

The Application of Parametric Models for the Evaluation of the Risk for Cardiac Death in Patients with Stable Angina Pectoris

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Introduction

Stable angina pectoris (SAP) is a chronic ischemic syndrome of an ischemic heart disease, a result of stenosis of the coronary arteries, which causes myocardial ischemia and cardiac pain. Annual morbidity with SAP is estimated to be 213/100,000 population over 30 years of age. According to the data presented by various authors, the annual mortality among patients with SAP is 2-4% [1]; nearly one-half of the patients (42%) experience myocardial infarction [1, 2]. The clinical course of SAP is conditioned by a number of various risk factors and treatment methods, and thus is a process that is difficult to prognosticate.

In cases of SAP, the determination of short-term and long-term prognosis including the evaluation of the risk of cardiac events – myocardial infarction (MI) and sudden cardiovascular death – as well as the estimation of the survival allows for the planning of individual treatment in high risk groups.

The evaluation of the short-term and the long-term prognosis of the patients' condition involves the determination of the following: (1) informative clinical variables for cardiovascular events (MI or cardiac death); (2) complexes of informative variables for an adverse cardiac event, selected during multivariate analysis; (3) quantitative evaluation of the risk; (4) the frequency of cardiac incidents, and survival in different risk groups [3, 4, 5].

According to the data of long-term follow-up of the patients, regression models of the survival function are designed and analyzed for the search for informative variables, and the prognostication cause of the disease. The most frequently applied method is Cox's proportional hazard model with constant regression coefficients. The assumption of the model is the following: the hazard function $h(t, \mathbf{x})$ in a patient with the clinical variable vector \mathbf{x} determined at the beginning of the study equals to $\exp(\mathbf{b}\mathbf{x})h_0(t)$, where $h_0(t)$ is the baseline hazard function. Using the $\exp(\mathbf{b}\mathbf{x})$ expression, the risk caused by the variable complex \mathbf{x} is evaluated, and the risk groups are

determined (the risk score model). Another group of survival models is parametric survival (and, at the same time – risk) function models. These models are used to evaluate the probability of unfavorable cardiovascular events during any given period, which is not possible using Cox's model. In addition to that, the parametric model is more suitable in cases when the relationship between hazard functions $h(t, \mathbf{x}_0)$ and $h(t, \mathbf{x}_1)$ is dependent on t .

A number of studies have been performed worldwide on the analysis of the survival of various groups of patients [1, 6]. On the basis of the findings of patients with stable angina pectoris during 1988 – 1997 follow-up analysis of the survival of these patients was performed [3]. The survival of patients was found to have been influenced by their age, number of narrowed of coronary arteries, perform coronary artery bypass surgery, angina pectoris and NYHA class, arterial hypertension, MI in the anamnesis, sinus tachycardia findings of the echocardiographic examination and exercise testing and data of biochemical blood analysis. The designed regression parametric models for the prognostication of myocardial infarction and coronary death, created on the basis of Veibul's and Bain's distributions were presented.

The aim of this study was, on the basis of the eliminal, demographic, electrocardiographic, angiographic data: (1) to create a parametric model of the survival function for patients with stable angina pectoris, including the employment of the information of the interventional treatment applied during the period of the observation; (2) and, on the basis of this model, to develop the algorithm for the stratification of patients into the low, medium, and high risk groups.

Contingent and methods

The development of the parametric models of survival was performed using the data of patient followed-up during 1988 – 2002 years. The contingent consisted of 781 patients with SAP (452 – without MI, and 329 – with previous MI). The duration of their follow-up was not less than 1 year. The patients' mean age was 52.6 ± 7.3 years, and the majority of patients (92.3%) were males (Table 1).

Cardiac death occurred in 112 patients, and 37 patients died from other causes. The data of the patients who died from other causes were not included into the further evaluation of survival. 744 patients were observed for 1 to 16 years (mean duration – 7.0 ± 4.8 years); mean duration of the follow-up of the survived patients was 9.8 ± 3.0 years, and in those who experienced cardiovascular death – 4.8 ± 3.7 years. 99 patients underwent coronary surgery during the follow-up period.

