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Overview of Frequentist and Bayesian Approach to Survival Analysis

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Abstract
Survival analysis is one of the main areas of focus in medical research in recent years. Survival analysis involves the concept of 'Time to event'. The event may be mortality, onset of disease, response to treatment etc. Purpose of this paper is to provide overview of frequentist and Bayesian Approaches to Survival Analysis. The paper starts with the overview of the basic concepts of survival analysis and then discusses the frequentist and Bayesian approaches to survival analysis in the biomedical domain with help of hypothetical survival dataset. The survival analysis of the hypothetical data sets showed that for the specific dataset and specific hypothesis, Bayesian approach provided direct probability that the null hypothesis is true or not and the probability that the unknown parameter (mean survival time) lies in a given credible interval wherein the frequentist approach provided p-values and confidence interval for interpreting whether the null hypothesis is true or not and the percentage of intervals which will contain the parameter when the experiment is repeated under same condition. The use of Bayesian survival analysis in biomedical domain has increased due to the availability of advanced commercial and free software, its ability to handle design and analysis issues in survival model and the ease of interpretation of the research findings.

Keywords: Survival analysis; Bayesian; Non-parametric method; Semi-parametric method; Parametric method

Introduction

Survival analysis techniques had an important development in the field of Biostatistics in recent years. Survival analysis [1, 2] involves the concept of 'Time to event'. The event may be mortality, onset of disease, response to treatment etc. The purpose of survival analysis is to estimate the survival rate for a single group, to compare survival rates among different groups, and to assess the effect of associated risk factors or covariates on the survival rate. Survival analysis is different from the normal statistical methods because of censoring [3] and involvement of a time variable. Survival analysis is normally carried out with the frequentist approach such as nonparametric methods, semi parametric and parametric methods [4-8]. Recently Bayesian methods are also used [4,9] to carry out the survival analysis due to its ability to handle design and analysis issues in clinical research involving survival analysis.

Basic Concepts of Survival Analysis

Survival analysis estimates two functions namely survival function and hazard function.

Survival Function. The survival function provides the probability of a time-to-event of interest. For example, it gives the probability of patient surviving at least to the specified time, or more than the specified time.

Hazard Function. The hazard function provides the probability of failure during a very small time interval $t+\Delta t$, given that the subject survived until time *t*. For example. it provides the probability that a patient who has survived until time x will die in the small interval of time represented by $[t, t + \Delta t]$.

Censoring. Survival analysis involves the concept called 'censoring' [2] which is a unique characteristic of the survival analysis. A studied case is said to be censored if the event or outcome of interest might not be observed until the end of the study, or cases might leave the study, or might die due to other reason than the event fixed in the design of the study, or might be lost during the follow up. When a study involves censored cases, a special type of analysis is required and the standard methods of analysis cannot be used in analyzing the survival time.

Right Censoring. Right censoring [10,11] occurs when the event has not occurred until the follow-up time(i.e. the true unobserved event will occur after the end of the study, or after the time of follow up). If the event under consideration is the survival time of a patient, then the survival time of the patient will be longer than the follow up time in the case of right censoring. There are three types of right censoring namely:

1. Type-I Censoring – Censoring time is fixed. Disease free period is fixed in case of Type-I Censoring. For example, recurrence of tumor is within 200 days after surgery or Recurrence of heart attack after 2 year of by-pass surgery.
2. Type-II Censoring – the study progresses until the failure of n^{th} subjects. This type of censoring is observed mainly in life testing studies where we cannot wait until all the components have failed.
3. Random censoring – subjects are withdrawn due to some other causes, for example death due to accident, in a cancer trail.

Left Censoring. For left censoring [12], event time is less than follow up time value. The event considered might have occurred before the study started. For example, when the event of interest is the recurrence of the cancer after surgery, then the exact time of the recurrence may not be known if the patient is observed 3 months after the surgery. The tumor might have developed before the follow up time i.e. 3 months after the surgery in this case.

Interval Censoring. For interval censoring [13], event might have occurred during an interval. The exact time of event may not be known but only the interval in which the occurrence of the event is known. Normally, the interval censoring happens when the patient is observed only at the specified time period like once 3 months or 6 months. The event (say recurrence of tumor) might have occurred between last visit and the current visit.

Frequentist approach of Survival Analysis

Survival analysis is normally carried out with the help of nonparametric methods, semi - parametric and parametric methods [4].

Non-Parametric Methods

Kaplan-Meier Estimator [14] is a non-parametric method that is used to estimate the overall likelihood of survival from the given set of survival data. The Kaplan Meier method does not assume any distribution for the survival time observed in the study.

