

# Influence of Ethnicity on Outcomes of Diabetes Inpatient Hypoglycemia: an Australian Perspective

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**Aims:** To evaluate outcomes of diabetic inpatient hypoglycemia among Aboriginal and Torres Strait Islander (ATSI) compared with Australian Caucasian patients.

**Methods:** A retrospective audit of diabetic patients aged > 18 years admitted at a regional hospital general ward between April 1, 2015, and March 31, 2016, was analyzed. The database contains clinical information at the time of admission and initial discharge and readmission within 4 weeks thereafter.

**Results:** A total of 1618 (of 6027) patients were admitted with diabetes representing 23.7% of the total ward admissions, of which 484 (29.9%) had inpatient hypoglycemia. Of the 91 patients with available data analyzed, ATSI origin with inpatient hypoglycemia was associated with longer length of stay (LOS) (hazard ratio [HR], 2.1, 95% confidence interval [CI], 1.2-3.5), whereas severe hypoglycemia ( $\leq 2.2$  mmol/L) in both ATSI and non-ATSI was significantly associated with longer LOS (HR, 2.3; 95% CI, 1.2-4.2). No significant differences in LOS were found for gender, age, and Carlson comorbidity index (CCI). The adjusted model for likelihood of readmission, gender, indigenous status, and CCI were not significant risk factors for readmission to the hospital. Readmitted patients were older (50-59 years vs < 50 years,  $P = 0.001$ ; 60-69 years vs < 50 years,  $P = 0.032$ ; 70+ years vs < 50 years,  $P = 0.031$ ).

**Conclusion:** We reported high rate of inpatient hypoglycemia in our study population. Indigenous Australian diabetic patients with inpatient hypoglycemia had significantly longer LOS compared with non-Indigenous Caucasian counterparts. Further prospective studies on a larger population are needed to confirm our findings.

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**Key Words:** Indigenous Australian, diabetes, inpatient hypoglycemia, length of hospital stay

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Abbreviations: ATSI, Aboriginal and Torres Strait Islander Australians; BGL, blood glucose level; CCI, Carlson comorbidity index; CI, confidence interval; HR, hazard ratio; LOS, length of stay; NHR, National Health Roundtable

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In Australia, there were more than 1 million hospitalizations in 2016 resulting from diabetes with disproportionately higher rates of hospitalization among Indigenous Australians compared with non-Indigenous counterparts [1]. Aboriginal and Torres Strait Islander Australians (ATSI) are 8 times more likely to have diabetes [1]. Although optimal glycemic control is needed to prevent chronic complications, diabetic patients on treatment are at risk of hypoglycemia, defined as a blood glucose level  $\leq 3.9$  mmol/L ( $\leq 70$  mg/dL). Both inpatient and outpatient trials have shown that the risk of hypoglycemia limits achievement of good blood glucose control [2].

Several studies have shown an association between severe hypoglycemia and all-cause mortality [2, 3]. Despite well-studied consequences of low blood glucose levels in critically ill admissions [4–7], the effect of hypoglycemia on outcomes in non-Caucasian cohorts in general is least studied [8]. Some studies have shown that general ward hypoglycemia in hospitalized Caucasian patients with diabetes is associated with increase in length of stay (LOS) [9], mortality [2, 3, 9], and costs [10] but extrapolation of these data onto indigenous subpopulations might not be realistic. Some of these studies suggest that the increased mortality is not associated with the hypoglycemia itself but rather with the patients' comorbidities [2, 3]. Furthermore, despite a high prevalence of diabetes and its complications among the Australian Indigenous population, there is no study on effects of inpatient hypoglycemia in its diabetic population.

The aim of this study was to evaluate outcomes of inpatient hypoglycemia in diabetic indigenous compared to non-Indigenous Australians.

