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ORIGINAL ARTICLE

The all-cause mortality and risk factors for mortality within five years among prevalent Type 1 Diabetes Mellitus Patients

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Abstract

Despite new comprehensive approach in diabetes care, type 1 diabetes is still facing considerable premature mortality. This study aims to examine associated risk factors for all-cause mortality among prevalent patients with type 1 diabetes mellitus (T1DM) within 5 years' period and subsequently develop a logistic regression model to predict the outcome. This was a cohort study where prevalent patients diagnosed with T1DM were notified in a national diabetes registry. Patients' particulars were recorded between 1 January 2009 and 31 December 2009. Their records were matched with national death record at the end of year 2013 to determine the status of mortality within 5 years. The factors associated with mortality were investigated, and a prognostic model was developed based on logistic regression model. There were 665 patients included in the study, and 105 patients died within 5 years. The mortality rate was 1.6 persons per 100 person-years and the standardized mortality ratio was 10.04. Majority causes of death were due to circulatory system (33.8%) and infection (32.5%). Multivariate analysis suggested that gender, age group, and ischemic heart disease (IHD) were the major contributing factors towards the outcome. Elderly male with IHD has a significant risk of mortality within 5 years with probability of event of 0.755, while elderly female with IHD has probability of event of 0.612. The main causes of death among prevalent T1DM patients were heart disease and infection. Male gender, elderly age group, and having IHD were significant risk factors of mortality in prevalent T1DM patients within 5 years.

Keywords Associated factors · Diabetes type 1 · Mortality · Prognostic model

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic illness caused by the body's inability to produce sufficient insulin. This noncommunicable disease is usually diagnosed in children and young adults and was previously known as juvenile diabetes. There were wide variations existing with regard to the incidence rates of T1DM in different countries. The annual incidence rates for childhood T1DM are between 0.1 and 37.4 per 100, 000. The lowest incidences are in China and Venezuela with 0.1 per 100,000 per year, and the top highest incidences are in Finland and Sardinia with 40 per 100,000 per year [1–3]. Currently, there are no official statistics reported regarding incidence rate of T1DM in Malaysia.

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In the past, the survivals for T1DM patients were poor until insulin therapy was introduced since 1922 [4]. Since then, a marked decrease in mortality was observed. Although there was a reduction in mortality, T1DM still contributes to risk of death reported in developed countries [5]. However, diabetes mellitus has not been acknowledged as major disease that could lead to fatality. The reason might be because diabetes mellitus is known to be underreported on death certificates as an underlying or contributing cause of death [6, 7]. Hence, few studies have attempted to examine the survival of T1DM patients and specific cause of death [8–11]. In a Swedish study, patients with T1DM have twice the risk of death from cardiovascular event even with good glycemic control [11]. There were limited data on Malaysia's all-cause mortality on T1DM patients.

Studies regarding predictive modeling for mortality among T1DM patients are scarce. This study aims to investigate the associated factors towards mortality within 5 years among patients with T1DM at any point of disease. Following to that, a predictive modeling was developed as a screening tool to predict potential risk of dying within 5 years' period among patients with prevalent T1DM. The predictive modeling tool potentially can be used as screening tool to classify patients who are at risk that may require more attention and to increase the awareness among the public.

Methodology

This was a cohort study where patients' demographic and clinical details were captured from national registry, an Audit of Diabetes Control and Management (ADCM) between 1 January 2009 and 31 December 2009. Full details of the design, methods, and recruitment for the ADCM have been published elsewhere [12]. This clinic-based prospective cohort study examined 665 T1DM patients. The patients were T1DM with minimum age of 18 years notified from government health clinics throughout Malaysia. Demographic profile, risk factors, and clinical parameters were recorded according to a standardized protocol during the baseline of study. Their records were matched with National Death Record (NDR) at the end of year 2013 to determine status of mortality within 5 years and also the causes of death based on ICD-10, 2016. The study was registered under the National Medical Research Registry and has obtained approval from the Medical Research Ethics Committee (MREC).

