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Long Term Survival of CABG Patients in Age Groups Using Complete and Incomplete Populations (A New Approach)

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Abstract— In this paper long term survival of Coronary Artery Bypass Graft Surgery (CABG) patients in four age groups is considered. A new approach of complete population from its incomplete population of CABG patients of 12 years observations is applied for the survival analysis. Complete and incomplete Populations of the age groups are used in a well known survival model. In the complete population, censored patients are proportionally included into the known survived and died patients respectively. The availability of a complete population may represent better behavior of lifetimes / survival proportions for medical research. Survival proportions of the CABG patients are obtained from lifetime representing parametric model (Weibull). A classical technique, maximum likelihood method, in-conjunction with Davidon-Fletcher-Powell (DFP) optimization method and Cubic Interpolation method is used in estimation of survivor's proportions from the parametric model. For complete population Drop Methodology is introduced i.e. we may drop the term for censored observations from likelihood function. The survival proportions of complete and incomplete populations of the CABG patients with respect to the four age groups are presented in term of statistics and graphs (survival curves) discussed and concluded.

Keywords—CABG Patients, Complete & Incomplete Populations, Age Groups, Parametric survival model (Weibull), Maximum likelihood method, Davidon-Fletcher-Powell optimization method, Drop Methodology and Survivor's Proportions.

1. INTRODUCTION

The Coronary Artery Disease (CAD) is due to accumulation of cholesterol and other material, called plaque, within inner walls of the coronary arteries (the arteries that supply blood with oxygen and nutrients to heart muscles). As this build-up grows (Arteriosclerosis), comparatively less blood can flow through the arteries. Over the time (which differs from individual to individual) heart weakens. This leads to chest pain (Angina) which is a symptom of Myocardial Infarction (MI). When the clot (thrombus) completely cuts off the hearts blood supply, this may leads to permanent heart damage, called as heart attack (MI). Heart failure means the heart cannot pump required blood to the rest of the body (Dorlands Medical Dictionary (2009)). CAD is the leading cause of disability and death worldwide (see William, Stephen, Van -Thomas and Robert (2003), John (2003), Hansson (2005), Axel, Yiwen, Dalit, Veena, Elaine, Catia, Matthew, Jonathan, Edward & Len (2010) and Sun & Hoong (2011). The symptoms and signs of coronary artery disease are noted in the advanced stage of the disease. Initially, most of the individuals with CAD show no evidence of disease, whereas the disease progresses before the first onset of symptoms and often there is a sudden heart attack. The CAD is the most common cause of sudden death of men and women over 20 years of age (Rao and Kiran (2011)). The medical scientists; William, Ellis, Josef, Ralph and Robert (2003), Heymann (2002), Goldstein, Adams, Alberts, Appel, Brass, Bushnell, Culebras, DeGraba, Gorelick & Guyton (2006) and Jennifer (2008) are of the opinion that CABG is an effective treatment option for CAD patients. The medical research organizations like Heart and Stroke Foundation Canada (1997) and American Heart Association (2007) have classified risk factors of CABG patients as modifiable and non-modifiable. Modifiable risk factors are those factors, which may be controlled by changing life style or taking medications to reduce cardiovascular risk. These risk factors include high blood pressure (hypertension), diabetes, smoking, high cholesterol, sedentary lifestyle and obesity. Non-modifiable risk factors are those factors, which may not be changed. These factors include age, gender and family history (Genetic predisposition). William, Ellis, Josef, Ralph and Robert (1995) carried out the survival study on incomplete population (progressive censoring of type 1) of CABG patients comprising 2011 patients using Kaplan Meier method (1958). The patients were grouped with respect to Male, Female, Age, Hypertension, Diabetes, and Ejection Fraction, Vessels, Congestive Heart Failure, Elective and Emergency Surgery. The patients were undergone through a first re-operation at Emory University hospitals from 1975 to 1993. This study also comprises the same data set of 2011 patients. The details of patients are given in the article (1995). We have carried out survival analysis of CABG patients by parametric estimations, in modifiable risk factors (Hypertension and Diabetes) in the paper; see Saleem M, Mahmud. Z and Khan.K.H); American Journal of Mathematics and Statistics, Vol. 2(5): 120-128, September 2012. In this paper we present survival analysis of the CABG patients with respect to non-modifiable risk factor (Age) i.e. Age Groups (Age less than 50; 50 to 59; 60 to 69 and 70 years & above (age groups I, II, III & IV respectively), in complete and incomplete Populations. In our paper, see Khan, Saleem and Mahmud (2011), we proposed a procedure, to make an incomplete population (*IP*), a complete population (*CP*). In the paper we also showed that the differences between the means of survival proportions of the CABG patients are statistically insignificant at 5% level of significance. The importance of parametric models for analysis of lifetime date has been indicated by Mann, Schefer and Singpurwala (1974), Nelson (1982), Cyrus (1981), Lawless (1982, 2003), Klein & Moeschberger (1997, 2003) and Sridhar and Mun Choon Chan (2009). The Exponential distribution model has been used by Lee, Kim and Jung (2006) in medical research for survival data of patients. The Weibull distribution model has been used for survival analysis by Cohen (1965), Gross and Clark (1975), Bunday (1981), Crow (1982), Klein & Moeschberger (1997, 2003), Lawrencce (1995), Abrenthy (1998), Hisada & Arizino (2002), Lawless (1982, 2003), David & Mitchel (2005) and Lang (2010). In particular, the survival study of chronic diseases, such as AIDS and Cancer, has been carried out by Bain and Englehardt (1991), Khan & Mahmud (1999), Klein & Moeschberger (1997, 2003), Lawless (1982, 2003) and Swaminathan and Brenner (1998, 2011) using Exponential and Weibull distributions. Lanju & William (2007) used Weibull distribution to human survival data of patients with plasma cell and in response-adaptive randomization for survival trials respectively. Lee, Kim and Jung (2006) used the exponential in medical research for survival data of the patients. We have concluded in our above article Saleem M, Mahmud. Z and Khan.K.H (2012) that the CABG patient's data has been adequately modeled by both distributions (Weibull and exponential).In this paper, the survivor proportions of the CABG patients are obtained for complete and in-complete populations of the CABG patients by parametric model (Weibull), using data of four age groups of CABG patients. Maximum likelihood method, in-conjunction with DFP optimization method and Cubic Interpolation method is used. A subroutine for maximizing log-likelihood function of the model is developed in FORTRAN program to obtain the estimates of the parameters of the model. The survival proportions of *IP* and *CP* of the CABG patients with respect to four age groups are presented in term of statistics and graphs (survival curves), discussed and concluded.

