Original Article

Application of Weibull Accelerated Failure Time Model on the Disease-free Survival Rate of Breast Cancer

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Abstract

Background and Purpose: The goal of this study is application of the proportional hazards model (PH) and accelerated failure time model (AFT), with consideration Weibull distribution, to determine the level of effectiveness of the factors affecting on the level of disease-free survival (DFS) of the patients with breast cancer.

Materials and Methods: Based on the retrospective descriptive studies, 377 female patients with primary breast cancer that had been treated at oncology section (Omid Hospital) in Mashhad, Iran, were considered for participation in the study.

Results: The median was 2 years and 10 months (mean 2 years and 4 months, interquartile range 3 years and 7 months, range 1-2920 days or 8 years). The average age of patients was 49.2 ± 11.5 (range 25-80 years). The rate of DFS determined with 52.5%. Base on the result of PHs Weibull model, the risk of the metastasis after surgery in the patients with invasive tumors to the skin and chest and positive lymph node was more than 2 times [hazard ratio (HR) = 2.53; confidence interval (CI): 1.26, 5.06] and (HR = 2.37 CI: 1.42, 3.98), respectively. Hormone therapy after surgery decreases the risk of the metastasis to 0.63% (HR = 0.63; CI: 0.41, 0.95). In the AFT model, characteristic tumor decelerated ($\gamma < 1$) the DFS time by a factor of 0.30 and 0.33, respectively. Furthermore, the hormonal therapy accelerated ($\gamma > 1$) the DFS time by factor of 1.8.

Conclusion: In this study, the PH and AFT assumption have been satisfied by data and characteristics tumor and the hormonal therapy decrease and increases time until recurrence, respectively.

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1. Introduction

Weibull model, is a parametric form of survival model, is one in which outcome, and is assumed to follow a known distribution Weibull. One of the properties of Weibull model is determined that if the accelerated failure time assumption (AFT) holds then the proportional hazards (PH) assumption also holds. The main assumption of a PH model is that hazard ratios are constant over time; the main assumption of an AFT model is that survival time accelerates by a constant factor when comparing different levels of covariates. This property is unique to the Weibull model. This assumption allows for the estimation of an acceleration factor which can describe the direct effect of an exposure on survival time (1). In the medical sciences, relapse and recurrence is one of the cases that are studied parallel to the evaluation of the treatment outcomes. In the field of cancer, relapse is observed as recurrence in the same organ or metastasis in another one (2). The metastasis puts the patient at risk because of both patients weakens or as a cause of it (3). The studies show that surgeries and type of the treatment after surgeries decrease the risk of recurrence and improves the disease-free survival (DFS) of the patient significantly. Based on the results of a clinical trial in the Oxford-Britain, more than 50% of breast cancer recurrence occurs 5 years after the early detection and using the hormone therapy has decreased the risk of relapse in the first 5 years after the surgery (4). The more recent studies have shown that the percent treatment difference or other factors in mean or median lifespan can be used, for summarizing treatment effects or factor effects on lifespan (5). The goal of this study is the application of Weibull PH models and Weibull AFT model to determine the rate of the DFS of the patient, after surgery, and the level of effectiveness of the factors affecting on the level of DFS of the patients with primary breast cancer.

2. Materials and Methods

Based on the retrospective descriptive studies, 377 female patients with primary breast cancer between April 2006 and April 2014 at oncology section (Omid Hospital) in Mashhad were considered for participation in the study.

Inclusion criteria were female with primary breast cancer who underwent mastectomy or breast-conserving surgery or lumpectomy and axillary node dissection. The patients were excluded if staging investigations at the time of diagnosis reveal evidence of disease progression such as distant metastases.

Patients with primary breast cancer were treated with either modified radical mastectomy or lumpectomy and axillary node dissection. Furthermore, they were treated chemotherapy in node-positive patients and hormone therapy in receptor-positive.

Vital status of patients was recorded. The effective factors on the metastasis-free or relapse-free period consisting of: Age (at the time of diagnosis), the pathologic size of tumor, axillary lymph node status, human epidermal growth factor receptor 2 (HER2) receptor level (6), hormone receptor status such as progesterone receptor (PR) and estrogen receptor (ER) (7,8). Hormone therapy during treatment was also considered.

