

ORIGINAL ARTICLE

Factors associated with prolonged length of stay in patients admitted with severe hypoglycaemia to a tertiary care hospital

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Summary

Severe hypoglycaemia carries considerable morbidity and potential mortality. We aim to elucidate the factors which were associated with a prolonged length of stay (LOS) among patients with diabetes who were admitted to the hospital with severe hypoglycaemia. Three hundred and four patients were included in the analysis, with a mean age of 70.6 ± 11.3 years, mean glycosylated haemoglobin of $6.9 \pm 1.3\%$ and median LOS of 3 days. Patients with a LOS >3 days had significantly higher Charlson Comorbidity Index (CCI) (4.9 ± 2.1 vs 4.1 ± 2.1 , $P < 0.01$), a lower glomerular filtration rate (GFR) (34.6 ± 31.4 mL/min vs 44.8 ± 28.9 mL/min, $P = 0.01$) and a higher proportion of these patients suffered from recurrent hypoglycaemia during the admission (38.9% vs 27.7%, $P = 0.04$). In addition, they had higher white cell counts ($11.1 \pm 4.8 \times 10^9/L$ vs $9.3 \pm 3.2 \times 10^9/L$) and lower albumin concentrations (32.9 ± 6.6 g/L vs 36.8 ± 4.9 g/L). Bivariate analysis showed that the same factors were associated with prolonged LOS. Identification of risk factors associated with prolonged LOS provides the opportunity for intervention to reduce the LOS and improve the outcomes for these patients.

KEYWORDS

diabetes complications, hypoglycaemia

1 | INTRODUCTION

Severe hypoglycaemia carries considerable morbidity and potential mortality. Clinicians around the world have embarked on the intensification of diabetes treatment after publication of landmark trials which demonstrated that intensive glucose control led to significant reduction of diabetes-related microvascular complications.¹ However, intensification of diabetes treatment increases the risk of severe hypoglycaemia.¹ In fact, the ACCORD study in 2008 demonstrated increased mortality in patients with type 2 diabetes and tight glycaemic control.² It would be informative and timely to look

at the characteristics of the diabetes patients who have been admitted with severe hypoglycaemia, the length of stay (LOS) and factors which are associated with a prolonged LOS.

2 | PATIENTS AND METHODS

2.1 | Study design

We performed a retrospective cohort study of patients admitted to the Singapore General Hospital (SGH) via the Accident and Emergency (A&E) Department with severe hypoglycaemia between

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January 2014 and January 2015. SGH is an acute tertiary care hospital with 1700 beds in Singapore. This study was approved by the institutional review board in SGH.

2.2 | Patients

Eligible participants were identified from Department of Accident and Emergency's database in SGH, using hypoglycaemia as the primary diagnostic code (ICD code 2512). Patients who passed away during the same admission were excluded from the analysis.

2.3 | Methods

The electronic medical records of eligible patients were reviewed by a member of the team, and relevant clinical and biochemical data were extracted.

The median LOS was 3 days. The patients were divided into two groups based on LOS of greater or lesser than and equal to 3 days. Clinical and biochemical characteristics of these patients were compared. The Charlson Comorbidity Index (CCI), a weighted index of the number and severity of comorbidities reflecting the 1-year mortality risk, was calculated for each patient. Each patient's glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault equation. We also examined the capillary blood glucose (CBG) at presentation and occurrence of recurrent hypoglycaemia during the admission.

Bivariate analyses were carried out to explore the factors which were associated with a prolonged LOS.

2.4 | Statistical analysis

All statistical data analyses were performed using Statistical Package for Social Sciences (SPSS) software for WINDOWS (version 23.0; IBM 2015, Armonk, NY, USA). Descriptive statistics and the differences between the means and proportions were analysed using Student's *t* test or χ^2 test. A *P* value of <0.05 was considered statistically significant. In addition, a Poisson regression model was used to examine the association between the LOS and the different clinical characteristics among patients who were admitted with severe hypoglycaemia.

