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Survival Analysis Of Coronary Artery Disease: A Case Study Of District Peshawar

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Abstract

Statistics plays a crucial role in modern research, particularly in the field of medicine, where various statistical techniques are applied to analyze data. One such technique is survival analysis, which has wide applications in biostatistics. In Pakistan, coronary artery disease (CAD) has been a major health issue, characterized by the narrowing of arteries supplying blood to the heart, leading to symptoms such as chest pain, shortness of breath, and even death. The study conducted at the Post Graduate Medical Institute, Lady Reading Hospital (LRH), Peshawar, analyzed data from 215 CAD patients to identify significant factors contributing to the disease and its severity. The results showed that most patients were male, with a small proportion of females. About 17% of patients experienced an event during the one-year study period, and 32% had diabetes while 9.3% had high cholesterol levels. The majority of patients had severe disease, with three blocked vessels, and 82 had total occlusion. Cox regression analysis revealed that hypercholesterolemia, Left Main Stem Disease (LMSD), total occlusion, and the combined effect of diabetes and smoking were significant factors contributing to the disease. Gender-specific findings indicated that male survival was associated with cholesterol levels, number of blocked vessels, LMSD, and the

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interaction between hypertension and smoking, with males showing high odds of events in cases of hypercholesterolemia, hypertension, and smoking. For females, diabetes, hypertension, and age were the primary risk factors. Age is a non-modifiable risk factor for females, while for males, hypercholesterolemia, hypertension, and smoking were modifiable and controllable risk factors. The study concludes that cholesterol levels, diabetes, and smoking are key risk factors for CAD, with gender-specific differences in the risk factors.

Keywords: *Coronary Artery Disease (CAD), Survival Analysis, Risk Factors, Cox Regression. Hypercholesterolemia.*

Introduction

Statistics is essential in various scientific fields, including medicine, where it plays a crucial role in research. Biostatistics, a branch of statistics, applies statistical methods to medical and biological sciences. As medical research increasingly relies on statistical evidence, understanding basic statistical techniques is vital for interpreting research articles and conducting one's own studies. Statistical inference has long been integral to medical research, with survival analysis being one of the most widely used statistical methods in this field. Overall, statistics is fundamental to medical research and its advancements.

Structure of Heart

The heart is a vital muscular organ located in the chest, functioning as a pump to circulate blood throughout the body. It has four chambers and valves, with the right side handling deoxygenated blood sent to the lungs, and the left side distributing oxygenated blood to the body. Blood is supplied to the heart muscle by coronary arteries, which include the left main stem, left anterior descending artery (LAD), left circumflex artery (CIRC), and right coronary artery (RCA). Coronary Artery Disease (CAD) involves the narrowing of these arteries due to atherosclerosis, leading to symptoms like chest pain, shortness of breath, irregular heartbeats, myocardial infarction, or sudden

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death. CAD is categorized by the number of affected vessels—single, two, or triple vessel disease—or as left main stem disease if the left main artery is involved.

What Causes Coronary Artery Disease

There are a number of conditions which may cause narrowing of the coronary arteries. However, most conditions are too rare to be mentioned. The main cause of CAD is atherosclerosis. It is the deposition of fatty material within the vessel wall along with changes in the vessel wall that cause narrowing of the vessel lumen. This is a progressive condition and may cause complete obstruction of the lumen either acutely or over many years.

What Causes Atherosclerosis

Atherosclerosis is a degenerative process in which fat and white blood cells accumulate in the vessel wall. This accumulation causes formation of cholesterol and white blood cell pockets inside the walls of the arteries. These pockets protrude into the lumen of the artery and cause in the diameter of the arterial lumen.

Risk Factors for CAD

Coronary Artery Disease (CAD) affects many people, with susceptibility influenced by modifiable and non-modifiable risk factors. Non-modifiable factors, which cannot be changed, include age, male gender, and family history. CAD risk increases with age, is higher in men, and is elevated for individuals with close relatives who developed CAD early. Modifiable factors, which can be managed, include diabetes, hypertension, high cholesterol, smoking, obesity, and physical inactivity. Diabetes is particularly critical, being almost equivalent to CAD in terms of risk. Hypertension and high cholesterol contribute to artery damage and plaque buildup, while smoking and inactivity further increase risk by affecting artery health and promoting

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related conditions. Managing these modifiable factors can reduce CAD risk significantly.

Survival Analysis

Survival analysis uses statistical methods to examine the time until specific events, like death or failure, and is widely applied in medical and biological research to understand factors affecting disease progression. Three main approaches can be used to fit survival models. The parametric approach is the most straightforward, where the model is fully specified, including both the hazard function and covariate effects, often using distributions like exponential and Weibull. The semi-parametric approach, such as Cox's model, adds flexibility by dividing time into small intervals and assuming a constant baseline hazard within each, allowing the hazard to depend non-parametrically on time but parametrically on covariates. The non-parametric approach, which includes the Kaplan-Meier estimator, makes no assumptions about the baseline hazard, allowing it to be estimated directly from the data. Each approach provides unique insights, balancing model complexity with assumptions to suit the analysis needs.

Objectives of the Study

Many studies have been conducted on Coronary Artery Disease. This study is an attempt to recognize the risk factors that are associated to the 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 in Peshawar. The main objectives of the study are:

1) To study the predominance of different risk factors in patients with coronary artery disease.

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2) To analyze event free survival of patient with coronary artery disease and the effect of different risk factors on the occurrence of events.
3) To check the severity of the disease.
4) To perform gender wise analysis in order to study the phenomenon of Coronary Artery Disease.

Literature Review

Nabel and Braunwald (2012) conducted a study on "Factors of Risk in the Development of Coronary Heart Disease," the study reveled that the main factors which increases the chances of ischemic heart disease and acute myocardial infarction is high cholesterol levels and blood pressure. Asians have been found to have a higher prevalence of CAD and mortality from CAD compared with Europeans and Chinese [Enas, et al. (1996); Hughes, et al. (1989); Anand, et al. (2000); Balarajan (1991)]. Mohan, et al. (2001) in Chennai Urban Population Study (CUPS 5) investigated the incidence and risk factors for CAD in Chennai. Total of 1262 individuals participated in the study. The prevalence rate of CAD in these patients was 11%. The incidence of CAD was high in patients with DM, higher cholesterol levels and in older age group.

Mehmood ul Hassan et al. (2005) conducted a study in rural areas of Peshawar. A total of 498 individuals were selected for this study. 309 were females and 189 were males. Mean age of individuals was 46.54±12.85 years. The prevalence of CAD among all the individuals was 11.2 %. CAD among females was 13.3%, while in males, it was 7.9 %.Wilson et al. (1998) conducted a prospective 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 males and 227 females developed CAD which was strongly associated with high blood pressure, total cholesterol and HDL cholesterol

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levels. 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 patients. Total of 5,696 deaths were reported after a median follow up of 2.3 years. It was found that central corpulence is directly associated with mortality in subjects with CAD.

Fontbonne et al (1989) conducted a study involving 943 male individuals with decreased glucose tolerance (diabetes). These individuals were analyzed for CAD mortality risk factors and were followed up for 11 years. Twenty six of the 943 subjects died of CAD. In multiple regression analysis, using the Cox proportional hazards model, plasma triglyceride levels were positively and significantly related to coronary heart disease deaths. This evidence suggests a role for dyslipidemia in extreme incidence of atherosclerotic vascular sickness in this class of subjects.

