REVIEW ARTICLE

Risk factors contributing to hypoglycemia among diabetes mellitus patients: a systematic review and meta-analysis

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ABSTRACT

Hypoglycemia is a dangerous, life-threatening condition affecting various populations, specifically diabetes mellitus (DM) patients. The condition has been reported to be influenced by several factors, such as gender, age, and body mass index (BMI). However, previous studies exploring these factors have yielded varying results, indicating the need for further investigations. This study aimed to identify factors contributing to hypoglycemia among DM patients through a systematic review and meta-analysis. The study procedures were carried out using PRISMA 2020 statement review reporting standards. In addition, a literature search was performed on four databases, including Pubmed, Scopus, Google Scholar, and Crossref, using Publish or Perish version 8 software. After the search, a total of 12 original articles were obtained based on the eligibility criteria. The results showed that eight factors significantly contributed to incidence of hypoglycemia, including elderly (OR 11.05; CI95%: 9.20-13.27), insulin use (OR 5.60; CI95%: 4.66-6.74), uncontrolled blood glucose (OR 4.07; CI95%: 3.41-4.85), have history of hypoglycemia (OR 3.52; CI95%: 2.27-5.45), overweight/obese (OR 2.63; CI95%: 1.89-3.64), sulfonylurea use (OR 1.98; CI95%: 1.37-2.85), longer DM duration (OR 1.29; CI95%: 1.20-1.38), and male gender (OR 1.31; CI95%: 1.21-1.42). Based on the results, the eight influential factors could be categorized into three domains, including medication-related hypoglycemia, non-modifiable medical conditions, and lifestyle-related hypoglycemia.

Keywords:
adverse event, diabetes mellitus, hypoglycemia, life-threatening, risk factor.

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INTRODUCTION

Diabetes mellitus (DM) is a progressive condition that has become a major health challenge in several countries.[1] There has also been a continuous annual increase in the number of affected patients. In 2019, a total of 1.5 million fatalities were directly related to DM, with 48% of these cases occurring before the age of 70. Several studies have shown that DM caused a 3% increase in age-standardized death rates between 2000 and 2019, as well as a 13% increment in mortality in lower-middle-income nations.[2] This indicates that the role of health workers, patients, and caregivers is essential in ensuring the success and safety of treatment.[2]

According to previous studies, hypoglycemia is a condition affecting the safety of patients receiving DM treatment. The condition is characterized by low plasma glucose level (<3,9 mmol/l), the presence of neuroglycemic or neurogenic symptoms, and symptoms that respond to treatment.[3] In addition, it has been reported to be the leading cause of death in DM patients, with the proportion of hypoglycemia-related mortality being 4.49 (95%CI: 4.44-4.55) per 1000 total DM deaths.[1] This has prompted scientists and health practitioners to develop various methods to reduce mortality. An effective method in this context comprises conducting comprehensive treatment for patients.[1,3,4]

Hypoglycemia has been shown to be associated with increased mortality and morbidity of the disease. Hypoglycemia causes an increase in the length of hospital stay and ultimately impacts the health costs incurred by both patients and the government[5-6,8]. Several studies have shown that the additional cost for hypoglycemia in DM patients ranges from $1353-2285 USD.[3-5] Hypoglycemia in DM patients in Indonesia is like an iceberg phenomenon. Many hypoglycemia incidents are not detected, so they are not reported or recorded in the health system. This condition is due to the low level of knowledge and awareness of patients about hypoglycemia.[5-6]

Patients who are discharged from diabetes medication may be at risk of hypoglycemia due to a lack of comprehensive understanding of how to start therapy, use medications, add therapy regimens without health worker consultation, review their diabetes medications, and when to stop their diabetes medications.[8-10] Hypoglycemia events in patients with diabetes mellitus have been reported to be triggered by medication-related, lack of nutritional intake, sudden or excessive increase in physical activity, and comorbidities such as chronic kidney disease (CKD).[11-14] Patients with diabetes mellitus undergoing therapy with diabetes medication are at risk of experiencing hypoglycemia. Hypoglycemia in ambulatory patients is difficult to track due to underreporting. Hypoglycemia is only identified when the patient comes to the emergency unit in an unconscious state. Patient knowledge regarding self-management support has also been reported to influence the incidence of hypoglycemia in patients with diabetes mellitus.[1,5,9]

To control the incidence of hypoglycemia in DM patients, there is a need to identify risk factors influencing its incidence. Risk factors causing hypoglycemia should be explored further to make it easier for health workers, patients, and caregivers to pay attention to controlling these risk factors. Risk factors reported to have an influence include gender, geriatrics, insulin, and sulfonylurea (SU) drug users, uncontrolled blood glucose, long duration of diabetes, non-ideal body mass index (BMI), history of recurrent hypoglycemia, poor adherence to treatment, limited patient knowledge related to self-management, and support system. The studies that reported risk

factors that contributed to hypoglycemia showed inconsistent and varied results. Therefore, this systematic study aims to identify the most influential factors contributing to hypoglycemia in DM patients. Variations in previously reported studies will be analyzed using Forest plots to obtain an idea of how strongly these risk factors influence the incidence of hypoglycemia in patients with diabetes mellitus. In the end, health workers can use the study results as evidence-based to develop more effective health interventions to prevent hypoglycemia, specifically for ambulatory DM patients, by focusing on the modifiable most influential risk factors and controllable risk factors. Health workers such as doctors can focus on disease prognosis, nurses can play a role in educating patients on self-management support, and pharmacists can focus on ensuring medication safety.[3-4] All health workers must collaborate in controlling risk factors so that patient safety can be achieved.

METHOD

Eligibility Criteria

Eligibility criteria were determined based on the inclusion and exclusion criteria. In this study, articles were included when 1) the design was observational, in the form of a cohort study, case-control study, and cross-sectional study, 2) the articles discussed the incidence of hypoglycemia in DM patients, 3) There was data on contributors causing hypoglycemia, and 4) Contributors were presented in the statistical analysis. Meanwhile, exclusion criteria included 1) articles that did not report the results, 2) did not focus on explaining factors that contributed to the incidence of hypoglycemia, and 3) data with extensive confidence intervals.