2. METHODOLOGY

In the paper, Khan, Saleem and Mahmud (2011) we have mentioned the method as proposed by Kaplan Meier (1958) and latter discussed by William (1995, 1997) and Lawless (1982, 2003) is: $S(t)=\prod_{j:t_j<t}(1-\frac{d_j}{n_j})$, where d_j and n_j are the number of items (individuals / patients) failed (died individuals) and number of individuals at risk at time t_j, that is, the number of individuals survived and uncensored at time t_{j-1}. This method may be applied to both censored and uncensored data, see Lawless (1982). In case of censored individuals (items) the analysis is performed on incomplete population (IP). In the above mentioned paper we proposed that the censored individuals c_j may be taken into account. The inclusion of splitted-censored individuals, c_j proportionally

$$\left[(1-\frac{d_j}{n_{j-1}-c_j})\times c_j \ and \ (\frac{d_j}{n_{j-1}-c_j})\times c_j\right]$$ into

known survived, n_j and died individual's d_j respectively makes the populations complete. Thus the survival analysis may be performed on the complete population (CP) from its IP. We, in our other paper see, Saleem, Mahmud and Khan (2012) have reproduced the form of likelihood function for a survival model, in the presence of censored data; as advocated by different researchers. The maximum likelihood method works by developing a likelihood function based on the available data and finding the estimates of parameters of a probability distribution that maximizes the likelihood function. This may be achieved by using iterative method, for details see Bunday & Al-Mutwali (1981). Khan & Mahmud (1999), Klein & Moeschberger (1997, 2003) and