Iqbal et al (2004) examined the risk factors and behaviors for CAD among ambulatory Pakistanis. This cross sectional study revealed that all were adults between the ages of 18-60 with no symptoms of CAD. Among those 370 Pakistanis, the proportions of most important risk factors for CAD were: inactive life style 72 %, family history 42 %, dyslipidemia 31 %, obesity 24 %, hypertension 19 % and diabetes mellitus 15 %. Diabetes, hypertension and dyslipidemia were badly controlled in the study population.

In the year 2000, total deaths due to Cardiovascular 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. This 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 the year 2002, almost 100,000 persons

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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 may have underlying CAD. Research revealed that in female there is a considerable increase in the rate of CAD in Pakistani population, compared to a decade ago (Asghar, et al. 2006).

METHODS OF ANALYSIS

Universe of the Study

This study focuses on coronary artery disease, with data collected from patients who underwent coronary angiography at the catheterization laboratory of the Post Graduate Medical Institute, Lady Reading Hospital in Peshawar. All patients who presented to this lab for angiography were included in the study.

Sampling Design

This study used convenient sampling, selecting only patients with significant coronary artery disease. Data were gathered from 215 patients through concise histories and lab investigations, recorded in a structured form developed with medical input. Collected data included patient demographics (name, age, gender), smoking history, diabetes status, family history, hypertension, and hypercholesterolemia. Information on the severity and extent of coronary artery disease was also documented.

Survival Analysis

Survival analysis is a branch of statistics focused on analyzing data that represents lifetimes, waiting times, or times until an event of interest occurs. This type of data, known as survival data, is commonly used in fields such as medicine, engineering, sociology, demography, and economics. For example, in medicine, it involves measuring survival times until an event like death

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occurs, while in engineering, it might measure time until failure, and in demography, it could involve studying how long a worker stays in a job.

Key assumptions of survival analysis

1. Events are independent across individuals over a given time interval.
2. The conditional probability of failure for an individual, given that they have survived up to time t is the same as the conditional probability of failure in the same interval.

Two main aspects of survival data

1. The data is often positively skewed, with most individuals experiencing shorter survival times, so normal distribution is not appropriate for analysis.
2. Some individuals may not have experienced the event by the end of the study, meaning their survival times are censored, and only the information that their survival time exceeds a certain point is known.

Censoring

In survival analysis, censoring occurs when the survival time of some individuals is unknown. This can happen if an individual has not experienced the event by the study's end, is lost to follow-up, or experiences another event making further follow-up impractical. Right censoring, the most common type, occurs when the event happens beyond the study period. Left censoring happens if the event occurs before the study starts, while interval censoring occurs when individuals are intermittently observed. Survival analysis focuses on two main terms: time, the duration from study start to the event, and event, the outcome of interest, like death or relapse.

Functions of Survival Time

Survival data are generally subject to random variations that are described and modeled in terms of two related probabilities, namely survival function and hazard function.

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Survival Function and Life Time Distribution Function

Survival function $S(t)$ calculates the probability of the individual that survives beyond some specified time t. In simple words $S(t)$ provides us the probabilities that random variable T exceeds some specific time t. Mathematically, it can be written as:

$$S(t) = P(an\ individual\ survives\ longer\ than\ t) \quad ----------(1)$$

$$S(t) = P(T > t) \quad ----------(2)$$

It is very important to a survival analysis as survival probabilities for different values of t provide important information from time to the occurrence of the event. These values give us the survival experience of a study cohort (Clark, et al. 2003).

The survival function $S(t)$ is always decreasing function with the following properties.

$$S(t) = \begin{cases} 1 & for\ t = 0 \\ 0 & for\ t = \propto \end{cases} \quad ----------(3)$$

The graph of $S(t)$ is called the Survival Curve. Which shows that the probability of surviving is one at initial time and is zero beyond the specified time [Johnson and Johnson, (1999); Lee and Wang, (2003)].

Survival function can also be defined in terms of cumulative distribution function, also known as life time distribution function,$F(t)$ as

$$S(t) = 1 - P(an\ individual\ fails\ before\ t) \quad ----------(4)$$

$$= 1 - F(t) \quad ----------(5)$$

$$F(t) = 1 - S(t) \quad ----------(6)$$

The derivative of $F(t)$, its density function is denoted by f(t) and is given by

$$f(t) = \frac{d\,F(t)}{dt} \quad ----------(7)$$

$$= \frac{d\{1 - S(t)\}}{dt} \quad ----------(8)$$

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$$f(t) = -S'(t) \quad \text{---------- (9)}$$

$f(t)$ is sometimes known as event density and as evident from the above equations, it is the rate of event per unit time [Johnson and Johnson, (1999)].

Hazard Function

The hazard function denoted by $h(t)$ or $\lambda(t)$ is the event rate at time t conditional on survival until time t or later. In other words, it is the instantaneous event rate of survival to time t.

$$h(t) = \lim_{d(t)\to 0} \frac{P(t < T < t + dt/T > t)}{dt} \quad \text{---------- (10)}$$

in the above equation, it is clear that the numerator gives us the conditional probability that an event will occur in interval $(t, t + dt)$ such that the event has not occurred and the denominator gives us the interval width. In short, the above equation tells us the occurrence of event per unit time and applying limit gives us the instantaneous rate of occurrence.

According to conditional probability numerator can be written as the ratio of joint probability that the event is in the interval $(t, t + dt)$ and $(T > t)$to the probability $(T > t)$. The joint probability can be written as $f(t)dt$ while probability $(T > t)$ can be written as $S(t)$. Putting the values in the above equation we will get:

$$h(t) = \frac{f(t)}{S(t)} \quad \text{---------- (11)}$$

$$\text{Where } f(t) = -S'(t) \quad \text{---------- (12)}$$

$$\text{So} \quad h(t) = -\frac{(S'(t))}{(S(t))} \quad \text{---------- (13)}$$

$$h(t) = -\frac{d\{\log S(t)\}}{dt} \quad \text{---------- (14)}$$

Arranging the equation and integrating from 0 to t we will get

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$$S(t) = exp\left(-\int_0^t h(x)dx\right) \text{-----------------------(15)}$$

Only the integral part of the above equation is known as the cumulative hazard or cumulative risk and is given by $\Psi(t) = \int_0^t h(x)dx$ (Clark, et al. 2003).

Model Fitting

Survival analysis aims to assess the impact of predictive factors on disease outcomes by modeling survival time in relation to covariates. There are three main modeling approaches: the parametric approach, which fully specifies the hazard function and covariate effects; the semi-parametric approach, which makes limited assumptions about the baseline hazard; and the non-parametric approach, which assumes no specific form for the baseline hazard. Each approach offers unique methods for modeling survival data based on differing assumptions about distributions and covariate relationships.

Parametric Approach

The parametric approach is a straightforward method where both the hazard function and the effects of covariates are fully specified. Common models used in this approach include Exponential, Weibull, Gamma, lognormal, log-logistic, and Generalized-F distributions. However, these models can be sensitive and may deviate from the exponential model, so they should be applied with caution.

Semi Parametric Approach

Semi-Parametric approach is the most popular strategy in the survival analysis. It is also called flexible approach where mild assumptions are made related to the baseline hazard $h_0(t)$. In this strategy the time is divided into small intervals and assumption is made about baseline hazard that it is

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constant in each interval. Hazard function depends on time non-parametrically while it depends parametrically on covariates [Cox, (1972); Prentice, et al. (1981); Bradburn, et al. (2003); Reid, (1994)].

