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Original Article

Survival Prognostic Factors of Male Breast Cancer Using Appropriate Survival Analysis for Small Sample Size: Three Center Experience

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ABSTRACT

Introduction: Breast cancer in men is a rare disease that has been increasing in recent decades. Identifying factors influencing the survival rate of these patients is particularly important considering the small sample size. The aim of this study was to present the results of the conventional Cox- LASSO method and compare it with the newer refined generalized log-rank (RGLR) method for analyzing survival data with a small sample size.

Methods: Available information related to men with breast cancer referred to 3 treatment centers in the country (Iran) between 2012 and 2020 were reviewed. Cox-LASSO and RGLR models were fitted on the data. The analyzes were done using R.4.1.2 software and the significance level of 0.05 was considered.

Results: About 60% of the conflicts are reported on the left side. About 53% of men have been diagnosed at a low stage. The tumor size of 75% of the patients was between 2 and 4.3. Most patients have received modified radical mastectomy (MRM) treatment and adjuvant radiotherapy. 80% of patients had received chemotherapy and most had received anthracycline-taxane base. According to Akaike's criterion, RGLR model (AIC=289.32) was better than Cox-LASSO (AIC=314.76) model. Results of RGLR model indicated that, age (p-value= 0.038, HR >50 vs <50 = 6.75, 95% CI: 2.70–17.30), left laterality (p-value = 0.019, HR left vs right = 3.45, 95% CI: 1.48–8.02), larger tumor size (p-value=0.033, HR T2 vs T1 = 3.70, 95% CI: 2.92–6.68; HR T3 vs T1 = 4.34, 95% CI: 3.17–5.95), higher tumor grades (p-value<0.001, HR grade 2 or 3 vs grade1 = 8.67, 95% CI: 5.10–14.71), are influential factors decreasing male breast cancer patient's survival.

Conclusion: Although the results of the two existing models in the field of small sample size survival analysis (Cox-LASSO and RGLR) are close to each other, the RGLR model has performed better than the Cox-LASSO. With smaller AIC and SE of parameter estimation, RGLR model was choose compared to Cox-LASSO model.

Introduction

Male breast cancer (MBC) is a rare disease; however, its incidence has been slowly increasing in the past two decades.[1] As MBC is a rare disease, there is a lack of prospective studies especially in clinical trial phases.[2] In Iran, MBC incidence rate increased from 36 to

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120 over 1990-2019.[3] Due to the low awareness of people in different communities about the signs and symptoms of this disease, it is often diagnosed late and has a high morbidity and mortality rate.[4]

In recent decades, studies have been conducted to better understand this disease and classify its risk factors for better prognosis. In these studies, some factors such as demographic, clinical and pathological factors have been investigated.[5-7] In addition to the risk factors related to the occurrence of the disease, one of the main goals of treating male breast cancer, like other cancers, is to increase the life expectancy of patients.[8] Researchers have always used different methods of analyzing the life span of patients to find factors affecting the survival rate of patients. Survival analysis has always been developed to achieve the most accurate statistical models to help researchers.[9] Types of Cox models are among the most well-known survival analysis methods. These models are based on assumptions and most researchers need a relatively large sample size to obtain high accuracy in fitting these models. Considering that most of the sample size in studies related to MBC are small, in these studies, the appropriate model of survival analysis should be used to fit when the sample size is small. In 1997, Tibshirani et al proposed the Cox LASSO model to analyze survival times when the sample size is less than the risk factors under consideration.[10] In 2018, Rengyi Xu et al proposed a refined generalized log-rank (RGLR) model for survival analysis in cases of sample size less than 40.[11] The latest introduced model has less bias in parameter estimation than parametric and non-parametric Cox models. This method of analysis is used in studies to investigate the survival of patients in clinical trials as well as observational studies with the aim of investigating the survival of patients in rare diseases. In cases of small sample size, in addition to lower bias, this model has more relative efficiency than Cox models.[11]

In this study, we applied both proposed methods for survival analysis with small sample size on male breast cancer data in three cancer centers in Iran and compared the results.

