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Survival Analysis: A Major Decision Technique in Healthcare Practices

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İlker Etikan*, Ogunjesa Babatope

**Near East University Faculty of Medicine Department of Biostatistics. Nicosia/ Cyprus*

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ABSTRACT

Aim The study seeks to explain the concept of survival analysis and the various methods used in analyzing survival data. **Methods** In order to have a practical application of these methods as regards clinical investigation, the data of the first 250 patients of the Worchester acute myocardial infarction (AMI) study (1975-2011), USA was extracted and analyzed using the SPSS version 20 computer package. The focus is to establish if there is any significant difference in the survival time relative to the gender of the patients after suffering from a heart attack. Variables such as the age, gender, heart rate, systolic blood pressure and the body mass index (BMI) of the patients were analyzed in order to discover if they have effects on the occurrence of death of the patients. **Results** From the descriptive analysis of the heart attack patients, 95 (38%) are male, while 155 (62%) are female. Patients between the ages 30-49 years old are 23 (9.2%), patients between 50-69 years old are 80 (32%), patients between 70-89 years old are 133 (53.2%) while patients between 90-109 years old are 14 (5.6%). At a significant level of 0.05, the Log rank, Brelow and Tarone Ware tests of the Kaplan Meier method all shows that there is no significant difference in the survival time between the male and female patients. Result from the Cox regression shows that there is no significant difference in death risk occurrence between the male and the female patients while the effects of Patients' Age, Heart Rate, Systolic Blood Pressure and Body Mass Index (BMI) are found significant. **Conclusion** It can, therefore, be concluded that gender difference does not have any significant impact on the survival time for patients with heart attacks. However, the study found that the increment in systolic blood pressure and the BMI covariates tend to reduce risk of death occurring in attack patients. The older a patient becomes increased the risk of death while the heart rate equally have a tendency to increase the risk of death occurrence.

INTRODUCTION

The pursuit of precision is a core objective of nearly all human field endeavors. In the healthcare settings, evidence-based medicine is essential in tackling the scourge of diseases occurrence from causes that could be attributed to factors such as genetics, changes in social lifestyles, nutrition, environmental changes, and so on.

In a more specific term, medical practitioners in oncology may be interested to understand the effect of some genetic or proteomic biomarkers on prognosis of cancer patients. In Nephrology research, treatment, Nephrologists interest could lie on what impact does risk factors such as diabetes, hypertension and other cardiovascular diseases have on chronic kidney diseases (CVD) while Cardiologists in heart studies would desire to know the outcome of physical exercises, diets or family health history in understanding cardiac heart problems in patients.

Therefore, various Health and Health Allied Professionals rely on vital decision tools in drawing inferences such as what type of drug medication is best suited for a disease cure or management as well as what the best safety inclined procedure is best suited for a surgical operation. In making conclusions like these, the statistical results of experimental and observational studies usually play a key role in this decision making.

Under this study, some application of survival analysis methods will be employed to draw inferences using the first 250 patients from the famous Worchester heart attack study (1975-2011) conducted by Dr. Robert J Golderg of the University of Massachusetts Medical School, USA. The Worchester Study has the objective to evaluate the pattern trends of heart attack occurrence as well as the acute myocardial infarction (AMI) survival rate in the Worchester metropolitan area. The data are culled from the Hosmer et al., a textbook on Applied Survival Analysis [1]

Research Objectives

(1) The study seeks to explain the concept of survival analysis

(2) The study will also give descriptions of various survival analysis methods and their underlying assumptions

(3) Survival method's application to the first 250 patients of the Worchester heart study in order to evaluate the significant difference in the survival time of patients hinged on gender criterion.

(4) Explaining the effects of covariate variables such as BMI, Age, Heart rate, and Systolic blood on risk of death for patients suffering from a heart attack.

