of insulin, sulfonylurea, or both in combination. This condition was ideal for exploring more deeply the risk of developing hypoglycemia in the patients and exploring which types of medications were at more risk of causing hypoglycemia. Averagely 85% of the study participants did not have good glucose control, where the average HbA1C level was >7%, average fasting blood >126 mg/dL, random blood, and 2 hours postprandial glucose was above 200 mg/dL.

Evaluation of Insulin and Sulfonylurea Types on Severe Hypoglycemia Event Among Ambulatory Type 2 Diabetes Mellitus Patients

The incidence of hospitalized hypoglycemia in the case and control groups in the variables of patients using insulin, sulfonylurea, a combination of both, and non-users of both was found to be significantly different from bivariate analysis ($p<0.05$). These results are shown in Table 2. Based on the type of insulin and sulfonylurea, it was found that differences in insulin type significantly influenced the incidence of hypoglycemia in the case group compared to controls when explored. However, no significant difference was observed in the type of sulfonylurea between the case and control groups. For the sulfonylurea type, it was found that the p-value was d"0.25, so the sulfonylurea-type variable was

eligible for inclusion in the multivariate analysis to observe the interaction between variables on the outcome of hypoglycemia.

Table 3 presented the multivariate analysis, showing that patients using insulin tended to be at risk of experiencing hypoglycemia 2.9 times greater than the control group (CI95%: 1.6-5.2). Meanwhile, sulfonylurea (SU) users had a 2.3 times risk (CI95%: 1.1-4.8) of experiencing hypoglycemia compared to the control group. When insulin and sulfonylurea were combined, the results increased the risk of hypoglycemia events up to 4.5 times (CI95%: 1.6-12.8) compared to the control group.

Multivariate analysis still observed the types of insulin and sulfonylurea that were found to cause the most hypoglycemia hospitalizations. In this study, it was found that patients who used basal-bolus insulin had a risk of experiencing hypoglycemia 4.3 times (CI95%: 2.2-7.7) compared to the control group. Meanwhile, the use of glimepiride sulfonylurea was found to have 2.2 times (CI95%: 1.1-4.1) higher risk of causing hypoglycemia compared to the control group, as shown in Table 4. An interesting result was found in this original study, which includes the use of basal insulin, bolus insulin, or mixed insulin alone, which did not have a significant effect on the incidence of hypoglycemia in the case or control groups. However, sulfonylurea types Glibenclamide, Glikazide, and Gluquidone were found to be insignificant causes of hypoglycemia.

