➜ **Original Article**

Assessing the Effect of Carcinoembryonic Antigen Tumor Marker Progression on Survival after Mastectomy in Patients With Breast Cancer: A Joint Survival Longitudinal Approach

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Abstract

Background: Breast cancer remains the most prevalent neoplasm in women, with more than 450 000 deaths each year, worldwide. In cancer researches, several factors such as serum tumor markers have an important role in screening, treatment, and recurrence of the disease. Carcinoembryonic antigen (CEA) is one of the most widely used serum tumor markers in the clinical evaluation of patients with breast cancer. This study aimed to evaluate whether increasing serum CEA levels is an indicator of breast cancer patient's survival or not.

Materials and Methods: This retrospective study was done at Hematology Department of Shafa Hospital of Ahvaz, southwest of Iran. Only those patients who had mastectomy during 2006-2014 and regularly referred to the hospital were included. The joint survival longitudinal model was applied to analyze the data. JM package in R software was used for joint modeling analysis.

Results: The five-year survival rate was 73.0%. Age and follow-up time were associated with CEA tumor marker values. Higher age is associated with higher CEA values over time ($P=0.0156$). There was a significant linear increasing trend in CEA values over time ($P=0.0465$). There was a significant difference between patients with and without nodal involvement (HR [95% CI]: 1.880 [1.330-5.565]; $P=0.0298$). There was a positive correlation between CEA tumor marker levels and death (HR [95% CI]: 2.770 [1.369-5.603]; $P=0.0046$).

Conclusion: Higher age is associated with higher CEA values over time. The involvement of lymph nodes increases the hazard of death. Death is more likely to occur in patients with higher CEA tumor marker levels.

Keywords: Breast cancer, Carcinoembryonic antigen (CEA), Joint modelling of longitudinal, Survival data

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Introduction

Worldwide, breast cancer remains the most prevalent neoplasm in women, with more than 1 300 000 new cases and 450 000 deaths each year (1, 2). It is the second and third cause of death in developed and less developed countries, respectively (3). According to the GLOBOCAN 2018 report, 13 776 new cases and 3526 cancer deaths occurred in Iran (4). Breast, colorectal, stomach, and esophageal cancers are the most frequent cancers among Iranian women (5). The estimated disability adjusted life years (DALYs) rate attributed to all neoplasms in both sexes had a descending trend from 1990 to 2010, worldwide (6, 7). However, in patients with breast cancer, DALYs increased from 167 in 1990 to 174 in 2012, and Iranian women also showed increasing DALY rates from 1990 to 2013 (7, 8).

Although the incidence of breast cancer has risen in recent years, the application of biotechnologies in the last decade has improved the survival rates of patients (9, 10). Most of the patients undergo mastectomy as treatment and also receive other treatments such as chemotherapy, hormone therapy, or radiation before or after surgery

(11, 12). If the treatment protocol failed, the survival rate might be affected (11, 13). Therefore, choosing the best treatment with a lower failure rate is very important. Seeking a reliable prognostic factor may lead to better prognosis and improvement in decision-making process.

In cancer researches, several pathological factors such as involvement of lymph nodes, tumor grade, tumor size, hormone receptor status, human epidermal growth factor receptor 2 (HER2) expression, and serum tumor markers have important roles in screening, treatment, and recurrence of the disease (14-16). Carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA15-3) are the most frequently used tumor markers which are used in the clinical evaluation of patients with breast cancer. The prognostic value of these tumor markers in patients with breast cancer has gained much attention in recent studies (17-19). Since the variation of serum CEA level is an important indicator of cancer progression, it should be monitored in a systematic manner.

In many medical studies, time to an event (death, recurrence, and recovery) is the primary outcome. Survival analysis is a suitable statistical method that could estimate the median "time to event" and identify the relationship between covariates and survival time. Some of the predictors were measured repeatedly over time because of the effect of their fluctuations on survival time. These predictors were considered as secondary outcome measures because they are influenced by other risk factors at the same time. In this setting, separate analyses of longitudinal predictors and survival data may result in biased estimates (20, 21). Using the joint survival longitudinal model, one can include all information from the two processes simultaneously and estimating unbiased results (22, 23). However, serum CEA levels were measured repeatedly over time and to assess the relationships between serum CEA fluctuations across follow-up time and post-mastectomy survival, joint modeling was considered to be a suitable statistical modeling method. In chronic disease researches, it is common to use the joint modeling method to explore the relationship between longitudinal measurements and time to event outcome (24-26). This study is one of the first efforts aimed at evaluating whether increasing serum CEA level is an indicator of a patient's survival after (mastectomy) surgery in patients with breast cancer or not.

