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Joint Frailty Modeling for Multiple Recurrent Events and Its Application in Patients with Breast Cancer

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ABSTRACT

Aims Breast cancer is one of the most prevalent recurrent cancers among women. Several factors affecting multiple recurrences of this disease have been studied and recognized in various studies. One of the various types of models used to analyze recurrent events considering the lack of homogeneity among patients is a frailty model. The aim of the present study was to investigate joint frailty modeling for multiple recurrent events and its application in patients with breast cancer.

Materials and Methods In this survival and retrospective analysis, 342 patients with breast cancer whose records were registered for follow-up in a Cancer Research Center at Shohadaye Tajrish Hospital, Tehran, Iran, from 2006 to 2015, were selected. The sampling method was purposive. These patients were monitored for at least 6 months after diagnosis and their latest statuses. For data analysis, the joint frailty survival model was used. Running the model and conducting the data analysis were performed by codes in Frailtypack using R 3.4.1 statistical software.

Findings Three-year and five-year survival rates for the patients were 0.79 and 0.68, respectively. The risk of multiple recurrences (Local and metastases) increased for the patients with tumor grades greater than I. It was found that when neglecting the relationship between multiple recurrences in the patients with breast cancer, a significant correlation was missed.

Conclusion With regard to the significant variance of the frailty component of the metastases event, the patients with the same predictive variables are prone to different levels of metastases risk.

Keywords Breast Cancer; Frailty; Retrospective Study; Metastases

CITATION LINKS

[1] Estimating the world cancer burden: Globocan 2000 [2] Breast cancer in Iran: Results of a multi-center study [3] AMechanisms of bone metastases of breast cancer [4] Automated quantitative analysis of E cadherin expression in lymph node metastases is predictive of survival in invasive ductal breast cancer [5] Regulation of collagenase-3 expression in human breast carcinomas is mediated by stromal-epithelial cell interactions [6] Brain metastases in breast cancer: Prognostic factors and management [7] Human oestrogen receptor cDNA: sequence, expression and homology to v-erb-A [8] Quantitative analysis of changes in ER, PR and HER2 expression in primary breast cancer and paired nodal metastases [9] Analysis of repeated events [10] Shared frailty models for recurrent events and a terminal event [11] On the regression analysis of multivariate failure time data [12] Regression analysis of multivariate incomplete failure time data by modeling marginal distributions [13] Analysis of risk factors for psoriasis recurrence using proportional rates model [14] Marginal regression models for multivariate failure time data [15] Survival and event history analysis: A process point of view [16] Estimation of seasonal effect on the psoriasis recurrence using time dependent coefficient rates model for recurrent events [17] Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials [18] Joint frailty models for recurring events and death using maximum penalized likelihood estimation: Application on cancer events [19] Cerebral metastases in metastatic breast cancer: Disease-specific risk factors and survival [20] Breast cancer in Iran: A survival analysis [21] Recurrence in breast cancer, analysis with frailty model [22] The role of prognostic factors on breast cancer recurrence in patients at radiation oncology ward in Imam Hossain hospital [23] Defining prognosis for women with breast cancer and CNS metastases by HER2 status [24] Separate and combined analysis of successive dependent outcomes after breast-conservation surgery: Recurrence, metastases, second cancer and death

Introduction

Breast cancer, after lung cancer, is the leading cause of cancer death in women and, after skin cancer, it is the most prevalent cancer among women [1]. Besides the high prevalence rate of breast cancer among Iranian women, this fact that 16% of all cancers in Iran are related to breast cancer and that Iranian women, compared with women in developed countries, develop this disease at least a decade earlier [2] double the importance of studying this issue.

