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Accelerated Failure Time Frailty Model in Survival Analysis

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ABSTRACT

Breast cancer and its etiologic factors have been widely studied worldwide. Statistics has shown that around the nation people living with breast cancer are in need of identifying risk factors of breast cancer and prognostic factor of breast cancer for their survival, and this research is specific to South Indian population. This study attempts to explore the survival experience of breast cancer patients treated under adjuvant and Neo-adjuvant therapy. The important prognostic variables in response to treatment survival were identified using accelerated failure time model with and without frailty. About 90% received Neo-adjuvant therapy, and 94% had favorable response to treatment. The Accelerated failure time model with frailty performed better than model without frailty.

Keywords: *Accelerated failure time model, Frailty model, Gamma, Weibull.*

1. INTRODUCTION

In cancer studies, the main outcome of interest is the time to occurrence of event like death, response, relapse or toxicity etc. The cancer survival data are skewed and consist of complications in the pattern of early events and in the end stage [2], [3]. In general, cancer studies measure the length of survival after diagnosis of cancer and treatment. It is common for a proportion of individuals to remain alive and respond to treatment at the end of the follow-up period, and only a lower limit on their actual time to event is known [5]. Survival time is the time to occurrence of an event. The survival times are often censored which make the problem of modeling and inference difficult [1]. This paper presents the survival probabilities of breast cancer patients attending a Government Cancer Hospital in Tamil Nadu, South India.

2. MATERIALS AND METHODS

This paper considers the data of 522 Breast cancer patients diagnosed and treated with adjuvant and Neo- adjuvant therapy between January 2000 and December 2008 at the Government Cancer Hospital, Tamil Nadu, South India and follow-up period up to May 2010. The event of interest is response to cure. The stages of the disease are classified based on the five point scale (Stage 2A, 2B, 3A, 3B, 4) [4], [14]. Apart from survival time the following covariates information were collected- Stage, Abortions, and Number of children, Chemotherapy, Radiotherapy, and Menopause status and etc. About 6% of the survival times were censored. The Accelerated failure time models with frailty using different lifetime distributions were fitted [17] using Stata-9 software.

2.1 Frailty Model

In clinical trials, survival analysis implicitly assumes a homogeneous population to be studied. That is, all individuals are in principle subject under the same risk [2]. In most of its the applications, the study population cannot be assumed to be homogeneous for following reasons that is the effect of drug may be individual specific or group specific or each subjects has its own biological response to treatment the notion of frailty provides a convenient way to introduce random effects, association and unobserved heterogeneity into models for survival data [16]. Heterogeneity in frailty may be a factor observed in declines and reversals with age of mortality differentials between pairs of populations. This study attempts with univariate frailty model [9]. The univariate frailty models are not identifiable from the survival information alone, provided a frailty model with finite mean is identifiable with univariate data, when covariates are included in the model. Many distributions can be chosen for the frailty, but the most common frailty distribution is the gamma distribution[11]. The gamma distribution has been widely applied as a mixture distribution. From a computational point of view gamma distribution is convenient, because it is easy to derive the closed form expression of survival and the hazard function [20]

2.2 Accelerated failure time model without Frailty

The Accelerated failure time model is an attractive alternative to the popular Cox proportional regression model. The accelerated failure time model is a linear regression model in which the response variable is the logarithm or a known monotone transformation of a failure time [8]. The proportional hazards model is appropriate when there is a permanent difference between the groups in the longer term in the context of the follow-up period [10],[14].The accelerated failure time model is more appropriate when the group differences are seen over a shorter timeframe while in longer term the probability of remaining event free is similar in the two groups. This is consistent when there is a delay in the event occurring in one group compared to the other but no

permanent effect [19]. The presence of such a delay is seen in many therapeutic settings and a range of time to event end points. The Accelerated failure time model describes a relationship between the survivor functions of any two individuals.

Let T_i be a random variable denoting the failure time for the i^{th} subject, and let $x_{i1}, x_{i2}, ..., x_{ip}$ be the values of *p* covariates of the subject. The model is then

$$log\, T_i = \beta_0 + \beta_1 x_{i1} + \ldots + \beta_p x_{ip} + \sigma \varepsilon_i \text{ where } \varepsilon_i \sim h_0(t) \quad (1)$$

where ε_i is a random disturbance term, and $\beta_0, \ldots, \beta_p$, and σ are parameters to be estimated, $h_0(t)$ is a known baseline survival, T_i is actual survival time sometimes observed, σ is a scale parameter and x_i is fixed $p \times 1$ vector of covariates. The σ can be omitted, which requires that the variance of ε_i be allowed to be different from equation1. But it is simpler to fix the variance of ε_i at 1 and let σ change. All Accelerated failure time models are named for the distribution of T rather than the distribution of ε or log T. The reason for allowing different distribution assumptions is that they have different implications for the shapes of hazard function [6], [7].

