Short Communication

J Babol Univ Med Sci
Vol 20, Issu 5; May 2018. P: 74-80

Assessment of AFT and Cox Models in Analysis of Factors Influencing the survival of Women with Breast Cancer in Yazd city

H. Fallahzadeh (PhD)[1], M. Mohammadzadeh (MSc)[1], N. Pahlavani (MD) [2], Sh. Taghipoor (PhD)[3], V. Pahlavani (MSc)[•1]

1. Department of Biostatistics and Epidemiology, Faculty of Health, Shahid Sadoughi University of Medical Sciences, yazd, I.R.Iran
2. Faculty of Medicine, Kashan University of Medical Sciences, Kashan, I.R Iran
3. Department of Pathology, Shahid Sadoughi University of Medical Sciences and Health Services, yazd, I.R.Iran

J Babol Univ Med Sci; 20(5); May 2018; PP: 74-80

Received: Aug 9th 2017, Revised: Dec 2nd 2017, Accepted: Dec 25th 2017.

ABSTRACT

BACKGROUND AND OBJECTIVE: Breast cancer is one of the most common cancers in women. The statistical methods in the survival analysis of these patients are accelerated time models and Cox model. The purpose of this study is to evaluate two models in determining the effective factors in the survival of breast cancer.

METHODS: The study was an analytical and cohort study of survival analysis. The 538 of the patients referred to Ramezanzade Radiotherapy Center who had breast cancer and recorded survival status as a census from the April 2005 until March 2012 in Yazd. and survived by phone call. The Kaplan-Meier estimate was used to describe the survival of the patients. The research variables included clinical and demographic factors. The choice of final variables in the model was done by the methods of diminishing the dimension and all possible Cox regressions by the acaian criterion. Then, the best accelerated time model was considered Getting different distributions was also determined by the Akayake criteria.

FINDINGS: The most effective Cox model among all Cox models was variables including Age, Her2 and Ki67 variables (AIC=30270). The generalized gamma model was the most optimal accelerated time model (AIC 463.966). Her2 was significant in both accelerated and cox models ($p<0.05$), but the Ki67 variable was not significant. ($p>0.05$).

CONCLUSION: In both accelerated time- Generalized Gamma- models and Cox Models, the Her2 variable was identified as a risk factor for breast cancer and There is a positive impact on the risk of death and reduced survival.

KEY WORDS: *Breast Cancer, Ki-67 Antigen, HER2/neu protein, Survival Analysis*.

Please cite this article as follows:

Fallahzadeh H, Mohammadzadeh M, Pahlavani N, Taghi poor Sh, Pahlavani V. Assessment of AFT and Cox Models in Analysis of Factors Influencing the survival of Women with Breast Cancer in Yazd city. J Babol Univ Med Sci. 2018;20(5):74-80.

•Corresponding Author: **V. Pahlavani (MSc)**
Adress: Faculty of Public Health, Shahid Sadoughi University of Medical Sciences and Health Services, yazd, I.R.Iran.
Tel: +98 35 37241742
E-mail: vida.pahlevani@yahoo.com

Introduction

Cancers are chronic diseases that in many societies have had a high rate of death in recent decades. Cancer treatments in addition to several side effects are generally costly and response rate to treatments are not usually complete (1). In the meantime, breast cancer is the most common cause of death in women aged 44-40 in many advanced and developing countries, and is also the second leading cause of cancer death after lung cancer (2). It is estimated that deaths from cancer will reach 13.1 million in 2030, with early diagnosis and control of risk factors can lead to 40% of decrease in deaths from cancer. Breast cancer is the abnormal proliferation and malignant in breast tissue cells, which is generally divided into in situ carcinoma (non-invasive) and invasive cancer (3).

According to the latest statistics, the incidence of breast cancer in Iranian women is 27.5 per thousand. The 5-year survival rate in these patients ranges from 48% to 84% in total and overall survival is 72% (4). This cancer is a type of hormone-related disease and malignant proliferation of epithelial cells that cover the ducts or lobules (5). In Iran, 16% of all cancers are related to breast cancer, which is ranked first among women (6). Therefore, in our country, especially in the last few decades, the recognition of the most important factors in the prevention of breast cancer as well as the treatment of this disease has been seriously addressed by medical centers (7).