Information Sources

Articles in this study were obtained through 4 databases, including Pubmed, Scopus, Google Scholar, and Crossref. The software used was Publish or Perish version 8. The search process was carried out in stages, starting from 1st August – 16th November 2023, and every 1st of the search period, an article search update was carried out. The duplication screening stage was conducted using Mendeley Desktop, and two authors performed the search and screen duplication process.

Search Strategy and Selection Process

Articles were searched on Publish or Perish software with a limit setting of 200 reports in one search run. The article publication year was not limited to compiling the development of factors that contributed to causing hypoglycemia from year to year, and searches were carried out by sorting per database. This information could be collected directly from Pubmed, Google Scholar, and Crossref databases. However, the authors needed API code obtained from the institution's Scopus account for the database. The article selection process was carried out after duplicate screening was completed. A total of 4 authors carried out the selection by carefully reading the abstract following the inclusion and exclusion criteria established through the Rayyan software. Each author had the right to determine which candidate articles must be included according to the protocol. However, the selection of full-text papers was carried out with the agreement of all authors. All records downloaded in full text were reviewed in parallel by four authors according to the protocol to obtain outcome data for extraction.

Data Items and Collection Process

The data collection process was carried out by distributing reports to all authors, and the work was done

independently to develop the results of data collection further. When there were differences in the results from several articles, the authors wrote down the differences to be discussed with the team. Data items collected included information on the study's authors, year of publication, location/country, subjects, number of subjects, variables observed as results, and results in the study. The focus of the results to be studied was factors that contributed to the cause of hypoglycemia in DM patients, such as medication factors, lifestyle, social-demographic factors, and other factors related to the incidence of hypoglycemia. Comparative statistical data, statistical power, and confidence interval data were the priorities that were extracted from articles that met eligibility criteria.

Study Risk and Reporting Bias Assessment

Bias in this study was assessed using the Newcastle-Ottawa Quality Assessment Form instrument for analytical observational studies.[5] The aspects assessed by this instrument included study selection, test group comparison methods, and measurement of observational study outcomes. Each aspect assessed in this instrument contained a score where the total score for all aspects assessed was grouped into Good, Fair, and Poor quality categories. All authors considered bias independently and then conveyed it to the team discussion to determine the final score to be reported. When there were differences in scoring results, solutions were carried out through team discussions. Furthermore, reporting could be carried out by presenting a score table for the Newcastle-Ottawa Quality Assessment Form instrument, which was agreed upon by the authors. During the review process, articles with poor-quality evidence were dropped out, and only studies with fair quality could be included.

Effect Measure, Synthesis Methods, and Statistical Analysis

The data synthesis method was carried out by extracting the primary data from the inclusion and exclusion criteria into tabular form. Furthermore, the different results continued in a meta-analysis using forest plot visualization using Review Manager 5.3 software. The original data in the studies taken to proceed to meta-analysis were only data with cohort and case-control study designs. The data were reanalyzed using the Mantel Haenszel statistical method, with a fixed effect analysis model, dichotomous data type, and the odd ratio as the effect measure. Confidence interval for studies and the total confidence interval used was 95%.

Certainty Assessment

During the full-text article review process, all authors paid attention to studying ethical considerations and cross-checked ethical approval numbers to ensure there were no ethical violations in the report. The authors also ensured that the articles in this study had no conflict of interest with the funders.

RESULTS

This systematic review and meta-analysis investigated the risk factors that contributed to the incidence of hypoglycemia in DM patients. All procedures performed and reporting for this study followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement review reporting standards. This study had also been registered on PROSPERO by the National Institute for Health Report (NIHR) with registration ID CRD4202449805.[7]

Study Selection

This study began in August 2023, starting with the search for articles according to the study objectives. After 4

months of searching the literature, 1466 articles were identified, reporting on the incidence of hypoglycemia in DM patients with the keywords "Hypoglycemia AND Diabetes Mellitus AND Risk Factor OR Contributor AND Adverse Outcomes." The process of identifying articles, screening articles, and determining articles involved in this study through a very selective process with a series of round reviews. In total, 12 articles could proceed to the data extraction stage, and 10 articles could enter the meta-analysis stage. The diagrammatic depiction of the stages in the study selection stage is shown in Figure 1.