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Lawless (1982, 2003), The likelihood function for all observed died and censored individuals is of the form:

$$L(t;\underline{\theta}) = \prod_{i=1}^{n} [f(t_i;\underline{\theta})]^{f_{t_i}} \prod_{i=1}^{n} [S(t_i;\underline{\theta})]^{c_{t_i}},$$ where

f_{t_i} & c_{t_i} are the number of died & censored individuals in interval *i* each of length *t*, $f(t;\underline{\theta})$ is *pdf* in a parametric model with survivor function, $S(t;\underline{\theta})$ & hazard function, $h(t;\underline{\theta})$ *and* $\underline{\theta}$ is vector of parameters say $\underline{\theta} = (\alpha, \beta)$ of the model . To obtain maximum likelihood estimates of parameters of a parametric model using DFP optimization method, we take negative log on both the sides of above equation and therefore by setting $l = -\ln(L(t;\underline{\theta}))$, we get:

$$l = -\sum_{i=1}^{n} f_{t_i} \ln f(t_i;\underline{\theta}) - \sum_{i=1}^{n} c_{t_i} \ln\left(S(t_i;\underline{\theta})\right)$$ or

$$l = -\sum_{i=1}^{n} f_{t_i} \ln h(t_i;\underline{\theta}) - \sum_{i=1}^{n} (f_{t_i} + c_{t_i}) \ln\left(S(t_i;\underline{\theta})\right);$$

(As $f(t_i;\underline{\theta}) = h(t_i;\underline{\theta})\, S(t_i;\underline{\theta})$)

Where, the first sum is for failure and the second sum is for all censored individuals.

Setting $N_{t_i} = (f_{t_i} + c_{t_i})$, where N_{t_i} represents total no of individuals at time t_i we get:

$$l = -\sum_{i=1}^{n} f_{t_i} \ln h(t_i;\underline{\theta}) - \sum_{i=1}^{n} (N_{t_i}) \ln\left(S(t_i;\underline{\theta})\right) \text{ --- (1)}$$

In this study time is partitioned into intervals, which are of unit length *t* starting from zero. Moreover, failures and censoring of the patients occur in each interval *i* of equal length of time *t*, $i = 1, 2, ..., 12.$.

For complete population, we propose that the Term of the likelihood function which represents Censored Observations may be Dropped from the likelihood function.

3. APPLICATION

We present detail application of above methodology for parametric model (Weibull distribution). Same procedure may be followed for other parametric models (Exponential distribution with $\beta = 1$; Gompertz, logistic,Log-Logistic, Gumbel etc.) and suitability of a survival model may be tested for a given data.

The probability density function (*pdf*) of Weibull distribution is: $f(t;\underline{\theta}) = \left(\frac{\beta}{\alpha}\right)\left(\frac{t}{\alpha}\right)^{\beta-1} e^{-\left(\frac{t}{\alpha}\right)^{\beta}}$,

where $\underline{\theta}$ is vector of parameters α and β; α is a scale parameter and β is a shape parameter; α, β and $t > 0$.

The survival and hazard functions of Weibull distribution are: $S(t;\underline{\theta}) = e^{-\left(\frac{t}{\alpha}\right)^{\beta}}$ and $h(t;\underline{\theta}) = \left(\frac{\beta}{\alpha}\right)\left(\frac{t}{\alpha}\right)^{\beta-1}$

For incomplete population replacing values of the survival and hazard functions of Weibull distribution in equation (1), we get

$$l = -\sum_{i=1}^{n} f_{t_i} \ln\left[\left(\frac{\beta}{\alpha}\right)\left(\frac{t_i}{\alpha}\right)^{\beta-1}\right] - \sum_{i=1}^{n} N_{t_i} \ln\left(e^{-\left(\frac{t_i}{\alpha}\right)^{\beta}}\right)$$

or

$$= -(F)\ln\left(\frac{\beta}{\alpha}\right) - (\beta - 1)\sum_{i=1}^{n} f_{t_i} \ln\left(\frac{t_i}{\alpha}\right) + \sum_{i=1}^{n} N_{t_i} \left(\frac{t_i}{\alpha}\right)^{\beta} \text{ --- (2)}$$

where, $F = \sum_{i=1}^{n} f_{t_i}$ is the total number of failures in a given time.