3 | RESULTS

Three hundred and eleven patients were admitted with severe hypoglycaemia to the hospital in 2014. Seven patients passed away during the admission and were excluded from the analysis. Therefore, 304 patients were included in the analysis. The mean age of the cohort was 70.6 ± 11.3 years. The mean duration of diabetes was 13.4 ± 8.6 years, and the mean glycated haemoglobin (HbA1c) level of the cohort was $6.9 \pm 1.3\%$. The clinical and biochemical characteristics of the patients are presented in Table 1.

Patients who had a LOS >3 day had more comorbidities with a higher CCI (4.9 ± 2.1 vs 4.1 ± 2.1 , $P < 0.01$). In addition, they had

more severe renal impairment with a lower GFR (34.6 ± 31.4 mL/min vs 44.8 ± 28.9 mL/min, $P = 0.01$). A greater proportion of patients with LOS >3 days experienced recurrent hypoglycaemia (38.9% vs 27.7% , $P = 0.04$) during their inpatient stay. They were also more ill, with higher white cell counts ($11.1 \pm 4.8 \times 10^9/L$ vs $9.3 \pm 3.2 \times 10^9/L$) and lower albumin concentrations (32.9 ± 6.6 g/L vs 36.8 ± 4.9 g/L).

3.1 | Determinants of prolonged LOS

Bivariate analysis revealed CCI, renal impairment, white cell count and albumin concentrations significantly influenced the LOS (Table 2). The LOS increased by 11.3% with each point of increment in the CCI, 6.5% with each point of increment in white cell count ($\times 10^9/\mu L$). On the other hand, the LOS decreased by 1% with each point increment in GFR (mL/min) and 5.7% for every point of increment in albumin (g/L), $P < 0.01$. Presence of recurrent hypoglycaemia trended towards significant in the bivariate analysis with *P* value of 0.06.

4 | DISCUSSION

Recent studies have highlighted a change in patterns of diabetes-related hospital admissions with an increase in hypoglycaemia related admissions.^{3,4} To the best of our knowledge, there are no studies which have examined the factors associated with the LOS of patients with diabetes who have been admitted with severe hypoglycaemia. Our study adds new knowledge and understanding of the factors that contribute to a prolonged LOS in patients admitted with severe hypoglycaemia.

There are about 4 million individuals residing in Singapore, with a high prevalence of diabetes at 13.7%.⁵ Our cohort of patients consists of mainly elderly patients with tight glycaemic control. Elderly patients are at a higher risk of developing hypoglycaemia as a result of their frailty, multiple comorbidities, polypharmacy and poor nutrition. In addition, the elderly are also more vulnerable to the adverse consequences of hypoglycaemia. Severe hypoglycaemia is associated with strokes, myocardial infarctions and increased risks of falls and fractures.⁶ Hence, there is a strong impetus to apply a less stringent HbA1c target in treating elderly type 2 diabetes patients and avoid hypoglycaemia. In addition, the proportion of patients experiencing recurrent hypoglycaemia was significantly higher in patients with a longer LOS and this trended towards significance with a *P* value of 0.06 on bivariate analysis. A tailored approach with less stringent inpatient glycaemic targets would reduce the risks of recurrent hypoglycaemia.

Our data also showed that nearly 60% of patients who were admitted with severe hypoglycaemia were on sulphonylureas. This differs from previous studies published in Europe, which revealed higher proportions of patients admitted with severe hypoglycaemia were on insulin therapy. Fadini et al⁷ reported that 50% of patients who were admitted with severe hypoglycaemia were