The following hypothetical example uses Statistical Analysis System [15] (SAS®) code (SAS® 9.1.3 version) to compare Survival time of patients who have undergone either Coronary Artery Bypass Surgery (CABG) or Percutaneous Coronary Intervention (PCI).

```
SAS Code
proc lifetest data=work.cph plots=(s);
time surtime * cstatus(0);
strata group;
run;
```

The median survival rate for the PCI group and CABG group obtained using the non-parametric

Method is shown in the below **Table 1.** The median survival rates indicate that the CABG patients have better survival times than the PCI patients.

Table 1. Survival rate between groups using Non Parametric Method

	Median Survival Time
PCI Group (0)	69.5
CABG Group (1)	89

PCI - Percutaneous Coronary Intervention
CABG - Coronary Artery Bypass Surgery

The Kaplan Meier Survival curves obtained from the analysis is shown in Figure 1. The survival curves indicate that the CABG patients have greater survival times than the PCI patients.

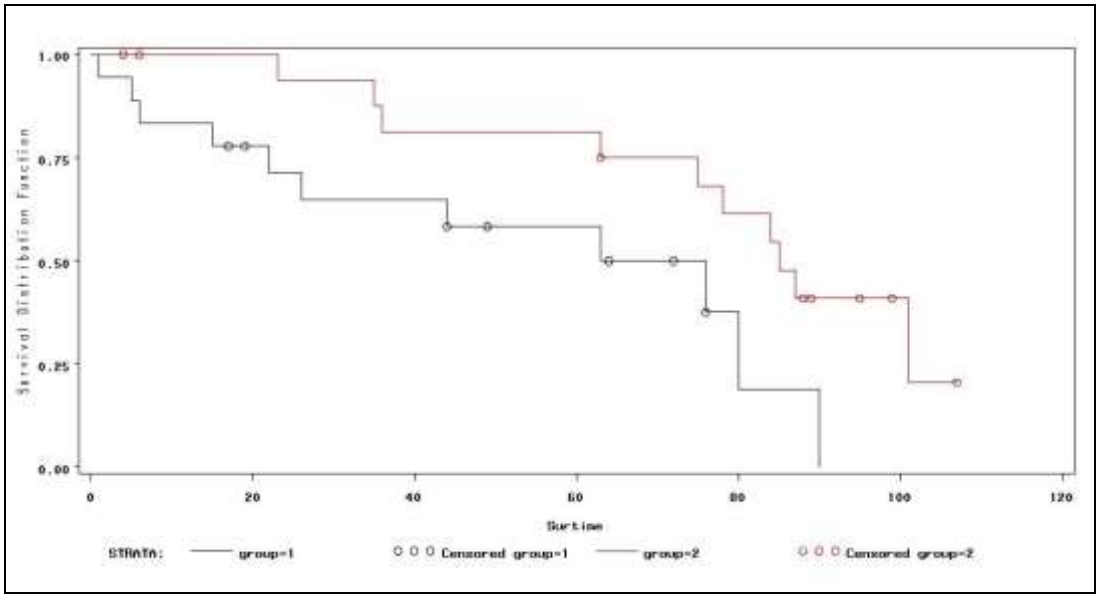

Figure 1. Comparison of Survival rate between Group1 (Percutaneous Coronary Intervention) and Group-2(Coronary Artery Bypass Surgery) Patients

The log rank test results given in the **Table 2** shows that the survival times CABG Patients is significantly greater than the PCI patients' survival time ($p<0.05$)

Table 2. Test of Equality over Strata (output from SAS)

Test	Chi-Square	df	Pr > Chi-Square
Log-Rank	10.96	1	0.0001
Wilcoxon	17.32	1	0.0008
-2Log(LR)	5.53	1	0.0491

LR – Log Rank; DF = degrees of freedom

Benefits and Limitations of Non-Parametric Survival Analysis Methods

Benefits

- Simple method to estimate the survival rate
- Useful in comparing survival rate for two groups graphically

Limitation

- Kaplan Maier Survival method cannot directly control for covariates in the study
- It is not useful when the variable of interest is a time dependent variable

Semi-Parametric Methods

Cox Proportional Hazard (CPH) [16,17] method is a semi parametric method which does not require any particular distribution to represent the survival time, and it is used to study the relationship between survival rate and covariates in the model. CPH assumes the hazard is proportional during the course of the study for the sub groups in the model. CPH can include both discrete as well as continuous measures of event times. The covariates in the model can be time dependent covariates (for example age and blood pressure), or time independent covariates (for example gender). The CPH model helps us to compare the two groups of patient's survival rate through their hazard ratios. The Cox Proportional Hazard method uses partial likelihood method for estimating the parameters in the model

```
SAS Code
proc phreg data = work.cph;
model surtime*cstatus(0) = group age1 sex cursmoke diabetes
totchol1 hypertens;
run;
```

Table 3 provides the survival model obtained using the semi parametric method.

