ORIGINAL ARTICLE

Comparing of Cox model and parametric models in analysis of effective factors on event time of neuropathy in patients with type 2 diabetes

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Background: Cox proportional hazard model is the most common method for analyzing the effects of several variables on survival time. However, under certain circumstances, parametric models give more precise estimates to analyze survival data than Cox. The purpose of this study was to investigate the comparative performance of Cox and parametric models in a survival analysis of factors affecting the event time of neuropathy in patients with type 2 diabetes. **Materials and Methods:** This study included 371 patients with type 2 diabetes without neuropathy who were registered at Fereydunshahr diabetes clinic. Subjects were followed up for the development of neuropathy between 2006 to March 2016. To investigate the factors influencing the event time of neuropathy, significant variables in univariate model ($P < 0.20$) were entered into the multivariate Cox and parametric models ($P < 0.05$). In addition, Akaike information criterion (AIC) and area under ROC curves were used to evaluate the relative goodness of fitted model and the efficiency of each procedure, respectively. Statistical computing was performed using R software version 3.2.3 (UNIX platforms, Windows and MacOS). **Results:** Using Kaplan–Meier, survival time of neuropathy was computed 76.6 ± 5 months after initial diagnosis of diabetes. After multivariate analysis of Cox and parametric models, ethnicity, high-density lipoprotein and family history of diabetes were identified as predictors of event time of neuropathy ($P < 0.05$). **Conclusion:** According to AIC, "log-normal" model with the lowest Akaike's was the best-fitted model among Cox and parametric models. According to the results of comparison of survival receiver operating characteristics curves, log-normal model was considered as the most efficient and fitted model.

Key words: Cox proportional hazards model, diabetes, Kaplan–Meier, neuropathy, parametric models

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INTRODUCTION

Diabetic neuropathy (DN) is a common and dangerous complication of diabetes accounting for highest healthcare spending and morbidity in diabetic patients and may cause profound disability in diabetic patients. Major clinical symptoms of DN include numbness, tingling, muscle weakness, loss of sensation, and severe pain that may progress to diabetic foot ulcers and finally lead to limb amputation in diabetic patients.[1,2]

The prevalence of DN varies from one country to another and has been reported within a wide range of 1.5%–100% in patients with type 2 diabetes. This variation can be attributed to various diagnostic methods for DR.[3] A meta-analysis on 21 studies by Sobhani *et al*. between 1991 and 2013, estimated the prevalence of diabetic peripheral neuropathy as 53% in Iran showing high prevalence of DR in Iran, to the extent which more than half of diabetic patients are affected with one type of DN.[4] Nevertheless, it can be concluded that one-third of diabetic patients suffer from DR.[5]

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Many studies have focused on contributing factors associated with neuropathy in diabetic patients. Accordingly, the most significant variables for the event of neuropathy included gender, age, family history of diabetes, type of treatment, cholesterol level, duration of diabetes, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glycated hemoglobin (HbA1c) level, habitat (rural or urban), smoking, creatinine, blood urea nitrogen (BUN), fasting blood sugar (FBS), hypertension (systolic and diastolic), height, weight, triglycerides, and body mass index (BMI).

Survival analysis was applied to study for occurrence of event and the time of occurrence of an event.[6] Unlike linear and logistic regression, in survival analysis, if censoring occurs through the follow-up, all data available on each participant will be used over the entire presence of participant during the study.[7] There are two types of regression models for survival data; (1) Cox proportional hazard model as a semi-parametric model; and (2) parametric models such as Weibull, exponential, log-logistic, and log-normal models. Cox model as a common method for survival modeling has been shown in some settings to be more widespread in use despite its limitations.[8] However, under certain circumstances, parametric models estimate the parameter more efficient than Cox.[9]

A number of studies have been conducted to compare various survival regression methods, of which some proposed parametric models as the most appropriate modeling method[10-18] and some implied to semi-parametric methods such as Cox regression.[19-21]

