Clinical Cancer Investigation Journal-ISSN: 2278-0513

Evaluation of Event Time of Neuropathy in Type 2 Diabetic Patients: Application of Surrogate Endpoints Method

Abstract

Diabetic neuropathy is the most common complication of diabetes, the effective control of which requires an accurate diagnosis of neuropathy regularly. The present study aimed to investigate the factors affecting the event time of neuropathy using the Clayton copula model in type 2 diabetic patients in the presence of a surrogate response variable.

The data of all the people whose diabetes test results were negative in the 2006 screening by the health centers in Fereydun Shahr, Isfahan, but whose diabetes re-tests were positive in 2007, and their neuropathy status was followed up for at least 10 years. To investigate the factors affecting the event time of neuropathy in the patients, the Clayton copula model as well as the true variable, ten-point monofilament test, surrogate variable, and Michigan questionnaire including interviews and examinations by a trained physician were used. All the statistical analyzes were performed using the R software (version 3.6.2) and tests were done with an error of 0.05.

Of the total of 371 diabetic patients studied, 114 (30.7%) were male and their mean age was 63.93 (±0.568) years. According to the Clayton copula model, individuals with a family history of diabetes and Hemoglobin A1c of >=8.1, BMI of >=35, HDL of <54, and under treatment with oral and insulin injections would develop neuropathy more quickly.

In this study, using the survival ROC curve, was shown that the Copula model was more efficient than the surrogate model, so it is suggested that the Copula model be used to predict the occurrence of neuropathy for patients who do not have access to the monofilament test.

Keywords: *Type 2 Diabetes, Neuropathy, Michigan Questionnaire, Monofilament Test*

Jamileh Abolghasemi[1], Mina Motamedi Rad[1*], Fahimeh Soheilipour[2], Hamid Reza Baradaran[3], Shahnaz Rimaz[3], Sadegh Kargarian Marvasti[4]

1. Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

2. Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran

3. Radiation Biology Research Center, Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

4. Fereydunshahr Health Center, Isfahan University of Medical Sciences, Isfahan, Iran

** Correspondence to: Mina Motamedi Rad, Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran Hemat Highway 14496 14535, Iran. E-mail: mina.motamedi@outlook.com*

Background

Peripheral neuropathy and vascular diseases are major causes of diabetic foot. Diabetic foot problems are the cause of many of these patients' hospitalization, and foot ulcers and amputation are common complications of diabetes. Neuropathy pain can be severe and may limit mobility and cause depression as well as disruption of the patient's social activities (1). All the patients are needed to be examined for peripheral neuropathy after diagnosis of type 2 diabetes (2). In a prospective study, about 10% of diabetic patients had neuropathy at the time of diagnosis (3). Diabetic neuropathy is one of the most common complications of diabetes (4), occurring in 40-50% of the patients who have been diagnosed with diabetes for at least 25 years (5). Motor and sensory neuropathy often occurs in the legs and is chronic and progressive, with pain in the extremities. The legs gradually become numb and prone to ulcers, burns, infections, gangrene, and Charcot joints (6). Early detection and control of diabetes and its risk factors (7) can help prevent or delay the progression of diabetic neuropathy (8). Early diagnosis of neuropathy is also of particular importance and can prevent more severe complications and huge economic costs. The use of a simple and inexpensive in-clinic method to screen for peripheral neuropathy would be of great value. Using the Michigan Questionnaire and the Monofilament Test is a simple, inexpensive, and clinically applicable method for screening for peripheral neuropathy in diabetic patients. All patients with type 2 diabetes should be examined annually based on their medical history and simple clinical tests for peripheral diabetic neuropathy after diabetes diagnosis (9).

In this study, the time of neuropathy diagnosis through probabilistic and rapid diagnosis in clinical conditions (Michigan questionnaire including interviews and examinations by a trained physician) and the time of neuropathy diagnosis through definitive diagnosis with the monofilament test were considered as surrogate and true endpoints, respectively. This study aimed to evaluate the event time of neuropathy in type 2 diabetic patients, using surrogate endpoint methods.

Methods

To collect the data, all the people whose diabetes test results were negative in the 2006 screening by the health centers in Fereidounshahr, Isfahan, underwent diabetes re-tests in 2007, and those with positive test results were enrolled in the study in case they were ≥30 years of age, and their neuropathy status

was followed up for at least 10 years. In this study, the response variable was the time of diabetes diagnosis until the time of neuropathy diagnosis. Thus, the Michigan questionnaire was first used to take the patient's medical history, and they were asked about the symptoms of neuropathy. Their skin and nail conditions were also checked. In the Michigan Questionnaire, the four factors including the appearance of foot skin (in terms of dryness or cracks, calluses, infection, and deformity), ulcers, Achilles tendon, and vibration sense measured with a 128 Hz tuning fork in the big toe are assessed, and the scores higher than 2 indicate the incidence of neuropathy (10). This method was used to diagnose neuropathy in all the patients studied in the present research. To detect neuropathy, the 10g monofilament and 128 Hz tuning fork are used, and the ten-point monofilament test is performed on ten points on the sole and dorsum of the foot. The lack of monofilament at one or more points indicates peripheral neuropathy (11). The test is performed on a small number of patients and is not available to all patients.