Methods. The survival function model chosen for the analysis of survival was the widely used two-parametric Weibull's distribution: $S(t) = \exp\{-(\lambda t)^\gamma\}$, where $S(t)$ – survival function. The parameters λ_i and γ_i of the survival function $S_i(t) = \exp\{-(\lambda_i t)^{\gamma_i}\}$ of every i^{th} patient are the functions of the patient's variables (covariates) vector \mathbf{x}_i : $\lambda_i = \exp\{\mathbf{a}\mathbf{x}_i\}$, $\gamma_i = \exp\{\mathbf{b}\mathbf{x}_i\}$, where \mathbf{a} and \mathbf{b} are the vectors of unknown coefficients. Unknown coefficients were evaluated with the help of the maximum likelihood method, using the MatLab software package. The significance of the patients' covariates in the model was verified using the likelihood ratio criterion. The patient's covariate was considered informative if its inclusion into the survival function model reliably decreased the likelihood function. The multivariate model included only the covariates that significant ($p < 0.05$) decreased the likelihood function. For the comparison of the models, we used Akaike's information criterion [7] $AIC = -2 \cdot \ln L + 2k$, where L – the value of the likelihood function, and k – the number of parameters in the model.

Table 1. Clinical characteristics of patients with stable angina pectoris (n=781)

Variables	Number	%	
Mean age	52.6±7.3		
Men	721	92.3	
Arterial hypertension	292	37.5	
Diabetes mellitus	20	2.6	
Dyslipidemia	555	71.1	
Metabolic syndrome (n=460)	180	39.1	
Experienced myocardial infarction	329	42.1	
Angina pectoris > II K	499	63.9	
Stenosis of coronary arteries ≥ 70%	One Two-three	241 253	30,9 32,4
Pathological VEM (n=451)	264	58.5	
LV EF < 40% (n=485)	43	8.8	
Surgery of the junction of coronary arteries	206	26.4	

Two $S(t)$ models were created. The 1st model (I) was developed using the data from the patient's anamnesis, clinical examination, ECG, and angiography obtained only during the initial examination (the regression model with constant covariates), and the 2nd regression model (II) included the time-dependent covariate x_i :

$$x_i = x_i(t) = \begin{cases} 0, & 0 \leq t < t_0, \\ 1, & t_0 \leq t \leq t_1, \end{cases} \quad (1)$$

where $x_i(t)$ – information about the interventional treatment of coronary artery performed during the follow-up, t_0 – time between the beginning of the follow-up observation and the operation.

The composition of the risk groups was based on the estimate of the survival function $S(t)$. The patient at the moment t is attributed to the low risk group if his/her survival function estimate is $\hat{S}_i(t) > c_0$, and to the high risk group, if the survival function estimate is $\hat{S}_i(t) < c_1$, where c_0 and c_1 are constants between 0 and 1.

Results

At first, we evaluated the parameters of Weibull's distribution, considering them to be constant for all patients. The results showed that the values of the parameters λ and γ were, respectively, 0.0113 and 0.7527, the logarithm of likelihood function $\ln L_0$ was 594.5, and $AIC = 1193$. After that, we analyzed the survival function model: $\exp\{-(\lambda t)^\gamma\}$ with $\lambda = \exp\{a_0 + a_1x\}$, $\gamma = \exp\{b_0 + b_1x\}$, where x – the values of the covariates of the anamnesis, clinical examination, ECG, or angiography. We found that the likelihood function was significant decreased by the inclusion into the model of the following: the presence of the variables (age, arterial hypertension (AH), diabetes mellitus, Q-wave MI, angina pectoris class, and sinus tachycardia) recorded at the beginning of the follow-up, as well as by the NYHA class, T-negative wave, a number stenosed coronary arteries, and interventional treatment of coronary arteries.

