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Original Article

The Influence of Diabetic Family History on the Development of Neuropathy in Type 2 Diabetes Patients: A Survival Analysis

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Abstract

Introduction: Neuropathy is a common and dangerous complication of diabetes mellitus with the highest mortality rate, as well as high costs for diabetic patients. This study aimed to identify the factors affecting the event time of neuropathy incidence in diabetic patients using cure models. **Material and Methods:** For data collection, all the patients whose diabetic screening tests conducted by the Fereidounshahr Health Centers and were negative in 2006, but were diagnosed with diabetes mellitus in 2007 through rescreening and were at least 30 years of age were enrolled in the study, and their neuropathy status was monitored for at least ten years. Mixture and non-mixture cure models were used for data analysis, and the survival-specific receiver operating characteristic curve was also used to compare the efficiency of the models. **Results:** Of the 371 diabetic patients, 257 were females (69.3%), and 178 (47.97%) had a family history of diabetes mellitus. Having fitted the exponential mixture and non-mixture cure models, as well as Weibull, log-normal, and log-logistic ones, we found the log-logistic model as being the most efficient. In the final fitted log-logistic mixture cure model, the variables such as a family history of diabetes mellitus, fasting blood sugar, ethnicity, and gender were significantly associated with the time of neuropathy incidence. **Conclusion:** The results of this study showed that female patients from Fars who had a positive family history of diabetes mellitus needed to more precisely control their fasting blood sugar in order to delay the incidence of neuropathy.

Keywords: Cure Models, Survival Analysis, Type 2 Diabetes Mellitus, Diabetic Neuropathy.

Introduction

Diabetes mellitus (DM) is one of the most common non-communicable diseases in the world and the Eastern Mediterranean Region (in which Iran is also located). DM is known as the leading cause of blindness, kidney failure, lower limb amputation, and death in the electronic medical record (EMR). Diabetic foot is one of the most common complications of DM that is often overlooked. Not only the costs of caring and treating diabetic foot problems are high due to the increased likelihood of hospitalization and amputation, but also, the disease has a high burden [1]. An estimation of the burden of DM and its complications based on the lost years in Iran, indicated in 2001 that neuropathy, diabetic foot, and amputation accounted for 18% of the total DM burden altogether [2]. The prevalence of diabetic foot is 4.6-12% in the world [3, 4] and 3% in the Iranian diabetic population. Neuropathy is one of the most common microvascular complications of DM observed in both type 1 and type 2 DM. The incidence of polyneuropathy in diabetic patients is 11-31%. Severe pain that decreases and can lead to loss of sensation, increased risk of foot ulcers and amputation are

among the complications of diabetic neuropathy [5] with many negative effects on the patients' quality of life. Previous studies reported that neuropathic pain was present in 33-47% of diabetic patients. According to the information obtained, the pain gets severe at night and rest and may lead to insomnia, restlessness, and many other problems for the patients. The incidence of neuropathy and its severity depend on the duration of DM [6]. Semi-parametric and parametric models can be used to determine the factors influencing the event time of neuropathy incidence in patients with type 2 DM. The condition for using such models is the gradual failure of all the subjects under investigation for a sufficiently long time. For example, in chronic diseases that are usually incurable and continue to progress, all the patients are expected to experience the incidence gradually, but this condition is not always met, and a certain proportion of patients may not experience the intended incidence during the follow-up period, in which case, common parametric and semi-parametric models cannot be used. For instance, not every patient rejects a transplanted organ or not everyone infected with the Human Immunodeficiency Virus (HIV) gets AIDS. Generally, in survival studies, cure models are used if a percentage of the population is immune to the incidence. In this case, the people are divided into two groups of susceptible and non-susceptible. The people in the susceptible group have long-term survival and are immune to the incidence in question [7, 8]. Hence, a cure model can be used, the most important objectives of which are to estimate the proportion of cured (immunized) individuals, to estimate the survival function for susceptible and at-risk groups, and to examine the factors affecting the aforementioned items [8, 9]. It should be noted that the high censorship rate in the survival data causes biased estimates of maximum likelihood in standard survival models of various types [10]. However, these models are not capable of separating the factors affecting short- and long- term survival. The use of cure models is recommended to analyze the survival of patients separately. As long- and short-term survival is examined in these models, censorship rates may be too low or too high. With a censorship rate of > 0.6 for patients with at least one diabetic first-degree relative and a censorship rate of 0.4 for other patients (the survival rates of whom are shown separately in Figure 1), the need for using mixture and non-mixture cure models seems obvious. Thus, the aim of this study was to investigate the effect of family history of DM on the event time of neuropathy in type 2 DM patients using mixture and non-mixture cure models.

