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Survival Analysing of the Breast Cancer Patients Using Cure Model

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Abstract

Background: Breast cancer (BC) is the most leading cause of cancer and the second most common cause of cancer-related death among females worldwide. The survival time of the disease and its risk factors are important for physicians.
Objectives: The current study aimed at applying the Cox, cure, and frailty models to identify the risk factors related to the survival of patients with BC.
Methods: The current historical cohort study investigated 499 patients with a confirmed diagnosis of BC, from March 2010 to March 2014, and followed-up to March 2015 in Besaat hospital in Tehran, Iran. The Cox regression, cure, and frailty models were used for the survival analysis (SA) of the patients. Data analysis was carried out by R3.2.2 software.
Results: The mean (± SD) age of the patients was 50.39 (± 11.13) years and the mean survival time was 53.44 months (95% CI: 51.41 - 55.48). In addition, the 1-year overall survival rate was 0.92 (95% CI: 0.89 - 0.94). Age at diagnosis, tumor size, and metastasis covariates were significant in all models ($P < 0.05$). Stage covariate were significant in frailty, cure, and failure time distribution model ($P < 0.001$). Familial history ($P = 0.016$) and pathology ($P = 0.012$) were significant only in the frailty model.
Conclusions: The cure and frailty models were better than the Cox model to estimate the parameters. When some patients have a long-term survival, cure models can be an interesting method to study survival and also describe the short-term and long-term effects.

Keywords: Survival Analysis, Breast Cancer, Cox Proportional Hazards Models, Cured Model

1. Background

Breast cancer (BC) is the most leading cause of death after non-melanoma skin cancer (1), and the second most common cause of cancer-related death among females worldwide (2, 3). In recent years, approximately 1.7 million new cases were diagnosed annually and 0.5 million deaths (per year) were caused by BC worldwide (3, 4). In the US, BC caused approximately 231 000 newly diagnosed cases and about 40 000 deaths (17.3%) in 2015 (5, 6). In Iran, BC is the most frequent cancer among malignancies in females and it caused 24.4% of all neoplasms with an incidence rate of 17.81 in 2006 (6). There are many risk factors related to BC such as older age (55 years and above), genetic risk factors (BRCA1 and BRCA2), a positive family history, late menopause, early menstruation, using oral contraceptive pill (OCP), prolonged nulliparity, hormone replacement therapy (HRT) after menopause, obesity after menopause, and alcohol use (7, 8). For metastasis of BC, there are several prognostic and predictive factors such as high tumor grade, lack of estrogen-receptor (ER) expression, over expression of human epidermal growth factor receptor 2 (HER2), and large tumor size (9). Despite some developments in systemic neoadjuvant or adjuvant therapies such as chemotherapy, radiotherapy, and hormonal therapy that can largely improve the prognosis of BC in recent years, the survival outcomes of patients with BC, especially in the elderly and the patients with long-term use of oral contraceptives, are still not optimistic (3). Due to the advances in early detection and the understanding of the molecular bases of the BC biology, the majority of patients are diagnosed at the early stage and a 5-year survival rate after treatment is nearly 90% (3), but the disease is recurrent in almost 30% of females with early-stage BC (1). Approximately one-third of the patients after surgery have the outcome of local recurrence and/or distant metastasis. Both local recurrence and distant metastasis tend to decrease the survival time in patients with BC. Recurrence of BC has a major role in cancer-related deaths in patients and overall survival after occurrence of metastasis is even

shorter (9). As cancer survival is a key index of the overall effectiveness of health services to manage patients (10), therefore, identifying the BC risk factors is important to determine therapeutic and preventive strategies to improve overall survival of patients and also their disease-free survival (DFS).

In time-to-death studies, survival analysis is used as a statistical method to study and model the relationship between the risk factors of the disease (11, 12). In survival analysis of medical data, using the Cox regression model, also named the Cox proportional hazard model, is most popular (11-14); compared with parametric models, it relies on fewer assumptions (11, 14).