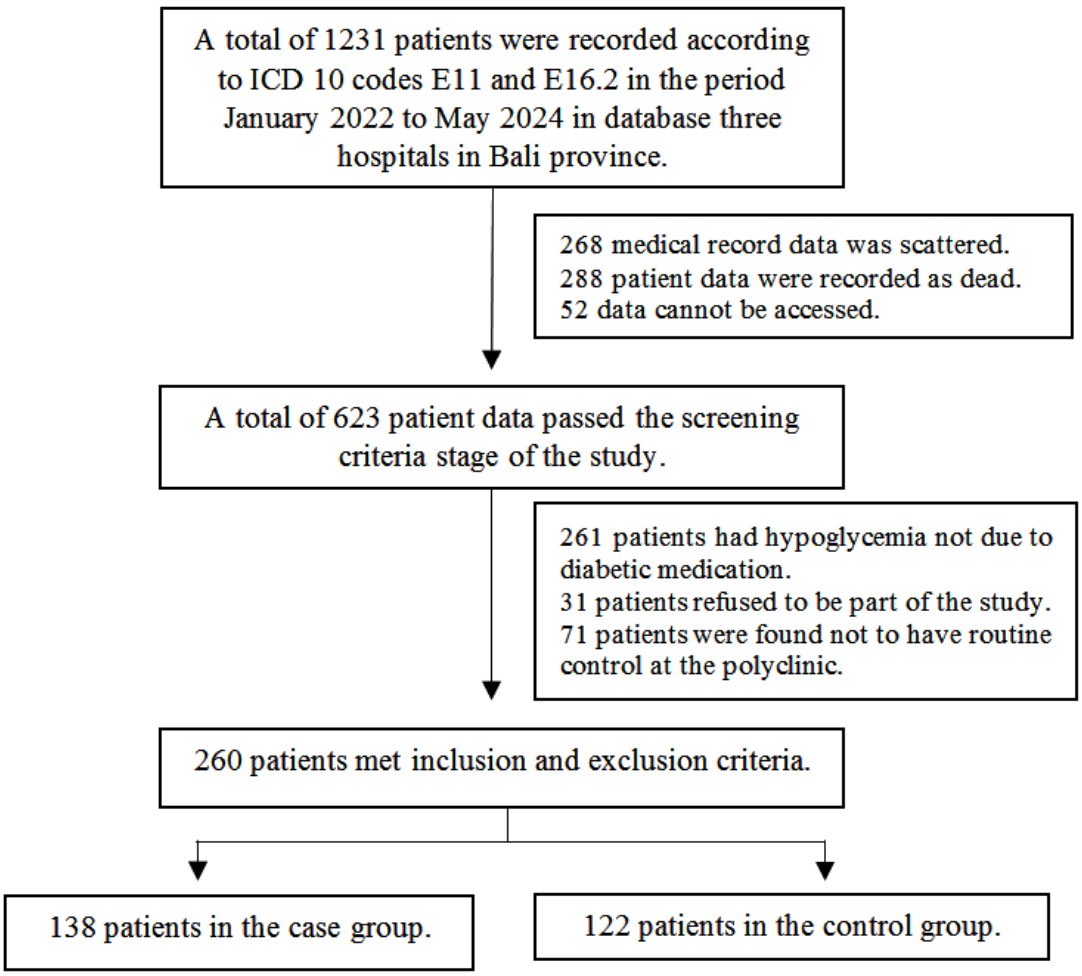

Fig. 1. Flow diagram summarizing patients selection criteria for a case-control study.

DISCUSSION

Hypoglycemia was often found in T2DM patients when discharged with diabetes medication, which insulin and sulfonylurea caused. A Cochrane systematic study found that hypoglycemic events were 2.0 to 2.6 events per participant taking insulin alone compared with 2.2 to 6.1 events per participant for patients taking insulin and sulfonylurea[8]. Another study also reported that the overall incidence of hypoglycemia (defined as hospitalization) was more frequent in the elderly, with an OR for hypoglycemia of 4.7 with sulfonylurea and insulin compared with 4.2 for insulin and 3.9 for sulfonylurea[9,16]. These results were consistent with several of these studies and need to be highlighted as there was a tendency for the incidence of hypoglycemia to be more often found when using basal-bolus insulin and glimepiride as a kind of sulfonylurea. The risk increased two times more when basal-bolus insulin was combined with glimepiride than when combined alone.

The risk of hypoglycemia in insulin users was due to the non-fixed dose of basal-bolus insulin. Patients who adjusted the basal-bolus insulin dose according to nutritional intake were at risk of developing hypoglycemia. Those who fail to understand this dose adjustment are at high risk of hospitalized hypoglycemia. Patients who consume oral antidiabetes (OAD), specifically the sulfonylurea group, must know the most

Table 1. T2DM Patients' Characteristics

No	Characteristics	Case Group (Hypoglycemia) (n=138)	Control Group (Non-Hypoglycemia) (n=122)	P Value (χ2)
1	Gender			0.227
	Male (n %)	70 (50.72)	71 (58.20)	
	Female (n %)	68 (49.28)	51 (41.80)	
2	Ages (Years)			0.036*
	20-30 (n %)	2 (1.45)	3 (2.46)	
	30-45 (n %)	12 (8.70)	20 (16.39)	
	46-55 (n %)	34 (24.64)	43 (35.25)	
	56-65 (n %)	46 (33.33)	30 (24.59)	
	>65 (n %)	44 (31.88)	26 (21.31)	
3	BMI (kg/m^2)			0.100
	Under Weight (n %)	4 (2.90)	3 (2.46)	
	Normal (n %)	44 (31.88)	52 (42.62)	
	Overweight (n %)	75 (54.35)	48 (39.34)	
	Obese (n %)	15 (10.87)	19 (15.57)	
4	T2DM Duration (year)			0.001*
	e"5 (n %)	118 (85.51)	75 (61.48)	
	< 5 (n %)	20 (14.49)	47 (38.52)	
5	Blood Glucose(HbA1C, fasting, prandial, random)			0.001*
	Uncontrolled	129 (93.48)	91 (74.59)	
	Controlled	9 (6.52)	31 (25.41)	
6	Comorbidity			
	CKD (n %)	45 (32.61)	18 (14.75)	0.001*
	Neuropathy DM (n %)	65 (47.10)	36 (29.51)	0.004*
	Cardiovascular diseases (n %)	3 (2.17)	3 (2.46)	0.879
	Retinopathy DM (n %)	19 (13.77)	16 (13.11)	0.878
	Diabetic foot (n %)	26 (18.84)	22 (18.03)	0.867
	Gastropathy DM (n %)	84 (60.87)	69 (56.56)	0.481

