Investigation of Prognostic Factors of Survival in Breast Cancer Using a Frailty Model: A Multicenter Study

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ABSTRACT

BACKGROUND: Using data from different health centers can provide more accurate knowledge of the survival prognostic factors and their effect on the patient's survival. In this multicenter study, we aimed to investigate the role of prognostic factors on breast cancer survival with large data set.

METHODS: This historical cohort study was carried out using data from 1785 participants with breast cancer. Data were gathered from medical records of patients referring to 4 breast cancer research centers in Tehran, Iran, between 1997 and 2013. Age at diagnosis (year), size of the tumor, involve lymph nodes, tumor grade, type of surgery, auxiliary treatment of chemotherapy, radiotherapy, recurrence, and metastasis were the prognosis factors considered in this study. A shared frailty model with a gamma distribution for frailty term was used.

RESULTS: The median follow-up period was 29.71 months with the interquartile range of 19 to 61 months. During the follow-up period, 337 (18.9%) patients died from breast cancer and 1448 (81.1%) survived. The 1-, 3-, 5-, and 10-year survival rates were 96%, 84%, 76%, and 58%, respectively. In the Cox model by centers, in Center A, the type of surgery, number of nodes involved, and the grade 3 tumor; in center B, age, radiotherapy, metastasis, and between 1 and 3 involved nodes; in center C, age, radiotherapy, recurrence, metastasis, tumor size, and grade 3 tumor; and in center D, chemotherapy, metastasis, and lymph nodes involved were significant. Shared frailty model showed that type of surgery, number of lymph nodes involved, metastasis, radiotherapy, and the tumor grade are the prognostic factors survival in breast cancer. The frailty variance was significant, and it affirmed there was significant variability between centers.

CONCLUSIONS: This study showed it is necessary to consider the frailty term in modeling multicenter survival studies and confirmed the importance of early diagnosis of cancer before the involvement of lymph nodes and the onset of metastasis and timely treatment could lead to longer life and increased quality of life for patients.

KEYWORDS: breast cancer, frailty model, prognostic factor, survival

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Introduction

Breast cancer is the second most common type of cancer after lung cancer. About 1 in 4 (24.2%) of all new cancer cases diagnosed in women worldwide is breast cancer. Breast cancer is also the leading cause of cancer death in women (15.0%), followed by lung cancer (13.8%) and colorectal cancer (9.5%).[1] As the most prevalent type of cancer among women in Iran, breast cancer accounts for 24.4% of malignancy among women with a crude incidence rate of 17.4 per 100 000.[2] In the 5-year survival analysis, breast cancer survival rates vary greatly worldwide, ranging from 80% in high-income countries to less than 40% in low-income ones.[3] In Iran, the survival rate of breast cancer has been reported to be 70%.[4]

Awareness of the prognostic factors associated with the survival in breast cancer plays an important role in the process of treatment and patient care. Several studies have proposed various survival prognostic factors in breast cancer. Age at diagnosis, stage of the disease, number of involved lymph nodes, tumor size and grade, type of auxiliary treatment (radiotherapy, chemotherapy, hormone therapy), metastasis, and recurrence are among these factors.[5,6] Various studies have been performed in Iran to determine the factors affecting the survival in breast cancer patients and estimate the survival time.[7-10] However, the factors identified in each study have been different from other studies and the extent of the effects of some of these factors has also been controversial. For example, the effects of the type of surgery (modified radical mastectomy [MRM] and breast conservation surgery [BCS]), chemotherapy, and radiotherapy on the survival of patients are the most discussed issues in recent years.[11-13]

Using data from different health centers can provide more accurate knowledge of the survival prognostic factors and their effect on the patient's survival. The data structure of these studies is heterogeneous due to the treatment of patients in different centers or being under the care of different physicians or similar