## 1. Methods

Data from patients with diabetes who were admitted to a 775-bed teaching hospital between April 1, 2015, and March 31, 2016, were reviewed. The study was based on a retrospective audit carried out using the National Health Roundtable (NHR) registry, electronic medical record, and laboratory data (Auslab) provided by the hospital's Medication Safety Committee and the study was approved by the regional ethics committee. The NHR database contains clinical information complemented by manual extraction of medication and laboratory details from the electronic medical record and Auslab, respectively. Adult patients aged  $> 18$  years admitted to the hospital's general wards were included in the study. Information extracted includes gender, age, primary and secondary diagnoses according to the International Classification of Diseases, Ninth Revision, Clinical Modification code showing admission and discharge status, LOS, indigenous status (dichotomized as ATSI and non-ATSI). Medications for diabetes (insulin and/or oral hypoglycemic agents) and blood glucose (point of care and/or laboratory) levels were also collated and analyzed.

The NHR database also contains a field that identifies readmission within the 30-day period after discharge. The readmission variable is a new hospitalization in the month following discharge with the same major diagnostic category as the initial diagnosis. The analysis includes patients discharged within the period of the study with a primary or secondary diagnosis of diabetes and a secondary diagnosis of hypoglycemia. Analysis also included demographic characteristics and the presence or absence of coexisting conditions, including congestive heart, coronary heart disease, hypercholesterolemia, chronic renal failure, exacerbation of chronic pulmonary disease, atrial fibrillation, cerebrovascular disease, dementia, gastric hemorrhagic bleeding, neoplasm, hypertension, anemia, nursing home residence, peripheral arterial disease, malnutrition, obesity, and cirrhosis. A diagnosis was considered primary if it was the reason for admission; all other diagnoses were considered secondary.

Descriptive analyses for demographic and clinical characteristics were presented as means and SDs for continuous variables and frequencies and percentages for categorical variables. We used the Charlson Comorbidity Index (CCI) [11] to rank patient illness severity based on the number and importance of comorbid diseases. The overall comorbidity score ranges were calculated showing the cumulative increased likelihood of 1-year mortality. CCI contains 19 groups of comorbidities, each weighted 1 to 6 to reflect their

potential influence on mortality. Furthermore, patients were classified into groups based on their total CCI scores (mild: 1, 2; moderate, 3, 4; severe,  $\geq 5$ ); hypoglycemia was classified based on lowest blood glucose values and categorized as previously described [12]: mild (3.9-3.1 mmol/L; 70.0-55.0 mg/dL), moderate (3.0-2.3 mmol/L; 54.0-40.0 mg/dL), and severe ( $\leq 2.2$  mmol/L;  $\leq 40.0$  mg/dL).

Associations between all explanatory variables and categorical response variables (inpatient mortality and the likelihood of readmission) were assessed separately using univariate logistic regression as preliminary analysis. Multivariable logistic regression was applied to inpatient mortality and readmission separately to investigate their association with hypoglycemia while adjusting for age, gender, indigenous status, lowest blood glucose level (BGL) during hypoglycemic event and the Charlson index score. Adjusted odds ratios and 95% confidence interval (CI) were presented for categorical variables. The survival risk (hazard ratio [HR]) was computed with the HR estimated from the Cox regression model. In this study, survival refers to patients who survived after being discharged from the hospital.

Because of the small events size and limited data, we used Firth penalized likelihood method to fit the logistic models and Cox regression. Inference was based on 5% level of significance and all statistical analyses was performed in SAS 9.4 software (SAS Institute Inc., Cary, NC) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

## 2. Results

A total of 6027 patients were admitted during the period of the study. We identified 1618 patients admitted with diabetes, representing 23.7% of the total ward admissions. Of these, hypoglycemic events were documented in 484 patients (29.9%). A follow-up retrospective study of a cohort of 91 patients whose data were available for review and fulfilled inclusion criteria were analyzed. We present in [Table 1](#) the baseline demographic and clinical characteristics of the study population. The age range of the cohort was 21 to 87 years old (mean, 60.6 years), males 51.6% and had type 2 diabetes (96.7%). Among the patients, 30 (33.0%) were identified as ATSI and 70.3% of them were on insulin. The mean lowest BGL was 2.9 mmol/L (52.2 mg/dL) (range, 1.1-3.9 mmol/L; 20.0-70.0 mg/dL). A total of 44 (48.3%) patients had lowest BGL between 3.9 mmol/L (70.0 mg/dL) and 3.1 mmol/L (55.0 mg/dL), 28 (30.8%) had BGL between 3.0 mmol/L (54 mg/dL) and 2.3 mmol/L (41.0 mg/dL), whereas the remaining 19 (20.9%) patient had a BGL  $\leq 2.2$  mmol/L ( $\leq 40$  mg/dL) during their hospitalization. The mean number of hypoglycemic events with inpatient hypoglycemia was 2.9 episodes/patient (range, 1-15 episodes/patient).

