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SURVIVAL ANALYSIS OF ACUTE MYOCARDIAL INFARCTION PATIENTS USING NON-PARAMETRIC AND PARAMETRIC APPROACHES

Gurprit Grover, Rumi Dutta*

Department of Statistics, University of Delhi, Delhi, India.

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Abstract: *In this paper, an investigation about the survival pattern of acute myocardial infarction (AMI) patients was explored, using non-parametric and parametric modeling strategies. Median survival time and their associated confidence intervals are often used to summarize the survival pattern of a group of patients in clinical data with failure- time end points. Although there is an extensive literature on this topic but there is no study that compares the survival pattern of AMI patients using the non-parametric and parametric modeling strategies. Life table estimates of cumulative survival function of AMI patients stratified by age and marital status show a poor prognosis for older and married patients respectively. The estimated median survival time of overall AMI patients by clinical life table method is 3.31(95% confidence interval, 2.80-3.82) years. Probability plotting and Anderson-Darling goodness of fit test were used to compare the theoretical distributions viz. Weibull and Gamma distributions. Among these, the Weibull distribution is found to be the best fit to the observed data. The median survival time of overall AMI patients using Weibull distribution is 2.45(95% confidence interval, 1.87-3.03) years.*

Keywords*: Acute myocardial infarction (AMI), hazard function, life table estimate, probability plot, survival analysis.*

1. Introduction

Acute Myocardial Infarction (AMI) continues to be a major health problem both in the developed, and developing countries like India despite the impressive strides in the diagnosis and

* Corresponding Author. Email: datadutta@yahoo.co.in

management over the past three decades. Although the death rate from AMI has declined by approx 30% over the last decade, its development is still a fatal event [29]. Approximately two out of every three incidents of myocardial infarction (MI) occur without warning and of note, one third of first MIs are fatal; 20% of patients die out of hospital and 13% die within the first 24 to 48 hours of hospitalization [18]. These data emphasize the need for better strategies of primary prevention to significantly impact on the incidence and mortality of AMI.
Moreover, data showing survival trend in Indian patients after AMI are scarce in the current era. Hence, prognosis and possible cure from AMI are important measures of lifetimes which can be assessed by analyzing the survival pattern of AMI patients in India.
Survival analysis or time- to- event data analysis is predominately in biomedical science where the interest is in observing the length of time to death of patients. For their analysis, what researcher is interested is most the determination of the distribution of the survival time, taken for an event of interest to occur. The results of survival analysis for AMI patients have been widely presented and reported for different human subpopulations of the globe [25, 31]. McGarty [24] has mentioned that for adopting any suitable statistical technique for analyzing survival data it should be assumed that the statistical model embodies the evaluation of some natural process with the belief that the model is a useful approximation of the real process. Several approaches have been proposed in the literature for analyzing the survival data [20, 21]. So far, there is no study that compares the survival pattern of AMI patients using the non-parametric and parametric modeling strategies. The major advantage of this study is to help the physicians to develop strategies for preventive cardiology by knowing median survival time, so that survival time of new AMI patients could be improved.

2. Methods

This was a hospital based retrospective study carried out among patients who experienced atmost two AMIs at the Coronary Care Unit (CCU) of Dr. Ram Manohar Lohia (RML) Hospital, New Delhi between 1996-2005. Patients were excluded if they were pregnant, had a history of cancer, or had a chronic disease of the kidney, lungs, liver, gastrointestinal tract, or thyroid. A written informed consent for history, examination and investigations was obtained from all the patients or their families. The data extracted included gender, age and marital status. The study sample comprised 303 patients according to eligibility criteria.

2.1 Nonparametric approach

Berkson and Gage (1950) and Cutler and Ederer (1958) presented a non-parametric approach to estimate survival function using clinical life table method [4, 9]. Clinical life table reflects the thinking and notation of population life table but use data from clinical studies of patients instead of census vital statistical data [14]. Since AMI cases lost to follow up and withdrawn alive are very few hence considering only completed data, the clinical life table is considered.
In this method, the time of study $(0,t)$ is divided into k subintervals viz. $I_i = (t_i, t_{i+1}), i = 1,2,....k.$ Let d_i be the deaths or events occur at the i^{th} interval and n_i, the number of individuals who are at risk of death at the start of the i^{th} interval. The life-table estimate of the survivor function is given by:

$$\hat{S}(t) = \begin{cases} 1 & if \quad t < t_1 \\ \prod_{t_1 \le t} \left[1 - \frac{d_i}{n_i} \right] & if \quad t_1 \le t \end{cases} \tag{1}$$