Concept of Survival Analysis

Survival Analysis is a widely used inferential statistical operation in clinical studies; especially in prospective studies. Though, its application is also found in epidemiology when testing for associations in epidemiology studies [2]. Prospective studies which are also called cohort studies are studies in which subjects are assigned randomly to certain exposure(s) and are followed up for a specific period of time to understand resulting impact the exposure(s) have on the subjects [3,4]. The longitudinal effect behind this type of study gives an allowance to succinctly examine change occurrences in the subjects as a result of the exposures as well as context of time such event happens. An example of a prospective study is the conduct of clinical trials. While on the other hand, retrospective studies lay emphasis on past or historical data measurement from subjects and reference groups to find out any likely changes resulting from a risk factor [5]. Examples of this include case control study and so on.

The usage of survival analytical methods is more pronounced in handling measurements derived from prospective studies by evaluating event occurrence, time of such event and the nature of the event. However, its usage can also be found in some retrospective studies in which this research work is an example of.

What is Survival Analysis?

The method of data processing in which the outcome variable is the time prior the event of interest occurring is widely called as survival analysis [6]. According to [7], he considered it as a timeline analysis that understudies some groups of individuals with some prior experience with a view to looking forward to the occurrence of an event of interest. The survival analysis is done to majorly help describe the pattern of survival over a time period; evaluate risk factors or treatment effect that affects survival duration; make comparison between different survival patterns of risk factors or treatments under investigations and as

well make some estimated predictions of survival for a group of subjects or individuals with unique attributes [8].

The event of interest varies according to the objectives of the field of study. In non-clinical settings such as engineering, it could be an event of machinery breakdown, product defects or failure of an industrial process. In the field of economics and management sciences, it could be loaned payment default, business foldup. But in the context of biological or clinical field, it could be the death of a patient or organism, treatment relapse, patient recovery, entering or departing a clinical phase, duration of surgical procedures, time for a couple to conceive, duration of birth occurrence, treatment cure and so on [9,10].In another other way round, it could be to examine the best of interventions among various alternatives e.g. Drugs potency comparisons. However, in medical studies, the most common event of interest anticipated is death occurrence [11]. The time prior this event occurrence is called the survival time. According to [12], the survival time is defined as the time commencing from a definite point (baseline) up to the time of event occurrence. Such time could be in minutes, hours, days, weeks or in years. Suppose, the event of interest is until the blood sugar level drops to an expected level, then the time until when that expected drop happens is called the survival time.

However, the occurrence of an event of interest is often plagued with some uncertainties arising from patients undergoing a study. These uncertainties arise from the inability of some patients to witness the event of interest due to some factors. According to [9], the following factors were identified:

1. When Patients have not witnessed the event of interest when the study came to an end

2. Patients lost to follow up in the course of the study

3. A different event was experienced by patients, which was quite not similar to what was being expected.

This scenario is regarded as censoring.

Censoring

From another dimension, censoring in survival analysis occurs when there is incomplete information on the status of subjects (s) as regard to experiencing the event of interest. For an

example in a clinical study to examine the preventive strength of a new drug medication to manage a heart attack diseases. Given that a group of patients are enrolled in this study to last for 53 weeks and the event of interest is death. Patients who dropped out of the study, thereby not completing the study, or patients who do not experience the event of interest and perhaps experience other events, not of interest, or patients who are alive throughout the duration of study are all considered censored patients or subjects.

The diagram below gives a description of censored events in a study.

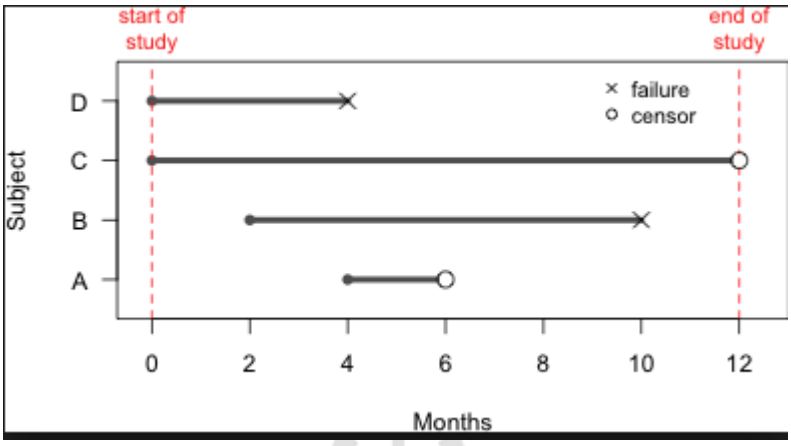

Figure 1: Censoring in survival analysis

There are two types of censoring in survival analysis, namely right censoring and left censoring as shown in the diagram below.