TABLE 1 Characteristics of patients admitted with severe hypoglycaemia

Characteristics	All patients	LOS ≤3 d	LOS >3 d	P-value
Number	304	173	131	
Gender—Male (%)	123 (40.5)	70 (40.5)	53 (40.5)	1.00
Age, y	70.6 ± 11.3	69.6 ± 10.6	71.9 ± 12.0	0.09
Diabetes type				
Type 1 diabetes or others, n (%)	9 (3)	6 (3.5)	3 (2.3)	0.74
Type 2 diabetes, n (%)	295 (97)	167 (96.5)	128 (97.7)	
Diabetes duration, y	13.4 ± 8.6	13.3 ± 8.5	13.6 ± 8.9	0.76
HbA1c, %	6.9 ± 1.3	6.8 ± 1.2	7.0 ± 1.5	0.27
On sulphonylurea, n (%)				
Glibenclamide	7			
Glimepiride	4			
Gliclazide/gliclazide MR	25			
Glipizide	133			
Tolbutamide	10			
On insulin, n (%)				
Insulatard only	4			
Insulin glargine only	4			
Multidose insulin				
Insulatard and actrapid	7			
Insulin glargine and insulin aspart	3			
Insulin detemir and insulin aspart	1			
Premixed insulin				
Novomix (aspart 30%, protamine aspart 70%)	25			
Mixtard (soluble 30%, isophane 70%)	47			
Other combinations				
Mixtard (soluble 30%, isophane 70%) and actrapid	2			
On both sulphonylurea and insulin, n (%)	21 (6.9)	9 (5.2)	12 (9.2)	0.18
BMI, kg/m ²	24.7 ± 6.2	25.0 ± 6.7	24.3 ± 5.4	0.34
Charlson Comorbidity Index	4.5 ± 2.1	4.1 ± 2.1	4.9 ± 2.1	0.00
CBG on admission, mmol/L	2.3 ± 0.7	2.4 ± 0.7	2.2 ± 0.8	0.17
Recurrent hypoglycaemia, %	99 (32.6)	48 (27.7)	51 (38.9)	0.04
WBC on admission, ×10 ⁹ /L	10.1 ± 4.1	9.3 ± 3.2	11.1 ± 4.8	<0.01
Glomerular filtration rate, mL/min	40.3 ± 30.4	44.8 ± 28.9	34.6 ± 31.4	0.01
Albumin on admission, g/L	35.0 ± 6.1	36.8 ± 4.9	32.9 ± 6.6	<0.01

Data expressed as n (%) or mean ± SD.

on sulphonylureas and 50% were on insulin. Another multicentre study from Portugal showed 55% of patients who presented to the Emergency Department with severe hypoglycaemia were on insulin therapy and 31.5% were on a secretagogue based regimen.⁸ This may reflect different patient characteristics and management practices of physicians locally with a larger proportion of patient on oral glucose-lowering agents as compared to insulin therapy. In addition, the risk of hypoglycaemia with sulphonylurea use is increased in the elderly and in patients with renal impairment.⁹⁻¹¹ Thus, strategies to reduce complications of hypoglycaemia could be targeted at sulphonylurea dose reductions or using alternative

agents with a lower risk of hypoglycaemia such as DPP-4 inhibitors or SGLT-2 inhibitors, especially so in elderly patients and patient with renal impairment.

The CCI is a measure of a patient's burden of comorbidities.¹² Our data showed that a higher CCI was associated with a longer LOS. Polypharmacy in patients with multiple comorbidities increases their risk for hypoglycaemia. In addition, patients with multiple comorbidities have less physiological reserves to cope with acute insults such as an inter-current illness or episodes of severe hypoglycaemia. We also found that renal impairment was significantly associated with a longer LOS. The kidneys play a critical role in the counter-regulation

of hypoglycaemia via gluconeogenesis, accounting for up to 20% of systemic glucose production during hypoglycaemia.¹³ Reduced renal mass in patients with CKD impairs renal gluconeogenesis. In addition, many patients with chronic kidney disease suffer from anorexia and poor nutrition, decreasing substrates available for gluconeogenesis. In patients with renal impairment and diabetes, altered metabolism of drugs increases their risks of developing hypoglycaemia. Both renal and hepatic metabolism of insulin are decreased in patients with CKD, as a result of reduced glomerular filtration and the effects of uraemic toxins on the liver.¹⁴ Many oral glucose-lowering agents such as metformin and sulphonylureas also undergo renal excretion.¹⁴ In patients with impaired renal function, the duration of action of these medications are prolonged, potentiating risks of hypoglycaemia. Renal impairment should be a key consideration in deciding therapeutic regimens and glycaemic targets for these patients.

