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19

Abstract

20 **Objective**

21 The main aim of this study is to identify the direct cost and economic burden of hypoglycaemia among
22 patients with Type II diabetes mellitus in Malaysia.

23 **Methods**

24 The incurred cost for hypoglycaemia among patients admitted to University Kebangsaan Malaysia Medical
25 Centre (UKMMC) was explored from a cross sectional study. 20-79 year patients discharged between Jan
26 2010 to Sept 2015 and having an ICD-10 code of hypoglycaemia as a primary diagnosis in the casemix
27 database were included in the study. Costing analysis from the perspective of health providers was
28 completed using step-down approach. Data related to hospital cost were collected using hospital-costing
29 template, based on three levels of cost centres. The costing data from UKMMC was used to estimate the
30 national burden of hypoglycaemia among type II diabetics for the whole country.

31 **Results**

32 Of 244 diabetes patients admitted primarily for hypoglycaemia to UKMMC, 52% were female and 88%
33 were over 50 years old. The cost increased with severity. Managing a hypoglycaemic case requires 5 days
34 (median) of inpatient stay with a range of 2-26 days; and costs RM 9,083 (USD 2,323). 30% of the cost
35 came from the ward services cost (final cost centre), 16% of the cost came from ICU services and 15%
36 from pharmacy services (secondary level cost centres). Based on the prevalence of hypoglycaemia-related
37 admissions of 3.2%, the total cost of care for hypoglycaemia among adult diabetes in Malaysia is estimated
38 to be RM 117.4 (USD 30.0) million, which is translated as 0.5% of Ministry of Health budget.

39 **Conclusion**

40 Hypoglycaemia imposes substantial economic impact even without the direct and indirect cost incurred by
41 patients and other cost of complications. Proper diabetic care and health education is needed in diabetic
42 management to reduce episodes of hypoglycaemia.

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46 **Introduction**

47

48 Hypoglycaemia is a not an uncommon presentation at accident and emergency (A& E) department. An
49 estimate of 2-4% of diabetes deaths is due to hypoglycaemia [1]. Hypoglycaemic episode is inevitable in
50 90% of diabetics with insulin therapy[2], and those with certain antihyperglycaemic medicine are also at
51 risk. Elderly and those with comorbid conditions are more likely to get severe hypoglycaemia. [3] The
52 incidence of hypoglycaemia varies with studies. On average, type 1 diabetics had two symptomatic
53 hypoglycaemia episodes per week [4]and one severe hypoglycaemia episode per year[5]; with a lesser
54 occurrence among type II diabetes patients.[2] However, type II diabetes with progressive insulin
55 deficiency, long duration of diabetes, and tight glycaemic control also have similar risk of hypoglycaemia
56 as type 1 diabetes.[5]

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58 Eleven percent of type 2 diabetic patients with different anti-diabetic regimens suffered one or more
59 hypoglycaemic episodes per year. Miller et al reported that 24.5% of patients reported at least one
60 hypoglycaemic episode in 3 months period [6, 7]. Mild hypoglycaemic attacks occurs frequently, as high as
61 1-2 episodes per week[8] and severe hypoglycaemic attacks occurs less frequently with an incidence rate of
62 1 to 2.7 episodes by per patient per year [8, 9].

63

64 DM is one of the commonest chronic non-communicable diseases globally. Its incidence and prevalence
65 are escalating, and Asia-Pacific region is at the forefront of the current epidemic. As of 2015, it is estimated
66 that 8.8% of adult population in Southeast Asia region has diabetes [10]. Prevalence of DM among
67 Malaysian over 20-79 years is estimated to be 17.5%[11], ranking third in Asia-Pacific region. [12, 13] It
68 was estimated that in 2030, Malaysia would have a total number of 2.48 million diabetics compared to 0.94
69 million in 2000 that can be translated as 164% increase [14].

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71 The chronic nature of diabetes and its devastating complications make it a very costly disease. To prevent
72 the risk of acute and chronic complication, diabetic patients required continuous medical care [2, 15].

