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Survival Analysis of Iranian Patients with Breast Cancer Using Joint Frailty Model with a Cure Rate

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Abstract

Background: Breast cancer is a common disease among women around the world. In Iran, it is the most prevalent cancer diagnosed in women. The objective of this study was to assess the cure rate of patients and the associated risk factors.

Method: A retrospective cohort study was conducted on 446 patients with breast cancer admitted to the Shahid Ramezanzadeh Radiotherapy Center. Using R 3.2.2 software, the Kaplan-Meier curve, log-rank test, and cure joint frailty model were utilized in the analysis.

Results: Of the 446 patients, 17.3% died, 20% experienced relapse, and 62.7% were censored. The 1-5-7-year disease-free survival rates were 95.3%, 73.4%, and 69.3%, respectively. In the cure model, stage, involved lymph node, and surgery were statistically significant. In the recurrence model, stage, involved lymph node, lymphovascular invasion, and hormone therapy were statistically significant. In the death model, stage, lymphovascular invasion, and involved lymph node had a statistically significant effect on the survival time.

Conclusion: The cure joint frailty model is a good model when there is a high fraction of patients who do not experience any recurrence or death. In addition, this model allows for the separate estimation of explanatory variable effect on recurrence, death, and cure. The findings of our study can be conducive to preventing the unfavorable effects of breast cancer and increasing the survival of patients.

Keywords: Breast, Cure, Cohort, Joint model, Frailty, Survival

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Introduction

With an annual 1.7 million new cases, breast cancer is the second most common cancer preceded by lung cancer; it is also the fifth most common cause of mortality due to

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cancer worldwide.[1] In 2017, a total of 252.710 new cases and 40610 deaths caused by breast cancer were reported in the United States.[2] According to the new statistics in Iran, 6160 new cases of breast cancer are diagnosed per year, where almost 1063 cases pass away. The Yazd province in Iran had a high prevalence rate during 2004-2008.[3] Although the incidence of breast cancer is lower in Iranian women compared with western countries, the onset of breast cancer occurs at a relatively younger age and more than 30% of the patients are under 30 years of age.[3,4]

The advancement in pharmaceutical research and the development of new drugs can increase the survival rate up to 95% with early-stage diagnosis and treatment; as a result, the breast cancer is not experienced by the patients during the follow-up period. This means that these individuals can be stated as cured.[5] The common survival methods, such as the Cox proportional hazard model, are not suitable for assessing the factors affecting the survival of patients. The reason is that such methods assume that individuals experience the event of interest until the end of the study. These models also lead to biased estimates of the overall survival and the parameter estimates.[6] Cure models can be useful in these situations. Baghestani et al. determined the survival rate and prognostic factors on the cure rate of patients with breast cancer using the cure rate models.[7,8] There is substantial evidence on the risk factors and prognostic factors associated with breast cancer.[9-14] Recurrence of breast cancer is an important determining factor for the progression of the disease and represents the main cause of breast cancer-related mortality.[15] A joint frailty model was used to assess the factors related to recurrence and death due to breast cancer. In these models, a latent variable for the dependence between recurrence and death is incorporated into the model.[16] According to statistics, no studies have been published on the joint modeling of recurrent events and death in the presence of the cure fraction of breast cancer data.

We aimed to investigate the survival rate and clinical factors in Iranian women with breast cancer using the joint frailty model in the presence of cure fraction.

Materials and Methods

We included a retrospective cohort of breast cancer patients undergoing their first breast surgery in Shahid Ramezanzadeh Radiotherapy Center from 2004 to 2012; they were followed up until April 2016. Patients with incomplete information