This cohort of patients shows a higher burden of comorbidity with an average CCI score of 7.2 (range, 1-15) and 86.81% had a CCI of  $\geq 5$ . The mean LOS was 9.0 days (range, 0.3-49.7). About one-third (36.3%) of the patients were treated with basal-bolus insulin regimen. [Table 1](#) reveals no significant associations between baseline demographic (and clinical) characteristics and readmission (and mortality). About one-half (53.9%) of the patients in this cohort had hypertension; other primary diagnosis and major comorbidities are presented in [Table 2](#). Further summary of the data and the data fields are included in [Table 3](#). Although non-ATSI had higher mortality and readmission, quantitative comparisons with ATSI were not statistically significant. We observed that, separately, comorbidity rates, LOS, and number hypoglycemia were significantly higher for non-ATSI than ATSI ([Table 3](#)).

The adjusted model for likelihood of readmission showed that gender, indigenous status, CCI, and BGL level were not significant risk factors for an increased readmission ([Table 4](#)). Having a CCI score between 3 and 4 did not reach nominal statistical significance ( $P = 0.06$ ). However, readmitted patients were older (50-59 years vs  $< 50$  years,  $P < 0.05$ ; 60-69 years vs  $< 50$  years,  $P < 0.12$ ; 70 + years vs  $< 50$  years,  $P < 0.05$ ).

The results from multivariate Cox regression displayed in [Table 4](#) shows that being of ATSI origin is associated with longer LOS (HR, 2.1; 95% CI, 1.2-3.5). Having severe hypoglycemia ( $\leq 2.2$  mmol/L) is significantly associated with longer LOS (HR, 2.3; 95% CI,

**Table 1. Demographic and Clinical Characteristics of Patients with Hypoglycemia**

Characteristics	Mean (Range) or N (%) <sup>a</sup>	Readmission OR (95% CI)	Mortality OR (95% CI)
<b>Overall</b>	<b>91</b>	<b>20 (22.0%)</b>	<b>6 (6.6%)</b>
Gender			
Male	47 (51.6%)	0.9 (0.3–2.5)	0.2 (0.0–1.2)
Female	44 (48.4%)	Reference	Reference
Age (years)	60.6 (21–87)	1.0 (0.9–1.0)	1.0 (0.9–1.0)
Age			
< 50 years	21 (23.1%)	Reference	Reference
50–59 years	19 (20.9%)	0.1 (0.0–0.5)	2.9 (0.4–32.1)
60–69 years	24 (26.4%)	0.3 (0.1–1.1)	1.5 (0.2–17.6)
70+ years	27 (29.7%)	0.2 (0.1–0.7)	0.3 (0.0–4.9)
Surgical procedure	18 (19.8%)	1.1 (0.3–3.4)	0.5 (0.1–5.3)
No surgical procedure	73 (80.2%)	Reference	Reference
Indigenous status <sup>b</sup>			
ATSI	30 (33.0%)	0.9 (0.3–2.4)	0.5 (0.1–2.8)
Non-ATSI	61 (67.0%)	Reference	Reference
LOS	9.0 (0.3–49.7)		
Number of hypoglycemia	2.9 [1–15]	0.8 (0.5–1.0)	1.0 (0.5–1.2)
Mean lowest BGL	2.9 (1.1–3.9)	0.9 (0.4–1.8)	1.6 (0.5–6.5)
BGL group			
Mild (3.9–3.1 mmol/L)	44 (48.3%)	Reference	Reference
Moderate (3.0–2.3 mmol/L)	28 (30.8%)	0.8 (0.2–2.4)	1.6 (0.3–8.2)
Severe ( $\leq$ 2.2 mmol/L)	19 (20.9%)	1.2 (0.4–4.1)	0.3 (0.0–3.4)
CCI	7.2 [1–15]	0.9 (0.7–1.0)	1.1 (0.9–1.5)
CCI subgroups			
Mild: CCI score [1, 2]	6 (6.6%)	Reference	Reference
Moderate: CCI score [3, 4]	6 (6.6%)	0.1 (0.0–2.5)	1.0 (0.0–81.0)
Severe: CCI score ( $\geq$ 5)	79 (86.8%)	0.3 (0.1–1.5)	1.2 (0.5–28.5)
Number on insulin	66 (77.7%)	5.5 (0.9–32.6)	0.3 (0.1–1.4)
Hospital diabetes treatment			
Basal only	10 (11.0%)	Reference	Reference
Basal + bolus	33 (36.3%)	1.0 (0.2–4.6)	2.4 (0.2–34.4)
Mixed	26 (28.6%)	0.7 (0.2–3.4)	0.4 (0.0–75.5)
Unknown	22 (24.2%)		
Types of diabetes			
T2DM	58 (63.7%)		
T1DM	29 (31.8%)		
Unknown	4 (4.4%)		