Rajaeefard *et al*. used both parametric and nonparametric methods in a survival analysis of patients with gastric cancer. As such, the results of Cox regression and parametric models were almost consistent.[11]In addition, Ghadimi *et al*. applied log-logistic model as the best-fitted model in a survival analysis of patients with gastrointestinal cancer.[18] Furthermore, Weibull model was selected as the best-fitted model in Grover and Sabharwal study that estimated survival time of diabetic nephropathy,[14] and Roshany *et al*. study analyzing the survival of patients with acute myocardial infarction.[15] In addition, log-normal model showed an excellent fit to the data in Askarishahi *et al*. study analyzing factors affecting the event time of retinopathy[16] and Baghestani *et al*.[17] and Orbe *et al*.[12] In addition, regression model was shown to be the best-fitted model in studies by Laclé and Valero-Juan determining the risk factors associated with lower-limb amputation due to neuropathy[20] as well as the study of risk factors for diabetic nephropathy by Viswanathan *et al*.[21]

This study was aimed to analyze contributing factors in event time of neuropathy in patients with type 2 diabetes, using Cox and parametric models including exponential, Weibull, log-normal, and log-logistic.

MATERIALS AND METHODS

This cohort study recruited 371 patients with type 2 diabetes (diabetic patients without neuropathy from all 440 diabetic patients) referring to Fereydunshahr diabetes clinic in Fereydunshahr, Iran, by census method. They were continuously followed for the development of DR until the end of 2016. For the diagnosis of diabetes (type 2), fasting blood sugar test was used.[22] First, patients were investigated by an expert physician using The Michigan Neuropathy Screening Instrument (MNSI). This questionnaire provided information on condition of foot skin, ulceration, Achilles tendon reflex, and vibration sensation. The MNSI examination has 61% sensitive and 79% specific in defining confirmed clinical neuropathy and has a positive predictive value of 56% and a negative predictive value of 83%.[23] We also performed 10-g monofilament testing on the palm and back of the feet.[24] Tabatabaei-Malazy *et al*. proposed simultaneous use of both MHQ questionnaire and monofilament testing to more effectively detect DN in diabetic patients.[25] The sensitivity and specificity of the 10-g monofilament testing were computed 65%–86% and 58%–71%, respectively.[26]

Serum total cholesterol and triglycerides, LDL, HDL, HbA1c, and glucose level were measured by standard biochemical kits and glucose oxidase method kit (Pars Azmoon, Tehran, IR Iran). The sensitivity of these kits for measuring of serum total cholesterol, triglycerides, LDL, and HDL were 95%, 99%, 99%, and 99%, respectively.[27] The precision of these kits for measuring of HbA1c, BUN, creatinine and glucose level was 99%, 99%, 100%, and 99%, respectively. Reference range of these variables are including triglycerides (normal: <200 mg/dl), cholesterol (normal: <200 mg/dl), HbA1c (change of therapy: >8%), urea UV (13–36 g/24 h), creatinine (men: 0.7–1.4 mg/dl and women: 0.6–1.3 mg/dl), and HDL (≥35 mg/dl).

Data regarding age, gender, ethnicity, BMI, smoking, family history of diabetes, age at diagnosis, educational level, height, weight, diabetes duration, habitat, occupation, systolic and diastolic hypertension (based on the classification of the seventh report of the joint national committee on prevention, detection, evaluation, and treatment of hypertension; JNC7), type of treatment, blood cholesterol and triglycerides level, Fasting blood sugar (FBS), LDL and HDL levels, BUN, creatinine, and HbA1c levels were extracted from patient's health-care records. Measurement and calibration of the independent variables were done based on "national programme for diabetes prevention and control" and "Iran's package of essential noncommunicable disease interventions for primary health care (IRAPEN).

The event (or failure) in this study was diagnosis of neuropathy in diabetic patients. Subjects who were not diagnosed with DN, as well as missing persons (immigrants) at the end of the study, were considered as censored cases (loss to follow-up).