The failure time was by month and based on the censored cases including those who were not diagnosed with neuropathy at the end of the study, those who died, and the ones missed in the follow-up (immigrants) before the end of the study. Reviewing the patient's medical records and, if necessary, doing in-person interviews and telephone calls, the researchers obtained information on variables such as demographic variables (gender, age, occupation, education, place of residence, region of residence, Race, diabetes in first-degree relatives, diabetes treatment methods, smoking), laboratory variables (FBS, height, weight, BMI, cholesterol, triglyceride, HDL, LDL, Creatinine, HbA1c, diastolic and systolic blood pressures, and clinical diagnostic and questionnaire variables of neuropathy).

In statistical modeling, the researcher seeks to estimate the response variable. If measuring the response variable is difficult in terms of cost, difficulty, and such factors, it should be replaced with a surrogate variable that can be measured with a lower cost or in a shorter time to diagnose the disease or can be measurable for more people through generalized methods. Modeling in surrogate endpoint methods is performed with regard to the type of true and surrogate endpoints (12).

When both endpoints are of the failure time type, the co-survival model can be applied, in which a bivariate distribution function with a copula function of any distribution type can be used for the survival function or the marginal risk of the two endpoints (12). The co-survival model (the one with surrogate endpoints) is a model in which both true and surrogate endpoints are of the failure time and correlated. The model is defined as follows:

$$F(s,t) = P\left(S_{ij} \geq s\,, T_{ij} \geq t\right) = C_{\theta}\left\{F_{Sij}(s), F_{Tij}(t)\right\}, s,t \geq 0. \quad (2.1)$$

Where F_{Sij} and F_{Tij} are marginal survival functions, and C_θ is the copula function, i.e. bivariate distribution functions are defined in $[0,1]^2$. In this model, any copula function can be used.

When the risk functions are known, the estimation of the paired model parameters will be through maximum likelihood estimation. In this model, various copulas can be used, depending on the probable intrinsic relationship between the surrogate and true endpoints. General assumptions for fitting the best copula model are not available, and the relation parameter can be difficult to interpret, but the following relation can be obtained by Kendall tau:

$$\tau = 4\int_0^1\int_0^1 C_\theta(s,t)C_\theta(ds,dt) \quad (2.2)$$

This coefficient indicates the relationship between the surrogate and true endpoints (12, 13).
The Kendall's τ in the Clayton copula model (14) is as follows:

$$\tau_{kendall} = \theta - 1/\theta + 1 \quad (2.3)$$

The survival function of the Clayton copula model is as follows:

$$S(t_1,t_2;\beta,\theta) = [S_1(t_1,\beta)^{1-\theta} + S_2(t_2,\beta)^{1-\theta} - 1]^{\frac{-1}{\theta-1}} \quad (2.4)$$

Where S_1 (t_1; β) and S_2 (t_2; β) are the marginal survival functions for each pair of neuropathy diagnosis times (T_1, T_2), θ> 1 is the parameter measuring the positive relationship between survival times, and β is a vector of marginal parameters. If the pairs are ranked, the β vector will be the model parameters. Otherwise, marginal distributions will be completely equal. If θ = 1, the survival times will be independent (15). The Weibull marginal survival distribution is as follows:

$$S(t) = exp\{-\left(\frac{t}{\lambda}\right)^k e^{z^\theta\beta} \quad (2.5)$$

Where λ> 0 is the scale parameter, k> 0 is the shape parameter, and β shows the parameters related to the variables. According to this model, the variables effects are proportional in the context of the risks (13).
To perform the modeling, each model was fitted with an auxiliary variable using simple regression, and the variables with a P value of <0.2 were nominated to enter the multiple

models. Through the employment of progressive and regressive methods, the Clayton copula multiple model was fitted with Weibull distribution, and the efficiency of the fitted model was then determined using survival curves.

The survival-related ROC curve is a method for evaluating the efficiency of fitted survival models. The curve graphically presents accurate prediction or sensitivity versus false prediction by time. It can also be plotted to examine the survival prediction trends in 3-month, 6-month, 24-month, and 36-month sections (16-18). The AUC was used in this study to compare the accuracy of the models. The closer the AUC value to 1 or the larger the area under the curve, the higher the accuracy of the model would be. The Weibull Clayton copula survival model and the surrogate Weibull survival model were used for survival analysis in the present research.