Table 3. Survival model using semi-parametric method

Variable	DF	Estimate	Error	Chi-Square	Pr> ChiSq	Hazard Ratio
Group	1	-1.50	0.36	16.88	<0.0001*	0.22
Age1	1	-0.005	0.012	0.22	0.63	0.99
Sex	1	0.61	0.31	3.75	0.05	1.84
Cursmoke	1	-0.65	0.33	3.80	0.05	0.52
Diabetes	1	-1.09	0.47	5.38	0.02*	0.33
Totchol1	1	-0.0003	0.004	0.006	0.93	1
Hypertens1	1	-0.32	0.42	0.55	0.45	0.726

DF = degrees of freedom; * Significant at 5% level of significance

From the above table D. it can be inferred that the independent variable diabetes has an effect on the survival and also the survival rate between two groups significantly differs.

Benefits of Cox Proportional Hazard Method

- Useful for both time independent and time dependent covariates
- Useful for both continuous and discrete time variable of interest
- Robust compared to the parametric method as it does not assume any specific distribution for survival time

Limitation

- When the proportional hazard assumption is not valid then the CPH method is not suitable for the analysis For example in case of surgery, the hazard rate will be initially higher and tends to decrease over time

Parametric Methods

Parametric methods [2,18-20] use known distributions such as Weibul distribution, exponential distribution, or log normal distributions for the survival time.

The parametric models assume specific distributions for the baseline hazard function whereas the Cox Proportional Hazard model does not assume any specific distribution for hazard function. The coefficients are estimated using maximum likelihood method in parametric methods.

Weibul distribution: If the survival time follows a Weibul distribution, then the survival and hazard rate is defined by shape (when the shape parameter changes, it changes the shape of the survival density) and scale parameter (when the scale parameter changes it rescales the survival density without changing the shape of the survival density) of the Weibul Distribution. The hazard rate will increase if shape parameter >1 and decreases if the shape parameter is < 1.

Exponential distribution: Exponential distribution is a special case of Weibul distribution wherein the shape parameter is equal to 1. If the survival time follows an exponential distribution then the hazard rate will be constant over time

Log normal distribution: Log normal distribution which estimates the hazard rate where the hazard rate is not constant but monotonic in nature. Log normal distribution is defined by mean and standard deviation.

Gamma distribution: Gamma distribution is represented by two parameters: shape and scale. When the shape parameter is equal to 1 it becomes an exponential distribution.

The following example using the SAS program code used the same sample data to exemplify the parametric survival analysis methods.

```
SAS Code
proc lifereg data = work.cph;
model surtime*cstatus(0) = group age1 sex1 cursmoke1 diabetes1
totchol1 hyptens / dist=exponential;
run;
proc lifereg data = work.cph;
model surtime*cstatus(0) = group age1 sex1 cursmoke1 diabetes1
totchol1 hyptens / dist=weibull;
run;
proc lifereg data = work.cph;
model surtime*cstatus(0) = group age1 sex1 cursmoke1 diabetes1
totchol1 hyptens / dist=lnnormal;
run;
proc lifereg data = work.cph;
model surtime*cstatus(0) = group age1 sex1 cursmoke1 diabetes1
totchol1 hyptens / dist=llogistic;
run;
proc lifereg data = work.cph;
model surtime*cstatus(0) = group age1 sex1 cursmoke1 diabetes1
totchol1 hyptens / dist=gamma;
run;
```

Table 4 provides survival model obtained using parametric method.

Table 5 shows the goodness of fit for different semi parametric methods obtained through the likelihood ratio test.

From the above table it can be observed that the Weibul distribution fits the sample data better than the other distributions for the given data set.

Table 4. Survival Model using parametric method

	Estimate (Weibul)	p value	Estimate (exponential)	p value	Estimate log normal	p value	Estimate (Gamma)	p value
Intercept	4.86	<0.0001*	5.34	<.0001*	4.70	<.0001*	4.8	<.0001*
Group	0.62	<0.0001*	0.78	0.011*	0.78	0.00*	0.65	0.00*
Age1	0.004	0.46	0.009	0.42	0.00	0.54	0.0	0.65
Sex1	-0.31	0.03*	-0.40	0.17	-0.27	0.22	-0.28	0.11
Diabetes1	-0.56	0.01*	-0.97	0.02*	-0.93	0.00*	-0.73	0.01*
Hypertens	-0.20	0.29	-0.24	0.53	-0.00	0.99	-0.07	0.77
Cursmoke1	-0.36	0.01*	-0.69	0.02*	-0.41	0.09	-0.43	0.02*
Scale	0.4788		1		0.88		0.40	
Shape	2.0887		1		4.70			

