RESEARCH ARTICLE

Fitting Cure Rate Model to Breast Cancer Data of Cancer Research Center

Ahmad Reza Baghestani[2], Farid Zayeri[2], Mohammad Esmaeil Akbari[1], Leyla Shojaee[1], Naghmeh Khadembashi[4], Parviz Shahmirzalou[1,2,3,*]

Abstract

Background: The Cox PH model is one of the most significant statistical models in studying survival of patients. But, in the case of patients with long-term survival, it may not be the most appropriate. In such cases, a cure rate model seems more suitable. The purpose of this study was to determine clinical factors associated with cure rate of patients with breast cancer. Materials and Methods: In order to find factors affecting cure rate (response), a non-mixed cure rate model with negative binomial distribution for latent variable was used. Variables selected were recurrence cancer, status for HER2, estrogen receptor (ER) and progesterone receptor (PR), size of tumor, grade of cancer, stage of cancer, type of surgery, age at the diagnosis time and number of removed positive lymph nodes. All analyses were performed using PROC MCMC processes in the SAS 9.2 program. Results: The mean (SD) age of patients was equal to 48.9 (11.1) months. For these patients, 1, 5 and 10-year survival rates were 95, 79 and 50 percent respectively. All of the mentioned variables were effective in cure fraction. Kaplan-Meier curve showed cure model's use competence. Conclusions: Unlike other variables, existence of ER and PR positivity will increase probability of cure in patients. In the present study, Weibull distribution was used for the purpose of analysing survival times. Model fitness with other distributions such as log-N and log-logistic and other distributions for latent variable is recommended.

Keywords: Breast neoplasms - cure fraction - cure rate model - negative binomial distribution - survival analysis

Introduction

Breast cancer (BC) is the most common cancer among women worldwide (Lotfnezhad et al., 2015). In 2012, there were 1.67 million incident cases from 140 of 184 countries. Around 39% of all cases in 2012 were from Asian countries (Kim et al., 2015). Unfortunately, BC incidence is rising among Iranian women. That includes 16% and 22.9% of all and invasive cancers respectively (Veisy et al., 2015). Incidence rate of BC in Isfahan province of Iran rates to 30 per 100,000 population (Movahedi et al., 2012; Baghestani et al., 2015). Taghavi et al states that there is increasing trend of BC in Iran, although mortality rate of BC in Iran proves to be lower than in western countries (Taghavi et al., 2012).

Another study in patients with more than 9 involved lymph nodes, manifested that young age and estrogen tumor positivity was associated with improved outcomes. Race of patients was significant at 0.1 levels (Zaichner et al., 2014). Some researchers also surveyed the effect of fat diet and obesity on BC patient's survival (Kaviani et al., 2013; Xing et al., 2014).

Survival analysis is a collection of statistical procedures in which the outcome of interest is time until an event occurs. Time can be weeks, months or years; outcome can be death, disease, incidence or relapse from remission, recovery and so on (Kleinbaum et al., 2012). The purpose of most studies is to identify effective factors on survival of patients. In fact for the purpose of monitoring the effectiveness of cancer treatment and identifying prognostic factors of the disease, studies of cancer patient survival are required (Rahimzadeh et al., 2014). Some studies surveyed role of age, age at menarche, total reproductive age, age at first child birth, and menopausal status (Akhtar et al., 2015). Some other study surveyed role of obesity, alcohol consumption, inactivity, and hormone replacement therapy (Colditz et al., 2014; Howell et al., 2014). The Cox Proportional Hazards (PH) model is the most popular, semi-parametric model for the analysis of survival data (Kleinbaum et al., 2012). It assumes that all patients will eventually experience the main outcome (relapse or death). Therefore, Cox PH model cannot be used to identify prognostic factors associated with the cure procedure (Asano et al., 2013). In some circumstances, despite the fact that the follow-up period is long, some patients will not experience main event; hence, the

[1]Cancer Research Center, Shahid Beheshti University of Medical sciences, Tehran, [2]Department of Biostatistics, [3]Committee Research, [4]Department of Englishsh language, School of Allied Medical Sciences, Shahid Beheshti University of Medical sciences, Tehran, Iran *For correspondence: pshkhoei@gmail.com

censoring rate increases, leading to the overestimation of the survival rate (Mirzaei et al., 2014). Cure rate models can be used to investigate the heterogeneity between patients with cancer who are long-term survivors and those who are not. Kaplan-Meier curve can be used to identify long-term survivors. Survival curve has a plateau among long-term survivors. Then cure rate model may be useful to analyze data (Othus et al., 2012).