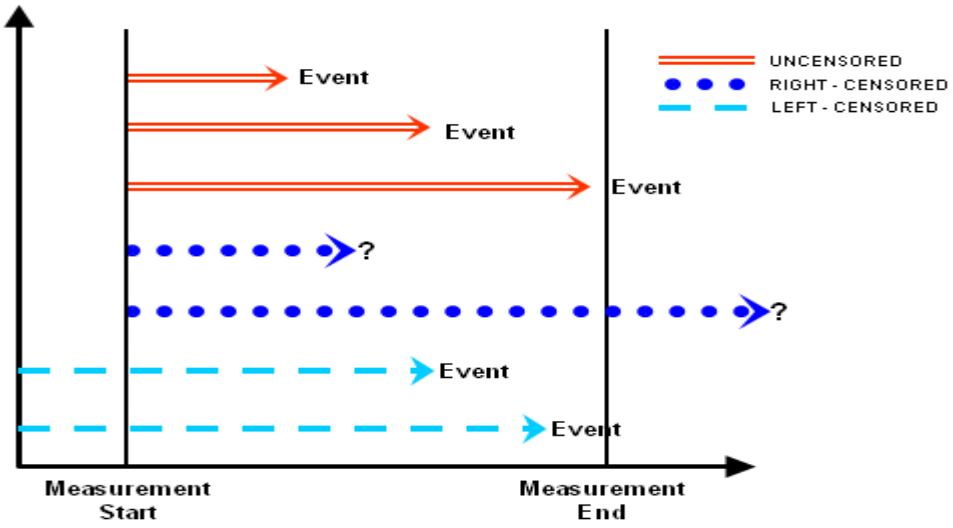

Figure 2: Right and Left Censoring in Survival Analysis

A right censoring occurs when the event of interest by some patients are beyond the set timeline of the study. That is some patients do not experience the event in the course of the study by dropping off. Though not often considered in many studies, a left censoring occurs in the circumstance in which the time to an event cannot be ascertained, well defined or the said event has happened before the commencement of the study. For an instance in a study to examine the recurrence of cancer growth in a group of patients, if some certain patients have begun to experience the recurrence of cancer growth before the study commence then we can consider them as left censored observations. Another form of censoring is the interval censoring. This censoring thus occurs when the event of interest for a subject lies within a range of time [13]. Hence it means that rather for the event to be observed holistically (on point measurement), it can only be observed in an interval measure (the event of interest occurrence lies between a time interval). This type of censoring is common in HIV/AIDS studies when the event of interest is the occurrence of diagnosing of AIDS (Acquired Immune Deficiency Syndrome) from an infected group. Since the test diagnosing can only be done periodically, therefore the time of diagnosing would be within a time interval. However, in the context of this research work, we are considering the right censoring approach.

Another similar phenomenon to censoring in survival analysis is truncation. Truncation occurs via sampling bias from investigators enlisting patients in a study. It pertains to the selection of who is qualified or not qualified to be enrolled in the study. Criteria for selection could be what age or category of age should be selected, what percentage of gender should be chosen, the severity level of initial diagnosis of an ailment, socioeconomic status of patients, weight or height level and so on.

The Survival and Hazard Functions

The survival analysis methodology help develop two major mathematical concepts to model data from survival analysis. These two mathematical concepts are probabilities with, which helps to describe the event of interest as related to time. The first one is known as Survival function or survival probability [S(t)] which emphasis on not experiencing the event of interest while the second one is the Hazard function or hazard probability [(λ (t)] which emphasis on an instantaneously occurrence of the event of interest at a point in time.

The survival function is written as:

$$S(T) = Pr\{T \geq t\}.$$

Given that T indicates the time until an event of interest (death in this context of this article), this function above gave the probability that the event of interest has not yet happen with time (t). Therefore, the survival function S (T) can be stated as the probability of a subject surviving beyond time (t). The survival curve is derived when the proportion of the surviving subjects is plotted against the time.