Results

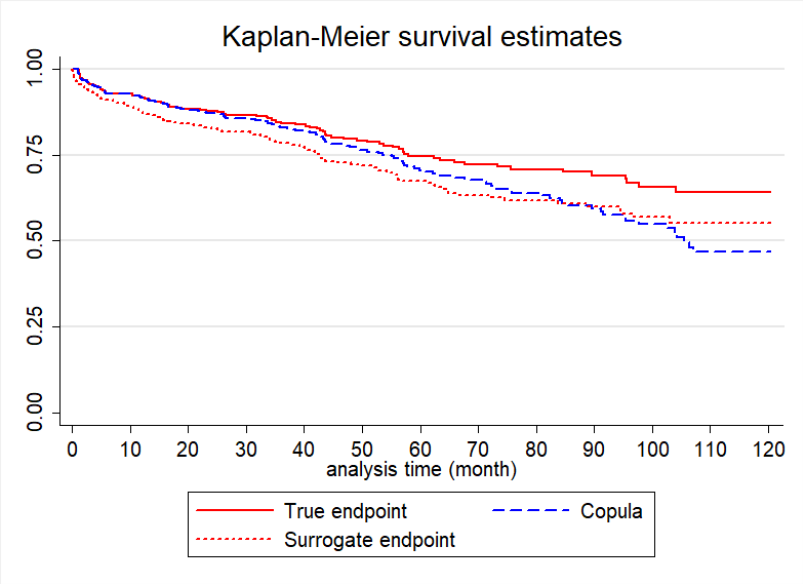

Figure 1: Estimation of survival time in the neuropathic event with monofilament ten-point test (true endpoint), Michigan questionnaire including interview and examination by a trained physician (surrogate endpoint), and both Michigan questionnaire and monofilament ten-point test (Copula)

Figure 1 indicates that the estimate of survival time in the neuropathic event with a monofilament ten-point test (true endpoint), was higher than the Michigan questionnaire because in this study the monofilament test was performed for patients later.

The Michigan questionnaire consisting of interviews and examinations by a qualified physician was used on 371 diabetic patients. (100%), and 244 patients (65.8%) underwent the ten-point monofilament test for neuropathy diagnosis. Table (1) shows the comparison of demographic information and laboratory results of the studied patients by the type of neuropathy diagnosis. The table also represents the frequency of the individuals for each diagnosis method.

In the survival analysis with an auxiliary variable (single regression) using the Clayton copula model with Weibull distribution, the variables including gender, family history, type of treatment, occupational activity, BMI, HbA1c, HDL, BUN, and Race were significant at 0.2 level.

Table 1: Comparison of descriptive demographic and laboratory variables

variables	**Diagnosis by Michigan questionnaire Frequency (%)**	**Diagnosis by Monofilament test Frequency (%)**	**Statistic** X^2	**P**
Gender				
Male	41 (32.3%)	73 (29.9%)	0.220	0.639
Female	86 (67.7%)	171 (70.1%)		
Race				
Georgia	47 (37%)	90 (36.9%)		
Bakhtiari	41 (32.3%)	76 (31.1%)	0.153	0.985
Persia	12 (9.4%)	26 (10.7%)		

Tork	27(21.3%)	52 (21.3%)		
Job activity				
low	20 (15.7%)	37 (15.2%)		
moderate	85 (66.9%)	168 (68.9%)	0.155	0.925
high	22 (17.3%)	39 (16.0%)		
Family History				
Yes	45 (35.4%)	133 (54.5%)	12.177	<0.001
No	82 (64.6%)	111 (45.5%)		
Treatment				
Oral	113 (89%)	194 (79.5%)		
Insulin injections	6 (4.7%)	22 (9.0%)	9.957	0.019
Both	4 (3.1%)	25 (10.3%)		
No.med	4 (3.1%)	3 (1.2%)		
	Mean (±s.e)	**Mean (±s.e)**	**statistic t**	**P**
Age	62.23±1.018	64.82±0.676	-2.173	0.030
FBS	166.11 (±6.302)	168.81 (±4.380)	-0.356	0.722
BMI	28.53 (±0.312)	28.52 (±0.296)	0.002	0.998
Hb1Ac	8.13 (±0.211)	8.10 (±0.132)	0.115	0.909
Cholesterol	189.59 (±3.797)	200.00 (±3.272)	-1.962	0.050
triglyceride	186.15 (±8.188)	191.57 (±7.705)	-0.444	0.657
HDL	47.89 (±1.345)	47.70 (±1.178)	0.102	0.919
LDL	105.62 (±3.469)	109.86(±2.505)	-0.990	0.323
BUN	15.02 (±0.346)	16.93 (±0.476)	-2.706	0.007
Creatinine	0.81(±0.191)	0.84 (±0.192)	-1.099	0.272

s.e: standard error

In the final Clayton copula model, the relationship between the time of neuropathy diagnosis using the Michigan Questionnaire (surrogate endpoint) and the time of neuropathy diagnosis using the monofilament test (true endpoint) was about 89%, which was acceptable for the nomination of the intended endpoint for replacing the true endpoint (13). In this model, the timing of neuropathy diagnosis using the Michigan Questionnaire with single-strand test was considered as the appropriate survival time. According to this model, people with a family history of diabetes and a body mass index of >=35 who were under treatment with both oral and insulin injections and whose Hemoglobin A1c was higher than 8.1 would develop neuropathy sooner, but those with an HDL of >=54 would develop it later. These results are given in Table (2).