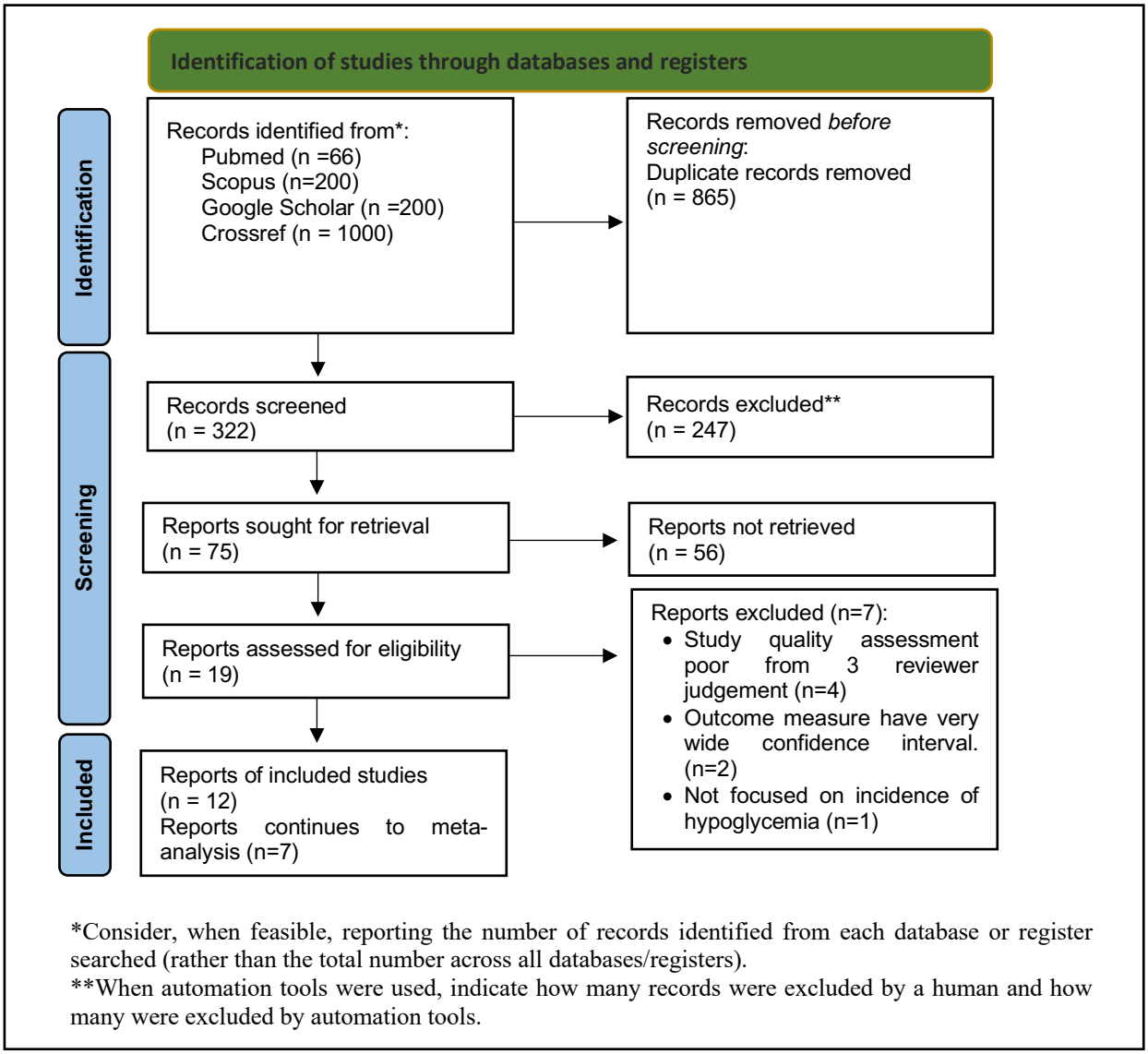

Figure 1. PRISMA flow diagram in the study selection stage[6–8]

Study characteristics

The articles were characterized by observational designs, and they began to be published from 2001 to 2023. The studies involved came from several countries around the world, such as the USA[9–11], Australia[12], Germany[13], China[14], Israel[15], Taiwan[16], Indonesia[17–19], and Saudi Arabia.[20] The study subjects were DM patients of all age groups who had reported experiencing the adverse drug event of hypoglycemia, to observe predictors that

contributed to it. The independent variables observed included a history of severe hypoglycemia, insulin treatment, DM duration, sulfonylurea treatment, education level/status, time on insulin/duration use of insulin, age, gender, and uncontrolled blood glucose (HbA1C, fasting glucose, random glucose). Detailed results of data extraction on study characteristics are presented in Table 1.

Table 1. Characteristics of Selected Articles

Author	Years	Country Study	Subject	Number of Subject (n)	Study Design	Observed Variables	Incidence and Factor Contribution (Results of Study)
Miller, C.D, et al.[9]	2001	Atlanta, Georgia, USA	All type two DM patients with hypoglycemia had been followed up for at least two months.	1,055 Participants	Retrospective Cross-sectional	Demographics, laboratory tests, current diabetes treatment, answer questions about hypoglycemia.	• Insulin treatment (insulin user, higher risk, OR: 3.44 [CI95%: 2.07 –5.73]). • History of severe hypoglycemia (having a history of hypoglycemia, higher risk OR: 2.65 [CI95%: 1.80–3.80]). • Age (younger, higher risk, OR: 0.98 [CI95%: 0.97-1.00], p<0.05). • HbA1C (controlled blood glucose, lower risk, OR: 0.87 [CI95%: 0.78–0.96])
Maynard, G.A, et al.[10]	2008	California, San Diego, USA	Adults ≥ 18 years of age with serum glucose value ≤ 60 mg/dl and event occurring while on a glucose-lowering agent.	130 Patients	Case-Control Study	Demographics and possible hypoglycemia risk factors include medications (outpatient and inpatient, nutritional status, presence or absence of a prior hypoglycemic, and the presence or absence of potential nutritional interruption or discordance of nutrition with anti-hyperglycemic regimen.	• Prior hypoglycemic day (having a history of hypoglycemia higher risk, OR: 31.18 [CI95%: 2.9–333.6]). • Insulin as outpatient treatment (insulin user, higher risk, OR: 15.57 [CI95%:1.39–174.8]). • Nutritional interruption/discordance (inadequate food intake higher risk, OR: 12.09 [CI95%: 1.23–118.05]).

Author	Years	Country Study	Subject	Number of Subject (n)	Study Design	Observed Variables	Incidence and Factor Contribution (Results of Study)
Davis, T.M.E., et al.[12]	2010	Western Australia	All DM patients with hypoglycemia from January 1999 until June 2006.	616 Patients	Retrospective Cohort Study	All medical conditions and their management, demographic, Socio-economic and lifestyle data.	• History of severe hypoglycemia (having a history of hypoglycemia, higher risk HR: 6.59 [CI95%: 2.62–16.60]). • Insulin treatment (insulin user, higher risk, HR: 4.29 [CI95%: 2.44 –7.55]). • Diabetes duration (>8 years, HR: 2.92 [CI95%: 1.60 –5.32]). • CKD (eGFR <60 ml/min per 1.73m2, higher risk, HR: 2.90 [CI95%: 1.68 – 5.00]). • Sulfonylurea treatment vs. lifestyle/other oral agents (Sulfonylurea user, higher risk, HR: 2.50 [CI95%: 1.16 –5.38]). • Education (higher level of education, lower risk, RR: 2.33 [CI95%: 1.14–4.76]) • Time on insulin/ duration use (increase risk > 1 year, HR: 1.42 [CI95%: 1.24 – 1.63]. • HbA1C (uncontrolled blood glucose, higher risk, RR: 1.39 [CI95%: 1.10–1.76])

