Chapter 7
SUMMARY AND CONCLUSION

7.1. Introduction

Late stage progressive hepatic fibrosis characterized by distortion of hepatic architecture, necrosis of hepatocyte and formation of regenerative nodules leads to cirrhosis. The liver has a fantastic regenerative capacity but, following chronic liver damage, this begins to fail, and then fibrosis, and eventually cirrhosis develops. Currently the only curative treatment for advanced liver cirrhosis is liver transplant. Although liver transplant has become a procedure with a relatively good 5-year survival, organ donation has not kept up with demand, which has resulted in an increasing number of patients on the liver transplant waiting list waiting longer for a donor organ, which leads to increased morbidity and mortality. Although there is emerging evidence that extending the donor organ criteria may impact on this mortality rate, there is clearly still an urgent need to develop alternative strategies for the treatment of advanced liver disease, and numerically cirrhosis is the most important target. The disease severity in patient with liver cirrhosis is measured through the model for end stage liver disease (MELD). It is continuous disease severities scale with highly predictive of the risk of dying from liver. The score is adopted by UNOS (the United Network for Organ Sharing) for use in allocating livers to patients on the liver transplantation waiting list. Set of respondent are divided into two parts as cured and non-cured. The main goal of this work is to look on the cure and non-cured rate among liver cirrhosis patients through MELD score. The MELD score is considered as the standard of reference for the diagnosis and staging of liver Cirrhosis. The different biochemical parameters viz. serum creatinine, bilirubin & INR (International Normalized Ratio) are used to calculate the MELD score. The details to calculate the MELD score can be cited with http://en.wikipedia.org/wiki/Model_for_End-Stage_Liver_Disease . The low MELD score is positively associated for mortality. Correlation among repeated measurement of MELD scores indicates that independence can no longer be assumed. Therefore, most standard statistical analyses cannot be used to analyze this type of data. If standard analyses (for example ANOVA test used without accounting for dependency within the subjects) are used, the likelihood of Type
I errors will be increased. A number of approaches like repeated measure ANOVA, repeated measures ANCOVA etc. are available for analyzing correlated data. However, selecting which approach is the best to analyze a particular study is unimportant, because each of these methods has a different theoretical paradigm, and its own strengths and weaknesses.

7.2. Contribution and Innovations

It is an effort which might or might not be helpful. But one should put his intact powered attempt to carry out the real foundation to place of the people for its utilization. Improvement to the subsistence of problem among the longitudinal and survival data is very much important and based on it required finding is also play an important role. I am not sure how much it will add to these types of data analyses mainly to the field of liver cirrhosis researches. However, I attempt to put my best effort on the matters relating to longitudinal and survival data analysis. This thesis inspects the understanding the Effectiveness of New Surgical Procedure on Liver Transplantation Patients through Longitudinal and Survival Data Analysis Techniques. It faces missing observation hitches, binary response appearance, various types of correlation structures and count data problem. This dissertation extends and proposes choice approaches to some usual frequency approach in longitudinal data analysis. This work also introduces Bayesian approach in cure rate modeling and consideration of heterogeneity factor into the model using shared frailty model.

7.3. Summary and findings

In scrutiny of the outlined objectives, this present study is prepared into seven chapters as follows: The chapter 1, is Introduction and Review of Literature. This provides the basic background information about liver cirrhosis and liver transplantation. Further, a review of existing studies related to approach considered to assess the effectiveness of liver transplantation procedures through different techniques.

The chapter 2 presents the results pertaining to the cure rate modeling with Bayesian approach and explored the risk of death due to liver transplantation in Cirrhosis patients including time-dependent effects terms. The Bayesian prior assumption is applied to formulate the posterior mean from the cure rate modeling. The model proposed in this paper assumed that the covariates affect only the probability of being cured. A more general model may be proposed that also includes the effects of covariates on the failure time distribution. An R and Winbugs package are
available for download at the web site http:// http://cran.r-project.org/ and http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml. Using these programs, cure rate modeling can be applied in situations similar to those presented in this paper. The applied method may also be suitable in other experimental studies. The model can be valid in the small-size data set. The regression co-efficient of covariate (age) refers to the positive impact of age on cure rate for patients in the treated group as compared to the control group. The male patients have higher odds of getting cured as compared to female patients when treated with study therapy. The work from chapter 2 has been published in the Journal of Data Science, and most of the contents are taken from the published article in this thesis.

In chapter 3, we introduce the shared frailty model to adjust heterogeneity factors that were not possible in earlier chapters. This paper has explored different baseline hazard and frailty distributions to identify the best suitable distributions on Liver Cirrhosis patient’s data. With Weibull and exponential baseline distributions, lognormal frailty model gives slightly lower frailty variance compared to the other frailty models. To compare all frailty models, we use the AIC and BIC methods. All five frailty models have the same number of parameters. Comparing the five models, lognormal frailty model has the smallest AIC and BIC values, suggesting that it is a good fit for these covariates in the data. There were few instances when we have considered baseline hazard distribution in our data and the distribution of frailty as lognormal distribution, in that scenario we could not estimate the parameters and also in few instances the frailty term could not be estimated. The concept of frailty provides a suitable way to introduce random effects in the model to account for relationship and unobserved heterogeneity. The dependence usually arises because individuals in the same group are related to each other or because of the recurrence of an event for the same individual. Multivariate frailty models have been used frequently for modeling dependence in multivariate time-to-event data. Many distributions can be chosen for the frailty, but the most common frailty distribution is the gamma distribution. The gamma distribution has been widely applied as a mixture distribution. The lognormal frailty model gives slightly lower frailty variance compared to the other frailty models when Weibull distribution considered baseline hazard. From this we can conclude that therapy and Meld scores have significant roles on liver transplant subjects when distribution of frailty considered as lognormal with Weibull baseline hazard for fitting the model. The work from chapter 3 has been
published in journal of clinical epidemiology and global health, and most of the contents are taken from published article in this thesis.