The aim of this study was to use cure rate model to determine the prognostic factors on survival of BC patients.

Materials and Methods

The present study is a prospective cohort study on 557 patients with BC who were admitted at Cancer Research Center (CCC) of Shahid Beheshti University of Medical Sciences, Tehran Iran, during 1994 to 2013. All patients went under Mastectomy Modified Radical (MRM) or Breast Conserving Surgery (BCS). Some of patients experienced the recurrence of the disease. In some cases, the patients or patient's family members were contacted to confirm if the patients were still alive. Variables recurrence cancer, status of and Human Epidermal growth factor Receptor-2 (HER2), Estrogen Receptor (ER), Progesterone Receptor (PR), size of tumor, grade of cancer, stage of cancer, type of surgery, age at the diagnosis time and Number of Removed Positive Lymph Nodes (NRPLN) were selected. Stage and grade of cancer were categorized to 3 and 4 degrees respectively. Size of tumor was categorized to 3 sizes (less than 2, 2-5 and more than 5 cm).

BC seemed be more aggressive in younger patients; Consequently age at the diagnosis time was categorized to 4 age groups (less than 40, 40 to 50, 50 to 60 and older than 60) and NRPLN to 3 groups (zero NRPLN, between 1 to 9 and more than 10). For data analysis, Non-Mixed cure rate model with negative binomial distribution was employed. Weibull and uniform distribution were proposed for survival time and prior distribution of all
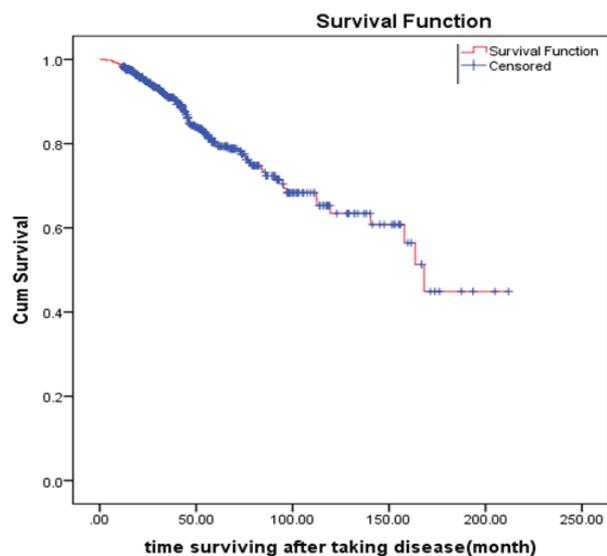
parameters in the model respectively. To identify the significant prognostic factors, credible intervals were used. Credible interval is a Bayesian form of confidence interval in domain of posterior probability distribution.

In cure rate models, covariates depend on θ through the following relationship: $\theta = \exp(x'\beta)$. where x is a $p*1$ vector of covariates and β is a $p*1$ vector of regression coefficients. Using, $\theta = \exp(x'\beta)$ in $P_0 = \{1 + \eta\theta\}^{-1/\eta}$ the role of the regression coefficients for the cured and non-cured group can be interpreted. Since $\eta > 0$, the relation between the covariates and the cure rate is inverse (Cancho et al., 2015). For instance, if a covariates has a positive coefficient, an increase in its value implies a reduction in the cure rate (where all other covariates are kept constant). All analyses were carried out using PROC MCMC in SAS version 9.2 and the parameters were estimated through a Bayesian approach.