73 Hypoglycaemia is unpredictable and undesirable side effects among diabetic patients. Frequent and

74 potentially fatal complication may occur among hypoglycaemic patients with Type 1 or Type 2 diabetes
75 treated with insulin, and in patients with Type 2 diabetes treated with certain oral anti-diabetic medicine.

76
77 Hypoglycaemic attacks require defence mechanism against falling serum glucose, and frequent attack result
78 in increasing cycles of recurrent hypoglycaemia [13]. Fear of hypoglycaemia is not uncommon in patients
79 with diabetes. Experiences of severe hypoglycaemic episodes increase the fear for future hypoglycaemic
80 event. Approximately 40% of patients admitted that fear of hypoglycaemia caused them to maintain their
81 blood glucose levels at higher than recommended values [14]. This questions compliance of anti-diabetic
82 medicine with possible complication due to uncontrolled diabetes and increased health care cost.

83 Regardless of bearing a significant burden by hypoglycaemia, the cost of hypoglycaemia in Malaysia is yet
84 known. This study identifies the direct cost and economic burden of hypoglycaemia among patients with
85 type II diabetes mellitus on insulin in Malaysia.

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87 **Methods**

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89 A cross sectional study was conducted to identify the incurred cost due to hypoglycaemia among patients
90 admitted to Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Using the electronic medical
91 database kept at UKMMC, patients discharged from January 2010 to September 2015 were classified into
92 diagnosis related groups (DRG) with MY-DRG® grouping software. 20-79 year old patients having
93 hypoglycaemia as a primary reason for admission in the casemix database is identified using ICD 10 codes.

94 The ICD 10 codes associated with hypoglycaemia: E16.0 (Drug Induced Hypoglycaemia without coma,
95 E16.1 (Other Hypoglycaemia) and E16.2 (Hypoglycaemia Unspecified) were included in the study.

96 Costing analysis was carried out using step-down approach. Financial staffs in the hospital were given a
97 costing template to retrieve financial data from the hospital records. The templates classifies the
98 departments into three levels of cost centres: overhead cost centres (e.g.; administration, utilities,

99 maintenance etc.), intermediate cost centres (e.g.; pharmacy, radiology etc.) and final cost centres (all

100 wards and all clinics). Information on financial expenditures and output for each cost centre was recorded.

101 The information recoded includes the total expenditure, total number discharges, inpatient days, number of

102 patient visits for outpatient clinics and floor space. All the information of the activities reflecting the
103 workload such as number of discharges, inpatient days, floor space and number of outpatient visits were
104 gathered for appropriate allocation.

105

106 Both capital cost (building, equipment and furniture cost) and recurrent cost (staff salary and other
107 recurrent cost) were combined in estimating the cost for each cost centre. The final allocated costs for each
108 inpatient cost centres were then divided by the total units of inpatient days to obtain the cost of providing
109 services on a per-patient per-day of stay basis, which is referred as unit cost. The unit cost is finally
110 multiplied with the individual patient's length of stay to obtain the cost of care per patient per discharge.
111 All these steps were simplified by using the Clinical Cost Modelling Software Version 2.1 (CCM Ver. 2.1).
112 CCM is the step-down costing tool that is being used by the casemix system in UKMMC.

113

114 The cost is triangulated by developing clinical pathways for a hypoglycaemic episode. An expert group
115 meeting was held to develop the common clinical pathways of managing hypoglycaemia. These experts
116 include physicians, endocrinologists, and pharmacists who are working in the A&E department and also in
117 the clinical departments of the hospital.

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119 In imputing the national burden, estimates for incidence and prevalence of diabetes were obtained from
120 NMHS 2015 [8] and the International Diabetes Federation.[9] The possible episode of hypoglycaemia
121 incidence was estimated from the Malaysian Hypoglycaemia Assessment Tool Study (HAT study) [16].
122 The unit cost for management of hypoglycaemia calculated in the step-down approach was used to estimate
123 the burden. Sensitivity analysis was carried out by varying the incidence of hypoglycaemia to obtain the
124 worst-case scenario and best-case scenario.

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130 **Results**

131 903 cases (0.54% of the total cases) discharged from UKMMC between January 2010 and September 2015
 132 had a diagnosis of hypoglycaemia (Table 1).