reasons; such that intra-center patients have a relatively high correlation and the inter-center ones have a low correlation. Ignorance of this issue can cause errors in identifying the prognostic factors and their effects. Conventional survival analysis models, such as the Cox proportional hazards model, ignore the effects of correlations and lead to an overestimation of model parameters. One of the well-known models that are used to model the clustered correlated data is shared frailty model.[14] A shared frailty model is a random effects model for time-to-event data, where the random effect (the frailty) has a multiplicative effect on the baseline hazard function. The effect of inter-center distinction and intra-center correlation can be controlled by frailty term. In this model, we assume that persons in the same center share the same frailty term. The frailty term is random and therefore a frailty distribution needs to be specified in the frailty model. The standard assumption is to use a gamma distribution for the frailty, but other distributions are also possible.[15] Early considerations of these models can be found in Clayton[16] and Clayton and Cuzick[17] and extensively studied in Hougaard,[18] Therneau and Grambsch,[19] Duchateau et al,[20,21] and Duchateau and Janssen,[22] and much of the development in this area stems from the extension of methods used to measure correlation in bivariate survival data with arbitrary individual hazard functions (including Cox models).[16,17]

In this study, we used the patients' data from 4 different health centers in Tehran. These health centers include the private and public centers, and there are differences in treatment facilities and treatment teams. We used the shared frailty model to control center effects and estimate the survival of breast cancer patients and determine the prognostic factors affecting the survival of breast cancer.

Materials and Methods

In this historical cohort study, the data set was collected as a secondary data and it contains information on 1785 breast cancer patients without any missingness, (based on the diagnosis of breast cancer pathology) referring to 4 breast cancer research centers in Tehran, Iran, between 1997 and 2013 who completed the follow-up period. The median follow-up time in the 2 centers of C and D was 65.70 and 51 months, and in centers A and B, follow-up time was 22.32 and 29 months, respectively. The median follow-up time in total data was 29.71 months with the interquartile range of 19 to 61 months.

The event is death from breast cancer, and all other deaths are regarded as censored observations. The survival time was defined as the duration (months) from diagnosis to death due to breast cancer. Age at diagnosis (year); tumor characteristics including size of tumor (>2 cm, between 2 and 5 cm, > 5 cm), the number of lymph nodes involved (no lymph nodes, 1-3 lymph nodes, 4-9 lymph nodes, and >9 lymph nodes), grade of malignancy (grades 1-3), and type of surgery (MRM or BCS); and auxiliary treatment of chemotherapy, radiotherapy, recurrence, and metastasis were the prognosis factors considered in this study.

In our study to investigate the relation between the survival time and risk factors, first, the Cox proportional hazard model was used for each center separately and for total data without considering centers. In the second model, Cox model with center term as covariate was used and in the third model a shared frailty model with a gamma distribution for center term as random effect (frailty term) was used.

The Cox proportional hazard is the most common method for analyzing the effects of several variables on survival time. In this model, the hazard function for individual i is written as

$$\lambda_i(t) = \lambda_0(t)\exp\left(\beta^T X_i\right)$$

$\lambda_0(t)$ is a baseline hazard function, left unspecified and $\exp(\beta^T X_i)$ is the relative risk of individual i, where X_i is the covariate vector of individual i.[14]

In multicenter studies, outcomes are typically more heterogeneous. Heterogeneity usually arises because individuals in the same center are related to each other and each center is different due to variations in patients as well as provider care and other latent factors can be different in centers. Heterogeneity decreases the power to detect important risk factors and can introduce bias into the analysis. Ordinary methods like Cox model implicitly assume that populations are homogeneous, meaning all individuals have the same risk of death. Heterogeneity between centers in multicenter studies with time to event outcome can be modeled by the shared frailty model. A shared frailty model is a random effects model for time-to-event data, where the random effect (the frailty) has a multiplicative effect on the baseline hazard function and frailty is defined as a measure of the relative risk which individuals in a group share.[15,20] In this situation, individuals j in a center i are supposed to share the same frailty Z_i. The conditional hazard for individual j in center i is

$$\lambda\left(t_{ij}|Z_i\right) = Z_i\lambda\left(t_{ij}\right)$$

where $\lambda(t_{ij})$ is the Cox model. The Z_i are independent identically distributed following a chosen distribution. Many distributions can be chosen for the frailty, but the most common frailty distribution is the gamma distribution. From a computational and analytical point of view, the gamma distribution is convenient because it is easy to derive the closed-form expressions of survival, density, and the hazard function. The model assumes that all time observations are independent given the values of the frailties. In other words, it is a conditional independence model. The value of Z is constant over time and common to the individuals in the center and thus responsible for creating dependence. The interpretation of this model is that the between-centers variability (the random variation of Z) leads to different risks for the centers, which then show up as dependence within the centers.[14] The variance of Z is interpretable as a measure of heterogeneity across the population in baseline risk. When it is small, then the values of Z are closely concentrated around one.