Table 2: Results of multiple analysis of weibull Clayton Copula

Covariate	**estimate**	**SE**	**stat**	**P**
Scale				
λ	977.758	214.8661	20.707	<0.001
Shape				
K	0.686	0.0424	260.986	<0.001
Family.History				
No (base)				
+	0.748	0.1477	25.670	<0.001
Treatment				
Oral (base)				
Oral & Insulin injections	0.973	0.1647	34.882	<0.001
BMI				

<35 (base) >=35	0.717	0.2440	8.645	0.003
HbA1c <8.1 (base) >=8.1	0.471	0.1483	10.088	0.001
HDL <54 (base) >=54	-0.496	0.2013	6.069	0.013
θ (Relationship parameter)	17.287	2.4396	50.212	<0.001
AIC	2108.812			

AIC: Akaike Information Criterion

The results of comparing the survival from the Clayton copula modeling with Weibull distribution in which neuropathy in diabetic patients was assessed using the Michigan Questionnaire for all the patients and the Clayton copula model in which neuropathy diagnosis was assessed using the Michigan questionnaire for all the patients and the monofilament test for a smaller number is shown in Figure 2, where the AUC values for comparing the efficiency of the two Clayton copula models and the surrogate model can be seen. The AUC values of the Clayton copula Weibull model were always higher than that of the surrogate model so the Wilcoxon test indicated a significant difference between these values (P <0.001), showing the higher efficiency of the Clayton copula model in estimating survival. As observed in (Figure 2), the copula model was better than the surrogate one, indicating the accuracy of the diagnostic method using the monofilament test along with the Michigan questionnaire.

In order to investigate the survival prediction trend using the Clayton Copula model with Weibull distribution in 3-month, 24-month, and 36-month periods, the ROC curve was plotted and the values of the area under the curve were 0.958, 0.897, and 0.835, respectively. As a result, trends exhibit predictive strength in the first months of being weaker than in later periods. (Figure 3).

Figure 4 presents that the copula model is more accurate than the surrogate model in predicting the event time of neuropathy in patients with neuropathy.

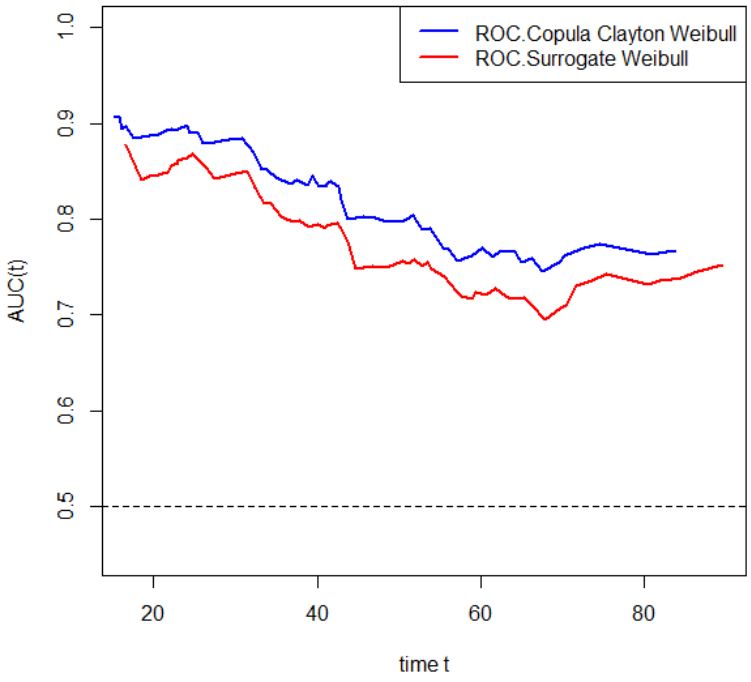

Figure 2: Accuracy of the Copula diagnosis (blue line) using the covariates of Family.History, Treatment, BMI, HbA1c and HDL vs. Surrogate Diagnosis (red line). Line Plot the Estimates of Incident/Dynamic AUC(t) Versus Time Under the Assumption of Proportional Hazards.