Model I. Creating the optimal multidimensional regression model, we used the variables that significant decreased the likelihood function. As a result, we found that the model with the following parameters:

$$\begin{aligned} \lambda &= \exp\{-5,787 + 0,758 \cdot \text{inag} + 0,623 \cdot \text{VA} + 1,01 \cdot \text{Tneg} + \\ &\quad 1,49 \cdot \text{CD} + 0,41 \cdot \text{AH} + 0,6 \cdot \text{Tach}\}, \\ \gamma &= \exp\{-0,098 + 0,228 \cdot \text{I1} - 0,133 \cdot \text{KA}\} \end{aligned} \quad (2)$$

had the lowest value of Akaike's information criterion – $AIC = 1124$. The abbreviations λ and γ in the expression are the following: $\text{inag} = 1$, if the age is >60 years, (0 – elsewhere), VA – the number of coronary arteries stenosed over 70%, $\text{CD} = 1$, if diabetes mellitus is present, Tneg (T-negative wave) = 1, if a negative T wave is present, $\text{AH} = 1$, if arterial hypertension is present, $\text{Tach} = 1$, if sinus tachycardia is detected, KA = the angina pectoris class minus 1, and $\text{I1} = 1$, if interventional treatment of coronary arteries was applied prior to the inclusion into the study. Using Model I, the number of expected deaths reliably corresponded to the observed number of deaths – the p value of the χ^2 criterion was lower than 0.001 (Table 2).

The composition of risk groups using Model I. Since $S(t)$ belongs to the family of two-parametric Weibull's distributions, inequalities $\hat{S}_i(t) > c_0$ and $\hat{S}_i(t) < c_1$ are equivalent to inequalities $\hat{\gamma}_i \ln(\hat{\lambda}_i) < c_1(t)$, $\hat{\gamma}_i \ln(\hat{\lambda}_i) > c_2(t)$, or $(\mathbf{a}\mathbf{x}) \cdot \exp(\mathbf{b}\mathbf{x}) < c_1(t)$ and $(\mathbf{a}\mathbf{x}) \cdot \exp(\mathbf{b}\mathbf{x}) > c_2(t)$, where $\hat{\lambda}_i$, $\hat{\gamma}_i$, \mathbf{a} and \mathbf{b} are estimate of respective parameters. For this reason, the determination of risk groups was performed after the introduction of two total score indices – one proportional to the value $\mathbf{a}\mathbf{x}$, and the other – to $\exp(\mathbf{b}\mathbf{x})$. These indices were used to evaluate the risk of death for various t , where t is the time since the beginning of the follow-up.

Using the values of the λ and γ coefficients of Model I, the following total score indices were created:

$$BI1 = 4*inag + 3*VA + 5*Tneg + 8*CD + 2*AH + 3*Tach; BI2 = -1*I1 + KA. \quad (3)$$

BI1, like Veibul's distribution parameter λ , characterizes the scale of the hazard function, while BI2 (like parameter γ) defines the tendency of the change in the hazard function. Using classification tree CARDS method, risk groups for death within the follow-up period of 1, 5 and 10 years were determined. The rule for the attribution to the risk groups is presented in Table 2.

Model II (the model with time-varying covariate).

In model I, the variable I1 (equal to 1 when the patient underwent interventional treatment of coronary arteries prior to the inclusion into the study, and equal to 0 when the patient did not undergo such treatment) was established at the beginning of the follow-up, and remained constant during the whole period of the follow-up. In model II, it is assumed that

$$I1 = I1(t) = \begin{cases} 0, & 0 \leq t < t_0, \\ 1, & t_0 \leq t \leq t_1, \end{cases} \quad (4)$$

where t_0 – the time of the interventional treatment of coronary arteries since the beginning of the follow-up, and t_1 – the time of the patient follow-up. If the interventional treatment was applied prior to the inclusion of the patient into the study, it is assumed that $t_0 = 0$, and $I1(t) \equiv 1$. If the patient did not undergo an interventional treatment during the follow-up period, then $t_0 = t_1$, and $I1(t) \equiv 0$, if $t \leq t_1$. Using this variable and all the aforementioned informative covariates, we created a multivariate regression model with the lowest AIC value. The parameters of this model are equal to:

$$\lambda_1 = \exp\{-5,67 + 0,703*inag + 0,613*VA + 1,03*Tneg + 1,454*CD + 0,377*AH\}, \quad (5)$$

$$\gamma = \exp\{-0,077 + 0,265*I(t - t_0) + -0,13*KA - 0,32*Tach\}, \quad (6)$$

AIC = 1121,26,

where $I(t)$ – indicatory function. The number of death prognosticated with the help of this model is presented in Table 2.