The time after surgery until the first recurrence, metastasis or death, determined as the time scale or the depended variable.

A statistical analysis was performed using the STATA software (version 13; Stata Corporation, College Station, TX, USA).

To determine the affective factors on the disease relapse and the rate of their effectiveness, the methods of linear regression was used. In these models, the outcome (survival time) is assumed to a follow known distribution such as the exponential or the Weibull.

Because of more flexibility, the shape parameter added to the exponential distribution. The generalization of the exponential distribution is the Weibull distribution.

$$f(t) = \gamma\theta t^{\gamma-1} \exp\{-\theta t^{\gamma}\}, t > 0$$

That the hazard and survival function are respectively (9):

$$h(t) = \gamma\theta t^{\gamma-1}, s(t) = \exp\{-\theta t^{\gamma}\}$$

In the Weibull model, the shape parameter (θ) determines the shape of the hazard function. If $\theta > 1$, then the hazard increases as time increases. If $\theta = 1$ then the hazard is constant, and if $\theta < 1$, then the hazard decreases over time (1).

The scale parameter consider as a function of covariates, that is,

$$\theta = \exp\{\beta_0 + \beta_1 x_1\} \text{ or } \log(\theta) = \beta_0 + \beta_1$$

The hazard and baseline hazard function is respectively (9):

$$h(t|x) = \exp\{\beta_0 + \beta_1 x_1\}\gamma t^{\gamma-1}, h_0(t) = \gamma t^{\gamma-1}$$

The underlying assumption for PH models is that the effect of covariates is multiplicative (proportional) with respect to the hazards whereas for AFT models the underlying assumption is that the effect of covariates is multiplicative (proportional) with respect to the survival time that is consistent over time.

The AFT assumption can be expressed as $S_2(t) = S_1(\gamma t)$ for $t \geq 0$, where γ is a constant called the acceleration factor. In the other words, the acceleration factor describes the stretching out or contraction of survival functions, when comparing one group to another.

In a regression framework, the acceleration factor could be parameterized as exp (α) [$\gamma = \exp(\alpha)$] where α is a parameter to be estimated (1).

3. Results

The median was 869 days or 2 years and 10 months (mean 869 days or 2 years and 4 months, interquartile range 1317 days or 3 years and 7 months, range 1-2920 days or 8 years). Among the patients, 249 (66%) patients did not have any relapse and 128 (34%) patients were relapsed. The recurrence occurred in 128 (34%) patients [first relapse: local recurrence n = 24 (19%), distant metastasis n = 104 (81%)]. Based on the log-rank test, the DFS rate was compared between groups (Table 1). The average age of patients is 49.2 ± 11.5 (range 25-80 years). The rate of overall survival without disease or metastasis and recurrence was to 52.5% (Figure 1).

Base on the result of PH Weibull model (Table 2), although the increase of the tumor at the level of 0.05 did not lead to increase in the relapse risk or metastasis, but in patients whose tumor have had invasive to their skin and chest; the risk of

Table 1. Patients characteristics and comparison DFS rates between categories, with log rank test

Variable	Variable levels	Metastasis occurrence	Metastasis none-occurrence	Final DFS	Log rank test
Type of carcinoma	Ductal	84.4 (108)	80.7 (201)	82.0 (309)	0.51
	Lobular	6.3 (8)	9.6 (24)	8.5 (32)	0.72
	Medullary	0.0 (0)	4.4 (11)	2.9 (11)	-
	Other	7.0 (9)	5.3 (13)	5.8 (22)	0.39
	Unknown	2.3 (3)	0.0 (0)	0.8 (3)	P < 0.030
Size of tumor	< 2 cm	14.8 (19)	16.1 (40)	15.6 (59)	0.54
	2-5 cm	30.5 (39)	55.8 (139)	47.2 (178)	0.67
	> 5 cm	26.6 (34)	13.7 (34)	18.1 (68)	0.41
	Invasive to the skin and chest	16.4 (21)	6.4 (16)	9.8 (37)	0.28
	Unknown	11.7 (15)	8.0 (20)	9.3 (35)	P < 0.001
Lymph node status	Negative	21.1 (27)	40.6 (101)	33.9 (128)	0.71
	Positive	73.4 (94)	56.2 (140)	62.7 (234)	0.52
	Unknown	5.5 (7)	3.2 (8)	3.4 (15)	P < 0.001
Hormone therapy	Untreated	53.1 (68)	50.6 (126)	51.5 (194)	0.47
	Treated	46.1 (59)	48.9 (122)	48.0 (181)	0.57
	Unknown	0.8 (1)	0.5 (1)	0.5 (2)	P < 0.004