Table 1. Profile of follow-up time (in months), event, and survival quartiles by 4 centers.

CENTER	PATIENT (N)	EVENT N (%)	MEDIAN FOLLOW–UP TIME	25% SURVIVAL *(SE)*	50% SURVIVAL *(SE)*	75% SURVIVAL *(SE)*
A	800	143 (17.9)	22.32	–	–	40.29 (6.36)
B	393	50 (12.7)	29.00	130 (24.16)	100 (9.9)	85 (28.03)
C	413	112 (27.1)	65.70	236.55 (14.07)	235.07 (77.24)	68.99 (7.34)
D	179	32 (17.9)	51	–	–	84 (10.48)
Total	1785	337 (18.9)	29.71	236.55 (1.21)	235.07 (67.89)	63.70 (4.86)

Abbreviation: *SE*, standard error.

If it is large, then values of Z are more dispersed, inducing greater heterogeneity in the individual hazards.[14]

To compare the efficiency of models, Akaike information criterion (AIC) was used.[23] The likelihood ratio test was used to test significantly frailty variance from zero. The proportional hazards assumption was investigated using a Schoenfeld residual test. Distributions of characteristics were compared using chi-square test (for categorical variables) and the analysis of variance (ANOVA) test (for continuous variables). The adjusted P values (with the Benjamini and Hochberg[24] procedure for multiple comparisons) less than .05 was considered to be significant. The analysis was performed using STATA, version 12.

Results

The center-specific number of patients studied, the number of deaths, follow-up times, and survival quartiles are provided in Table 1 by different centers; 800, 393, 413, and 179 (in total, 1785) patients were studied from the 4 health centers A to D. During the follow-up period, 337 (18.9%) patients died from breast cancer and 1448 (81.1%) survived, so 17.9% died in center A also D, 12.7% in center B, and 27.1% in center C.

Number (percent; mean [standard deviation] for continuous variables) of the studied variables by the centers and P value of Pearson chi-square test (P value of ANOVA test for age) are presented in Table 2. Characteristics of the study population by survival status (number (%); mean [standard deviation] for continuous variables) who died are presented in Table 3. The mean (standard deviation) of age at diagnosis was almost the same in all centers and in total data was 48.78 (12.63). Totally, MRM was used for 67.1% and BCS for 32.9% of patients; 249 (13.9%) of patients diagnosed with metastasis and 159 (8.9%) patients experienced recurrent. Auxiliary radiotherapy and chemotherapy were performed in 914 (51.2%) and 1145 (64.1%) of patients, respectively.

According to the survival curve (Figure 1A), the 1-, 3-, 5-, and 10-year survival rates were 96%, 84%, 76%, and 58%, respectively. Figure 1B shows the survival rate estimation by the Kaplan-Meier method in the different studied centers. During the first 100 months of follow-up, center A has a lower survival curve than 3 other centers.

The assumption of proportional hazards was confirmed in Cox models at the significance level of 0.05. The results of the Cox model by centers and Cox model for all centers are provided in Table 4, and the results of the Cox model with the center term as covariate and a shared frailty model with a gamma distribution for center term as random effect (frailty term) for total data are provided in Table 5. Age at diagnosis in B and C centers was significant, and the hazard of death increases by 1.02 with every year (for both centers). The hazard of death reduces 0.624 times with the BCS compared to MRM method significantly, in shared frailty model, and it reduces significantly 0.510 times in center A. Radiotherapy at B and C centers and in shared frailty model was significant and reduced the hazard of death 0.662 times compared to those who did not receive this treatment. In shared frailty model, metastasis increased the hazard of death significantly by 5.384 times. In centers A to D, the hazard ratio of death in metastatic patients was 6.535, 10.784, 3.182, and 5.575, respectively. The increase in the number of involved lymph nodes increased the hazard of death. In shared frailty model, the hazard of death in the patients with 1-3, 4-9, and above 9 involved nodes was 1.694, 1.947, and 2.336 times the patients with no involved nodes. In the examination of the tumor grade, the hazard of death for patients with grade 3 tumors was 2.512 times the grade 1 tumor, and the grade 2 tumor than grade 1 had a statistically significant effect on the survival of patients with hazard ratio of 1.670.