All the listed categories and variables were not statistically significant.

ATSI, Aboriginal and Torres Strait Islander Australians; BGL, blood glucose level; CCI, Carlson comorbidity index; CI, confidence interval; LOS, length of stay; OR, odds ratio; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

<sup>a</sup>Number of events (percentage).

<sup>b</sup>Aboriginal and/or Torres Strait Islander.

1.2–4.2) than mild hypoglycemia (3.9–3.1 mmol/L). No significant differences in LOS were found for gender, age, and CCI score.

### 3. Discussion

To the best of our knowledge, this is the first study to estimate, in a hospital-based Australian diabetic population, incidence of inpatient hypoglycemia on general ward admissions. It shows a high rate of hypoglycemia, 29.9% in our cohort, which is much higher than the 3.5% to 10.5% reported by others [9, 13, 14]. In our series, 70% of the study population were treated with insulin, in contrast to 24.5% reported by others in earlier studies [8]. The relatively higher rate of insulin-treated patients in our series might have contributed to high

**Table 2. Characteristics of Subjects with Inpatient Hypoglycemia Showing Primary Diagnoses and Major Comorbidities at the Time of Admission**

Variables	n	%
Primary diagnosis		
Infection	27	29.67
Metabolic	24	26.37
Cardiovascular	14	13.38
Cancer	10	10.99
Mental	6	6.59
Musculoskeletal	10	10.99
Comorbidities <sup>a</sup>		
Hypertension	49	53.85
Ischemic heart disease	25	27.47
Dyslipidemia	23	25.27
Osteoarthritis	15	16.48
Depression	13	14.29
Stroke	8	8.79
Gastroesophageal reflux disease	9	9.89