Differentiating (2) with respect to α *and* β and simplifying we get

$$\frac{\partial l}{\partial \alpha} = F\left(\frac{\beta}{\alpha}\right) - \left(\frac{\beta}{\alpha}\right)\sum_{i=1}^{n} N_{t_i} \left(\frac{t_i}{\alpha}\right)^{\beta}$$

(3)

$$\frac{\partial l}{\partial \beta} = -\frac{F}{\beta} - \sum_{i=1}^{n} f_{t_i} \ln\left(\frac{t_i}{\alpha}\right) + \sum_{i=1}^{n} N_{t_i} \left(\frac{t_i}{\alpha}\right)^{\beta} \ln\left(\frac{t_i}{\alpha}\right)$$

(4)

By using (2), (3) and (4) in the DFP optimization method, we find the parameters estimates for which value of the likelihood function is maximum.

For complete population Drop Methodology may be applied i.e. we may drop the term for censored observations from likelihood function, equation (2) instead of using the likelihood function for a complete population s mentioned by Lawless (1982, 2003). FORTRAN program for the parameters estimation of the Weibull model is developed. The optimal estimates of the scale and shape / location parameters (α and β respectively) of Weibull distribution using *CP* and *IP* of

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four age groups are obtained by maximizing the log-likelihood function. The *t*-ratios of the parameters are given in parenthesis. The values of parameters estimates, *t*-ratios, log-likelihood function and variance–covariance matrix are given below: -

4. AGE GROUPS (MALE AND FEMALE CABG PATIENTS)

The survival proportions $\hat{y}_t$ and $\tilde{y}_t$ of *CP* and *IP* respectively of age groups I, II, III and IV of CABG patients are obtained using Weibull distribution as explained earlier. Both the male and female CABG patients are included in the *CP* and *IP* of age groups I, II, III and IV. The optimal estimates of parameters obtained by maximizing the log-likelihood function are given below in table 1.

TABLE 1 Estimates of Parameters of Weibull Distribution Using *CP* and *IP* of Age Groups I,II,III and IV of CABG Patients:

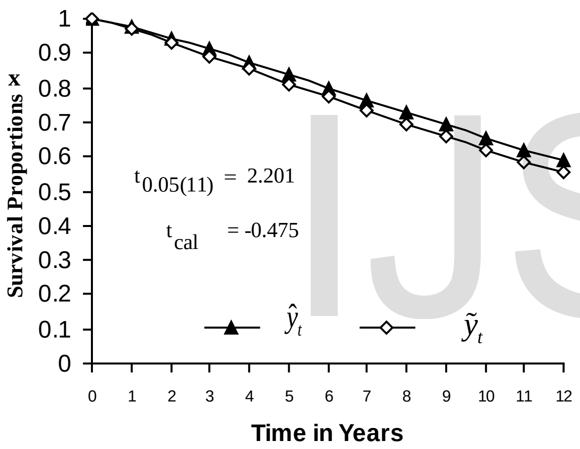
Parameters	Age Groups							
	I				II			
	CP		*IP*		*CP*		*IP*	
	Estimates/ (t-ratio)	Gradients	Estimates/ (t-ratio)	Gradients	Estimates/ (t-ratio)	Gradients	Estimates/ (t-ratio)	Gradients
α	19.918 (10.31)	1.5×10^{-9}	18.574 (5.88)	$-1.277\times10^{-}$	20.966 (15.25)	5.65×10^{-11}	18.413 (8.99)	$-4.58\times10^{-}$
β	1.253 (10.63)	4.43×10^{-8}	1.197 (8.34)	$-4.196\times10^{-}$	1.197 (16.76)	$-4.17\times10^{-}$	1.217 (13.13)	$-2.02\times10^{-}$
Log-Likelihood	415.9276		209.6061		1043.354		499.7652	
Variance–Covariance Matrix	$\begin{pmatrix} 3.735 & -0.131 \\ -0.131 & 1.39\times10^{-2} \end{pmatrix}$		$\begin{pmatrix} 9.981 & -0.329 \\ -0.329 & 2.06\times10^{-2} \end{pmatrix}$		$\begin{pmatrix} 1.889 & -5.83\times10^{-2} \\ -5.83\times10^{-2} & 5.1\times10^{-3} \end{pmatrix}$		$\begin{pmatrix} 4.195 & -0.140 \\ -0.140 & 8.59\times10^{-3} \end{pmatrix}$	
	III				IV			
	CP		*IP*		*CP*		*IP*	
	Estimates/ (t-ratio)	Gradients	Estimates/ (t-ratio)	Gradients	Estimates/ (t-ratio)	Gradients	Estimates/ (t-ratio)	Gradients
α	11.547 (29.81)	2.61×10^{-10}	12.089 (13.00)	5.6×10^{-6}	8.758 (25.39)	-1.96×10^{-8}	9.745 (9.5)	2.88×10^{-6}
β	1.330 (25.00)	9.74×10^{-9}	1.220 (17.22)	2.81×10^{-6}	1.414 (20.47)	1.97×10^{-8}	1.186 (12.66)	2.26×10^{-5}
Log-Likelihood	1783.982		729.3413		997.2853		362.5588	
Variance–Covariance Matrix	$\begin{pmatrix} 0.150 & -3.56\times10^{-3} \\ -3.56\times10^{-3} & 2.83\times10^{-3} \end{pmatrix}$		$\begin{pmatrix} 0.864 & -4.32\times10^{-2} \\ -4.32\times10^{-2} & 5.02\times10^{-3} \end{pmatrix}$		$\begin{pmatrix} 0.119 & 2.73\times10^{-3} \\ 2.73\times10^{-3} & 4.77\times10^{-3} \end{pmatrix}$		$\begin{pmatrix} 1.053 & -6.07\times10^{-2} \\ -6.07\times10^{-2} & 8.78\times10^{-3} \end{pmatrix}$	