Log rank test: Comparison test of DFS rate between groups. DFS: Disease-free survival

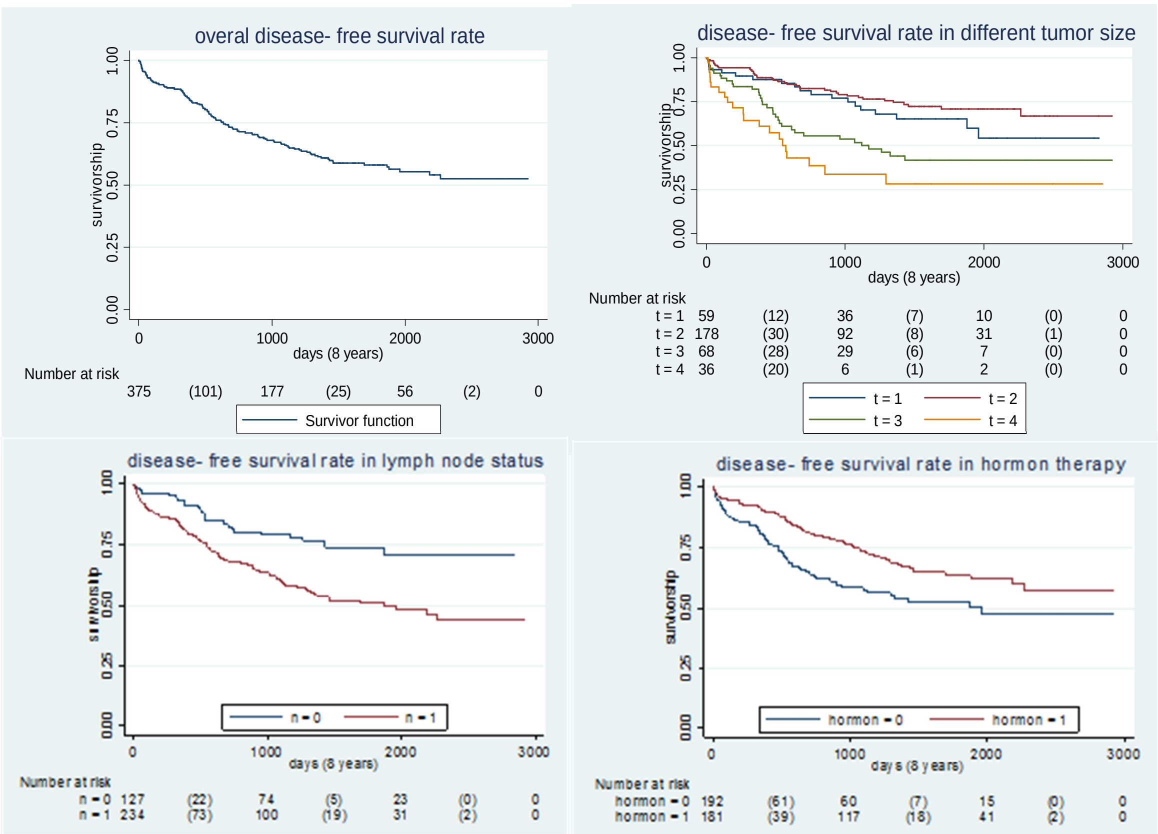

Figure 1. The diagram of the disease-free survival rate in different groups. (1) Tumor size < 2 cm, 0 = Negative lymph node, 0 = Untreated, (2) tumor size between (2, 5), 1 = Positive lymph node, 1 = Treated, (3) tumor size ≥ 5, (4) invasive tumor to skin and chest

Table 2. Multivariate analysis of prognostic factors for DFS rate of patients with Weibull model

