ORIGINAL ARTICLE

Application of additive hazards models for analyzing survival of breast cancer patients

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Background: Survival rates for breast cancer (BC) are often based on the outcomes of this disease. The aim of this study was to compare the performance of three survival models, namely Cox regression, Aalen's, and Lin and Ying's additive hazards (AH) models for identifying the prognostic factors regarding the survival time of BC patients. **Materials and Methods:** This study was a historical cohort study which used 1025 females' medical records that underwent modified radical mastectomy or breast saving. These patients were admitted to Besat and Chamran Hospitals, Tehran, Iran, during 2010–2015 and followed until 2017. The Aalen's and Lin and Ying's AH models and also traditional Cox model were applied for analysis of time to death of BC patients using R 3.5.1 software. **Results:** In Aalen's and also Lin and Ying's AH models, age at diagnosis, history of disease, number of lymph nodes, metastasis, hormonal therapy, and evacuation lymph nodes were prognostic factors for the survival of BC patients ($P < 0.05$). In addition, in the Lin and Ying's AH model tumor size ($P = 0.048$) was also identified as a significant factor. According to Aalen's plot, metastasis, age at diagnosis, and number of lymph nodes had a time-varying effect on survival time. These variables had a different slope as the times go on. **Conclusion:** AH model may yield new insights in prognostic studies of survival time of patients with BC over time. Because of the positive slope of estimated cumulative regression function in Aalen's plot, metastasis, higher age at diagnosis, and high number of lymph nodes are important factors in reducing the survival BC, and then based on these factors, the therapists should consider a special therapeutic protocol for BC patients.

Key words: Additive hazards model, breast cancer, metastasis, survival analysis

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INTRODUCTION

Nowadays, cancer is one of the most important health problems in the world.[1] It is a serious and prevalent problem that all of the countries of the world are faced with.[1,2] In 2018, 18.1 million cancer cases and 9.6 million cases of death due to cancer were estimated from around the world.[3] In 2015, breast, lung, and colorectal cancers were the most common cancers,[1,2] and in 2018, breast, colorectal, and lung cancers were the most commonly diagnosed cancers.[3]

Breast cancer (BC) is the most common type of cancer diagnosed in women and is the main cause of cancer-related death in females in 2015[1,2] and also in 2018.[3] BC was ranked second and fifth in terms of incidence and mortality worldwide, respectively. It alone comprises 11.6% of all cancers and 6.6% of cancer-related deaths, the leading cause of cancer-related death in over 100 countries worldwide.[3]

BC has a high incidence rate in the world.[3] This cancer is growing in South America, Africa, and Asia. BC is increasing in incidence among Southeast Asian women and also West Europe.[4]

In Iran, cancer is the third leading cause of deaths after injuries and cardiovascular diseases, accounting for more than 53,000 annual deaths. Current evidences suggest

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that stomach, breast, prostate, leukemia, and lung are the most common incident cancers in both sexes in Iran.[5] BC is the most common cancer occurring among Iranian women as well as in those from other countries. Similar to that in the Middle East countries, the mean age of BC diseases in Iran is 10 years lower than that in the developed countries.[6]

The survival of patients with BC was dependent on access to medical facilities and BC screening.[7] In the recent decade, prevention, early diagnosis, and proper treatment had improved survival rate of cancer.[7-9]

The main goal of survival analysis is to investigate and model the probable relationship between risk factors and the death time of a patient. When the response variable usually is time to death, disease recurrence, or metastasis, there are three major approaches to analysis of the data: (a) Cox proportional hazards as a semiparametric;[10] (b) parametric functions such as Weibull, Gompertz, and log-normal;[11] and (c) nonparametric methods such as Aalen's additive risk model and Kaplan–Meier method.[12] Survival analysis has traditionally been performed using the Cox model and preferred by most researchers.[13] This model is simple to fit, and the results are easy to explain, but there are two potential drawbacks: proportionality and ignoring the effect of time-varying covariate.[14-16] In contrast, the Aalen's additive model is nonparametric and propounds time-varying covariates.[16,17] Unlike the PH model which estimates hazard ratios, in the additive model, the difference in hazards is used to describe the association between the risk factors and disease occurrence.[17,18]

This study aimed to compare the performance of three survival models, namely Cox regression, Aalen's, and Lin and Ying's additive hazards (AH) models for identifying the prognostic factors regarding the survival time of BC patients.

MATERIALS AND METHODS

Patient population

This study was a historical cohort study which used data gathered from medical records of 1025 BC patients who were admitted to Besat and Chamran Hospitals, Tehran, Iran, during 2010–2015 and followed until 2017. Females with a confirmed diagnosis of BC who underwent either modified radical mastectomy (MRM) or breast saving (BS) from 2010 to 2015 were enrolled in the study. This study approved by the Ethics Committee, affiliated to University of Social Welfare and Rehabilitation Sciences (IR.USWR.REC.1399.050).