133 **Table 1. Number of Hypoglycaemia Patients By Year in UKMMC Casemix Database**

Year	Nos.	Total Discharges	% Hypoglycaemia of Total Discharges
2010	199	32,144	0.62%
2011	157	26,262	0.60%
2012	180	28,728	0.63%
2013	177	33,473	0.53%
2014	119	27,303	0.44%
2015	71	18,623	0.38%
Total	903	166,533	0.54%

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136 Among these cases, 33.4% were classified into MY-DRG® casemix groups of Endocrine, Nutrition and
 137 Metabolism Group followed by Respiratory System Group (12.6%) and Cardiovascular System Group
 138 (9.7%). Central Nervous System and Nephro-urinary System contributed 6.4% of the hypoglycaemia
 139 individually (Table 2).

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141 **Table 2. Hypoglycemia by Casemix Main Group (CMG)**

No	Casemix Main Groups (CMG)	Frequency	Percent
1	Endocrine system, nutrition & metabolism Groups	302	33.4
2	Respiratory system Groups	114	12.6
3	Cardiovascular system Groups	88	9.7
4	Central nervous system Groups	58	6.4
5	Nephro-urinary System Groups	58	6.4
6	Infectious & parasitic diseases Groups	51	5.6
7	Musculoskeletal system & connective tissue Groups	47	5.2

8	Digestive system Groups	45	5
9	Hepatobiliary & pancreatic system Groups	38	4.2
10	Female reproductive system Groups	26	2.9
11	Skin, subcutaneous tissue & breast Groups	23	2.5
12	Haemopoietic& immune system Groups	17	1.9
13	Ear, nose, mouth & throat Groups	10	1.1
14	Myeloproliferative system & neoplasms Groups	7	0.8
15	Mental Health and Behavioral Groups	5	0.6
16	Injuries, poisonings & toxic effects of drugs Groups	4	0.4
17	Eye and Adnexa Groups	3	0.3
18	Male reproductive System Groups	2	0.2
19	Deliveries Groups	2	0.2
20	Factors influencing health status & other contacts with health services Groups	2	0.2
21	Substance abuse & dependence Groups	1	0.1
Total		903	100

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144 Most of the hypoglycaemic conditions were admitted to the medical ward (91.7%), and 8.1% were
 145 admitted to the surgical unit.

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147 Of the 302 hypoglycaemic cases with endocrine problems, diabetes in particular, 244 cases were admitted
 148 primarily for hypoglycaemia and 58 were admitted for hypoglycaemia as a secondary reason (Table 3).

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153 **Table 3. Type of Hypoglycemia among cases in CMG Endocrine System, Nutrition & Metabolism**

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Type of Hypoglycaemia	Frequency	Percent
Hypoglycaemia as main diagnosis	244	80.8%
Hypoglycaemia as secondary diagnosis	58	19.2%
Total	302	100

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157 Only 244 cases with hypoglycaemia as primary reason were included in the study for further analysis.

158 Females were more likely to suffer from hypoglycaemia, as almost 52% of the cases were female. 99.2% of

159 all cases were discharged home well. In the MY-DRG® system, patients are classified into one of the three

160 levels of severity. Cases in severity level 1 do not have complications or co-morbidities where as those in

161 severity level 2 have minor complications and co-morbidities. Patients in severity level 3 have major

162 complications and co-morbidities. About 57.4% of the primary hypoglycaemia cases were in severity level

163 3. Most (88.1%) of the patients suffering from hypoglycaemic attacks were in the age group of 50-79 years

164 old, with 55.3% of the cases required not more than 5 days of hospital admission (Table 4).