* Significant at 5% significance level

Table 5. Goodness of Fit using Maximum Likelihood Method

	Maximum Likelihood
Log normal	-80.82
Weibul	-68.43
Exponential	-82.16
Gamma	-73.8

Benefits and Limitations of the Parametric Survival Analysis

Benefits

- When the baseline hazard is specified correctly, the parametric survival analysis methods are efficient.
- Useful for predictive and multivariate analysis

Limitation

- If the hazard function is not correctly specified the parameter estimates will be biased

Bayesian Approach to Survival Analysis

Bayesian methods can also be used [4,9,21-26] to carry out the survival analysis due to its ability to handle design and analysis issues in survival model. The use of Bayesian methods are becoming more and more common in the design and analysis of clinical research and clinical trials [27] especially in adaptive designs and interim monitoring [28,29]. One main reason for this is due to its flexibility and operating characteristics.

The Bayesian method differs from the frequentist method [30,31] in terms of uncertainty about unknown parameters in a model which is expressed through a distribution, called the prior distribution. The main inferential tool in the Bayesian method is called the posterior distribution, which is constructed from the data, and the prior distribution. The proper choice of priors plays an important role in the success of the Bayesian survival analysis in achieving its objectives.

Bayesian vs. frequentist approach [32-37]

- In frequentist approach, the probability of an event is measured as a frequency of the event under the same repeatable condition whereas in the Bayesian approach probability of an event is measured as a degree of belief.
- Frequentist approach treats parameters as fixed but Bayesian approach treats parameters as random
- Frequentist approach does not make direct statements about parameters whereas Bayesian approach makes direct statements about parameters

- Frequentist approach calculates likelihood of data from the parameter whereas Bayesian approach calculates the likelihood of parameter given the actual data
- Frequentist approach estimators have properties of unbiasedness, minimum variance, efficient and sufficient, and are weak in robustness
- Bayesian estimators are robust– statistical models maintain stability when new samples are pooled in.

Interpretation of Probability

Null Hypothesis

H_0: There is no significant difference between the survival rate of treatment 1 and treatment 2

Rejecting null hypothesis at p=0.05 or 5%

a. Frequentist approach

When the treatments are repeated under the same condition with new data each time, only in 5% of the times the null hypothesis will be rejected wrongly (when it is actually true).

b. Bayesian approach

Bayesian approach will give exact probability of null hypothesis being true which is straight and easily interpretable. In the above case, the probability of null hypothesis being true is only 5%.

Interpreting Confidence Interval

a. Frequentist approach

In frequentist approach, the traditional confidence interval is interpreted as if we construct confidence intervals over time from the samples drawn from the population, the 95% of confidence intervals constructed will contain the parameter. It will not specify the probability that the parameter lies in interval i.e. 95% chance that the mean survival years lies in the interval [6, 9] years.

b. Bayesian approach

In the Bayesian approach, the credible interval or the Bayesian highest posterior density interval gives us the 95% probability that the unknown parameter mean survival years lies in the interval [6,9] years.

Benefits of Bayesian approach

1. For specific dataset and specific hypothesis, Bayesian approach will be able to construct the probability that the hypothesis is true or not
2. It is able to revise the estimate in orderly manner when new data comes in
3. It will give the scope for dynamically optimizing the trial size and stopping rule
4. More useful and natural inferences are possible
5. Makes use of more available information
6. Addresses complex problems
7. More transparent in making inferences
8. Ideal for decision making

Limitation of Bayesian approach

1. Subjectivity
2. Specifying additional information is not reliable
3. Bayesian methods are complex to implement and need special software

Prior Distribution: Prior information is identified and expressed in terms of prior distribution for the unknown parameters of the model. The prior distribution explains what is known before collecting data. The following are the types of prior distribution

a. Conjugate prior: Prior and posterior are from the same family of distributions
b. Informative prior: Represents reliable prior information
c. Non informative prior: Lacks reliable prior information
d. Skeptical prior: Guesses on the likelihood of null hypothesis
e. Structural prior: Represents the relations between the parameters

Posterior Distribution: Posterior distribution is obtained by synthesizing the Prior distribution with

the data. The posterior distribution is explained with the help of following example:

> *Let us consider that data on the survival distribution of patients who have undergone surgery which is expressed in terms of parameters, mean survival years and extreme values. Let us assume that the mean survival year is 10 years and with range of values of the distribution from 6 to 16 years. The prior distribution say for example is expressed in terms of mean survival years as 8 years and extreme values of the distribution as 3 and 12 years.*
>
> *The posterior distribution will be a synthesis of the prior distribution with the evidence obtained from the data which will be with mean 9 years and extreme values 6 and 12 years discarding the minimum value of prior distribution as it was not supported by the data and discarding the maximum value from the data as it was not supported by the prior. The mean survival rate (9 years) is obtained as the average of the two mean values, prior (8 years) and the data (10 years).*

Markov Chain Monte Carlo Model. Monte Carlo simulation technique [38] (MCMC) is normally used to generate samples of parameter values and Markov Chain links these parameters and produces the sample from the desired posterior distribution.