The composition of risk groups using Model II.

In Model II, the value of the survival function equals to:

$$S(t) = \begin{cases} S_1(t), & t < t_0, \\ [S_1(t_0)/S_2(t_0)]S_2(t), & t \geq t_0, \end{cases} \quad (7)$$

where $S_1(t)$ – Veibul's survival function with parameters λ_1 and $\gamma_1 = \exp\{-0,077 - 0,13*KA - 0,32*Tach\}$, and $S_2(t)$ – Veibul's survival function with parameters λ_1 and $\gamma_2 = \exp\{0,182 - 0,13*KA - 0,32*Tach\}$ (γ value when $t > t_0$). The value $[S_1(t_0)/S_2(t_0)]$ for patients operated during the follow-up period varied from 0.91 to 1, and therefore the influence of this value on the margins of the risk groups was not high. For this reason, the risk groups of death within the periods of 1, 5 and 10 years were created analogically, using the indices of 2 scores:

$BIII = 7*inag + 6*VA + 10*Tneg + 15*CD + 4*AH$, and the index, dependent on t : $BII2(t) = -2*I(t - t_0) + KA + 2*Tach$. Using classification tree CARDS method and the BII1 and BII2(t), we created the risk groups for death within the periods of 1, 5 and 10 years. The rule of the attribution to the risk groups is presented in Table 3.

Table 4 presents the number and the percentage of deaths within the periods of 1, 5 and 10 years in different risk groups, created according to Models I and II.

Discussion and conclusions

On the basis of Veibul's survival model (I-II), two risk score indices were developed, allowing for the stratification of the patients into 3 risk groups.

The information about the application of interventional treatment of coronary arteries during the late period (the use time-varying covariate) improved the prognostic capabilities of the model. For instance, in the creation of the risk groups for death within the period of 5 years using Model II, the uncertainty coefficient was greater (0.1751) than in case of Model I (0.1386).

Table 2. The number of actual and prognosticated deaths

t interval	Actual number of deaths	Number of deaths prognosticated using Model I	Number of deaths prognosticated using Model II	Number of patients observed during the interval
(0; 0.5]	13	14.4	14.3	744
(0.5; 1.5]	21	18.3	17.5	729
(1.5; 2.5]	13	14.5	13.9	695
(2.5; 3.5]	12	12.4	12	665
(3.5; 4.5]	5	10.9	10.6	645
(4.5; 5.5]	7	10	9.8	632
(5.5; 6.5]	13	9	8.8	598
(6.5; 7.5]	9	7.8	7.7	547
(7.5; 8.5]	7	6.8	6.8	499
(8.5; 9.5]	5	5.8	5.8	448
(9.5; 10.5]	3	4.4	4.4	354
(10.5; 11.5]	5	3.4	3.4	279
(11.5; 12.5]	4	2.7	2.7	218
(12.5; 15.5]	5	6.2	6.3	169
Total	122	126.6	124	
χ^2 . degrees of freedom		6.9; 10; p<0.001	6.9; 10; p<0.001	