Material and Methods

In order to collect the data, all the people whose DM screening tests were conducted at the Fereidounshahr health centers and were negative in 2006, but were di-

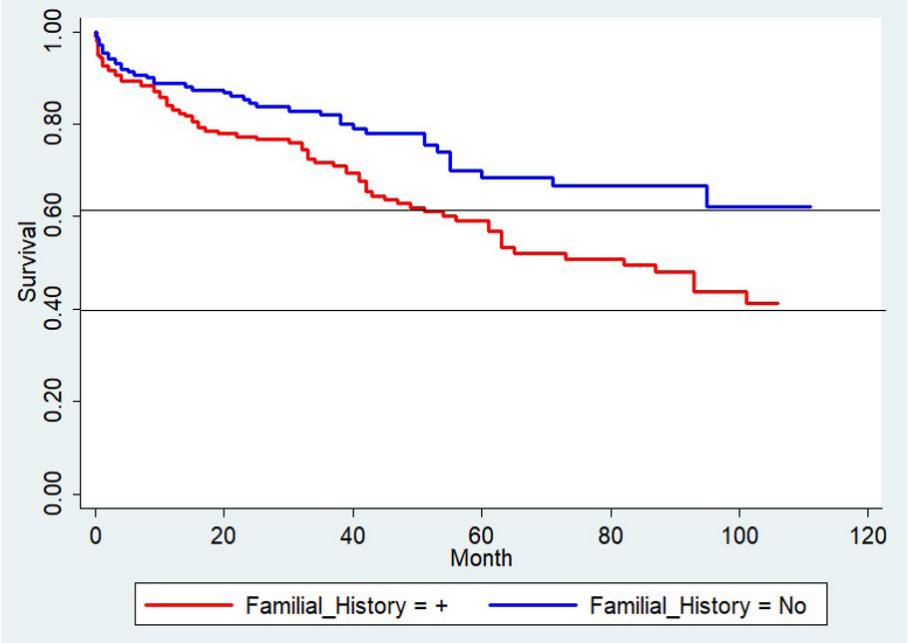

Figure 1: Estimation of survival time in the absence of neuropathy in patients studied by the history of diabetes mellitus in first-degree family members.

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agnosed with type 2 DM in 2007 through rescreening, and were at least 30 years of age, were included in the study, and their neuropathy status was monitored for at least ten years.

In this survival study, the response variable was the time from the diagnosis of DM until the diagnosis of neuropathy. The failure time was by month, and censored cases included those who had not been diagnosed with neuropathy at the end of the study, those who died, and those missing at the follow-up (migrants) before the end of the study. The data on demographic variables including gender, age, occupation, education, place of residence, race, history of DM in first-degree relatives, DM treatment method, smoking, along with laboratory variables including fasting blood sugar, height, weight, body mass index (BMI), total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, creatinine, HbA1c, diastolic and systolic blood pressure, as well as the clinical diagnostic and questionnaire variables of neuropathy and neuropathy diagnosis using nerve conduction studies were recorded through reviewing the patients' records and interviewing them if necessary.

The Akaike information criterion was used to fit the models. The criterion is defined as Akaike Information Criteria (AIC)= -2L (b)+2p, where p is the number of parameters in the model, and the smaller the criterion is, the more appropriate the proposed model will be. L is also defined as the likelihood function for b parameters.

The survival-specific receiver operating characteristics (ROC) curve is one of the methods used to evaluate fitted survival models. It is a benchmark for measuring model efficiency by measuring the area under the ROC curve. The curve graphically shows the correct sensitivity or prediction against false prediction [11]. The Area Under Curve (AUC) was used to compare the accuracy of the models. The closer its value was to 1 or the greater the area under the curve, the higher the accuracy of the model would be. In this study, exponential mixture and non-mixture cure models, as well as Weibull, log-logistic and log-normal, were used.