Plateaus at tails of survival curves or long plateaus at survival plots lead to failure in the assumption of proportional hazards. In this case, cure models can be used to determine risk factors with either short-term or long-term effects (15). This model can be used in medical research, especially in breast cancer studies (16). Regardless of proportionality of hazards (as a fundamental assumption), a restriction of this model occurs with time-dependent covariate. In this case, misleading effect estimates can be resulted (12, 17). For time variable model, frailty model can be used. It is a random-effects model, where the random effect (the frailty) has a multiplicative effect on the hazard. Indeed, it is an extension of the proportional hazards model in which the hazard function depends on an unobservable random quantity, which acts multiplicatively (18). However, using appropriate survival models to analyze data, non-misleading effect (regression coefficient) estimates can be derived.

2. Objectives

The current study aimed at applying the Cox, cure, and frailty models to determine the risk factors related to the survival of patients with BC.

3. Methods

The current historical cohort study was carried out at Besaat Nahaja general hospital in Tehran, Iran. Females with a confirmed diagnosis of BC who underwent either MRM (modified radical mastectomy) or BCS (breast-conserving surgery) from March 2010 to March 2014 were enrolled in the study. Only the patients with a non-metastatic condition (M0) at the diagnosis time were included. Patients with missing information on important prognostic factors or unknown current status were excluded. All patients had undergone adjuvant therapy after surgery and were followed-up to March 2015. According to these criteria, 499 females were enrolled in and 47 patients were excluded from the study. All data were gathered by a single observer. The research ethics committee of University of social welfare and rehabilitation sciences approved the study (code no. : IR.USWR.REC.1395.1).

3.1. Characteristics of Data

The following variables at the time of diagnosis were selected and analyzed based on the expert medical opinion and review articles: age, ethnicity (Fars, other), job status (housewife, other), level of education (illiterate, primary and secondary, and postsecondary school), kind of surgery (radical mastectomy, breast saving), type of treatment (hormone therapy, chemotherapy, and radiotherapy), progesterone receptor (PR), estrogen receptor (ER), histological tumor grade (I, II, III), tumor size, stage of disease (I, II, III, IV), metastasis (no, yes), human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR) at initial diagnosis, pathology (invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS) and lymph node ratio (LNR). LNR was calculated as the percentage of involved lymph nodes to total lymph nodes excised by the surgeon. Overall follow-up time was considered from the date of treatment to the date of death (ie, event) or censoring (ie, alive).

3.2. Statistical Analysis

Descriptive statistical analysis was carried out to explore the patient and disease characteristics using mean $\pm$ SD for continuous variables, median (for times), and also frequency table for categorical variables. To analyze the data; first, the Kaplan-Meier estimator was used to quantify the median follow-up time and also as the empirical evidence of cure (Presence of a long and stable plateau with heavy censoring at the tail of the Kaplan-Meier plots indicated as the empirical evidence of cure.) (16). Then, the proportional Cox regression model was used to analyze the survival times. After univariate analysis, all significant factors were analyzed using multiple analyses. Finally, gamma frailty model with exponential baseline hazard distribution and also cure model were used to analyze the data. A P value < 0.05 was considered statistically significant. All statistical analyses were conducted using survfit, CoxPH, smcure and parfm packages in R software, version 3.2.2.

4. Results

A total of 499 females with BC were included in the current analysis. The mean $\pm$ SD for age at the time of diagnosis was 50.39 $\pm$ 11.19 years. In addition, the mean $\pm$ SD for

tumor size was 3.60 ± 3.0 mm. Of the 499 patients, 85.0% were housewives, 91.2% had no familial history, 67.5% were Fars ethnicity, 52.7% had postsecondary education, 63.3% were in stage II, 53.3% were in grade III, 77.4% had no metastasis, 54.3% were negative for Her2, 61.5% carried LNI, 66.1% had ER+ and PR+, 88.0% had DCIS, 66.7% received hormonal therapy (HoR+), 89% undergone radiotherapy, 97.8% undergone chemotherapy, and only 26.9% of the patients undergone breast conserving surgery (Table 1). In the current study, 113 (22.6%) patients died of BC until March 2015. Mean survival time was 53.44 months (95% CI: 51.41 - 55.48). Using the life-table method, the 1-year overall survival rate was 0.92 (95% CI: 0.89 - 0.94). Figure 1 shows a long and stable plateau with heavy censoring, which means cure.