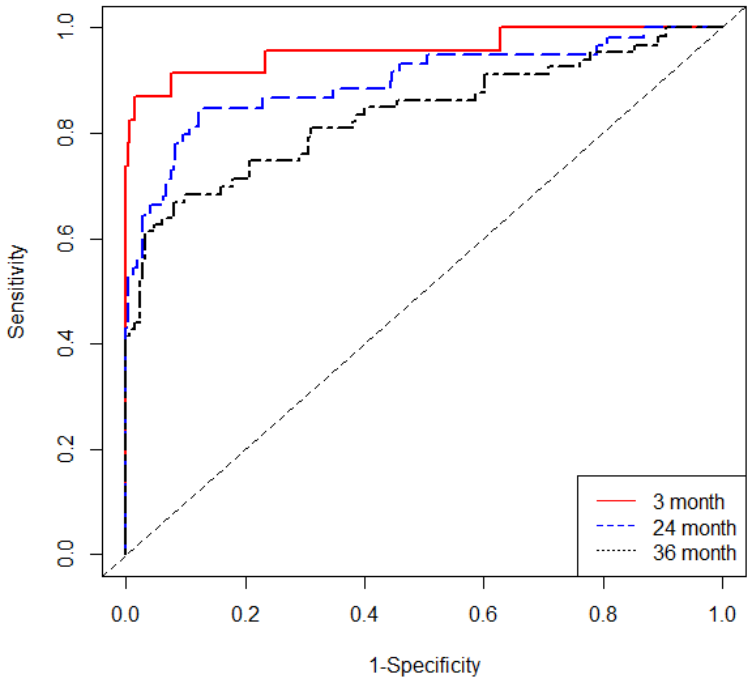

Figure 3: Comparison of the Area Under ROC Curves (AUC) for Predicting the event time of neuropathy at 3(AUC = 0.958), 24(AUC = 0.897), 36(AUC = 0.835) Months for Copula Diagnosis.

