A Fuzzy Approach to Fleming-Harrington Estimator

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Abstract
Apart from randomness and other characteristics which are embedded with survival data, impreciseness in the observations is a quite common phenomenon. Statistical methods deal with randomness, however, not with impreciseness. The theory of fuzzy helps to deal with the impreciseness in the data. In this paper, the Fleming-Harrington estimator (1984) which is developed for estimating the survival function of the survival data in the presence of censoring is modified through the implementation of the fuzzy concept in the observations. The survival times are normally measured as crisp observations, but in reality, they are "more or less fuzzy" (Viertl (2015)) and so in this article, the fuzziness is introduced to the survival times and related fuzzy survival curves and median survival time are obtained. As there is no specific article related to fuzzy orientation to the Fleming-Harrington estimator (1984), this method paves the way by proposing a new methodology by finding a fuzzy Fleming-Harrington estimator.The proposed methodology has been illustrated through an example. The suggested fuzzy technique brings out an enhancement in the estimation of the survival probabilities.

Keywords: Survival Data; Fleming-Harrington Estimator (F-H); Fuzzification; Impreciseness; Fuzzy Numbers; Fuzzy Intervals; Survival Curves.

1. Introduction

The topic of survival analysis encompasses a wide range of techniques that analyze the time taken for a specified event to occur in living beings or working objects from a fixed epoch. Hence, survival analysis is also called time-to-event data analysis. The time until an event occurs can be quantified in days, weeks, years, etc. Death, illness occurrence, disease relapse, divorce, employment, etc., are examples of events that may happen to everyone. Though estimating and understanding the behaviour of the survival function or hazard (instantaneous failure) function are the primary aims of survival analysis, it is necessary to compare the survival/hazard curves when we have data relating to two or more groups of people/patients with different basic characteristics. The effect or impact of various suspected explanatory variables on survival time can also be studied in survival analysis **[16]**.

Censoring is the nature of most of the survival data. It is the presence of incomplete records of the observations relating to a survival study. That is, censored data cannot provide full information for all the persons involved in a survival study, some will have just a portion of the data. The presence of censored data makes survival analysis complicated and challenging when compared with other types of studies that use the full information. Under censoring, usually non-parametric procedures are recommended to estimate the survival function or

hazard function. It is because the non-parametric procedure does not necessitate any particular assumption concerning the distribution of survival times [**22**].
Generally, there are two types of non-parametric estimators used in survival analysis. First, the Kaplan-Meier Estimator (1958), which is a familiar and pioneer method for estimating the survival function through conditional probabilities [**18**]. The Kaplan-Meier analysis is most commonly used in both observational and interventional investigations. The Kaplan-Meier (K-M) technique has the advantage of using censored data. That is, the information regarding patients who are lost at any point in time, for any cause, can be included in the analysis. Another familiar non-parametric estimator is suggested by Nelson-Aalen (1972). This provides an estimator of the cumulative hazard function through which one may also estimate the survival function **[26].**
The Nelson-Aalen Estimator (N-A) can be applied to both censored and uncensored types of survival data, with the assumption that censoring is independent of the risk **[1]**, estimating the cumulative hazard only. Fleming – Harrington (1984) have used Nelson-Aalen estimator for finding a survival proportion. In general, the survival estimates of the Fleming-Harrington estimator (F-H) will be slightly higher than the Kaplan-Meier estimator [**8**].
In 1965, Zadeh first introduced the fuzzy theory as an expansion of the traditional idea of classical set algebra [**34**]. Zadeh developed his work on probability theory into a formal system of mathematical fuzzy logic and provided a new method for applying fuzzy concepts. This new logic for expressing and manipulating fuzzy words was called fuzzy logic, and Zadeh became the expert in that field. The fuzzy theory is a well-known and useful technique for formulating and analyzing imprecise and subjective circumstances in which perfect analysis is either a difficult or impossible situation [**33**]. In the recent past, the fuzzy set theory has received attention as being more applicable than the traditional set theory and fuzzy logic and fuzzy set theory have been used in survival analysis [**28**].
In this article, survival times are assumed to be fuzzy numbers and as a result, the Fleming-Harrington Estimator (1984) has been modified in accordance, making use of the fuzzy concepts by utilizing the concept of triangular fuzzy numbers and hence which may be more appropriate and realistic than the traditional method.

