



SURVIVAL ANALYSIS OF CORONARY ARTERY DISEASE

Gohar Ayub¹, Dr. Qamruz Zaman², Saba Saeed³, Muhammad Atif⁴, Muhammad Farooq⁵

¹Department of Mathematics & Statistics, University of Swat

²Department of Statistics, University of Peshawar

³PhD Scholar, Department of Statistics, University of Peshawar

⁴Department of Statistics, University of Peshawar

⁵Department of Statistics, University of Peshawar

***Corresponding Author:** Gohar Ayub

^{*}Department of Mathematics & Statistics, University of Swat

ABSTRACT

Objective: This research study concerns with the survival analysis of Coronary Artery Disease (CAD). Also the study compares the survival function both empirically and graphically gender wise and the other significant factors.

Material and Methods: For this study a sample of 215 patients selected from the Peshawar region, visited the Post Graduate Medical Institute, Lady Reading Hospital (LRH), Peshawar. The patient's record collected for the purpose of discovering significant factors that causes Coronary Artery Disease. To analyze the survival data, cox regression and the KM curve is used.

Results: Most of the male patients with a very low proportion of female endowment. Amongst these patients almost 17 % experienced an event during the study period of one year. Cox regression model reveals that hypercholesterolemia, Left Main Stem Disease (LMSD), Total Occlusion and joint effect of Diabetes Mellitus (DM) and smoking are significant factors. The study compare the survival time based on gender, Hypertension, Hypercholesterolemia, Smoking and Diabetes Mellitus of the selected patients using Kaplan Maier (KM) curve.

Conclusion: The impact of gender on the risk factors is investigated and found that the survival time of male is associated with their cholesterol level, number of vessels blocked, LMSD and interaction effect of hypertension and smoking. Male patients have very high odds of event occurrence in hypercholesterolemia, hypertension and smoking. On the other hand, females are more at risk if they are diabetic, hypertensive or if they are aged.

Key words: CAD, Cox Regression, Survival time, KM-Curve

INTRODUCTION

Knowledge of statistics is necessary in medicine for empirical verification of any theoretical evidence.

Medical researches has become deeply involved using the techniques of statistical inference. In

shorts, statistics plays a significant role in medical research and survival analysis is considered to be widely used set of statistical methods. Survival analysis is the collection of statistical methods that are used to analyze data regarding the time to occurrence of an event such as death, recovery etc. Survival time means, the time to follow-up of an individual until an event occurs. Events such as failure, death, or some other response of interest. Alternatively the survival age can be referred as the time until an event occurs (Kleinbaum, 2004). The main objective of survival analysis is to identify the effects of key factors that relate to the course of disease. This can only be achieved by relating the survival time to a set of covariates. Survival analysis can be performed using three different approaches i.e. parametric, semi-parametric and non-parametric approaches.

Coronary Artery Disease (CAD) is the narrowing of the arteries supplying blood to the heart muscle due to atherosclerosis. This process causes many symptoms in the individual like chest pain (Angina pectoris), shortness of breath, irregular heart rhythm, myocardial infarction and even sudden death. Coronary Artery Disease is classified according to the number of vessels involved, from among the main coronary arteries (LAD, CIRC or RCA), i.e. single vessel disease, two vessel disease or triple vessel disease. Disease in the left main stem is classified separately as left main stem disease. This study is an attempt to recognize the risk factors that are associated to the Coronary Artery disease and to quantify the degree of the problem of the disease in Peshawar by using the Kaplan Meier (Non-parametric) and Cox Regression (Semi-parametric) techniques of survival analysis.

LITERATURE REVIEW

Wilson et al. (1998) conducted a study with a 12 years follow up, to analyze the effects of hypertension and cholesterol levels on incidence of Coronary Artery Disease. In this study 2489 men and 2856 women were included. During the 12 years follow up, 283 men and 227 women developed CAD which was strongly associated with high blood pressure, total cholesterol and HDL cholesterol levels.

Mohan et al. (2001) investigated the prevalence and risk factors for CAD in Chennai, India. A total of 1262 individuals participated in the study and the prevalence rate of CAD in these patients found 11%. The study concluded that prevalence of CAD was higher in patients with DM, higher cholesterol levels and in older age group.

Iqbal et al. (2004) examined the risk factors and behaviors for CAD among ambulatory Pakistanis. This cross sectional study revealed that adults between the ages of 18-60 with symptoms of CAD, most important risk factors for CAD are: inactive life style, family history, dyslipidemia, obesity, hypertension and diabetes mellitus.