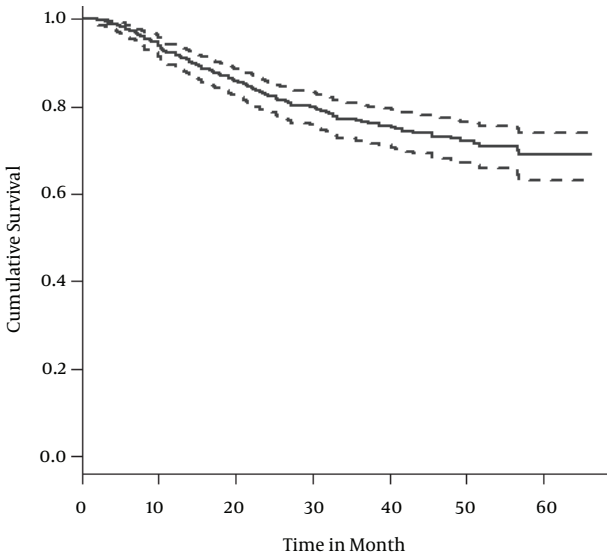

Figure 1. The Kaplan-Meier Survival Curve of the Patients with BC

In univariate analysis of age at diagnosis, tumor size, employment, level of education, stage of the disease, metastasis, and pathology had a statistically significant effect on the survival of patients with BC (Table 1). Multivariate analysis was used for all biological, clinical, and pathological variables. The results of CoxPH and frailty model are presented in Table 2. The Kaplan-Meier plots for survival function of patients with BC indicate that there may be a long plateau (with some long-term survivors); ie, there is an evidence of cure (Figure 1). Therefore, the results of cure probability and failure time distribution models are presented in Table 3.

According to the results of multivariate analysis presented in Table 2, in the CoxPH model, age at diagnosis ($P < 0.001$), tumor size ($P = 0.001$) and metastasis ($P < 0.001$) covariates, and in frailty model age at diagnosis ($P = 0.003$), tumor size ($P < 0.001$), familial history ($P = 0.016$), stage III ($P = 0.005$) and IV ($P < 0.001$), metastasis ($P < 0.001$), and DCIS pathology ($P = 0.012$) had a statistically significant effect on the survival of patients with BC. In addition, according to the results of multivariate analysis presented in Table 3, in cure probability model, age at diagnosis ($P = 0.003$), tumor size ($P < 0.001$), stage IV ($P < 0.001$) and metastasis ($P < 0.001$) covariates had a statistically significant effect on cure of the patients with BC; and in failure time distribution model, tumor size ($P = 0.003$), stage IV ($P = 0.028$), and metastasis ($P = 0.001$) had a statistically significant effect on the death of patients with BC. In cure model, the hazard ratio estimate for tumor size was HR = exp (0.315) = 1.37, adjusted for other variables; it means that the tumor size had a hazard rate about 1.37 times more than that of the event, if 1 unit increased in the tumor size. The hazard ratio estimate for stage IV was HR = exp (0.945) = 2.57. It means that the stage IV had a hazard rate about 2.8 times more than that of the stage I on the hazard of the event. The hazard ratio estimate metastasis was HR = exp (3.26) = 26.05. It means that the metastasis group had a hazard rate about 26 times more than that of the non-metastasis group on the hazard of the event.

Finally, the standard errors (SE) in cure and frailty models were better than the Cox model (Tables 2 and 3).

5. Discussion

BC is second most common cause of cancer related death (2, 3), which has high incidence rate among females worldwide (4). In many studies, the CoxPH model was used as a standard method to determine the prognostic factors of survival of patients with BC. However, this method cannot support long-term survival (19). Now, if a model assesses the risk factors for long-term survival, it is more appropriate. In the current paper, the CoxPH, frailty, and cure models were used to analyze the survival of patients with BC and their results were reported.