For values of t beyond the largest observation this estimator is well defined. The estimated probability density function is:

$$\hat{f}(t) = \frac{\hat{S}(t_i) - \hat{S}(t_{i-1})}{b_i},\ b_i = t_{i+1} - t_i,\ \ i = 1, \ldots\ldots, k-1. \tag{2}$$

The estimated hazard function is:

$$\hat{h}(t) = \frac{d_i}{b_i (n_i - \frac{1}{2} d_i)},\ b_i = t_{i+1} - t_i, \qquad i = 1, \ldots\ldots, k-1. \tag{3}$$

Cox and Oakes [8] also established the variance of life table estimate of the survivor function using Greenwood's relation [13] as:

$$\hat{V}[\hat{S}(t)] = \hat{S}(t)^2 \sum_{t_1 \le t} \frac{d_i}{n_i (n_i - d_i)} \tag{4}$$

Gehan generalized Wilcoxon test [10,11] has been applied to compare survival distributions of two groups.

2.2 Parametric approach

Considering the following lifetime parametric model as a useful approximation of the real process, two lifetime models viz Weibull and Gamma distribution are considered.

Gamma Model:

$$f(t) = \frac{\lambda}{\Gamma(\gamma)} (\lambda t)^{\gamma - 1} e^{-\lambda t}, \qquad t > 0, \lambda, \gamma > 0\,. \tag{5}$$

$$S\ t\ = \sum_{k=0}^{n-1} \frac{e^{-\lambda t} (\lambda t)^k}{k!}, t > 0, \lambda > 0. \tag{6}$$

$$h\left(\right) = \frac{\lambda (\lambda t)^{n-1}}{(n-1)! \sum_{k=0}^{n-1} (1/k!)(\lambda t)^k}, \ t > 0, \lambda > 0. \tag{7}$$

Weibull Model:

$$f(t) = \lambda\gamma t^{\gamma-1} e^{-\lambda t^{\gamma}}, t > 0, \lambda, \gamma > 0. \quad (8)$$

$$S(t) = \exp\{-\lambda t^{\gamma}\}, \ t > 0, \lambda > 0. \quad (9)$$

$$h(t) = \lambda\gamma t^{\gamma-1}, t > 0, \lambda > 0. \quad (10)$$

Parameters of the chosen distributions can be estimated from the probability plots [19] without tedious numerical calculations. The additional accuracy of numerical methods is usually not great enough in practice to warrant the effort involved. When an appropriate distribution is chosen, the probability plot result to a straight line fit to the data.
The Anderson-Darling test [3, 2] which makes the use of these specific lifetime distributions in calculating critical values, is defined with the following hypothesis

- H_0 : The data follow a specified parametric model.
- H_1 : The data do not follow a specified parametric model.

The Anderson and Darling (1954) test statistic is defined as:

$$A^2 = -\sum_{i-1}^{n} \frac{(2i-1)}{n} [\log F(t_i) + \log(1 - F(t_{n+1-i})] - n, \quad (11)$$

where F is the cumulative distribution function of the specified distribution, t_i are the ordered data. The test is a one-sided test and the hypothesis H_0 is rejected if the test statistic A^2 is greater than the critical value. Among the class of specified parametric lifetime distributions, the one that has the minimum Anderson-Darling value, confer the best fit to the given data set. A probability value of <0.05 is considered statistically significant.
95% confidence interval (CI) [7] for the median survival time is:

$$\hat{t}(50) \pm 1.96 SE\{\hat{t}(50)\} \quad (12)$$

where $\hat{t}(50)$ is median survival time (MST) and $SE\{\hat{t}(50)\}$ is standard error of median survival time. Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) Windows version 14 (Chicago, IL).

3. Results

3.1 Descriptive analysis

Overall, 185 subjects were studied according to eligibility criteria during a period of 10 years. Out of 185 subjects died, 64.9% (120/185) died after experiencing first MI and 35.1% (65/185) died after experiencing second MI.