One of the possible complications of breast cancer after conducting a treatment (Surgery) is either metastases or local recurrence of the disease and it is observed that the primary causes of death in breast cancer are tumor invasion and metastases [3, 4]. Despite notable advances in the diagnosis and treatment of breast cancer, a high mortality rate and incidence of metastases breast cancer in affected women treated by performing a surgery and applying necessary treatments still remain as medical issues [5]. Various studies have indicated that patients with metastases had shorter lifespans compared to other patients [6]. On the other hand, metastatic recurrence of the disease decreases a patient's physical and mental dimensions of quality of life. Therefore, recognizing factors affecting the incidence of metastases and examining the relationship between the two types of recurrences, i.e. metastases and local recurrences, among patients with breast cancer is very important in the process of identifying and treating this disease [7]. Different factors affecting the incidence of metastases have been studied and recognized in number of studies [8]. However, being aware of these factors alone cannot predict the onset of metastases since some of these factors are individual-specific, are attributed to personality and environmental characteristics, and establish a correlation among the incidences of different recurrent events in patients. Due to the existence of such factors, despite the similarity between two patients in terms of predictive factors, a patient, compared to the other, becomes more or less likely to develop various types of recurrences like metastases or local recurrence.

In many longitudinal medical studies, each person can experience an event, such as a recurrence of a tumor in various parts of the body, several times. The times of these recurrent events are inherently interdependent. Objectives related to analyzing such recurrent events can include describing the status of recurrent events in people, changing the recurrence rate of a process from a person to another person, and investigating the relationship of fixed dependent variables or time-dependent variables with the occurrence time of recurring events. These objectives can be verified by models associated with analyzing recurrent events. Due to their ability to conduct a simultaneous investigation of two processes of recurrent events and to achieve unbiased and efficient estimates for parameters, in survival analyses, joint models are applied for analyzing follow-up studies including carrying out a simultaneous examination of two survival events [9].

The simplest way of analyzing recurrent events is only to consider the first occurrence for each patient and use Cox's proportional hazards model for just one of the events. This is a direct method and it avoids considering complexities such as the effect of the first event on the risk of the occurrence of the next event. Furthermore, only considering the first event is not satisfactory for evaluating the natural history of the disease and examining the effects of therapeutic interventions. Additionally, by the sole consideration of the first event, this kind of analysis does not apply all available data and does not estimate all advantages of performing a therapeutic approach correctly. Various models have been presented to fit data on recurrent events which are all essentially generalizations of the Cox's proportional hazards model. In addition, in studies where several failures occur during the follow-up period, there are always individual factors which create a correlation between the time of the occurrence of events in the same people and the reason for the differences among people (Dispersion among individuals).

Standard survival models, like the Cox's proportional hazards model, ignore the effects of unobserved individual factors and lead to an incorrect estimation of model parameters. In recent studies, a random component was used to express these unknown factors and correlations among the incidence of recorded events in a patient. This random component is known as frailty. Frailty often expresses a random effect and unobserved correlations and dispersions in survival data. Accordingly, joint modeling is suitable for such a condition, since it is able to study two processes at the same time and achieve unbiased and efficient estimates for parameters to analyze several follow-up studies [10]. On the other hand, people may be exposed to more than one recurrent event during their lifetime with the disease. Since data related to recurrent events have existed in most medical longitudinal studies and, sometimes, more than one type of recurrent events have been considered in these studies, a multivariate joint frailty model was proposed in the current study for analyzing such data and examining hazard functions of various types of recurrent events with respect to the effect of frailty. The complexity of the mentioned modeling was that it simultaneously modeled two types of recurrences, i.e. local and metastases recurrences.

The aim of the present study was to investigate joint frailty modeling for multiple recurrent events and its application in patients with breast cancer.

Materials and Methods

This is a survival and retrospective analysis, in which all patients with breast cancer were considered as a statistical population who referred to Shohadaye Tajrish Hospital, Tehran, Iran from 2006 to 2015. During the years, patients with definite diagnoses of breast cancer were studied and examined in a cancer ward at the hospital as a historical cohort. The data were extracted from the patient's medical records. Their latest conditions in terms of the recurrence of the disease were recorded by this center via telenursing.

The inclusion criterion was following-up at least 6 months after the surgery. It should be noted that alive patients who, at the end of the study, did not experience any local and metastases events and patients who, after a certain period of time, provided no data about their survival statuses were eliminated from the study. Finally, by eliminating variables overlapped with the results of the study, the final sample size was considered 342 patients. The sampling method was purposive. In this historical cohort study, all patients with definite pathological diagnosis whose records could be used were included in the study.

