Survival Analysis of Time to Amputation Event Data in Patients with Severe Foot Problems in Vascular Practice

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Abstract

Objective: To estimate time to amputation event in patients with severe foot problems in vascular practice and investigate the relationship of factors influencing the amputation event and time of patients with severe foot problems in vascular practice.

Methods: The study design was a retrospective cohort study using data collected from medical records in the Faculty of Medicine Vajira Hospital, Navamindradhiraj University. The study included patients who were diagnosed with patients with severe foot problems in vascular practice (patients who were diagnosed with critical limb ischemia (CLI) and/or diabetic foot) between January 1, 2009 and December 31, 2010, and follow-up times started from January 1, 2009 to December 31, 2014.

Results: There were 372 patients, the follow-up time ranged from 0.066 to 72.933 months (median 50.466 months). There were detected amputation event in 89 of 372 patients (23.9%). The 10th percentiles were 1.66 months. According to Cox's proportional hazard model, there were 3 significant variables affecting the amputation event rates, that were smoking, HbA1c ≥ 7.5% and presence of renal disease (p-value = 0.034, <0.0001 and 0.021, respectively).

Conclusion: In vascular practice, patients with severe foot problems who smoked, had HbA1c ≥ 7.5% and had renal disease were more prone to have amputation events.

Keywords: Time to event analysis, Amputation, Severe foot problems, Vascular practice

การวิเคราะห์ระยะเวลาปลอดการตัดขาในผู้ป่วยที่มีปัญหาเท้ารุนแรงในเวชปฏิบัติทางด้านหลอดเลือด

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บทคัดย่อ

วัตถุประสงค์: เพื่อประมาณค่าระยะเวลาปลอดการตัดขาในผู้ป่วยที่มีปัญหาเท้ารุนแรงในเวชปฏิบัติทางด้านหลอดเลือด และศึกษาปัจจัยที่มีความสัมพันธ์กับการถูกตัดขาในผู้ป่วยที่มีปัญหาเท้ารุนแรงในเวชปฏิบัติทางด้านหลอดเลือด

วิธีดำเนินการวิจัย: รูปแบบการศึกษาติดตามไปข้างหน้าโดยใช้ข้อมูลในอดีตจากเวชระเบียนผู้ป่วยที่คณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช ประกอบด้วยผู้ป่วยที่มีปัญหาเท้ารุนแรงในเวชปฏิบัติทางด้านหลอดเลือด (ผู้ป่วยที่ได้รับการวินิจฉัยเป็นแผลเท้าเบาหวานและ/หรือภาวะขาขาดเลือดชนิดรุนแรง) ระหว่างวันที่ 1 มกราคม 2552 ถึงวันที่ 31 ธันวาคม 2553 และติดตามจนถึงวันที่ 31 ธันวาคม 2557

ผลการวิจัย: กลุ่มตัวอย่างมีจำนวน 372 ราย โดยช่วงระยะเวลาของการติดตามอยู่ระหว่าง 0.066-72.933 เดือน (ค่ามัธยฐาน = 50.466) ผู้ป่วยที่ได้รับการตัดขามี จำนวน 89 ราย (23.9%) พบอัตราการปลอดการตัดขาที่เปอร์เซ็นไทล์ที่ 10 เท่ากับ 1.66 เดือน และการวิเคราะห์ Cox's proportional hazard model พบว่ามี 3 ตัวแปรที่เพิ่มความเสี่ยงต่อการตัดขา ได้แก่ ประวัติการสูบบุหรี่ ระดับน้ำตาลเฉลี่ยสะสมในเลือด ≥7.5% และโรคไต (p-value = 0.034, <0.0001 และ 0.021 ตามลำดับ)

สรุป: ผู้ป่วยที่มีปัญหาเท้ารุนแรงในเวชปฏิบัติทางด้านหลอดเลือดที่สูบบุหรี่ ระดับน้ำตาลเฉลี่ยสะสมในเลือด ≥7.5% และเป็นโรคไต เป็นกลุ่มผู้ป่วยที่มีความเสี่ยงสูงต่อการเกิดการตัดขา

Introduction

Time to event analysis or survival analysis starts where a cohort of subjects or individuals was continuously followed-up until some event of interest occurred or the study ends.[1] Survival analysis consists of analyzing of the survival time of a subject, usually measured in days, weeks, months, or year and the event of interest occur as failure, death, response to a treatment, relapse, the development of a disease. A significant aspect of survival analysis is that the outcome or event of interest may not occur to all patients during follow-up.[2-4] There are certain aspects of survival data, such as censoring, that generate great difficulty when trying to analyze the data using traditional statistical models such as multiple linear regression analysis due to censoring or censored observation is defined as an observation with incomplete information and we do not know the exact duration of survival time.[2] Survival analysis methods correctly use both the censored and uncensored observations. Therefore, survival analysis has become a popular tool used in clinical trials where it is well suited for work dealing will incomplete information.