Table 1 gives the distribution of MI patients with respect to social characteristics. Males are known to be more prone to MI diseases as sustained by the sample, which has 60.5% male patients. This may be the effect of male attitude and lifestyle. They are more repressive on what they feel, which may contribute to the increase of their blood pressure. 14.6% of the patients aged below 45. 83.8% are married and 16.2% are single. The mean age (± SD) of overall patients at the time of first MI was 53.86 (± 8.77) years.

Table 1. Distribution of MI Patients with respect to social characteristics

Variable	*Category*	*Count*	*Percentage*
Sex	Male	112	60.5
	Female	73	39.5
Age	Below 45	27	14.6
	45-87	158	85.4
Marital Status	Single	30	16.2
	Married	155	83.8

The mean age (± SD) of second MI patients at the time of first MI and second MI were 54.09(± 8.09) years and 57.32(± 8.37) years respectively. However, significant differences ($p<0.0001$) have been observed between mean age of patients at the time of first and second MI.

Figure1 represents distribution of MI patients between months. There was a peak increase on MI cases at the month of August and October. Figure 2 represents distribution of MI patients between years. It shows that peak was observed among MI cases in the year 2001 and 2004. Since, end of study was mid of 2005, the number of patients in year 2005 was not available, hence data of 2005 was not considered.

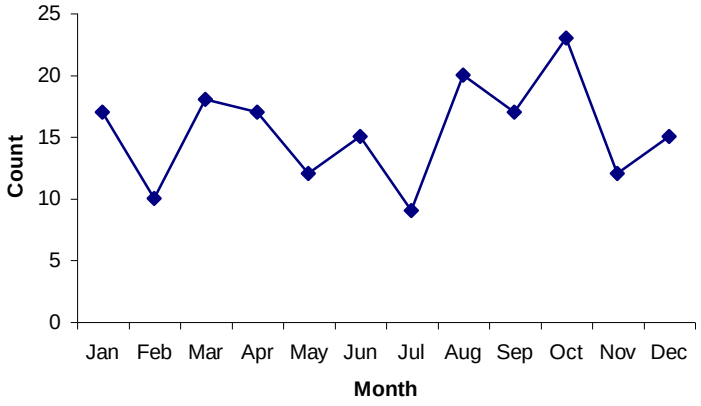

Fig.1. Distribution of MI patients between months.

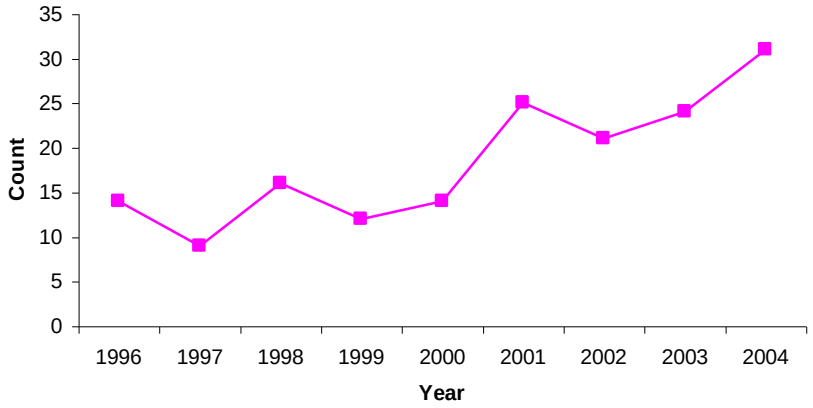

Fig.2. Distribution of MI patients between years.

3.2 Non-parametric analysis

Under this analysis, clinical life table method has been applied to study the survival pattern of MI patients. Table 2 is related to life table analysis of clinically diagnosed MI patients. 22.7% (42/185) have experienced death within 1 year. The five-year survival rate is 0.2270.

Table 2. Life table analysis of clinically diagnosed MI patients

Time Interval (Years)	Number Entering This Interval	Number of Death	Cumulative Survival Function	Hazard function
0-1	185	42	0.7730	0.2561
1-2	143	15	0.6919	0.1107
2-3	128	28	0.5405	0.2456
3-4	100	24	0.4108	0.2727
4-5	76	15	0.3297	0.2190
5-6	61	19	0.2270	0.3689
6-7	42	9	0.1784	0.2400
7-8	33	14	0.1027	0.5385
8-9	19	11	0.0432	0.8148
9-10	8	8	0.0000	2.0000

Table 3 gives the descriptive characteristics of interest of MI patients by clinical life table procedure. The median survival time for this data has been estimated 3.31 years. It means 50% of the patients have been survived less than 4 years after experiencing MI. 95% CI for median survival time is (2.80,3.82).