Variable levels	Weibull PH model			Weibull AFT model		
	HR	CI	P value	Coef	CI	P value
Size of tumor						
< 2 cm	-	-	-	-	-	-
2-5 cm	0.62	(0.34, 1.15)	NS	0.59	(−0.19, 1.39)	NS
> 5 cm	1.45	(0.77, 2.75)	NS	-0.48	(−1.3, 0.33)	NS
Invasive to the skin and chest	2.53	(1.26, 5.06)	< 0.010	−1.19	(−2.09, −0.29)	< 0.010
Lymph node status						
Negative	-	-	-	-	-	-
Positive	2.37	(1.42, 3.98)	< 0.010	−1.11	(−1.79, −0.43)	< 0.010
Hormone therapy						
Treated	-	-	-	-	-	-
Untreated	0.63	(0.41, 0.95)	< 0.050	0.59	(0.05, 1.13)	< 0.050

Coef: Estimated parameter in the AFT model, CI: Confidence interval, HR: Hazard ratio, DFS: Disease-free survival, AFT: Accelerated failure time

the both relapse or metastasis was more than 2 times [hazard ratio (HR) = 2.53] rather than the people whose tumor's size were to < 2 cm and this effect is significant if the effect of the other variables is controlled. In the group of patients with positive lymph node, the risk of the metastasis after surgery was more than 2 times (HR = 2.37) than the people with a negative lymph node. In the patients who were treated with hormone therapy after surgery, the risk of the both relapse or metastasis is equal to 0.63% rather than patients not under hormone therapy. In other words, the type of treatment decreases the risk of metastasis, and this decrease has a significant effect on the DFS time of the patients.

However, other variables such as age, HER2 receptor, ER, PR did not have the significant impact, on the increase or decrease risk of relapse.

According to the result of AFT model (Table 2), exp (−1.19) = 0.30 (acceleration factor), shows that, the increase of tumor size, decreases the DFS time by a factor of 0.30 for the invasive tumor to the skin and chest. The positive lymph node in the patients decreases the DFS time by a factor of 0.33 [exp (−1.11) = 0.33]. However, the results show that the hormonal therapy increase the DFS time after the surgery by a factor of 1.8 [exp (0.59) = 1.8].

4. Discussion

The object of many medical and epidemiological studies is to estimate the DFS rate in disease. In this context, DFS rates and the risk of covariates were determined using Weibull PH and AFT model in the female patients with primary breast cancer.

Base on the other studies, between the tumor characteristics such as tumor size, status of lymph node, and DFS time, there was a significant relationship. These results, based on the survival analysis by semi-parametric cox model, have been obtained (2,10-12). Cox regression model is the most common way of analyzing prognostic factors in clinical research and widely popular. Because of is that, it does not rely on distributional assumptions for the survival time (1,13). But in the parametric form of survival such as Weibull, if the log-log survival curves look like straight lines with log survival time, then can be said that the time (outcome) variable follows a Weibull distribution (Figure 2) (1).