The important for survival analysis was dependent variables include outcome or event of interest and time to event or survival time and presented by estimated median survival time or 50% of survivors.[5-7] The model used for the analysis of the determinants of differences in the occurrence of events or Cox's proportional hazard model which was developed by Cox and principle similar to the multiple regression analysis but in the Cox's proportional hazard model variables as a function of the risk of an event of interest at time t ($h(t)$)[8] and can be exploring the relationship between the survival of subjects and several covariates. In addition, it allows us to estimate the risk of death or event of interest occurred for an individual, given their prognostic variables.

Critical limb ischemia and diabetic foot is one of the major problems for national health care causing major limb loss and death. Hence, early detection of this disease and correction of the risk factors should be the most effective strategy to improve the overall outcome of the management of this complicated problem. In the previous studied, the natural history of Critical limb ischemia in 20 publications on 6,118 patients found that the cumulative probability of survival of the entire group was 74%, 58%, 56%, 48%, and 44% at 1, 2, 3, 4, and 5 years, respectively.[9] In addition, Engelharat M, et al. report a 3 years amputation rate of 31%, and factors related to amputation event in Critical limb ischemia patient was patients who were diagnosed as heart disease with kidney disease (HR 3.68, 95% CI 1.51-8.94; p<0.001).[10] The risk factors related to amputation event of Critical limb ischemia patient was severity of the patients, infection, smoking and underlying disease of patients, especially diabetes mellitus, kidney disease, hypertension, dyslipidemia, ischemic heart disease and ischemic stroke.[11] And the studied of factors associated with amputation-free survival in patients with diabetic foot were 173 cases found that amputation-free survival at 1-year were 65.9%. Factors associated for amputation was the severity of diabetic foot (HR 7.99 95%CI 3.12-20.47), followed by Ankle Brachial Index <0.9 (HR 2.64 95%CI 1.52-4.59).[12]

Faculty of Medicine Vajira Hospital, a tertiary care hospital that provides medical treatment this patients. Thus, the researcher interest studied time to event analysis in this patients group to estimate amputation-free survival time and identify factors that influenced amputation event and time of Critical limb ischemia and/or diabetic foot patients.

Methods

This study was a retrospective cohort study of patients presenting with patients with severe foot problems in vascular practice based on inclusion criterions consisted of patients who were diagnosed with Critical limb ischemia and/or diabetic foot all ages and gender between January 1, 2009 and December 31, 2010. And exclusion criterions consisted of patients cloud not find the medical records or had history of independent variables in this study incomplete. The observation period continued until the event occurred

(amputation event) or, if no event occurred, individuals were followed up until the end of study (December 31, 2014) from medical records.

Sample size requirements for survival study carried out as follows[13] the required number of patients will be found from $n = \frac{d}{\Pr(event)}$. To calculate the number of events that would be required in a study to compare the two groups of patients, we will take α = 0.1 and 1 – β = 0.8. With these values of α and β, the value of the function c(0.1, 0.2) = 6.18 and taking θ_R = log(2.64) 0.42, the number of events required to have a 80% chance of detecting a hazard ratio of 0.42 to be significant at the 90% level is then given by $d = \frac{4\left(Z_{\frac{\alpha}{2}}+Z_{\beta}\right)^2}{\theta_R{}^2}$ therefore, $d = \frac{4\times6.18}{0.42^2} = 137.44$.
Allowing for possible underestimation, this can be rounded up to 138 events (amputation) in total.
From equation; $n = \frac{d}{\Pr(event)}$, the probability of amputation can be taken as

$$\Pr(event) = 1-\tfrac{1}{6}\left\{\bar{S}(f)+4\bar{S}(0.5a+f)+\bar{S}(a+f)\right\}$$

Where $\bar{S}(t)$ = Average amputation-free survival of diabetes patients with diabetic foot ulcer have ABI<0.9 (experimental group) and patients with diabetic foot ulcer have ABI >=0.9 (control group) at time *t*

$$\bar{S}(t) = \frac{S_N(t)+S_S(t)}{2}$$

F = Follow – up time, A = Accrual time

The patients are to be recruited to the study over an 24-months accrual time and that there is to be a subsequent follow-up time of 48 months. From equation,

$\Pr(event) = 1-\tfrac{1}{6}\left\{\bar{S}(f)+4\bar{S}(0.5a+f)+\bar{S}(a+f)\right\}$, the probability of amputation in the 72 months of the study will then be given by

$$\Pr(event) = 1-\tfrac{1}{6}\left\{\bar{S}(48)+4\bar{S}(60)+\bar{S}(72)\right\}$$