2. Literature Review

Indrayan A and Tripathi C B [12] have analyzed the subject of survival analysis from a broad perspective. The necessity of using non-parametric procedures to censored survival data has been explained. It is stated that under specific conditions, the Kaplan-Meier approach examines the overall survival pattern at various points of time. The Cox's methodology for studying the hazard is also discussed. **Musavi S *et.al* [25]** have stated that even though the Kaplan-Meier estimator (K-M) behaves well in dealing with censored data, when the sample size is small and the censoring is heavy the K-M estimators are not reliable. Hence, a new methodology is proposed using fuzzy logic to obtain more reliable estimates. Two types of estimators, namely, the fuzzy product-limit estimator and a modified fuzzy product-limit with estimators are proposed. These methods were applied to the data on the survival of AIDS patients and were proven to yield better results than the classical one.

Gonzalez D G *et.al* [9] used fuzzy probability theory and prior knowledge of the process estimation for dealing with the high degree of uncertainty involved in the censored data. An application of the method proposed is made for risk-based inspection which substantiates the claim of obtaining more reliable estimates. A new way of inference called Fuzzy EuroSCORE (European System for Cardiac Operative Risk Evaluation) was introduced by **Khanmohammadi S *et.al* [20]** for predicting the risk of mortality after cardiac surgery. The developed system is based on a fuzzy inference system and reliability analysis. **Lv X *et.al* [24]** have introduced a dynamic treatment assignment model for survival data which relaxes the restriction of simultaneous and independence of prospective treatment gains in regression discontinuity design.

Janurova K and Bris R [15] have quantified the probability of mortality with uncertainties for the data from patients who underwent colectomy. The first approach is using both Kaplan-Meier and Nelson-Aalen estimators and the second approach is an innovative one, called the non-parametric predictive inference which is based on lower and upper probabilities and provides a model of the predictive survival function rather than the population survival function. **Brunel E *et.al* [3]** have considered the problem of censored indicators missing at random and estimated the hazard rate in the presence of covariates using non-parametric adaptive strategies on the basis of model selection.

Kenah E [19] has developed a non-parametric method of survival analysis which is based on a contact interval for the analysis of infectious disease data and used an expectation-maximization algorithm to average the Nelson-Aalen estimates observed from the combinations of who infected whom observations. The newly developed procedure is called the marginal Nelson- Aalen estimator. **Dehkordi A N *et.al* [5]** described a survival model which is based on a system of adaptive neuro-fuzzy-inference and used the age of the patients and the dynamic contrast-enhanced magnetic resonance imaging data for the prediction of survival time for patients with glioblastoma multiforme (GBM).

Liu K F R *et.al* [23] used fuzzy logic to generate conditional probabilities in the Bayesian perspective which is used in Bayesian belief networks. The methodology proposed was used to assess the possible feature population status of the Pheasant-tailed jacana. **Wu C Q *et.al* [32]** considered an estimator of the change points in hazard function models which allows for random censoring and unknown baseline hazard function. It is shown that the estimators so developed are consistent. **Jaisankar R *et.al* [14]** proposed a new methodology for calculating the Nelson-Aalen estimator using fuzzy survival times and survival probabilities.