The estimated values of scale parameter $\alpha > 0$ and shape parameter $\beta > 0$ for *CP* and *IP* of age groups I,II,III and IV of CABG patients are given in the table 1 along with *t*-ratios in the parenthesis, indicating that the estimates of scale and shape parameters are significant at 5% level of significance. The estimated values of β is greater than 1 (for *CP* and *IP* of the age groups I,II,III and IV) which indicates increasing failure rate with the increase in age. The negative values of co-variances (for *CP* and *IP* of the age groups I,II,III and IV of CABG patients) indicates that the movements of $\hat{\alpha}$ and $\hat{\beta}$ are in the opposite directions.

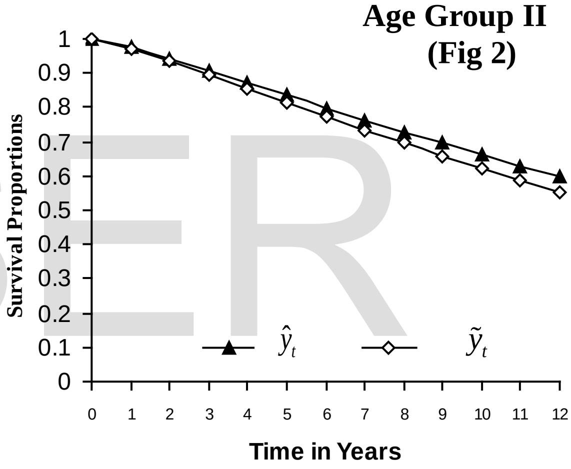
The values of estimated survival proportions of *CP* and *IP* of age groups I, II, III and IV of CABG patients are given in table 2 and corresponding graphs (survival curves) in fig 1 to 4.

Table 2 Survival Proportions $\hat{y}_t$ and $\tilde{y}_t$ of *CP* and *IP* respectively of Age Groups I, II,III and IV from Weibull Distribution

