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ORIGINAL ARTICLE

Risk Factors for Inpatient Hypoglycemia in a Tertiary Care Hospital in Indonesia

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Abstract

Introduction. Hypoglycemia is an important and harmful complication that often occurs in inpatient and outpatient settings. This study aims to assess the incidence of inpatient hypoglycemia and its related factors. We also assessed mortality and length of hospital stay.

Methodology. We performed a retrospective cohort study among patients with type 2 diabetes mellitus admitted to a tertiary hospital in Indonesia. Using multivariate regression, we analyzed age, sex, body mass index, comorbidities, history of hypoglycemia, hyperglycemia treatment administered, nutritional intake, and medical instruction as the related risk factors for inpatient hypoglycemia.

Results. From 475 subjects, 80 (16.8%) had inpatient hypoglycemia, of which, 7.4% experienced severe hypoglycemia. We found that patients with a history of hypoglycemia (RR: 4.6; 95% CI: 2.8-7.6), insulin and/or sulfonylurea treatment (RR 6.4; 95% CI: 1.6-26.5), and inadequate nutritional intake (RR 2.6; 95% CI: 1.5-4.3) were more likely to have hypoglycemic events compared to those who did not. The length of hospital stay for patients in the hypoglycemic group is significantly longer than those in the non-hypoglycemic group (13 vs 7 days, $p<0.001$), but their mortality rates did not differ (16% vs 10.9%, $p=0.18$).

Conclusion. Inpatient hypoglycemia may be affected by a history of hypoglycemia and inadequate nutritional intake. Patients who had inpatient hypoglycemia tend to have a longer median length of hospital stay.

Key words: hypoglycemia, diabetes mellitus, insulin, mortality, length of stay

INTRODUCTION

Hypoglycemia is an important and harmful complication of diabetes that often occurs in outpatient as well as inpatient settings. According to the American Diabetes Association (ADA), hypoglycemia is defined as a blood glucose level of ≤70 mg/dL.[1]

Hypoglycemia can be divided into two types: primary and secondary. Hypoglycemia is termed primary if it is the indication for hospital admission, whereas secondary hypoglycemia is hypoglycemia that occurred during hospitalization.[2] In 2012, the National Diabetes Inpatient Audit in the UK found that the prevalence of inpatient hypoglycemia was 22%, with 11% being severe.[3] A Spanish study by Gomez et al., found the incidence of secondary hypoglycemia was higher than primary hypoglycemia (2.8% vs 1.7%).[2]

Several risk factors for inpatient hypoglycemia include age, type of diabetes, comorbidities (sepsis, impaired liver and renal function, malignancy,[1,4] heart failure,[5] endocrine disorders[6]), history of hypoglycemia,[1,4] low body mass index (BMI),[5] anti-hyperglycemic agents, lack of blood glucose monitoring, limited healthcare personnel, and the discordance between nutritional intake and anti-hyperglycemic agents administered.[5]

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Inpatient hypoglycemia may cause serious clinical and non-clinical consequences. In terms of clinical trajectory, inpatient hypoglycemia could lead to increased mortality, cardiovascular and cerebrovascular diseases.[1,4,5] A study that involved >100,000 patients with diabetes found that in patients who had hypoglycemic episodes during hospitalization, the length of hospital stay was three days longer and the medical cost was 39% higher than the control group.[7]

It is important to discuss inpatient hypoglycemia because of the serious impact that could occur. A study on the incidence and related risk factors for inpatient hypoglycemia has never been conducted in Indonesia, which has different patient characteristics, hospital policies, and healthcare resources compared to other countries. Therefore, we aimed to determine the incidence of inpatient hypoglycemia and its related risk factors among admitted patients with type 2 diabetes in Fatmawati General Hospital, Jakarta, Indonesia, a tertiary care center with integrated diabetes healthcare services. We also set out to determine whether the mortality rate is higher, and the length of hospital stay longer, in patients who experienced hypoglycemic episodes during hospitalization.