Methods

In the form of a retrospective study, the files in three cancer treatment centers in Iran were reviewed. Due to the cooperation of these centers in the research plan, three centers were included in the study. Patients between September 2013 and September 2020, referred to Shohadaye Tajrish hospital, Tehran, Iran, were included in study. Also, patients from Shahid Sadoughi hospital, Yazd, Iran, from September 2012 to February 2020, and patients from Mehraneh cancer center, Zanjan, Iran, between March 2012-February 2020 were included in this study. All patients' races were white.

The variables studied were general characteristics including the patient age at diagnosis, marital status, and residence, family history of Breast Cancer, history of alcohol use, history of smoking and history of benign tumor, clinical characteristics including nipple discharge, nipple ulceration, nipple retraction, skin fixation, skin retraction, skin redness, palpable axillary lymph node and arm swelling, pathological characteristics including tumor size, histological grade, axillary lymph node involvement, laterality, chest wall invasion and staging and treatment characteristics including

surgery, adjuvant radiation, chemotherapy, chemotherapy regimen and type of endocrine therapy. In some cases, telephone contacts were made to complete the information about survival data and death times. The tumor stage was based on the 6th American Joint Committee on Cancer (AJCC) criteria and grading followed Notting-ham modification of the Bloom- Richardson system.

Descriptive statistics of these four categories of patient characteristics were summarized using SPSS software. Also, the survival time of the disease and the factors affecting the survival rate were investigated using two models presented for the analysis of survival data with a small sample size. LASSO – Cox model and RGLR models were fitted on the data. Akaike's criterion was used to compare the two models and analyzes were performed using R.4.1.2 software. Some packages like survival, perm, truncdist, mvtnorm were used. Right censor was applied from the final day to those who survived the study period, and other certain deaths for those who were lost to follow up. P-value less than 5% was considered significant.

Results

In total, 34 patients were studied, 14 patients lived in Tehran, 11 patients lived in Zanjan, and 9 patients lived in Yazd. About 76% of men are over 50 years old when the disease is diagnosed. About 40% of patients have a history of this disease in their families. Most of the patients did not have nipple discharge (83.3), nipple ulceration (77.7), nipple retraction (83.3), skin fixation (83.3), skin retraction (77.7), skin redness (72.2), palpable axillary lymph node (77.7), arm swelling (91.3) problems (table1). About 60% of the conflicts are reported on the left side. About 53% of men have been diagnosed at a low stage. The tumor size of 75% of the patients was between 2 and 4.3. Most patients have received MRM treatment and adjuvant radiotherapy. 80% of patients had received chemotherapy and most had received anthracycline-taxane based (table2).

According to Akaike's criterion, RGLR model (AIC=289.32) was better than Cox-LASSO (AIC=314.76) model. Results of RGLR model indicated that, age (p-value= 0.038), left laterality (p-value = 0.019), larger tumor size (p-value=0.033), higher tumor grades (p-value<0.001), are risk factors that affect the survival of male breast cancer patients. Higher age (HR >50 vs <50 = 6.75, 95% CI: 2.70–17.30), Left Laterality (HR left vs right = 3.45, 95% CI: 1.48–8.02), larger tumor size (HR T2 vs T1 = 3.70, 95% CI: 2.92–6.68; HR T3 vs T1 = 4.34, 95% CI: 3.17–5.95), higher tumor grades (HR grade 2 or 3 vs grade1 = 8.67, 95% CI: 5.10–14.71), were associated with significantly higher risks of cancer-related death (table3).