To address the presence of uncertainty with fuzziness in the measurements of lifetimes **Shafiq M and Atif M [27]** have developed a new type of estimator in case of accelerated life testing (ALT) which takes account of both fuzziness and stochastic variations. Survival models for Step-Stress based on fuzzy lifetimes are proposed. **Del Sarto N *et.al* [6]** have proposed a model for the survival of start-up based on internal resources and their corresponding interactions through the fuzzy set qualitative comparative analysis. The proposed model has been applied to the data set of 38 start-ups accelerated in Italy in 2013. An adaptive network fuzzy inference system (ANFIS) has been introduced by **Hamdan H and Garibaldi J M [10].** This system consists of the partitioning of the input space to define

the membership functions based on the factors like expert knowledge, fuzzy c-means clustering, etc. The proposed framework has been applied to the data on ovarian cancer.
Burn treatment management is a specific kind of medical field which is used to minimize the after-burn progression and severity. **Suha S A *et.al* [30]** have stated that several factors are involved in such studies and the traditional survival methods and also the methods based on artificial intelligence systems fail to reflect the correct estimates. In such a situation, they have developed a fuzzy logic system with multiple forms of fuzzy membership functions and different defuzzification procedures. The method proposed has been shown to provide better results. **Jaisankar R *et.al* [13]** suggested a generalized approach to a fuzzy Kaplan-Meier estimator based on fuzzified survival times and compared the methodology with the classical procedure.

2.1 Motivation and Contribution

The motivation behind current work is the fact that the survival times are normally measured as crisp observations; but in reality, they are more or less fuzzy, since the measurements of observed lifetimes are recorded during the conditions which are with unusual environments. So in this article fuzziness is introduced to the survival times and related fuzzy hazard rate and median survival time are obtained based on fuzzy set theory which can be used in ambiguous situations.

There is no research work which involves fuzziness related to the Fleming-Harrington Estimator (1984) so far. This method paves the way by proposing a new methodology for finding the Fuzzy Fleming-Harrington estimator.

3. Preliminaries

Some basic concepts of survival function, cumulative hazard function (Nelson-Aalen estimator), survival probabilities (Fleming-Harrington estimator), fuzzy numbers, fuzzy α-cuts and triangular fuzzy numbers are presented in this section.

Definition 3.1 [29] The survival function simply describes the probability that the event of interest has not occurred by time t. That is, the survival function $\hat{S}(t)$ estimates the probability of an individual in the study surviving beyond time t.

$$\hat{S}(t) = \Pr(T > t) = 1 - \Pr(T \leq t) \tag{1}$$

Definition 3.2 [4] The hazard rate or hazard function, which is sometimes expressed as the instantaneous failure rate, is denoted by $\hat{h}(t)$, estimates the probability that the event of interest for an individual occurs within the short infinitesimal time interval (Δt). It is calculated by,

$$\hat{h}(t) = \lim_{\Delta t \to 0} \frac{Pr[(t \leq T < t + \Delta t \mid T \geq t)]}{\Delta t} = \frac{\hat{f}(t)}{\hat{S}(t)} \tag{2}$$

where, the probability density function of the survival $\hat{f}(t)$ is given by,

$$\hat{f}(t) = -\frac{d(\hat{S}(t))}{dt} \tag{3}$$

The survival function is related to the cumulative hazard function $\widehat{H}(t) = \int_0^t \hat{h}(t)$ by,

$$\hat{S}(t) = exp(-\widehat{H}(t)) \tag{4}$$

Definition 3.3 [21] Let $t_1 < t_2 <, \cdots, t_n$ denote the times at which the event of interest has been observed as occurred. The Nelson-Aalen estimator (1972) for calculating the cumulative hazard function is given by,

$$\widehat{H}(t) = \begin{cases} 0 & if \quad t < t_1 \\ \sum_{t_i \le t} \frac{\dot{d}_i}{\dot{Y}_i} & if \quad t_1 < t. \end{cases} \tag{5}$$

where, $\dot{d}_i$ is the number of events that occurred by time t, $\dot{Y}$ is the number of subjects at risk just before the time t. From the observed $\widehat{H}(t)$ the Fleming-Harrington estimator (1984) of the survival function $\hat{S}_{FH}\,(t)$ is obtained by,

$$\hat{S}_{FH}\,(t) = \exp(-\widehat{H}(t)).$$

Definition 3.4 [2] A fuzzy set $\tilde{\eta}$ of universe set U, is defined with membership function, such that,

$$\tilde{\eta} = \{(x/ f_{\tilde{\eta}}(x)), x \in U\} \tag{6}$$

$$f_{\tilde{\eta}}(x) : U \to [0,1]$$

where, $f_{\tilde{\eta}}\,(x)$ is the membership function of x in $\tilde{\eta}, \forall x \in U$.