In particular, the amputation-free survival rates for diabetes patients with diabetic foot ulcers have ABI >=0.9 at time 48, 60 and 72 months are 0.43, 0.25 and 0.25, respectively. For diabetes patients with diabetic foot ulcers have ABI<0.9 at time 48, 60 and 72 months are 0.05. Therefore,

$$\bar{S}(48) = \frac{S_N(48)+S_S(48)}{2} = \frac{0.05+0.43}{2} = 0.24$$

$$\bar{S}(60) = \frac{S_N(60)+S_S(60)}{2} = \frac{0.05+0.25}{2} = 0.15$$

$$\bar{S}(72) = \frac{S_N(72)+S_S(72)}{2} = \frac{0.05+0.25}{2} = 0.15$$

and thus the probability of event (amputation) is

$$\Pr(event) = 1-\tfrac{1}{6}\left\{0.24+(4\times0.15)+0.15\right\} = 0.83$$

From equation; $n = \frac{d}{\Pr(event)}$, the required number of patients is

$$n = \frac{138}{0.83} = 166.2$$

and thus a total of 334 patients were included in the study or 167 patients will need to observed in each patients group. Adjust sample size to prevent for dropout from equation; $n_{adj} = \frac{n}{1-R}$ Instead, the formula is $n_{adj} = \frac{334}{1-0.1} = 371.1 \sim 372$ patients.

The collected data for patients with severe foot problems in vascular practice based on inclusion and exclusion criterions at the medical record and medical statistic department, Faculty of Medicine Vajira Hospital, Navamindradhiraj University. The data recorded included of variables following: time to amputation event in months, last status of patients with severe foot problems in vascular practice. The patients were classified into two groups: amputation event and censored data, and twelve of independent variables of patients with severe foot problems in vascular practice consisted of age at initial diagnosis, gender, smoking, infection, Ankle-brachial index, hypertension, dyslipidemia, renal disease, HbA1c, duration of diabetes and group of patients. And the data preparation for variables coding based on the criterion of determine reference group from literature review and research reports.

The data analysis by SPSS program version 22 and STATA program version 12 and statistical analysis for time to event analysis or survival analysis, according to the following: Descriptive statistics were used to describe categorical variables, univariate analysis to examine the relationship between the independent variables and amputation event, the continuous variables were tested by t-test or Mann-Whitney U test and categorical variables were tested by Chi-Square test or Fisher's

exact test. Each independent variable has p-value of 0.10 or less will be included for analysis in the next step but in this study the researcher used to total independent variables for analysis in Log-rank test. Kaplan-Meier method was used to estimate amputation-free survival time, Log-rank test was produced to compare amputation-free survival time between subgroups of each potential risk factors, Cox's Proportional Hazards Model was used to determine potential risk factors of amputation event of CLI and/or Diabetic foot patients, assessing the proportional hazards assumption using graphical approaches by the plot the log-log Kaplan-Meier survival estimates against time (or against the log of time) and the Schoenfeld residual tested to confirm the result obtained from log-log Kaplan-Meier survival estimates. In addition, we tested for Goodness of Fit by plot of the Cox-Snell residuals: Cox-Snell residuals are useful in assessing overall model fit.

Results

Characteristics of the sample

There were 372 patients with severe foot problems in vascular practice in which 170 patients (45.7%) in Diabetic foot group 76 patients (20.4%) in Critical limb ischemia group and 126 patients (33.9%) in Critical limb ischemia and diabetic foot group. The follow-up time ranged from 0.066 to 72.933 months (median 50.466 months). Detected amputation event in 89 cases of 372 patients (23.9%) 30 from 170 patients (17.6%) for diabetic foot 16 from 76 patients (21.1%) for Critical limb ischemia 43 from 126 patients (34.1%) for Critical limb ischemia and diabetic foot.

In patients with severe foot problems in vascular practice, the age at diagnosis ranged from 17 to 98 years old (62.46±13.86). Of all patients with severe foot problems in vascular practice, 49.5% were male and 50.5% were female. 58.1% of patients were smoker and 41.9% were non-smoker. 74.7% of patients had infection and 25.3% had no infection. The Ankle Brachial Index ranged from 0.10 to 1.70 [0.9(0.58-1.10)]. The HbA1c ranged from 4 to 16.20% [7(6-8)]. 77.2% of patients had hypertension and 22.8% had no hypertension. 44.4% of patients had dyslipidemia and 55.6% had no dyslipidemia. 27.2% of patients had renal disease and 72.8% had no renal disease. The duration of diabetes ranged from 1 to 40 years [11(9-15)]. (Table 1).