Cured models

Cured models are divided into two general categories:

- Mixture models: As the name implies, a mixture model is a combination of total survival for both cured and uncured patients. The former group consists of patients who are immune to the incidence. They are considered cured. The latter consists of the patients who are not immunized to the incidence at all and are at risk until the end of the study. The survival function for mixture cure models is defined as [12]:

$$S_p(t) = P + (1 - P)S^*(t), S^*(\infty) = 0, S_p(\infty) = P > 0$$

In this model, the p ratio of the cured or immunized individuals can be modeled by logistic regression, probit function, complementarity log-log link function, and linear regression. It should be noted that cure models are the standard survival models in the absence of immunized individuals.

- Non-mixture Models: These models are defined for populations with an incomplete distribution function of the survival time for the whole population, i.e., the value of the cumulative distribution function does not reach one. The survival function for these models is defined as:

$$S(t) = p^{(1-S(t))}$$

In these populations, the difference between the cumulative distribution function and the value 1 shows the proportion of cured people; so, in these models, the proportion of cured individuals is within the model and can be directly obtained by having an infinite survival limit. If the data under study are i=1,...,n (t_i, δ_i, X_i, Z_i) (where the values of 1 and 0 for δ_i indicating the incidence of the event and the censorship, respectively, t_i indicates the survival time, and X_i and Z_i represent the variables related to the survival rate and cure probability, respectively), the likelihood function for the i^{th} person will be as follows:

$$if \quad \delta_i = 1 \Rightarrow L = \pi_i(Z_i) f(t_i|U = 1, X_i)$$
$$if \quad \delta_i = 0 \Rightarrow L = 1 - \pi_i(Z_i) + \pi_i(Z_i) S(t_i|U = 1, X_i)$$

In the formula, $f = S\lambda$ and is the probability density function T. Thus, the likelihood function will be as follows:

$$L(\gamma, \beta) = \prod^{n} [(1 - \pi_i(Z_i) S(t_i|U = 1, X_i))]^{1-\delta_i} \times [\pi_i(Z_i) f(t_i|U = 1, X_i)]^{\delta_i}$$

Results

Of the 371 DM patients, 257 were females (69.3%), and 178 (47.97%) had a family history of DM. Table 1

Table 1: Comparison of descriptive of demographic and laboratory variables.

Variables	Neuropathy + Frequency (%)	Neuropathy NO Frequency (%)	Statistic X^2	P-Value
Gender				
Male	26 (22.4%)	88 (34.5%)	5.480	0.019
Female	90 (77.6%)	167 (65.5%)		
Race				
Georgia	36 (31%)	101 (39.8%)	9.263	026
Bakhtiari	32 (27.6%)	85 (33.5%)		
Persia	18 (15.5%)	19 (7.5%)		
Turkey	30 (25.9%)	49 (19.3%)		
Job activity				
Low	15 (12.9%)	42 (16.5%)	2.010	0.366
Moderate	85 (73.3%)	168 (65.9%)		
High	16 (13.8%)	45 (17.6%)		
Family History				
Yes	74 (64.3%)	104 (44.4%)	12.223	<0.001
No	41 (35.7%)	130 (55.6%)		
Treatment				
Oral	85 (73.3%)	222 (87.1%)	20.813	<0.001
Insulin	13 (11.2%)	15 (5.9%)		
Both	18 (15.5%)	11 (4.3%)		
No medication	0 (0.0%)	7 (2.7%)		
	Mean (± s.d)	**Mean (± s.d)**	**statistic t**	**P-Value**
FBS	172.25 (± 55.170)	164.57 (± 54.762)	-1.971	0.048
BMI	28.36 (± 4.485)	28.52 (± 4.201)	0.310	0.757
Hb1Ac	8.15 (± 1.631)	7.71 (± 1.919)	-2.040	0.420
Cholesterol	200.98 (± 46.347)	192.38 (± 46.953)	-1.586	0.114
Triglyceride	196.74 (± 124.232)	193.15 (± 108.830)	-0.272	0.786
HDL	49.37 (± 22.022)	48.44 (± 16.892)	-0.404	0.687
LDL	112.6 (± 42.897)	110.16(± 40.185)	-0.500	0.617
BUN	16.42 (± 7.836)	15.89 (± 6.462)	-0.640	0.523
Creatinine	0.79(± 0.241)	0.82 (± 0.291)	0.987	0.324

Note: s.d: standard deviation. Abbreviations: BMI, Body Mass Index; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; BUN, Blood Urea Nitrogen; FBS, Fasting Blood Sugar

shows demographic data and laboratory results of the included patients by the final neuropathy status.