The **Hazard Function** according to [14] provides the rate of event occurrence (risk of death as regards this study) at a time (t). It is mathematically stated as:

$$\lambda(t) = \lim_{\Delta t \to 0} P(t \leq T < t + \Delta t \mid T \geq t)\,\Delta t$$

Generally stated, the survival function gave an insight into the overall non –occurrence of events of interest while the hazard function measures the rate of event occurrence.

Methods for Estimating Survival Data

Majorly, the analysis of survival data can be done using parametric and non-parametric methodologies. The decision about which method is to be adopted is reached by identifying if the data follows some probability distribution assumptions. Often time, insight about a pattern of distribution is given by the graphical plots of the survival curve. If found that the data follows some distribution properties, the parametric method can be adopted for the study and essential derivation of parameters can be inferred to describe the survival pattern. Otherwise, the non- parametric methods are used.

Parametric Survival Methods: These methods are used when the survival data have some predictive distribution pattern in line with some probability distributions. These methods offer greater precision in the prediction of the time of an event of interest. Examples of these survival distributions are Exponential distribution, Weibull distribution, Gompertz and Log-Logistic distribution [15].

One commonly used distributions of survival distribution is the exponential distribution. For the exponential distribution, the instantaneous hazard is plotted against the time to infer if the distribution of the survival data can be fitted into the distribution. A straight line plot is generated by this method. Measured by mean λ, the instantaneous hazard function of the exponential distribution remains relatively constant with time. The logarithm of the cumulative hazard rate can equally be plotted against the logarithm of the time.

Non -Parametric Survival Methods: Theses methods are adopted when there is no definite probability distribution pattern in the survival data. They comprise nonparametric and semiparametric methods. In the context of this study, the examples of these methods will be used to analyze our heart attack study data. Examples of these methods include Life table, Kaplan Meier, Nelson –Aalen method, Cox regression and so on.

Life Table

When there are large data sets of patients or subjects to be considered with a goal also to cut costs, life table is given a greater preference. A typical assumption of the life table is that dropped out subjects experience a uniform event of interest. The life table gives the timeline proportion of the cumulative hazard function, the time of survival and the rates of hazard of the patients or subjects undergoing the study. Both subjects that witness the event of interest and those that do not (censored) are included in the resultant analysis of this table. Interval censored observation are mostly best fitted for a life table analysis. However, due to more advancement in survival data analysis, the usage of the Kaplan Meier method is used in the place of life table in recent times.

Kaplan Meier Survival Analysis

This is an example of a non-parametric method to derive survival curves of various treatments under consideration. It puts emphasis on the survival time of each of the subjects, and that for a subject to be censored is not connected to the occurrence of the event of interest. In computing the survival of the patients or subjects, the exact time of when the event of interest occurred (death in this case) is being used [16]. Likewise, computation of the survival function can only be done when there is a declared outcome while withdrawals are ignored.

The Kaplan Meier survival function mathematical expression is given as:

$$\hat{S}(t) = \prod_{t_i \leq t} \frac{n_i - d_i}{n_i}$$

Where *ni* is the number of subjects at risk and *di i*s the number of subjects who fail both at time *t*. Aside the assumptions of randomness of subjects which are also considered independent in the population of interest, this method also assumes that subjects that are

being censored have equal probabilities of surviving like those who remain in the study. At each distinctly survival time, the survival time estimates changes, but remain unchanged when censoring occurs except the fact that there is a coincidence of a censored subject at a time that another subject experience the event of interest(death or failure).

Flemington-Harrington Estimator

This method makes use of Nelson-Aalen computation of the cumulative hazard to estimate the survival function of a survival data. The survival function is given as shown below.

$$S(t) = e^{-H(t)}$$

Where *H* (t) is the total hazard for all time up to time *t.*

Cox Regression Model

The Cox Regression model is an advanced semi parametric analytical method that evaluates the differences among the survival curves of groups of subjects under study consideration and equally examining the effects other variable factors called coverts have in the event of interest [17]. Irrespective of the form of the covariates whether they are discrete or continuous, the Cox regression model computes individual tests for each of them as well as an overall test for all groups in consideration. Its account for being a parametric model stemmed from the fact that the covariates are parametric in nature whiles its non- parametric properties stemmed from the fact that the baseline hazard function is not clearly defined [18].