The mean age of the patients in the current study was 50.4 years (median = 51 years), consistent with other studies from Iran (9, 20-22) and also similar to that of Arab nations (23). In the current study, age was a significant factor for the survival of patients with BC in all models. Compared with Western countries, Iranian females had a higher risk of developing breast cancer in their middle age (24). This may be due to young population structure of the I.R. Iran and also lower age at the first pregnancy (average of 28 years) (25).

Metastasis and tumor size covariates were the significant risk factors in all models. These risk factors were also reported as significant factors in other studies (9, 10, 20,

Table 1. Characteristics of Patients with BC and Their Association with Survival Time Using Univariate Analysis[a]

Risk Factors	Levels	No. (%)	Estimate	SE	P Value
Age	Mean ± SD, median	50.39 ± 11.19, 51.0	0.041	0.100	< 0.001
Tumor size	Mean ± SD, median	3.60 ± 2.37, 3.0	0.225	0.026	< 0.001
Job status	Housewife	424 (85.0)			
	Employee	75 (15.0)	0.427	0.329	0.194
Familial history	No	455 (91.2)			
	Yes	44 (8.8)	0.563	0.335	0.093
Ethnicity	Fars	337 (67.5)			
	Other	162 (32.5)	0.050	0.225	0.823
Level of education	Illiterate	42 (8.4)			
	Primary and secondary school	194 (38.9)	-0.890	0.345	0.009
	postsecondary school	263 (52.7)	0.879	0.338	0.001
Stagea	I	77 (15.5)			
	II	316 (63.3)	0.217	0.333	0.515
	III	87 (17.4)	1.115	0.359	0.002
	IV	19 (3.8)	2.575	0.429	< 0.001
Grade	I	26 (5.2)			
	II	207 (41.5)	0.352	0.570	0.538
	III	266 (53.3)	1.002	0.561	0.074
Metastasis	No	386 (77.4)			
	Yes	113 (22.6)	2.464	0.212	< 0.001
Her2	Negative	271 (54.3)			
	Positive	228 (45.7)	-0.341	0.225	0.129
LNI	No	192 (38.5)			
	Yes	307 (61.5)	-0.034	0.219	0.878
ER and PR	Negative	169 (33.9)			
	Positive	330 (66.1)	-0.327	0.218	0.134
Pathology	IDC	60 (12.0)			
	DCIS	439 (88.0)	1.235	0.448	0.006
HoR	Negative	166 (33.3)			
	Positive	333 (66.7)	-0.371	0.218	0.089
Radiotherapy	Without	55 (11.0)			
	With	444 (89.0)	0.427	0.348	0.219
Chemotherapy	Without	11 (2.2)			
	With	488 (97.8)	-0.304	0.673	0.651
Kind of surgery	Radical Mastectomy	365 (73.1)			
	Breast saving	134 (26.9)	-0.290	0.267	0.277

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HoR, hormone receptor; IDC, invasive ductal carcinoma; LNI, lymph node involvement; PR, progesterone receptor.
[a] Stage classification according to 7th edition of AJCC staging.

Table 2. Survival Analysis of Patients with BC Using Multivariate Survival Analysis[a]