Coutinho et al. (2011) did a meta-analysis of 6 studies involving 15,923 subjects to examine the relationship of different measures of corpulence (obesity) with mortality in Coronary Artery Disease (CAD) patients. Total of 5,696 deaths were reported after a median follow up of 2-3 years. The study concluded that central corpulence is directly associated with mortality in subjects with CAD.

Nabel & Braunwald (2012) conducted a research study for the determination of risk factors involved in development of coronary heart disease. They concluded that increase in blood pressure and cholesterol levels are strongly associated with an increased incidence of ischemic heart disease and acute myocardial infarction.

In 2000, total deaths due to Cardio Vascular Diseases (CVDs) were 16.7 million in the world (Lopez et al, 2006). Gupta et al. (2006) concluded that two thirds of deaths due to CVD are reported

among developing countries which may rise drastically by 2020. The study showed that South Asians are amongst those who have the highest rates of coronary artery disease. CAD is now amongst the prime cause of death in the Indo-Pak subcontinent (Joshi, et al. 2007).

In 2002, almost 100,000 persons suffered from severe myocardial infarction in Pakistan (Samad, 2003). According to Jafar et al (2008), in urban areas of Pakistan, one out of five middle aged adults had CAD. A research study revealed that in female there found a considerable increase in the rate of CAD in Pakistani population, compared to a decade ago (Asghar, et al. 2006).

MATERIAL AND METHODS

Data for this study was collected from the patients presenting to the catheterization laboratory Post Graduate Medical Institute, Lady Reading Hospital, Peshawar for coronary angiography. All those patients who were found to have significant coronary artery disease were included in this study. With the help of a concise history and laboratory investigations, data of 215 patients were collected through a Performa which was prepared with the help of medical expertise.

Cox Regression was fitted to the data by considering survival time as response variable and age, gender, diabetes, hypertension, hypercholesterolemia, smoking, family history, number of vessels involved, left main stem disease, total occlusions and number of lesions as explanatory variables, while death is considered as event. The initial model that was considered is given below

$$y_i = \beta_0 + \sum \beta_i x_i + \epsilon_i$$

Where

y_i =survival time of CAD

Age =Age

$Gender$ =Gender

DM = Diabetes Mellitus

HYP =Hypertension

$HYPCHOL$ =Hypercholesterolemia

SMK =Smoking

FM =Family History

$Vessels$ =No.of vessels involved

$LMSD$ =Left main Stem Disease

$Occlusion$ =Total occlusion

$Lesions$ =Number of lesions

Backward elimination technique was used to select the parsimonious model that adequately fit the data. The model after eliminating insignificant variables is

$$y_i = 0.860 HYPCHOL + 0.852 LMSD + 0.817 Occlusion + 0.907 DM * SMK$$

The above estimated model suggests that the survival time of the patients significantly depends on hypercholesterolemia, left main stem disease, total occlusion and the interaction between diabetes mellitus and smoking.

Gender wise Analysis

In order to analyze the impact of gender on these factors, gender wise analysis was carried out. The Cox-regression model was fitted separately for both males and females respectively. After applying the backward elimination criteria the model that adequately fits the for male patients is given below

$$y_{i,m} = 1.129 \text{ HYPCHOL} + 0.609 \text{ Vessels} + 1.043 \text{ LMSD} + 0.674 \text{ HYP} * \text{SMK}$$

This suggests that the survival time of the male patients significantly depends on hypercholesterolemia, number of vessels involved, left main stem disease and the interaction between hypertension and smoking.

Similarly the survival time for female is given by the model

$$y_{i,f} = 0.087 \text{ Age} + 9.859 \text{ DM} + 10.443 \text{ HYP} + 0.230 \text{ Lesions} + 15.653 \text{ DM} * \text{HYP}$$

This is an indication of the fact that the survival time of female patients depends on age, diabetes, hypertension, number of lesions and the joint effect of diabetes and hypertension.

KM Curves

The Kaplan-Meier (KM) curve is computed for the different significant risk factor of the cox regression.