According to the results of the chi-square test, the number of diabetic women with neuropathy was three times as much as that of the men. Also, there was a significant difference between Georgian, Bakhtiari, Persian, and Turkish ethnic groups in terms of the number of neuropathy patients. In other words, of the 37

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Persian subjects, 18 (49%) had neuropathy, and the proportion was 26%, 27%, and 38% in Georgian, Bakhtiari, and Turkish ones, respectively. In this study, no significant relationship was found between occupational activity and suffering from neuropathy, but family history and treatment type had a significant relationship with neuropathy. The independent t-test also showed a significant relationship between fasting blood sugar and neuropathy (P-value = 0.048), but no significant relationship was found between BMI, HbA1c, creatinine, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol and blood urea nitrogen (BUN) (P-value <0.05).

The one-year, three-year, and five-year survival rates are presented in Table 2. The five-year survival rate was 0.64 in the studied patients, necessitating the use of a cure model (Table 2).

In the survival analysis with an auxiliary variable (single regression) for the four models used as mixture and non-mixture, the family history of diabetes, fasting blood sugar, ethnicity, and gender were significant.

The results of the mixture and non-mixture exponential, Weibull, log-logistic and log-normal cure models obtained through single and multiple regression, respectively, are shown in Table 3.

In the final model, the Akaike values were 1469.8 (1467.4), 1360.8 (1371.4), 1347.3 (1357.6), and 1349.2 (1361.8), respectively, amongst which the log-logistic mixture model with the lowest Akaike value had the best fitness. The results of the multiple regression for log-logistic and Weibull mixture cure models are shown in Table 4. In fitting the two models, the cure fraction with Fasting Blood Sugar (FBS) and family history of diabetes, and the scale section with ethnicity and gen-

Table 2: One-year, three-year and five-year survival rates and 95% confidence intervals in the studied patients.

Survival	Survival rate	S.d	95% Confidence Interval	
			Lower bound	Upper bound
One-year	0.86	0.018	0.828	0.898
3-year	0.77	0.023	0.723	0.817
5-year	0.64	0.031	0.582	0.704

Table 3: Results of the mixture and non-mixture exponential, Weibull, log-logistic, and log normal single regression cure model in the studied patients.

Model	exponential		Weibull		log-normal		log-logistic	
Variable	mixture	non-mixture	mixture	non-mixture	mixture	non-mixture	mixture	non-mixture
-	1281.86	1281.51	1264.35	1269.56	1282.46	-	1272.23	1270.83
Gender	1278.08	1278.66	1260.40	1265.32	1280.44	-	1268.88	1264.88
Age	1274.05	1272.48	1256.33	1255.03	1274.46	-	1264.05	-
FBS	1283.85	1281.81	1266.34	1265.10	1283.28	-	1273.62	1266.62
Job activity	1283.66	1283.42	1266.24	1271.54	1284.40	-	1274.07	1272.80
Tobacco	1281.91	1281.00	1263.90	-	1280.55	-	1270.86	-
Education	1283.24	1283.02	1265.86	1271.06	1283.90	-	1273.76	-
Zone	1283.30	1282.08	1265.70	1268.33	1283.72	-	1273.60	-
Race	1281.86	1281.51	1258.96	1263.86	1281.72	1293.00	1267.36	1267.60
Family history	1281.86	1281.51	1271.12	1275.92	1315.56	1329.82	1277.20	1281.01
Treatment	1283.82	1283.28	1265.54	1270.82	1283.21	-	1273.20	-