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177 Table 4: Characteristics of hypoglycemic cases among CMG Endocrine System, Nutrition and Metabolism

Characteristics	Hypoglycemia as primary diagnosis (n =244)	
Gender (Female, %)	127 (52%)	
Discharged status	- Discharged to home	242 (99.2%)
	- Others	2 (0.8%)
Severity Level	- Severity Level 1	23 (9.4%)
	- Severity Level 2	81(33.2%)
	- Severity Level 3	140 (57.4%)
Age group	- 20 - 29 years	3 (1.2%)
	- 30 - 39 years	8 (3.3%)
	- 40 - 49 years	18 (7.4%)
	- 50 - 59 years	34 (13.9%)
	- 60 - 69 years	84 (34.4%)
	- 70 - 79 years	97 (39.8%)
	- >= 80 years	15 (6.1%)
Length of stay	- <=5 days	135 (55.3%)
	- 6 – 10 days	77 (31.6%)
	- 11 – 15 days	18 (7.4%)
	- 16 – 20 days	10 (4.1%)
	- 21 – 25 days	3 (1.2%)
	- 26 – 30 days	1 (0.4%)

178

179 The cost for a patient to be treated at UKMMC A&E department for hypoglycaemia is RM 741 (USD 190).

180 Generally, the cost of hypoglycaemic cases admitted to the medical unit is less costly than other units: RM

181 1,375 (USD 352) at medical unit compared toRM 1,679 (USD 430) for obstetrics and gynaecology unit,

182 and (RM 2,611 (USD 668) at surgical unit. Out of 903 cases with hypoglycaemia as diagnosis, 828 cases

183 are from medical ward, 73 are from surgical ward and only 2 are from O&G unit.

184

185 As an average, the cost of care for hypoglycaemia varies with severity level. Although the mean cost of
 186 care for hypoglycaemia at severity 1 and 2 is RM7,054 (USD 1,804) and RM7,333 (USD 1,875)
 187 respectively, the mean cost reaches RM10,401 (USD 2,660) when the condition becomes severity level 3.
 188 The median cost for cases diagnosing hypoglycaemia as the primary diagnosis was RM 6,875 (USD
 189 1,758) and cases of hypoglycaemia as secondary diagnosis was found to be RM 11,000 (USD 2,813) The
 190 median length of stay for hypoglycaemic cases was 5 days for primary diagnosis and 8 days for secondary
 191 diagnosis. In this study, the focus is on the diabetic cases with hypoglycaemia as primary reason for
 192 admission and the median cost found was RM 6,875 (USD 1,758) with a median length of hospital stay of
 193 5 days (Table 5).

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196 **Table 5. The cost (RM) of Hypoglycemia by diagnosis type and severity level**

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Type of	Severity	N	Mean	SD	Med	Min	Max	%
Hypoglycaemia			(RM)	(RM)	(RM)	(RM)	(RM)	
Hypoglycaemia as main diagnosis	Severity Level-1	23	7,054	3,807	5,500	2,750	15,125	9.3%
	Severity Level-2	81	7,333	4,165	6,875	2,750	26,125	32.8%
	Severity Level-3	140	10,401	7,346	8,250	2,750	36,554	57.9%
	Total	244	9,083	6,363	6,875	2,750	36,554	100.0%

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200 The cost by different cost centres was explored. 30% of the cost came from the final cost centre (the ward
 201 services cost), 16% of the cost came from ICU services and 15% from pharmacy and drug services.

202

203 Using the information from International Diabetes Federation [8], the HAT study [16] and the NMHS 2015
 204 [9], the assumption on incidence and prevalence were made. From the NMHS 2015, 17.5% of adult
 205 Malaysians are estimated to have diabetes mellitus, with 8.3% of them with known diabetes. 25.1% of the
 206 known diabetics are on insulin therapy, which is equivalent to 404,619 people. Using a conservative