Materials and Methods
Study Setting and Participants
This retrospective study was conducted at Hematology Department of Shafa Hospital of Ahvaz, southwest of Iran. Only those patients who underwent mastectomy during 2006-2014 were included. A total of 112 patients were included in the study. Time to death after mastectomy and CEA tumor marker levels were the primary outcomes. Patients' information was obtained from the

hospital records. Other required data such as clinical characteristics measured at a pathobiology laboratory on each visit were also recorded.

Statistical Analysis
As illustrated, the joint survival longitudinal model was applied. Joint survival longitudinal models could be divided into two sub-models. First, the linear mixed effects model (LME) is used for modeling the longitudinal predictor. The proportional hazards (PH) Cox model to model the survival time is the second sub-model. These sub-models link together via a shared parameter as follows:

To illustrate the joint model, let Yit (CEA tumor marker level) denote the tth repeated observation for ith patient under study (I = 1, 2,…, n; t = 1, 2,…, Ti) and Xit and Zit are the p and q-dimensional (q ≤ P) covariate vectors (age, grade, …) for the fixed and random part of the model. Thus, for analyzing the longitudinal part of the joint model, the linear mixed effect (LME) model can be written as:

$$y_i(t) = m_i(t) + \varepsilon_i(t)$$
$$m_i(t) = x_i^T(t)\beta + z_i^T(t)b_i$$

Where β is a fixed effects parameter and b is a q dimensional random effect. ε_i shows the error term; $\varepsilon_i(t) \sim N(0, \sigma^2)$ and $b_i \sim N(0, D)$.

Let T indicate the survival time after mastectomy and w is the predictors (age, lymph node involvement, and so on). The Cox proportional hazards model will be written as:
$$h(t) = h_0(t) \exp[\gamma w + \alpha\, y_i(t)]$$

Where h_0 is the baseline hazard, γ is the parameter vector and α is the association parameter which indicates the association between the CEA levels and time to event process. In the joint survival longitudinal framework, the association parameter must have a significant effect (20, 21).

Mastectomy time was considered as the beginning of the event process ($T_{i0} = 0$). Baseline covariates in the joint model included age at diagnosis, estrogen receptor status, grade, and lymph node involvement. We were also interested in the rate of change of CEA over time; therefore, the time since mastectomy was considered as a covariate in the sub-model of the longitudinal process. JM package in R software version 3.5.1 was used for joint modeling (22).

Results
In this retrospective study, a total of 112 patients were studied. The mean ± SD age at diagnosis was 46.52 ± 9.87 years and the mean of follow-up time was 105.53 months. The baseline characteristics of the patients are presented in Table 1. The five-year survival rate was at least 80.0%. Kaplan-Meier (KM) method was applied for preliminary

Table 1. Patient's Characteristics

Variable	Statistics
Age at diagnosis (y), mean ± SD	46.52 ± 9.87
Follow-up time (mon), mean ± SD	105.53 ± 6.77
Grade; No. (%)	
I	12.00 (10.70)
II	30.00 (26.80)
III	70.00 (62.50)
Estrogen receptor (positive), No. (%)	75.00 (67.00)
Lymph node involvement (yes), No. (%)	68.00 (60.70)

Table 2. Results of the Joint Modeling Analysis

Variable	Estimate (95% CI)	P Value
Longitudinal sub-model		
Age at diagnosis (y)	0.01 (0.003-0.03)	0.015
Follow-up (mon)	0.01 (0.0001-0.02)	0.046
Grade		
I	-	-
II	0.31 (-0.22-0.84)	0.252
III	0.19 (-0.29-0.68)	0.441
Estrogen receptor (positive)	0.25 (-0.50-0.55)	0.102
Variable	**HR (95% CI)**	**P-value**
Survival sub-model		
CEA marker	2.77 (1.36-5.60)	0.004
Age at diagnosis	0.95 (0.86-1.05)	0.377
Grade		
I	-	-
II	0.29 (0.03-2.89)	0.297
III	0.09 (0.01-0.85)	0.035
Lymph node involvement (yes)	1.88 (1.33-5.56)	0.029

analysis of survival time. KM graph is shown in Figure 1. Table 2 presents the joint model results. Age and follow-up time were significantly associated with the values of CEA tumor marker in patients with breast cancer. Higher age is associated with higher CEA values over time ($P = 0.015$). There was a significant linear increasing trend in CEA values over time ($P = 0.046$).