Table 3. Descriptive characteristics of MI patients

Descriptive characteristics	
Median survival time(MST)	3.31
SE(MST)	0.51
95% CI for MST	(2.80; 3.82)

Fig. 3 presents life table estimates of survival function of clinically diagnosed MI patients. The graph of the estimated survivor function is a step- function in which the estimated survival probabilities are constant between adjacent death times and decrease at each death time.

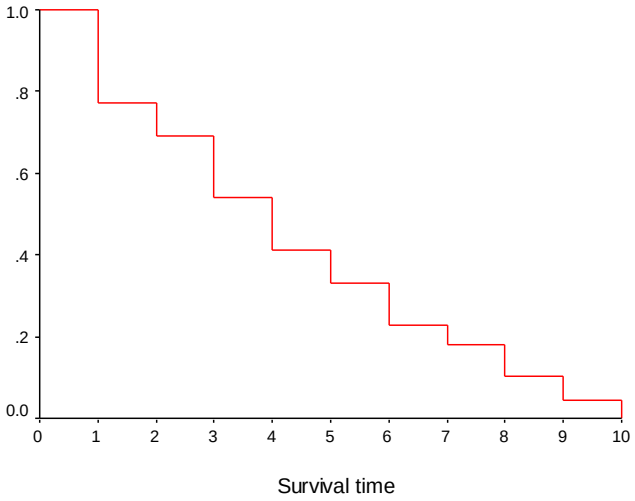

Fig 3. Life table estimates of survival function of clinically diagnosed MI patients

Fig. 4 presents life table estimates of hazard function of clinically diagnosed MI patients. The graph of the estimated hazard function shows that the death rate remains relatively constant from the beginning of the first year to the beginning of the seventh year fluctuating between 0.11 and 0.37.The hazard rate is higher after the seventh year and is highest at the beginning of tenth.

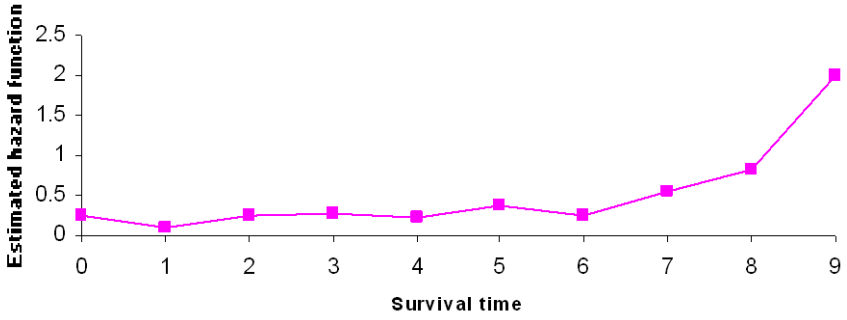

Fig 4. Life table estimates of hazard function of clinically diagnosed MI patients

Fig. 5 presents life table estimates of survival function of clinically diagnosed MI patients stratified by gender. Gehan's generalized Wilcoxon test shows no significant difference between males and females (p=0.16). The median survival time for males is 2.93 years and for females is 3.77 years.

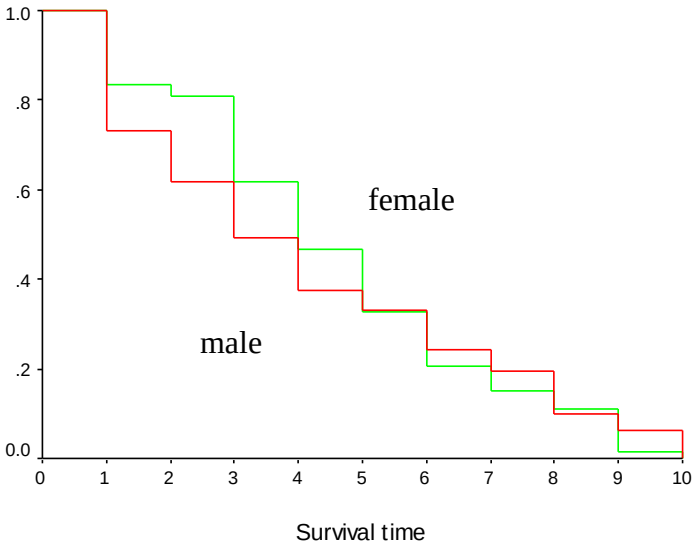

Fig 5. Life table estimates of survival function of clinically diagnosed MI patients stratified by gender

Fig. 6 presents life table estimates of survival function of clinically diagnosed MI patients stratified by age. Gehan's generalized Wilcoxon test shows a significant difference between age<45 and age>=45 (p<0.001). A poor prognosis for older patients has been seen. The median survival time for older patients is 2.92 years and for younger patients is 5.55 years.