Obtained results of comparing 3 models such as Cox model, Cox model with the center term, and shared frailty model indicated that the hazard ratio and confidence intervals changed. Chemotherapy and recurrence were significant in the Cox model while were not significant in the shared frailty model, but recurrence was significant in the Cox model with center term; also center term was significant (P value = .002) in this model. Shared frailty model had AIC less than 2 other models. In the shared frailty, variance of frailty term (0.0369; SE = 0.0364) was significantly different from zero using the likelihood ratio test, and it affirmed that there was significant variability between the centers (P value = .021).

Discussion

In this study, we used the data collected from 4 health centers in Tehran, Iran, to investigate the effect of prognostic factors of survival. As the data were collected from different centers, in

Table 2. Profile of patient demographics and clinical characteristic.

RISK FACTORS	CENTER A (N = 800)	CENTER B (N = 393)	CENTER C (N = 413)	CENTER D (N = 179)	*P* VALUE	ALL CENTERS
N (%)						
Surgical procedure						
MRM	674 (84.2)	106 (27.0)	338 (81.8)	80 (44.7)	<.001	1198 (67.1)
BCS	126 (15.8)	287 (73.0)	75 (18.2)	99 (55.3)		587 (32.9)
Metastases						
Yes	79 (9.9)	51 (13.0)	91 (22.0)	28 (15.6)	<.001	249 (13.9)
No	721 (90.1)	342 (87.0)	322 (78.0)	151 (84.4)		1536 (86.1)
Recurrence						
Yes	100 (12.6)	14 (3.6)	32 (7.7)	13 (7.3)	<.001	159 (8.9)
No	700 (87.5)	379 (96.4)	381 (92.3)	166 (92.7)		1626 (91.1)
Radiotherapy						
Yes	201 (25.1)	310 (78.9)	256 (62.0)	147 (82.1)	<.001	914 (51.2)
No	599 (74.9)	83 (21.1)	157 (38.0)	32 (17.9)		871 (48.8)
Chemotherapy						
Yes	341 (42.6)	280 (71.2)	376 (91.0)	148 (82.7)	<.001	1145 (64.1)
No	459 (57.4)	113 (28.8)	37 (9.0)	31 (17.3)		640 (35.9)
Tumor size						
<2 cm	233 (29.1)	147 (37.4)	95 (23.0)	65 (36.3)	<.001	540 (30.3)
2-5 cm	444 (55.5)	206 (52.4)	235 (56.9)	92 (51.4)		977 (54.7)
>5 cm	123 (15.4)	40 (10.2)	83 (20.1)	22 (12.3)		268 (15.0)
Tumor grade						
1	95 (11.9)	49 (12.5)	58 (14.0)	20 (11.2)	.007	222 (12.4)
2	487 (60.9)	219 (55.7)	243 (58.8)	85 (47.5)		1034 (57.9)
3	218 (27.3)	125 (31.8)	112 (27.1)	74 (41.3)		529 (29.6)
Involved lymph node						
0	162 (20.3)	207 (52.7)	181 (43.8)	83 (46.4)	<.001	633 (35.5)
1-3	216 (27.0)	86 (21.9)	99 (24.0)	36 (20.1)		437 (24.5)
4-9	253 (31.6)	49 (12.5)	83 (20.1)	41 (22.9)		426 (23.9)
>9	169 (21.1)	51 (13.0)	50 (12.1)	19 (10.6)		289 (16.2)
Age	48.86 (13.62)	48.54 (11.83)	46.73 (11.39)	53.68 (11.15)	<.001	48.78 (12.63)

Abbreviations: ANOVA, analysis of variance; BCS, breast conserving surgery; MRM, modified radical mastectomy; N, number; SD, standard deviation. *P* value: significant value of Pearson chi-square test (*P* value of ANOVA test for age).

addition to the covariates considered, other factors such as treatment methods, conditions of patients referring to each center, and therapeutic equipment cause a correlation between patients at each center. Disregarding this correlation in the modeling leads to a biased estimation of the effects of the factors studied. A shared frailty model considers this correlation

Table 3. Characteristics of study population by survival status.