Data collection

Data were gathered from patients' medical records and histopathology reports by trained data collectors. Age at diagnosis, number of lymph nodes, tumor size, family history (no, yes), Stage (I, II, III, IV), Grade (I, II, III), metastasis (no, yes), human receptor of epidermal growth factor 2 (minus, plus), excapsular (no, yes), evacuation lymph nodes, history of disease (no, yes), estrogen receptors (minus, plus), progesterone receptors (minus, plus), pathology report (ductal carcinoma *in situ*, invasive carcinoma, both), hormonal therapy (no, yes), and surgery (MRM, BS) variables were gathered through patient's medical records. Finally, time to death was considered from the date of surgery (MRM/BS) to the date of current status (death/censoring).

Statistical analysis

At first, preprocessing of the data was made on Excel software, and the cases with missingness in these variables or unknown current status were excluded. After that, almost all of the patients had chemotherapy and radiotherapy. Hence, these variables exclude from the analysis. After that, the sample size was decreased to 933. Subsequently, by performing a univariate analysis, all variables with $P < 0.2$ were selected for modeling. By this strategy, age at diagnosis, number of lymph nodes, tumor size, metastasis, excapsular, evacuation lymph nodes, history of disease, hormonal therapy, and kind of surgery variables were selected for multiple analysis.

Finally, the Aalen's and Lin and Ying's AH models and also Cox proportional hazards model, as a traditional model, were applied for data analysis. In this way, the Schoenfeld residual plot was used to evaluate the proportionality assumption of Cox model. A nonzero slope is an indication of a violation of the proportional hazard assumption. Moreover, 95% pointwise confidence intervals were used to estimate cumulative regression functions based on Aalen's additive model. An estimated cumulative regression function plot (Aalen's plot) is obtained to see the effect of covariates over time. The smoothed line in the Aalen's plot with a slope was approximately equal to zero, suggesting that there may be no time-varying effect, and this is in agreement with the test. The slope of an estimated cumulative regression function is positive when covariate increases, and this fact corresponds to an increasing hazard rate. On the other hand, if the slope is negative while the covariate increases, then this fact points to a decreasing hazard rate. Data analysis was carried out with *survival* and *addhazard* packages in R 3.5.1 software. In this sense, *coxph*, *survfit*, *ah*, and *aareg* functions were used to fit the models. $P < 0.05$ was considered statistically significant.

Cox proportional hazards model

In the analysis of censored failure time observations, the standard Cox proportional hazards model assumes that the regression coefficients are time independent. This model, also known as the Cox model, has the form:

$$\lambda\left(t \mid Z(t)\right) = \lambda_0(t)\exp\left(\beta' Z(t)\right) = \lambda_0(t)\exp\left(\sum_{j=1}^{p}\beta_j Z_j(t)\right) \quad (1)$$

where λ (t | Z) is the hazard at time t given predictor values $Z = (Z_1, Z_1, \ldots, Z_p)$ and $\lambda_0(t)$ is an arbitrary baseline hazard function and β is unknown time-independent parameters.

In the Cox proportional hazards model, the effect of the covariates acts multiplicatively on the baseline hazard rate, and the hazard for each covariate is assumed to be constant over time.[12]

LIN AND YING'S ADDITIVE HAZARDS MODEL

This model is semiparametric AH, and the effect of covariates is additive on the baseline hazard rate. According to this model, hazard function for failure time (T_i) has the form:

$$\lambda\left(t \mid Z(t)\right) = \lambda_0(t) + \beta' Z(t) = \lambda_0(t) + \sum_{j=1}^{p}\beta_j Z_j(t) \quad (2)$$

Where $\lambda_0(t)$ is baseline hazard function and β is unknown time-independent additive effects.[12,19]

Aalen's additive hazards model

This model is nonparametric AH, and the effect of covariates is additive on the baseline hazard rate. According to this model, hazard function for failure time (Ti) has the form:

$$\lambda\left(t \mid Z(t)\right) = \lambda_0(t) + \beta'(t) Z(t) = \lambda_0(t) + \sum_{j=1}^{p}\beta_j(t) Z_j(t) \quad (3)$$

Where β(t) is unknown time-dependent additive effects and Z (t) is a ($P \times 1$) vector of covariates. This model is useful when the main interest is risk difference rather than relative risk, and the model allows covariate effects to vary with time. In addition, this model provides a cumulative regression function plot to display the change of covariates over time.[12,20]

RESULTS

The mean age of patients at diagnosis was 50.71 (standard deviation [SD] = 11.30) years, and the mean of tumor size was 3.03 (SD = 1.85) cm. Of the 933 patients with BC, 90.2% were without metastasis, 78.8% had hormonal therapy, and 54.1% had mastectomy surgery. Other characteristics were reported in Table 1.