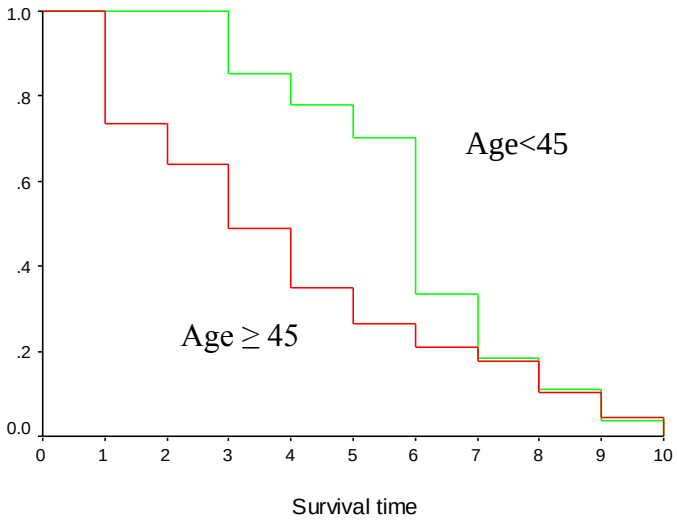

Fig. 6. Life table estimates of survival function of clinically diagnosed MI patients stratified by age

Fig. 7 presents life table estimates of survival function of clinically diagnosed MI patients stratified by marital status. Gehan's generalized Wilcoxon test shows a significant difference between single and married patients ($p<0.0001$). A poor prognosis for married patients has been seen. The median survival time for married is 2.73 years and for single is 7.20 years.

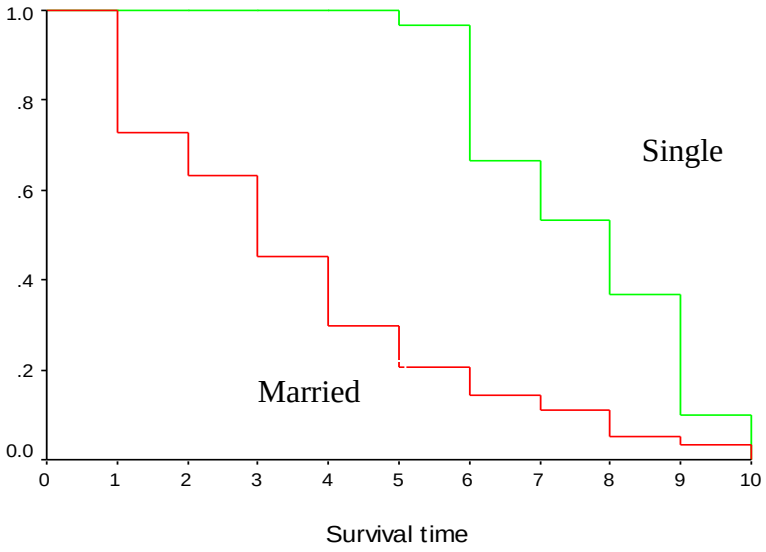

Fig 7. Life table estimates of survival function of clinically diagnosed MI patients stratified by marital status.

3.3 Parametric analysis

Non–parametric techniques show that the survival pattern of MI patients has increasing hazard function in the course of time. So under this analysis, we have considered survival time of MI patients follows Weibull and Gamma distributions.

Fig. 8 and fig.9 show the different probability plots of the survival time of MI patients using the two right- skewed distributions to the survival data. Looking at a glance to fig.8 and fig.9 of Gamma and Weibull distributions show that most of the points are much closer to the fitted line of Weibull distribution as compared to gamma distribution. Also, Anderson-Darling goodness of fit test show that Weibull distribution has the minimum Anderson-Darling value [A^2=-78.707<0.757(critical value) at 5% level of significance [1]. Hence, Weibull distribution is a better fit to this data set.