Statistical analyses

Descriptive analysis was conducted to determine the incidence of cause of death based on ICD-10 code. Meanwhile, multivariate analyses were conducted to determine the major-associated factors contributing to mortality rate within 5 years. Following to that, a predictive model to predict mortality after 5 years was formulated using logistic regression model. The flow analysis was done as follows:

1. A univariate analysis based on Pearson's chi-square test was conducted to determine the associated factors towards risk of mortality within 3 years.
2. The significant factors from the univariate analysis were tested again using multivariate analysis based on logistic regression using forward likelihood ratio method. The cut off probability for variable selection was set at 0.05 for both inclusion and exclusion criteria. The coefficients, odds ratio with respective confidence interval, and p values were recorded.
3. The equation model was derived based on the selected variables' coefficients in the logistic regression model. Then, the z-score and probability of event were calculated for each combination among the significant variables in predicting the outcome. The probability of the outcome of interest, the Z value, was then transformed into the probability of event using the following link function: $P[\text{event}] = e^z/1 + e^z$. This probability value range from 0 to 1.

All analyses were carried out using SPSS (IBM Corporation, Released 2011, IBM SPSS Statistics for Windows, Version 20.0; Armonk, NY: IBM Corp.) and Microsoft Office Excel 2007.

Results

There were 70,279 records in the registry with only 665 patients recorded as T1DM, and thus, the prevalence of T1DM was 0.95%. There were 105 deaths (15.8%) out of T1DM patients where incidence of mortality within 5 years was 15.8% with average of 3.2% in each year. The incidence of mortality in 2009, 2010, 2011, 2012, and 2013 was 1.8%, 3.2%, 4.1%, 3.5, and 3.3%, respectively. The mortality rate was 1.6 persons per 100 person-years. The standardized mortality ratio (SMR) was 10.04 where male and female reported the SMRs with 13.38 and 8.00, respectively. Majority of patients died due to diseases of circulatory system (33.8%), infectious and parasitic diseases (32.5%), and respiratory system (6.5%). Majority of younger patients died due to infection and diabetes, whereas majority of elder patients died due to diseases circulatory system or heart disease (Table 1).

Out of 665 patients, majority were female (63.8%), between 40 and 64 years (61.9%) and Malay (87.0%). More than half have hypertension (58.1%) and 17.8% with dyslipidemia. (Table 2). Based on univariate analysis, age group at notification ($p < 0.001$), gender ($p = 0.001$), comorbidity such as hypertension ($p = 0.026$), diabetes complications such as

Table 1 Causes of death among T1DM patients based on age group

	18–39 years ($n = 6$)		40–64 years ($n = 50$)		≥65 years ($n = 49$)	
Cause of death	n	%	n	%	n	%
Diseases of the circulatory system	0	0.0	15	35.7	11	40.7
Certain infectious and parasitic diseases	4	50.0	14	33.3	7	25.9
Diseases of the respiratory system	1	12.5	2	4.8	2	7.4
Endocrine, nutritional, and metabolic diseases	2	25.0	5	11.9	0	0.0
Diseases of the genitourinary system	0	0.0	1	2.4	2	7.4
External causes of morbidity and mortality	1	12.5	0	0.0	1	3.7
Diseases of the nervous system	0	0.0	5	11.9	1	3.7
Diseases of the blood and blood-forming organs and certain disorders involving the immune m	0	0.0	0	0.0	1	3.7
Diseases of the digestive system	0	0.0	0	0.0	2	7.4
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	0		14		25	

*The percentage excludes the cause of death for symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified

ischemic heart disease (IHD) ($p = 0.018$), and foot problem ($p = 0.018$) were associated with the outcome (Table 2, Table 3, and Table 4).

Multivariate analysis based on stepwise analysis suggested that only gender and age group were the major contributing factors towards the outcome. Further multivariate analysis was carried out to incorporate status of IHD in the analysis. Status of IHD was slightly more than $p = 0.05$, but the effect size based on odds ratio was large (Table 5). Thus, the prediction model was incorporating age group, gender, and status of IHD. Elderly with IHD has a significant risk of mortality within 5 years with probability of event of 0.612 and 0.755 for female and male, respectively. Regardless of age, patients without IHD have lower risk of dying within 5 years' period (less than probability of 0.5) (Table 6).