Univariate analysis was used to describe the difference of independent variables in two outcomes of patients (amputation event and censored), there were 7 variables that showed statistically significant association with amputation event. These variables were smoking, infection, renal disease, Ankle Brachial Index, HbA1c, duration of diabetes and group of patients and we conclude that the others were not different between two groups of last status (Table 1).

Description of amputation event rate and amputation event-free survival functions by Kaplan-Meier

In this study, at the end of observation, the number of patients that suffered from cause of amputation event did not reach 50%, so we could not identify median time of amputation event-free survival. But at 10th percentiles of amputation event-free survival of patients with severe foot problems in vascular practice was 1.66 months (Figure 1).

Model fitting by Cox's proportional hazard model

Consideration of the relationship among prognostic factors and amputation event of patients with severe foot problems in vascular practice was analyzed by Cox's proportional hazard model. In the methods of the model selection, the researcher used to forward selection methods. The result of the final model of the patients with severe foot problems in vascular practice group showed in Table 2; there were 3 statistically significant variables affecting on amputation event rate and time. They were smoking, HbA1c and renal disease (p-value<0.05). AIC and BIC were 365.830 and 374.339, respectively. The Cox's proportional hazard model for the patients with severe foot problems in vascular practice group in the final step was the following:

$$\mathrm{Ln}\frac{h_{it}}{h_{0t}} = 0.841\mathrm{smoking} + 1.423\mathrm{HbA1c} \geq 7.5\% + 0.727\mathrm{Renal\ disease}$$

Table 1 :

Descriptive characterizations and univariable analysis of predictors of amputation event in patients with severe foot problems in vascular practice

Independent variables	Patients with severe foot problems in vascular practice	Amputation event (n=89)	Censored (n=283)	p-value
Age at diagnosis (years) (n=372)	62.42±13.86[a]	62.37±14.51[a]	62.43±13.68[a]	0.972[c]
- < 65	204 (54.8%)			
- ≥ 65	168 (45.2%)			
Gender (n=372)				0.996[d]
- Male	184 (49.5%)	44 (49.4%)	140 (49.5%)	
- Female	188 (50.0%)	45 (50.6%)	143 (50.5%)	
Smoking (n=372)				<0.0001[d*]
- No	156 (41.9%)	20 (22.5%)	136 (48.1%)	
- Yes	216 (58.1%)	69 (77.5%)	147 (51.9%)	
Infection (n=372)				<0.0001[d*]
- No	94 (25.3%)	6 (6.7%)	88 (31.1%)	
- Yes	278 (74.7%)	83 (93.3%)	195 (68.9%)	
Ankle Brachial Index (n=76)	0.90 (0.58-1.10)[b]	0.70 (0.44-0.90)[b]	0.94 (0.70-1.10)[b]	<0.0001[f*]
- ≥ 0.5	161 (79.7%)			
- < 0.5	41 (20.3%)			
HbA1c (%) (n=296)	7 (6-8)[b]	7.8 (7.20-8.65)[b]	6.7 (6.00-7.70)[b]	<0.0001[f*]
- <7.5	182 (61.5%)			
- ≥7.5	114 (38.5%)			
Hypertension (n=372)				0.499[d]
- No	85 (22.8%)	18 (20.2%)	67 (23.7%)	
- Yes	287 (77.2%)	71 (79.8%)	216 (76.3%)	
Dyslipidemia (n=372)				0.537[d]
- No	207 (55.6%)	47 (52.8%)	160 (56.5%)	
- Yes	165 (44.4%)	42 (47.2%)	123 (43.5%)	
Renal disease (n=372)				0.016[d*]
- No	271 (72.8%)	56 (62.9%)	215 (76%)	
- Yes	101 (27.2%)	33 (37.1%)	68 (24%)	
Duration of diabetes (n=296)	11 (9-15)[b]	12 (10-15)[b]	10 (8-15)[b]	0.003[f*]
- No	84 (28.4%)			
- Yes	212 (71.6%)			
Patient groups (n=372)				
- Diabetic foot	170 (45.7%)	30 (33.7%)	140 (49.5%)	0.004[d*]
- Critical limb ischemia	76 (20.4%)	16 (18%)	60 (21.2%)	
- Diabetic foot and Critical limb ischemia	126 (33.9%)	43 (48.3%)	83 (29.3%)	

[a] mean±SD; [b] median(Q1-Q3); [c] t-test; [d] χ^2-test; [e] Fisher's Exact-test; [f] Mann-Whitney test; [*] Significant with p-value ≤0.10