2.3 Accelerated failure time model with Frailty

In survival analysis, deviations from proportional hazards may sometimes be explained by unaccounted random heterogeneity, or frailty [12]. This work also discuss about on omitted covariates in survival analysis and shows in a case study how unstably frailty models might behave when asked to account for unobserved heterogeneity in standard survival analysis with no replications per heterogeneity unit[15], [18]. It would be advantageous to upgrade the accelerated failure time approach alongside the hazard modeling approach to survival analysis

$$T_{ij} = x_{ij}\beta + \varepsilon_{ij} \text{ and } h_{ij}(t/z_i) = z_i h_0(t) \quad (2)$$

where $h_0(t)$ is unknown baseline hazard is independent of the covariates and z_i are the frailties, the conditional on z_i and ε_{ij} are independent, and z_i is Gamma frailty.

3. RESULTS

Table1: Distribution of patients according to treatment and stages

Neo-Adjuvant therapy				Adjuvant therapy		
Stage	**No. of cases**	**Censored**	**Response (%)**	**No. of cases**	**Censored**	**Response (%)**
2A	125	5	120(96)	22	4	18(22)
2B	91	2	89(98)	10	1	9(90)
3A	100	3	97(98)	7	1	6(86)
3B	133	9	124(93)	9	1	8(89)
4	22	10	12(55)	3	1	2(67)
Total	471	29	442	51	8	43

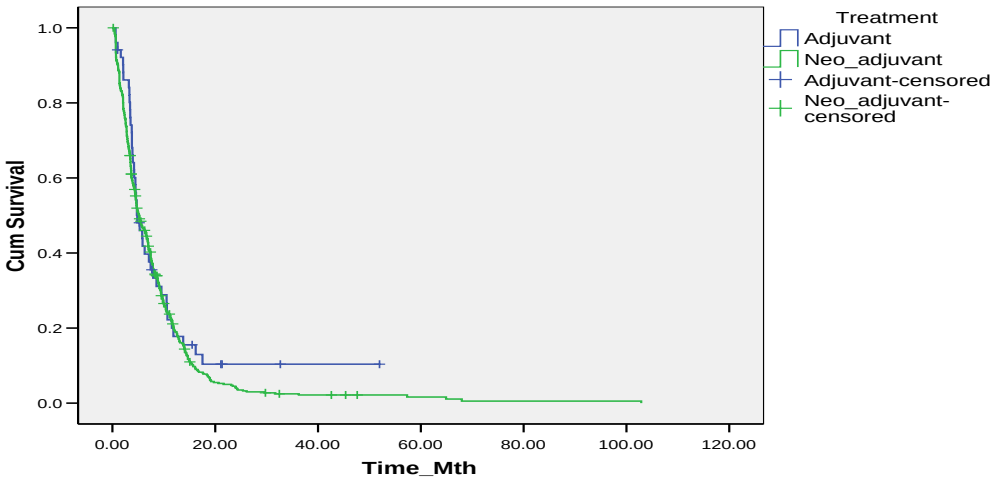

Figure: 1. Kaplan-Meier survival estimates for Neo-Adjuvant and Adjuvant groups

The table1 describes the different stages of breast cancer between two types of treatment namely Neo-adjuvant (90%) and adjuvant (10%). The disease recovery 93% and 55% respectively. The recovery rates for adjuvant among various stages are 82%, 90%, 86%, 89% and 67% respectively. As expected the early stages usually give higher response than later stages. However the rates for neo-adjuvant among various stages are 96%, 98%, 97%,

difference between neo-adjuvant and adjuvant was not significant (See Figure1). Hence for the analysis we combined both the treatment groups [13].

Table2: Accelerated Failure Time with and without Frailty

Covariates	AFT Model without frailty			AFT Model with frailty		
	Weibull	Exponential	Log Normal	Weibull	Exponential	Log Normal
Stage	0.8940* (0.0327)	0.8970* (0.0327)	0.1269* (0.0375)	0.8299* (0.0447)	0.8901* (0.0347)	0.1269* (0.0375)
Abortions	1.2002 (0.1368)	0.9715 (0.0242)	-0.0685 (0.1173)	1.1578 (0.1767)	1.1589 (0.1386)	-0.0685 (0.1173)
No. of children	0.9687 (0.0240)	0.9715 (0.0242)	0.0143 (0.0270)	0.9714 (0.0361)	0.9736 (0.0263)	0.0413 (0.0270)
Chemotherapy	3.0910 (0.7916)	2.7916 (0.6969)	-0.4557* (0.2507)	2.0867* (0.8167)	2.5154* (0.7093)	-0.4557* (0.2507)
Radiotherapy	1.1900	1.1737*	-0.0706	1.1650	1.1633	-0.0706