Table 3. The rule of the creation of risk groups

Risk groups	Within 1 year	Within 5 years	Within 10 years
Model I			
Low	$BI1 \leq 5$	$BI1 \leq 5$	$BI1 \leq 5$
Medium	$BI2 = -1, bI1 \geq 6,$ $BI2 = 0, bI1 \in [6; 14],$ $BI2 = 1; 2, bI1 \in [6; 12]$ $BaI2 = 3; bI1 \in [6; 8]$	$BI2 = -1, bI1 \geq 6,$ $BI2 = 0; 1 \in bI1 \in [6; 14],$ $BI2 = 2, bI1 \in [6; 12],$	$BI2 < 2, 1 bI1 \in [6; 14],$ $BI2 \geq 2, bI1 \in [6; 12]$
High	$BI2 = 0, bI1 \geq 15,$ $BI2 = 1; 2, bI1 \geq 13,$ $BI2 = 3; bI1 \geq 9$	$BI2 = 0, 1 bI1 \geq 15,$ $BI2 = 2, bI1 \geq 13,$ $BI2 = 3; bI1 \geq 6$	$BI2 < 2, 1 bI1 \geq 15,$ $BI2 \geq 2, bI1 \geq 13$
Model II			
Low	$BII1 \leq 11$	$BII1 \leq 11, baI2 < 3$	$BII1 \leq 11$
Medium	$BII2 = -2, bIII \geq 12$ $BII2 = -1; 0, bIII \in [12; 32],$ $BII2 = 1; 2, bIII \in [12; 24]$	$BII2 = -2, bIII \geq 12$ $BII2 = -1; 0, bIII \in [12; 28],$ $BII2 = 1; 2, bIII \in [12; 24]$ $BII2 = 3, bIII \leq 9$	$BII2 \leq 0, bIII \in [12; 28],$ $BII2 = -1; 0, bIII \in [12; 28],$ $BII2 = 1 - 3, bIII \in [12; 24]$ $BII2 > 3, bIII \leq 11$
High	$BII2 = -1; 0, bIII \geq 33,$ $BII2 = 1; 2, bIII \geq 25,$ $BII2 \geq 3.$	$BII2 = -1; 0, bIII \geq 29$ $BII2 = 1; 2, bIII \geq 25$ $BII2 = 3, bIII \geq 9$ $BII2 > 3$	$BII2 \leq 0, bIII \geq 29$ $BII2 = 1 - 3, bIII \geq 25$ $BII2 = 3, bIII \geq 9$ $BII2 > 3, bIII \geq 12$

Table 4. The number of deaths (%) in different risk groups, and the uncertainty coefficient UC(Y)

Risk groups	Within 1 year		Within 5 years		Within 10 years	
	N	Deaths, %	N	Deaths, %	N	Deaths, %
Model I						
Low	349	1.15	342	2.92	342	5.56
Medium	334	5.39	332	11.14	345	18.55
High	61	16.39	55	41.82	42	59.52
UC(Y)	0.0973		0.1386		0.1262	
Model II						
Low	364	1.10	338	2.66	349	5.73
Medium	325	5.54	319	9.4	330	17.27
High	55	18.18	72	43.06	50	62.00
UC(Y)	0,1084		0.1751		0.1443	

The parametric regression models allow for the evaluation of the change in the risk following the interventional treatment: Model I – when the operation was performed prior to the inclusion of the patient into the study, and Model II – when the operative treatment was applied during the follow-up period. The estimate of hazard function $\lambda\gamma t^{\gamma-1}$ in Weibull's model, where $\lambda = \lambda(\mathbf{x})$, $\gamma = \gamma(\mathbf{x})$, allows possibility analysis of the hazard function with respect to the patient's covariates \mathbf{x} . The parameter γ characterizes the tendency of the increase ($\gamma > 1$) or the decrease ($\gamma < 1$) in the hazard function in dependence of the changes in t . Since in case of angina pectoris Class I, interventional treatment is practically not applied, in Model I we have $\gamma < 1$. The application of the interventional treatment prior to the inclusion into the study increases the γ value, and thus the hazard function in operated patients during the early period is lower than that in the non-operated patients. With time, the hazard function in the operated patients decreases more slowly, compared to that in the non-operated patients. At a certain point of time, depending on the risk group of the patients, the hazard in the operated and the non-operated patients becomes equal; after this point, the risk of operated patients becomes higher compared to the non-operated ones.

The analysis of the hazard function value with respect to Model I shows that in patients with one narrowed coronary artery and without other risk factors,

interventional treatment prior to the inclusion into the study decreases the risk of cardiovascular death in the following way: after half a year – by 3.8 times, after 1 year – by, 3.1 times, and after 10 years – by 1.56 times. In patients with 3 narrowed coronary arteries ($VA=3$) and without other risk factors, interventional treatment decreases the risk of death after 0.5, 1, and 10 years by 2.7; 2.2, and 1.1 times respectively. In patients with $VA=3$, diabetes mellitus, and negative T wave, interventional treatment decreases the risk of death after 0.5 year by 1.3 times, after 1 year – by 1.06 times, whereas it increases the risk of death after 5 years by 1.4 times, and after 10 years – by 1.65 times.