Definition 3.5 [7] The fuzzy α-cuts of $\tilde{\eta}$ be defined by,

$$\tilde{\eta}[\alpha] = \{x \in U : f_{\tilde{\eta}}(x) \ge \alpha\} = [\tilde{\eta}_\alpha^l, \tilde{\eta}_\alpha^u] \tag{7}$$

where, $\tilde{\eta}_\alpha^l = \inf\{x : x \in \tilde{\eta}[\alpha]\}$ and $\tilde{\eta}_\alpha^u = \sup\{x : x \in \tilde{\eta}[\alpha]\}$.

Definition 3.6 [11] The triangular fuzzy number (TFN), say, $\tilde{\eta} = (\tilde{\eta}^l, \tilde{\eta}^c, \tilde{\eta}^u)_T$ with its membership function and α-cuts are given by,

$$f_{\tilde{\eta}}\,(x) = \left\{ \begin{matrix} 0 & x < \tilde{\eta}^l, \\ \frac{x-\tilde{\eta}^l}{\tilde{\eta}^c-\tilde{\eta}^l} & \tilde{\eta}^l \le x < \tilde{\eta}^c, \\ \frac{\tilde{\eta}^u-x}{\tilde{\eta}^u-\tilde{\eta}^c} & \tilde{\eta}^c \le x < \tilde{\eta}^u, \\ 0 & x > \tilde{\eta}^u, \end{matrix} \right\} \forall x \in \mathbb{R}, \tag{8}$$

$$\tilde{\eta}[\alpha] = [\tilde{\eta}^l + (\tilde{\eta}^c - \tilde{\eta}^l)\alpha,\ \tilde{\eta}^u - (\tilde{\eta}^u - \tilde{\eta}^c)\alpha] \tag{9}$$

4. Proposed Methodology: A Fuzzy Approach to Fleming-Harrington Estimator

Fleming-Harrington (1984) proposed a non-parametric estimator that approximates the true survival function, determined by the conditional probability calculated based on the number of events and individuals at risk. Both the number of events and the number of people at risk are unique, and so treating them as ambiguous may be inappropriate. However, the time of survival durations are continuous, and therefore treating them as accurate measures may be unreasonable. Hence, it would be appropriate to treat each survival time by applying some fuzzification method. Here, this method adopted is based on fuzzy survival intervals obtained with a fuzzification factor proportional to the associated survival probability.

- **Step 1.** Let $(t_1,\ t_2, \dots, t_n)$ be the survival times at which the event of specified interest is known to have occurred. At first, the hazard function $\hat{h}(t)$ is calculated using the classical Fleming-Harrington procedure on the basis of the Nelson-Aalen estimator. The cumulative hazard function $\widehat{H}(t)$ and the survival proportion $\hat{S}(t)$ are observed.
- **Step 2**. The survival probabilities for each t_i are calculated and from which the fuzzification factor $(\tilde{\psi}_i)$ is introduced to each of the survival times (t_i) with proportionality constant to c for $0 < c < 1$, generated based on the survival probabilities. The observed fuzzified triangular survival time (T_i^{*F}) is given by,

$$T_i^{*F} = \left[\left(t_i - \tilde{\psi}_i\right), \tilde{\psi}_i, \left(t_i + \tilde{\psi}_i\right)\right] \tag{10}$$

where, $0 \leq \tilde{\psi}_i < 1$.

Therefore, for each survival time, *n* triangular fuzzy numbers are obtained. Since most of the survival data are skewed, the measure of "Median" is taken. For finding the median, ordering data is necessary which is required even in the case of fuzzy numbers. For this, a method of ranking fuzzy intervals has been selected appropriately among various procedures available in the literature. However, specific to each of such methods, one may obtain different ordering outcomes.