Author	Years	Country Study	Subject	Number of Subject (n)	Study Design	Observed Variables	Incidence and Factor Contribution (Results of Study)
Quilliam, B.J. et al.[11]	2011	Rhode Island, Kingston, USA	Patients aged ≥18 years with type 2 DM are taking at least one antidiabetic medication.	14,725 Patients (1,339 in the cases group and 13,390 in the controls group)	Case-Control Study	Antidiabetic medication availability, other medication availability, previous visits for hypoglycemia, complications of diabetes, and other comorbidities.	• Previous inpatient emergency hypoglycemia (OR: 9.48 [CI95%: 4.95–18.15]). • Previous outpatient hypoglycemia event (OR: 7.88; [CI95%: 5.68–10.93]). • CKD (eGFR <60 ml/min per 1.73m2, higher risk, HR: 2.22 [CI95%: 1.56–3.25]). • Insulin treatment (insulin user, higher risk, OR: 2.23 [CI95%: 1.83–2.72]). • Sulfonylurea treatment (Sulfonylurea user, higher risk, OR: 2.25 [CI95%: 1.93 –2.63]). • Gender (male higher risk, OR: 0.84 [CI95%: 0.73-0.96])
Bramlage, P., et al.[13]	2012	Jena, Germany	Type-2 diabetes aged ≥ 40 years on oral mono or dual oral combination antidiabetic treatment	3810 Patients	Case-Control Study	Antidiabetic medication, previous visits for hypoglycemia, complications of diabetes, and other comorbidities.	• Sulfonylurea treatment (Sulfonylurea user, higher risk, OR: 1.82 [CI95%: 1.25 –2.63]). • SMBG (uncontrolled blood glucose, higher risk, OR: 2.00 [CI95%: 1.24–3.24])

Author	Years	Country Study	Subject	Number of Subject (n)	Study Design	Observed Variables	Incidence and Factor Contribution (Results of Study)
Kong, A.P.S., et al.[14]	2014	Hong Kong, China	All DM patients attend medical clinics with hypoglycemia.	10,129 Patients	Prospective Cohort Study	Demographics, laboratory tests, current diabetes treatment.	• Insulin treatment (insulin user, higher risk, HR: 2.75 [CI95%: 1.56–4.86]). • Age (per 10 years) (older, higher risk, HR: 1.50 [CI95%: 1.24–1.81]) • HbA1C (uncontrolled blood glucose, higher risk, HR: 1.21 [CI95%: 1.13–1.29]) • CKD (eGFR <60 ml/min per 1.73m2, higher risk, HR: 1.91 [CI95%: 1.36 – 2.69]). • BMI (BMI >30 kg/m2, higher risk, HR: 0.96 [CI95%: 0.92- 0.99])
Akirov, A., et al.[15]	2018	Petach Tikva, Israel	All DM patients with hypoglycemia and serious hypoglycemia (BG: ≤ 70 and <54 mg/dl) during hospitalization	5301 Patients	Prospective Cohort Study	Age, gender, BMI, comorbidities, glycemic control based on glycated hemoglobin, drug treatment, and DM duration.	• Insulin treatment (insulin user, higher risk, OR: 3.94 [CI95%: 3.11–4.98]). • CKD (having renal impairment higher risk, OR: 1.42 [CI95%: 1.1–1.85]). • Gender (female higher risk, OR: 1.31 [CI95%: 1.1–1.60]). • HbA1C (uncontrolled blood glucose, higher risk, OR: 1.06 [CI95%: 1.02–1.1]) • Diabetes duration (longer duration (>15 years) higher risk, OR: 1.03 [CI95%: 1.02–1.03]). • Age (older higher risk, OR 1.01 [CI95%: 1.01–1.02]). • BMI (BMI >30 kg/m2, higher risk, OR: 0.97 [CI95%: 0.95-0.98])

Author	Years	Country Study	Subject	Number of Subject (n)	Study Design	Observed Variables	Incidence and Factor Contribution (Results of Study)
Li, T.S., et al.[16]	2018	Taichung, Taiwan	All patients with type 2 DM had at least one year of follow-up.	32,653 Patients	Retrospective Cohort Study	Sociodemographic characteristics and patient health data, including age, gender, BMI, comorbidities, glycemic control based on glycated hemoglobin, drug treatment, and duration of DM.	• Insulin in combination with sulfonylurea, higher risk, HR: 3.97 (CI95%: 3.36, 4.68) • Insulin treatment (insulin user, higher risk, HR: 3.76 [CI95%: 3.18 –4.45]). • Diabetes duration (longer duration (>20 years) higher risk, OR: 2.07 [CI95%: 1.75–2.46]). • CKD (eGFR <60 ml/min per 1.73m2, higher risk, HR: 1.89 [CI95%: 1.66 – 2.16]). • Gender (male higher risk, HR: 1.82 [CI95%: 1.63-2.03]). • Sulfonylurea treatment (Sulfonylurea user, higher risk, HR: 1.63 [CI95%: 1.43 –1.86]). • HbA1C >7% (uncontrolled blood glucose, higher risk, HR: 1.42 [CI95%: 1.31–1.53]). • History of hypoglycemia (having a history of hypoglycemia higher risk, OR 1.39, [CI95%: 1.23-1.58]). • Age (older, higher risk, HR: 1.08 [CI95%: 1.07-1.09]). • BMI (BMI >30 kg/m2, higher risk, HR: 0.69 [CI95%: 0.57-0.84])

Author	Years	Country Study	Subject	Number of Subject (n)	Study Design	Observed Variables	Incidence and Factor Contribution (Results of Study)
AlKhaldi, Y.M., et al.[20]	2019	Abha, Saudi Arabia	All patients aged 12 until > 40 years with type 1 and 2 DM.	378 Patients	Cross-sectional	Sociodemographic characteristics and patient health data (type of DM, duration, history of chronic health problems, types of drugs in use).	• Age (younger, higher risk p<0.05). • Type of diabetes (T1DM higher risk p<0.05). • Diabetes duration of (longer duration (>11 years) higher risk p<0.05). • Insulin use (rapid-acting higher risk) • Gender (female higher risk [59%] compared to male [46%] p<0.05).
Bakar, A., et al.[19]	2020	Indonesia	Adults aged between 20-60 years with type 2 DM who consume DM drugs from doctors for more than three years.	37 Patients	Cross-sectional	Sociodemographic characteristics and patient health data, including age, education, occupation, gender, knowledge, and blood sugar levels.	• Gender (CV: 3.417; male higher risk). • Occupation (CV: 1.322, worker higher risk). • Knowledge (CV: 1.025, low level of knowledge, higher risk). • Education (CV: 0.731, high level of education lower risk). • Age (CV: 0.091, older higher risk).
Pratiwi, C., et al.[18]	2022	Indonesia	Patients aged ≥18 years with type 2 DM.	475 Patients	Retrospective Cohort Study	Sociodemographic characteristics (age and gender), comorbidities (chronic kidney disease, heart failure, liver failure, malignancy, sepsis or septic shock, and other endocrine disorders), BMI, history of hypoglycemia, hyperglycemia treatment administered, and daily nutritional intake.	• Anti-hyperglycemia agent (insulin and sulfonylurea users higher risk, RR 6.4 [CI95%; 1.6-26.5]). • History of hypoglycemia (having a history of hypoglycemia higher risk, RR 4.6 [CI95%: 2.8-7.6]). • Nutritional intake (inadequate food intake higher risk, RR 2.6 [CI95%; 1.5-4.3]). • BMI (BMI >30 kg/m2, higher risk, RR: 0.68 [CI95%: 0.45-1.03]).