The Cox hazard proportional regression model is given as follows:

$$\lambda(t;z) = \lambda o(t) \exp\left(\sum_{i=1}^{p} \beta i z i\right)$$

Where λo (t) is the initial hazard function when all z is zero. βi are unknown co-efficient and the *Zi* are p-dimensional covariates.

The Cox hazard proportion model assumes that censoring occurs randomly, the time is continuous and that the hazard function for two subjects relative to covariates combinations are independent of time.

Test of Goodness of fit

In a bid to test for significant difference among various survival curves; it could be a survival time curve for a group of patients that are assigned a new drug and another group of patients assigned a placebo, the comparison of their respective survival curves can be done and test of significant difference can be conducted. Most popular of these tests is the Log rank test which is an approximated chi-square distribution that makes comparison of the several survival time curves of the Kaplan Meier analysis of the groups under consideration. It tests if there is a significant difference in the time of survival between different independent groups under study.

Having considered the various methods used in analyzing survival data, some of these procedural methods will be used in analyzing a heart study data culled from Hosmer et al., [1].

The study seeks to establish the influence of several factors such as Age, Gender, Heart Rate(HR), Systolic Blood Pressure (SYSBP), and Body Mass Index (BMI) on the time of survival following a heart attack. The event of interest is death while patients without this experience are right censored.

RESULT PRESENTATION

Table 1: Descriptive Statistics of Heart Attack Patients

		Frequency	Percentage (%)
Gender	Male	95	38.00
	Female	155	62.00
	Total	250	100.00
Status	Alive (follow up)	133	53.20
	Death	177	46.80
	Total	250	100.00
Age category	30-49	23	9.20
	50-69	80	32.00
	70-89	133	53.20
	90-109	14	5.60

The descriptive data analysis shows that male patients account for 38% of the heart attack patients while 62% of the patients are females. 53.2 % of the patients were alive while 46.8% experienced the event of interest which is death. In terms of age, patients between 30-49

years are 9.2%, 32 % are between 50-69 years, 53.2% are between 70-89 years and 5.6% are between 90-109 years old.

Kaplan Meier Result Analysis

Table 2: Events and censored output

Case Processing Summary				
GENDER	Total N	N of Events	Censored	
			N	Percent
Female	155	64	91	58.7%
Male	95	53	42	44.2%
Overall	250	117	133	53.2%

Table 3: Means and Survival Times

Means and Medians for Survival Time								
GENDER	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Female	1475.762	73.358	1331.980	1619.543	2160.000	.	.	.
Male	1392.495	101.361	1193.828	1591.162	1577.000	307.709	973.891	2180.109
Overall	1492.305	62.911	1368.998	1615.611	2160.000	166.924	1832.829	2487.171
a. Estimation is limited to the largest survival time if it is censored.								

The above table shows that the mean survival time for male patients is 1392.495 ± 101.361 at 95% confidence interval while that of females is 1475.762 ± 73.358 at 95% confidence interval. The result above seems to indicate that female patients have longer survival times compared to their male counterparts. However, the significance of these values needs to be tested. And this is shown in the overall comparison table below.

Table 4: Overall Comparison Table

Overall Comparisons			
	Chi-Square	**df**	**Sig.**
Log Rank (Mantel-Cox)	2.310	1	.129
Breslow (Generalized Wilcoxon)	1.570	1	.210
Tarone-Ware	1.989	1	.158
Test of equality of survival distributions for the different levels of GENDER.			

The overall comparison table shows that the p-values of 0.129, 0.210 and 0.158 for the log rank test, Breslow and Tarone –Ware test, respectively are higher than the significance level α= 0.05, which indicates that the survival curves for the males and female patients are not significant.