Risk Factors	Levels	CoxPH Model			Frailty Modela		
		Estimate	SE	P Value	Estimate	SE	P Value
Age		0.047	0.012	< 0.001	0.032	0.011	0.003
Tumor size		0.240	0.072	0.001	0.205	0.030	< 0.001
Job status	Housewife						
	Employee	0.336	0.339	0.322	0.421	0.336	0.210
Familial history	No						
	Yes	0.464	0.307	0.130	0.718	0.299	0.016
Ethnicity	Fars						
	Other	0.162	0.220	0.461	0.135	0.211	0.523
Level of education	Illiterate						
	Primary and secondary	-0.467	0.306	0.127	-0.562	0.288	0.051
	postsecondary	-0.088	0.339	0.794	-0.301	0.309	0.329
Stage	I						
	II	-0.207	0.368	0.575	0.190	0.339	0.574
	III	-0.120	0.495	0.809	1.052	0.372	0.005
	IV	-0226	0.794	0.776	2.305	0.473	< 0.001
Grade	I						
	II	-0.316	0.553	0.567	-0.531	0.540	0.325
	III	-0.344	0.545	0.528	-0.544	0.536	0.311
Metastasis	No						
	Yes	2.470	0.225	< 0.001	2.374	0.213	<0.001
Her2	Negative						
	Positive	-0.322	0.212	0.129	-0.167	0.195	0.393
LNI	No						
	Yes	-0.327	0.223	0.143	-0.321	0.196	0.101
ER and PR	Negative						
	Positive	1.580	29.3	0.995	-0.272	0.193	0.158
Pathology	IDC						
	DCIS	0.183	0.528	0.728	1.412	0.559	0.012
HoR	Negative						
	Positive	-0.162	29.3	0.995	-0.320	0.217	0.140
Radiotherapy	Without						
	With	0.201	0.470	0.669	-0.316	0.482	0.512
Chemotherapy	Without						
	With	-0.569	0.739	0.441	-0.283	0.773	0.714
Kind of surgery	Radical mastectomy						
	Breast saving	0.339	0.261	0.193	-0.257	0.264	0.330

[a] Survival frailty model was conducted using gamma frailty distribution with exponential baseline hazard distribution.

Table 3. Cure Probability and Failure Time Distribution Model to Analyze the Survival of Patients with BC

Risk Factors	Levels	Cure Probability Model			Failure Time Distribution Model		
		Estimate	SE	P Value	Estimate	SE	P Value
Age		0.070	0.023	0.003	0.025	0.017	0.150
Tumor size		0.315	0.095	< 0.001	0.162	0.055	0.003
Job status	Housewife						
	Employee	-0.060	0.295	0.840	-0.110	0.418	0.793
Familial history	No						
	Yes	0.555	0.488	0.255	0.448	0.432	0.299
Ethnicity	Fars						
	Other	0.152	0.316	0.631	-0.246	0.382	0.520
Level of education	Illiterate						
	Primary and secondary	0.152	0.316	0.631	0.214	0.291	0.464
	postsecondary	0.098	0.165	0.554	0.168	0.240	0.484
Stage	I						
	II	0.521	0.368	0.887	-0.225	0.360	0.532
	III	0.058	0.264	0.827	0.219	0.449	0.625
	IV	0.945[a]	0.209	< 0.001	0.994	0.451	0.028
Grade	I						
	II	-0.420	0.248	0.0.90	-0.189	2.329	0.935
	III	-0.146	0.192	0.446	-0.737	2.292	0.748
Metastasis	No						
	Yes	3.260	0.298	< 0.001	1.590	0.469	0.001
Her2	Negative						
	Positive	-0.182	0.435	0.677	-0.094	0.231	0.685
LNI	No						
	Yes	-0.558	0.424	0.188	-0.304	0.280	0.277
ER and PR	Negative						
	Positive	-0.409	0.437	0.350	-0.083	0.301	0.782
Pathology	IDC						
	DCIS	0.580	0.604	0.337	0.951	0.645	0.140
HoR	Negative						
	Positive	-0.363	0.293	0.216	0.951	0.645	0.140
Radiotherapy	Without						
	With	0.651	0.443	0.142	-0.193	0.494	0.696
Chemotherapy	Without						
	With	-0.459	0.548	0.402	-0.249	1.109	0.822
Kind of surgery	Radical mastectomy						
	Breast saving	0.261	0.360	0.470	-0.128	0.319	0.687

[a] The hazard ratio estimate for stage IV was HR = exp (0.945) = 2.57. It means that the stage IV had a hazard rate about 2.8 times more than that of the stage I on the hazard of the event.

22, 26). In these cases, some studies suggested a linear and others suggested a nonlinear effect of tumor size (27). It is mentioned that some studies reported that tumor size increased the risk of metastasis in patients with BC (20, 28-30).

Stage covariate was a significant risk factor in cure and frailty models. This risk factor was also reported as a significant factor in other studies (9, 13, 20, 26).