Results

Data from 557 female patients with breast cancer were analyzed. The mean (SD) age was equal to 48.86 (11.31).

Table 1. Baseline Characteristics of the Patients

Variable	Category	No (%)	Survival mean in month (percent of death)
Recurrence of cancer			
	Yes	96 (17.2)	56.85(65.6)
	No	461(82.8)	49.70(6.3)
Type of surgery			
	BCS	348(62.5)	43.46(8)
	MRM	209(37.5)	63.38(30.6)
ER			
	Yes	388(69.7)	49.75(13.4)
	No	169(30.3)	53.65(23.7)
PR			
	Yes	369(66.2)	49.95(13.6)
	No	188(33.8)	52.86(22.3)
HER2			
	Yes	127(22.8)	57.93(29.9)
	No	430(77.2)	48.86(12.6)
Age			
	Less than 40	120(21.5)	52.69(20)
	40-50	210(37.7)	53.37(13.8)
	50-60	137(24.6)	50.25(13.1)
	More than 60	90(16.2)	43.93(23.3)
tumor size(cm)			
	less than 2	190(34.1)	49.81(7.9)
	2-5	291(52.2)	52.65(16.2)
	More than 5	76(13.6)	47.17(39.5)
NRPLN			
	0	268(48.1)	56.10(6)
	0-9	241(43.3)	46.51(22)
	10 and More	48(8.6)	44.32(47.9)
stage of cancer			
	1	126(22.6)	52.05(5.6)
	2	252(45.2)	52.69(8.3)
	3	163(29.3)	48.51(32.5)
	4	16(2.9)	39.09(68.8)
Grade of cancer			
	1	61(11)	53.09(6.6)
	2	312(56)	51.69(12.5)
	3	184(33)	48.94(26.6)

Figure 1. Kaplan-Meier Curve for Overall Cumulative Survival of Women with BC

and Minimum and maximum follow-up times of patients were equal to 3.23 and 211.97 months, respectively, with the average of 50.93 and the median of 39.96 months. Among the patients, 92 of the patients died from breast cancer and the rest survived. Other descriptive statistics are shown in Table 1.

For these patients 1, 5 and 10-years survival rate was 95, 79 and 50 percent, respectively. Since cured models are appropriate for data with cured fraction, the Kaplan-Meier curve showed cured patients in the data (Figure 1).
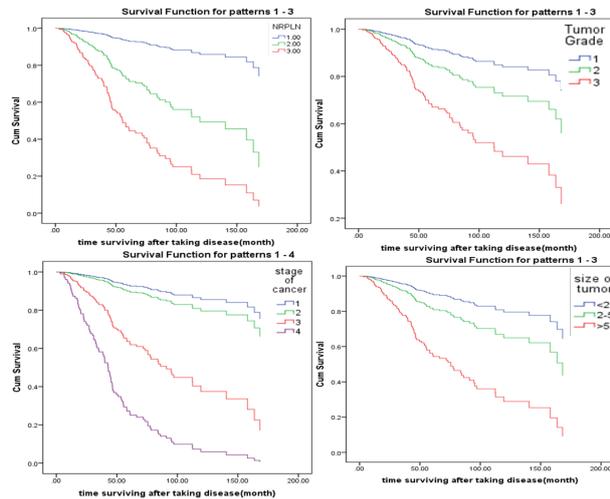
Figure 2. Kaplan-Meier Analysis Showing Disease-free Survival for Variables Stage and Grade of Cancer, Size of Tumor, NRPLN

Because of Figure1, the above mentioned variables were entered in Non-Mixed cure rate model with negative binomial distribution for the purpose of determining factors associated with cure rate of patients (Table 2).

These results manifested that all of the variables were significant on the cure rate of patients (Table 2). Sign in the mean of parameters shows role of variable in increase or decrease cure rate. For instance, positive sign causes a decrease in the cure rate. Kaplan-Meier analysis showed disease-free survival for variables such as stage of cancer, Tumor grade, size of tumor, NRPLN and age at the time of diagnosis (Figure 2).