- **Step 3.** Here, Lee and Li (1988) **[31]** algorithm is taken to rank fuzzy survival time intervals. Lee and Li method for ranking into triangular fuzzy numbers is based on the quantity,

$$f_{\tilde{\eta}}(t_i) = \frac{\tilde{\eta}_{il}+\tilde{\eta}_{ic}+\tilde{\eta}_{iu}}{4} \tag{11}$$

After the ranking of the triangular fuzzy numbers the *α*-cuts associated with each fuzzy survival time are calculated. Corresponding to the *α*-cuts, *n* fuzzy intervals are obtained.

- **Step 4.** Nguyen and Wu (2006) **[17]** proposed a method for finding the median of fuzzy interval-valued data. Let *U* be the set of the universe, and $\{\tilde{\mathfrak{F}}_{xi} = [\tilde{p}_i, \tilde{q}_i], \tilde{p}_i, \tilde{q}_i \in \mathbb{R}, i = 1,2, \dots, n\}$ is a collection of arbitrary fuzzy interval samples from *U*. Let $\tilde{c}_i$ represent the center of the interval of $[\tilde{p}_i, \tilde{q}_i]$, and $\tilde{l}_i$ be the length of $[\tilde{p}_i, \tilde{q}_i]$. The Median of the fuzzy sample is defined by,

$$\tilde{\mathfrak{F}}_{\text{Med}} = (\tilde{c},\ \tilde{r}) \tag{12}$$

$$\text{where, } \tilde{c} = \text{Med}\,\{\tilde{c}_i\},\ \tilde{r} = \frac{\text{Med}\{\tilde{l}_i\}}{2}.$$

- **Step 5.** It is necessary to calculate the crisp value from the fuzzy median calculated. This can be obtained by defuzzifying the median obtained above by converting it to a triangular fuzzy number. The defuzzification value of the isosceles triangular fuzzy number so obtained is given by the centroid point

$$C_{\tilde{\eta}} = \frac{\tilde{\eta}^l + \tilde{\eta}^c + \tilde{\eta}^u}{3} \quad (13)$$