Family history and pathology covariates were significant only in the frailty model. These risk factors were also reported as significant factors in other studies from Iran (20, 31) and USA (30).

Use of adjuvant chemotherapy tends to increase in cure fraction, particularly for the oldest age group. Huang for the first time estimated the cure fraction for the patients with ER breast cancer (32). The cure fraction was 58% (26), 20% (33), and was estimated 68% in the current study. This controversy may be due to different follow-up intervals.

In the current study, other covariates had no significant effects on the survival of patients with BC. Some of these risk factors, such as ER and PR, HoR, and Her2, are still controversial and a number of studies reported their importance (34-37).

It was mentioned that the results of the cure models can provide estimates of the probability of being a long-term survivor, which the other models cannot. For cancers in which some patients may have a long and stable plateau with heavy censoring, the cure models can be an interesting method to analyze data (12).

5.1. Limitation

All data were collected retrospectively. The sample size in the current study was related to the armed forces and their families. In the current study, it was assumed that patient censoring was not related to the BC death. In addition, an increase in the follow-up time (in years) may make stronger results for BC survival parameters in the cure model.

5.2. Conclusion

Cure models are an underused statistical tool and not yet very popular in the survival studies on cancer. This statistical method could be useful for a wide range of cancers such as head and neck, colon cancer, stomach, breast, etc. However, when some patients are the long-term survivors, cure models can be interesting methods to study survival and also describe their short-term and long-term effects. The current study showed that the tumor size had an increased effect on the hazard of the event, adjusted for other variables. In addition, stage IV of the disease and also metastasis increased the effects on the hazard of the event. Finally, a large cohort study of BC survival and comparison between cure fractions in different categories is suggested.

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Footnotes

Authors' Contribution: Enayatollah Bakhshi, Ayeh Sheikhaliyan, Keivan Atashgar, and Akbar Biglarian: study design; Ayeh Sheikhaliyan and Akbar Biglarian: data collection and entries; Enayatollah Bakhshi, Ayeh Sheikhaliyan, Maryam Koosheh, and Akbar Biglarian: writing of the manuscript; none of the authors had personal or financial conflicts of interest.

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References

1. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. *Adv Exp Med Biol.* 2007;**608**:1–22. [PubMed: 17993229].
2. Tavani A, Gallus S, La Vecchia C, Negri E, Montella M, Dal Maso L, et al. Risk factors for breast cancer in women under 40 years. *Eur J Cancer.* 1999;**35**(9):1361–7. [PubMed: 10658528].
3. Li SJ, Chen DL, Zhang WB, Shen C, Che GW. Prognostic value of stromal decorin expression in patients with breast cancer: a meta-analysis. *J Thorac Dis.* 2015;**7**(11):1939–50. doi: 10.3978/j.issn.2072-1439.2015.11.29. [PubMed: 26716032].
4. Stewart BW, Wild CP. World cancer report 2014. Lyon: IARC; 2014. pp. 517–9.
5. Xie J, Hao Y, Li N, Lin PL, Ohashi E, Koo V, et al. Clinical outcomes among HR+/HER2- metastatic breast cancer patients with multiple metastatic sites: a chart review study in the US. *Exp Hematol Oncol.* 2015;**4**:31. doi: 10.1186/s40164-015-0023-0. [PubMed: 26693096].
6. Harirchi I, Kolahdoozan S, Karbakhsh M, Chegini N, Mohseni SM, Montazeri A, et al. Twenty years of breast cancer in Iran: downstaging without a formal screening program. *Ann Oncol.* 2011;**22**(1):93–7. doi: 10.1093/annonc/mdq303. [PubMed: 20534622].
7. Ghoncheh M, Mirzaei M, Salehiniya H. Incidence and Mortality of Breast Cancer and their Relationship with the Human Development Index (HDI) in the World in 2012. *Asian Pac J Cancer Prev.* 2015;**16**(18):8439–43. [PubMed: 26745098].
8. American Cancer Society. . What are the risk factors for breast cancer? [cited 09/13]. Available from: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors.
9. Gohari MR, Khodabakhshi R, Shahidi J, Fard ZM, Foadzi H, Soleimani F, et al. The impact of multiple recurrences in disease-free survival of breast cancer: an extended Cox model. *Tumori.* 2012;**98**(4):428–33. doi: 10.1700/1146.12635. [PubMed: 23052157].