Factors affecting the event time of DN were investigated using univariate and multivariate analysis according to Cox and four parametric models, Weibull, exponential, log-logistic and log-normal to identify the fitted model. Data were analyzed using R software version 3.2.3 (UNIX platforms, Windows and MacOS). After univariate analysis, five variables with statistical significance ($P < 0.20$) were submitted in a multiple regression model. In addition, data analysis was conducted using regressive-progressive approach ($P < 0.05$).[26,28] We also compared survival curves using the Kaplan–Meier method with log-rank test.[22]

We used Akaike's information criterion (AIC) to evaluate the goodness of fit. In addition, receiver operating characteristics curves (ROC) and area under ROC curves (AUCs) were applied to determine the efficiency of models. ROC curve is the most common measure to estimate sensitivity and specificity in two-state events. However, ROC curves are used to estimate the survival time data in time-dependent events.[29] The accuracy of the model is measured by the AUC so that an area of one represents a perfect test; an area of 0.5 represents a worthless test.[30]

RESULTS

A total of 371 diabetic patients without DN entered the study, of whom 114 were male (30.7%) and 257 were female (69.3%). The mean age of the patients was 64 ± 1.15 years (ranged from 31 to 93 years), and the median age was 64.5 years (standard deviation: 11.03 years). Figure 1 shows number and annual trend of diabetic patients and event of neuropathy and Table 1 shows demographic and clinical characteristics of participants with and without DN.

All 371 patients were followed up for 15,544 months (1295 person-year), and the average follow-up for each patient was 41.9 months. According to nonparametric Kaplan–Meier approach, neuropathy was diagnosed 76.6 (5±) months after the initial diagnosis of diabetes (83.8 ± 8 months male vs. 72.7 ± 6 months female). At the end of 10-year follow-up, DN was diagnosed in 31% of the patients (n = 115) and 60.4% (n = 224) were diagnosed without DN (right-censored). In addition, 8.6% of the patients were lost to follow-up (69% of the patients were censored in the study). Cox regression revealed the 1-, 2-, 5- and 8-year survival rates (event-free survival) as 0.867, 0.819, 0.647, and 0.527, respectively.

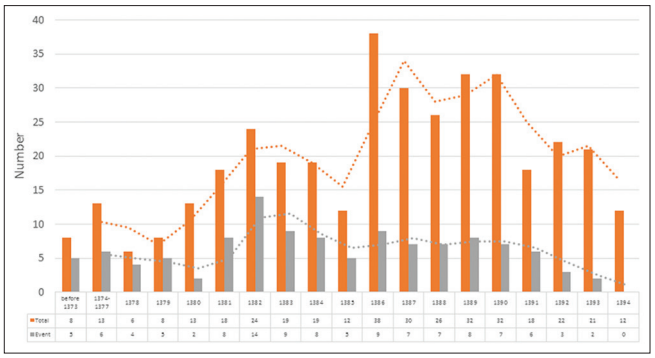

Figure 1: Number and annual trend of diabetic patients and event of neuropathy

Results of univariate analysis for all models are shown in Table 2. In all-fitted models, variables including gender, ethnicity, familial history of diabetes, treatment type of diabetes, height, fasting blood sugar, weight, HDL, HbA1c levels, and duration of diabetes were significant. However, systolic blood pressure was significant only in exponential model. These variables were submitted in multiple regression models.

Figure 2 indicates cumulative hazard function of DN in patients with type 2 diabetes, and Table 3 shows the results of multivariate analysis, in Cox regression and parametric models.

According to multivariate analysis, ethnicity in all models, familial history of diabetes in Cox, Weibull, exponential and log-logistic models, and HDL levels in exponential model were identified as contributing factors associated with event time of DN ($P < 0.05$).

Although univariate analysis results were not different between parametric and semi-parametric models, parametric models showed an excellent fit to the data based on AIC [Table 4]. In addition, "log-normal model" with the lowest values of AIC, provided the excellent fit to the data.

In addition, according to the results of survival ROC, "log-normal model" was recognized as model with the highest efficiency in parametric and semi-parametric models [Figure 3].

DISCUSSION

The main objectives of this study were to (1) investigate contributing factors in the event time of DR in patients with type 2 diabetes using semi-parametric and parametric models; (2) compare the fitness of the models based on AIC; and (3) compare the accuracy and efficiency of models based on the AUC.