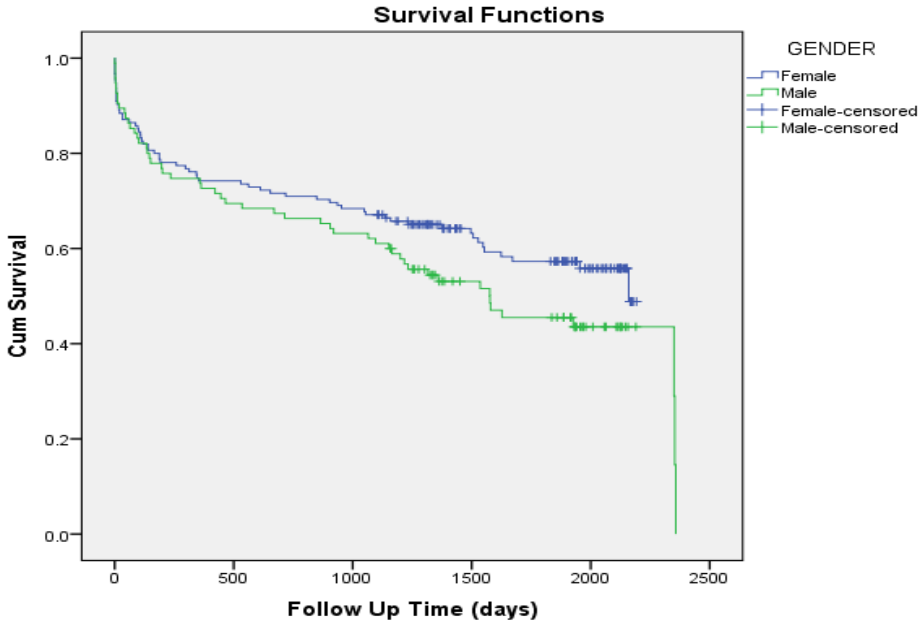

Figure 3: The survival curves for the male and female patients

The survival curve shows that both the male and female patients seem to have a similar death occurrence pattern at the early start of the study, but towards the middle and the end of the curve, the survival time of the male patients were lower compared to the female patients. However, their respective survival times are not significant to each other according to the overall comparison tests of Log rank, Breslow and Tarone-ware tests.

Cox Regression Output

Table 5: Omnibus Tests of Model

Omnibus Tests of Model Coefficients[a]									
-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
1088.102	87.600	5	.000	92.261	5	.000	92.261	5	.000
a. Beginning Block Number 1. Method = Enter									

From the Omnibus tests of model coefficients, it is found that the overall score of the model is significant since the p-value (0.000) is less than the value of alpha (α=0.05). It is therefore revealed that the five covariates namely Age, Gender, Heart Rate (HR), Systolic Blood Pressure (SYSBP) and Body Mass Index (BMI) significantly explain the variability in the hazard occurrence of the heart attack patients.

Table 6: Coefficient and Hazard Ratios Analysis

Variables in the Equation								
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
AGE	.055	.009	36.433	1	.000	1.057	1.038	1.076
GENDER	.169	.194	.762	1	.383	1.185	.810	1.733
HEART RATE	.016	.004	15.979	1	.000	1.016	1.008	1.024
SYSTOLIC BLOOD PRESURE	-.008	.003	6.726	1	.010	.992	.985	.998
BMI	-.048	.021	5.453	1	.020	.953	.915	.992

Hazard Function Interpretation [Exp (B)]

The Age hazard function is 1.057. This indicates that for a year increment in the age, the patient's chance not to survive after an attack increases by 1.057. However, the 95% confidence level for the age hazard function indicates that this is not significant. The hazard function for the gender covariate shows that male patients are 1.185 likely to experience death compared to the female patients. However, the 95% confidence level for the Gender hazard function indicates that this is not significant A unit increment in the heart rate increases the risk of death occurrence after a heart attack by 1.016.This also tends not to be significant considering the 95% confidence interval of the Heart rate hazard function. A unit increment in the systolic blood pressure reduces the risk of death by 0.992 or 0.9 % [(1-0.991)* 100=0.9%]. At 95% confidence interval, this measure is significant. A unit increment in BMI reduces the risk of death hazard of patients by 0.953 or 4.7 % [(1-0.953*100=4.7%]. At 95% confidence interval, the BMI hazard function measure is significant.

P-value with Alpha value Interpretation.