In chapter 4, we introduce different type of correlation structure under GEE in linear regression modeling. The goal of this chapter is to compare the surgical procedures on biochemical parameters among the liver transplanted patients at seven times observations. This work is also involved to identify the existing covariance and explain their effects on the model. The presence of different type of correlation structure has been addressed and compared by GEE method. The results in different correlation structure under QIC and CIC information criteria.

The MELD score is found useful tool to evaluate the liver cirrhosis disease. Although, it is based on three objective laboratory variables, it can be influenced by other clinical variables based on situations. It's also useful for management of patients with a wide spectrum of liver disease. The MELD score is applicable as working models and it served as an outline for further improvement to achieve the goal of equitable distribution of a scare resource. There are several types of suitable model to apply into the repeatedly measured correlated data. It is not possible to detect the perfect model. The approach is to search the most suitable model among selected models. A different model generation is being driven by several correlated structures. Generalized estimating equations are attractive for several reasons, including their relative simplicity. They can include any kind of response distribution among the exponential family. They are hence promising for liver cirrhosis data that are longitudinal. However, the QIC performed not well in our study. Therefore we cannot advise this information criterion. Consequently GEEs should only be used when the biological rationale for selecting the covariance structure is obvious (see also a qualitative comparison that can be considered. In this framework, it can be stated that the CIC is useful for selecting appropriate correlation structures.

In chapter 5, we illustrated the application of analyzing incomplete follow data, where the response variable is missing throughout visit. We gave attention on the situation in which responses are continuous. The model that considered was the selection model. The study focused on the precise cases of selection model; that is, a Diggle and Kenward's, (1994) model. In applying the selection model, we used logistic regression for modeling drop-out. However, a number of various probabilities can be used, i.e., using survival analysis approach, the span of duration on treatment or placebo before drop-out can also be modeled. However, in our study,
the survival model for drop-out cannot be used because the time to event is not exactly decided by design. For example, if any patient is not seen at month 12, the exact time to drop-out could hypothetically be any time between month 6 and 12. The aim was to investigate the possible influence that drop-out might have or exert on the response measurement on the liver cirrhosis data and to deal with incomplete sequences.

In chapter 6, we introduce the application of Bayesian computation of Concordance Correlation Coefficient (CCC) which is described by agreement of measurement between two continuous random variables. This application is an effort on Biochemical marker to get prominent evidence about test statistics on relation between variables. Concordance correlation coefficient may seem to be convenient to have a single measure of agreement. CCC has attractive characteristics. It is simple to use. Its estimate using the sample counterparts is consistent and has asymptotic normality for bivariate normal data. Even though, its statistical properties (consistency and asymptotic normality) could be improved by using the inverse hyperbolic tangent transformation (Z-transformation). It is also robust against samples from the uniform and Poisson distributions even with small sample sizes. The further studies should be done to explore CCC approach in more than two raters.

7.4. Scopes of Further Research

The research on longitudinal and survival data analysis has broad scopes. It is difficult to lay a hand on all area in a single work. The present thesis only focuses on studying the effectiveness of new surgical procedure through longitudinal and survival data analysis techniques. Second and third chapters involve the Bayesian counterpart of cure modeling to find out the effectiveness of new surgical procedure as compared to conventional procedure. And adjust the heterogeneity factor through shared frailty model to assess the effectiveness of surgical procedures. Fourth and fifth chapters use the GEE model to compare surgical procedure by selecting the appropriate working correlation structure by QIC and CIC information criteria and handling of missing data through selection modeling approach. Sixth chapter introduces the application of Bayesian computation of Concordance Correlation Coefficient (CCC) which is described by agreement of measurement between two continuous random variables. In this thesis, surgical procedure to liver transplantation has been studied through different biochemical parameters in liver cirrhosis patients. The present work considers the assumption of balanced
longitudinal data set in clinical trial on liver cirrhosis patient. Therefore, an extension of the work is possible in presence of unbalanced data set in longitudinal and survival data set.

7.5. Concluding Comments

Cirrhosis is special state of liver to be get trapped within the sea of scar and struggle to regenerate. It influences the gradual shrinkage of the size of the liver. Liver transplantation is surgery to remove a diseased or injured liver and replace it with a healthy one from another person. In liver cirrhosis problem, the duration between transplantation to recover is crucial period for patients. Patients are generally measured through follow up periods with liver functioning effects. The disease severity in patient with liver cirrhosis is measured through the model for end stage liver disease (MELD). In longitudinal studies, missing data are the rule, not the exception, and pose a major challenge for data analysis. In this work we tried to incorporate the selection modeling approach to handle missing data problem and established that it produce more consistent results as compare to the widely used imputation techniques. More recently, there have been important advances in methods for handling missing data in semi-parametric models for longitudinal data. It is our limitation to incorporate the semiparametric modeling approach and applied in the liver cirrhosis patient data.