In this study, two tumor markers Ki67 and Her2 were used for a novel treatment method. Generally, survival analysis is a set of statistical methods for analyzing data whose outcome variable is the time to occurrence of a particular event. The time spent in survival analysis can be the number of years, months, weeks or days from the onset of an individual's follow-up to the event.

It can also be considered the age of an individual when an event occurs. An incident in survival analysis may be death, illness, relapse after recovery, recovery (for example, return to work), or any other possible experience that may occur to the individual. In survival analysis, we usually call the time variable a survival time, because this determines the duration of a person's "survival" during the follow-up period (8). In most medical research that aims to assess the survival distribution, methods such as Cox regression are used. The unnecessary probability distribution for survival times is an important feature of this semi-parametric model, but the assumption that the risk fit for all predictor variables in the final model is an important and fundamental assumption for this model (9). If the assumption is made, the interpretation of the obtained model will be simpler than the parametric models. So far, many studies have been conducted using the Cox regression model, but according to a systematic study, only 5% of these studies have considered the appropriateness of hazards (10). If assumptions are made, parametric models have more robust analysis than Cox's semi-parametric model. In these models, survival times have a certain probable distribution, such as Wybol, Exposure, Normal Log and Log Logic (11). Having a probability distribution for the survival times will make the statistical deduction more precise and reduce the standard deviation of the estimates than when there are no assumptions (12).

Many studies on breast cancer have been carried out around the world and in Iran, and in most medical research centers, more studies are still in the focus of attention, which expresses this vital need for public health, especially for women (13). In this study, various parametric survival distributions including exponential, Weibull, logging, normal log, generalized Fisher, and generalized gamma and pseudo-parametric Cox model were tested on the data (14) and based on the Akaike model, the final model was selected and factors influencing breast cancer survival were determined. The basic software for survival analysis in this study is R, and the flexsurvreg and survival packages were used to complete the analysis of the model's relevance (15). The aim of this study was to identify the most important prognostic factors of breast cancer and their effect on the survival time of patients using accelerated and coaxial time models.

Methods

This analytical and survival analysis study was conducted in August of 2016 after approval by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, with code IR.SSU.SPH.REC.1395.64. Firstly, a checklist containing the characteristics of the patients and all the factors examined (age, size of the tumor, lymph node involvement, primary metastasis, disease stages, pathology, vascular and neurological invasion, gradient, tumor markers (Her2, ER, PR, Ki67) Lymph nodes removal, involved lymph nodes, opposite breast involvement, type of breast surgery (mastectomy or BCT), accompanying treatments (post-operative radiotherapy, post-operative chemotherapy, hormone therapy), subject recurrence, distant metastasis , the incidence and survival of patients, and the presence of connective tissue disease) was prepared and then the survival status of all 538 patients diagnosed with breast cancer referring to the Shaheed Ramezanzadeh Radiotherapy Center in Yazd were recorded from 2005-2012 by phone call. Kaplan-Meier estimates were used to describe the survival of patients. Regarding the Ki67 protein, there is always a discussion that has a positive or negative effect on patient survival. The Ki67 gene is a proto-oncogene that is active in the process of cell proliferation. 20% of breast cancers are Her2 positive. Breast cancer with Her2 gene amplification in the Fish Test or overexpression in the IHC Test is called Her2 +, which responds to Her2 receptor blocker drugs such as Herceptin (16).

Before performing the survival regression, due to the high number of predictor variables for entering the model, firstly exploratory factor analysis is used to identify correlated predictor variables and to avoid coherent consequences in regression and reduce the dimension of data (17). Therefore, the variables considered by the expert physician especially the tumor markers were also considered in their linearity. Finally, according to the results of factor analysis and expert physician opinion, seven variables including Her2, ki67, estrogen receptor (ER), age (less than 40 or more than 40 years old), surgical procedure (mastectomy or BCT), stage of disease (initial or advanced), lymph node involvement (or not) were considered as a risk factor for the survival time of breast cancer.