In the study, variables were age, diagnosis time, family history of breast cancer, tumor size, levels of the involvement of lymph node removed after surgery, metastases, surgical type, tumor grade, estrogen receptor levels, progesterone receptor levels, undergoing a chemotherapy, the stage of the disease, and the time until local and metastases recurrences.

The following hazards model was used for modeling joint recurrent events:

$$h_{1i}\left(t_{1ij}\right) = h_1\left(t_{1ij}\right) \exp\left(\beta_1^T Z_i^L + \theta_{1i}\right)$$

$$h_{2i}(t_{2ij'}) = h_2\left(t_{1ij}\right) exp(\beta_2^T Z_i^{(D)} + \theta_{2i})$$

In this model, $h_1\ (t)$ and $h_2\ (t)$ are basic hazard functions for local and metastases recurrences in i^{th} person, respectively. Moreover, $Z^{(L)}$ and $Z^{(D)}$ are auxiliary vectors for local and metastases recurrences, respectively. Furthermore, $\beta_1{}^T$ and $\beta_2{}^T$ are vectors for corresponding regression parameters. Specific parameters to each part are bivariate frailties logarithms $\{(\theta_{1i}, \theta_{2i})\}_{i=1}^{n}$ which are patient-specific. In this regard, θ_{1i} and θ_{2i} indicate frailties. These frailties can demonstrate that patients with higher levels of frailty, compared to others, are more prone to the risk of recurrence. The effects of θ_{1i} and θ_{2i} work on the time of recurrence type 1 (T_1) and the time of recurrence type 2 (T_2). Hence, it was assumed that effects of these two types of recurrences were not the same. Finally, a bivariate normal distribution for $\{(\theta_{1i}, \theta_{2i})\}$ was presented as follows:

$$N\left(\begin{pmatrix}0\\0\end{pmatrix},\begin{pmatrix}\sigma_1^2 & \rho\sigma_1\sigma_2\\ \rho\sigma_1\sigma_2 & \sigma_2^2\end{pmatrix}\right)$$

It should be noted that, in this study, a frailty pack was applied via the R statistical software version 3.4.1 for running the joint frailty model and estimating the parameters using a maximum penalized likelihood estimation.

A total of 342 patients were investigated as the sample. Univariate and multivariate analysis were conducted on these patients. Using Kaplan-Meier estimator, a median of disease-free survival time (the time till the occurrence of the first recurrence after surgery is known as disease-free survival time) for breast cancer patients was estimated. The joint frailty model was fitted with an approximated basic hazard function using smoothing methods. The maximum penalized likelihood estimation was applied for estimating the parameters. The maximum likelihood estimation was used for models with a fixed basic hazard function.

The data were analyzed by codes in Frailtypack using R 3.4.1 statistical software.

Findings

The patients aged 22 to 84 years with the statistical mean age of 47.84±11.75 years, and a median of 47.81 years. The median follow-up time was 113 months. Among these 342 patients under study, 87 patients (25.4%) experienced the incidences of recurrences and the other 255 patients (74.6%) did not experience such recurrences (Table 1).

The median disease-free survival time was 30.57 months with a minimum of 6 months and a maximum of 187 months. Disease-free one-year, three-year, and five-year survival rates were 96%, 79%, and 68%, respectively (Table 2).

Given the results obtained from the fitted model, the risk of local and metastases recurrences was higher in the patients with at least one N+ lymph node and/or in the patients with a tumor grade of greater than 1.

Moreover, no significant difference was found in terms of the risk of death between the patients who were younger than 40 years old and those who were older than 60 years old. However, there was a slightly significant difference between the patients aged 40 to 60 year old and the patients older than 60 years old.

The risk of multiple local and metastases recurrences was higher in the patients who were younger than 40 years old compared to the patients who were older than 60 years old.