Author	Years	Country Study	Subject	Number of Subject (n)	Study Design	Observed Variables	Incidence and Factor Contribution (Results of Study)
Yunir, EM., et al.[17]	2023	Indonesia	Patients aged ≥ 18 years with type 2 DM.	291 Patients	Retrospective Cohort Study	Age, level of education, subject's understanding of hypoglycemia symptoms, HbA1c levels, duration of T2DM, CKD, CLD, history of previous severe hypoglycemia, self-monitoring of blood glucose (SMBG), sulfonylurea, and insulin use.	• History of hypoglycemia (having a history of hypoglycemia higher risk, RR: 4.105 [CI95%: 2.64-6.38]). • Insulin use (insulin user higher risk, RR: 1.50 [CI95%: 1.27-1.77]). • CKD (eGFR less than 60 mL/min/1.73m2, higher risk, RR: 1.38 [CI95%: 1.06-1.80]). • HbA1C (controlled blood glucose, lower risk, RR: 0.65 [CI95%: 0.43-0.98]) • Sulfonylurea treatment (Sulfonylurea user, lower risk RR: 0.61 [CI95%: 0.40-0.93]).

Table information: OR: odd ratio, RR: risk ratio, HR: hazard ratio, CI: confidence interval, CKD: Chronic kidney diseases, BMI: body mass index, DM: diabetes mellitus, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus, CLD: chronic liver diseases, eGFR: estimated glomerular filtration rate, CV; coefficient value, and SMBG: self-monitoring blood glucose.

Risk of Bias in Studies

The bias assessment results found that seven articles were of good quality, and five articles were of fairly good quality. The five articles categorized as fairly good quality had several weaknesses, such as the data not being presented in a representative manner and the small number of subjects with wide variations between subjects. However, when viewed from the aspect of outcome measurement, the analysis was carried out sensitively and comprehensively. The results of the bias analysis are presented in Table 2.

Table 2. Risk of bias in studies using New Castle Ottawa Scale and Quality Assessment using AHRQ standard

No	Study	Newcastle-Ottawa Scales/Score			Total Score	Quality of Study
		Selection	Comparability	Outcome/ Exposure		
1	Miller, C.D, et al. 2001[9]	4	2	3	9	Good
2	Maynard, G.A, et al. 2008[10]	3	1	2	6	Fair
3	Davis, T.M.E., et al. 2010[12]	4	2	3	9	Good
4	Quilliam, B.J. et al. 2011[11]	3	1	2	6	Fair
5	Bramlage, P., et al. 2012[13]	3	1	2	6	Fair
6	Kong, A.P.S., et al. 2014[14]	4	2	3	9	Good
7	Akirov, A., et al. 2018[15]	4	2	3	9	Good
8	Li, T.S., et al. 2018[16]	4	2	3	9	Good
9	AlKhaldi, Y.M., et al. 2019[20]	2	1	2	5	Fair
10	Bakar, A., et al. 2020 [19]	2	1	1	4	Fair
11	Pratiwi, C., et al. 2022[18]	4	2	3	9	Good
12	Yunir, EM., et al. 2023[17]	4	2	3	9	Good

Overall, twelve studies that met the research criteria were declared eligible for further analysis related to the reported findings. Table 2 is the result of a critical appraisal obtained from the review of 4 independent reviewers. At the end of the review, a discussion was held on the results of different review items to obtain the results of the forum further and determine the conclusion of the study quality. The New Castle Ottawa Scale and Quality Assessment using the AHRQ standard was chosen because the type of studies selected in this research was observational with the advantages of sensitive, valid, reliable, and simple critical appraisal items.

Risk Factors Contributing to the Incidence of Hypoglycemia

Based on the results of data extraction from the 12 articles involved, factors that influenced the incidence of hypoglycemia in DM patients were identified, including insulin and sulfonylurea treatment, having a history of hypoglycemia, longer DM duration, chronic kidney diseases as DM comorbidity, and duration of insulin treatment. Others included uncontrolled blood glucose, age, gender, body mass index (BMI), patient occupation, patient knowledge about their medication, patient level of education, type of DM (type 1 DM higher risk), and nutritional intake (inadequate food intake higher risk).

There were exciting things found in these studies, such as differences in results between the factors that were exposed. Some differences in results included insulin and sulfonylurea treatment factors, having a history of hypoglycemia, longer DM duration, uncontrolled blood glucose, age, gender, and BMI. These were differences between factors that significantly contributed and those that did not. The difference could also be seen in the power of statistics. These conditions allowed investigators to conduct forest plot analysis

to understand further the factors that contributed the most. The forest plot analysis stage was carried out by extracting data on the proportion of patients who experienced hypoglycemia against contributing factors. Only studies that presented proportion data could carry out this analysis, and the results of the forest plot analysis were presented in Figures 2 to 9.

Forest Plot Analysis of Factors that Contribute to Hypoglycemia

A total of 15 reported factors contributed to hypoglycemia. Based on these factors, eight factors constantly emerged from the articles. These factors included insulin treatment, sulfonylurea treatment, history of hypoglycemia, DM duration, uncontrolled blood glucose, age, gender, and BMI.