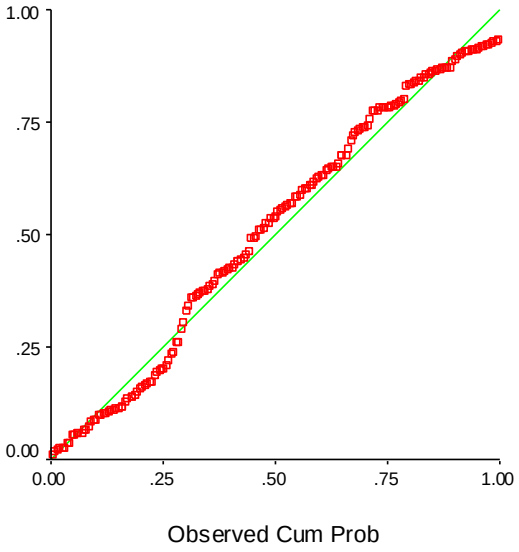

Fig. 8. Probability plot of survival time of AMI patients using Weibull distribution.

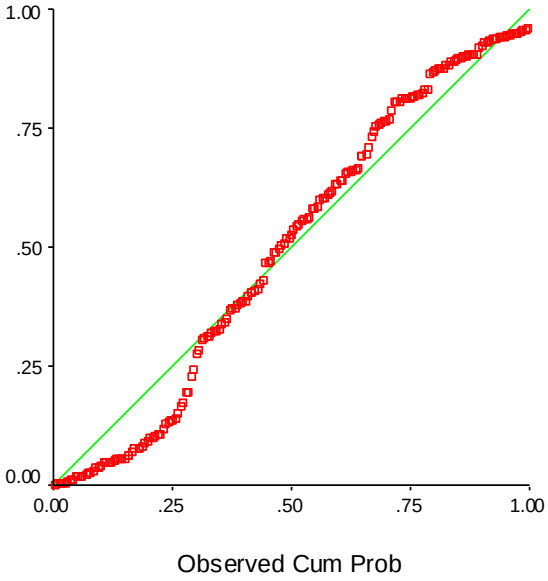

Fig. 9. Probability plot of survival time of AMI patients using Gamma distribution.

Table 4 gives the parameter estimates and descriptive characteristics of interest of Weibull distribution for MI patients. The median survival time for this data has been estimated as 2.45 years. It means 50% of the patients have been survived less than 3 years after experiencing MI. 95% CI for median survival time is (1.87,3.03).

Table 4. Parameter estimates and descriptive characteristics of interest of Weibull Distribution for MI patients.

Parameter estimates and desriptive characteristics	
Shape	1.16
Scale	0.25
Median survival time(MST)	2.45
SE(MST)	0.71
95% CI for MST	(1.87; 3.03)

Table 5 gives the estimated survival and hazard functions of Weibull distribution for MI patients. The five- year survival rate is 0.2055.

Table 5. Estimated survival and hazard functions of Weibull distribution for MI patients.

Time Interval (Years)	Survival function	Hazard function
0-1	1.0000	0.0000
1-2	0.7825	0.2841
2-3	0.5785	0.3171
3-4	0.4166	0.3381
4-5	0.2947	0.3539
5-6	0.2055	0.3666
6-7	0.1417	0.3774
7-8	0.0967	0.3867
8-9	0.0654	0.3950
9-10	0.0439	0.4024

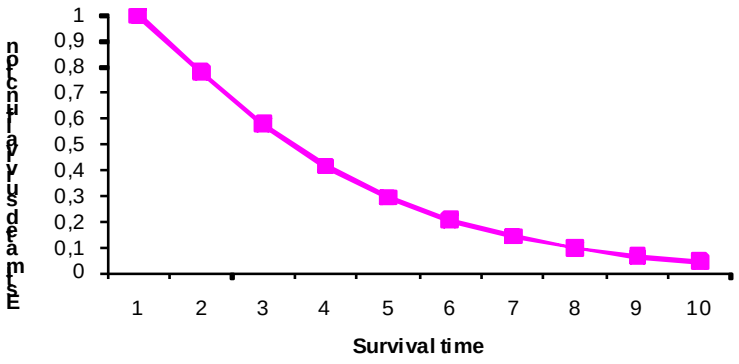

Fig. 10. Estimated survival function of Weibull distribution for clinically diagnosed MI patients.