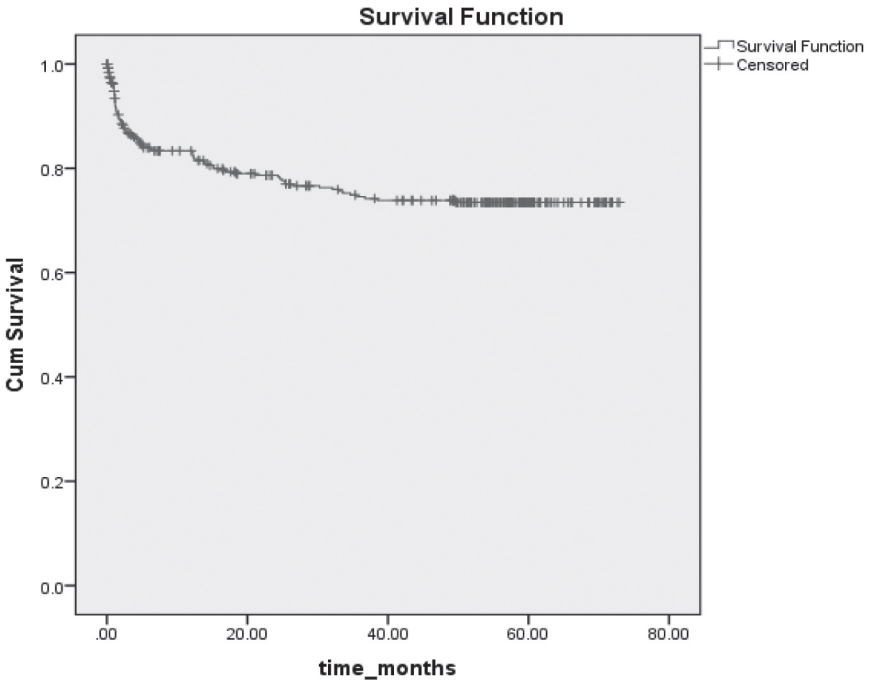

Figure 1 Overall amputation event-free survival functions in patients with severe foot problems in vascular practice

Table 2 :

Cox's proportional hazard model for patients with severe foot problems in vascular practice

Independent variables	95% CI of RR				
	$\hat{\beta}$	RR	Lower	Upper	p-value
Smoking					0.034*
- No	-	1			
- Yes	0.841	2.319	1.066	5.042	
HbA1c (%)					<0.0001*
- <7.5	-	1			
- ≥7.5	1.423	4.150	2.121	8.122	
Renal disease					0.021*
- No	-	1			
- Yes	0.727	2.069	1.116	3.836	

AIC=365.830 BIC=374.339 -2LL=359.830 * = significant with p-value <= 0.05

Assessing the proportion hazards assumption

1. Test of proportional-hazards assumption

The most important assumption of the Cox's proportional hazards model is that the hazard ratio is proportional over time. The test of proportional hazards implemented by plotting the -ln[-ln(survival)] curve. To examine whether the proportional hazards model is appropriate for the patients with severe foot problems in vascular practice with HbA1c, smoking and renal disease independent variables. Two curves of each independent variable were roughly parallel (Figure 2-4). In addition, we tested the Schoenfeld residual (Table 3) to confirm the result obtained from -ln[-

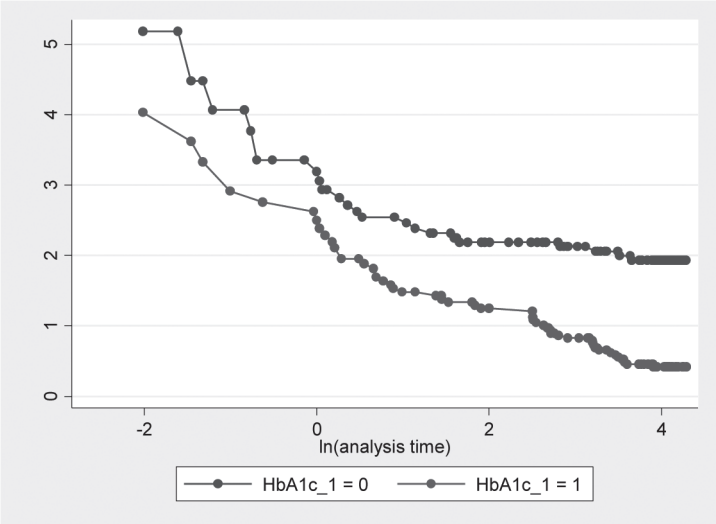

Figure 2: Amputation event-free survival curves for patients with severe foot problems in vascular practice stratified by HbA1c plotted on a -ln-ln scale