METHODOLOGY

This retrospective cohort study used secondary data from patients with type 2 diabetes mellitus admitted to Fatmawati General Hospital from January 2016 to December 2018. We used the hospital registry and searched entries under the ICD-10 codes E10-E14. We included patients ≥18 years old with type 2 diabetes mellitus hospitalized during the pre-determined periods. Exclusion criteria were patients diagnosed with hypoglycemia or with documented blood glucose levels ≤70 mg/dL upon admission, and patients who had only reactive hyperglycemia and were not proven to have diabetes during hospitalization (medical records were incomplete or could not be found).

The primary outcome of this study was inpatient hypoglycemia. The subjects were followed during hospitalization. Blood glucose levels were regularly checked using a point-of-care glucose meter in accordance with the ADA guidelines.[8] A blood glucose level of ≤70 mg/dL is defined as inpatient hypoglycemia. Hypoglycemia was further classified as either mild-moderate or severe hypoglycemia if the hypoglycemia caused cognitive dysfunction and required external assistance to recover from the hypoglycemia.

The independent variables in this study were age, sex, BMI, comorbidities (chronic kidney disease grade 4-5 according to KDIGO 2012,[9] heart failure, liver failure, malignancy, sepsis or septic shock, and other endocrine disorders), history of hypoglycemia, hyperglycemia therapy administered, and daily nutritional intake (it was considered to be adequate if the subject consumed up to 75% of their daily portion[10]). Older individuals should be regarded as a special population more prone to inpatient hypoglycemia. The ADA and the Endocrine Society Clinical Practice Guidelines defined older patients as those aged >65 years old.[11,12] However in this study, we modified this criterion and classified age as either <60 or ≥60 years old. BMI was classified according to the WHO BMI classification for the Asian population.[13] Hyperglycemia therapy was classified into 2 groups: insulin and/or sulfonylurea vs non-insulin and non-sulfonylurea. We included patients using various insulin regimens (basal only, basal-bolus, basal with correction dose, prandial only, sliding scale, and insulin drip) and patients using either first or second-generation sulfonylureas. We also studied in-hospital mortality and length of hospital stay as secondary outcomes.

The calculated sample size was based on the formula for the comparison of hypoglycemic events between the two groups.[14] Akirov et al., reported that inpatient hypoglycemia occurred in 24.7% of patients using insulin compared to 8.0% of patients using non-insulin treatment.[15] Using this proportion, the minimum sample size required for a 2-tailed analysis was 178 subjects, with a 95% confidence level and 80% statistical power. The samples were selected using proportionate stratified random sampling. The data analysis was performed using SPSS Statistics 20.0 software.[16] Bivariate analysis was done using chi-square test or Fisher's exact test if chi-square was inappropriate. To give a more precise statistical analysis that was suitable for our cohort design, cox regression was used for estimating relative risk (RR) in the multivariate analysis.[17] Multivariate analysis was carried out with a p-value <0.25[18] in the bivariate analysis and other factors that are clinically associated with hypoglycemia to provide complete control of confounding. The related factors were supposed to be statistically significant if the p-value is <0.05. Mortality rates between hypoglycemic and non-hypoglycemic groups were analyzed using chi-square or Fisher's exact test if chi-square was inappropriate. Length of hospital stay was analyzed as numerical data. Normality test was conducted using Kolmogorov-Smirnov and the difference between the two groups was analyzed using independent t-test or Mann-Whitney test if results had a skewed distribution.

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, with Ethical Approval No.0822/UN2.F1/ETIK/2018.

RESULTS

From 9,071 patients with diabetes who were hospitalized from January 2016 to December 2018, a total of 565 subjects met our inclusion criteria. We excluded 90 patients (18 subjects were re-hospitalized during the study period, 19 subjects were admitted due to hypoglycemia, 17 subjects were not diagnosed with type 2 diabetes mellitus, and 36 subjects had incomplete/missing medical records). Our final sample size was 475 subjects.