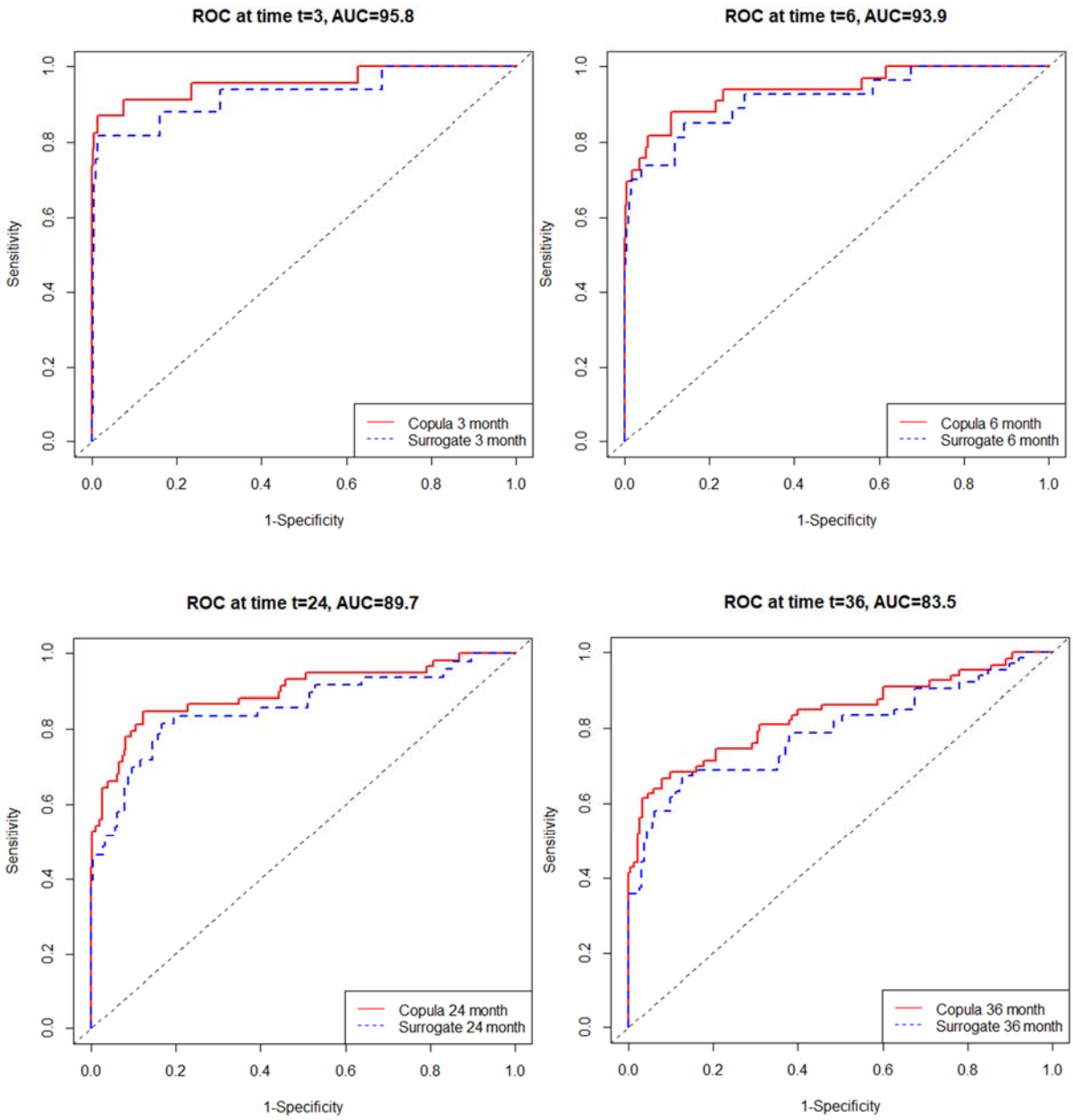

Figure 4: Comparison of the Area Under the ROC Curves (AUC) for predicting the event time of neuropathy at 3, 6, 24, and 36 Months Between Copula Diagnosis (solid line) and Surrogate Diagnosis (dash line). AUC for Prediction of event time of neuropathy using the Copula at 3 (AUC=0.958), 6 (AUC=0.939), 24 (AUC=0.897), 36 (AUC=0.835) Month, and AUC for Prediction enent time of neuropathy using the Surrogate at 3 (AUC=0.926), 6 (AUC=0.915), 24 (AUC=0.856), 36 (AUC=0.790) Month

Discussion

Diabetic neuropathy refers to a group of heterogeneous disorders with different clinical manifestations. Therefore, prompt and immediate diagnosis of neuropathy in patients with diabetes is of particular importance. Diagnosing diabetic peripheral neuropathy is a unique process given the presence of non-diabetic neuropathy that is usually curable. There are numerous treatments for symptomatic non-diabetic neuropathies, but more than 50% of peripheral diabetic neuropathies may be asymptomatic. If the symptoms are not diagnosed and preventive foot care is not taken, the patient will be at risk of diabetic foot ulcer due to the numbness of the feet (2). In the current literature, neuropathy diagnosis was conducted by employing the Michigan questionnaire comprising interviews and examinations by a trained physician for all patients (surrogate variable) and the ten-point

monofilament test for a smaller number of patients (true variable). AUC criterion was also used to compare the efficiency of surrogate and copula models. The AUC value for the model that used the Clayton Copula model (Michigan questionnaire along with the ten-point monofilament test) was close to 1, indicating a higher accuracy of the model than the surrogate variable (Michigan questionnaire). Furthermore, the values of the area under the curve (AUC) for the 3-, 24-, and 36-month sections were declining, indicating a better fit of the model in the time near present. The accuracy of the estimation decreased as the time increased so the AUC decreased from 0.958 in the 3-month section to 0.835.

Based on the findings, a family history of diabetes in first-degree relatives was one of the important risk factors for neuropathy in this study (P <0.001). The hazard ratio for the patients with a family history of diabetes was about 2 times more than that of the ones without a family history of the disease (HR = 2.11, P <0.001). Thus, it could be hypothesized that there were genetic effects in the acceleration of neuropathy (19, 20). Numerous studies such as the ones by Nicholson G, Trivedi JR, and Tavakkoly-Bazzaz J emphasized the role of genetics (VEGGF polymorphism gene) in neuropathy development (19-21).

This study observed that the type of treatment affected neuropathy patients. The ratio of the disease in the patients taking oral medication and insulin simultaneously was 15.4%, while it was 84.6% in those who were only taking oral medication. The hazard ratio for neuropathy was 2.64 times higher in the former group than in the latter group, which may be due to the severity of the former disease. Unlike our study, the studies by Booya et al. (22) and Abbott (23) showed no significant relationship between the type of diabetes treatment and developing neuropathy. This might be due to the difference between the types of studies and the response variable (survival analysis versus logistic regression).

In the present study, about 18.9% of the subject had HDL >=54 and 81.1% had HDL < 54. The Chi-square test showed that there was a significant difference between higher and lower HDL than 54 and the incidence of neuropathy (P = 0.012). Other studies such as the ones by Tesfaye S et al. (7) and Maser RE et al. (24) also confirmed this relationship. high-density lipoproteins (HDL), also known as good cholesterol, are responsible for transporting excess cholesterol to the liver and removing it from the body, and the higher its level, the lower the risk of heart disease will be. In this study, high HDL levels were associated with a reduced risk of neuropathy (HR = 0.61, P = 0.013).