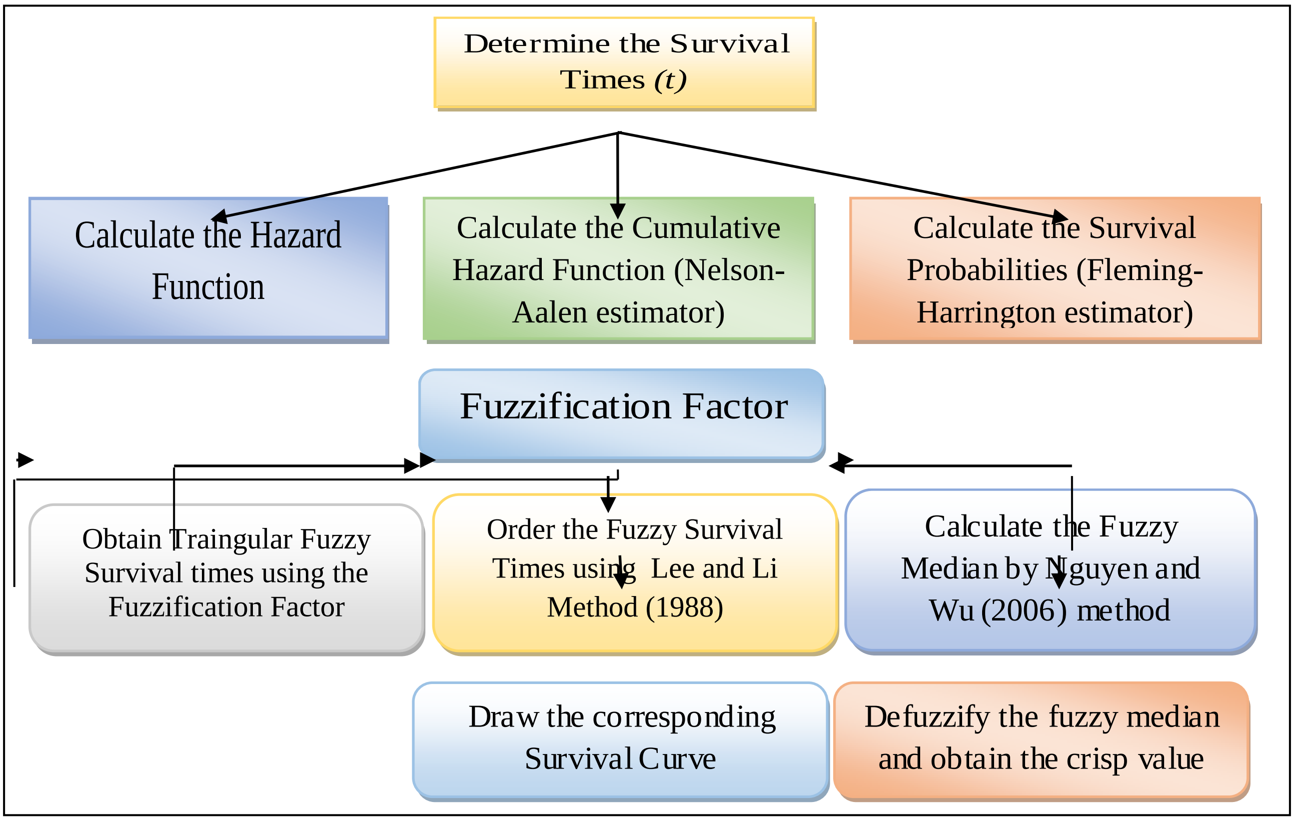

Fig 1: Hierarchical Structure of Fuzzy Fleming-Harrington estimator

5. Illustration

5.1 The Fleming-Harrington Estimator (1984) – Classical Version

In this section, for the illustration of the above method, self-coined survival data with 15 survival times are taken and given in the following Table 1. By using the Classical Fleming-Harrington procedure, the survival probabilities $\hat{S}_{FH}(t)$ are calculated. The details are given in Table 1. The survival curve is plotted in Fig 2.

Time (Months)	Vital Status (1-event, 0-censoring)	Cumulative Hazard Function $\hat{H}(t)$	F-H Survival Probabilities $\hat{S}_{FH}(t)$
6	1	0.06	0.94
8	1	0.07	0.93

26	1	0.16	0.85
34	1	0.25	0.78
75	1	0.35	0.70
82	1	0.46	0.63
95	1	0.58	0.55
102	0	-	-
109	1	0.73	0.48
117	1	0.89	0.40
127	1	1.09	0.33
129	1	1.34	0.26
137	1	1.68	0.19
138	1	2.18	0.11
155	1	3.18	0.04

Table 1: Calculation of the F-H Survival Probabilities

From the calculated survival proportions, the median survival time is observed as 95 months and given in the following Fig 2.