Findings of the current study show that ethnicity, HDL level, and family history of diabetes were identified as

Table 1: Demographic and clinical characteristics of type 2 diabetic patients

Variables	Neuropathy		Total (*n*)	*P* (χ^2)
	With, *n* (%)	Without, *n* (%)		
Gender				
Male	25 (21.7)	89 (34.8)	114	0.008
Female	90 (78.3)	167 (65.2)	257	
Age				
<55	20 (17.4)	57 (22.3)	77	0.018
55–70	68 (59.1)	105 (41.0)	173	
≤70	26 (22.6)	79 (30.9)	105	
Missed	1 (0.9)	15 (5.8)	16	
Job				
Housekeeper	82 (71.3)	160 (62.5)	242	0.435
Worker, farmer, stockbreeder, self-employment	17 (14.8)	50 (19.5)	67	
Employee	3 (2.6)	8 (3.1)	11	
Effete, retired, dead	13 (11.3)	38 (14.9)	51	
Smoking				
Yes	11 (9.6)	18 (7.0)	29	0.284
No	104 (90.4)	231 (90.3)	335	
Missed	0	7 (2.7)	7	
Education				
Illiterate	86 (74.8)	171 (70.4)	257	0.280
Primary education	26 (22.6)	56 (23.0)	82	
Diploma and higher	3 (2.6)	16 (6.6)	19	
Missed	0	13 (5.1)	13	
Habitat				
Rural	48 (41.7)	101 (39.5)	149	0.496
Urban	67 (58.3)	145 (56.6)	212	
Missed	0	10 (3.9)	10	
Ethnicity				
Georgian	35 (30.4)	102 (39.8)	137	0.022
Bakhtiari (Lor)	32 (27.8)	85 (33.2)	117	
Tork	30 (26.1)	50 (19.5)	80	
Fars	18 (15.7)	19 (7.4)	37	
Familial history of diabetes				
+ (Yes)	74 (64.3)	104 (40.6)	178	0.0001
- (No)	40 (34.8)	131 (51.2)	171	
Missed	1 (0.9)	21 (8.2)	22	
Treatment type of diabetes				
Oral	84 (73.0)	223 (87.1)	307	0.004
Insulin injected	13 (11.3)	15 (5.9)	28	
Both (oral and insulin injected)	18 (15.7)	18 (7.0)	36	
Fasting blood sugar				
<130	29 (25.2)	93 (36.3)	122	0.009
≤130	83 (72.2)	144 (56.3)	227	
Missed	3 (2.6)	19 (7.4)	22	
Duration of diabetes (months)				
<36	5 (9.1)	50 (90.9)	55	0.0001
36-<72	21 (25.6)	61 (74.4)	82	
72-<108	23 (24.5)	71 (75.5)	94	
≤108	66 (47.1)	74 (52.9)	140	
BMI				
<25	21 (18.3)	42 (16.4)	63	0.915
25–30	49 (42.6)	99 (38.7)	148	
≤30	33 (28.7)	74 (28.9)	107	
Missed	12 (10.4)	41 (16.0)	53	

BMI = Body mass index

Table 2: Comparison of the final results of fitted Cox and parametric models in univariate analysis for diagnosis of diagnosis of neuropathy in patients with type 2 diabetes (*P*<0.20)

Variables	Cox	Log-normal	Log-logistic	Weibull	Exponential
Gender	0.028	0.072	0.048	0.028	0.024
Age	0.775	0.974	0.874	0.750	0.748
Job	0.398	0.701	0.551	0.384	0.437
Smoking	0.504	0.331	0.382	0.471	0.505
Education	0.256	0.426	0.304	0.263	0.257
Habitat	0.963	0.645	0.903	0.978	0.950
Ethnicity	0.012	0.002	0.011	0.015	0.014
Familial history of diabetes	0.006	0.006	0.008	0.005	0.006
Treatment type of diabetes	0.128	0.098	0.098	0.078	0.200
Height	0.085	0.128	0.167	0.099	0.08
FBS	0.006	0.003	0.004	0.006	0.003
Weight	0.033	0.022	0.043	0.038	0.029
BMI	0.449	0.373	0.43	0.490	0.417
Cholesterol	0.361	0.592	0.442	0.350	0.409
Triglycerides	0.795	0.607	0.713	0.784	0.842
HDL	0.024	0.051	0.039	0.028	0.025
LDL	0.410	0.530	0.446	0.415	0.408
BUN	0.696	0.749	0.689	0.695	0.629
Creatinine	0.935	0.814	0.887	0.946	0.716
HbA1c	0.020	0.009	0.021	0.019	0.016
Systolic blood pressure	0.221	0.401	0.305	0.280	0.182
Diastolic blood pressure	0.547	0.661	0.716	0.648	0.513
Duration of diabetes	0.008	0.001	0.006	0.004	0.033