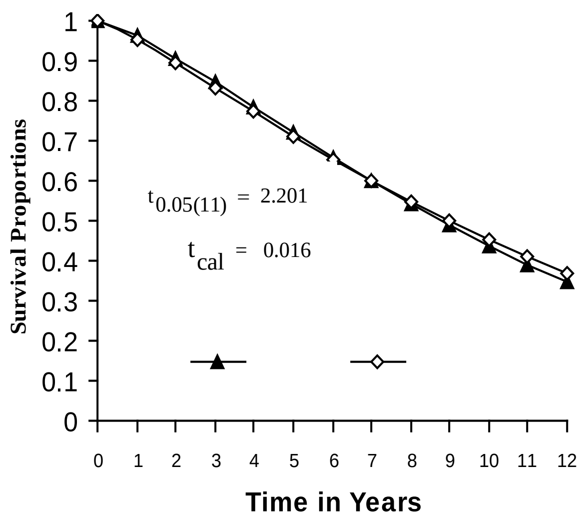
Years (t)	Age Groups							
	I		II		III		IV	
	CP	IP	CP	IP	CP	IP	CP	IP
0	1	1	1	1	1	1	1	1
1	0.976	0.97	0.974	0.972	0.962	0.953	0.954	0.935
2	0.945	0.933	0.941	0.935	0.907	0.895	0.883	0.858
3	0.911	0.893	0.907	0.896	0.846	0.833	0.802	0.781
4	0.874	0.853	0.871	0.856	0.783	0.772	0.718	0.707
5	0.837	0.812	0.835	0.815	0.720	0.711	0.636	0.636
6	0.800	0.772	0.799	0.775	0.658	0.654	0.556	0.57
7	0.763	0.733	0.764	0.735	0.598	0.599	0.482	0.509
8	0.727	0.694	0.729	0.696	0.541	0.547	0.414	0.453
9	0.691	0.657	0.695	0.658	0.487	0.498	0.353	0.403
10	0.656	0.621	0.662	0.622	0.437	0.452	0.299	0.357
11	0.621	0.586	0.630	0.586	0.391	0.41	0.251	0.315
12	0.588	0.553	0.598	0.552	0.349	0.371	0.209	0.278



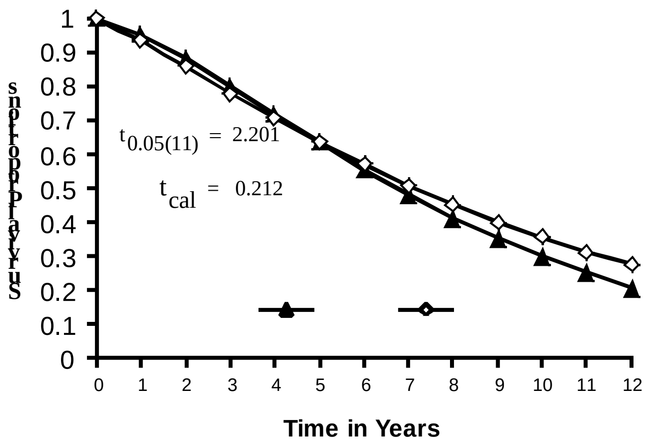
Age Group II
(Fig 2)



Age Group III
(Fig 3)



Age Group IV
(Fig 4)



STATISTICAL ANALYSIS

The differences between the means μ_C and μ_I of survival proportions obtained by using Weibull distribution, of *CP* and *IP* respectively, of CABG patients, age groups I, II, III and IV, are tested using *t*-statistic under the null hypothesis $H_o : \mu_C < \mu_I$, against an alternative hypothesis $H_1 : \mu_C \geq \mu_I$. The values of *t*-statistic for the age groups I, II, III and IV are -8.362, 5.407, -0.328 and -1.827 respectively when compared with $t_{0.05(11)} = -20201 - 20201$, suggest that H_o is accepted in case of age groups III and IV which means that the differences between the means of *CP* and *IP* for age groups III and IV are statistically insignificant at 5% level of significance and it shows that the data has been suitably modeled.

DISCUSSION

The graphs in fig 1to 4 of survival proportions obtained by using Weibull distribution of CP and IP for age groups I, II, III and IV of CABG patients indicates that for the age groups I and II, the difference between survival proportions of CP and IP is small at the start, continuously increasing and the survival proportions of CP are higher than those of IP. This is due to less mortality in age groups I & II. Whereas for age groups III and IV the survival proportions of CP are slightly higher at the start and lower at the end than those of IP. This is due to more mortality in age groups III & IV, as is true in real lif.

5. CONCLUSION

The complete population gives true picture of survival. Further, the survival proportions of age group IV (age 70 years and above) are lower than those of age groups I, II and III as observed by world over by the medical scientists. These survival proportions of CP may be used as reliable estimates for forecasting of survival proportions of the CABG patients using Kalman Filteration technique.

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