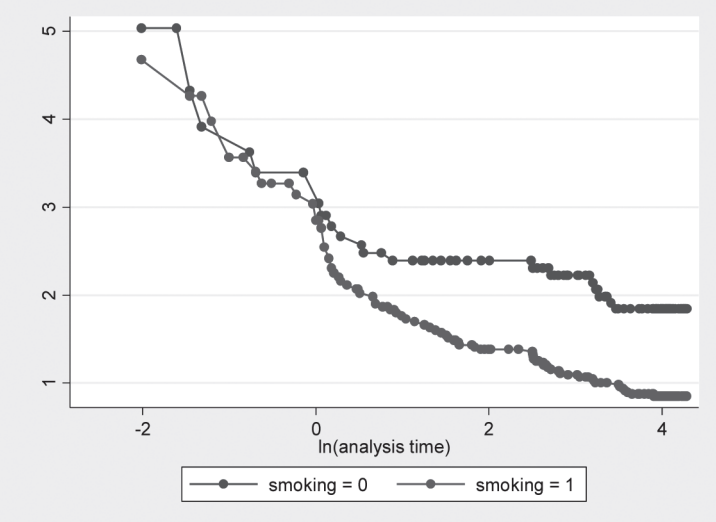

Figure 3: Amputation event-free survival curves for patients with severe foot problems in vascular practice stratified by smoking plotted on a -ln-ln scale

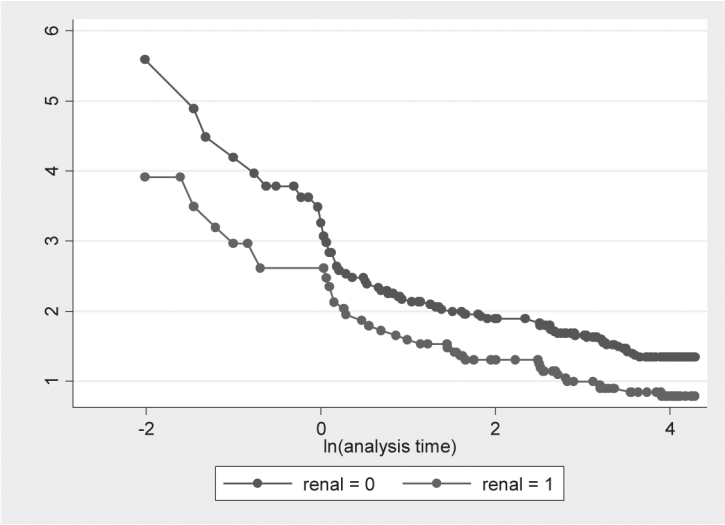

Figure 4: Amputation event-free survival curves for patients with severe foot problems in vascular practice stratified by renal disease plotted on a -ln-ln scale

Table 3 :

Test of proportional-hazards assumption by Schoenfeld residuals for patients with severe foot problems in vascular practice

Independent variables	rho	x^2	df	p-value
1. HbA1c	0.251	4.73	1	0.029
2. Smoking	0.093	0.65	1	0.420
3. Renal disease	-0.081	0.48	1	0.488
Global test		5.83	3	0.120

ln(survival)] curve. The p-value of the testing for departure from proportional hazard assumption was equal to 0.120. There was no evidence that the proportional hazard assumption had been violated.

Test for Goodness of Fit

1. Plot of the Cox-Snell residuals

Cox-Snell residuals are useful in assessing overall model fit. If the Cox model fits the data, these residuals should have a standard censored exponential distribution with hazard ratio equal to 1. Therefore, if the model fits the data, the plot of the cumulative hazard versus Cox-Snell residual should approximate a straight line with slope equal to 1. From Figure 5, they showed that graphs of Cox model for patients with severe foot problems in vascular practice. Cox model of patients, there is a reasonably good fit to the data.

Discussion

For this study, the time to event analysis counted for month from the patients who first date of diagnosed for Critical limb ischemia and/or diabetic foot to the end point of follow-up. At the end of observation, the number of patients that suffered from cause of amputation event cloud not reach 50%, so the researchers choose to present the 10th percentile of time to event. An