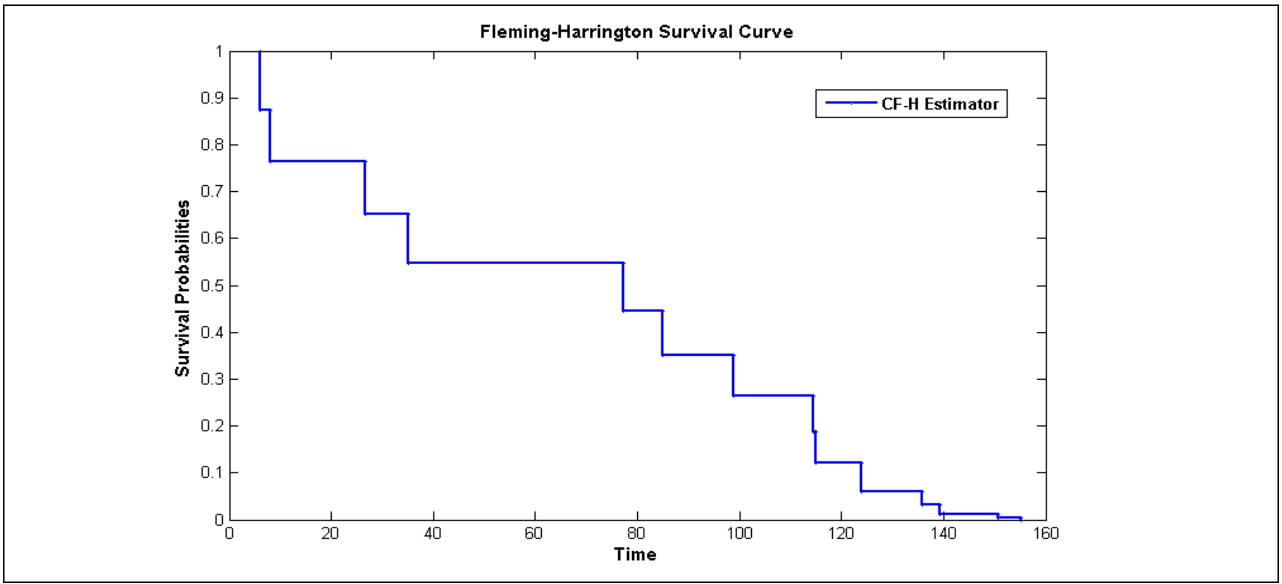

Fig 2: Plot of FH-Survival Probabilities

5.2 Fuzzification of Survival Times

Using the procedure described above, triangular fuzzy numbers $\tilde{\eta}$ are generated for each of the survival times and are shown in Table 2. From the triangular fuzzy numbers, the α-cuts are calculated and corresponding to each α-cut a lower value and higher value have been found, from which the survival curve has been drawn and presented in Fig 5.

The triangular fuzzy numbers (TFN) $\tilde{\eta} = (\tilde{\eta}^l, \tilde{\eta}^c, \tilde{\eta}^u)_T$, generated are given in Table 2.

$\tilde{\eta}_1 = (6,6,6)_T$	$\tilde{\eta}_8 = (108,109,110)_T$
$\tilde{\eta}_2 = (7.98,8,8.02)_T$	$\tilde{\eta}_9 = (116.18,117,117.82)_T$
$\tilde{\eta}_3 = (25.8,26,26.02)_T$	$\tilde{\eta}_{10} = (126.4,127,127.6)_T$
$\tilde{\eta}_4 = (33.72,34,34.28)_T$	$\tilde{\eta}_{11} = (128.43,129,129.57)_T$
$\tilde{\eta}_5 = (74.33,75,75.67)_T$	$\tilde{\eta}_{12} = (136.6,137,137.4)_T$
$\tilde{\eta}_6 = (81.27,82,82.73)_T$	$\tilde{\eta}_{13} = (137.63,138,138.37)_T$
$\tilde{\eta}_7 = (94.13,95,95.87)_T$	$\tilde{\eta}_{14} = (155,155,155)_T$

Table 2: Calculation of the Triangular Fuzzy Numbers

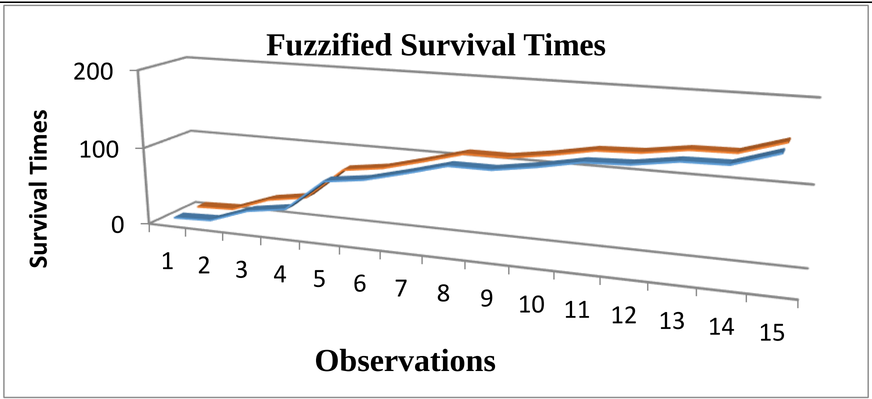

Fig 3: Lower and Upper Fuzzified Survival Times

The lower and higher α-cuts are position functions considering the fuzzy survival times described in Fig 4.