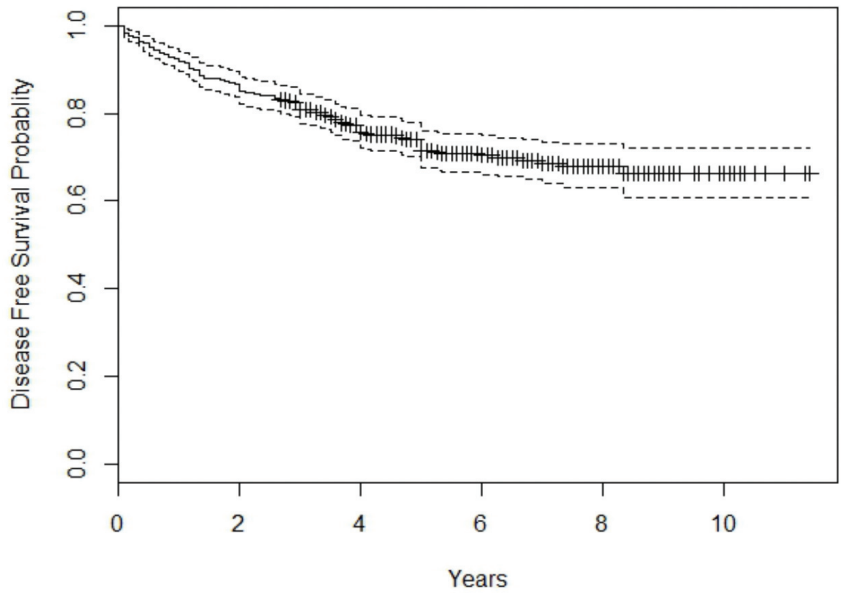

Figure 1. Kaplan-Meier estimate of the disease-free survival of patients. The patients with more than seven years of breast cancer had nearly the same disease-free survival.

were excluded from the study.[17] The cure joint frailty model was employed for data analysis. This model consists of three submodels: a model for recurrent events (relapse), a model for the terminal event (death), and a logistic model used to describe the cure probability. Two outcomes were simultaneously analyzed through the joint model. The occurrence of relapse time and the time of the terminal event (death) were considered as dependent variables in the model. The patients with no relapse or lost to follow-up were respectively censored for recurrence and death. The tumor size, cancer stage, age at diagnosis, lymphovascular invasion (LVI), lymph node status, and systemic treatment (types of surgery included modified radical mastectomy(MRM), breast conserving therapy (BCT), chemotherapy, and hormone therapy) were considered as independent variables. The software used in this analysis was R 3.3.2.

Ethical issues

The Ethics Committee of Beheshti University of Medical Sciences approved this study (IR.SBMU.RETECH.1382.).

Statistical analysis

In the cure model, the population is divided into two subpopulations where the subject is either cured with probability $1=\pi$ or has a survival function with probability π. The model for the distribution of survival times that contains a cured fraction $S_0(t)$ is given by $S(t)=(1-\pi)+\pi S_0(t)$. A logistic regression model is used to assess the impact of independent variable (z) on probability cure (π):

, where γ is a parameter associated with the cure rate through the covariate.

$$\pi(z)=\frac{\exp(\gamma z)}{1+\exp(\gamma z)}$$

The joint model for the hazard functions of the recurrent event and death is:

, where r_0 and λ_0 are the baseline hazards for recurrence and death. In addition, β and β^* are

$$\begin{cases} r_i(t \mid \omega_i)=\omega_i r_0(t)\exp(\beta Z_i)=\omega_i r_i(t) \\ \lambda_i(t \mid \omega_i)=\omega_i \lambda_0(t)\exp(\beta^* Z_i)=\omega_i \lambda_i(t) \end{cases}$$

the regression coefficient vectors for recurrence and death. The random effect frailties (ω_1) consider the dependence between recurrence and survival times, meaning a frailty variance denotes the dependency between recurrence and death time.[16]

Results

Of 446 women with breast cancer, 77 (%17.3) passed away, 89 (%20) patients experienced the occurrence of relapse, and 280 (%62.7) cases were censored. The mean age at diagnosis was 48.89±13.22 years. Table 1 depicts the characteristics of the patients under investigation and the log-rank test results. Increased tumor size and stage, presence of LVI and lymph node, MRM surgical treatment, and absence of hormone therapy can reduce the disease-free survival (DFS) (the time until the first tumor recurrence or death).

The Kaplan-Meier curve shows the 1-3-5-7-year DFS of patients with breast cancer: %95.3, %85.9, %73.4, %69.3, respectively. Therefore, DFS for patients with more than seven years of breast cancer was approximately the same, meaning these patients were cured. (Figure 1)

Table 2 shows the estimate of parameters in the joint frailty model in the presence of a cure fraction.

The cure rate in the patients with age<=50 was 1.47 times higher than age>50; there was no significant decrease in the risk of death and recurrence in these two age groups. The difference was not statistically significant among the three models. The women with stage 1 breast cancer had a higher probability of being cured compared with those with stage 3+. As a result, their cure rate was 2.2 times higher than the patients with stage 3+. In stage 1, there was a statistically significant reduction in the risk of death (66%) and recurrence (67%).