Furthermore, the tumor size (>20mm) had a significant effect on the risk of recurrences. The risk of multiple local and metastases recurrences was higher among patients with HER2+ (Table 3).

Table 1) Frequency distribution of independent variables among the patients with breast cancer (n=342; the numbers in parentheses represent percentage)

Variables	Frequency
Family history	
None	233 (68.1)
Immediate family member	52 (15.2)
Extended family member	57 (16.7)
Tumor size (mm)	
<2	72 (21.0)
2-5	211 (61.7)
>5	59 (17.3)
Stage of the disease	
Stage 1	44 (12.9)
Stage 2	168 (49.1)
Stage 3	121 (35.4)
Stage 4*	9 (2.6)
Chemotherapy	
Yes	330 (96.5)
No	12 (3.5)

Table 2) Statistical average of the disease-free one-year, three-year, and 5-year survival rates of the patients with breast cancer

Follow-up time	Survival probability
One-year	0.96±0.01
Three-year	0.79±0.03
Five-year	0.68±0.03

Survival probability: The time till the occurrence of the first recurrence after surgery is known as disease-free survival time

Table 3) Results of the joint frailty modeling for multiple recurrent events, local recurrence, and metastases recurrence in the breast cancer patients

Variables	Hazard Ratio (HR)	95%CI
Local recurrence		
Age (years)		
≤40	2.86	1.76-4.64
40-50	1.32	0.94-1.86
Reference group: >55		
Tumor grade		
II	2.79	1.53-5.09
III	4.79	1.33-3.17
Reference group: Grade I		
Tumor size (mm)		
≥20	1.61	1.15-2.25
Reference group: <20		
HER2+		
Yes	1.83	1.18-2.82
Without a reference group		
Metastases		
Age (years)		
≤40	2.81	1.31-6.03
40-50	0.8	0.49-1.29
Reference group: >55		
Tumor grade		
II	1.63	1.15-2.3
III	4.56	2.26-9.2
Reference group: Grade I		
Tumor size (mm)		
≥20	5.92	2.53-13.86
Reference group: <20		
HER2+		
Yes	2.19	1.1-4.34
Without a reference group		
θ=var(ui) (SE)	1.1	0.11
η=var(vi) (SE)	7.39	0.63

Discussion

The aim of the present study was to investigate joint frailty modeling for multiple recurrent events and its application in patients with breast cancer.

In the survival analysis literature, different methods were proposed for estimating recurrent events of a type. Conditional models [11] and marginal models [12] were all presented for analyzing recurrent events of a type. These models are based on modeling a hazard function. Despite the advancement in methods of analyzing data on recurrent events of a type, methods used to analyze recurrent events of several types, including nonhomogeneous Poisson processes by using random and fixed effects with inferential procedures, are all based on the maximum likelihood estimation [13] Such parametric methods require identifying the correctness of the considered in Pearson correlation structure which is difficult to achieve for multiple recurrent events. Semi-parametric robust methods are desirable when a correlation structure is not considered. Marginal regression models for multivariate failure time data was proposed by Spiekerman and Lin [14] and Aalen *et al.* [15] and can be generalized to the analysis of multiple recurrent events [16].

In the present study, in order to simultaneously consider two recurrent events and to achieve more accurate results, the joint frailty model was used for modeling multiple recurrent events and the maximum penalized likelihood estimation was applied for estimating the hazard functions. This approach is also consistent with informative censoring of recurrent events. The proposed model showed that there was a correlation between the two types of recurrences. This method also can cover the relationship between recurrent events and the terminal event. It can be indicated that this method is better for practical situations and is better and more efficient compared to applying two separated models (Having a separate joint frailty model for each type of recurrences). On the other hand, also this method considers the correlation between events and unobserved heterogeneity in data. As inferred from the concept of joint frailty models, a joint frailty component can improve the fitness of a model. In addition, ignoring it when fitting a model, can cause an impairment in the fitness of the model. Another advantage of this proposed model is that the effects of various covariates are evaluated by two types of hazard functions. These variables can be independent of time and/or time-dependent. Generally, there are several reasons for using frailty models to provide time to recurrence responses, include achieving an overall possible correlation by applying a bias correction for a regression coefficient in survival analysis and whether one or both types of recurrences can be used as an alternative endpoint.