HbA1c is one of the most important factors in diabetes, indicating the quality of diabetes control within the last three months. It is also a major indicator of diabetes care, which reflects the quality of self-care in the last three months. Many studies found high HbA1c effective in the incidence of neuropathy (7, 22, (25, 26)). During diabetes, the speed and ability of the body to use up and metabolize glucose decreases; therefore, blood sugar increases, and this is called hyperglycemia. The prolonged increase in sugar means an increase in diabetes duration (27). Macrovascular complications (atherosclerosis) begin with damage to the walls of the arteries, leading to chronic inflammation of the arteries, infiltration of immune cells, deposition of fat from LDL particles inside the arteries, and smooth muscle expansion (28). Microvascular complications of diabetes are caused by the destruction of very small blood vessels and can affect different parts of the body, such as the kidneys, eyes, and nerves. Sustained hyperglycemia destroys peripheral nerve cells, which are at high risk because they cannot consistently regulate blood glucose uptake and can lead to neuropathy over years. Hyperglycemia causes nerve cells to accumulate glucose. It is converted to sorbitol and fructose over time, which in turn leads to impaired axonal transmission, the fragility of nerve membranes, and eventually, destruction of nerve cells. According to the Clayton copula model with Weibull distribution used in this study, the patients with a mean 3-month blood sugar of >=8.1 were about 1.60 times more likely to develop neuropathy (HR = 1.60, P <0.001). Several studies also found high HbA1c effective in the development of neuropathy (7, 22, 25, 26).

Neuropathy exposes the feet to ulcers by causing numbness and impaired proprioception in them. The reason is that the numbness and impaired proprioception of the feet cause them to be imposed excessive and inappropriate loads, and ulcers will appear in the areas that are exactly the points of pressure transfer, i.e. increased body mass index is associated with ulcer formation. In this study, BMI was another factor influencing the incidence of neuropathy. Foot care is also necessary for diabetic patients. Using appropriate medical tools and necessary training, they must avoid excessive pressure on their feet as much as possible. To this end, weight loss will also be effective. In the present study, the patients with a body mass index of >=35 were about twice as likely as those with lower BMIs to develop neuropathy (HR = 2.04, p = 0.003). This might be due to the greater pressure on their feet and also due to obesity.

There is currently no specific treatment for nerve damage other than optimal blood sugar control that can effectively prevent peripheral neuropathy in diabetic patients and reduce the progression of peripheral neuropathy to a great extent (29). However, blood sugar control does not reverse the loss, and treatment strategies (pharmacological and non-pharmacological) to relieve the pain of diabetic peripheral neuropathy can potentially reduce pain (9) and improve the quality of life.

Conclusion

In this study, the Michigan questionnaire including interviews and examinations by a trained physician was used for all type 2 diabetic patients, and the ten-point monofilament test was performed on a limited number of them (65.8%) in order to diagnose neuropathy. Thus, the model which was fitted based on surrogate response variables (Michigan questionnaire) along with the true response variable (ten-point monofilament test) could efficiently estimate the event time of neuropathy.
People with a family history of diabetes, Hemoglobin A1c of >=8.1, BMI of >=35, HDL of <54, and under treatment with oral and insulin injections will develop neuropathy more quickly. Thus, it is recommended to provide more care and control to these patients once they are diagnosed with type 2 diabetes.
…

List of abbreviations
HbA1c (Hemoglobin A1c), 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), s.e (standard error), AIC (Akaike Information Criterion), ROC (Receiver Operating Characteristics), AUC (Area Under Curve), VEGGF (Vascular Endothelial Growth Gene Factor).

Acknowledgments
None.

Conflict of interest
None.

Financial support
Iran University of Medical Sciences.

Ethics statement
Ethics committee approval was obtained (IR.IUMS.REC.1398.322). Design code was 98-1-2-14867.

References

.1 Galiero R, Caturano A, Vetrano E, Beccia D, Brin C, Alfano M, Di Salvo J, Epifani R, Piacevole A, Tagliaferri G, Rocco M, Iadicicco I, Docimo G, Rinaldi L, Sardu C, Salvatore T, Marfella R, Sasso FC. Peripheral Neuropathy in Diabetes Mellitus: Pathogenetic Mechanisms and Diagnostic Options. International Journal of Molecular Sciences. 2023;24(4):3554.

.2 Effects of 12-week integrated exercise training on glycemic and peripheral sensation control in diabetic peripheral neuropathy. Research in Sport Medicine & Technology. 2021;19(22):113-29.

.3 Carmichael J, Fadavi H, Ishibashi F, Shore AC, Tavakoli M. Advances in Screening, Early Diagnosis and Accurate Staging of Diabetic Neuropathy. Frontiers in Endocrinology. 2021;12.

.4 Dhiaa S, Thanoon AI, Fadhil NN .VITAMIN E VERSUS PROPOLIS AS AN ADD-ON THERAPY TO SITAGLIPTIN/METFORMIN ON OXIDANT/ANTIOXIDANT STATUS AND LIPID PROFILE IN TYPE 2 DIABETIC PATIENTS. MMSL. 2022.

.5 Bodman MA, Varacallo M. Peripheral Diabetic Neuropathy. StatPearls. Treasure Island (FL) :StatPearls Publishing
Copyright © 2022, StatPearls Publishing LLC.; 2022.