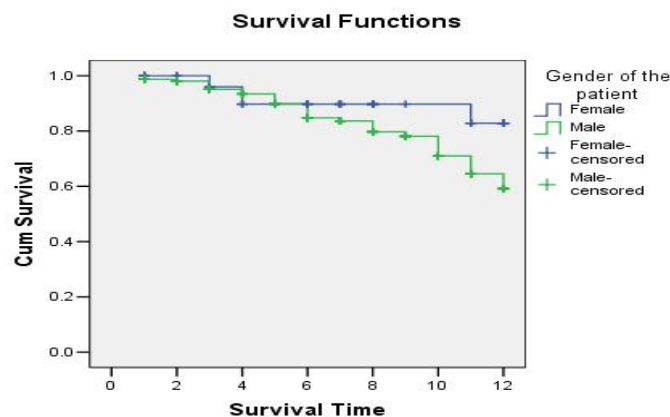


Figure1: Gender Wise Survival Function

In figure 1, it is observed that the survival of patients from death having coronary artery disease is same till 7 months. After that the male patients have higher probability of experiencing the event while the female's life stabilizes.

The following table shows the mean survival time of CAD for patients with and without hypertension. Result shows that mean survival time of CAD for patients with hypertension is 9.733 and for those without hypertension it is 11.271.

Table 1: Means for Survival Time of Hypertension

HYP				
	Mean	Estimate Std. Error	95% C. I Lower Bound	95% C. I Upper Bound
No	11.271	.247	10.787	11.755

Yes	9.733	.383	8.983	10.484
Overall	10.556	.228	10.109	11.003

The above results can be verified with the help of Figure 2, which gives us the survival function for patients of CAD with and without hypertension. It clearly shows that the life of CAD patient with hypertension reduces significantly as compared to those without hypertension.

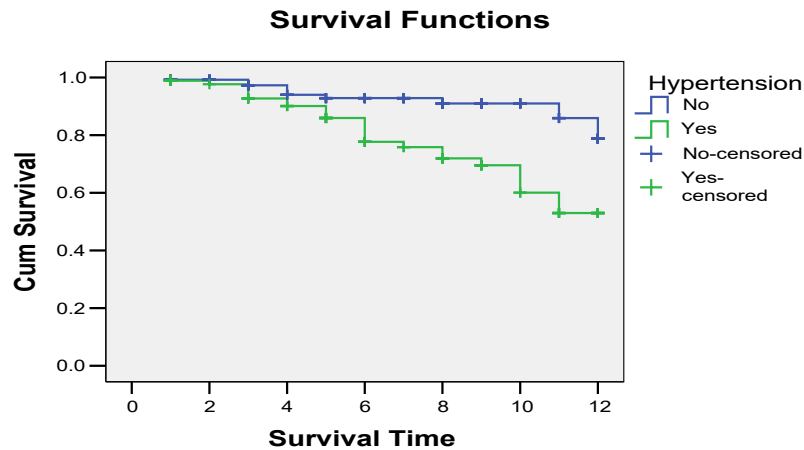


Figure2: Survival Function for Hypertension

The following table shows the mean survival time of CAD for patients with high cholesterol level is 8.170 and for those with low cholesterol levels it is 11.033.

Table2: Means for Survival Time of Hypercholesterolemia

HYPOCHOL				
	Mean	Estimate Std. Error	95% C. I Lower Bound	95% C. I Upper Bound
No	11.033	.215	10.611	11.455
Yes	8.170	.706	6.786	9.555
Overall	10.556	.228	10.109	11.003

The above survival time can also be verified with the help of Figure 3, which gives us the survival functions of patients having low and high cholesterol levels. It is evident that the life of CAD patient with high cholesterol level reduces significantly as compared to those having low cholesterol level.