10. Lee ES, Han W, Kim MK, Kim J, Yoo TK, Lee MH, et al. Factors associated with late recurrence after completion of 5-year adjuvant tamoxifen in estrogen receptor positive breast cancer. *BMC Cancer.* 2016;**16**:430. doi: 10.1186/s12885-016-2423-x. [PubMed: 27388210].
11. Efron B. The efficiency of Cox's likelihood function for censored data. *JASA.* 1977;**72**(557-65).
12. Therneau TM, Grambsch PM. Modeling survival data: Extending the cox model. New York: Springer; 2000.
13. Abadi A, Saadat S, Yavari P, Bajdik C, Jalili P. Comparison of Aalen's additive and Cox proportional hazards models for breast cancer survival: analysis of population- based data from British Columbia, Canada. *Asian Pac J Cancer Prev.* 2011;**12**(11):3113–6. [PubMed: 22393999].
14. Abadi A, Yavari P, Dehghani-Arani M, Alavi-Majd H, Ghasemi E, Amanpour F, et al. Cox models survival analysis based on breast cancer treatments. *Iran J Cancer Prev.* 2014;**7**(3):124–9. [PubMed: 25250162].
15. Othus M, Barlogie B, Leblanc ML, Crowley JJ. Cure models as a useful statistical tool for analyzing survival. *Clin Cancer Res.* 2012;**18**(14):3731–6. doi: 10.1158/1078-0432.CCR-11-2859. [PubMed: 22675175].
16. Rondeau V, Schaffner E, Corbiere F, Gonzalez JR, Mathoulin-Pelissier S. Cure frailty models for survival data: application to recurrences for breast cancer and to hospital readmissions for colorectal cancer. *Stat Methods Med Res.* 2013;**22**(3):243–60. doi: 10.1177/0962280210395521. [PubMed: 21632696].
17. Bellera CA, MacGrogan G, Debled M, de Lara CT, Brouste V, Mathoulin-Pelissier S. Variables with time-varying effects and the Cox model: some statistical concepts illustrated with a prognostic factor study in breast cancer. *BMC Med Res Methodol.* 2010;**10**:20. doi: 10.1186/1471-2288-10-20. [PubMed: 20233435].
18. Glidden DV, Vittinghoff E. Modelling clustered survival data from multicentre clinical trials. *Stat Med.* 2004;**23**(3):369–88. doi: 10.1002/sim.1599. [PubMed: 14748034].
19. Cox DR. Summary comments on evolution of cancer survival analysis. *Surg Oncol.* 2010;**19**(2):61.
20. Rezaianzadeh A, Peacock J, Reidpath D, Talei A, Hosseini SV, Mehrabani D. Survival analysis of 1148 women diagnosed with breast cancer in Southern Iran. *BMC Cancer.* 2009;**9**:168. doi: 10.1186/1471-2407-9-168. [PubMed: 19497131].
21. Harrirchi I, Ebrahimi M, Zamani N, Jarvandi S, Montazeri A. Breast cancer in Iran: A review of 903 experimental records. *Public Health.* 2000;**114**(2):143–5.
22. Hajihosseini M, Faradmal J, Sadighi-Pashaki A. Survival Analysis of Breast Cancer Patients after Surgery with an Intermediate Event: Application of Illness-Death Model. *Iran J Public Health.* 2015;**44**(12):1677–84. [PubMed: 26811819].
23. Najjar H, Easson A. Age at diagnosis of breast cancer in Arab nations. *Int J Surg.* 2010;**8**(6):448–52. doi: 10.1016/j.ijsu.2010.05.012. [PubMed: 20601253].
24. Fregene A, Newman LA. Breast cancer in sub-Saharan Africa: how does it relate to breast cancer in African-American women?. *Cancer.* 2005;**103**(8):1540–50. doi: 10.1002/cncr.20978. [PubMed: 15768434].