	(0.1152)	(0.1129)	(0.0954)	(0.1520)	(0.1173)	(0.0954)
Family History of Cancer	1.0687 (0.2401)	1.0540 (0.2366)	0.1009 (0.2288)	0.9420 (0.2857)	1.0228 (0.2411)	0.1009 (0.2288)
Menopause	0.9734 (0.0953)	0.9728 (0.0951)	0.0750 (0.0997)	0.9857 (0.1337)	0.9747 (0.1005)	0.0750 (0.0997)
-2LL (Deviance)	1515.95	1519.50	**1488.23**	**1483.97**	1518.53	1488.23
* Indicates $p < 0.05$ and (values) indicates standard error						

The table2 describes the Accelerated failure time model without frailty and it shows the significant for the covariates stage in Weibull exponential and lognormal, except lognormal where as chemotherapy is significant factor in log normal and radio therapy is significant factor in exponential models, the deviance for lognormal is 1488.23 which is less compared to other models. The Accelerated failure time model with gamma frailty and it shows that the covariate stage and chemotherapy is significant in weibull, exponential and log normal models. The deviance Of Weibull model is 1483.97 which are less compared with other models with gamma frailties, as well as Weibull model without frailties.

4. DISCUSSIONS

The Accelerated failure time model is an important alternative to the Cox-proportional hazard model in survival analysis. The early stages usually give higher response than later stages. The Accelerated failure time with gamma frailty model accounts more heterogeneity in Weibull distribution compared with other models. The lognormal model better fits Accelerated failure time without frailty.

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REFERENCES

[1]Aalen.O., (1988): Heterogeneity in Survival Analysis. Statistics in Medicine. 7,121-37.

[2]Cox, D.R., Oakes, D., (1984): Analysis of Survival Data. London Chapman and Hall.

[3]Duncan, Kerr G.R., (1976): The curability of breast cancer. British Medical Journal. 2, 781-783.

[4]Haybittle, J.L., (1959): The estimation of the proportion of patients cured after treatment for cancer of the breast. British Journal of Radiology. 32, 725–733.

[5]Hosmer, D.W., and Lemeshow S., (1999): Applied Survival Analysis: regression modeling of time to event data. New York, Willey.

[6]Keiding, N., Anderson, P.K., and Klein J.P., (1997): The role of frailty models and accelerated failure time models in describing heterogeneity due to omitted covariates. Statistics in Medicine.16, 215-24.

[7]Klein Baum, D.G., (1996): Survival analysis: a self learning text, New York, Springer.

[8]Lee E.T. Wang J.W., (2003): Statistical Methods for survival Data Analysis. New Jersey: John Willey.

[9]Manatunga, A.K., Oakes, D. (1999): Parametric Analysis of Matched pair survival Data. Life time Data Analysis.5, 371-387

[10]Maggard M.A., Thompson J.E., and KOC.Y. (2003): Why do breast cancer mortality rates vary across states? American Journal Surgery .69, 59–62.

[11] McGilchrist,C.A.,Aisbett,C.W(1991):Regression With Frailty in Survival analysis.Biometrics. 47, 461-4 66.

[12] Venkatesan, P., and Ponnuraja, C., (2010): Survival Models for exploring tuberculosis clinical trial data-an empirical comparison. Indian Journal of Science. and Technology. 3, 755-758.

[13] Venkatesan, P., and Raman T.T, Ponnuraja, C., (2011): Survival Analysis of Women with Breast Cancer under Adjuvant Therapy in South India. Asian Pacific Journal of Cancer Prevention.12, 1543-1545.

[14]Rajaeefard, A.R., Baneshi, M.R., Talei, A.R., and Mehrabani, D.,(2009): Survival Models in Breast

Cancer Patients. Iranian Red Crescent Medical Journal. 11,295-300.

[15]Rama, R., Swaminathan, R., and Venkatesan, P., (2010): Cure models for estimating hospital-based breast cancer survival, Asian Pacific Journal Cancer Prevention. 11,387-91.

[16]Vaupel, J. W., Manton, K.G., Stallard, E. (1997): The Impact of Heterogeneity in individual frailty on the dynamics of Mortality. Demography 6,439-454.

[17]Wei, L.J., (1992): The Accelerated failure time model: A useful alternative to the Cox regression model in survival analysis (with discussion).Statistics in Medicine.11, 1871-79.

[18]Weipan., (2001): Using frailties in the accelerated failure time model. Life time Data Analysis. 7, 55-64.

[19]Zahl, P.H., Tretli, S., (1997): Long-term survival of breast cancer in Norway by age and clinical stage. Statistics in Medicine. 16, 1435–1449

[20] Zahl, P.H (1997): Frailty modeling for the excess hazard. Statistics in Medicine.16, 1573-1585.