Table 1. Baseline characteristics of the subjects

Variable	Value N=475
Age, n (%)	
≥60 years old	213 (44.8)
<60 years old	262 (55.2)
Sex, n (%)	
Male	243 (51.2)
Female	232 (48.8)
Body mass index, n (%)	
Underweight (<18.5 kg/m^2)	39 (8.2)
Overweight (23.0 – 27.5 kg/m^2)	84 (17.7)
Obese (>27.5 kg/m^2)	154 (32.4)
Normal weight (18.5 – 22.9 kg/m^2)	198 (41.7)
Comorbidities, n (%)	
Chronic kidney disease	101 (21.3)
Heart failure	52 (10.9)
Liver failure	19 (4.0)
Malignancy	29 (6.1)
Other endocrine disorders	2 (0.4)
Sepsis or septic shock	50 (10.5)
History of hypoglycemia, n (%)	
Yes	36 (7.6)
No	439 (92.4)
Anti-hyperglycemic agents, n (%)	
Insulin and/or sulfonylurea	370 (77.9)
Non-insulin and non-sulfonylurea	105 (22.1)
Nutritional intake, n (%)	
Inadequate	38 (8.0)
Adequate	397 (83.6)
No data	40 (8.4)
Unreadable or unclear medical instruction, n (%)	
Yes	5 (1.1)
No	470 (98.9)
Hypoglycemia, n (%)	
Yes	80 (16.8)
No	395 (83.2)
Mortality, n (%)	
Yes	56 (11.8)
No	419 (88.2)

Table 2. Bivariate analysis of risk factors for inpatient hypoglycemia

Variables	Hypoglycemia		*p*-value
	Yes	No	
Age, n (%)			
≥60 years old	42 (19.7)	171 (80.3)	0.131
<60 years old	38 (14.5)	224 (85.5)	
Sex, n (%)			
Male	37 (15.2)	206 (84.8)	0.336
Female	43 (18.5)	189 (81.5)	
Body mass index, n (%)			
Underweight (<18.5 kg/m^2)	13 (33.3)	26 (66.7)	0.008
Overweight (23.0 – 27.5 kg/m^2)	13 (15.5)	71 (84.5)	
Obese (>27.5 kg/m^2)	17 (11.0)	137 (89.0)	
Normal weight (18.5 – 22.9 kg/m^2)	37 (18.7)	161 (81.3)	
Chronic kidney disease, n (%)			
Yes	23 (22.8)	78 (77.2)	0.073
No	57 (15.2)	317 (84.8)	
Liver failure, n (%)			
Yes	5 (26.3)	14 (73.7)	0.342
No	75 (16.4)	381 (83.6)	
Heart failure, n (%)			
Yes	10 (19.2)	42 (80.8)	0.626
No	70 (16.5)	353 (83.5)	
Sepsis or septic shock, n (%)			
Yes	8 (16.0)	42 (84.0)	0.866
No	72 (16.9)	353 (83.1)	
History of hypoglycemia, n (%)			
Yes	33 (91.7)	3 (8.3)	<0.001
No	47 (10.7)	392 (89.3)	
Anti-hyperglycemic agents, n (%)			
Insulin and/or sulfonylurea	78 (21.1)	292 (78.9)	<0.001
Non-insulin and non-sulfonylurea	2 (1.9)	103 (98.1)	
Nutritional intake (n=435), n (%)			
Inadequate	28 (73.7)	10 (26.3)	<0.001
Adequate	51 (12.8)	346 (87.2)	
Unreadable or unclear medical instruction, n (%)			
Yes	2 (40.0)	3 (60.0)	0.199
No	78 (16.6)	392 (83.4)	
Insulin Therapy, n (%)			
Non-fixed dose	21 (23.6)	68 (76.4)	0.650
Fixed dose	45 (21.2)	167 (78.8)	

In this study, 55.2% of the subjects were <60 years old and 41.7% had normal body mass index. The most common comorbidity was chronic kidney disease (21.3%). A previous history of hypoglycemia was present in 7.6% and 63.4% received insulin therapy. Sixty-nine subjects (14.5%) were on sulfonylurea monotherapy, of which 53.7% were on gliquidone and 2.9% were on glibenclamide. Blood glucose levels were not adequately monitored in 11.8% of subjects, and 1% had unreadable or unclear medical instructions. The mortality rate was 11.8%. The incidence of inpatient hypoglycemia was 16.8%, 7.4% of which were severe cases (Table 1).