Cox's Proportion Hazard Model

If T is the random variable used to measure time until the occurrence of an event , that is, duration, and X represents the covariates required to explain T, then we use Cox proportional hazard and is given by

$$h(t,x) = h_0(t).exp(x,\beta) \quad \text{(16)}$$

In the above function $h_0(t)$ is the baseline function. It is evident from above that hazard function $h(t,x)$ is the product of baseline function $h_0(t)$ and the effect of covariates in the model, that is, $exp(x,\beta)$. The advantage and the main reason for the popularity of this model are the simplicity and possibility to estimate the parameters without any assumption on the distribution of time variable. In other words, no parametric restrictions are applied on baseline hazard function. However, estimation for this model can be done by using partial likelihood function (Cox, 1972; 1975).

Non-Parametric Approach

This approach focuses on the estimation of β, the regression coefficients, and assuming $h_0(t)$, the baseline hazard function totally unspecified. Kaplan Meier is the most popular non-parametric approach for the survival analysis (Cox, 1972).

Kaplan-Meier Estimator

Kaplan-Meier estimator is an estimator used for the estimation of the survival function which depends on lifetime data. In this the intervals are taken so small that at the most one observation can occur within that interval. Let $d(x)$ be the number of deaths at time (x). Generally it is taken as 0 or 1, but provision can be given for tied survival times where $d(x)$ might be greater

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than 1. Let $n(x)$ is the number of survivors just prior to time (x). Then the Kaplan-Meier estimator can be written as

$$S(t) = \prod_{x \le t} \frac{(n(x) - d(x))}{n(x)} \text{------------------------}(17)$$

This was first proposed by Kaplan and Meier (1958). It is very much evident that the product will only change if we observe an event, that is, death (Sveltana, 2002).

Model Selection Methods

In regression analysis, selecting the best-fitting model becomes challenging as the number of variables increases due to more interaction terms. While a complex model may fit the data well, a simpler model is easier to interpret. Various techniques for model selection, similar to those used in regression and analysis of variance, have been developed for contingency tables.

Stepwise Method

The stepwise method for model selection adjusts terms in a model to identify the best fit. It includes three approaches: forward selection, which adds significant terms to a small model; backward elimination, which removes insignificant terms from a large model; and a composite method that combines both adding and removing terms. These methods, introduced by Goodman (1971), are widely used in regression analysis to systematically refine models.

Initial Model Selection Techniques

Various model selection methods exist to determine an initial model for identifying an optimal fit. One recommended approach, proposed by Brown (1976), Whittaker and Aitkin (1978), and Aitkin (1980), involves a simultaneous testing procedure to control the error rate when comparing models of different orders.

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Brown Test

Brown test is one the most simple and widely used famous method for the selection of initial model. Brown proposed two test, marginal association and partial association, to look for the importance of each and every effect.

In the first test, the most complicated parameter in the simple model is the term. For example, taking the model (XY, XZ, YZ), we want to see whether to include or exclude the three factor interaction effect, that is, (XYZ). In second test all the parameters of its level of complexity are included. Suppose, to check whether the two factor interaction term (XZ) is needed in the model having variables $(X, Y, and\ Z)$. The criterion used is the marginal test and can be given by $G^2\{(X,Y,Z)/(XZ,Y)\}$; this test is the marginal $(X-Z)$ association. This can also be written as

$$G^2\{(X,Y,Z)/(XZ,Y)\} = G^2(X,Y,Z) - G^2(XZ,Y) - - - - - - - - - - - - - - - (18)$$

Main effects cannot be tested with the help of marginal association (Gottman, 1990).

Marginal Association: To check any specific term using marginal association collapsed over any factors not to be included in the model since for such association all other factors are completely overlooked. Which means that, this test depends on marginal tables and consists of testing that model which involve a specific term whose significant is to be tested with the higher model which is without that specific term. For example, taking the three dimensional table, the test of marginal association for the term (XYZ) is the test of (XY, YZ, XZ) versus (XYZ). Test of marginal association for the term (XY) is the test of (X, Y, Z) versus (XY, Z) (Gottman, 1990).

Partial Association: This takes into account a number of factors involved in the term. Brown test of partial association involving S factors is actually the difference between the model of order S and the model involving all marginal

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of the same order dropping the S-factor interaction of interest. Partial association is the conditional test, where all the other effects are fixed at certain level of interaction. For instance, partial association between (X) and (Y) in four dimensional table is the difference between the models having the factors (WX, WY, WZ, XY, XZ, YZ) and (WY, WZ, XY, XZ, YZ) , that is, (WX) interaction term is dropped in the second model. It can be seen clearly that in both the models the same order interaction terms appear which are compared (Gottman, 1990).There are four approaches for selecting the initial model in statistical analysis. The first approach includes terms that are significant in the marginal test, while the second includes terms that are significant in the partial test. The third approach involves including terms that are significant in either the marginal or partial test, and the fourth includes only those terms that are significant in both tests. The first method typically uses forward selection to simplify the model, whereas the second approach utilizes backward elimination (Gottman, 1990).

Data Source

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 and entered into a Performa which was prepared with the help of medical expertise. The data collected for this study include name, age, gender, smoking history, presence or absence of diabetes mellitus, family history, hypertension and hypercholesterolemia. Different aspects of the severity and degree of coronary artery disease were also entered.

Preliminary Analysis

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Diabetes Mellitus

Figure 1 given below shows the patients of CAD with and without Diabetes Mellitus (DM). The result shows that 68 (31.63 %) out of 215 patients have DM whereas 147 (68.37 %) out of 215 patients do not have DM.

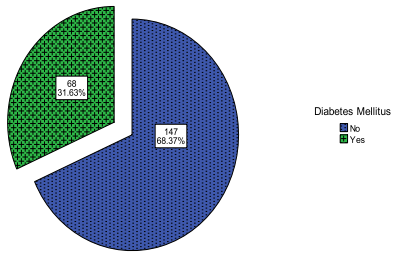

Figure1: Patients of CAD With and Without Diabetes Mellitus

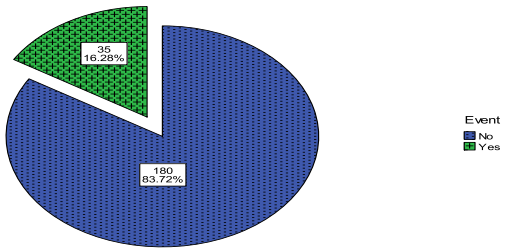

Figure2: Occurrence of Event Among The Patients

Events among the Patients

Figure 2 shows the occurrence of events among the patients of CAD. This figure shows that out of 215 patients, 35 (16.28 %) patients got the event and 180 (83.72 %) were event free.

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Family History of the Patients

In Figure 3, family history of the patients is taken into account. It represents that any member, who is in blood relation with the patient have CAD or not. "Yes" means at least one of family member has got CAD and "NO" means none of the family member has CAD. It is very much evident that the percentage CAD patients having positive family history is very high, that is, 28.84 %.

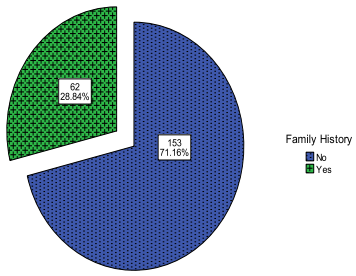
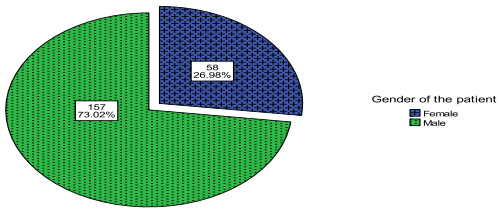


Figure3: Family History of The Patients

4.4 Gender of the Patients

It is very much clear from Figure 4 that (58/215) patients are female, whereas (157/215) are male patients. In terms of percentage 26.98 % of females have



got CAD, while 73.02 % of males have CAD.