The P-value of the age is 0.000 and is lesser than the alpha value of 0.05, which means that age has a significant effect on the risk of death hazard from a heart attack. The P-values of the Heart Rate, Systolic Blood Pressure (SYSBP) and the Body Mass Index (BMI) given as

0.000, 0.010 and 0.020 respectively, are lesser than the alpha value of 0.05, hence these covariates are considered significantly to the patients' risk of experiencing death hazard.

However, the Gender with a P-value of 0.383 has no significant effect since its P-value is greater than an alpha value of 0.05 which entails that Gender has no significant effect on the risk of death occurrence.

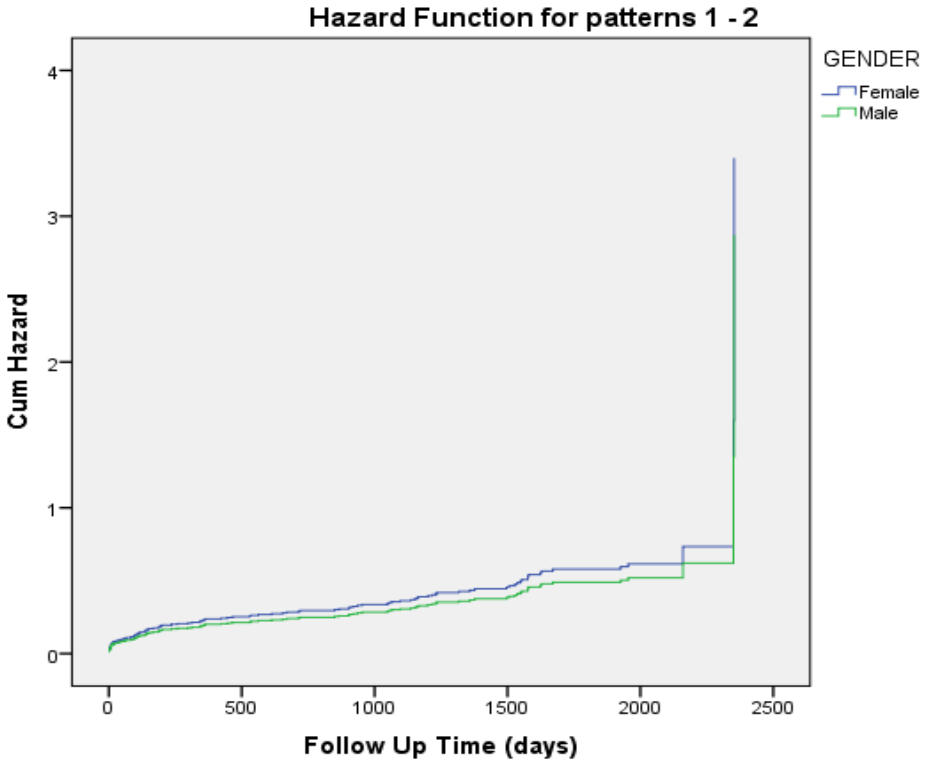

Figure 4: Hazard Function Graph showing comparison between male and female patients.

CONCLUSION

From the Kaplan Meier result outputs above, the mean survival time for male patients is 1392.495 ± 101.361 at 95% confidence interval while that of females is 1475.762 ± 73.358 at 95% confidence interval. However, the overall comparison statistic for the survival time given by the Log Rank test, Breslow test and Tarone ware test with p-values of 0.129, 0.210 and 0.158 respectively are all greater than the alpha value of 0.05. This indicated that there is no significant difference in the survival time of the male and female patients. This means that the male patients and the female patients have relatively the same time chance of surviving after a heart attack episode.

From the Cox regression result output, the gender hazard function shows that the male patients are at more risk to die compared to the female patients. However, the test shows that gender has no significant effect on the risk of dying. The Age, Heart Rate, Systolic Blood Pressure and Body Mass Index (BMI) covariates are all found to be significant at α=0.05. Also, a unit increment in the systolic blood pressure tends to reduce the risk of death by 0.9 % and a unit increment in BMI tends to reduce the risk of death hazard of patients 4.7 %.

However, the increment in age was found to increase the risk of death for patients.

Conflict of Interest

None

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