The cure rate in patients with tumor size T1 was 2.15 times greater than tumor size T3. Moreover, with tumor size T1, the rates of death and recurrence decreased by 34% and 47%, respectively, compared with tumor size T3+. The difference was not statistically significant among

Table1. Characteristics of patients with breast cancer

Variable	Frequency (%)	Death N (%)	Relapse N (%)	Mean of survival time (DFS) year(SD)	*P*-value (log-rank)
Age at diagnosis					
≤50	271(60.8)	37(8.2)	54(12)	8.461(0.25)	0.112
>50	175(39.2)	40(8.9)	35(7.8)	7.843(0.33)	
Stage					
I	52(11.7)	4(0.8)	5(1.1)	8.26(0.39)	0.001*
II	258(57.8)	42(9.4)	46(10.3)	8.155(0.39)	
III+ (III & IV)	136(30.5)	31(6.9)	38(8.5)	7.28(0.39)	
Tumor size					
T1	71(15.9)	6(1.34)	6(1.3)	9.27(0.31)	0.004*
T2	290(65)	50(11.2)	58(13)	8.17(0.25)	
T3+(T3 & T4)	85(19,1)	21(4.7)	25(5.6)	8.1(0.43)	
Lymphovascular invasion					
Positive (+)	272(61)	55(12.3)	65(14.5)	8.92(0.28)	0.028*
Negative (-)	174(39)	22(4.9)	24(5.3)	7.89(0.25)	
Lymph node status					
Positive (+)	285(63.9)	64(14.3)	70(15.6)	9.25(0.25)	0.001*
Negative (-)	161(36.1)	13(2.9)	19(4.2)	7.63(0.25)	
Surgery					
MRM	280(62.8)	14(3.1)	71(15.9)	9.04(0.23)	0.001*
BCT	166(37.2)	63(14.1)	18(4)	7.6(0.26)	
Chemotherapy					
Yes	412(92.4)	68(15.2)	80(17.9)	8.29(0.25)	0.251
No	34(7.6)	9(2.01)	7.09(0.71)	9(2)	
Hormone therapy					
Yes	173(30.7)	1(0.22)	13(2.9)	9.53(0.22)	0.001*
No	309(69.3)	76(17.04)	76(17)	7.63(0.24)	

*Significant; MRM: Modified radical mastectomy; BCT: Breast conserving therapy; DFS: Disease-free survival

the three models. The cure rate in women without lymph node was 3.12 (1/0.32=3.12) times greater than the patients with lymph node. On the contrary, in the presence of lymph node, the risk of death and recurrence was 2.18 and 2.87 times greater, respectively, which was statistically significant in the three models. The cure rate in women without LVI was 10 (1/0.1=10) times more than those with LVI. Furthermore, in the presence of LVI, the risk of death and recurrence increased up to 2.96 and 2.6 times, respectively. This difference was statistically significant among three models. The cure rate in patients receiving MRM surgical treatment was 5.25 times higher than those with BCT. However, this variable was not significant in death and recurrence models. The cure rate in patients undergoing chemotherapy was 1.35 higher than those without chemotherapy. In addition, death and recurrent rates in women with chemotherapy were 0.43 and 0.58 lower than patients without chemotherapy. However, this factor was not significant in the three models. The cure rate of patients undergoing hormone therapy was 1.13 times greater than those without hormone therapy. Besides, hormone therapy decreased the risk of death and recurrence by 94% and 90%, respectively, which was statistically significant in death and recurrent models.

Discussion

Using a general cure joint frailty model, we assessed the influence of prognostic factors on recurrence and death among patients with breast cancer. The importance of the model is two-fold: first of all, patients with no experience of recurrence and death during follow-up can enter the model. Secondly, the dependence between the occurrence of relapse and death is incorporated through shared frailty, in which the variance of shared frailty (θ) indicates the degree of correlation between recurrence and death events. Here, the estimate of frailty variance was 2.1, indicative

Table2. Estimation based on joint frailty model in the presence of cure rate

	Cure logistic model			Death			Recurrence events		
Variable	**β(SE)**	**OR**	***P*-Value**	**β(SE)**	**HR**	***P*-Value**	**β(SE)**	**HR**	***P*-Value**
Age at diagnosis									
≤50	0.39(0.37)	1.47	0.23	-0.01(0.4)	0.99	0.39	0.02(0.51)	1.02	0.38
>50	REF								
Stage									
I	2.2(0.22)	2.2	<0.001*	-1.07(0.42)	0.34	0.015*	-1.09(0.46)	0.33	0.02*
II	-1.13(0.64)	0.32	0.0	-0.1(0.41)	0.92	0.38	-0.04(0.46)	0.9	0.39
III+ (III & IV)	REF								
Tumor size									
T1	0.79(0.68)	2.2	0.20	-0.41(0.83)	0.66	0.35	-0.63(0.75)	0.53	0.28
T2	0.10(0.41)	1.01	0.38	-0.47(0.43)	0.62	0.22	-0.28(0.38)	0.75	0.30
T3+(T3 & T4)	REF								
Lymphovascular invasion									
Positive (+)	-2.29(0.67)	0.1	0. 039*	1.08(0.37)	2.96	0.005*	0.95(0.39)	2.6	0.02*
Negative (-)	REF								
Involved lymph node									
yes	-1.13(0.49)	0.32	0.028*	0.78(0.37)	2.18	0.041*	1.05(0.42)	2.87	0.01*
no	REF								
Surgery									
MRM	1.65(0.45)	5.22	0.001	-0.01(0.46)	0.99	0.39	0.02(0.51)	1.02	0.39
BCT	REF								
Chemotherapy									
Yes	0.31(0.67)	1.35	0.35	-0.56(0.6)	0.57	0.2	-0.87(0.68)	0.42	0.17
No	REF								
Hormone therapy									
Yes	0.11(1.35)	1.13	0.39	-2.8(1.06)	0.06	0.025*	-2.3(1.06)	0.1	0.001*
No	REF								
θ	2.1(0.21)	2.1	<0.001	-	-	-	-	-	-