Figure4: Gender of The Patients

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Patients of CAD with Hypertension

Figure 5 shows the distribution of CAD patients with or without hypertension. The results show that 81 out of 215 patients are hypertensive, while 134 out of 215 are non hypertensive. Talking in terms of percentage 37.67 % are hypertensive patients, whereas 62.33 % patients are not hypertensive.

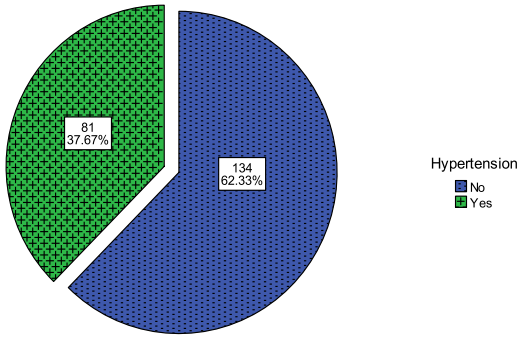

Figure 5: Pie Chart Showing The Presence of Hypertension

Distribution of Hypercholesterolemia

The result shows that 20 out of 215 (9.30 %) patients have high cholesterol level while 195 out of 215 (90.70 %) have normal cholesterol level.

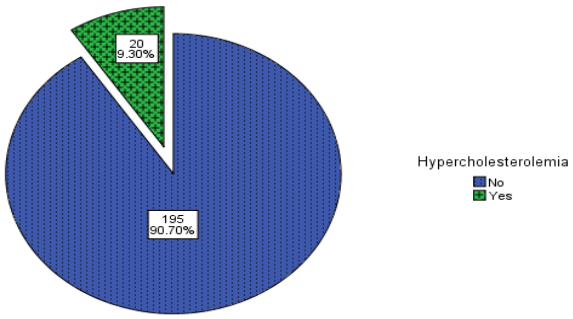

Figure 6: Pie Chart Showing The Presence of Hypercholesterolemia

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Left Main Stem Disease

The Pie graph given in Figure 7 shows that 30 out of 215 patients of coronary artery disease have got left main stems disease. This means that 13.95 % of patients have left main stem disease.

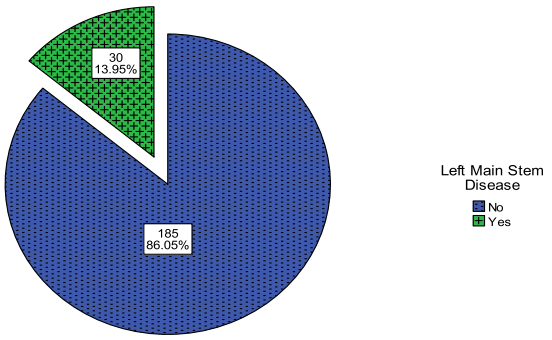

Figure7: Distribution of Left Main Stem Disease

Number of Lesions

Figure 8 shows the distribution of coronary artery disease patients having different number of lesions.

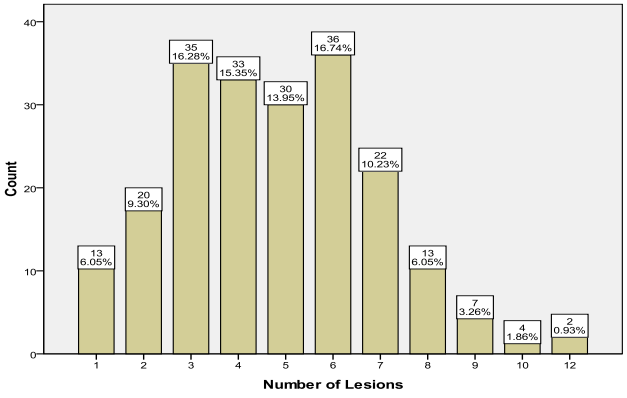

Figure8: Distribution Showing Number of Lesions

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Number of Vessels Involved

Result shows that maximum number of patients has 2 and 3 vessels blocked. In other words, out of 215 patients 179 patients are such that they have 2 and 3 vessels blocked. That constitutes almost 83.25 % of the total patients. Figure 9 shows that the percentage of the patient having 3 vessels blocked is 45.58%, which means that almost half of the patients have severe CAD.

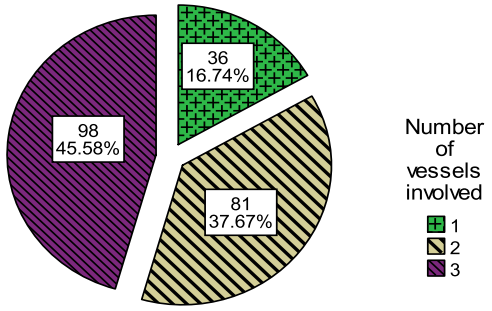
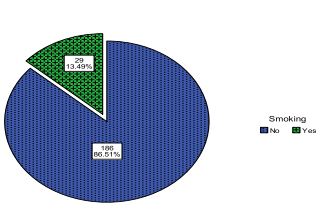


Figure9: Pie Chart Showing Number of Vessels Blocked Distribution of Smoking

Figure 10 given below shows that only 29 out of 215 patients are those who are smokers and remaining 186 are non smokers.

Distribution of Total Occlusion



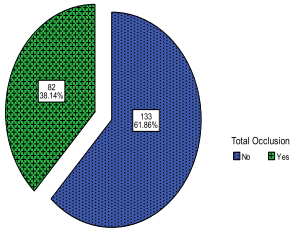


Figure10: Pie Chart Showing Distribution of Smoking

Figure11: Distribution of Total Occlusion

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The graph given in Figure 11 shows those 82 out of 215 patients of coronary artery disease have got total occlusion. This means that 38.14 % of patients have total occlusion.

Age of Patients

Table 1 shows that the mean age of the patients of CAD is 54.97 (±10.472), with maximum age 82 and minimum 28.

Table 1: Age of The Patients

Descriptive Statistics			
	N	Mean	Std. Deviation
Age of the Patient	215	54.97	10.472
Valid N (listwise)	215		

Cox Regression

Cox Regression is 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,

$$y_i = \beta_0 + \sum \beta_i x_i + \varepsilon_i \quad ----------(19)$$

In the study, the variables are defined as follows: yi represents the survival time of patients with Coronary Artery Disease (CAD), while the other factors include Age, Gender, Diabetes Mellitus (DM), Hypertension (HYP), Hypercholesterolemia (HYPCHOL), Smoking (SMK), Family History (FM), Number of vessels involved (Vessels), Left Main Stem Disease (LMSD), Total

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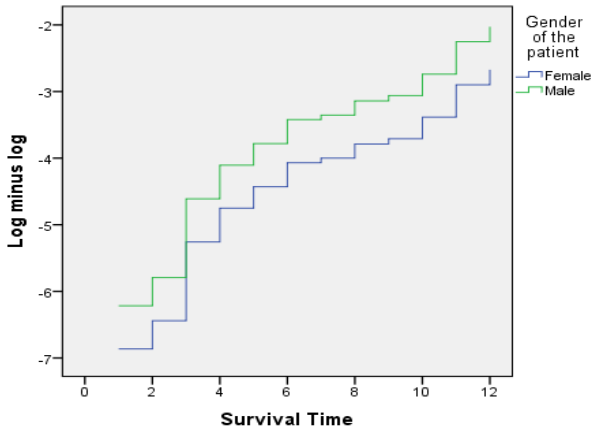
Occlusion (Occlusion), and the Number of lesions (Lesions). These variables are used to analyze the survival times of CAD patients and identify significant risk factors.