.6 Niajalili M, Sedaghat M, Reazasoltani A, Akbarzade Baghban AR, Naimi SS. Effect of Capacitive Tecar Therapy on Foot Pain and Tactile Sensation in Patients with Type 2 Diabetes. Archives of Rehabilitation. 2020;21(3):304-19.

.7 Tesfaye S, Stevens LK, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, Nuber A, Pozza G, Ward JD. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia. 1996;39(11):1377-84.

.8 Won JC, Park TS. Recent Advances in Diagnostic Strategies for Diabetic Peripheral Neuropathy. Endocrinol Metab. 2016;31(2):230-8.

.9 Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017;40(1):136-54.

.10 Park JH, Park JH, Won JC. Associations of nerve conduction study variables with clinical symptom scores in patients with type 2 diabetes. acn. 2019;21(1):36-43.

.11 Deng L, Du C, Song P, Chen T, Rui S, Armstrong DG, Deng W. The Role of Oxidative Stress and Antioxidants in Diabetic Wound Healing. Oxid Med Cell Longev [Internet]. 202:2021 ;2021 1[8852759 p.]. Available from: http://europepmc.org/abstract/MED/33628388
https://doi.org/10.1155/2021/8852759
https://europepmc.org/articles/PMC7884160
https://europepmc.org/articles/PMC7884160?pdf=render.

.12 Buyse M, Molenberghs G, Paoletti X, Oba K, Alonso A, Van der Elst W, Burzykowski T. Statistical evaluation of surrogate endpoints with examples from cancer clinical trials. Biom J. 2016;58(1):104-32.

.13 Sun T, Liu Y, Cook RJ, Chen W, Ding Y. Copula-based score test for bivariate time-to-event data, with

application to a genetic study of AMD progression. Lifetime Data Anal. 2019;25(3):546-68.
.14 Burzykowski T, Molenberghs G, Buyse M, Geys H, Renard D. Validation of Surrogate end Points in Multiple Randomized Clinical Trials with Failure Time end Points. Journal of the Royal Statistical Society Series C. 2001;50:405-22.
.15 Achcar JA, Martinez EZ, Tovar Cuevas JR. Bivariate lifetime modelling using copula functions in presence of mixture and non-mixture cure fraction models, censored data and covariates. Model Assisted Statistics and Applications. 2016;11:261-76.
.16 Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: current methods and applications. BMC Medical Research Methodology. 2017;17(.53:(1
.17 Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Stat Med. 2013;32(30):5381-97.
.18 Hung H, Chiang C-T. Estimation methods for time-dependent AUC models with survival data. Canadian Journal of Statistics. 2010;38(1):8-26.
.19 Axelrod FB, Gold-von Simson G. Hereditary sensory and autonomic neuropathies: types II, III, and IV. Orphanet J Rare Dis. 2007;2:39.
.20 Boonsuth R, Samson RS, Tur C, Battiston M, Grussu F, Schneider T, Yoneyama M, Prados F, Ttofalla A, Collorone S, Cortese R, Ciccarelli O, Gandini Wheeler-Kingshott CAM, Yiannakas MC. Assessing Lumbar Plexus and Sciatic Nerve Damage in Relapsing-Remitting Multiple Sclerosis Using Magnetisation Transfer Ratio. Frontiers in Neurology. 2021;12.
.21 Barus J, Setyopranoto I, Sadewa AH, Wibowo S. Vascular Endothelial Growth Factor 936 C/T Gene Polymorphism in Indonesian Subjects with Diabetic Polyneuropathy. Open Access Maced J Med Sci. 2018;6(10):1784-9.
.22 Booya F, Bandarian F, Larijani B, Pajouhi M, Nooraei M, Lotfi J. Potential risk factors for diabetic neuropathy: a case control study. BMC Neurology. 2005;5(1):24.
.23 Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care. 2011;34(10):2220-4.
.24 Haji Naghi Tehrani K. A study of nerve conduction velocity in diabetic patients and its relationship with tendon reflexes (T-Reflex). Acta Biomed. 2020;91(3):e2020066.
.25 Al Odhayani AA, Al Sayed Tayel S, Al-Madi F. Foot care practices of diabetic patients in Saudi Arabia. Saudi Journal of Biological Sciences. 2017;24(7):1667-71.
.26 Sonawane PP, Shah SH, Shah SH, Vaidya SM, Vaidya SM, Nahar PS, Nahar PS, Khare AS, Khare AS, Buge KH, Buge KH. Effect of glycemic status on peripheral nerve conduction in lower limbs in type 2 diabetes mellitus patients. International Journal of Research in Medical Sciences. 2017;3(6):1505-10.
.27 Mansoor H, Tan HC, Lin MT, Mehta JS, Liu Y-C. Diabetic Corneal Neuropathy. Journal of Clinical Medicine [Internet]. 2020; 9(12).
.28 Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016;20(4):546-51.
.29 Smith DI, Tran H. Pathogenesis of Neuropathic Pain: Diagnosis and Treatment: Springer International Publishing; 2022.