MCMC model uses the following algorithms

1. Metropolis–Hastings algorithm [39]
2. Gibbs sampling [40]

MCMC procedures needs to be run for several iterations (say 10000) to get the sample converged to the target distribution. Normally, the samples generated until initial period, called Burn-in Period, will be discarded (i.e. 500 iterations), and the remaining sample is used to represent a sample from the posterior distribution. The convergence of the sample can be tested using Gleman Rubin [41], Geweke [42] and Heidelberg-Welch stationary test [43].

Bayesian survival analysis is explained through the following examples with the data used in the frequentist approach

A Bayesian Approach for Parametric Survival using Weibul Distribution

The Bayesian survival analysis process starts with the maximum likelihood estimation of the parameters. It uses the maximum likelihood parameters as the initial value for the Monte Carlo Markov Chain procedure. The posterior distribution is obtained by combining the maximum likelihood estimate and the prior distribution. If there are non-informative priors then the posterior distribution and the maximum likelihood estimators will be more or less same. The Posterior distribution is used to estimate the following:

1. Confidence interval for the posterior parameters are obtained from the credible and HPD intervals which can be directly interpreted as there is a 95% chance that the parameters lie in the given interval
2. The effect of the dependent variable on the survival time can be estimated through checking whether the probability of the coefficient is greater than zero or not
3. If the hazard ratio between groups is significant or not, it can be tested using the posterior distribution

The following example uses a non informative prior in calculating the posterior distribution.

```
SAS code
proc Blifereg data= sasdr.cph;
class sex1 diabetes1 hypertens cursmoke1;
model surtime*cstatus(0) = group age1 sex1 diabetes1 hypertens
cursmoke1/dist=weibull;
bayes;
run;
```

Table 6 gives the posterior sample, mean, standard deviation, quantiles along with the credible interval and HPD interval. Here the HPD interval will directly give the probability that the sample parameter lies within the specified values.

Table 6. Descriptive Statistics of the Posterior Samples

Parameter	N	Mean	Standard Deviation	Quartiles		
				25%	50%	75%
Intercept	10000	4.97	0.4	4.7	4.96	5.23
Group	10000	0.65	0.17	0.53	0.65	0.77
Age1	10000	0.004	0.006	0.0005	0.004	0.008
Sex=Female	10000	-0.3223	0.16	-0.43	-0.31	-0.2
Diabetes=No	10000	-0.63	0.25	-0.79	-0.61	-0.45
Hypertens=No	10000	-0.23	0.22	-0.37	-0.22	-0.08
CurSmoke=No	10000	-0.41	0.18	-0.53	-0.4	-0.29
Scale	10000	0.54	0.07	0.49	0.53	0.58

As the model uses the non-informative priors, Bayesian estimates are closer to the maximum likelihood estimates obtained through Frequentist approach. Here the coefficients of the model are greater than zero except for the parameter age. Table 7 provides the interval statistics of the posterior samples.

Table 7. Interval Statistics of the Posterior Samples

Parameter	Alpha	Credible Interval		HPD Interval	
Intercept	0.05	4.22	5.79	4.2	5.77
Group	0.05	0.32	1.01	0.31	1.007
Age1	0.05	-0.006	0.01	-0.006	0.01
Sex=Female	0.05	-0.65	-0.01	-0.64	-0.001
Diabetes=No	0.05	-1.16	-0.16	-1.16	-0.16
Hypertens=No	0.05	-0.69	0.19	-0.67	0.19
Cursmoke=No	0.05	-0.78	-0.07	-0.77	-0.06
Scale	0.05	0.42	0.7	0.4	0.68

Autocorrelation should be close to zero to get a better model which is also reflected in the Lag 50 column in Table 8**,** where autocorrelation values are close to zero for variables such as group, gender etc.