Fig. 10 represents estimated survival function of Weibull distribution for clinically diagnosed MI patients.
Fig. 11 represents estimated hazard function of Weibull distribution for clinically diagnosed MI patients. The graph of the estimated hazard function shows that the death rate remains zero at the beginning of the first year and then gradually increases.

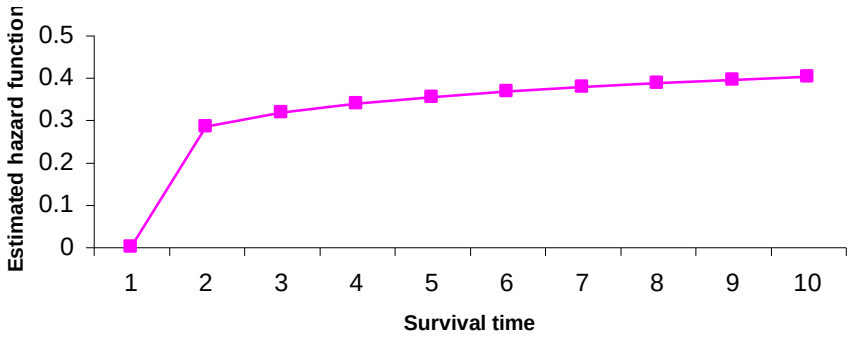

Fig. 11. Estimated hazard function of Weibull distribution for clinically diagnosed MI patients.

4. Discussion

Survival is the major outcome measure for studies of AMI [16]. The survival time for these studies is most commonly taken to be the duration of hospital stay, or sometimes it is fixed as one month. Less frequently, survival is documented for a one-year period and, rarer still, five years or duration from first AMI till death. A longer term survival pattern is important because long-term survival may be subject to different influences than short-term survival. In our study, we have considered survival time as duration from first MI till death (occurs within ten years). Non- parametric and parametric techniques have been employed to compare the survival pattern of AMI patients in India.
Clinical lifetable method is quite useful because it uses the information that is available and it provides the type of information that medical investigators often desire [14]. It is utilized to compute and plot the survival and hazard probabilities for each interval. As seen in the lifetable results, the median survival time is 3.31 years. The hazard plot shows survival pattern of overall AMI patients has increasing hazard function in the course of time. The greater the hazard function, the shorter is the survival time [27] and hence the prognosis for a patient worsens. Probability plotting and Anderson-Darling goodness of fit test were used to compare the theoretical distributions. Among these, the Weibull distribution is found to be the best fit to the observed data. The median survival time of overall AMI patients using Weibull distribution is 2.45 years. According to a previous study conducted in Europe, the median survival time was 6.2 years [17]. This might be due to variation in medical practices between various countries, reflecting to a large extent their economical and cultural development. Substantial differences may also exist between regions within the same country.

The findings of this study showed that there is no significant impact of gender on the survivability of AMI patients which is similar to the previous finding [28]. In contrast, a large number of studies among hospitalized patients with MI have found a worse prognosis in women [15, 22, 23]. Patient selection may account for some of the differences i.e. women who were admitted may have had more serious infarctions than other women with MI.

Age is also a very important determinant of survivability in most studies. Our study revealed that older patients hospitalized with MI have a poorer prognosis compared to younger patients. Similar findings have been reported earlier, in larger studies [12, 30].

The results of this study indicated that unmarried men and women who experience an AMI have a significantly better survival prospect, both in hospital and after discharge, independent of other risk factors. Previous research on the impact of marital status, as a measure of social support, on outcomes in patients after an MI showed conflicting results. Some authors [5, 6] found strong independent relationships between marital status and survivability in patients after an MI. Others found that although there was a difference in outcomes between patients living alone and patients not living alone, marital status was not an independent risk factor for mortality in MI patients [26]. They concluded that advanced age, and not social support, seemed largely responsible for the decreased survivability in patients living alone.

Our study shows that there was a peak increase on AMI cases at the month of August and October. There was also a peak increase on MI cases in the year 2001 and 2004.

Knowledge of median survival time will enable the physicians to develop strategies for preventive cardiology so that survival time of new AMI patients could be improved. This can be considered as a baseline for further studies by taking into consideration other risk factors viz. hypertension, cholesterol, diabetes mellitus etc. This study can also be extended further by taking into consideration censored and truncated survival time data.

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