Bivariate analysis showed that a previous history of hypoglycemia, hyperglycemia treatment, and nutritional intake were related to inpatient hypoglycemia (Table 2). We decided to include all variables with $p<0.25$ in our multivariate analysis (age, BMI, chronic kidney disease, history of hypoglycemia, hyperglycemia treatment and nutritional intake). We added the type of insulin therapy to the variables because we considered it to have a substantial effect on the incidence of hypoglycemic events.

Our final model (Table 3) showed that patients with a history of hypoglycemia (RR: 4.6; 95% CI: 2.8-7.6), insulin and/or sulfonylurea treatment (RR: 6.4; 95% CI: 1.6-26.5), and inadequate nutritional intake (RR 2.6; 95% CI: 1.5-4.3) have a higher risk for inpatient hypoglycemia.

In our cohort, 13 subjects with hypoglycemia (16%) and 43 subjects without hypoglycemia (10.9%) died (p=0.18).

Table 3. Multivariate analysis for the related risk factors of inpatient hypoglycemia

Variable	RR (95% CI)	*p*
History of hypoglycemia		
No	Reference	-
Yes	4.6 (2.8-7.6)	<0.001
Anti-hyperglycemic agents		
Non-insulin and non-sulfonylurea	Reference	-
Insulin and/or sulfonylurea	6.4 (1.6-26.5)	0.010
Nutritional intake (N=435)		
Adequate	Reference	-
Inadequate	2.6 (1.5-4.3)	<0.001

Variables included in the multivariate analysis were: age, body mass index, history of chronic kidney disease, history of hypoglycemia, anti-hyperglycemic agents, nutritional intake, and insulin therapy.

The median length of hospital stay in subjects with hypoglycemia was 13 days (min-max, 1-58 days), whereas, for subjects without hypoglycemia, the median was seven days (min-max, 1-48 days), $p<0.001$).

DISCUSSION

Our study aimed to evaluate factors affecting the incidence of inpatient hypoglycemia. We found that patients with a history of hypoglycemia, insulin and/or sulfonylurea treatment, and inadequate nutritional intake were more likely to have hypoglycemic events.

The incidence of inpatient hypoglycemia in this study was 17% with 7.4% of them being severe cases. Our findings were similar to the 18% incidence of hypoglycemia reported by the Voluntary Hospitals of America (VHA Inc.) in a cohort study of 15 hospitals in the United States.[19] In the VHA Inc. study, hypoglycemia was defined as a blood glucose level below 60 mg/dL, whereas in our study, we followed the cut-off value of the International Hypoglycemia Study Group (blood glucose level ≤70 mg/dL).[20]

In this study, patients with diabetes who had a history of hypoglycemia were four times more likely to have inpatient hypoglycemia (RR: 4.6; 95% CI: 2.8-7.6). Quilliam et al., stated that previous emergency department hypoglycemia visits (OR = 9.48; 95% CI = 4.95–18.15) and previous outpatient hypoglycemia visits (OR = 7.88; 95% CI = 5.68–10.93) were strongly associated with inpatient hypoglycemia.[21] Patients with diabetes who had recurrent hypoglycemia may have hypoglycemia-associated autonomic failure where the counter-regulatory mechanism mediated by the adrenomedullary catecholamines was blunted and led to recurrent hypoglycemia with more severe manifestations, known as hypoglycemia unawareness.[22]

