

RESEARCH ARTICLE

Estimation of the Cure Rate in Iranian Breast Cancer Patients

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Abstract

Background: Although the Cox's proportional hazard model is the popular approach for survival analysis to investigate significant risk factors of cancer patient survival, it is not appropriate in the case of log-term disease free survival. Recently, cure rate models have been introduced to distinguish between clinical determinants of cure and variables associated with the time to event of interest. The aim of this study was to use a cure rate model to determine the clinical associated factors for cure rates of patients with breast cancer (BC). **Materials and Methods:** This prospective cohort study covered 305 patients with BC, admitted at Shahid Faiazbakhsh Hospital, Tehran, during 2006 to 2008 and followed until April 2012. Cases of patient death were confirmed by telephone contact. For data analysis, a non-mixed cure rate model with Poisson distribution and negative binomial distribution were employed. All analyses were carried out using a developed Macro in WinBugs. Deviance information criteria (DIC) were employed to find the best model. **Results:** The overall 1-year, 3-year and 5-year relative survival rates were 97%, 89% and 74%. Metastasis and stage of BC were the significant factors, but age was significant only in negative binomial model. The DIC also showed that the negative binomial model had a better fit. **Conclusions:** This study indicated that, metastasis and stage of BC were identified as the clinical criteria for cure rates. There are limited studies on BC survival which employed these cure rate models to identify the clinical factors associated with cure. These models are better than Cox, in the case of long-term survival.

Keywords: Breast cancer - long-term survival analysis - cure rate model

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Introduction

Breast cancer is considered to be the most common cancer in women throughout the world (Parkin et al., 2005). In Iran, breast cancer ranks first among cancers diagnosed in women (Sadjadi et al., 2005) and the most frequent cancer in women population in Tehran (Mohagheghi et al., 2009). Its mortality rate increased (Taghavi et al, 2012), with similar pattern to expected mortality rates in general Iranian women population (Haghighat et al, 2012).

The survival analysis is one of the most important measures of cancer care. Studies of cancer patient survival are essential for monitoring the effectiveness of the diagnosis and treatment of cancer and identifying the prognostic factors of the disease (Dickman and Hakulinen, 2000). The relationship between survival time and stage at diagnosis is considered in many studies (Gakwaya et al., 2008; Lee et al., 2007). Detection at an earlier stage of the disease is the key to improve the life expectancy

of breast cancer patients (Bray et al., 2004).

Although the Cox's proportional hazard model is the popular survival analysis to investigate the significant risk factors of cancer patient's survival (Al-Naggar et al., 2009; Fouladi et al., 2011), this model would not appropriate in the case of log-term disease free survival. The ordinary Cox model assumes that all patients will eventually experience the events of interests (relapse or death). Therefore, for breast cancer patients who achieved long-term disease-free survival and did not experience recurrences, or death during the follow-up, this model could not accurately identify the clinical factors associated with cure (Asano et al., 2013).

Recently, cure rate models, introduced to explain the remaining cancer cells after treatment, using latent variable. These models can distinguish between clinical determinants of cure and variables associated with the time to event of interest (relapse or death) (Cooner et al., 2007; Borges et al., 2012). Cure rate models cover the situations in which there are sampling units insusceptible to the

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occurrence of the event of interest, which can be caused by different competing causes. If such sampling units are not present, the analysis reduces to standard approaches of survival analysis (Cancho et al., 2013).

The aim of this study was to use these cure rate model to determine the clinical associated factors on cure rate of patients with breast cancer.

Materials and Methods

This is a prospective cohort study on 345 patients with BC who admitted at Shahid Faiazbakhsh Hospital, Tehran, during 2006 to 2008 and followed until April 2012. These patients had no metastasis at the time of entering in the study. All patients were gone under Mastectomy Modified Radical or Breast Conserving Surgery (BCS). The case of metastasis was confirmed by an oncologist, using biochemical technique, X-ray, Ultrasound or changing blood biomarker. The patients or patients' family members were contacted through the phone to confirm if the patients are still alive and the last situation of metastasis. 40 patients excluded from the study due to incomplete information or lost in follow up. Finally 305 patients were entered in the analysis. Age at diagnosis, metastasis and the stage of BC were selected as the prognosis factors in cure rate model.

For data analysis, unmixed cure rate model with Poisson distribution and Negative Binomial distribution were employed. A Weibull distribution was proposed for survival time. Credible interval was used to identify the significant prognostic factors. Credible interval is the Bayesian analogue of a confidence interval. In Bayesian statistics, credible interval (also called Bayesian confidence interval) is an interval in the domain of a posterior probability distribution.

All analysis carried out using a developed Macro in WinBugs and the parameters were estimated by a Bayesian approach. In order to model comparison and finding the best model, the deviance information criterion (DIC) was calculated. This criteria is corresponding to AIC information criteria (Tomohiro, 2007) and according to this, the model with lower DIC is the better one.

Results

A total of 305 women with breast cancer were included in this analysis. The mean (SD) of age was 49.8 (11.3) years. The age ranged from 23 to 79.

13.4% of patients experienced metastasis. The mean (SD) age of metastasis was 50.9 (13.2) years and the mean (SD) age for patients without metastasis was 49.6 (10.66) simultaneously. There was no statistically difference between age of two groups (p=0.48).

The longest period of follow-up was 6.47 years (2356 days) and during the follow-up (52 subjects) 17% of patients were dead, 20 subjects (7.6%) without metastasis and 32 subjects with metastasis (78%). There is statistically significant difference between proportion of two groups (p<0.0001).