There are sensible difference between the categories stage of cancer, Tumor grade, NRPLN and size of tumor while at the age group of 40-50 and 50-60 an overlap in the graph was observed. Fourth column in Table 2 shows cure rate. For instance, probability of cure in patients without recurrence of disease was 30% more than patients with recurrence of BC while probability of cure in patients with ER was 8% more than patients without ER.

Discussion

BC is the most common cancer among Iranian women. Incidence rate of BC was 30 cases per 100,000 Iranian patients (Movahedi et al., 2012). It is essential that mortality and survival of disease be improved by an early diagnosis. In some forms of cancers, such as BC, we expect to see long-term survival by early diagnosis (Najafi et al., 2013).

Table 2. Promotion Time Parameters of the Negative binomial model

Parameters	Category	Mean (SD)	Credible Interval		Sig.	Cure rate
			2.50%=	97.50%		
Recurrence of cancer	Yes	0.83 (0.01)	0.81	0.84	*	0.71
	No	REF	-	-	-	-
Type of surgery	MRM	0.68 (0.02)	0.65	0.72	*	0.77
	BCS	REF	-	-	-	-
ER	Yes	-0.29 (0.01)	-0.31	-0.27	*	1.08
	No	REF	-	-	-	-
PR	Yes	-0.59 (0.01)	-0.61	-0.55	*	1.16
	No	REF		-	-	- -
HER2	Yes	0.89 (0.01)	0.87	0.92	*	0.69
	No	REF	-	-	-	-
Age	Less than 40	REF	-	-	-	-
	40-50	0.21 (0.01)	0.19	0.24	*	0.93
	50-60	0.60 (0.03)	0.55	0.65	*	0.79
	More than 60	0.46 (0.01)	0.43	0.49	*	0.84
tumor size(cm)	less than 2	REF	-	-	-	-
	2 - 5	0.69 (0.01)	0.67	0.71	*	0.76
	More than 5	-0.42 (0.01)	-0.44	-0.4	*	1.12
NRPLN	0	REF	-	-	-	-
	0-9	0.24 (0.01)	0.22	0.27	*	0.91
	10 and More	-0.85 (0.02)	-0.89	-0.81	*	1.21
stage of cancer	1	REF	-	-	-	-
	2	0.21 (0.01)	0.2	0.23	*	0.92
	3	-0.44 (0.01)	-0.46	-0.42	*	1.12
	4	-0.59 (0.01)	-0.6	-0.57	*	1.16
Grade of cancer	1	REF	-	-	-	-
	2	0.52 (0.01)	0.49	0.54	*	0.82
	3	1.05 (0.01)	1.03	1.08	*	0.63

Cure rate models are appropriate for determining effective factors on patient's survival and cure rate. Promotion time cure model was introduced first by Yakovlev and Tsodikov (1993). It was extended by Chen (1999) afterwards. In survival data analysis, we are facing a high percentage of individuals who will not experience the given event. These individuals are referred to as cured. There exists many cured individual in cancers like BC. Although it is more 20 years that cure rate models are introduced, they have not been addressed properly yet (Othus et al., 2012). These models are useful and effective, despite the fact that there are no cured patients. Under such conditions, these models will play the role of survival models appropriately.

In this study 1, 5 and 10-years survival rate was 95, 79 and 50 percent, respectively. Abdollahi et al estimated 5-years survival of patients equal to 49%. That is much lower than other studies estimations (Abdullah et al., 2013). On the other hand, Ziaie et al estimated 1, 5 and 10-years patients survival 96, 81 and 76%, respectively that is more than the present study's estimations (Ziaei et al., 2013).

All Variables were diagnosed as factors contributing to Iranian women cure with BC. Recurrence of BC occurred in 96 (%17) patients. Mean of survival time in patients with recurrence of BC have 7 month more than others. They also had 60 percent more death rate, comparatively speaking. Thus, recurrence of BC caused a decrease in the cure rate.