In this study, inadequate nutritional intake during hospitalization (<75% of daily portion)[10] was also a risk factor for inpatient hypoglycemia. Maynard et al., also showed that compared to the control group, the hypoglycemia group more commonly had nausea, vomiting, or anorexia (18 vs 8, $p=0.05$). They also found that changes in nutritional intake, inappropriate nutritional intake, and inappropriate anti-hyperglycemic therapy were the risk factors for inpatient hypoglycemia (OR 112.09; 95% CI = 1.23-118.05).[5] Reduced caloric intake with an unadjusted anti-hyperglycemic agent dose, particularly in those treated with insulin, or a delay in providing food would increase the incidence of inpatient hypoglycemia.[5]

Insulin and/or sulfonylurea therapy were also risk factors for inpatient hypoglycemia (RR: 6.432; 95% CI: 1.559-26.535). This result was in line with the study of Akirov et al.,[14] that found the proportion of insulin therapy to be higher in the hypoglycemia group (68% vs 37%, $p<0.01$). The use of basal (15% vs 8%) and basal-bolus (19% vs 8%) insulin were found to be higher in the hypoglycemia group. The FADOI-DIAMOND study[23] stated the opposite result: hypoglycemic events were more common in subjects who had sliding scale insulin compared to basal-bolus insulin (19.4% vs 11.4%, $p<0.01$).[24] In their study, Ignaczak et al., stated that 48% of type 1 diabetes and 20% of type 2 diabetes who received continuous intravenous insulin therapy experienced a hypoglycemic event.[24] In our study, we performed a sub-analysis for the method of insulin therapy to determine whether it affects inpatient hypoglycemia. We further grouped the subjects who were on insulin therapy into fixed dose and non-fixed dose, and we found that there was no difference in the incidence of hypoglycemia between the two groups ($p=0.650$).

Sulfonylurea use is widely known to cause hypoglycemic events. The majority of our subjects used gliquidone, a second-generation sulfonylurea with a lower risk for hypoglycemia compared to the first-generation sulfonylureas.[25] However, compared to other oral anti-diabetic drugs, sulfonylureas still contribute to a higher risk for hypoglycemia,[26] especially in patients with older age, lower renal function, lower BMI, and lower triglyceride levels.[27]

In this study, we decided to use 60 years old instead of 65 years old as our cut-off age because a previous study showed that individuals above 60 years of age were significantly more prone to hypoglycemia.[28] Moreover, the National Health Ministry of Indonesia used 60 years old as the age cut-off to classify geriatric patients.[29] Hence, in most national referral hospitals in Indonesia that have a geriatric department, inpatient and outpatient facilities for patients above 60 years old are separated from those below 60 years old. We expected this delineation to lead to better monitoring and care. However, our study showed no association between age and the risk of hypoglycemia. This finding was consistent with a case-control study by Maynard et al., which did not find a significant age difference between the cases and controls (mean 56 ± 15 vs 58 ± 13; $p=0.309$).[5] On the contrary, Akirov et al., stated that patients with inpatient hypoglycemia tend to be older (74 ± 14 (median 76)) compared to patients without hypoglycemia (72 ± 12 (median 74)) with adjusted OR = 1.01 (95%CI =1.01-1.02)[15] It should be noted that older age did affect hypoglycemic events, yet most of these studies were conducted in an outpatient setting,[30,31] where (glucose monitoring depends merely on the patients' self-monitoring, while our study was conducted in the inpatient setting, where glucose monitoring was scheduled and carefully watched by nurses.

In this study, we found that chronic kidney disease did not increase the risk of inpatient hypoglycemia. This result was similar to the study by Maynard et al., which found that heart failure and chronic kidney disease did not increase the incidence of inpatient hypoglycemia (OR = 6.35; 95% CI = 0.65-61.47; OR = 5.16, 95% CI = 0.61-43.3). Based on the literature, impaired renal function increases the risk of hypoglycemia due to the impairment of renal gluconeogenesis, as well as the impairment in the degradation process and clearance of anti-hyperglycemic

drugs, including exogenous insulin therapy.[32] Our finding may be due to the small number of patients with chronic kidney disease included in our study. The association between impaired renal function and inpatient hypoglycemia is beyond the scope of our study.