RISK FACTORS	CENTER A	CENTER B	CENTER C	CENTER D	*P* VALUE	ALL CENTERS
N (%) WHO DIED						
Surgical procedure						
MRM	131 (91.61)	23 (46.00)	99 (88.39)	22 (68.75)	<.001	275 (81.60)
BCS	12 (8.39)	27 (54.00)	13 (11.61)	10 (31.25)		62 (18.40)
P value	.008	.001	.035	.003		<.001
Metastases						
Yes	48 (33.57)	31 (62.00)	52 (46.43)	14 (43.75)	.004	145 (43.03)
No	95 (66.43)	19.38 (87.0)	60 (53.57)	18 (56.25)		192 (56.97)
P value	<.001	<.001	<.001	<.001		<.001
Recurrence						
Yes	18 (12.59)	2 (4.00)	16 (14.29)	5 (15.63)	0.264	41 (12.17)
No	125 (87.41)	48 (96.00)	96 (85.71)	27 (84.38)		296 (87.83)
P value	.972	.858	.002	.044		.020
Radiotherapy						
Yes	40 (27.97)	29 (58.00)	67 (59.82)	22 (68.75)	<.001	158 (46.88)
No	103 (72.03)	21 (42.00)	45 (40.18)	10 (31.25)		179 (53.12)
P value	.386	<.001	.581	.029		.078
Chemotherapy						
Yes	65 (45.45)	33 (66.00)	106 (94.64)	22 (68.75)	<.001	226 (67.06)
No	78 (54.55)	17 (34.00)	6 (5.36)	10 (31.25)		111 (32.94)
P value	.450	.380	.118	.022		.215
Tumor size						
<2 cm	36 (25.17)	15 (30.00)	8 (7.14)	9 (28.13)	<.001	68 (20.18)
2-5 cm	83 (58).04	26 (52.00)	65 (58.04)	15 (46.88)		189 (56.08)
>5 cm	24 (16.78)	9 (18.00)	39 (34.82)	8 (25.00)		80 (23.74)
P value	.507	.117	<.001	.050		<.001
Tumor grade						
1	9 (6.29)	5 (10.00)	8 (7.14)	1 (3.13)	.228	23 (6.82)
2	67 (46.85)	25 (50.00)	67 (59.82)	21 (65.63)		180 (53.41)
3	67 (46.85)	20 (40.00)	37 (33.04)	10 (31.25)		134 (39.76)
P value	<.001	.401	.027	.052		<.001
Involved lymph node						
0	15 (10.49)	16 (32.00)	28 (25.00)	6 (18.75)	0.001	65 (19.29)
1-3	31 (21.68)	16 (32.00)	25 (22.32)	9 (28.13)		81 (24.04)

(Continued)

Table 3. (Continued)

RISK FACTORS	CENTER A	CENTER B	CENTER C	CENTER D	*P* VALUE	ALL CENTERS
N (%) WHO DIED						
4-9	52 (36.36)	3 (6.00)	29 (25.89)	12 (37.50)		96 (28.49)
>9	45 (31.47)	15 (30.00)	30 (26.79)	5 (15.63)		95 (28.19)
P value	<.001	<.001	<.001	.007		<.001
MEAN (SE)						
Age						
Alive	49.03 (0.53)	48.08 (0.62)	46.28 (0.64)	54.21 (0.92)	0.001	48.76 (0.33)
Died	48.10 (1.09)	51.70 (1.99)	47.93 (1.13)	51.22 (1.90)	0.194	48.87 (0.69)
P value	.460	.043	.190	.169		**.881**

Abbreviations: ANOVA, analysis of variance; BCS, breast conserving surgery; MRM, modified radical mastectomy; N, number; SE, standard error. *P* value: significant value of Pearson chi-square test (*P* value of ANOVA test for age).