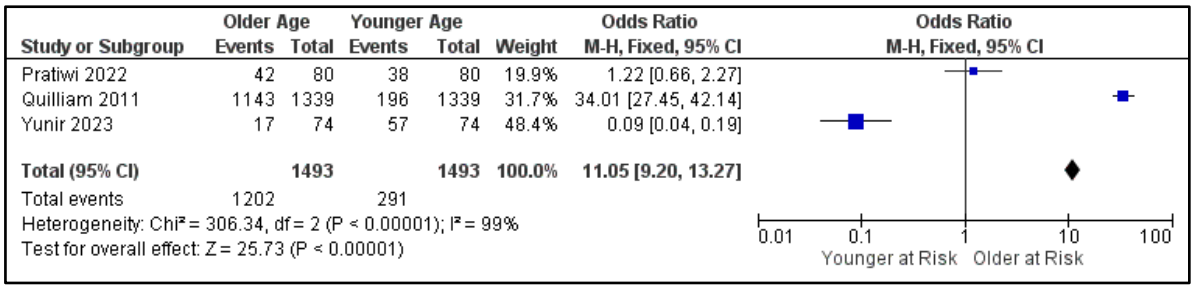

Figure 2. Forest Plot. Older age was a significant contributor to hypoglycemia.

Figure 2 shows that the study report by Pratiwi et al. 2022 stated that age does not affect the incidence of hypoglycemia (OR: 1.22 CI 95%: 0.66-2.27). A study by Quilliam et al. 2011 reported that the older age group was at greater risk of hypoglycemia (OR: 34.01 CI 95%: 27.45-42.14). A study by Yunir et al. 2023 reported that the younger age group was at greater risk (OR: 0.09 CI 95%: 0.04-0.19). The final analysis of the forest plot, by considering the statistical strength of each study, found that the older patients had a risk of 11 times greater than patients in the younger age group (OR: 11.05 CI 95%: 9.20-13.27).

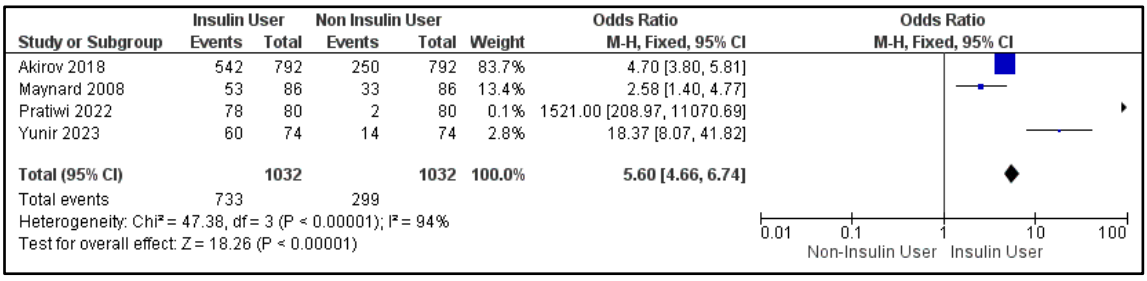

Figure 3. Forest Plot. Insulin use was a significant contributor to hypoglycemia.

Figure 3 shows that the study report by Akirov et al. 2018 showed that patients who use insulin have a higher risk of hypoglycemia than non-insulin users (OR: 4.70 CI 95%: 3.80-5.81). Similarly, Maynard et al. 2008 reported that patients who use insulin have a higher risk of hypoglycemia than non-insulin users (OR: 2.58 CI 95%: 1.40-4.77). Pratiwi et al. 2022 reported that patients who use insulin have a higher risk of hypoglycemia than non-insulin users (OR: 1521 CI 95%: 208.97-11070). A study by Yunir et al. 2023 also reported that patients who use insulin have a higher risk of hypoglycemia than non-insulin users (OR: 18.37 CI 95%: 8.07-

41.82). The final analysis of the forest plot found the use of insulin was proven to increase the risk of hypoglycemia five times more than those taking non-insulin (OR: 5.60 CI 95%: 4.66-6.74).

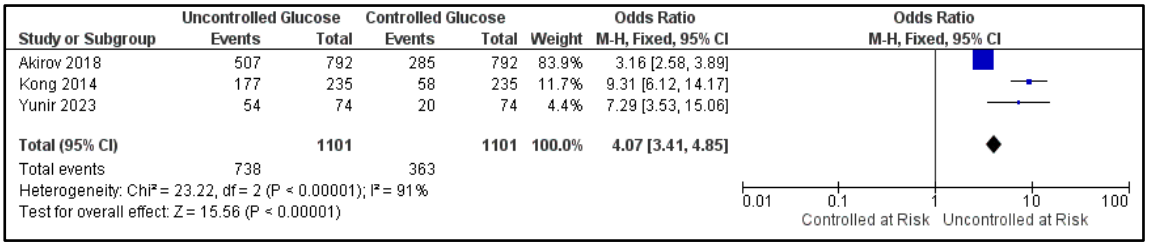

Figure 4. Forest Plot. Uncontrolled blood sugar was a significant contributor to hypoglycemia.

Figure 4 shows that the study report by Akirov et al. 2018 showed that patients who have uncontrolled blood sugar have a higher risk of hypoglycemia than those with controlled blood sugar (OR: 3.16 CI 95%: 2.58-3.89). Kong et al, 2014 reported that patients who have uncontrolled blood sugar have a higher risk of hypoglycemia than those with controlled blood sugar (OR: 9.31 CI 95%: 6.12-14.17). Yunir et al. 2023 also reported that patients who have uncontrolled blood sugar have a higher risk of hypoglycemia than those with controlled blood sugar (OR: 7.29 CI 95%: 3.53-15.06). The final analysis of the forest plot found that having uncontrolled blood sugar in DM patients was proven to increase the risk of hypoglycemia four times more than those controlled blood sugar (OR: 4.07 CI 95%: 3.41-4.85).