Assumptions

The proportional hazard assumption in survival analysis requires that the hazard ratio remains constant over time, meaning the hazard for one individual is proportional to that of another, with the constant being time-independent. In a study comparing two groups, the hazard functions should remain constant over time. If these functions cross at any point, it indicates that a Cox Proportional Hazard model is not suitable, as it assumes a constant hazard ratio across time. This is reflected in the Log-minus-Log plot, where parallel lines should appear for two or more groups.



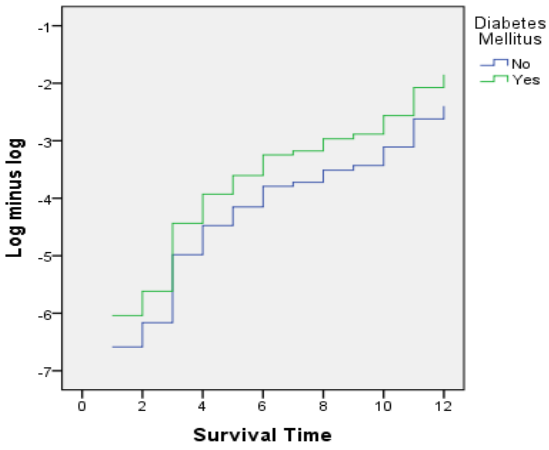


Figure 12: Log Minus Log Curve for Gender

Figure 13: Log Minus Log Curve for Diabetes Mellitus

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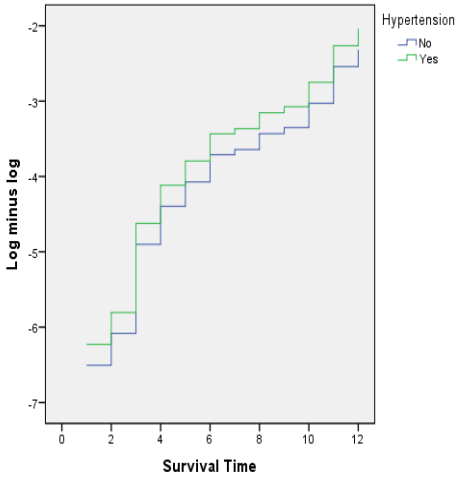

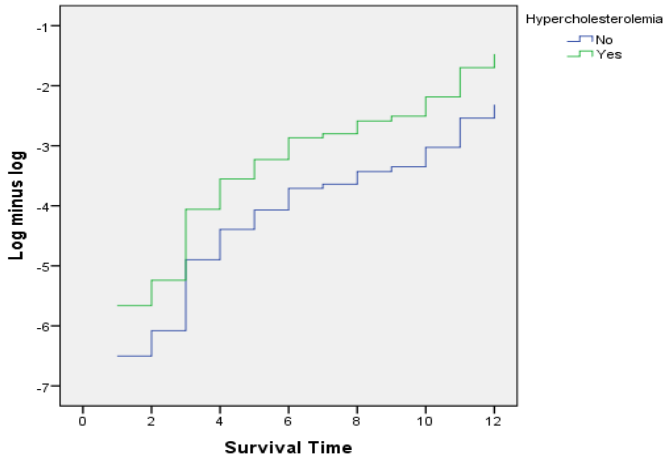

Figure 14: Log Minus Log Curve for Hypertensio

Figure 15: Log Minus Log Curve for Hypercholesterolemia

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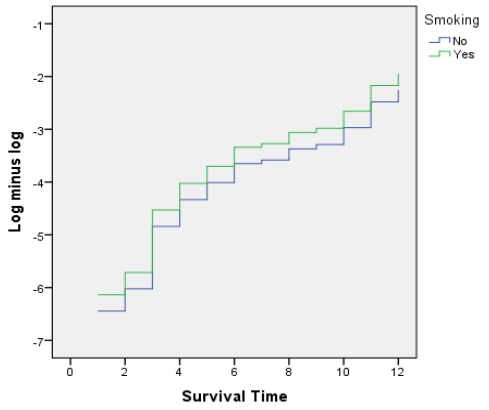


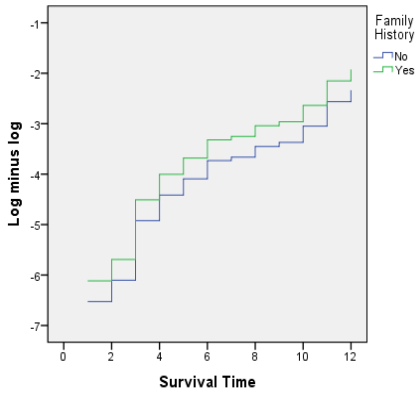
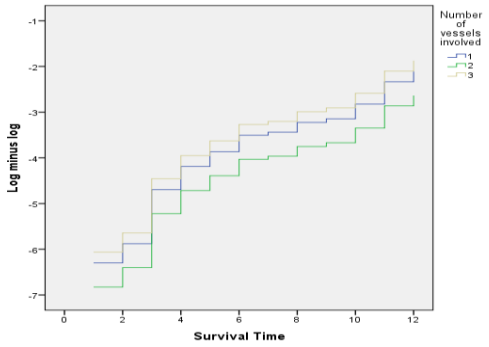


Figure 16: Log Minus Log Curve for Smoking

Figure 17: Log Minus Log Curve for Family History



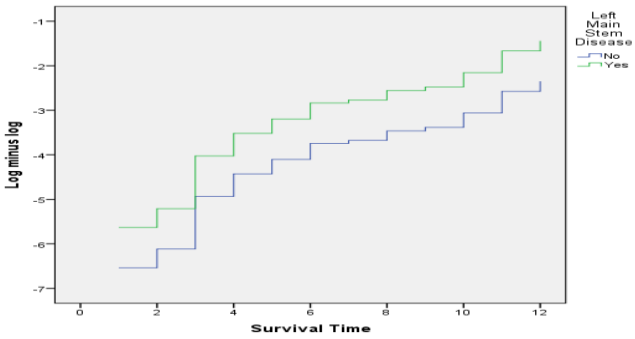


Figure 18: Log Minus Log Curve for Number of Vessels Involved

Figure 19: Log Minus Log Curve for Left Main Stem Dise

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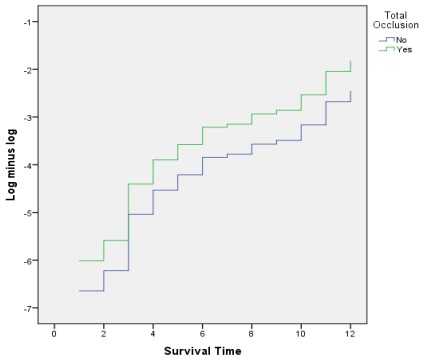

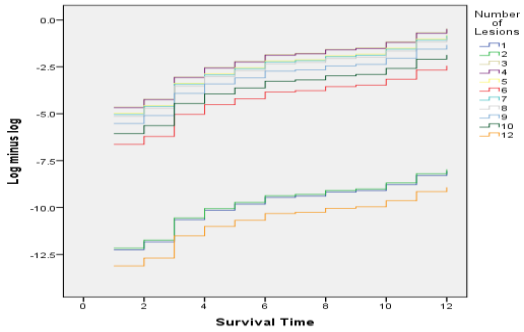

Figure 20: Log Minus Log Curve for Total Occlusion

Figure 21: Log Minus Log Curve for Number of Lesions

It can be clearly seen that the Log minus log curves for all the variables are constant or parallel over survival time. This means that proportion hazard model assumption is satisfied for all the variables. Backward elimination technique has been used to select the parsimonious model that adequately fit the data. The model after eliminating insignificant variables is;

$$y_i = 0.860\ HYPCHOL + 0.852\ LMSD + 0.817\ Oclusion + 0.907\ DM * SMK - -(20)$$

This suggest 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.