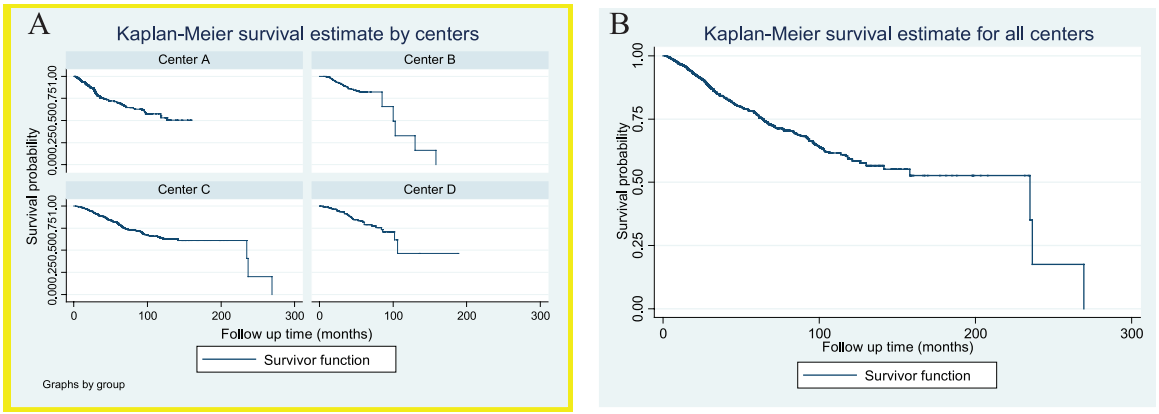

Figure 1. Kaplan-Meier curves in breast cancer patients (A) by centers and (B) all centers.

to control the effects of ignoring factors, by extending the Cox proportional hazard model. A frailty term is taken into account for every center in this model so that it can relate the unobserved shared frailty to the hazard function dispersion due to inter-center and the intra-center correlations.[25] The term "Share" in this type of modeling means that there is a common effect in each center which is constant over time.[26] We used the data collected from 4 centers with at least 179 patients in each center; therefore, according to Govindarajulu and Malloy,[27] we have enough power in using a shared frailty model to analyze breast cancer data.

The results of total data obtained using the shared frailty model (assuming gamma distribution for frailty) showed that the type of surgery, number of nodes involved, metastasis, radiotherapy, and tumor grade are the prognostic factors of survival in breast cancer. The frailty term had a significant effect on the model, which shows the necessity of using the frailty model to control the changes between the centers due to unconsidered covariates. In the separate analysis centers by the Cox model, in center A, the type of surgery, number of nodes involved, and the grade 3 tumor; in center B, age, radiotherapy, metastasis, and between 1 and 3 involved nodes; in center C, age, radiotherapy, recurrence, metastasis, size of the tumor, and grade 3 tumor; and in center D, chemotherapy, metastasis, and lymph nodes involved were significant.

Among the significant factors in this study, the effect of the surgical method on the survival of breast cancer patients is one of the most addressed issues in recent studies. Our study showed that the hazard of death in BCS surgery for women with breast cancer is less than the hazard of death due to MRM, which is consistent with the results of similar studies.[28-30] In the study of Hofvind et al.,[31] by controlling other factors, the hazard of death in MRM is 1.7 times higher than BCS. In a similar study, Hartmann-Johnsen et al.[30] provided similar results for women aged 50-69 years by controlling other factors. Meanwhile, there has been no significant difference between the 2 surgical methods in the study of Quan et al.[12] In the study of Baghestani et al.[32] in Iran, with univariate analysis, the surgical method had a significant effect on survival; however, in multivariate analysis, by controlling other factors, there was no significant effect.

In our study, more involved lymph nodes increased the hazard of death significantly. In Iran, in the study by Movahedi

Table 4. HR and 95% CI prognostic factors of death from Cox model by center and for all centers.