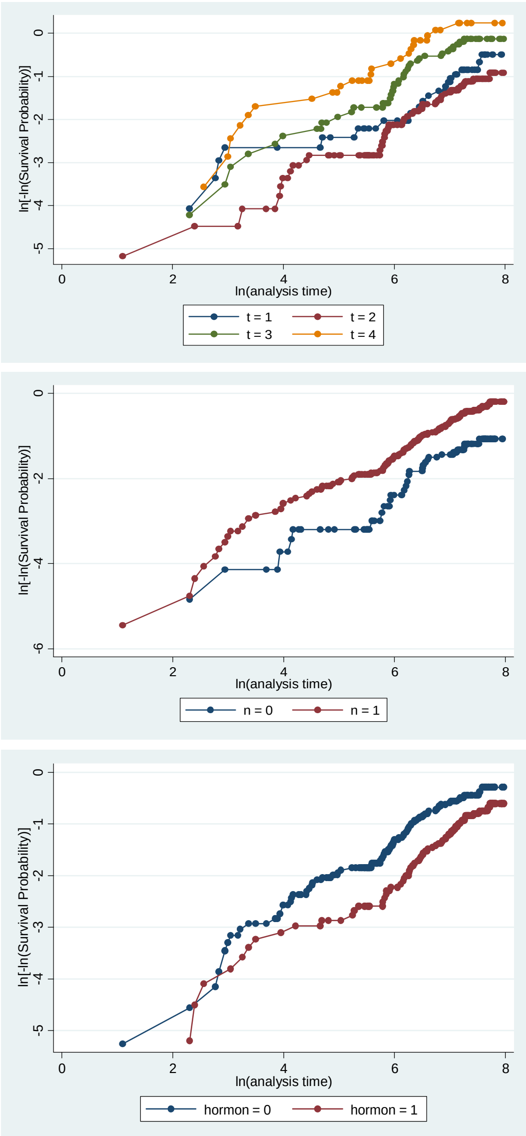

Figure 2. Distribution recognition of time to event

Before fitting PH model, the validity of the proportionality assumption must be check (13). This model, has the requirement of PHs, which has been satisfied by data (14). If the log-log survival for each group against the survival time was a parallel function, it would mean that the PH assumption holds (Figure 3) (13).

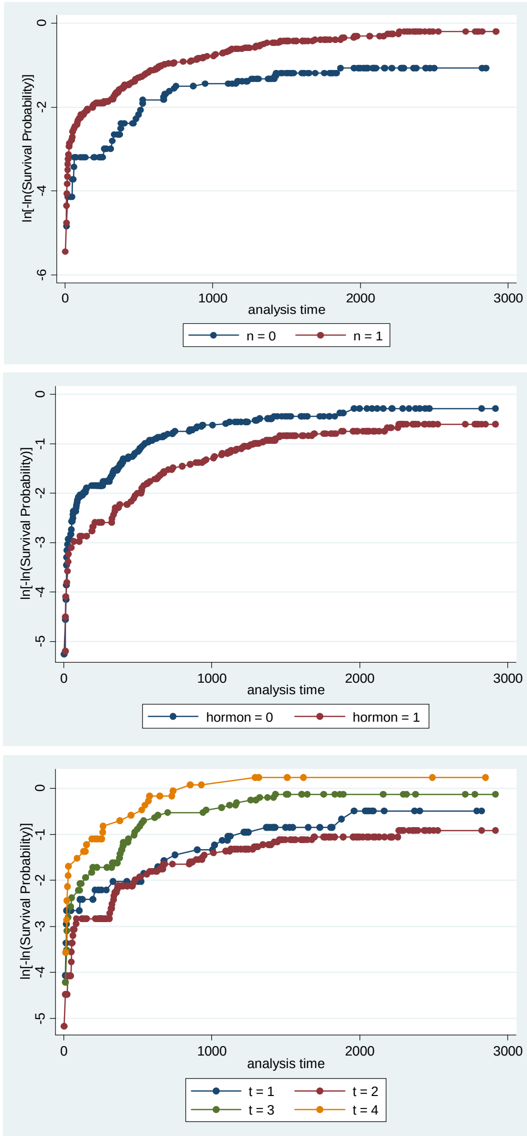

Figure 3. Graphical test of proportional hazard functions

If parallel straight lines were seen, the model is Weibull and PH and AFT assumptions hold. Otherwise, if lines, were parallel but not straight lines, AFT Weibull cannot be considered, instead, PH cox model can be used (1).

In these situations, parametric models or AFT model provide an alternative framework to fit the data. In this study, the PH and AFT assumption have been satisfied by data, so both models can be used in the analyzing. Parametric form of PHs, such as PH Weibull model, beside the AFT Weibull model been considered. Notice that the result under the different methodologies are not directly comparable because the AFT models measure the direct effect of covariates on the survival time while the PH model explains the effect of covariates on the hazard function (5,12-15). But if both models were correct inferential, analysis should agree in terms of the significance of the covariates (13).

Base on the PH and AFT models, tumor characteristics has increased the risk of recurrence or, in the other words, has decreased the survival time, according to the AFT model. The measure of stretching or reducing between survival in several groups is indicated, with acceleration factor, that as follows, is shown $\gamma = \exp(\alpha)$. If the acceleration factor, more than one, the survival rate has increased compared with baseline and viz.

Conflict of Interests

The Authors have no conflict of interest.

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