Table 8. Autocorrelations of the Posterior Samples

Parameter	Lag1	Lag5	Lag10	Lag50
Intercept	0.96	0.81	0.66	0.1
Group	0.52	0.15	0.1	0.01
Age1	0.93	0.72	0.53	0.09
Sex=Female	0.6	0.13	0.05	0.012
Diabetes=No	0.88	0.56	0.33	0.041
Hypertens=No	0.84	0.38	0.13	-0.049
Cursmoke=No	0.68	0.24	0.16	0.015
Scale	0.24	0.1	0.07	-0.003

From Table 9, it can be inferred that the model is converged as the Geweke diagnostic table consists of smaller z values.

For a survival model to be significant, the effective sample size and efficiency should be higher which is not reflected in the below mentioned Table 10. The effective sample size and efficiency can be increased with the help of more iteration.

Table 9. Geweke Diagnostics

Parameter	z	Pr > |z|
Intercept	1.79	0.07
Group	-0.4	0.68
Age1	-0.94	0.34
Sex=Female	1.23	0.21
Diabetes=No	-0.83	0.4
Hypertens=No	-1.57	0.11
Cursmoke=No	-2.22	0.02
Scale	1.17	0.23

Table 10. Effective Sample Size

Parameter	ESS	Correlation Time	Efficiency
Intercept	228	43.85	0.02
Group	1503.4	6.65	0.15
Age1	294.7	33.9	0.02
Sex=Female	1957.1	5.1	0.19
Diabetes=No	486.6	20.54	0.04
Hypertens=No	1019.5	9.8	0.1
Cursmoke=No	993.9	10.06	0.09
Scale	2045.4	4.88	0.2

The following Figure (2-5) shows diagnostics for intercept, age, group and gender with number of iterations, autocorrelation values and posterior density. Autocorrelation values for the parameters which reflects the model has converged to the solution with the given iterations.

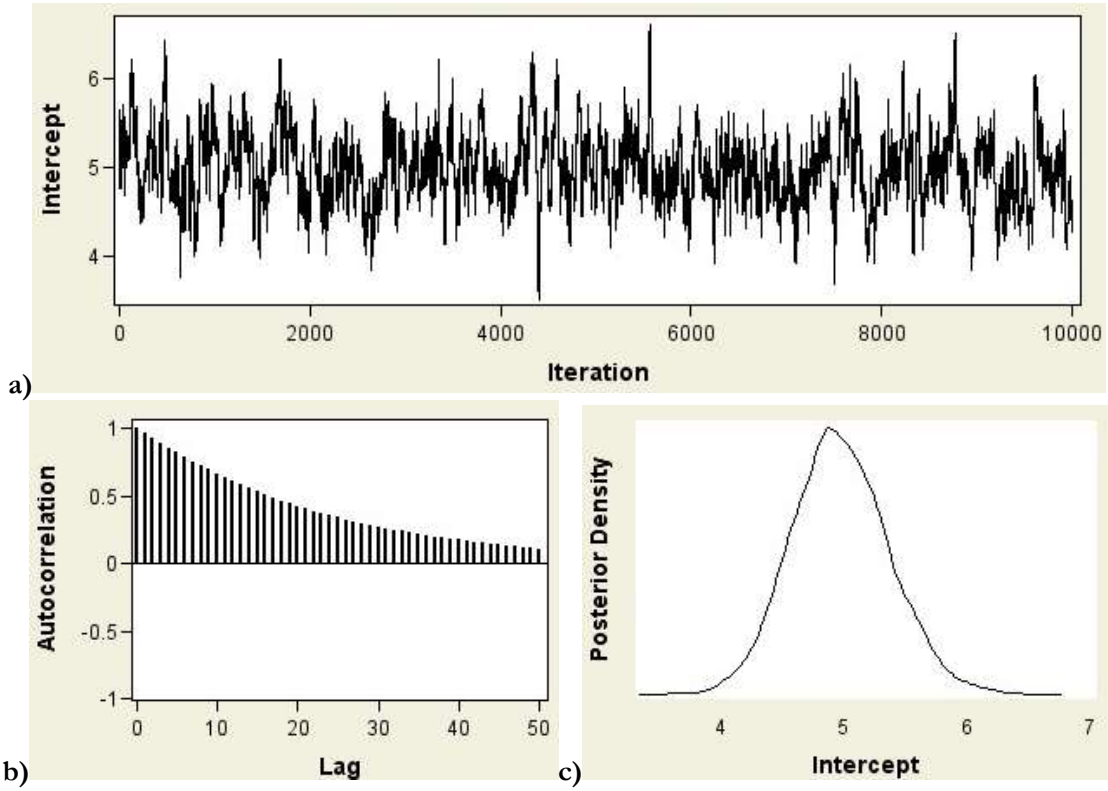

Figure 2. a) Iterations for intercept; b) Autocorrelation; c) Posterior density of intercept