We also demonstrated that hypoalbuminemia was associated with prolonged LOS. Albumin level is a predictor of outcomes in acutely ill patients, where lower albumin levels are associated with increased mortality, morbidity and LOS.¹⁵ It has been postulated that albumin exerts a protective effect in acute illness by maintaining colloid osmotic pressure, playing a role in protein transport and via antioxidant effects. Furthermore, hypoalbuminaemia is a marker of poor nutrition and low functional reserves. It is associated with the development of new-onset disability at discharge in elderly patients who were independent prior to hospitalization.¹⁶ This predicts the need for a period of rehabilitation and slower recovery, prolonging the LOS. Hypoalbuminemia is easily identifiable and interventions which focus on nutritional requirements are likely to positively impact on the well-being and long-term clinical outcomes of these patients.

An abnormal white cell count is one of the variables included in the definition of systemic inflammatory response syndrome (SIRS).¹⁷ We found that patients with LOS >3 days had higher white cell

counts, and there was a significant association on bivariate analysis. This suggests that superimposed infection or sepsis in patients admitted with severe hypoglycaemia prolonged recovery times and LOS. Early judicious use of antibiotics to treat concomitant infections is likely to accelerate recovery times and shorten LOS. Clinical pathways which focus on frequent capillary glucose monitoring, aggressive management of acute kidney injury with frequent monitoring of renal function and appropriate adjustment of the diabetes regimen can be instituted to prevent recurrent hypoglycaemia. A multidisciplinary team consisting of an endocrinologist, a diabetic nurse educator and a dietician should be involved in the care of these patients to optimise diabetes treatment and set appropriate glycaemic targets.

One of the major limitations in our study is that we did not account for confounding factors that may contribute to the patient's LOS, such as the complexity of an individual's clinical case or social factors. It is not possible to completely attribute the length of stay to events related to severe hypoglycaemia events. However, this study may confirm the observations of many physicians on the ground using an evidence-based approach.

5 | CONCLUSION

It is alarming to find that more than 300 elderly diabetes patients with tight glycaemic control had been admitted with severe hypoglycaemia and despite overwhelming evidence demonstrating adverse outcomes with intensive glycaemic control. In addition, a large percentage of these patients were on sulphonylureas. Individualising the glycaemic targets and choice of medications may help to avoid the severe hypoglycaemia and admissions. Our study has also highlighted several factors that are easily measured that can aid in predicting the LOS in patients admitted with severe hypoglycaemia. Interventions which address the factors associated with prolonged LOS should reduce the LOS and improve the care of these patients should they be admitted.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

TMM, BYM and GSY conceived the idea of this manuscript. CJM wrote the manuscript under the guidance of TMM. CJM, LWY, ECTC, ATXW, WZW, XX, ALC and HWM conducted data collection and statistical analyses. All authors reviewed the final manuscript.

TABLE 2 Bivariate analysis of association between length of stay and clinical characteristics using Poisson regression (N = 304)

Bivariate analysis	Change in LOS	
	% (95% CI)	P-value
Age, y	9.0 (-0.6 to 2.4)	0.25
Charlson Comorbidity Index	11.3 (4.2 to 18.9)	<0.01
BMI, kg/m ²	-1.0 (-3.2 to 1.4)	0.42
Diabetes duration, y	-0.2 (-1.7 to 1.3)	0.78
HbA1c, %	-8.0 (-18.3 to 3.6)	0.17
CBG on admission, mmol/L	10.7 (-9.2 to 34.9)	0.32
Presence of recurrent hypoglycaemia	42.9 (-1.8 to 107.8)	0.06
WBC on admission, ×10 ⁹ /L	6.5 (3.5 to 9.5)	<0.01
Glomerular filtration rate, mL/min	-1.0 (-1.7 to -0.4)	<0.01
Albumin on admission, g/L	-5.7 (-7.3 to -4.2)	<0.01

ETHICAL APPROVAL

This study was approved by the institutional review board at the Singapore General Hospital.

DATA ACCESSIBILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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