n: number; T2DM: type 2 diabetes mellitus; DM: diabetes mellitus; CKD: chronic kidney diseases; χ2: Chi-Square analysis; *:statistically significant

appropriate time to use the drug to avoid the risk of hypoglycemia[16-19]. The results recommended selecting a combination of basal-bolus insulin with glimepiride as the last choice for blood sugar control in T2DM patients.

In developed countries, there has been a shift in the use of diabetes medication to direct incretin mimetic agents (GLP-1) and indirect agents such as DPP4 inhibitors[2,19]. SGLT2-I is also widely reported to provide good glycemic control for DM patients. These drugs are considered effective in controlling blood sugar, minimizing hypoglycemia side effects, minimizing weight gain, and promoting weight loss[2]. The use of these agents is still limited due to cost and access constraints, especially in developing countries[2,19]. Developing countries such as Indonesia still rely on insulin and SU as blood sugar controllers for patients because they are cost-effective, covered by national health insurance, and have easy access to remote areas[12]. The findings of this original research were expected to provide a detailed picture of the incidence of hypoglycemia in the use of these agents, along with the types of insulin and SU with the highest incidence of severe hypoglycemia. Basically, ambulatory T2DM patients with insulin and SU have a high risk of hypoglycemia event. So, they are highly recommended to obtain comprehensive information regarding medication use from start, take, add, review, and stop medication

Table 2. Analysis of hypoglycemia events in patients using insulin, sulfonylurea, and their combination

Variable	Hypoglycemia Case (n=138)	Non Hypoglycemia Control (n=122)	Total	P Value
Non-insulin and non-SU user	30 (21.74%)	54 (44.26%)	84 (32.31%)	0.001*
Insulin all types	66 (47.83%)	41 (33.61%)	107 (41.15%)	
SU all types	27 (19.57%)	21 (17.21%)	48 (18.46%)	
Insulin and SU as a combination	15 (10.87%)	6 (4.92%)	21 (8.08%)	
Total	138 (100%)	122 (100%)	260 (100%)	
Non-insulin user	57 (41.30%)	75 (61.48%)	132 (50.77)	0.001*
Basal bolus insulin	62 (44.93%)	22 (18.03%)	84 (32.31%)	
Basal insulin	9 (6.52%)	14 (11.48%)	23(8.85%)	
Bolus insulin	3 (2.17%)	5 (4.10%)	8 (3.08%)	
Mixed insulin	7 (5.07%)	6 (4.92%)	13 (5.00%)	
Total	138 (100%)	122 (100%)	260 (100%)	
Non-SU user	96 (69.57%)	95 (77.87%)	191 (73.46%)	0.161
Glimepiride	34 (24.64%)	21 (17.21%)	55 (21.15%)	
Glibenclamide	4 (2.90%)	6 (4.92%)	10 (3.85%)	
Glikazide	3 (2.17%)	0 (0%)	3 (1.15%)	
Glikuidone	1 (0.72%)	0 (0%)	1 (0.39%)	
Total	138 (100%)	122 (100%)	260 (100%)	

P-value ≤0.25 continues multivariate analysis; *: statistically significant; SU: Sulfonylurea; n: number.

Table 3. Stepwise multivariate logistic regression analysis of hypoglycemia events in patients using insulin, sulfonylurea, and their combination

Variable	OR (CI95%)	P Value
Non-insulin and non-SU user	1 Reference	0.001*
Insulin all types	2.898 (1.602-5.240)*	
SU all types	2.314 (1.122-4.774)*	0.023*
Insulin and SU as a combination	4.500 (1.580-12.817)*	0.005*

P-value <0.05 is statistically significant; *: statistically significant; OR: odd ratio; CI: confident interval; SU: Sulfonylurea.