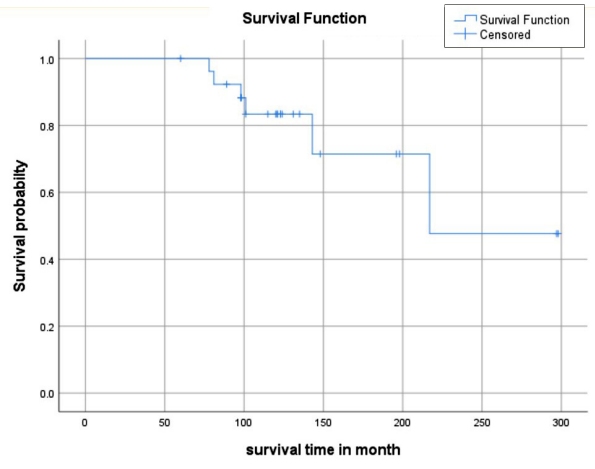

Figure1. Kaplan-Meier estimate for the survival curve of Male Breast Cancer data

Table1. General and Clinical characteristics of MBC patients

General characteristics	n (%)	Clinical characteristics	n (%)
Age (n=34)		Nipple Discharge (n=18)	
<49	8 (23.5)	No	15 (83.3)
50 – 59	6 (17.6)	Yes	3 (16.7)
60-69	7 (20.6)	Nipple Ulceration (n=18)	
>70	13 (38.3)	No	14 (77.7)
Residence (n=34)		Yes	4 (22.3)
Tehran	14 (41.1)	Nipple Retraction (n=18)	
Zanjan	11 (32.4)	No	15 (83.3)
Yazd	9 (26.5)	Yes	3 (16.7)
Family history of Breast Cancer (n=32)		Skin Fixation (n=18)	
No	19 (59.4)	No	15 (83.3)
Yes	13 (40.6)	Yes	3 (16.7)
History of Alcohol Use (n=32)		Skin Retraction (n=18)	
No	29 (90.7)	No	14 (77.7)
Yes	3 (9.3)	Yes	4 (22.3)
History of Smoking (n=32)		Skin Redness (n=18)	
No	17 (53.1)	No	13 (72.2)
Yes	15 (46.9)	Yes	5 (27.8)
Marital status (n=34)		Palpable Axillary Lymph Node (n=27)	
Married	30 (88.2)	No	21 (77.7)
Single	4 (11.8)	Yes	6 (22.3)
History of Benign tumor (n=14)		Arm Swelling (n=23)	
Negative	13 (92.9)	No	21 (91.3)
Positive	1 (7.1)	Yes	2 (8.7)

Table 2. Pathologic and Treatment characteristics of MBC patients

Pathologic characteristics	n (%)	Treatment characteristics	n (%)
Stage (n=34)		Surgery(n=30)	
0	18 (52.9)	Simple mastectomy	6 (20.0)
I (Well)	5 (14.8)	Modified radical mastectomy (MRM)	19 (63.3)
II (Moderately	9 (26.4)	Breast conserving surgery	2 (6.7)
III (Poorly)	2 (5.9)	No surgery	3 (10.0)
Tumor size (n=33)		Adjuvant radiation (n=34)	
<2 cm	4 (12.1)	Yes	22 (64.7)
2 – 4.9 cm	25 (75.8)	No	12 (35.3)
>4.9 cm	4 (12.1)	Chemotherapy (n=34)	
Histological Grade (n=32)		Yes	30 (88.2)
Grade 1	17 (53.1)	No	4 (11.8)
Grade 2 or 3	15 (46.9)	Chemotherapy regimen (n=30)	
Laterality (n=34)		Anthracyclin-taxane based	21 (70.0)
Left	19 (55.9)	Adriamycin, cyclophosphamide, pacliatxel, trastuzumab, pertuzumab	9 (30.0)
Right	13 (38.2)	Type of endocrine therapy (n=31)	
Bilateral	2 (5.9)	Tamoxifen	16 (51.6)
Chest Wall Invasion (n=33)		Anastrozole and leuprolide	13 (42.0)
No	18 (54.5)	Fulvestrant and leuprorelin	2 (6.4)
Yes	15 (45.5)		
Axillary Lymph Node Involvement (n=32)			
No	19 (59.4)		
Yes	13 (40.6)		

Table 3. Probable Prognostic Factors of Survival in Male Breast Cancer Patients by LASSO-Cox and RGLR Methods