Heart Disease	1280.13	1277.20	1262.04	-	1280.00	-	1259.66	-
BMI	1253.92	1254.74	1235.72	-	1252.36	-	1242.60	-
Cholesterol	1253.12	1252.04	1241.72	1242.26	1239.16	-	1248.50	-
Triglyceride	1264.45	1263.10	1250.29	1253.60	1265.24	-	1257.67	1254.51
HDL	1020.08	1017.16	998.20	-	1010.44	-	1003.66	-
LDL	1238.09	1237.47	1225.03	1228.73	1238.88	-	1231.92	-
BUN	1218.01	1214.19	1199.10	-	1214.96	-	1205.60	-
Creatinine	1213.12	1212.95	1198.91	-	1217.12	-	1206.75	-
HbA1c	1238.02	1236.19	1222.82	-	1238.40	-	1229.29	1222.66
BP sys	1115.58	1114.14	1094.20	-	1108.86	-	1100.75	-
BP dia	1114.48	1112.76	1094.05	1090.58	1109.10	-	1101.02	-

Abbreviations: BMI, Body Mass Index; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; BUN, Blood Urea Nitrogen; FBS, Fasting Blood Sugar; BP sys, Blood Pressure systolic; BP dia, Blood Pressure diastolic; VEGGF, Vascular Endothelial Growth Gene Factor.

Table 4: Results of multiple analysis of logistic and Weibull mixture of the cure models.

	coefficient		**s.d**		**z**		**p-value**	
Variables	**Log-Logistic**	**Weibull**	**Log-Logistic**	**Weibull**	**Log-Logistic**	**Weibull**	**Log-Logistic**	**Weibull**
Cure fraction								
FBS	0.005	0.005	0.0025	0.0023	1.970	2.090	0.049	0.037
Family history								
No (base)								
Yes	1.179	1.033	0.3218	0.2959	3.660	3.490	<0.001	<0.001
Scale								
Gender								
Male (base)								
Female	3.033	3.006	0.3569	0.2878	8.500	10.450	<0.001	<0.001
Race								
Georgia (base)								
Bakhtiari	-1.239	-2.105	0.5227	0.4408	-2.370	-4.780	0.018	<0.001
Persian	0.678	-0.123	0.6990	0.5661	0.970	-0.220	0.332	0.827
Turk	-1.012	-2.073	0.5505	0.4159	-1.840	-4.980	0.066	<0.001
Shape								
Gamma	-0.300	-0.627	0.0933	0.0763	-3.220	-8.220	0.001	<0.001

Abbreviations: FBS, Fasting Blood Sugar.

der were significant. Given that the variables of fasting blood sugar and family history of diabetes were significant in the cure fraction, these two variables divided the subjects into cured and uncured groups. According to the results, females developed neuropathy faster than males, and Persians faster than other ethnic groups.

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It was found out in the fitted log-logistic model that for 50 units of increase in fasting blood sugar, the patients were 1.3 times more likely to have neuropathy (uncured). Also, those with a positive family history of DM were over three times more likely to have neuropathy, but in the non-susceptible group, females were at risk of neuropathy for about 21 times as much as males. Besides, Persians got neuropathy faster than other ethnicities.

Figure 2 shows the AUC values to compare the efficiency of the Weibull and log-logistic mixture cure models. The AUC values of the log-logistic mixture cure model were always greater than those of the Weibull model so that the Wilcoxon test showed a significant difference between these values (P-value <0.001), indicating greater efficiency of the log-logistic model in survival estimation.

Discussion

DM reduces the body's speed and ability to utilize and metabolize glucose completely. As a result, blood sugar increases, resulting in hyperglycemia. If the increase in blood sugar lasts for a long time (i.e., increased time of DM occurrence) [14, 15], macrovascular complications (atherosclerosis) will begin to damage the arterial walls. Damage to the walls of the arteries may lead to chronic vascular inflammation, immune cell infiltration, lipid deposition of LDL particles into the vessels, and smooth muscle extension [16]. Microvascular complications of DM are caused by the destruction of very small veins in the body that can affect various parts of the body, such as kidneys, eyes, and nerves.