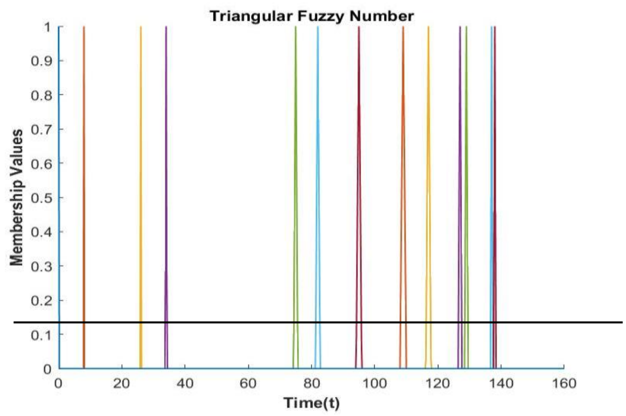

Fig 4: Plot of Triangular Fuzzy Numbers

5.3 Comparison of Classical F-H and Fuzzy F-H Estimator

The survival curves were observed both by the Classical Fleming-Harrington (CF-H) and the Fuzzy Fleming-Harrington (FF-H) procedures as suggested in this article and shown in Fig 5. Based on alpha cuts, the median survival time in the case of the Fuzzy Fleming-Harrington estimator is observed as 82 months instead of the median survival time of the Classical Fleming-Harrington estimator, 95 months.

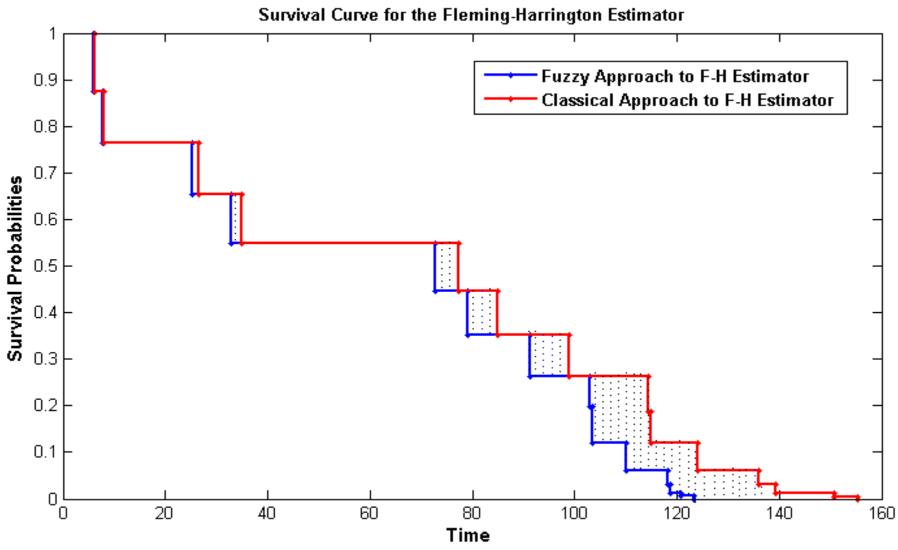

Fig 5: Survival Curves for Fuzzy F-H and Classical F-H Estimator

6. Conclusion

In this work, the perception of a fuzzy set is used for survival analysis concerning Fleming-Harrington estimates for finding the survival functions, which may have greater utility as it addresses the ambiguity that exists in lifetimes which are non-negative and continuous, because of which better results may be expected than the traditional approach. However, the selection of the fuzzification factor is vital and to be chosen with caution as per the problem under the study. Hence, fuzzy survival analyses are appropriate and pragmatic to describe data with fuzzy survival times.

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