Table 2: Variables in General Cox Regression Model

		B	SE	Sig.
Step 1	Age	-0.005	0.017	0.785
	DM	0.261	0.734	0.722
	HYP	0.016	0.738	0.983
	HYPCHOL	1.626	0.748	0.030
	SMK	0.280	1.080	0.796

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	FH	0.269	0.397	0.498
	Vessels	0.610	0.373	0.102
	LMSD	0.957	0.432	0.027
	Occlusion	0.714	0.440	0.105
	Lesions	-0.146	0.107	0.171
	DM*HYP	0.331	0.999	0.740
	DM*SMK	0.430	0.902	0.633
	HYP*SMK	0.044	1.035	0.966
	DM*HYPCHOL	-0.613	0.862	0.477
Step 2	Age	-0.005	0.017	0.782
	DM	0.255	0.683	0.709
	HYPCHOL	1.633	0.655	0.013
	SMK	0.282	1.073	0.793
	FH	0.269	0.395	0.496
	Vessels	0.611	0.366	0.095
	LMSD	0.959	0.425	0.024
	Occlusion	0.715	0.437	0.102
	Lesions	-0.146	0.105	0.165
	DM*HYP	0.346	0.733	0.637
	DM*SMK	0.426	0.877	0.627
	HYP*SMK	0.047	1.026	0.964
	DM*HYPCHOL	-0.620	0.801	0.439

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Step 3	Age	-0.005	0.017	0.770
	DM	0.246	0.656	0.708
	HYPCHOL	1.633	0.655	0.013
	SMK	0.320	0.676	0.636
	FH	0.273	0.389	0.483
	Vessels	0.611	0.366	0.095
	LMSD	0.961	0.423	0.023
	Occlusion	0.719	0.427	0.092
	Lesions	-0.146	0.105	0.165
	DM*HYP	0.365	0.601	0.544
	DM*SMK	0.422	0.871	0.628
	DM*HYPCHOL	-0.622	0.802	0.438
Step 4	DM	0.265	0.651	0.684
	HYPCHOL	1.597	0.642	0.013
	SMK	0.313	0.675	0.643
	FH	0.275	0.390	0.481
	Vessels	0.587	0.356	0.100
	LMSD	0.961	0.424	0.024
	Occlusion	0.692	0.416	0.096
	Lesions	-0.143	0.104	0.168
	DM*HYP	0.359	0.598	0.548
	DM*SMK	0.410	0.870	0.637

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	DM*HYPCHOL	-0.635	0.801	0.428
Step 5	HYPCHOL	1.544	0.627	0.014
	SMK	0.247	0.654	0.705
	FH	0.272	0.392	0.488
	Vessels	0.611	0.352	0.083
	LMSD	0.933	0.420	0.026
	Occlusion	0.699	0.416	0.093
	Lesions	-0.147	0.104	0.157
	DM*HYP	0.494	0.515	0.337
	DM*SMK	0.513	0.837	0.540
	DM*HYPCHOL	-0.509	0.740	0.492
Step 6	HYPCHOL	1.540	0.634	0.015
	FH	0.297	0.387	0.443
	Vessels	0.609	0.352	0.083
	LMSD	0.942	0.424	0.026
	Occlusion	0.693	0.415	0.095
	Lesions	-0.146	0.104	0.159
	DM*HYP	0.465	0.508	0.360
	DM*SMK	0.742	0.579	0.200
	DM*HYPCHOL	-0.519	0.745	0.486

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Step 7	HYPCHOL	1.200	0.428	0.005
	FH	0.323	0.386	0.402
	Vessels	0.663	0.344	0.054
	LMSD	1.004	0.410	0.014
	Occlusion	0.680	0.410	0.097
	Lesions	-0.154	0.102	0.134
	DM*HYP	0.411	0.494	0.405
	DM*SMK	0.618	0.547	0.258
Step 8	HYPCHOL	1.136	0.418	0.006
	FH	0.336	0.384	0.382
	Vessels	0.644	0.341	0.059
	LMSD	1.039	0.409	0.011
	Occlusion	0.666	0.416	0.109
	Lesions	-0.144	0.102	0.158
	DM*SMK	0.915	0.414	0.027
Step 9	HYPCHOL	1.141	0.418	0.006
	Vessels	0.656	0.344	0.056
	LMSD	1.045	0.411	0.011
	Occlusion	0.777	0.397	0.050
	Lesions	-0.146	0.103	0.158
	DM*SMK	1.034	0.396	0.009
Step 10	HYPCHOL	0.977	0.399	0.014

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	Vessels	0.377	0.276	0.171
	LMSD	0.795	0.384	0.039
	Occlusion	0.659	0.386	0.087
	DM*SMK	0.938	0.392	0.017
Step 11	HYPCHOL	0.860	0.402	0.032
	LMSD	0.852	0.388	0.028
	Occlusion	0.817	0.369	0.027
	DM*SMK	0.907	0.404	0.025

The odds of event occurrence increases by 2.363 times with hypercholesterolemia and 2.345 times with left main stem disease. Similarly the odd for occlusion is 2.265 times and for interaction term it is 2.476 times.

Table 3: Odds Ratio for Variables in General Equation

Factors	Odds
HYPCHOL	2.363
LMSD	2.345
Occlusion	2.265
DM*SMK	2.476

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 males and females.

After applying the backward elimination criteria the model that adequately fits the for male patients is given below

$$y_{i,m} = 1.129HYPCHOL + 0.609Vessels + 1.043LMSD + 0.674HYP * SMK - -(21)$$

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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.

Table 4: Variables in Cox Regression Model for Male

		B	SE	Sig.
Step 1	Age	-0.012	0.018	0.499
	DM	0.731	0.843	0.386
	HYP	-0.262	0.859	0.760
	HYPCHOL	1.338	0.845	0.113
	SMK	0.370	1.119	0.741
	FH	0.344	0.437	0.431
	Vessels	0.919	0.441	0.037
	LMSD	1.274	0.523	0.015
	Occlusion	0.798	0.479	0.096
	Lesions	-0.201	0.123	0.102
	DM*HYP	0.070	1.125	0.950
	DM*SMK	-0.807	1.049	0.442
	HYP*SMK	0.585	1.112	0.599
	DM*HYPCHOL	0.166	1.001	0.868
Step 2	Age	-0.012	0.018	0.497
	DM	0.762	0.677	0.260
	HYP	-0.229	0.675	0.734

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	HYPCHOL	1.316	0.770	0.087
	SMK	0.342	1.029	0.740
	FH	0.340	0.430	0.430
	Vessels	0.915	0.436	0.036
	LMSD	1.270	0.521	0.015
	Occlusion	0.794	0.476	0.095
	Lesions	-0.200	0.122	0.101
	DM*SMK	-0.785	0.985	0.426
	HYP*SMK	0.608	1.053	0.564
	DM*HYPCHOL	0.182	0.964	0.850
Step 3	Age	-0.012	0.018	0.507
	DM	0.808	0.633	0.202
	HYP	-0.268	0.646	0.678
	HYPCHOL	1.419	0.548	0.010
	SMK	0.347	1.031	0.736
	FH	0.335	0.428	0.434
	Vessels	0.893	0.420	0.034
	LMSD	1.261	0.519	0.015
	Occlusion	0.799	0.477	0.094
	Lesions	-0.197	0.121	0.104
	DM*SMK	-0.751	0.966	0.437
	HYP*SMK	0.623	1.049	0.553
Step 4	Age	-0.011	0.018	0.528