Table 2 Univariate analysis on patients' demographic characteristics

			Died		
Characteristics		N (%)	No	Yes	*p* value
Demographic					
Age group	18–39	85 (12.8)	79 (14.1)	6 (5.7)	< 0.001
	40–64	412 (61.9)	362 (64.6)	50 (47.6)	
	≥65	168 (25.3)	119 (21.3)	49 (46.7)	
Gender	Male	241 (36.2)	188 (33.6)	53 (50.5)	0.001
	Female	424 (63.8)	372 (66.4)	52 (49.5)	
Ethnicity	Malay	575 (87.0)	481 (86.5)	94 (89.5)	0.808
	Chinese	41 (6.2)	35 (6.3)	6 (5.7)	
	India	38 (5.7)	34 (6.1)	4 (3.8)	
	Others	7 (1.1)	6 (1.1)	1 (1.0)	
Comorbidity					
Hypertension	Yes	336 (57.0)	272 (55.1)	64 (67.4)	0.026
	No	253 (43.0)	222 (44.9)	31 (32.6)	
Dyslipidemia	Yes	105 (17.8)	90 (18.2)	15 (15.8)	0.571
	No	484 (82.2)	404 (81.8)	80 (84.2)	

Discussion

The mortality rate of T1DM was 1.6 persons per 100 person-years and is slightly higher compared with T2DM in the same

Table 3 Univariate analysis on patients' clinical characteristics

Clinical parameter		Died		
		No	Yes	*p* value
HbA1c	Good (≤7.0)	96 (29.7)	10 (17.2)	0.051
	Poor (>7.0)	227 (70.3)	48 (82.8)	
Systolic BP	Good (≤130)	239 (48.5)	39 (41.5)	0.214
	Poor (>130)	254 (51.5)	55 (58.5)	
Diastolic BP	Good (≤80)	304 (61.7)	55 (58.5)	0.565
	Poor (>80)	189 (38.3)	39 (41.5)	
BMI	Underweight (<18.50)	10 (2.1)	3 (3.2)	0.059
	Normal (18.50–24.99)	162 (33.4)	42 (45.2)	
	Overweight (≥25.00)	201 (41.4)	36 (38.7)	
	Obese (≥30.00)	112 (23.1)	12 (12.9)	
LDL	Good (≤2.6)	60 (18.5)	9 (16.7)	0.744
	Poor (>2.6)	264 (81.5)	45 (83.3)	
HDL	Good (≥1.1)	244 (76.5)	35 (68.6)	0.226
	Poor (<1.1)	75 (23.5)	16 (31.4)	
TG	Good (≤1.7)	192 (53.9)	31 (51.7)	0.745
	Poor (>1.7)	164 (46.1)	29 (48.3)	

BMI, body mass index; *BP*, cerebrovascular disease; *HbA1c*, glycated hemoglobin; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *TG*, triglyceride

Table 4 Univariate analysis on patients' complications

Complications		Died		
		No	Yes	*p* value
Retinopathy	Yes	25 (6.1)	9 (12.3)	0.053
	No	387 (93.9)	64 (87.7)	
IHD	Yes	3 (0.7)	3 (4.0)	0.018
	No	410 (99.3)	72 (96.0)	
CVD	Yes	4 (1.0)	2 (2.6)	0.230
	No	417 (99.0)	76 (97.4)	
Nephropathy	Yes	21 (5.0)	5 (6.6)	0.577
	No	397 (95.0)	71 (93.4)	
Foot problem	Yes	8 (1.7)	5 (5.9)	0.018
	No	466 (98.3)	80 (94.1)	
Amputation	Yes	1 (0.2)	1 (1.0)	0.184
	No	559 (99.8)	104 (99.0)	
Duration	< 5 years	252 (51.0)	40 (42.1)	0.272
	5–10 years	193 (39.1)	43 (45.3)	
	> 10 years	49 (9.9)	12 (12.6)	

CVD, cerebrovascular disease; *IHD*, ischaemic heart disease

country [13]. The SMR reported in this present study was higher compared to that of other countries especially in developed countries [14]. The SMR ratio among female compared to male is 0.60, and the result was about similar to Finland and Taiwan [10, 15], while majorities reported SMR ratio among female compared to male was more than one especially in developed countries [14]. Thus in general, our population showed poorer survival among male compared with female patients.