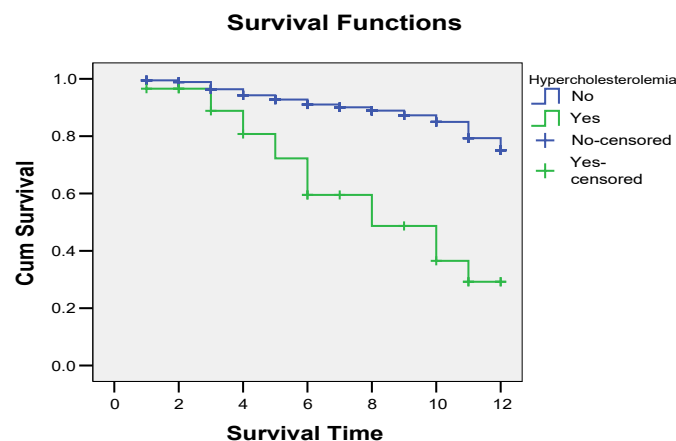


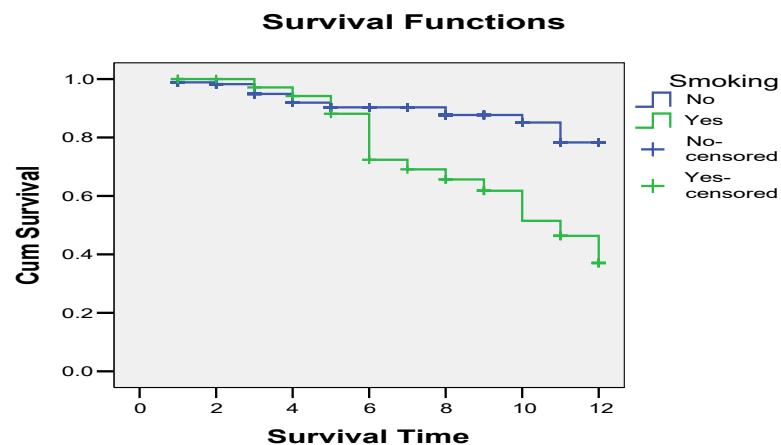
Figure3: Survival Function for Hypercholesterolemia

Similarly the following table indicates the mean survival time of CAD for patients having the habit of smoking is 9.462 comparing with non-smoking as 10.938.

Table 3: Means for Survival Time of Smoking

SMK				
	Mean	Std. Error	95 % C.I Lower Bound	95 % C.I Upper Bound
No	10.938	.229	10.489	11.387
Yes	9.462	.540	8.402	10.521
Overall	10.556	.228	10.109	11.003

Survival function for smokers and non-smokers is given in Figure 4, which shows that non-smoker CAD patient live longer than that of smokers.

**Figure4: Survival Function for Smoking**

The mean survival time of CAD for patients with and without diabetes mellitus. Result shows that mean survival time of CAD for diabetic patients are 9.675 and for non-diabetic it is 11.147.

Table4: Means for Survival Time of Diabetes Mellitus

DM				
	Mean	Standard Error	95 % C.I Lower Bound	95% C.I Upper Bound
No	11.147	.243	10.670	11.624
Yes	9.675	.419	8.854	10.496
Overall	10.556	.228	10.109	11.003

function for patients of CAD with and without DM. It clearly shows that the life of diabetic CAD patient reduces as compared to non-diabetic.

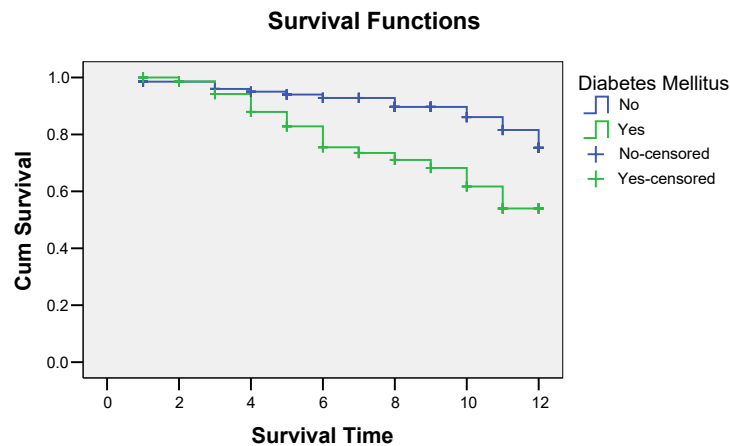


Figure5: Survival Function for Diabetes Mellitus

CONCLUSION

The study analyze the significance of various risk factors with the average survival time of the patients, Cox regression model is fitted to the patient's medical record. It was observed that the survival time is significantly associated with hypercholesterolemia, left main stem disease, total occlusion and the interaction between diabetes mellitus and smoking. In order to analyze the impact of gender on these factors gender wise analysis was carried out. The Cox-regression model was fitted separately for males and females. The survival time of the male patients significantly depends on hypercholesterolemia, number of vessels involved, left main stem disease and the interaction between hypertension and smoking. The survival time of female patients depends on age, diabetes, hypertension, number of lesions and the joint effect of diabetes and hypertension. The Kaplan Meier show that $S^{\wedge}(0) = 1$ which gives the probability of surviving past time zero. During the first 3 months as the number of events is less, significant change in the graph can be seen. In other words, the decrease in the probability is not very noticeable. On the other hand, the probability of failure starts with its minimum value zero and reaches to maximum value at time 12 months, while at the same time probability of surviving reaches to minimum value.

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