Age at diagnosis did not have any significant effect on time to death. There was a significant difference between patients with and without nodal involvement (HR [95% CI]: 1.88 [1.33-5.56]; $P = 0.029$). In patients with nodal involvement, the hazard of death increases by about 88.0%. In addition, there was a positive correlation between CEA tumor marker levels and death (HR [95% CI]: 2.77 [1.36-5.60]; $P = 0.004$), which means that death is more likely to occur in patients with higher CEA tumor marker levels.

Discussion

According to the latest cancer data, cancers of the lung and female breast are the leading types worldwide in terms of the number of new cases; for each of these types, approximately 2.1 million diagnoses were reported in 2018, contributing about 11.6% of the total cancer

incidence burden (27). The number of women with breast cancer seems to be increasing (9). The increasing incidence rate of breast cancer shows that it is a significant medical and social problem in Iran.

This study applied the joint modeling method to investigate the role of patient's characteristics in CEA fluctuations within the follow-up time and evaluate the association between the CEA levels and death after mastectomy.

To the best of our knowledge, a few prior studies have studied the factors that affect the CEA levels over time (28). Results show that the time to death was not significantly correlated with the patient's age. In the current study, the CEA tumor marker levels significantly increased over time. The patient's age was associated with CEA tumor marker values. The findings of the current study in the longitudinal sub-model regarding time, age, estrogen receptor status, and grade are consistent with those of other studies (28). A statistically significant relationship between age and the CEA levels was found in some reports (28). In our research, no significant association was found between the tumor grade and the CEA values. A previous study also found similar results (28).

The main finding of the current research is the direct association of CEA tumor marker levels and death after mastectomy. This direct association shows that death after mastectomy is more likely to occur in patients with higher CEA tumor marker levels. For one unit increase in the CEA level, an increased risk of death up to 5.60 times is estimated. Therefore, measuring CEA levels has an important role in monitoring the patient's status after mastectomy. There is agreement between other studies regarding the role of the CEA level in the likelihood of experiencing death after mastectomy (28).

The main advantage of the current research was the investigation of the determinants of both the longitudinal CEA tumor marker measurements and the time to death outcomes following mastectomy, as well as the evaluation of the correlation between the CEA levels and death
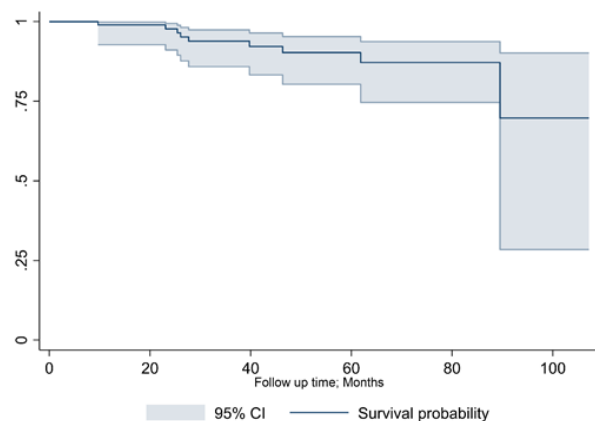
Figure 1. Kaplan-Meier Survival Plot for Death as the Survival Event.

through the simultaneous joint model.

One of the main limitations of this research was the lack of similar works. To the best of our knowledge, there is only one similar study for comparing the result of our research. Another limitation was related to the lack of a well-established medical registry for monitoring patients with cancer.

Conclusion

If the association between the longitudinal process and survival process is not suitably taken into account, bias can occur. Bias could affect results and inferences drawn from the model. Therefore, it is obvious that the utilization of joint models to study the association between the survival of the patients and the longitudinal progression of the CEA tumor marker values yields more reliable results. According to the joint survival longitudinal approach, death is more likely to occur in patients with higher CEA tumor marker levels.

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