On the basis on Model II, we can evaluate the changes in the patient's prognosis after the application of the diabetes mellitus CD, and negative T wave, the risk of death after the interventional treatment performed during the t period differed from that in patients who did not undergo interventional treatment. For instance, when $t=0.5$ year, the risk of death was lower by 1.2 times, and when $t=1$ year – by 1.1 times. When $t=2$ years, the risk of death in operated and non-operated patients became equal, and during the later periods even increased ($t=5$ years – by 1.3 times, and $t=10$ years – by 1.5 times). Thus, parametric models allow for judging about the time and the usefulness impact of interventional treatment in different patient groups depending on the degree of the risk.

The regression models of prognostication that we recommend help to stratify patients with chronic ischemic heart disease into the groups of risk for cardiovascular death, and to guide recommendations for best pharmaceutical and interventional treatment.

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Pateikta spaudai 2005 05 08

J. Vencloviene, M. R. Babarskienė, D. Lukšienė, B. Šlapikienė, I. Milvidaitė. Parametrinio modelio taikymas ligonių, sergančių stabilią krūtinės angina, rizikos kardialinei mirčiai vertinimui // *Electronics and Electrical Engineering. – Kaunas: Technologija, 2005. – Nr. 4(60). – P. 63–67.*

Pateikiami ligonių, sergančių stabilią krūtinės angina, išgyvenamumo funkcijos parametriniai regresiniai modeliai. Naudotas Veibulo skirstinys su parametrais, priklausančiais nuo ligonio rizikos veiksnių, T neigiamo dantelio buvimo EKG, bei intervencinio gydymo taikymo. Sudaryti du išgyvenamumo funkcijos modeliai: I – naudojant ligonio rodiklius, nustatytus stebėjimo pradžioje (regresinis modelis su pastoviomis kovariatėmis) ir II – naudojantis ir informaciją apie stebėjimo eigoje atliktą intervencinį gydymą (regresinis modelis su kintamomis kovariatėmis). Remiantis Veibulo parametru įvertius sudarytas algoritmas, leidžiantis stratifikuoti ligonius į mažos, vidutinės ir didelės rizikos grupes. Bibl. 8 (anglų kalba; santraukos lietuvių, anglų ir rusų k.).

J. Vencloviene, M. R. Babarskienė, D. Lukšienė, B. Šlapikienė, I. Milvidaitė. The Application of Parametric Models for the Evaluation of the Risk for Cardiac Death in Patients with Stable Angina Pectoris // *Electronic and Electrical Engineering. – Kaunas: Technologija, 2005. – No. 4(60). – P. 63–67.*

In this paper are presented parametric regression models of the survival function for patients with stable angina pectoris, and, on the basis of this model was developed the algorithm for the stratification of patients into the low, medium, and high risk groups. The survival function model chosen for the analysis of survival was Weibul's distribution with parameters, dependent on eliminal, demographic, electrocardiographic, angiographic data. Two survival models were created: I model - was developed using the data from the patient's obtained only during the initial examination (the regression model with constant covariates), and II model – included information about interventional treatment, during follow-up (model with the time-dependent covariate). Bib. 8 (in English; summaries in Lithuanian, English and Russian).

Й. Венцловиене, М. Р. Бабарскиене, Д. Лукшиене, Б. Шлапикене, И. Милвидайте. Использование параметрического модели выживаемости для оценки риска кардиальной смерти больных стабильной стенокардией // *Электроника и электротехника. – Каунас: Технология, 2005. № 4(60). – P. 63–67.*

Представлены регрессионные модели функции выживаемости для больных стабильной стенокардией. Использовалась распределение Вейбула с параметрами, зависящими от факторов риска, отрицательного зубца Т и проведенной реваскуляризации сердца. Составлены два модели функции выживаемости I – использующий показатели, полученные в начале наблюдения (регрессионная модель с постоянными ковариантами) и II – использующий информацию о реваскуляризации миокарда в течении наблюдения (регрессионная модель с ковариантами меняющимися во времени). На основе полученных моделей составлен алгоритм, позволяющий распределить больных на группы низкого, среднего и высокого риска смерти. Библ. 8 (на английском языке; резюме на литовском, английском и русском яз.).