	n (%)	LASSO – Cox AIC = 314.76		RGLR AIC = 289.32	
		Beta (SE)	HR*	Beta (SE)	HR
Age (34)		0.028**		0.038	
<50	8 (23.5)	-	-	-	-
>50	26 (76.5)	1.26 (2.19)	3.52	1.91 (0.48)	6.75
Family history of Breast Cancer (n=32)		0.105		0.139	
No	19 (59.4)	-	-	-	-
Yes	13 (40.6)	0.16 (2.61)	1.17	-0.13 (1.84)	0.87
Laterality (n=32)		0.021		0.019	
Right	13 (40.6)	-	-	-	-
Left	19 (59.4)	1.67(2.96)	5.31	1.24 (0.43)	3.45
Axillary Lymph Node Involvement (n=32)		0.157		0.264	
No	19 (59.4)	-	-	-	-
Yes	13 (40.6)	0.21 (2.09)	1.23	0.14 (1.84)	1.15
Stage (n=34)		0.167		0.108	
0	18 (52.9)	-	-	-	-
I (Well)	5 (14.8)	0.18 (1.32)	1.19	0.26 (1.07)	1.29
II (Moderately	9 (26.4)	0.28 (1.46)	1.32	-0.16 (1.02)	0.85
III (Poorly)	2 (5.9)	0.02 (2.9)	1.02	0.09 (1.18)	1.09
Tumor size (n=33)		0.083		0.033	
T1: <2 cm	4 (12.1)	-	-	-	-
T2: 2 – 4.9 cm	25 (75.8)	0.19 (1.04)	1.20	1.31 (0.12)	3.70
T3: >4.9 cm	4 (12.1)	0.32 (1.35)	1.38	1.47 (0.16)	4.34
Histological Grade (n=32)		0.002		<0.001	
Grade 1	17 (53.1)	-	-	-	-
Grade 2 or 3	15 (46.9)	2.52 (3.38)	12.42	2.16 (0.27)	8.67

*Hazard Ratio
** P-value

Discussion

Survival analysis was performed using two existing models for analyzing the survival times of rare patients, LASSO-Cox and RGLR. The results of the analysis of the male breast cancer in Tehran, Zanjan and Yazd showed that age, laterality, tumor size and grade, have significant effects on the survival rate in men with breast cancer.

Considering the smaller Akaike's criterion and the standard errors of the parameter estimation in the RGLR model compared to LASSO-Cox, it can be said that the first model provides a more accurate estimate of the factors affecting the survival rate of these patients.

In Shahraki et al.'s study, the standard errors values of the LASSO-Cox method were smaller than the standard Cox method, and they concluded that in cases such as male breast cancer, where the sample size is often small, it is better to use the LASSO-Cox model to identify factors affecting the survival rate of patients.[12] In this study, the LASSO-Cox method was compared with the newer RGLR method, and the use of both methods is suggested for a more detailed investigation. The results of these two methods are close

to each other, and more extensive studies are needed for further investigations, what is certain is that the use of these two methods is much more accurate than the conventional methods of survival analysis such as Cox and in analyzing data with sample size it is better to use these methods.

Among the factors identified in the present study, the study by Shahraki et al., who used the Lasso method, is similar to the present study in terms of factors such as age, tumor size, and grade.[12] However, in the study of Salehi et al., other factors have been defined, and the results are not in line with the present study.[13] Different studies, such as Salehi's study, have not used the appropriate method to analyze the survival of men with breast cancer, and therefore the contradiction in the results can be attributed to this.[14] Considering the effect of tumor size and stage on the survival rate of patients, it seems that early detection of this disease in men can be effective in increasing the survival rate as well as in women.[15]

One of the limitations of this study was the lack of sufficient information on the important BRCA genes of the patients,[16] as well as details of the treatment and their effects on the survival rate of the patients. It is suggested that in future studies, the effects of BRCA genes on the survival rate of patients should be investigated using the two suitable models presented.

Considering the few studies in the field of male breast cancer,[17] it is suggested that clinical trials be launched and implemented in different centers in the country, and by sharing data and using appropriate survival analysis methods, effective factors can be extracted.

Conclusion

Survival analysis is required in small sample size data, which are common in studies of rare diseases and early phase clinical trials. Thus, it is important to have methods that provide efficient hazard ratio estimation, control type I error and maintain confidence interval coverage in small sample settings. Although the results of the Cox-LASSO and RGLR models are close to each other, the RGLR model has performed better than the Cox-LASSO. With smaller AIC and SE of parameter estimation, RGLR model was choose compared to the Cox-LASSO model. Therefore, according to the results of the present study, we recommend that the RGLR method be examined and compared next to LASSO-Cox method.

Acknowledgments

Not applicable

Conflict of Interests

The authors of this article hereby declare that we have no conflict of interest in writing, ordering the names of the authors, and publishing the article.

Ethics

This study has been approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.316).

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