Long-term hyperglycemia causes the destruction of peripheral nerve cells. These cells are at higher risk because they are unable to regulate blood glucose uptake in the long run and lead to neuropathy over some years [17–19]. Increased blood glucose causes glucose accumulation inside the nerve cells and converts to sorbitol and fructose over time [20], which, in turn, impairs axonal transport, nerve membrane fragility, and ultimately leads to nerve cell destruction [21]. In this study, FBS and HbA1c variables were significant in single regression, but FBS was finally significant as a determinant of susceptible and immunized groups in the multiple regression.

A family history of DM in first-degree relatives was one of the most critical risk factors for the incidence of neuropathy in this study (P-value <0.001). The ratio of neuropathy was higher in those with a family history of DM than other patients [22-25]. Based on the aforementioned results, it can be hypothesized that genetic factors can affect the incidence of neuropathy [24, 25]. Numerous studies also emphasized the role of genetics

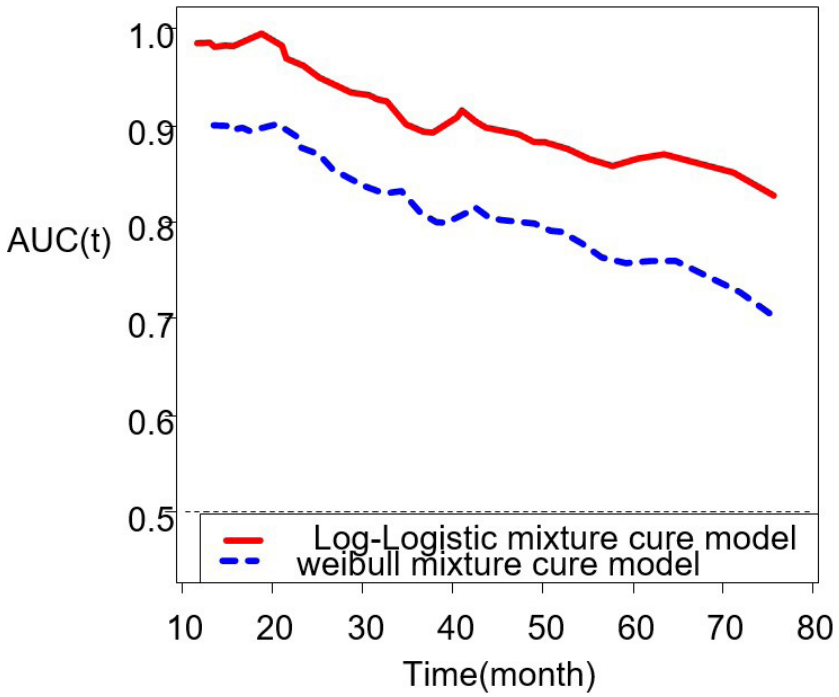

Figure 2: Comparison of accuracy between the Area Under Curve (AUC) of Receiver Operating Characteristics Curve (ROC) of Log-Logistic mixture cure model and Weibull mixture cure model.

- Vascular Endothelial Growth Gene Factor (VEGGF) - in the development of neuropathy [26–24].

The difference between males and females in terms of developing neuropathy could be attributed to hormonal imbalances in the two genders. Endocrine disorders result in hormonal imbalance and neuropathy. Inadequate production of thyroid hormones, for example, slows down the metabolism and leads to fluid retention and tissue swelling, which can put pressure on peripheral nerves. In contrast, overproduction of thyroid hormones can cause acromegaly and abnormal enlargement of bones and joints, trapping the adjacent nerves and causing neuropathic pain [27]. Some studies have proved the role of progesterone in the regeneration of damaged nerve myelin membrane [28]. In the present study, gender was identified as an effective predictor of developing neuropathy, i.e., females developed neuropathy faster than males.

Conclusion

According to the results of this study, it can be concluded that female patients, Persians, and those with a positive family history of DM needed to have more precise control of fasting blood sugar in order to delay neuropathy and increase the time of developing it.

Considering the efficiency of the mixture log-logistic cure model, it can be concluded that as the model is initially incremental and then decreasing, many uncured patients with DM experience neuropathy at the onset of the disease, and then a decrease in the number of neuropathy cases can be seen [29].

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Conflict of Interest

The authors declare no conflict of interest.

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