BMI = Body mass index; BUN = Blood urea nitrogen; FBS = Fasting blood sugar; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; HbA1c = Glycated hemoglobin

Table 3: Comparison of the final results of Cox and parametric models in multivariate analysis for diagnosis of neuropathy in patients with type 2 diabetes (*P*<0.05)

Variables	Model														
	Cox			Weibull			Exponential			Log-logistic			Log-normal		
	HR	*P*	95% CI	HR	*P*	95% CI	HR	*P*	95% CI	TR	*P*	95% CI	TR	*P*	95% CI
Ethnicity	1.83	0.019	1.1-3.0	1.82	0.020	1.1-3.0	1.98	0.014	1.1-3.4	2.21	0.027	1.1-4.5	2.12	0.050	1.1-4.6
Familial history of diabetes	4.58	0.025	1.2-17.3	4.87	0.018	1.3-18.1	4.52	0.028	1.2-17.4	7.47	0.037	1.1-14.9	No significance		
HDL	No significance			No significance			4.23	0.019	1.3-14.2	No significance			No significance		

HR = Hazard ration; TR = Time ratio; CI = Confidence interval; HDL = High-density lipoprotein

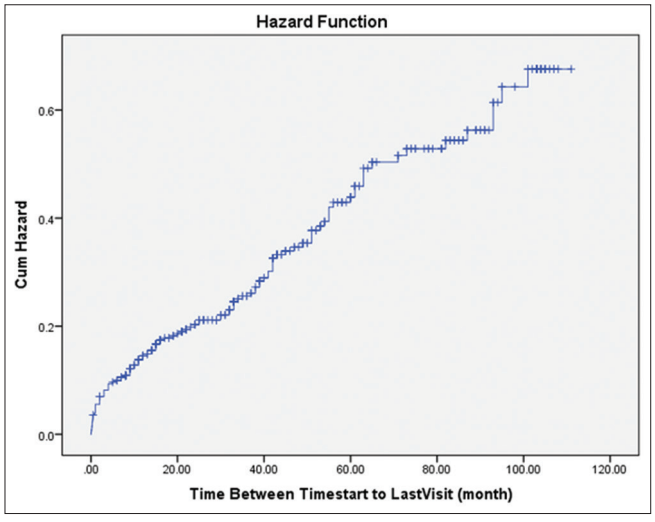

Figure 2: Cumulative hazard function of neuropathy in patients with type 2 diabetes

contributing factors in the event time of DN ($P < 0.05$). Fars ethnicity was positively associated with DR ($P = 0.016$). As such, 49% of the Fars diabetic patients reported DN. In addition, the prevalence of DN was reported 38, 27, and 26% in Turkish, Bakhtiari, and Georgian ethnicity, respectively.

Kaplan–Meier survival analysis showed that event time of DN was shorter in Fars ethnicity compared other ethnicities. As such, the Fars ethnicity developed DN about 22 and 15 months earlier than the Georgians and Bakhtiaris ethnicities, respectively. No research has been done on the relationship between ethnicity and DN in Iran. The family history of diabetes was shown as an important risk factor for DN in this study ($P = 0.001$).

The proportion of DN in patients with a family history of diabetes was higher compared other patients (41% vs.