In regression modeling, instead of simultaneously accommodating these seven variables and preventing the complexity of the final model, we first fitted all possible sub-models of them (including a model with principal effects and second-order interactions) using Cox regression and a model whose AIC value was lower than the others was chosen as the most efficient Cox model. In the next step, accelerated time models were fitted with different survival distributions including exponential models, Weibull, Normal logs, generalized gamma, generalized Fisher, and logistic fit on variables that were present in the most optimal Cox model (18) and the optimal acceleration time model was selected using the Akaike test and the likelihood ratio test. The Akaike criterion was presented by Akaike in 1974 to assess the goodness of fitting models and is defined as follows:

$$AIC = -2 \{\log (likelihood)\} + 2 (a + c)$$

In the above formula, a is the number of model parameters and c is a constant coefficient that is different from that of the applied model, and the lesser akaike criterion means better fitting (19). Modeling and data analysis were performed using flexsurvreg, muhaz, survMisc, survival and graphic charts with the survminer package under the R software version 3.4.0 (20). In all tests, p <0.05 was considered as a significant level.

Results

In this study, 538 patients with breast cancer were included in the study, of whom 109 died of the disease (20.3%). The incident in this study was death due to breast cancer. In Table 1, we report descriptive statistics, and in Kaplan Meyer's graph, Figure 1 shows the two variables Her2 and Ki67. The results of this test have been presented to evaluate the survival curves of raw materials.

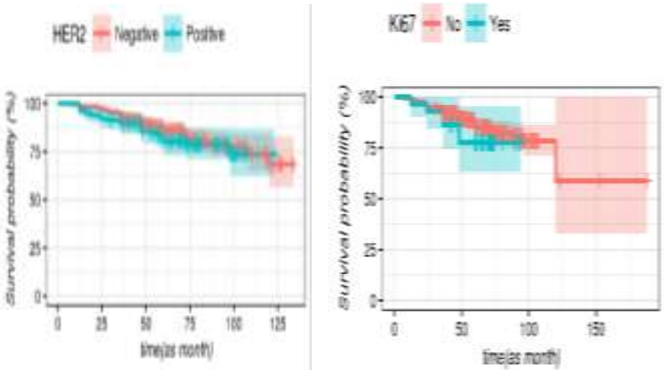

Figure 1. Kaplan-Meier charts for the two variables Her2 and Ki67

After single analyzing of variables and their meaningful raw materials to achieve the best subset of the variables studied on survival of breast cancer, in the next step, using Cox regression, all of the following sub-models of these seven variables (including the model with the main effects and Double-order interactions were fitted. As a result, a model that included the main effect of Her2, Ki67, age, and interactions of their second order was the lowest possible AIC among all 127 possible models. (AIC=330/718). Since the interaction between age and Ki67 was significant (p = 0.0103), the model was layered according to age. To investigate the Cox model hazards suitability assumption based on Schoenfeld test was used (21). The results of the test showed that the assumption of the appropriateness of the risks was established (Global P-value = 0.176).

After fitting the Cox model on this subset of the variables, we expanded the accelerated time models by taking into account the various survival distributions mentioned in the material and methods section on the data that the accelerated gamma-accelerated time model expanded the minimum AIC in other models. (AIC 463/98) and was chosen as the best model among accelerated time models (Table 2).