Table 4. Multivariate analysis of all types of insulin and sulfonylurea caused the highest incidence of hypoglycemia in T2DM patients

Variable	P Value	OR (CI95%)
Model 1		
Glimepiride	0.019*	2.231 (1.142-4.358)*
Glibenclamide	0.640	0.719 (0.181-2.853)
Glikazide	0.999	0.639 (0.001-20.277)
Glikuidone	1.000	0.286 (0.001-21.773)
Basal Bolus Insulin	0.001*	4.292 (2.286-8.057)*
Basal Insulin	0.936	0.961 (0.368-2.515)
Bolus Insulin	0.979	1.020 (0.229-4.537)
Mixed Insulin	0.339	1.765 (0.551-5.659)
Model 2		
Glimepiride	0.018*	2.228 (1.149-4.317)*
Glibenclamide	0.638	0.719 (0.182-2.846)*
Basal Bolus Insulin	0.001*	4.285 (2.305-7.968)*
Basal Insulin	0.933	0.960 (0.369-2.495)
Mixed Insulin	0.338	1.763 (0.552-5.623)
Model 3		
Glimepiride	0.015*	2.239 (1.168-4.293)*
Glibenclamide	0.634	0.717 (0.181-2.830)
Basal Bolus Insulin	0.001*	4.313 (2.364-7.871)*
Mixed Insulin	0.330	1.773 (0.561-5.609)
Model 4		
Glimepiride	0.013*	2.279 (1.193-4.353)*
Basal Bolus Insulin	0.001*	4.329 (2.373-7.896)*
Mixed Insulin	0.316	1.802 (0.570-5.693)
Model 5		
Glimepiride	0.018*	2.168 (1.140-4.123)*
Basal Bolus Insulin	0.001*	4.256 (2.363-7.665)*

P-value <0.05 is statistically significant; *: statistically significant;
OR: odd ratio; CI: confident interval.

when outpatient with insulin, sulfonylurea, or a combination of insulin and sulfonylurea. The role of health workers was essential to ensure the control of this condition. Health workers, caregivers, and patients should pay more attention to how to use drugs, review drug use, and provide information to carry out self-monitoring of blood glucose as well as how to get first aid when an emergency occurs[13-15].

This study had several limitations, such as the case-control design and exposure parameters, which were analyzed based on the three available hospital medical records. Therefore, it shared the essential limitations of a hospital-based study. The primary outcome data was analyzed based on the current therapy patients were undergoing. It was possible that patients previously used other types and conditions of treatment. Patients might have been diagnosed with T2DM and prescribed medication at Primary care or other hospitals before the index date, hence, patients were not limited to new users.

CONCLUSION

In conclusion, T2DM patients who used insulin and sulfonylurea were at risk of developing hypoglycemia while undergoing outpatient therapy compared to control. Furthermore, basal-bolus insulin and OAD sulfonylurea-type glimepiride

were discovered to be the types of treatment with the highest and most significant incidence of hospitalized hypoglycemia in T2DM patients.

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Connflict of Interest

The author(s) do not have any conflict of interest

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Data Availability

This statement does not apply to this article.

Ethics Statement

The Faculty of Medicine, Udayana University, Bali, ethics commission approved this study with an ethical clearance number 1165/UN.14.2.2.VII.14/LT/2024. Ethical clearance was obtained from the multicenter hospitals, namely Denpasar City Hospital, Badung Regency Hospital, and Buleleng Regency Hospital with ethical clearance number 052/EA/KEPK.RSBM.DISKES/2024, B/475/UN14.6/PT.01.04/2024, and 019/EC/KEPK-RSB/V/2023 respectively.

Informed Consent Statement

Consent was obtained from participants using an approved and locally translated digital consent form. Patients were informed about the details of the study, including the general overview, purpose, risks, and benefits, also confidentiality was maintained through all stages. This study was conducted following the Declaration of Helsinki.

Clinical Trial Registration

This research does not involve any clinical trials

Author Contributions

Zullies Ikawati was the research leader and drafter who prepared the manuscript. Made Krisna Adi Jaya contributed to collecting and processing data and writing the manuscript. Fita Rahmawati and Nananag Munif Yasin contributed to designing the data analysis and developing reporting standards for this research.

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