<sup>a</sup>Including those with multiple comorbidities

**Table 3. Demographic and Clinical Characteristics of Patients with Hypoglycemia Among ATSI<sup>a</sup> and Non-ATSI**

Characteristics	Total	Non-ATSI <sup>a</sup>	ATSI <sup>a</sup>
Overall, n (%)	91	61(67.0%)	30 (33.0%) <sup>b</sup>
Mortality	6 (6.6%)	5 (83.3%)	1 (16.7%)
Readmission	20 (3.0%)	14 (70.0%)	6 (30.0%)
Gender, n (%)			
Male	47 (51.6%)	36 (76.6%)	11 (23.4%)
Female	44 (48.4%)	25 (56.8%)	19 (43.2%)
Age, n (%)			
< 50 years	21 (23.1%)	13 (61.9%)	8 (38.1%)
50–59 years	19 (20.9%)	8 (42.1%)	11 (57.9%)
60–69 years	24 (26.4%)	17 (70.8%)	7 (29.2%)
70+ years	27 (29.7%)	23 (85.2%)	4 (14.8%)
Surgical procedure, n (%)	18 (19.8%)	11 (61.1%)	7 (38.9%) <sup>b</sup>
No surgical procedure, n (%)	73 (80.2%)	52 (71.3%)	21 (28.8%)
BGL group, n (%)			
Mild (3.9–3.1 mmol/L)	44 (48.3%)	29 (65.9%)	15 (34.1%)
Moderate (3.0–2.3 mmol/L)	28 (30.8%)	18 (64.3%)	10 (35.3%) <sup>c</sup>
Severe ( $\leq$ 2.2 mmol/L)	19 (20.9%)	14 (73.7%)	5 (26.3%) <sup>c</sup>
CCI subgroups, n (%)			
Mild: CCI score [1, 2]	6 (6.6%)	3 (50.0%)	3 (50.0%)
Moderate: CCI score [3, 4]	6 (6.6%)	4 (66.7%)	2 (33.3%)
Severe: CCI score ( $\geq$ 5)	79 (86.8%)	54 (68.4%)	25 (31.7%) <sup>b</sup>
Age (years)	60.6 (21–87)	63.4 (27–9)	55 (21–8) <sup>b</sup>
LOS, mean (range)	9.0 (0.3–49.7)	10.9 (0.6–49.7)	5.17 (0.3–13.4) <sup>d</sup>
Number of hypoglycemia, mean (range)	2.9 [1–15]	3.5 [1–15]	2.0 [1–6] <sup>c</sup>
Mean lowest BGL, mean (range)	2.9 (1.1–3.9)	7.4 [1–14]	7.2 [1–15]
CCI, mean (range)	7.24 [1–15]	7.4 [1–14]	2.9 (1.3–3.9)

ATSI, Aboriginal and/or Torres Strait Islander; BGL, blood glucose level; CCI, Carlson comorbidity index; LOS, length of stay.

<sup>a</sup>Based on the number of events within each category. Note that the first subcategory of a variable is the reference comparison.

<sup>b</sup> $P < 0.05$ .

<sup>c</sup> $P < 0.01$ .

<sup>d</sup> $P < 0.001$ .

**Table 4. Risk Factors for Readmission and Length of Hospital Stay Among Diabetic Subjects with Inpatient Hypoglycemia**

Characteristics	Readmission	Length of stay
	OR (95% CI)	HR (85% CI)
Gender (reference: female)		
Male	1.2 (0.4–3.7)	0.8 (0.5–1.3)
Indigenous status (reference: NATSI)		
ATSI	0.9 (0.3–2.8)	2.1 (1.2–3.5) <sup>a</sup>
Age (reference: <50 years)		
50–59 years	0.1 (0–0.6) <sup>b</sup>	0.7 (0.4–1.5)
60–69 years	0.3 (0.1–1.2)	0.8 (0.4–1.7)
70+ years	0.2 (0.1–0.8) <sup>b</sup>	0.7 (0.3–1.3)
CCI (reference: mild CCI score, 1–2)		
Moderate: CCI score [3, 4]	0.1 (0–3.6)	0.4 (0.1–1.3)
Severe: CCI score (>5)	0.9 (0.1–7.8)	0.8 (0.3–2.3)
BGL group (reference: mild, 3.1–3.9 mmol/L)		
Moderate (2.3–3.0 mmol/L)	0.8 (0.2–2.9)	1.2 (0.7–2.0)
Severe ( $\leq$ 2.2 mmol/L)	1 (0.3–3.9)	2.3 (1.2–4.2) <sup>a</sup>

ATSI, Aboriginal and Torres Strait Islander Australians; CI, confidence interval; HR, hazard ratio; NATSI, non-Aboriginal and Torres Strait Islander Australian; OR, odds ratio.

<sup>a</sup> $P < 0.01$ .

<sup>b</sup> $P < 0.05$ .

incidence of inpatient hypoglycemia in our report. In support of our study, Umpierrez et al. [15] reported similar incidence in their report on admitted insulin-treated type 2 diabetic patients, suggesting medication as a contributing factor. However, Malawana et al. and the International Hypoglycemia Study Group reported no significant differences in occurrence of inpatient hypoglycemia between insulin-treated and non-insulin-treated patients [8, 16].