The overall 1- year, 3-year and 5-year relative survival rate was found as 97%, 89% and 74%. Kaplan-Meier

analysis showed disease-free survival after 5 years for both metastasis and non-metastasis patients (Figure 1).

Age, metastasis and stage were taken into account as the prognosis factors in non-mixed cure rate model with both Poisson and Negative Binomial distributions (Table 1). According to the results, metastasis and stage of BC were the significant factors, but age was significant only in Negative Binomial model.

The DIC criteria showed that the Negative Binomial model had a better fit, comparing to Poisson model (DIC=251 in Negative Binomial model vs. DIC=267 in Poisson model).

The results regarding the estimation of cure rates for metastasis and stage (assumed that, age is fixed) revealed in Table 2, indicated that, the rate of cure in metastasis patients was lower than non-metastasis patients and the rate of cure decreases as the stage of BC increases consequently.

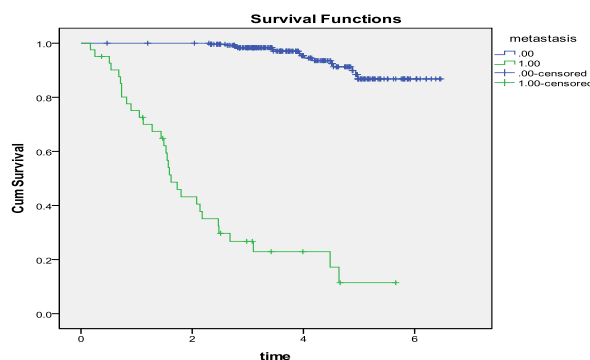


Figure 1. Kaplan-Meier Analysis Showing Disease-free Survival after 5 years for Both Metastasis and non-Metastasis Patients (blue=non-metastasis, green=metastasis)

Table 1. Promotion Time Parameters of the Poisson and NB Models

Model	Parameter	Mean	SD	2.5 Percentile	97.5 Percentile
Poisson	scale	5.18	1.55	-8.8	-2.92
	shape	1.69	0.21	1.37	2.12
	intercept	-4.21	3.32	-10.49	1.74
	stage 1	4.51	3.26	-0.21	12.61
	stage 2	5.05	3.27	0.28	13.26
	metastasis	3.39	0.33	2.78	4.05
	age	-0.01	0.01	-0.03	0.01
Negative Binomial	scale	-7.16	1.36	-10.08	-4.74
	shape	3.29	0.61	2.22	4.56
	intercept	-4.33	3.4	-12.66	1.44
	stage 1	4.53	3.19	-0.1	13.16
	stage 2	5.83	3.19	1.25	14.52
	metastasis	6.35	1.16	4.36	8.89
	age	-0.04	0.01	-0.06	-0.02

Table 2. Cure rate Estimation Based on the Negative Binomial

Stage1		Stage2		Stage3	
Metastasis	Non-Metastasis	Metastasis	Non-Metastasis	Metastasis	Non-Metastasis
34	99	2	14	1	9

Discussion

This study indicated that, metastasis and stage of BC were identified as the clinical criteria of cure rate, in Iranian women with breast cancer.

Iran is located in the western part of Asia which, breast cancer in women is number one, (Moore, 2010). The incidence of the BC is rising in Iran. (Mousavi et al., 2007) and its burden is increasing (Taghavi et al., 2012).

In this study, the overall 1- year, 3-year and 5-year relative survival rate was found as 97%, 89% and 74%. A study in Jordan showed that the overall 5-year survival rate for breast cancer was 59.6%. The 1-year rate was 91.6%, the 2-year rate was 80.1%, the 3-year rate was 70.2% and the 4-year rate was 65.8% (Arkoob et al., 2010). In Korea, the five-year survival rates for BC have improved significantly after National Cancer Screening Program, from 78.0% in early 1993-1995 to 90.0% in 2004-2008 (Park et al., 2011). However, in other studies conducted in different regions of Iran, five- year survival rate ranged from 56 to 62 percent was lower than this study (Babaei et al., 2005; Yaghmayee et al., 2007; Fouladi et al., 2011). In contrast, a cohort study in Malaysia indicated the overall 5 years survival as 49% (Abdullah et al., 2013).

Early detection of breast cancer plays the leading role in reducing mortality rates and improving the patients' prognosis among women (Elmore et al., 2005; Hoerger et al., 2011). So in some cancers like BC, we expected to see more long-term disease free survival (Najafi et al., 2013).

"Promotion time Cure Model" which was first introduced by Yakolev and Tsodikov (Yakolev and Tsodikov, 1996) and then "time required for tumor formation can be determined" developed by Chen et al, (Chen et al., 1999) has been lots of attention in recent decades. These models would appropriate in the case of log-term disease free survival in which most patients do not experience the events (death or recurrence) or totally cured.

Recently, cure rate models, introduced to explain the remaining cancer cells after treatment, using latent variable. These models can distinguish between clinical determinants of cure and variables associated with the time to event of interest (relapse or death) (Borges et al., 2012; Cooner et al., 2007). There are limited studies on BC survival, which employed these cure rate models to identify the clinical factors associated with cure (Asano et al., 2013) and this study is one of those pioneers who employed this new technique from theory to application on cure rate and survival of women with breast cancer.

These models would be beneficial, even though there are no cured patients. In this case, these models (at least) would make the rule of the survival models appropriately.

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