RISK FACTORS	CENTER A	CENTER B	CENTER C	CENTER D	ALL CENTERS
	HR (95% CI)				
Age	0.996 (0.982-1.009)	1.023 (1.001-0.045)*	1.025 (1.008-1.043)*	0.998 (0.963-1.034)	1.006 (0.997-1.015)
Surgical procedure					
MRM	1.00	1.00	1.00	1.00	1.00
BCS	0.510 (0.278-0.936)*	0.572 (0.287-1.138)	0.843 (0.449-1.580)	0.628 (0.262-1.501)	0.647 (0.487-0.861)*
Chemotherapy					
No	1.00	1.00	1.00	1.00	1.00
Yes	0.931 (0.660-1.315)	1.670 (0.801-3.478)	1.156 (0.456-2.928)	0.199 (0.078-0.506)*	0.772 (0.688-1.161)*
Radiotherapy					
No	1.00	1.00	1.00	1.00	1.00
Yes	1.195 (0.823-1.735)	0.322 (0.168-0.617)*	0.489 (0.319-0.749)*	0.608 (0.249-1.483)	0.604 (0.478-0.763)*
Recurrence					
No	1.00	1.00	1.00	1.00	1.00
Yes	1.135 (0.679-1.897)	1.233 (0.266-5.718)	2.124 (1.181-3.819)*	1.461 (0.385-5.543)	1.434 (1.029-1.999)*
Metastasis					
No	1.00	1.00	1.00	1.00	1.00
Yes	6.535 (4.404-9.696)*	10.784 (5.668-20.518)*	3.182 (2.108-4.802)*	5.575 (2.218-14.010)*	4.923 (3.921-6.182)*
Tumor size					
<2 cm	1.00	1.00	1.00	1.00	1.00
2-5 cm	1.086 (0.731-1.614)	0.506 (0.213-1.199)	3.073 (1.382-6.832)*	0.752 (0.299-1.893)	1.060 (0.794-1.413)
>5 cm	1.116 (0.656-1.899)	0.691 (0.208-2.294)	4.311 (1.815-10.238)*	0.886 (0.264-2.974)	1.181 (0.833-1.673)
Involved lymph node					
0	1.00	1.00	1.00	1.00	1.00
1-3	1.250 (0.668-2.338)	2.741 (1.185-6.343)*	1.526 (0.854-2.726)	6.009 (1.761-20.499)*	1.856 (1.323-2.604)*
4-9	1.491 (0.821-2.708)	0.733 (0.184-2.916)	2.386 (1.352-4.209)*	4.336 (1.345-13.971)*	2.218 (1.596-3.083)*
>9	1.885 (1.023-3.473)*	1.224 (0.410-3.649)	2.953 (1.598-5.456)*	8.406 (2.142-32.987)*	2.630 (1.862-3.714)*
Grade					
1	1.00	1.00	1.00	1.00	1.00
2	1.297 (0.636-2.645)	0.654 (0.227-1.887)	1.626 (0.764-3.460)	4.009 (0.501-32.087)	1.709 (1.101-2.650)*
3	2.731 (1.329-5.609)*	0.574 (0.179-1.842)	2.368 (1.082-5.183)*	1.746 (0.199-15.258)	2.624 (1.668-4.127)*
Log likelihood	–769.838	–209.384	–544.082	–111.723	–2070.681
AIC	1565.768	444.768	1114.162	249.446	4167.361

Abbreviations: AIC, Akaike information criterion; BCS, breast conserving surgery; CI, confidence interval; HR, hazard ratio; MRM, modified radical mastectomy.
*Significant adjusted *P* values with the Benjamini and Hochberg[24] procedure (<.05).

et al.[33] on 623 patients with breast cancer, involvement of lymph nodes was associated with a decrease in the survival rate of patients under study. Faradmal et al.[10] and Nematolahi et al.[34] presented similar results, using the shared frailty model (to control the effect of hidden factors) and a Bayesian model, respectively.

Table 5. HR and 95% CI prognostic factors of death from a shared frailty model and Cox model with a center term.

RISK FACTORS	SHARED FRAILTY MODEL	COX MODEL WITH A CENTER TERM
	HR (95% CI)	
Age	1.005 (0.996-1.014)	1.006 (0.997-1.015)
Surgical procedure		
MRM	1.00	1.00
BCS	0.624 (0.463-0.842)*	0.647 (0.486-0.860)*
Chemotherapy		
No	1.00	1.00
Yes	0.894 (0.688-1.161)	0.895 (0.688-1.165)
Radiotherapy		
No	1.00	1.00
Yes	0.662 (0.517-0.847)*	0.683 (0.534-0.874)*
Recurrence		
No	1.00	1.00
Yes	1.381 (0.989-1.928)	1.412 (1.013-1.968)*
Metastasis		
No	1.00	1.00
Yes	5.384 (4.256-6.810)*	5.379 (4.251-6.807)*
Tumor size		
<2 cm	1.00	1.00
2-5 cm	1.082 (0.811-1.442)	1.073 (0.805-1.430)
>5 cm	1.243 (0.878-1.759)	1.229 (0.868-1.740)
Involved lymph node		
0	1.00	1.00
1-3	1.694 (1.202-2.386)*	1.675 (1.187-2.363)*
4-9	1.947 (1.387-2.732)*	1.962 (1.400-2.749)*
>9	2.336 (1.644-3.318)*	2.294 (1.610-3.268)*
Grade		
1	1.00	1.00
2	1.670 (1.077-2.591)*	1.677 (1.081-2.602)*
3	2.512 (1.596-3.956)*	2.574 (1.636-4.049)*
Center	–	0.810 (0.706-0.928)*
Log likelihood	−2068.164	−2070.026
AIC	4162.327	4166.006