We have also shown ATSI diabetic patients with inpatient hypoglycemia having significantly longer LOS compared with non-ATSI counterparts. Interestingly, as far as we know, this is the first report on association of increased LOS with ethnicity. Our finding is relevant in that ATSI people are 5.7 times more likely to be hospitalized for diabetes and thus at risk of long LOS, than non-Indigenous people [1]. More research is needed to understand extent of racial differences in the association between inpatient hypoglycemia and LOS in the wider Australian diabetic population. This will assist in understanding other clinical and environmental risk factors to explain longer LOS among the diabetic ATSI patients. Future studies should assess avenues for addressing these potential causes of inpatient hypoglycemia in the indigenous diabetic inpatients and implement interventions to reduce hypoglycemia and LOS.

Our studies further highlight irrespective of ethnic background, severe hypoglycemia was associated with longer LOS as previously reported in the United Kingdom and United States [9, 12, 17]. The need to maintain higher or normal BGLs is further supported by previous landmark studies showing excess mortality in individuals with tighter glycemic control compared with those with higher glycemic levels [18, 19]. Although increased mortality during and after admission was reported to be associated with inpatient hospital hypoglycemia [17, 20], there was no significant mortality in our cohort. The reason for this is not obvious, but might be due to a small sample size compared with earlier studies as well as high CCI, signifying high comorbidities in both subjects with and without hypoglycemia in our study population.

We have also shown older patients with inpatient hypoglycemia were less likely to be at risk of hospital readmission. Significance of this is not clear because readmission for other comorbidities as measured by CCI was not significant in our study. Despite Indigenous status with inpatient hypoglycemia being associated with long LOS, readmission within 1 month of initial hospital admission did not appear to be a contributory risk factor in

diabetic ATSI subjects. This contrasts Zaccardi et al.'s report showing higher rate of readmissions among Caribbean diabetic subjects compared with Caucasians [21]. In the same report, Asians (Bangladeshi, Pakistani, and Indian) were found to have lower risk of readmission compared with Caucasians thought to be due to less aggressive management of glucose in the Asian patients [22]. More studies on a larger population in our setting is needed to characterize these findings.

Our data have an important strength: being, to the best of our knowledge, the first study to focus on Indigenous and non-Indigenous Australian patients with diabetes hospitalized in a general ward, by far the largest group of inpatients at high risk of hypoglycemia. On the other hand, some study limitations should be noted. The absence of randomization of patients in diabetic inpatient hypoglycemic group is an inherent problem in observational studies. Although we cannot be certain that hypoglycemia is the determining factor for LOS in the Indigenous and non-Indigenous cohort's analysis, matching the 2 patient groups on primary diagnosis and other background variables reduced confounding. In this retrospective study, although all patients had diabetes and were receiving antidiabetic medications including insulin, we cannot exclude the possibility that some non-antidiabetic medications and other conditions may have contributed to the inpatient hypoglycemia, for example, beta blockers, sepsis, or alcoholism, rather than antidiabetic medications alone. It is important to note that there is a limitation to retrospective studies in general. Observations derived from such studies may contain some missing information and thus may serve as a stimulus to further prospective work to clarify findings. Similarly, our study is based on a small sample of events, non-ATSI patients were twice higher than for ATSI patients, which is not surprising given that indigenous population is less than 10% of the local population [23]. The present study must be interpreted in the knowledge of the defects inherent in such studies. Despite these, we believe that our report is likely to be accurate because experienced health care professionals made the recordings; our results are in line with similar findings in other non-Caucasian diabetic inpatient populations [21].

#### 4. Conclusion

Our results are significant for promoting awareness of the effect of ethnicity on inpatient hypoglycemia risk. Intensification of strategies for prevention of hypoglycemia including education, frequent glucose monitoring, and glycemic pattern recognition should be emphasized to minimize inpatient hypoglycemia, particularly in the identified high-risk indigenous population. Further prospective studies on a larger population are needed to verify our findings.

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#### Additional Information

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**Disclosure Summary:** The authors have nothing to disclose.

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