amputation event-free survival of was 1.66 months. In the analysis of Cox's proportional hazard model for patients with severe foot problems in vascular practice found that patients who had smoking had higher risk of amputation event (RR=2.319, 95% CI 1.066 to 5.042; p-value =0.034), which is consistent with the research of Klomp et al.[14] that studied 120 patients with CLI and found that current smoking was independent variable associated with amputation. Yesil et al.[15] studied 670 consecutive patients with diabetic foot ulcer and found that smoker was a significant risk associated with amputation (p=0.041). Tseng[16] studied 12,531 patients with diabetic foot and logistic regression analysis showed that smoking was significantly associated with lower-extremity amputation (OR=1.64). For HbA1c, patients who had HbA1c ≥ 7.5 % had higher risk of amputation event (RR=4.150, 95% CI, 2.121 to 8.122; p-value <0.0001), which is similar to Zahra et al's study of 94 patients with diabetic foot ulcer[17], 34 (32%) had amputation and logistic regression analysis by exclusion of all confounders in the model, HbA1c ≥ 8 % was statistically significantly associated with amputation (OR=4.2). The receiver operating characteristics curves were generated to predictive of the levels of HbA1c and showed that a cutoff point of 9.75% for HbA1c demonstrated 75.2% specificity and 81.5% sensitivity for amputation and area under the curve yielded a value of 0.86 (p-value=0.05). Previous studies also showed that poor diabetic control is a risk factor for limb loss in diabetic patients. Miyajima et al.[18] studies 210 patients with diabetic foot and found that HbA1c ≥ 8 % was a risk factor for major amputation (HR=1.20). For renal disease, patients with renal disease are at risk of amputation event (RR=2.069, 95% CI 1.116 to 3.836; p-value =0.021), which is similar to Cheng et al.[19] that studied 665 patients with chronic lower extremity ischemia and multivariate cox regression analysis had been showed that renal disease was independent variable affecting survival time. The cumulative survival for all patients at 1, 3, and 5 years were 86.1, 71.2, and 55.8%, respectively. Markowitz et al.[20] studied patients with diabetic foot ulcer between January 2000 and December 2002 and found that renal disease was prognostic factor for increased amputation (OR=2.11), Ahmed et al.[21] studied 224 patients with CLI and found that ESRD was associated with major amputation (p-value <0.05), Owens et al.[22] studied 456 patients with CLI and found that subjects within the CKD 5 classification were more likely to have a major amputation (p-value = 0.018) compared to all other CKD classes, Shojaiefard et al.[23] studied 146

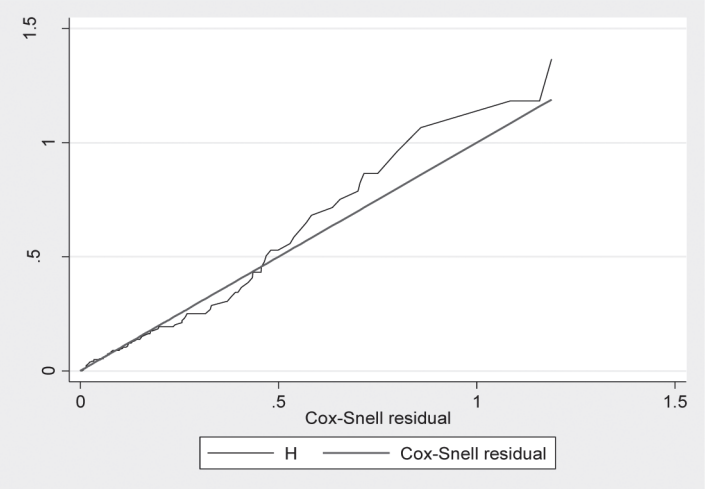

Figure 5: Overall goodness of fit test of Cox model for patients with severe foot problems in vascular practice.

patients with diabetic foot between January 2004 and February 2005 and stepwise logistic regression model revealed that nephropathy was independent predictor for limb amputation (OR=2.64; p-value = 0.03), Biancari et al.[24] studied 1,425 patients with critical limb ischemia and found that CLI with ESRD patients was significantly associated with lower amputation-free survival than patients without renal failure or less severe renal failure (at 3-year, 16.2% vs. 52.9%; p < 0.0001). Lastly, Mohammad et al.[25] studied 162 patients with diabetic foot ulcer and found that the overall amputation rate was 28.4% and nephropathy was a significant risk factor for amputation (RR=1.62).

Conclusion

Fitted the model by Cox proportional hazard, the final model for the patients with severe foot problems in vascular practice, found that there were 3 statistically significant variables affecting on amputation event; conclude that smoking (p-value = 0.034), HbA1c ≥7.5% (p-value <0.0001) and renal disease (p-value = 0.021).