β: Estimate, SE: Standard error, OR: Odds ratio, HR: Hazard rate; *Significant; MRM: Modified radical mastectomy; BCT: Breast conserving therapy

of a statistically significant correlation between the occurrence of relapse and death. The 1-3-5-year DFS rates were 95.3%, 85.9%, and 73.4%, respectively.

In this present analysis, a high proportion of patients with breast cancer were expected to live longer and never experience death or relapse. The high survival rate of breast cancer in Iran can be due to the development of new drugs and the increased level of awareness among people, which is in agreement with other studies.[10,11] However, this rate is lower compared to the U.S. and Europe.[18,19] The reason might be attributed to the process of patient selection, short-term follow-up period, or lack of awareness of such diseases.

Based on the results, the age at diagnosis was an important factor affecting the cure rate. The cure rate in patients under 50 years was greater than that in patients over 50 although the difference was not statistically significant, which is in line with one study.[20] However, some studies reported that age was a major risk factor in breast cancer. The older the patient, the higher the risk of breast cancer will be.[21,4,18,22] We revealed that the cure rate for lower stages was greater than that for higher stages. Lower stages were significantly associated with a lower rate of recurrence and death, which is similar to other studies.[21,20,23,7,13] Tumor size is a major factor for breast cancer. In our study, the cure rate of patients with T1 was greater than patients with T3+ and their recurrence and death rates were lower than patients with T3+. Several studies have indicated that a decrease in tumor size increases the cure rate, eventually reducing the risk of recurrence and death.[23,24,7] In contrast, a few studies have reported an inverse relationship between the size of tumor and survival. In a study by Kasangian et al., no statistically significant difference was observed between the size of tumors and death and recurrence in patients with breast cancer.[25] In our study, the risk of death and recurrence was greater in patients with LVI

in comparison with those without LVI. On the contrary, the cure rate of patients without LVI was higher than patients with LVI, which was statistically significant among the three models. Similarly, Meshkat et al. reported a greater cure rate in patients without LVI.[7] Baghestani et al. detected a statistically negative effect on the survival time in patients with LVI.[26] In the current paper, the cure rate in women without involved lymph node was more than patients with involved lymph node. Additionally, the risk of mortality and recurrence statistically increased in the presence of lymph node. Many studies have shown that the increase in the number of lymph nodes entails a reduction in the survival rate and an increase in death and recurrence.[26,28,13,29] Surgery is of prime importance for survival rate. According to the findings of this study, the cure rate of patients presented with MRM surgical treatment was statistically higher than those with BCT. The difference was not statistically significant in terms of death and the occurrence of relapse. In a study by Akbari et al., surgery did not have any significant relationship with survival time. Furthermore, in the present study, the cure rate was higher with chemotherapy and hormone therapy. However, the difference was not statistically significant in the cure rate model. Many studies have reported that the relative risk of death and recurrence can be reduced with chemotherapy and hormone therapy.[30-32] In the present paper, the risk of death and recurrence for patients undergoing chemotherapy was lower than those with hormone therapy or no therapy. Hormone therapy was the only statistically significant factor in recurrence and death models. This study had some limitations. Information for some explanatory factors was incomplete and some was recorded incorrect, entailing an inaccurate inference. Also, the strong relationship between the overall survival and the inflammatory biomarkers requires more investigation, in such a way that the reduction of inflammatory markers is effective for breast cancer recurrence and survival.

Conclusion

This study aimed to evaluate the effect of some factors on the survival time when recurrence and death did not occur in a high fraction of patients. For this purpose, a cure joint model was utilized to provide a more comprehensive analysis. The findings of our study can be employed to prevent the unfavorable effects of breast cancer and increase the survival of patients. We also suggest developing programs and better plans to raise awareness in women for early detection and screening.

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Conflict of Interest

None declared.

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