Many breast cancer patients normally select one of the two surgeries of MRM or BCS during their treatment period. In such cases examining patient's survival status and determining multi-year survival with surgical separation proves to be quite important. One study stated that patients who are undergoing BCS surgery have better performance and survival status than MRM ones(Acil et al., 2014). Patients with surgery of MRM had 20 month more survival, but near 23 percent more death rate than BCS ones. Another study showed that the long-term survival rate among women who undergo breast-conserving surgery is the same as those women who undergo radical mastectomy (Veronesi et al., 2002).

One important aspect of the role of pathology in the evaluation of BC is biomarker testing, as ER, PR and HER2. Biomarkers might be prognostics, predictive and both. Thus, it proves to be effective on treatment and survival of BC. This study proved that ER and PR inverse HER2 caused an increase in the cure fraction. One study was performed in order to ascertain the role of receptors (ER, PR and HER2) in four groups (luminal A and B, HER2 type and triple negative) with survival of patients with spinal bone metastases. The study showed that a survival time wasn't significant between groups; and yet patients with triple negative groups had shorter survival rate than luminal B (Bollen et al., 2015).

Rahimzadeh et al. in a study conducted on Iranian women patients with breast cancer, considered latent variable distribution (the number of remaining cancer cells in cancerous tissue after receiving treatment) as Poisson and negative binomial. In that study, patient's age was significant only in a model with negative binomial distribution. DIC criterion comparison of the two models revealed that this criterion was the least in a model with negative binomial distribution (Rahimzadeh et al., 2014). Another study that focused on age at the diagnosis time, showed age as an important factor in survival of patients with BC (Asif et al., 2014). Age at the diagnosis time was categorized into four groups in this study (less than 40, 40 to 50, 50 to 60, more than 60). Third and fourth age group had less survival mean compared to those in the first group. This difference was sensible in the fourth group.

Tumor size is related to BC recurrence and survival time. More study showed a reverse relationship between tumor size and BC survival. The present study proves that, with increasing tumor size, percentage of death (7.9, 16.2 and 39.5 %) increase which proves to be a significant factor in cure rate. However, there is a heterogeneity in significance between categories of tumor size (Table 2). One study indicated that a decline of 1 and 1.5 cm in size of tumor was associated with a 10.3% and 23% reduction in mortality rate respectively (Narod et al., 2014). Another study showed a significant effect between tumor size and some other variables with overall survival of BC patients in Pakistan (Mahmood et al., 2015).

Lymph node involvement is a very important factor for patients with breast cancer (Orang et al., 2013), affecting the patient's survival (Chen et al., 2014). Patients with more than 10 NRPLN had 12 month less survival time and more than 42% more probability of dying from BC compared to patients with less than 10 NRPLN.

Cancer stage is one of the variables that affect the survival of patients. According to one study, 5 and 10 years survival rate of patients for all stages was 64.2 and 52.6 respectively (Rama et al., 2010). In the present study, the values of 93, 91, 59 and 19 percent were estimated respectively.

Tumor grade is a description of normality status of cancer cells and therefore is an indicator of the ability of a tumor to grow and spread. The patients with tumor grade 1 (53.09) had better survival than patients with tumor grade 2 (51.69) and 3 (48.94). While, patients with tumor grade 3 had 20% more death than patients in grade1. This relationship was highly significant (p<0.001) in some studies (Sipetic-Grujicic et al., 2014).

BC is the most common cancer in women worldwide. Recognizing factors affecting cure rate of patients can be a significant factor in reducing death rate. There are limited studies on BC survival, which employed cure rate model to identify the clinical factors associated with cure (12). These cure rate models are introduced to explain the remaining cancer cells after treatment, using latent variable. Although them would be beneficial, even though there are no cured patients. Analysis showed that biologic variables (ER, PR and HER2) and recurrence of cancer, size of tumor, grade of cancer, stage of cancer, type of surgery, age at diagnosis and NRPLN were important on cure rate of BC. Meanwhile, there were heterogeneity in sign in mean of tumor size, NRPLN and stage of cancer, maybe for correlation between these with other variables.

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