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References

1. Dupont WD. Statistical modeling for biomedical researchers. 2th ed. New York, NY: Cambridge University Press; 2009. p. 287-310.
2. Lee ET. Statistical methods for survival data analysis. 2th ed. Hoboken, NJ: John Wiley & Sons, Inc; 1992. p. 8.
3. Kleinbaum DG, Klein M. Survival analysis: A Self-learning text. 2th ed. New York, NY: Springer Science & Business Media, Inc; 2005. p. 4-62.
4. Korosteleva O. Clinical statistics: Introducing clinical trials, survival analysis, and longitudinal data analysis. Burlington, MA: Jones & Bartlett Publishers; 2009. p. 33-59.
5. Dwyer JH, Feinleib M, Lippert P, Hoffmeister H. Statistical model for longitudinal studies of health. New York, NY: Oxford University press; 1992. p.163-209.
6. Morrell CH, Brant LJ. A Two-stage linear mixed-effects/Cox model for longitudinal data with measurement error and survival. The Biometrics Section of the American Statistical Association 2000; 198-203.
7. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportion-hazards regression model. Annu Rev Public Health. 1999; 20: 57-145.
8. Cox DR. Regression Models and Life-Tables. J R Stat Soc. 1972; 34: 187-220.
9. Allie DE, Hebert CJ, Lirtzman MD, Wyatt CH, Keller VA, Khan MH, et al. Critical limb ischemia: a global epidemic. A critical analysis of current treatment unmasks the clinical and economic costs of CLI. EuroIntervention. 2005; 1: 75-84.
10. Engelhardt M, Boos J, Bruijnen H, Wohlgemuth W, Willy C, Tannheimer M, et al. Critical limb ischaemia: initial treatment and predictors of amputation-free survival. Eur J Vasc Endovasc Surg. 2012; 43: 55-61.
11. Mutirangura P, Ruangsetakit C, Wongwanit C, Sermsathanasawadi N, Chinsakchai K. Atherosclerosis Obliterans of the lower extremities in Thai patients. J Med Assoc Thai. 2006; 89: 1612-20.
12. Won SH, Chung CY, Park MS, Lee TS, Sung KH, Lee SY, et al. Risk factors associated with amputation-free survival in patient with diabetic foot ulcers. Yonsei Med J. 2014; 55: 1373-8.
13. Collett D. Modeling survival data in medical research. 2th ed. London: Chapman & Hall/CRC; 1995. p. 253-67.

14. Klomp HM, Steyerberg EW, Wittens CHA, Van Urk H, Habbema JD. A prognostic model for amputation in critical lower limb ischemia. Vasc Med. 2009; 14: 109-15.
15. Yesil S, Akinci B, Yener S. Predictors of amputation in diabetics with foot ulcer: single center experience in a large Turkish cohort. Hormones. 2009; 8: 286-95.
16. Tseng CH. Prevalence and risk factors of diabetic foot problems in Taiwan: A cross-sectional survey of non-type 1 diabetic patients from a nationally representative sample. Diabetes Care. 2003; 26: 3551.
17. Yekta Z, Pourali R, Mezhadrahim R, Ravanyar L, Ghasemi-rad M. Clinical and behavioral factors associated with management outcome in hospitalized patients with diabetic foot ulcer. Diabetes Metab Syndr Obes. 2011; 4: 371-5.
18. Miyajima S, Shirai A, Yamamoto S, Okada N, Matsushita T. Risk factors for major limb amputations in diabetic foot gangrene patients. Diabetes Res Clin Pract. 2006; 71: 272-9.
19. Cheng SW, Ting AC, Lau H, Wong J. Survival in patients with chronic lower extremity ischemia: A risk factor analysis. Ann Vasc Surg. 2000;14(2):158-65.
20. Markowitz JS, Gutterman EM, Magee G, Margolis DJ. Risk of amputation in patients with diabetic foot ulcers: a claims-based study. Wound Repair Regen. 2006; 14: 11-7.
21. Abou-Zamzam AM Jr, Gomez NR, Molkara A, Banta JE, Teruya TH, Killeen JD, et al. prospective analysis of critical limb ischemia: Factors leading to major primary amputation versus revascularization. Ann Vasc Surg. 2007; 21: 458-63.
22. Owens CD, Ho KJ, Kim S, Schanzer A, Lin J, Matros E, et al. Refinement of survival prediction in patients undergoing lower extremity bypass surgery: stratification by chronic kidney disease classification. J Vasc Surg 2007; 45: 944-52.
23. Shojaiefard A, Khorgami Z, Larijani B. Independent risk factors for amputation in diabetic foot. Int J Diabetes Dev Ctries. 2008; 28: 32-7.
24. Biancari F, Arvela E, Korhonen M, Soderstrom M, Halmesmaki K, Alback A, et al. End-stage renal disease and critical limb ischemia: a deadly combination?. Scand J Surg. 2012; 101: 138-43.
25. Zubair M, Malik A, Ahmad J. Incidence, risk factors for amputation among patients with diabetic foot ulcer in a north Indian tertiary care hospital. Foot (Edinb). 2012; 22(1): 24-30.