207 assumption, the HAT study estimated that among type 2 DM patients, the annual incidence of any type of
 208 hypoglycaemic episode is 47.1% and severe hypoglycaemia is 16.8%. [16] Based on the assumptions on
 209 the number of cases requiring hospital admission and the mean cost for hypoglycaemia as main diagnosis
 210 in UKMMC for severity level 1 to 3, the calculation was developed as base case scenario, best case
 211 scenario and worst case-scenario. We estimated the worst case scenario based on the retrospective arm
 212 findings of the HAT Study which is 5.9% of severe hypoglycaemia cases (23,872 patient) assumed to
 213 require hospital admission. The base case scenario is calculated based on an expert group discussion with
 214 local clinicians, which reached a consensus of 3.2% prevalence (12,948 patients) for hypoglycaemia-related
 215 hospital admissions. In the best case-scenario, 2.5% prevalence (10,115 patients) was used, from the
 216 prospective arm findings of the HAT Study on hypoglycaemia hospital admissions. We assume that all
 217 these cases require hospital admission for at least once.
 218 The total cost of care for hypoglycaemia among adult diabetes in Malaysia was estimated to be RM 117.4
 219 (USD 30.0) million, approximately 0.5% of Ministry of Health annual budget allocation of RM 22.16
 220 (USD 5.67) billion in 2014. [17] The national economic burden estimates based on the bestcase-scenario
 221 and the worstcase-scenario range from RM 91.7 (USD 23.5) million to RM 216.5 (USD 55.4) million.
 222 (Table 6)

223 **Table 6. The Estimated Cost and Economic Burden of Hypoglycemia**

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Hypoglycemia as primary diagnosis	% of cases	Mean cost per admission (RM)	Worst case scenario (5.9% admission)	Base scenario; (3.2% Admission)	Best case scenario (2.5% Admission)
Severity Level 1	9.4	7,054	15,829,227	8,585,371	6,707,321
Severity Level 2	33.2	7,333	58,118,921	31,522,127	24,626,662
Severity Level 3	57.4	10,401	142,522,937	77,300,576	60,391,075
Total Cost		9,083	216,471,136	117,408,074	91,725,057
% MOH Budget (RM 22,160,380,300)			1.0	0.5	0.4

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230 **Discussion**

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232 Proper glycaemic control is required to minimize the risk of microvascular complication of diabetes among
233 diabetics. At the same time, diabetes management commonly result in hypoglycaemic episodes. The
234 occurrence of hypoglycaemia is widely variable. The frequency of severe hypoglycaemia requiring
235 emergency services in patients with type 2 DM receiving insulin therapy is comparable to type 1 DM
236 depending on how diabetes is being managed. Incidence rates were 11.5 and 11.8 events per 100 patient-
237 years for type 1 and type 2 patients treated with insulin, respectively [17]. A study in Canada stated that
238 1.9% of individuals had at least one hypoglycaemia related A&E visits, and 0.1% was admitted to hospital.
239 In terms of incidence rate, 5.2 cases and 0.3 cases per 1000 patient-year required A&E visits and hospital
240 admission respectively [18]. In the HAT study, hypoglycaemic episodes of hospital admissions among DM
241 cases in Malaysia were measured both prospectively and retrospectively. Findings from the prospective and
242 retrospective component of the HAT study were reviewed and the most conservative estimates was selected
243 and subsequently validated by specialists from different hospitals in Malaysia. 47.1% of the type II DM
244 cases with insulin experienced any type of hypoglycaemia and 16.8% had severe hypoglycaemic episodes
245 within a 6-month period [16]. Based on their clinical experience, the expert group of specialists determined
246 a 3.2% prevalence for hypoglycaemia requiring at least one hospital admission. The incidence of hospital
247 admission was conservatively estimated as 3.2 episodes per person year and also estimated with the worst
248 case-scenario with 10 episodes per person per year. Even with the best-case scenario, the incidence of
249 admission due to hypoglycaemic episodes is significantly higher than elsewhere [18, 19].

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251 Several investigations are required to confirm and manage hypoglycaemia cases appropriately. Based on
252 severity and management protocol, the duration of hospital stay may vary from place to place. The cost of
253 hospital care is also dependent on how long the patient was admitted to the hospital. The mean length of
254 hospital stay ranged from 5.5 to 9.8 days in most studies (20-22). The median length of stay is 4 days in the
255 Canada [19]. The findings from our study also provide similar estimates with the mean length of hospital
256 stay was 6.5 days and the median length of stay was 5 days. Due to the wide variation and huge standard
257 deviation, the median length of stay was selected as the common length of hospital stay in this study.

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259 Depending on the level of severity, a hypoglycaemic condition may be treated at home, at A&E department
260 or at hospital wards. The cost of care also varies with the level of severity. Our study showed that the cost
261 of care at A&E department was RM 741 (USD 190) per case. On the other hand, the mean cost of care for a
262 patient admitted for hypoglycaemia is RM 9,083 (USD 2,323).