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	DM	0.779	0.624	0.212
	HYP	-0.326	0.620	0.599
	HYPCHOL	1.460	0.539	0.007
	FH	0.339	0.429	0.428
	Vessels	0.901	0.419	0.032
	LMSD	1.219	0.504	0.016
	Occlusion	0.786	0.476	0.099
	Lesions	-0.199	0.121	0.100
	DM*SMK	-0.621	0.895	0.488
	HYP*SMK	0.874	0.753	0.246
Step 5	Age	-0.010	0.018	0.567
	DM	0.704	0.612	0.250
	HYPCHOL	1.372	0.506	0.007
	FH	0.314	0.425	0.460
	Vessels	0.852	0.406	0.036
	LMSD	1.175	0.499	0.019
	Occlusion	0.735	0.468	0.116
	Lesions	-0.189	0.119	0.112
	DM*SMK	-0.479	0.865	0.580
	HYP*SMK	0.661	0.640	0.301
Step 6	Age	-0.011	0.018	0.553
	DM	0.471	0.469	0.316
	HYPCHOL	1.299	0.486	0.008
	FH	0.291	0.426	0.493

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	Vessels	0.870	0.405	0.032
	LMSD	1.166	0.504	0.021
	Occlusion	0.766	0.468	0.102
	Lesions	-0.187	0.119	0.117
	HYP*SMK	0.438	0.509	0.389
Step 7	DM	0.433	0.464	0.351
	HYPCHOL	1.193	0.456	0.009
	FH	0.266	0.428	0.534
	Vessels	0.800	0.387	0.039
	LMSD	1.142	0.502	0.023
	Occlusion	0.723	0.460	0.116
	Lesions	-0.177	0.117	0.131
	HYP*SMK	0.472	0.512	0.357
Step 8	DM	0.431	0.460	0.349
	HYPCHOL	1.206	0.455	0.008
	Vessels	0.810	0.393	0.039
	LMSD	1.151	0.497	0.020
	Occlusion	0.776	0.453	0.087
	Lesions	-0.178	0.118	0.131
	HYP*SMK	0.581	0.478	0.224
Step 9	HYPCHOL	1.223	0.458	0.008
	Vessels	0.813	0.393	0.039
	LMSD	1.179	0.486	0.015

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	Occlusion	0.715	0.451	0.113
	Lesions	-0.179	0.119	0.135
	HYP*SMK	0.816	0.408	0.046
Step 10	HYPCHOL	1.049	0.439	0.017
	Vessels	0.474	0.306	0.122
	LMSD	0.873	0.445	0.050
	Occlusion	0.602	0.441	0.172
	HYP*SMK	0.632	0.398	0.112
Step 11	HYPCHOL	1.129	0.422	0.007
	Vessels	0.609	0.283	0.031
	LMSD	1.043	0.413	0.012
	HYP*SMK	0.674	0.393	0.087

The odds of event occurrence increases by 3.093 times with hypercholesterolemia and 1.839 times with number of vessels involved. Similarly the odd for left main stem disease is 2.838 times and for interaction term it is 1.962 times.

Table 5: Odds Ratio for Male

Factors	Odds
HYPCHOL	3.093
Vessels	1.839
LMSD	2.838
HYP*SMK	1.962

Similarly the survival time for female is given by the model

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$$y_{i,f} = 0.087Age + 9.859DM + 10.443HYP + 0.230Lesions + 15.653DM * HYP - -(22)$$

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.

Table 6: Variables in Cox Regression Model for Female

		B	SE	Sig.
Step 1	Age	0.087	0.091	0.039
	DM	9.859	101.948	0.023
	HYP	10.443	101.950	0.018
	HYPCHOL	-0.086	1.664	0.959
	SMK	-10.762	182.554	0.953
	FH	0.729	1.627	0.654
	Vessels	-1.591	1.345	0.237
	LMSD	1.139	1.562	0.466
	Occlusion	1.245	1.650	0.451
	Lesions	0.230	0.319	0.020
	DM*HYP	-10.552	101.965	0.018

The odds of survival in females are 1.091 times if the patient is younger. Likewise, it is 19.13 and 34.30 times if it is diabetes and hypertension respectively. Also the odds for the lesions it is 1.259 times and for the joint effect it is 6.28 times.Table 7 presents the odds ratios for female participants across various factors. Age has an odds ratio of 1.091, suggesting a slight

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increase in the odds of the condition with age. Diabetes Mellitus (DM) shows a substantially higher odds ratio of 19.13, indicating a strong association with the outcome. Hypertension (HYP) has an even higher odds ratio of 34.30, highlighting a very significant relationship. The presence of lesions has an odds ratio of 1.259, suggesting a mild increase in the odds. Finally, the combined effect of Diabetes Mellitus and Hypertension (DM*HYP) shows an odds ratio of 6.28, indicating a notable interaction effect between these two factors.

Kaplan-Meier

The preliminary analysis in the present study while computing Kaplan-Meier estimates is shown in the Figure 12. The Figure shows that $\hat{S}(0)= 1$ 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.

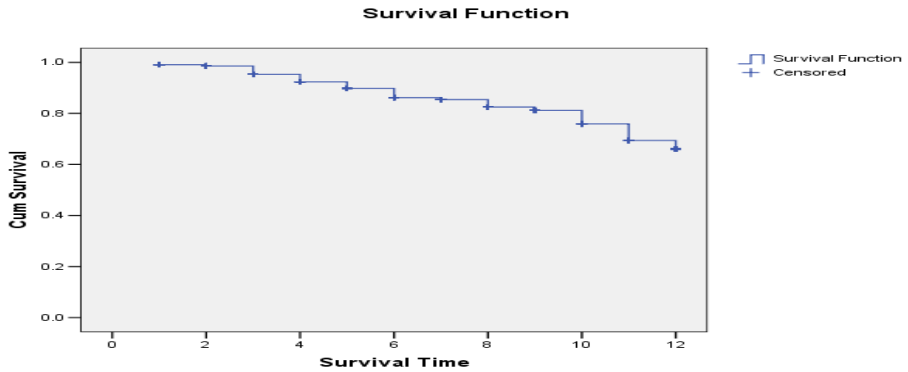

Figure 22: Survival Function

Analyzing Figure 13 it is observed that the survival of patients from death having coronary artery disease is same till 7 months. After that the male

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patients have higher probability of experiencing the event where the female's life stabilizes.

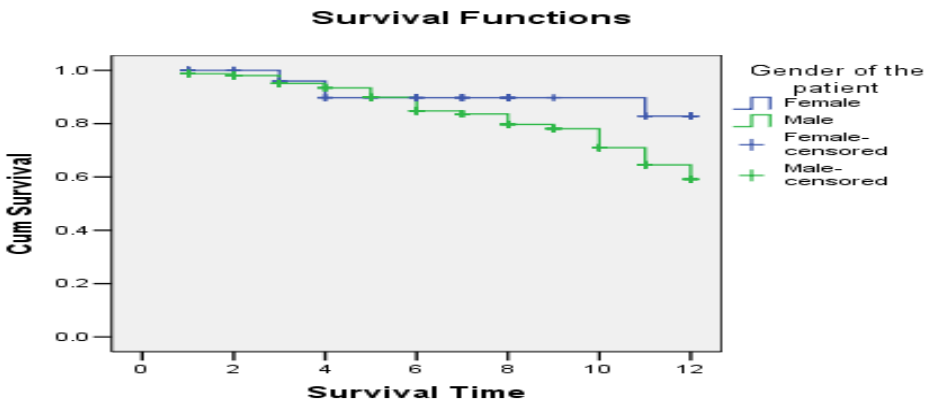

Figure 23: Gender Wise Survival Function

Kaplan-Meier for Hypertension

Table 8 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 7: Means for Survival Time of Hypertension

HYP	Mean			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
No	11.271	0.247	10.787	11.755
Yes	9.733	0.383	8.983	10.484
Overall	10.556	0.228	10.109	11.003

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The above results can be verified with the help of Figure 14 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.