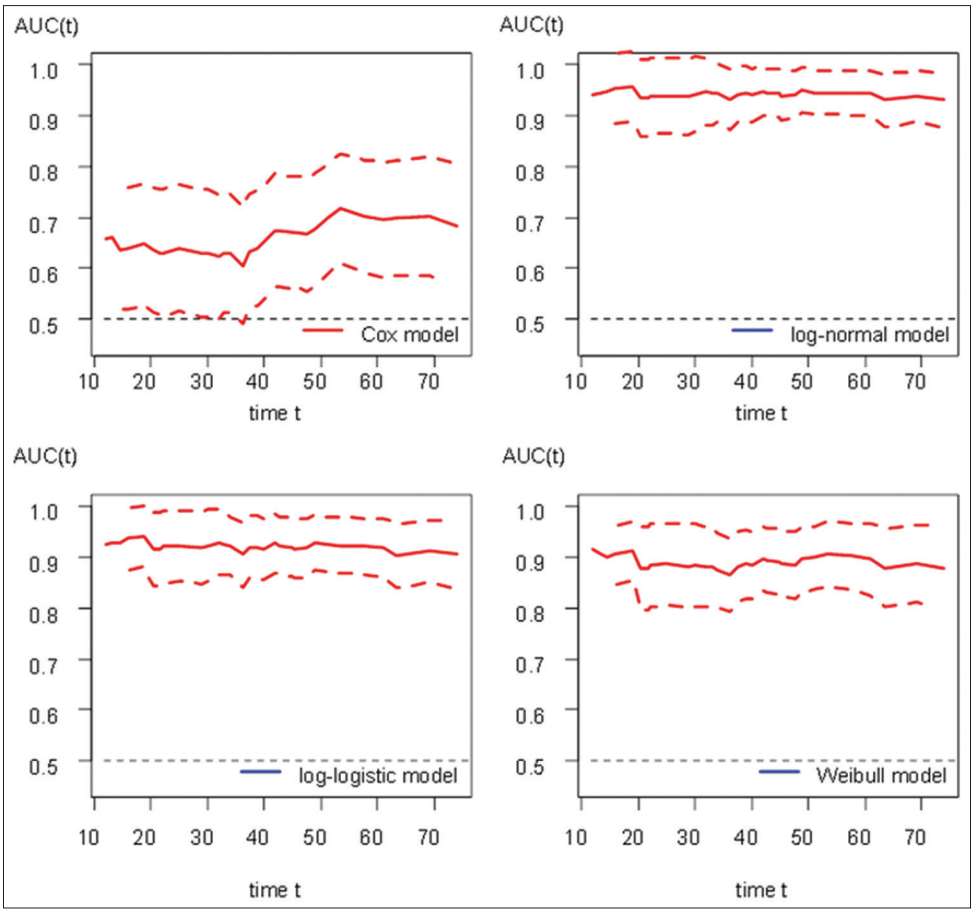

Figure 3: Accuracy of semi-parametric and parametric models by the area under operating characteristics curve in the prediction of event time of diabetic neuropathy in patients with type 2 diabetes

Table 4: Comparison of fitness of models based on Akaike information criterion

Model	AIC
Cox	404
Exponential	327.98
Weibull	326.02
Log-normal	319.32
Log-logistic	322.86

AIC = Akaike information criterion

23%). The odds of having DN were 2.3 times higher among those with a family history of diabetes compared to patients without a family history of diabetes. In addition, the event time of DN in patients with a family history of diabetes was 16 months shorter than patients without a family history of diabetes, which was supported by other studies.[31]

According to results of the current study, it can be assumed that genetic factors are likely to play an important role in the development of DN.[32,33] Several studies focused on the role of genetics (VEGF gene polymorphism) in developing DN.[32-35] In addition, reduced HDL level was positively associated with DR. HDL is known as "good" cholesterol in that it removes excess cholesterol in the arteries and transport it back to the liver for excretion and elevated HDL levels are associated with lower risk of cardiovascular disease.

According to Pittsburgh[36] and Tesfay study on the relationship between vascular risk factors and DN (EURODIAB),[37] reduced HDL levels were significantly associated with DN. Findings of the current study revealed a relationship between HDL level and the event of DN (P = 0.035). In addition, Kaplan–Meier survival analysis showed that the occurrence time of DN was 21.5 months shorter in patients with lower HDL levels than those who have high HDL levels (P = 0.02). In addition, the odds of having DN were higher in patients with lower HDL (41.7% vs. 23%).