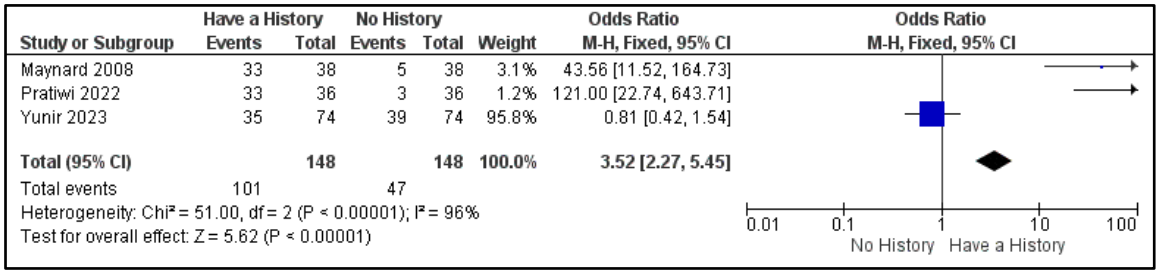

Figure 5. Forest Plot. Having a history of hypoglycemia was a significant contributor to hypoglycemia.

Figure 5 shows that the study report from Maynard et al. 2008 showed that patients who have a history of hypoglycemia have a higher risk of recurrent hypoglycemia than those who do not have a history (OR: 43.56 CI 95%: 11.52-164.73). Similarly, Pratiwi et al. 2022 also reported that patients who have a history of hypoglycemia have a higher risk of recurrent hypoglycemia than those who do not have a history (OR: 121 CI 95%: 22.74-643.71). However, Yunir et al. 2023 reported that having a history of hypoglycemia was not an influential factor causing hypoglycemia (OR: 0.81 CI 95%: 0.42-1.54). The final analysis of the forest plot found that patients with DM who have a history of hypoglycemia have a higher risk of recurrent hypoglycemia than those who do not have a history (OR: 3.52 CI 95%: 2.27-5.45).

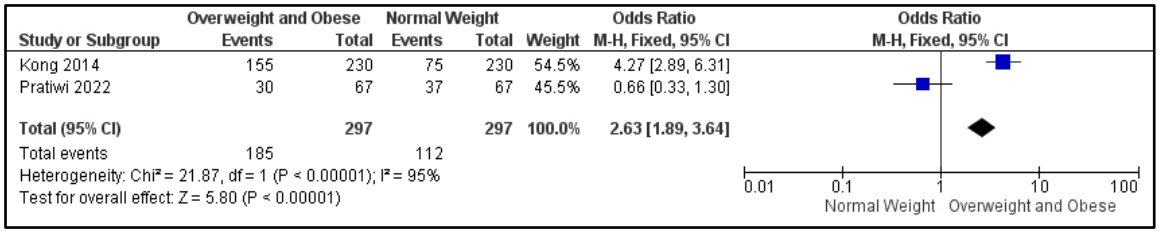

Figure 6. Forest Plot. Overweight was a significant contributor to hypoglycemia.

Figure 6 shows that the study report by Kong et al. 2014 showed that patients who were overweight had a higher risk of hypoglycemia than those who had ideal body weight (OR: 4.27 CI 95%: 2.89-6.31). Pratiwi et al. 2022 reported that body mass index (BMI) was not a contributor to the incidence of hypoglycemia (OR: 0.66 CI 95%: 0.33-1.30). The final analysis of the forest plot found that DM patients who are overweight have a higher risk of hypoglycemia than those who have ideal body weight (OR: 2.63 CI 95%: 1.89-3.64).

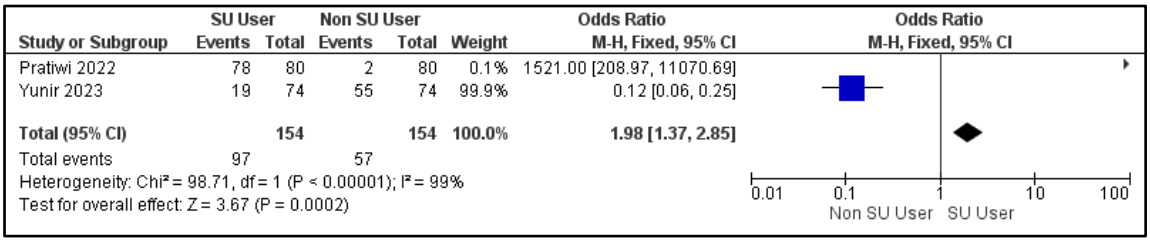

Figure 7. Forest Plot. Sulfonylurea use was a significant contributor to hypoglycemia.

Figure 7 shows that the study report by Pratiwi et al. 2022 showed that patients who use sulfonylurea have a higher risk of hypoglycemia than non-sulfonylurea users (OR: 1521 CI 95%: 208.97-11070.69). A study from Yunir et al. 2023 reported that patients who use sulfonylurea have a lower risk of hypoglycemia than non-sulfonylurea users (OR: 0.12 CI 95%: 0.06-0.25). The final analysis of the forest plot found the use of sulfonylurea was proven to increase the risk of hypoglycemia two times more than those taking non-sulfonylurea treatment (OR: (1.98 CI95%: 1.37-2.85).

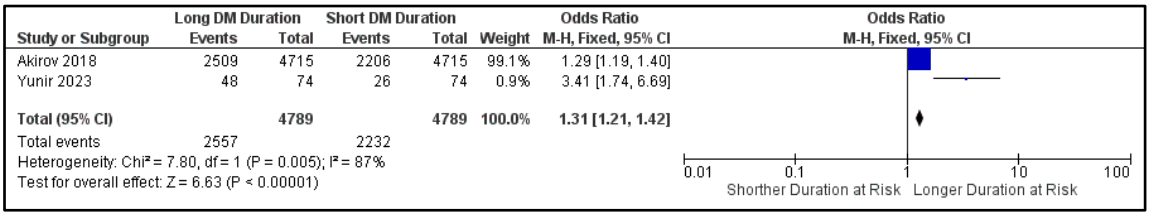

Figure 8. Forest Plot. DM duration was a significant contributor to hypoglycemia.

Figure 8 shows that the study report from Akirov et al. 2018 showed that patients who have a longer DM duration have a higher risk of hypoglycemia than those who were newly diagnosed (OR: 1.29 CI 95%: 1.19-1.40). A study by Yunir et al. 2023 also reported that patients who have a longer DM duration have a higher risk of

hypoglycemia than those who were newly diagnosed (OR: 3.41 CI 95%: 1.74-6.69). The final analysis of the forest plot found that DM patients who have a longer DM duration have a higher risk of hypoglycemia than those who were newly diagnosed (OR: 1.29 CI 95%: 1.20-1.38).