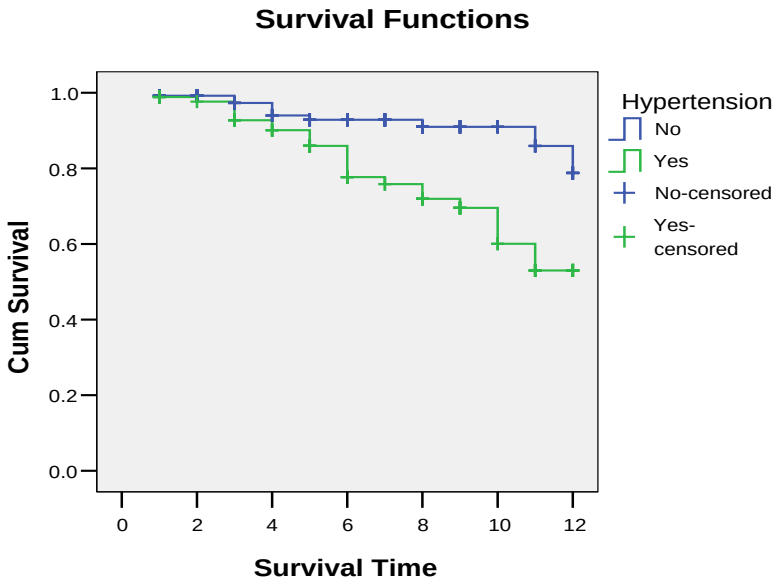

Figure 24: Survival Function for Hypertension

Kaplan-Meier for Hypercholesterolemia

As shown in Table 9 that 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.

Table 8: Means for Survival Time of Hypercholesterolemia

HYPCHOL	Mean			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
No	11.033	0.215	10.611	11.455

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Yes	8.170	0.706	6.786	9.555
Overall	10.556	0.228	10.109	11.003

The above survival time can also be verified with the help of Figure 15, 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.

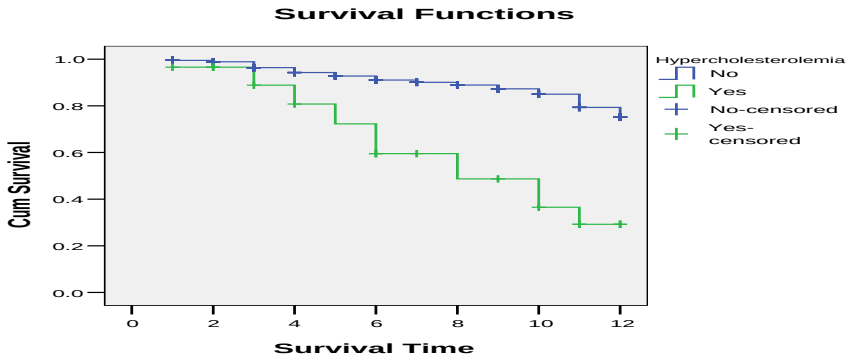

Figure 25: Survival Function for Hypercholesterolemia

Kaplan-Meier for Smoking

Table 10 shows that the mean survival time of CAD for patients having the habit of smoking is 9.462 and for non smokers it is 10.938.

Table 9: Means for Survival Time of Smoking

SMK	Mean			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
No	10.938	0.229	10.489	11.387
Yes	9.462	0.540	8.402	10.521

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Over all	10.556	0.228	10.109	11.003

Survival function for smokers and non smokers is given in Figure 16, which shows that non smoker CAD patient live longer than that of smokers.

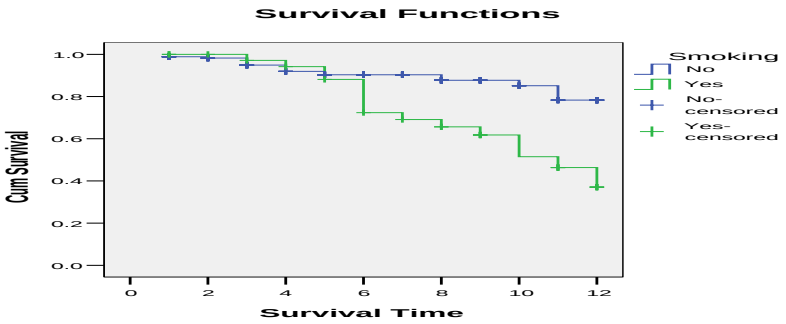

Figure 26: Survival Function for Smoking

5.3.4 Kaplan-Meier for Diabetes Mellitus

Table 11 shows 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. **Table 10: Means for Survival Time of Diabetes Mellitus**

DM	Mean			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
No	11.147	0.243	10.670	11.624
Yes	9.675	0.419	8.854	10.496
Overall	10.556	0.228	10.109	11.003

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The above results can be verified with the help of Figure 17, which gives us the survival 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.

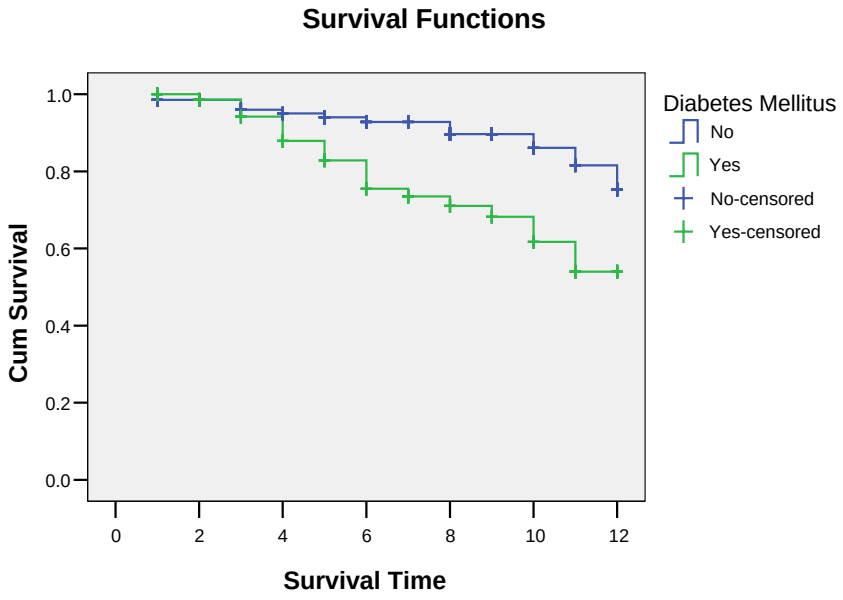

Figure 27: Survival Function for Diabetes Mellitus

5. Conclusion

The study results highlight that diabetes, hypertension, hypercholesterolemia, and smoking are key risk factors for coronary artery disease (CAD). Male patients with CAD are at higher risk and tend to have shorter life expectancy compared to females. Cox regression analysis identified hypercholesterolemia, Left Main Stem Disease (LMSD), total occlusion, and the combined effect of diabetes and smoking as significant factors. Gender-based differences show that male survival is linked to cholesterol levels, blocked vessels, LMSD, and the interaction of hypertension and smoking, with males having higher odds of events in these conditions. In

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contrast, females are more at risk if diabetic, hypertensive, or older. Major risk factors for CAD include a sedentary lifestyle, hypercholesterolemia, obesity, family history, old age, smoking, hypertension, and diabetes, with some being non-modifiable (e.g., family history, age) and others modifiable (e.g., lifestyle, diabetes, cholesterol, smoking, obesity).

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