Ghorbani-Gholiabad *et al.*,[6] Orbe *et al.*,[12] and Pourhoseingholi *et al.*[13] evaluated the parametric and semi-parametric models in the survival analysis of patients with gastric cancer. They have argued that parametric regressions had fitted better than Cox. In addition, log-normal model was shown to be the best fitness, which was in accordance with the present study. However, this was not supported by a number of studies (e.g., Teshnizi *et al.*,[19] and Askarishahi *et al.*[16]). They proposed Cox model as the best-efficient model.

In addition, a number of studies parallel with our study showed that accuracy and fitness of parametric regression were better than Cox regression.

Besides, Weibull model was selected as the best-fitted model in Grover and Sabharwal study that estimated the survival time of DN,[14] Roshany *et al*. in a study to analyze the survival of patients with acute myocardial infarction,[15] and Rajaeefard *et al*. in a survival analysis of patients with gastric cancer.[11] Ghadimi *et al*. in a study on the survival of the patients with gastrointestinal cancer,[18] log-logistic model had fitted better than Cox regression and other parametric models.

In this study, ROC curves and the AUC criterion were used to compare the accuracy of semi-parametric and parametric models to estimate the survival time of DN. As shown in Figure 2, in parametric models, AUC value is close to one, showing a higher accuracy than semi-parametric Cox regression (which is closer to 0.5). Thus, log-normal model was determined as the most efficient model.

At the end of 10 years follow-up, the cumulative incidence and prevalence of DN in patients with type 2 diabetes in Fereydunshahr was 31% and 41.8%, respectively, which is consistent with other studies in Iran and other parts of the world. The prevalence of DN in patients with type 2 diabetes found in this study was similar to other studies.[4,37]

The risk of DN (cumulative incidence) in three experimental studies including complications and control of diabetes in Europe with 7 years follow-up,[37] Pittsburgh study with two follow-ups for 4- and 10-year period,[36] and San luis effort with 5-year follow-up[38] was 23.5%, 13%, 34.2%, and 28.6%, respectively. These suggest that the time of follow-up was positively associated with the cumulative incidence of DN.

According to Kaplan–Meier analysis, female diabetic patients developed DN about 11 months earlier than the male patients (83.8 vs. 72.7 months). Moreover, the risk of DN was 13% higher in women than men ($P = 0.014$). In similar studies, gender has been found as an effective factor in developing DN.[32]

Limitation

For goodness of fit of parametric models, censoring should not exceed 40%–50%.[39] The frequency of right-censored data was 69% in this study which may be due to the limited study period.

Although this study was performed with a long-follow-up period (10-year), continuous follow-up is needed to achieve higher cumulative incidence (higher percentage of DN diagnosis) and reduce the right-censored data.

However, the strengths of this study were as follow as follows: low rate of lost to follow-up (<10%), use of census method for sampling, high sample size (440 patients in start of the study), patients' regular follow-up, and free medical examinations.

CONCLUSION

According to the results of this study, low-levels of HDL were a modifiable risk factor for DN. However, there were also nonmodifiable risk factors including Persian ethnicity and family history of diabetes. Therefore, educational intervention to achieve recommended HDL levels is of a great importance in patients with a family history of diabetes.

Consumption of unsaturated fats (e.g., olive oil, nuts, fish) instead of saturated fats, exercise and increased fiber intake are shown to increase HDL level, as mentioned in many literatures.

Despite the tendency of many researchers to use Cox regression models in survival analysis, parametric models have been shown to provide more precise results than the Cox model, especially, in when fewer right-censored data are presented. In this study, according to AIC and AUC, "log-normal"parametric model, was identified as the best fitted and efficient model in the analysis of the effective factors in the event time of DN.

However, parametric regression models are not selected as the best-fitted models in survival analysis. As a result, various models show different effectiveness in the analysis of different data sets and we need to evaluate the different models to find the most effective model.

Finally, we suggest further research to be done with more follow-up time to increase the rate of DN diagnosis and reduce the right-censored cases as well as using different comparison criteria between various models.

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Conflicts of interest

The authors have no conflicts of interest.

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