The incidence of mortality among prevalent T1DM patients was relatively low with less than 5% in a year, and this shows that patients with T1DM have relatively good survival, although some studies showed that survival among individuals with T1DM has an increased age-adjusted mortality risk of death compared to the general population [16, 17]. This excess mortality risk is driven by the results of the development of complications due to T1DM in the population [18–20]. In other words, when there is no diabetes complication, some studies suggested that T1DM patients may have long-term survival comparable to the general population [18, 21]. From our findings, prevalent T1DM patients with no diabetes complications have probability of event with less than 0.5 in getting risk of mortality within 5 years.

Based on our data, the leading cause of death among patients with T1DM was due to circulatory system. All of them died after 40 years, and majority were at 65 years and above. Heart disease is a common and a leading cause of death in most countries including developed country like the USA [22]. In addition, heart disease or cardiovascular is also a leading cause of death among diabetes population [14]. This showed that our result is consistent with previous findings. Based on our data, only six patients reported to have diabetes complication of IHD. However, 26 patients died of heart disease within 5 years' period after notified into the registry. This can be explained by majority of them having also other

Table 6 Probability of event between gender, age group and status of IHD

Combination of factors	Male Prob (e)	Female Prob (e)
Adult and no IHD	0.072	0.038
Middle age and no IHD	0.161	0.089
Elderly and no IHD	0.328	0.241
Adult and yes IHD	Nil	Nil
Middle age and yes IHD	0.489	0.383
Elderly and yes IHD	0.755	0.612

IHD, ischaemic heart disease; *Prob (e)*, probability of event

Table 5 Risk factors towards mortality within 5 years, a multivariate analysis

Stepwise method: backward likelihood ratio						Enter method					
Factors		*B*	OR	95%CI	*p* value	Factors		*B*	OR	95%CI	*p* value
Constant		− 3.236				Constant		− 3.236			
Gender	Male	0.673	1.960	1.162, 3.304	0.012	Gender	Male	0.673	1.96	1.162, 3.304	0.012
	Female	Ref	Ref				Female	Ref	Ref		
Age	Adult	Re	Ref			Age	Adult	Ref	Ref		
	Middle age	0.915	2.497	0.737, 8.465	0.142		Middle age	0.915	2.497	0.737, 8.465	0.142
	Elderly	2.087	8.059	2.339, 27.759	0.001		Elderly	2.087	8.059	2.339, 27.759	0.001
						IHD	Yes	1.603	4.967	0.906, 27.237	0.065
							No	Ref	Ref		

B, logistic regression's coefficient; *CI*, confidence interval; *IHD*, ischaemic heart disease; *OR*, odd ratio; *Ref*, reference group

underlying comorbidity such as hypertension besides factor of aging. It has been reported that the survival rates for onset IHD were 25.0% and 38.0% in both men and women, respectively, with median survival of only between 2 and 3 years [23].

The second leading cause of death was infection. It is a fact that patients with diabetes are at risk of developing wounds and sores that are difficult to heal well [24]. If the wounds are not treated well, the patients are at high risk of developing infection. It was reported there seems to be reduced immune regulation in subgroup of individuals with T1DM [25]. Therefore, in poorly controlled diabetes, infections can get severe faster. In the worst case scenario, when infection overwhelms the body, patients develop sepsis which can lead to septic shock and eventually death.

In the univariate analysis, IHD and foot problem were also associated with mortality within 5 years. These two important factors were not significant in the multivariate analysis because these variables were confounded with age group. In other words, although these variables were dropped from the stepwise analysis, IHD and foot problem were still important predictors in relation to the outcome. Therefore, prevention is necessary to avoid developing early diabetes complications.