The secondary outcomes of this study were mortality and length of hospital stay. The mortality rate of the hypoglycemia group was 16%, whereas in subjects without inpatient hypoglycemia, the mortality rate was 10.9%, a difference that was not statistically significant (p=0.18). This result contradicts the result of the FADOI-DIAMOND study that involved 3,167 subjects.[23] The FADOI-DIAMOND study found that inpatient mortality was higher in the hypoglycemia group (8.8% vs 4.8%, p<0.01).[23] In another prospective cohort study, Hsu et al., also found that patients with diabetes who had hypoglycemia episodes, either in an inpatient or outpatient setting, had a threefold higher mortality risk (HR = 3.49; 95% CI = 3.01-4.05).[33] Our study found most of the hypoglycemic events were mild to moderate (92.6%). Only 7.4% of them were severe which may account for the non-significantly increased mortality rate. In a study involving 5,404 elderly patients, they found that the incidence of hypoglycemia was associated with in-hospital mortality. However, further multivariate analysis adjusting for sepsis, malignancy, and hypoalbuminemia showed that hypoglycemia was not associated with mortality. Hypoglycemia was only considered as a marker of serious disease that can lead to mortality.[1,4]

Another secondary outcome of this study was the length of hospital stay. The subjects that had hypoglycemic episodes during hospitalization had a longer median length of stay (13 days vs 7 days, p<0.001). Our result echoes the FADOI-DIAMOND study which stated that patients with hypoglycemia had a longer length of stay (mean 12.7 ± 10.9 vs 9.6 ± 6.5, p<0.01).[23] Curkendall et al., also found that patients who had inpatient hypoglycemia would be hospitalized longer compared to control (11.7 days vs 5.1 days, p<0.001).[7]

This is the first study on inpatient hypoglycemia and its related factors conducted in Indonesia. It has several weaknesses though. First, this is a retrospective cohort study using medical records with its limitation of incomplete documentation of patients' internal risk factors and other institutional risk factors that might cause inpatient hypoglycemia that were not studied in this research, such as duration of the diseases, A1C level, other drugs that could induce hypoglycemia, prolonged fasting before an invasive procedure, therapy administered by nurses that was not in accordance with medical instructions, limited health personnel resources, and the lack of glucose meters to monitor patients' blood glucose levels. Second, in this study, we used the rule-of-thumb formula to calculate sample size. We did not calculate the minimum sample size for each variable to have a minimum statistical power of 80%. A qualitative study is needed to further assess the risk factors for inpatient hypoglycemia, particularly the institutional risk factors. Last, with our small sample size, our results may not be generalizable to the large population of diabetic patients in Indonesia.

From this study, we have shown that the related risk factors for inpatient hypoglycemia, both patients' internal risk factors (history of hypoglycemia) and institutional risk factors (nutritional intake, hyperglycemia therapy with insulin or insulin combined with sulfonylurea) should guide clinicians to be more cautious in treating patients with diabetes to prevent inpatient hypoglycemia which may increase the length of hospital stay and increase medical cost.

CONCLUSION

Patients with a history of hypoglycemia, insulin and/or sulfonylurea treatment, and inadequate nutritional intake were at higher risk for inpatient hypoglycemia. This can lead to a prolonged hospital stay, resulting in higher healthcare costs. Hence, clinicians need to take these risk factors into account to minimize inpatient hypoglycemia.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Contribution Statement
CP, MR, IAMK, PS conceived the study; conducted research; reviewed and edited the manuscript. CP, MR, IAMK, PS developed the study design. CP and MR developed the software, curated and synthesized the data. CP verified the research outputs and presented the data. CP and IAMK provided the study materials and prepared the original draft. MR, IAMK, and PS supervised the research activity planning. CP, IAMK, and PS coordinated the research activity planning. CP and PS acquired financial support for the study.

Author Disclosure
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