25. Mousavi SM, Harirchi I, Ebrahimi M, Mohagheghi MA, Montazeri A, Jarrahi AM, et al. Screening for breast cancer in Iran: a challenge for health policy makers. *Breast J.* 2008;**14**(6):605–6. doi: 10.1111/j.1524-4741.2008.00662.x. [PubMed: 19000044].
26. Baghestani AR, Moghaddam SS, Majd HA, Akbari ME, Nafissi N, Gohari K. Application of a Non-Mixture Cure Rate Model for Analyzing Survival of Patients with Breast Cancer. *Asian Pac J Cancer Prev.* 2015;**16**(16):7359–63. [PubMed: 26514537].
27. Verschraegen C, Vinh-Hung V, Cserni G, Gordon R, Royce ME, Vlastos G, et al. Modeling the effect of tumor size in early breast cancer. *Ann Surg.* 2005;**241**(2):309–18. [PubMed: 15650642].
28. Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol.* 2001;**19**(8):2263–71. doi: 10.1200/JCO.2001.19.8.2263. [PubMed: 11304780].
29. Dawood S, Broglio K, Esteva FJ, Ibrahim NK, Kau SW, Islam R, et al. Defining prognosis for women with breast cancer and CNS metastases by HER2 status. *Ann Oncol.* 2008;**19**(7):1242–8. doi: 10.1093/annonc/mdn036. [PubMed: 18334512].
30. Malone KE, Daling JR, Doody DR, O'Brien C, Resler A, Ostrander EA, et al. Family history of breast cancer in relation to tumor characteristics and mortality in a population-based study of young women with invasive breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2011;**20**(12):2560–71. doi: 10.1158/1055-9965.EPI-11-0781. [PubMed: 21960690].
31. Tehranian N, Shobeiri F, Pour FH, Hagizadeh E. Risk factors for breast cancer in Iranian women aged less than 40 years. *Asian Pac J Cancer Prev.* 2010;**11**(6):1723–5. [PubMed: 21338222].
32. Huang L, Johnson KA, Mariotto AB, Dignam JJ, Feuer EJ. Population-based survival-cure analysis of ER-negative breast cancer. *Breast Cancer Res Treat.* 2010;**123**(1):257–64. doi: 10.1007/s10549-010-0752-z. [PubMed: 20130982].
33. Tsutsui S, Kataoka A, Ohno S, Murakami S, Kinoshita J, Hachitanda Y. Prognostic and predictive value of epidermal growth factor receptor in recurrent breast cancer. *Clin Cancer Res.* 2002;**8**(11):3454–60. [PubMed: 12429634].
34. Habibi G, Leung S, Law JH, Gelmon K, Masoudi H, Turbin D, et al. Redefining prognostic factors for breast cancer: YB-1 is a stronger predictor of relapse and disease-specific survival than estrogen receptor or HER-2 across all tumor subtypes. *Breast Cancer Res.* 2008;**10**(5):R86. doi: 10.1186/bcr2156. [PubMed: 18925950].
35. Heitz F, Rochon J, Harter P, Lueck HJ, Fisseler-Eckhoff A, Barinoff J, et al. Cerebral metastases in metastatic breast cancer: disease-specific risk factors and survival. *Ann Oncol.* 2011;**22**(7):1571–81. doi: 10.1093/annonc/mdq625. [PubMed: 21059640].
36. Koizumi M, Yoshimoto M, Kasumi F, Iwase T. An open cohort study of bone metastasis incidence following surgery in breast cancer patients. *BMC Cancer.* 2010;**10**:381. doi: 10.1186/1471-2407-10-381. [PubMed: 20646320].
37. Akhlaghi AA, Najafi I, Mahmoodi M, Shojaee A, Yousefifard M, Hosseini M. Survival analysis of Iranian patients undergoing continuous ambulatory peritoneal dialysis using cure model. *J Res Health Sci.* 2013;**13**(1):32–6. [PubMed: 23772014].