Other interesting finding in the analysis was dyslipidemia and its marker such as LDL cholesterol, HDL cholesterol, and triglycerides which had no significant association with the outcome. The cholesterol markers among the patients seemed well controlled; this may probably be due to patients taking oral lipid-lowering medications. Despite most patients taking oral antihypertension medication which lowers the blood pressure (systolic and diastolic), hypertension was still significantly associated with the outcome. Patients having both diabetes and hypertension were reported to be at high risk for all-cause mortality as compared to only diabetes [26]. However, so far there is limited evidence that relates dyslipidemia and mortality among T1DM patients. On the other hand, taking lipid-lowering agents are still necessary to prevent diabetes complications especially cardiovascular disease [27, 28].

This study had successfully developed a simple and quick prognostic model to predict prevalent T1DM patients who are at risk of mortality within 5 years. A risk model in predicting the mortality can be subjective because it varies between individuals. However, based on large pool of data, researcher could find some common characteristics in the population. Our study found that gender, age group, and IHD were the major contributors for risk of mortality within 5 years. This study is considered as preliminary work to develop a prognostic model for predicting mortality among prevalent T1DM patients based on logistic regression model. Logistic regression is a very useful statistical model that can be applied to predict an outcome provided the predictors have sufficiently large effect size [29].

Our predictive modeling in predicting mortality within 5 years' period among prevalent T1DM patients can act as a screening tool to classify patients with severe conditions. Our finding concluded that elderly patient with IHD has relatively shorter survival period which was within 5 years' period. Therefore, this group of patients requires closer attention. This finding can be used to increase awareness among patients, healthcare workers, and the public. Besides reporting the odds ratio, this study also reported the probability of event based on combination of the three factors. The model was simple as it only involved three factors, and thus, the model is quite practical to be applied to screen high risk patients in clinical setting.

One of the strengths of this study was because the study was conducted based on large sample size. Large sample size is necessary since T1DM patients have lower prevalence among diabetes patients as compared to that of T2DM patients. Our data at least reached more than 500 patients. Previous studies have showed that studies that have recruited large sample size such as with minimum 500 subjects, the statistical analyses are likely to represent the parameter in the intended population [30, 31]. Hence, the result of this study could be inferred to the larger population. Secondly, the factors in the final model have sizeable effect size that has increased the accuracy of the model.

This study has several limitations. Our study population only involved government health clinics all over Malaysia. No records were captured from private clinics. However, majority of patients in Malaysia with diabetes are being follow up in government health clinics since it is heavily subsidized. Hence, the result from this study is likely to reflect the general finding for T1DM in Malaysia. Besides that, the variables that were tested as risk factors were captured based on variables observed during the notification period, while there may be other important factors which have not been investigated. Thus, this could influence the accuracy of the prediction model.

In addition, there were 39 causes of death which were not verified. This was probably due to their cause of death which was not verified by medical officers and the failure to get consent among family members to conduct autopsy [32]. Due to the survival outcome of T1DM patients as considerably good, therefore, only small events (mortality) were observed, and this may influence the power of analysis for some analysis. Hence, some of the results need to be interpreted with caution. Some of the significant predictors were nonmodifiable and have limited clinical or public health intervention such as age and gender. However, the findings from this study are still important for health care personals to screen and identify groups of high risk T1DM patients who are more likely for mortality. This can help clinicians and public health workers to identify T1DM patients that require closer monitoring or more aggressive treatment to prevent this group

from developing diabetes complications and ultimately reduce the mortality rate.

In conclusion, this study found that the associated factors of mortality within 5 years' period among T1DM patients were gender, age group, and history of ischemic heart disease. We have developed a simple and quick prognostic model that can be used as a screening tool to predict risk of mortality within 5 years among T1DM patients at any duration of disease. Future studies are recommended to validate the model.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required. The study was registered under the National Medical Research Registry and has obtained approval from the Medical Research Ethics Committee (MREC).

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