Table 1. Frequency of patients with breast cancer in terms of the variables affecting the disease

Risk Factors		N(%)	Average survival time (standard error) per month	P-value* (Fleming-Harrington)
age	<40 years	132(24.5)	84.81(6.17)	0.374
	≤40 years	132(75.5)	86.98(3.98)	
Esterogen receptor(ER)	positive	264(62.6)	104.24(4.31)	0.078
	negative	158(37.4)	90.97(7.29)	
Ki67	positive	287(90.8)	87.74(4.45)	0.826
	negative	29(9.2)	87.26(8.22)	
Lymph node involvment	does not have	176(33)	102.48(6.26)	0.024 ¥
	has	357(67)	98 .16(3.58)	
Breast surgery method	BCT	312(85)	100.71(3.43)	0.008
	mastectomy	226(42)	93.52(3.80)	
Her2	Positive	115(30.7)	48.13(3.94)	0.97
	negative	259(69.3)	78.06(2.48)	
stage	Initial stage	100(18.6)	78.06(2.48)	0.075
	Advanced stage	438(81.4)	67.12(3.77)	

¥ P-value with Renyi correction for cross-survival curves, * Significant level (0.05) for the Flemington Herrington test

Table 2. Classification of estimates for the Cox regression and generalized gamma

Risk factor		Cox model (PH)		Generalized Gamma model (AFT)	
		HR(CI-95%)	P-value	RR(CI-95%)	P-value
Her2	+	2.141(1.067-4.394)	0.031*	0.421(0.280-0.635)	0.001*
	-	1		1	
Ki67	+	0.908(0.3-275)	0.875	0.771(0.339-1.491)	0.44
	-	1		1	
AIC		302.707		463.976	

Discussion

In this study, the effect of Her2 variables was significant in both accelerated time and cox models. The most important finding of this study is the positive effect of Her2 on the risk of death and reduced survival time. According to the Cox model, the risk of death from breast cancer for patients with Her2 positive is 14.2 times that of Her2 negative patients. This study was also confirmed in other studies. Also, according to the generalized gamma model, patients with negative Her2 57.9% had a longer life span than patients with Her2 (22). There has always been a lot of disagreement over the role of Ki67 (23). In the study of Nishimura et al., higher Ki67 was associated with a higher degree of malignancy and lower survival(24). However, in a study by Bryan et al., no association was found between Ki67 and androgen receptor (25). In this study, the Ki67 effect was not significant. This can be due to the low number of deaths in subgroups of age and the reduced test power. Khodabakhshi et al. in a study during 2005 to 2007 on 153 women with breast cancer in Tehran concluded that the risk of death of Her2 positive patients was 1.64 more than patients with negative Her2 (26). This can be attributed to the use of the breakdown of age groups in the research analysis mentioned in the present study. Also, the mean age and mean survival time in the meta-analysis of yektakoshali et al. were consistent with our study (27). Cox models and accelerated time models are the most effective models that are in accordance with the goal of the researcher. If the aim of the study is to compare the risk of patients, the Cox model, and if the goal is to compare their survival time, accelerated time models are more valid. The important point is that you cannot compare the AIC coefficients of cox models and accelerated time. Because the Cox method is a semi-parametric one and it uses a slight likelihood ratio in the construction of AIC, while all the observations are used to construct AIC for accelerated time models. It can be concluded that the Cox and accelerated models are complementary and have different interpretations, each of them is used according to the purpose of the investigator. It is also recommended to use the accelerated time model while simpler interpretation, when appropriate assumption of hazards does not exist in the Cox model. According to the results of this study, Her2 variable was considered as a risk factor in both models and had a positive effect on the risk of death and reduced survival.

Acknowledgment

Hereby, we would like to thank the cooperation of the Shahid Sadoughi University of Medical Sciences as well as the Ramezanzadeh radiotherapy center in Yazd.

References

1. Nelson HD, Fu R, Cantor A, Pappas M, Daeges M, Humphrey L Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 us preventive services task force recommendationeffectiveness of breast cancer screening. Ann Intern Med. 2016;164(4):244-55.

2. moslemi d, gholizadeh pasha a, hajian k, sum sh, pourghasem m, jahantigh r. comparison of treatment outcomes between breast conserving surgery followed by radiotherapy and mastectomy alone in patients with t1-2 stage and 1-3 axillary lymph nodes in the era of modern adjuvant systemic treatments.j babol univ med sci. 2012;14(5):36-41. [in persian].

3. Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, et al. Breast cancer in Iran: an epidemiological review. Breast J. 2007;13(4):383–91.

4. Harirchi I, Ebrahimi M, Zamani N, Jarvandi S, Montazeri A. Breast cancer in Iran: a review of 903 case records. Pub Health. 2000;114(2):143-5.

5. Harirchi I1, Karbakhsh M, Kashefi A, Momtahen AJ. Breast cancer in Iran: results of a multi-center study. Asian Pac J Cancer Prev. 2004;5(1):24-7.

6. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. Cancer Epidemiol. 2015;39(4):519-27.

7. Kiaei M, Ferdosi M, Moradi R, Chelongar Q, Ahmadzadeh MS, Bahmanziari N. Association between self-efficacy and quality of life in women with breast cancer undergoing chemotherapy. J Qazvin Univ Med Sci. 2016;20(2):58-65. [In Persian].

8. Klein JP, Moeschberger M. Survival analysis: techniques for censored and truncated data. Springer Science & Business Media; 2005.

9. Cox DR, Oakes D. Analysis of survival data.1st ed. CRC Press; 1984.

10. Klein JP, Van Houwelingen HC, Ibrahim JG, Scheike TH. Handbook of survival analysis. CRC Press; 2016.

11. Cleves M. An introduction to survival analysis using Stata. Stata Press; 2008.

12. Kabacoff RI. R in Action. manning; 2010.

13. Moghaddam SE, Barzegar A, Nikbakhsh N. Study of the regulatory promoter polymorphism (- 938c> a) of b-cell lymphoma 2 gene in breast cancer patients of mazandaran province in northern iran. J Res Med Sci. 2017; 22: 21.

14. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Med Res Methodol. 2013;13(1):152.

15. Harrell Jr FE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Springer; 2015.

16. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American society of clinical oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25(33):5287-312.

17. Cureton EE, D'Agostino RB. Factor analysis: An applied approach. Psychology press; 2013.

18. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. Stata J. 2009;9(2):265.

19. Efron B. Logistic regression, survival analysis, and the Kaplan-Meier curve. J Am Stat Assoc. 1988;83(402):414-25.

20. Therneau TM, Lumley T. Package "survival." Verze; 2017.

21. Bennett S. Analysis of survival data by the proportional odds model. Stat Med. 1983;2(2):273-7.

22. Ansaripour A, Uyl-de Groot CA, Redekop WK. Adjuvant Trastuzumab Therapy for Early HER2-Positive Breast Cancer in Iran: A Cost-Effectiveness and Scenario Analysis for an Optimal Treatment Strategy. Pharmacoeconomics. 2018;36(1):91-103..

23. Vera-Badillo FE, Chang MC, Kuruzar G, Ocana A, Templeton AJ, Seruga B, et al. Association between androgen receptor expression, Ki-67 and the 21-gene recurrence score in non-metastatic, lymph node-negative, estrogen receptor-positive and HER2-negative breast cancer. J Clin Pathol. 2015;68(10):839-43.

24. Nishimura R, Osako T, Okumura Y, Hayashi M, Toyozumi Y, Arima N. Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer. Exp Ther Med. 2010;1(5):747-54.

[DOR: 20.1001.1.15614107.1397.20.5.10.6]

[DOI: 10.18869/acadpub.jbums.20.5.74]

25. Bryan RM, Mercer RJ, Bennett RC, Rennie GC, Lie TH, Morgan FJ. Androgen receptors in breast cancer. Cancer. 1984;54(11):2436–40.

26. Khodabakhshi R, Reza Gohari M, Moghadamifard Z, Foadzi H, Vahabi N. Disease-Free survival of breast cancer patients and identification of related factors. Razi J Med Sci. 2011;18(89).

27. YektaKooshali MH, Esmaeilpour-Bandboni M, Sharemi SH, Alipour Z. Survival Rate and Average Age of the Patients with Breast Cancer in Iran: Systematic Review and Meta-Analysis. J Babol Univ Med Sci. 2016;18(8):29-40. [In Persian].