263

264 The HAT study presented the proportion of patients admitted to hospital, but not the patients requiring
265 A&E visit prior to hospital admission. Other country studies stated that the proportion of hypoglycaemia-
266 related hospital admissions after the treatment in Emergency Department (ED) varies between 11-28% [18,
267 23]. We do not have local estimates for this information but based on our expert group review, it could be
268 as high as 50%. However, we used 5.9% of the cases require hospital admission as the worst case-scenario
269 and 2.5% as the best case-scenario from the findings in the Malaysian HAT Study [16].

270

271 Regardless of hypoglycaemia-related hospitalization is seemingly low, the actual number of hypoglycaemic
272 episodes requiring hospital care can impose both clinical and economic burden. In this study we have
273 focused more on the cost of care for severe episodes of hypoglycaemia at tertiary academic institutions and
274 the total economic burden introduced by hypoglycaemia. Comparing the economic cost of hypoglycaemia
275 is difficult due to the differences in health care systems and also in defining hypoglycaemia itself. Costing
276 studies from the literature showed that hypoglycaemia admissions in Scotland costs USD 303 (£218) per
277 person per day [22] whereas in Canada, where an average cost of USD 7,000 is required for an average
278 hospitalization due to hypoglycaemia for 7 days [19]. nIn case of Thailand, a patient with hypoglycaemia
279 requires 6 days of hospital stay as an average requiring nearly USD 700 (THB 22,000) per episode. [24] A
280 recent study in Korea estimated the medical costs for a hypoglycaemic event ranged from USD 17.28 to
281 USD 1,857 at secondary and tertiary hospitals [25].

282

283 Although the individual cost of care in Malaysia is not significantly high compared to other countries, the
284 number of episodes requiring health care services at the hospital is considerably higher, making the total
285 cost of care higher. This brings to an estimated cost of care for hypoglycaemia among type II DM patients

286 in Malaysia to be between USD 23.5 Million to 55. 4Million (RM 91.7 Million to RM 216.5 Million). In
287 Germany for example, the estimated annual direct cost of severe hypoglycaemia by Type II DM during
288 1997-2000 was USD 54,980 (€ 44,338) per 100,000 inhabitants (26,27), and in comparison, this study
289 found the cost estimate to be significantly higher in Malaysia, amounting to at least USD 526,585 (RM
290 2,058,963) per 100,000 inhabitants. Although the length of stay and the unit cost of care are not necessarily
291 higher, the number of admission required determined the possible burden for hypoglycaemic care at
292 hospitals.

293

294 A significant portion of hypoglycaemic episodes are treated at home without the assistance of medical
295 services either at the A&E or hospital admission [28], indicating that this study measures only the burden
296 visible at the tip of the iceberg. Higher frequency of hypoglycaemic events could also have significant
297 impact on quality of life as well as imposing indirect cost by limiting work capacity and work productivity.

298

299 **Conclusion**

300 The findings of this study showed that severe hypoglycaemia in patients with diabetes impose significant
301 impact on resource utilization. Regardless of seemingly a simple condition, hypoglycaemia can result in
302 substantial economic burden for national health care system. Preventing hypoglycaemic episode should be
303 included in diabetic management programs that emphasize on proper diabetic management and health
304 education. This could minimize hypoglycaemic risk, which may lead to reducing overall health spending,
305 minimizing the fear of hypoglycaemia episodes and improving the compliance of diabetes management.
306 The high cost of hypoglycaemia management calls for a personalized approach to glycaemic control and
307 development of better guidelines for clinical decision making in diabetes control strategies.

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324

325 **Contributions**

326 SM Aljunid Aniza Ismail and Yin New Aung designed the study and prepare the first draft of the

327 manuscript. Siti Zafrah Abdul Rashid and Amrizal N Nur conducted the data analysis and prepare the

328 tables. SM Aljunid, Julius Cheah and Priya Matzen reviewed that first draft and finalised the manuscript for

329 publication

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