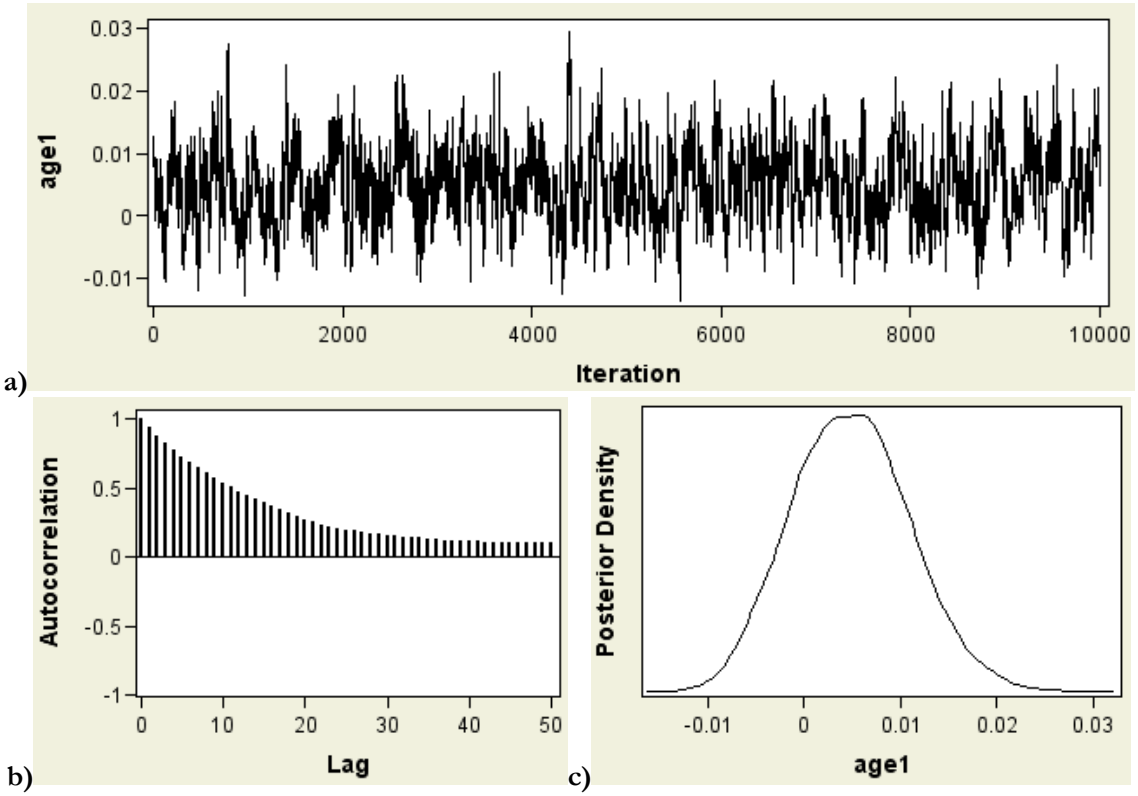

Figure 3. a) Iterations for age; b) Autocorrelation; c) Posterior density of age

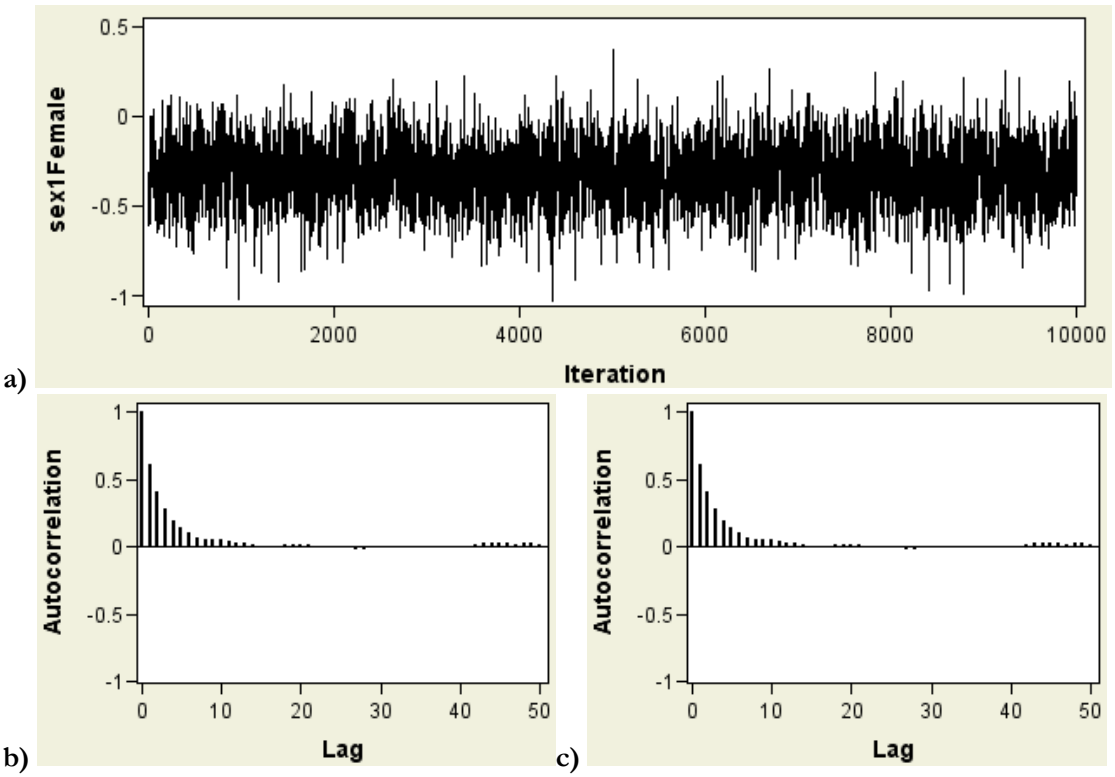

Figure 4. a) Iterations for gender; b) Autocorrelation; c) Posterior density of gender

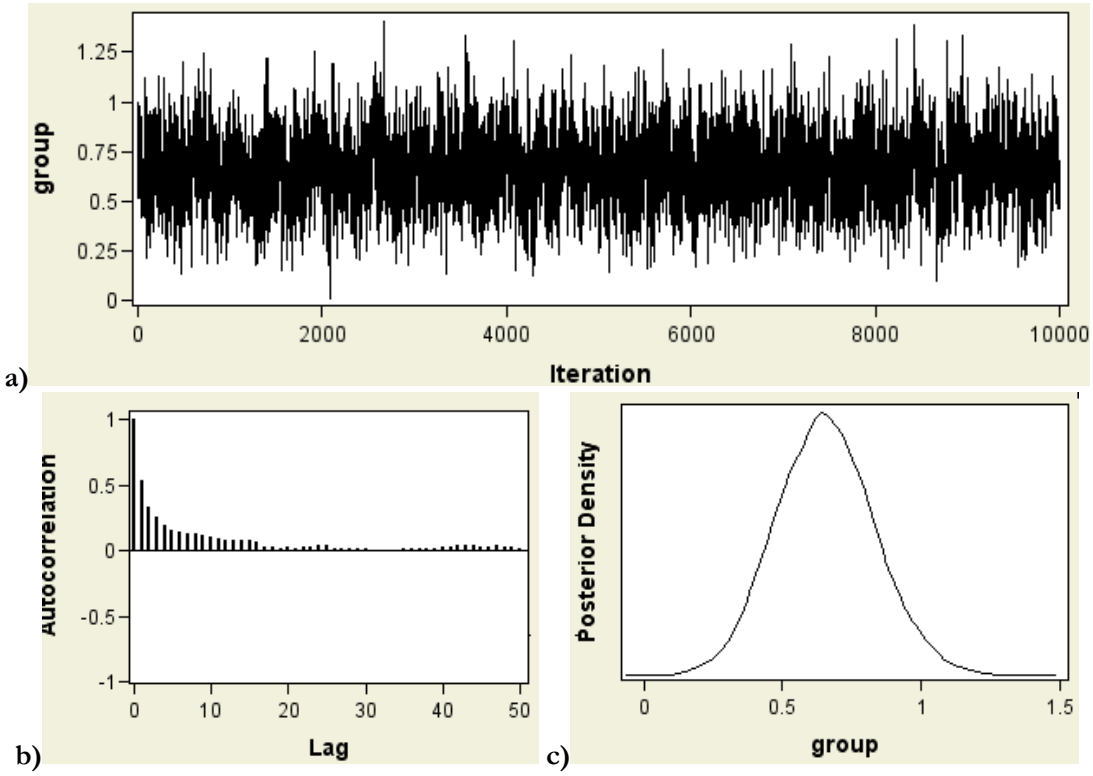

Figure 5. a) Iterations for group; b) Autocorrelation; c) Posterior density of group

The paper provided an overview of frequentist approach and Bayesian approach to survival analysis with the help of hypothetical data set using SAS software. Paper also discussed the benefits and limitation of non-parametric, semi-parametric, parametric and Bayesian approaches to survival analysis. The results showed that the interpretation of the probability and confidence interval is straight forward when Bayesian Survival analysis method is used. The use of Bayesian survival analysis in biomedical domain is increased due to the availability of advanced commercial & free software and the ease of interpretation of the research findings.

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