Accordingly, of the fitted model, it can be concluded that the risk of local recurrence was associated with the risk of metastases. Although Wapnir *et al.* [17] demonstrated the relationship between local recurrence and death [17], when there was a significant difference in a subgroup of patients, a frailty model can be used to evaluate such heterogeneity in the population under study. Used of the frailty component in Cox's relative hazards model leads to a more accurate assessment of regression coefficients and the effect of individual characteristics of patients is also included in the model. Several studies have used the frailty model for data analysis [18]. A number of authors have also applied the frailty model to analyze data on breast cancer [19].

In the present study, the mean age of the patients was 47.81 years, which is consistent with findings of other studies that carried out in Iran. According to studies, the mean age of breast cancer patients is between 45 and 50 years. The age distribution of women with breast cancer in Iran indicates that the diagnosis age is lower in Iran compared to that in Western Europe and North America. This means that Iranian women are more likely to suffer from this disease earlier. This was confirmed by a number of studies examined the issue in Iran [20, 21]. The median disease-free survival time in this study was 30.57 months and the five-year survival rate for the patients was 68%. In the study carried out by Mirzaei *et al.*, [22] a disease-free 5-year lifespan was reported to be 77.3%. HER2+ was not considered as a prognostic factor for metastases recurrence in the frailty model in patients; however, some studies indicated that it can be regarded as a prognostic factor in the recurrence of metastases [23]. The degree of tumor malignancy was recognized as a significant factor in the prognosis of local and metastases recurrences in the patients, which is in line with the results of study that conducted by Rondeau *et al.*, [24] showing that patients with the first-degree malignancy had more survival rate than patients with the second-degree and third-degree malignancy. Moreover, during the follow-up period of the patients, none of the two events, i.e. death or metastases, were observed in the patients with the first-degree malignancy. In some studies, the tumor size was proved to be a prognostic factor for patients' survival rate [21].

In the current study, tumor size was also significant in the joint model for two types of local and metastases recurrences. The variance in the distribution of frailty in the above model for local recurrence was 1.1, which did not differ significantly with the value of 1 and for metastases recurrence, this value was 7.39, it was indicated that only the effect of auxiliary variables did not determine the state of recurrence of the disease and individual characteristics were also effective in the recurrence of tumors. In other words, the effect of unknown variables or variables that are not included in the model was also important in predicting metastases recurrences of the disease and these factors, a small part of which are individual characteristics of patients, play significant roles in predicting the patients' statuses. In a study conducted by Gohari *et al.*, [21] the variance of frailty was 0.31 and in the study that carried out by Rondeau *et al.*, [18] it was 0.35. This suggested a high degree of non-homogeneity among breast cancer patients participating in this study compared to those participating in the studies conducted by Gohari *et al.* [21] and Rondeau *et al* [18].

With regard to the results obtained from fitting the joint frailty model used for analyzing the data on the patients with breast cancer, it can be concluded that even the patients with the same explanatory variables presented different risks of metastases recurrence. Similarly, in a sample selected from a large population of women with breast cancer, it was inferred that there was a positive relationship between multiple recurrences among the patients. In other words, it can be stated that the presented model used in the current study for modeling the data set converged correctly.

In this study, a small number of both types of local and metastases recurrences were observed. Therefore, the random effects of u_i and v_i reflected the relationship between the two types of recurrences rather than the interpersonal dependence of the patients. In this particular case, achieving the independence of the two answers (Multiple recurrences) may be difficult. Since this study included a small number of recurrent events, cautions should be exercised when considering the obtained data.

According to few numbers of recurrent events observed in the application, several multistate models could be investigated. Contrary to the frailty modeling, multistate modeling does not directly provide information about the dependence between events of interest.

Conclusion

With regard to the significant variance of the frailty component of the metastases event, the patients with the same predictive variables are prone to different levels of metastases risk.

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