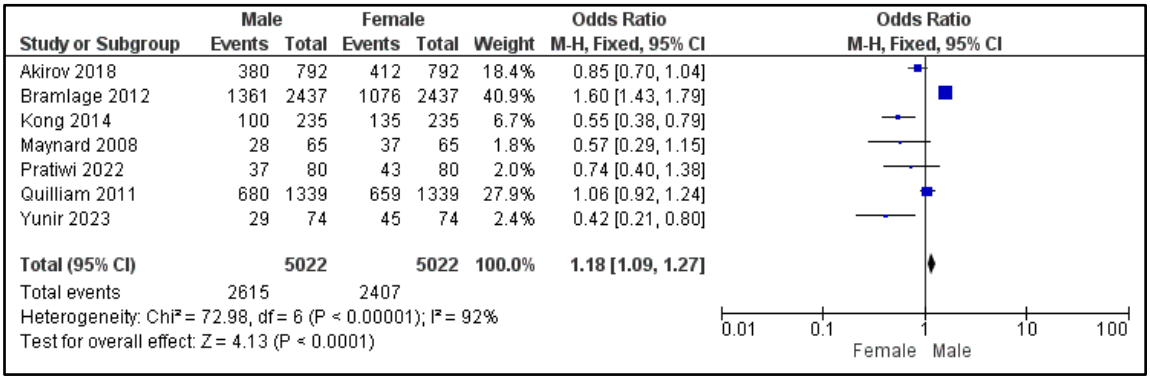

Figure 9. Forest Plot. Males had a greater tendency to experience hypoglycemia than females.

Varying results were found for the gender factor (Figure 9). Akirov et al. 2018 (OR: 0.85 CI 95%: 0.70-1.04), Maynard et al. 2008 (OR: 0.57 CI 95%: 0.29-1.15), Pratiwi et al. 2022 (OR: 0.74 CI 95%: 0.40-1.38), and Quiliam et al. 2011 (OR: 1.06 CI 95%: 0.92-1.24) reported that gender was not a risk factor for the incidence of hypoglycemia. Males and females have a risk of hypoglycemia events. Bramlage et al. 2012 reported that males tend to be at risk of developing hypoglycemia (OR: 1.60 (CI 95%: 1.43-1.79). Kong et al. 2014 reported that females tend to be at risk of developing hypoglycemia (OR: 0.55 CI 95%: 0.38-0.79). The final pooled results found that there was a tendency for males to be at risk of developing hypoglycemia (OR: 1.31 (CI 95%: 1.21-1.42).

DISCUSSION

The results of this systematic study showed that eight factors contributed most to causing hypoglycemia, namely age, insulin use, sulfonylureas use, having a history of hypoglycemia, DM duration, uncontrolled glucose levels, gender, and BMI. These factors could be categorized into three domains, namely medication-related hypoglycemia, non-modifiable medical conditions, and lifestyle-related hypoglycemia.

Older age, in this case, the elderly group, was the risk factor with the highest contribution to causing hypoglycemia, and this factor could not be modified. This risk factor could only be controlled by giving special attention to elderly DM survivors to remain safe in carrying out their treatment. In addition, geriatrics are considered unable to carry out self-management support.[28] A caregiver must accompany them to provide necessary support for their safety during DM therapy.[27,28]

Treatment of patients with insulin and sulfonylureas has been widely reported to result in a high risk of hypoglycemia. The death rate due to hypoglycemia associated with using this class of drugs ranged from 4-10%.[28–30] An extensive increase in the amount of insulin in the blood without being accompanied by adequate nutritional intake was what most often caused this incident.[29,31,32] In developed countries, the use of insulin and SU as diabetes mellitus therapy has been abandoned. The management of treatment has been a shift in the use of diabetes medication to direct incretin mimetic agents (GLP-1) and indirect agents such as DPP4 inhibitors. Developing countries still rely on insulin

and SU as blood sugar controllers for patients because they are cost-effective and have easy access to remote areas.[31-35]

Having a history of hypoglycemia was one of the unique contributors to the risk of experiencing a repeat event in the future. This phenomenon could not be confirmed clearly, but it was often related to the patient's behavior, knowledge, and skills in managing DM.[21,36-38] Some studies reported recurrent hypoglycemia blunts the brain's ability to sense and respond to subsequent hypoglycemic episodes.[39-40]

Longer diabetes duration, uncontrolled blood glucose, and overweight/obese were found to be contributors because they were often associated with DM complications. The longer a patient remained a survivor without stable sugar control, the risk of complications, medication errors, and ADRs increased. Excess BMI was also a condition that worsened the shape of the heart and blood vessels and was often associated with chronic systemic inflammation.[21,22,28–30,32-40]

Males were found to be more at risk of experiencing hypoglycemia than females. From the results of the forest plot analysis, it can be seen that gender has the most varied evidence reports. The cause of this could not be known, but it was most likely related to social, behavioral, and epidemiological reasons.[38–43]

In general, based on the findings of this study, patients and caregivers were also important aspects to pay attention to in ensuring patient safety from the risk of hypoglycemia. The behavior, skills, and knowledge of patients and caregivers must also be improved to become a center for supervision and monitoring of outpatients. This condition was considered more complicated because it required a sustainable health program.[44–48] Visits to patient's homes, mapping social problems, training, and patient education must be carried out to create ideal conditions. The government was deemed to need to take part in formulating policies to optimize the role of patients and caregivers in managing DM at home.[45-51]

CONCLUSION

Risk factors that significantly contributed to the incidence of hypoglycemia among DM patients were age, insulin use, sulfonylureas use, having a history of hypoglycemia, DM duration, uncontrolled glucose levels, BMI, and gender. These factors could be classified into three domains, namely medication-related hypoglycemia, non-modifiable medical conditions, and lifestyle-related hypoglycemia. Health workers, care providers, and patients should work together to minimize the risk of hypoglycemia in DM patients.

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CONFLICT OF INTEREST

This study was written independently, and the authors declared no financial or personal relationships with other people or organizations that could inappropriately influence the work.

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AUTHOR CONTRIBUTION

Zullies Ikawati was the study 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 study.

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