Abbreviations: AIC, Akaike information criterion; BCS, breast conserving surgery; CI, confidence interval; HR, hazard ratio; MRM, modified radical mastectomy.
*Significant adjusted *P* values with the Benjamini and Hochberg[24] procedure (<.05).

In our study, metastasis was one of the most important and effective factors in reducing the survival of breast cancer patients. Metastasis increased the hazard of death by 5.384 times. In other studies, metastasis has been one of the most important factors affecting the survival of breast cancer patients.[34-36] A systematic review stated that with metastasis, the survival probability is .18.[37] In Iran, Rezaianzadeh et al.[38] showed that metastasis to the bones and the lung increases the hazard of death by 2.25 and 3.21 times, respectively. In a study by Karimi et al.,[39] the survival rate of patients without metastasis was twice that of metastatic patients.

Cancer patients receive different auxiliary therapies after surgery, which can affect the survival of the patient, recurrence of the tumor, and the incidence of metastasis. In the present study, radiotherapy decreased the hazard of death in patients who received this treatment compared to others. Several studies have shown that the hazard of recurrence can be reduced with radiotherapy by BCS.[40,41] The study of Daugherty et al.[11] suggested that radiotherapy enhances survival. Eighteen studies in the systematic review by Whelan et al.[42] showed that radiotherapy reduces the hazard of death.

In our study, grade 2 and 3 tumor increased the hazard of death compared to grade 1. Also, in other studies, higher grade tumor has been introduced as a prognostic factor for survival.[43-45] In a study by Rezaianzadeh et al.,[38] the hazard of death was double with the increase in tumor grade. In a review of the literature published between 1995 and 2006, Soerjomataram et al.[37] concluded that tumor grade is one of the most important factors in the long-term survival of breast cancer patients. Grade 3 malignancy shows no distinction between cancer cells and healthy cells, which is an indication of the spread and growth of cancer cells.

The average age of the patients was 48.86 years, which is similar to other studies in Iran that have reported an average age of breast cancer patients between 45 and 50 years,[34] and this is lower than those in Western Europe and North America.[46] In the present study, age was recognized as a prognostic factor for survival in 2 centers and suggested that increasing age increases the hazard of death. Previous studies have reported different outcomes about the significance of the effect of age.[47,48] Heydari studied the 5-, 10-, and 15-year survival rate in breast cancer among 863 patients who referred between 2001 and 2006. In their study, the age of breast cancer diagnosis was 46.3 years and the survival rate had a significant negative relation to the age of diagnosis.[47]

The size of the tumor and recurrence were significant only at center C that indicated an increase in tumor size and recurrence increases the hazard of death. Many studies have identified these factors as risk factors for death in breast cancer.[44,49] One of the reasons for the insignificance of tumor size in the other centers could be that any size of the tumor has been dissected in the surgery, and if the large size of the tumor was indicative of the progression of the disease, this could be expressed by factors such as the grade of the tumor.

One of the limitations of this study was failure to measure some variables, such as family history, marital status, estrogen and progesterone receptors, and other factors addressed in all health studies, and because of this reason, it was not possible to be analyzed in our multicenter study.

Based on this multicenter study, the type of surgery, number of lymph nodes involved, metastasis, radiotherapy, and the tumor grade are the prognostic factors survival in breast cancer. Consequently, early diagnosis of cancer before the involvement of lymph nodes and the onset of metastasis and timely treatment can lead to longer life and increase the quality of life for patients. Also, the significance of frailty term showed there was significant variability between the centers.

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Author Contributions

AY, HZ and MY designed the model and the computational framework and analyzed the data. AY wrote the manuscript with support from HZ and MY. SH and AK contributed to sample preparation. All authors discussed the results and contributed to the final manuscript. All authors have read and approved the manuscript.

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