According to Cox proportional hazards model, the age at diagnosis ($P < 0.001$), history of disease ($P < 0.001$), number of lymph nodes ($P < 0.001$), metastasis ($P < 0.001$), hormonal therapy ($P < 0.001$), and evacuation lymph nodes ($P = 0.004$) were identified as significant factors [Table 2]. For example,

Table 1: Demographic and clinical characteristics of breast cancer patients

Covariates	Number (%)
History of disease, *n* (%)	
No	606 (65.00)
Yes	327 (35.00)
Metastasis, *n* (%)	
No	842 (90.20)
Yes	91 (9.80)
Hormonal therapy, *n* (%)	
No	198 (21.20)
Yes	735 (78.80)
Excapsular, *n* (%)	
No	883 (94.60)
Yes	50 (5.40)
Kind of surgery, *n* (%)	
Mastectomy	505 (54.10)
Breast Saving	428 (45.90)
Covariates, mean±SD	
Age at diagnosis	50.71±11.30
Number of lymph node	2.9 8±4.48
Tumor size	3.03±1.85
Evacuation_ L node	9.71±5.72

SD=Standard deviation

tumor size coefficient was positive, which indicates a worse prognosis effect, and this variable is associated with increased risk of BC (hazard = 1.10). Based on the scaled Schoenfeld residual plots, it seems that the proportionality is not exactly satisfied for metastasis, age at diagnosis, and hormonal therapy [Figure 1]. Hence, Aalen's additive model was used to analyze the data. The age at diagnosis ($P < 0.001$), history of disease ($P < 0.001$), number of lymph nodes ($P = 0.030$), metastasis ($P < 0.001$), hormonal therapy ($P = 0.001$), and evacuation lymph nodes ($P = 0.011$) had a significant effect on survival time. The other covariates had no effect on BC's lifetime. For example, the tumor size coefficient was 4.54e-4, which indicates the absolute difference in the BC rate per-unit change in the tumor size. In Lin and Ying's AH model, the age at diagnosis ($P < 0.001$), history of disease ($P < 0.001$), number of lymph nodes ($P = 0.026$), metastasis ($P < 0.001$), hormonal therapy ($P = 0.002$), tumor size ($P = 0.048$), and evacuation lymph nodes ($P = 0.012$) were identified as significant factors [Table 2]. For example, the coefficient of tumor size was 4.54e-4, which indicates that patients with per-unit change in the tumor size had an increase in hazard of 0.0005.

Figure 2 indicates that the estimates of cumulative regression function for all variables used in this data set. For patients who had history of disease, or gave hormonal therapy, or evacuation Lymph node; the risk decreases as the time goes on, i.e., the slope of the graph is negative for this patient during 80 month. For patients with metastasis, patients with higher age, and patients with high number of lymph nodes, the slope of an estimated cumulative

Table 2: Results of fitting Aalen's additive hazards, Cox PH, and Lin and Ying's additive hazards models for breast cancer data

Covariates	Beta (95% CI)	HR (95% CI)*	Z (*P*)
Cox proportional hazards model results			
Age at diagnosis	5.60e-2 (3.32e-2, 7.86e-2)	1.058 (1.034–1.082)	4.80 (<0.001)
No_ L node	1.15e-1 (4.75e-2, 1.83e-1)	1.122 (1.049–1.201)	3.33 (<0.001)
Tumor size	9.6e-2 (1.79e-2, 1.75e-1)	1.101 (1.018–1.191)	2.40 (0.016)
History of disease	−1.11e-0 (−1.70e-0, −5.13e-1)	0.331 (0.183–0.599)	−3.66 (<0.001)
Metastasis	1.58e-0 (1.09e-0, 2.08e-0)	4.880 (2.983–7.984)	6.31 (<0.001)
Hormonal therapy	−1.19e-0 (−1.69e-0, −6.93e-1)	0.303 (0.184–0.450)	−4.68 (<0.001)
Excapsular	8.74e-1 (1.81e-1, 1.57e-0)	2.396 (1.199–4.790)	2.47 (0.013)
Surgery breast saving	−7.82e-1 (−1.47e-0, −9.63e-2)	0.458 (0.846–0.970)	−2.24 (0.025)
Evacuation_ L Node	−9.90e-2 (−1.68e-1, −3.08e-2)	0.906 (0.231–0.908)	−2.84 (0.004)
Aalen's additive model results			
Age at diagnosis	1.24e-03 (6.36e-05, 1.84e-04)	-	4.02 (<0.001)
No_ L Node	2.11e-04 (2.05e-05, 4.01e-04)	-	2.17 (0.030)
Tumor size	3.79e-04 (−1.27e-04, 8.85e-04)	-	1.47 (0.142)
History of disease	−2.21e-03 (−3.36e-03, −1.06e-03)	-	−3.79 (<0.001)
Metastasis	9.30e-03 (5.03e-03, 1.36e-02)	-	4.27 (<0.001)
Hormonal therapy	−2.92e-03 (−4.72e-03, −1.12e-03)	-	−3.18 (0.001)
Excapsular	2.66e-03 (−4.72e-03, −1.12e-03)	-	1.28 (0.199)
Surgery breast. saving	−7.17e-04 (−1.87e-03, 4.41e-04)	-	−1.21 (0.225)
Evacuation_ L Node	−1.07e-04 (−1.89e-04, −2.45e-05)	-	−2.54 (0.011)
Lin and Ying's AH model results			
Age at diagnosis	1.34e-4 (7.01e-05, 1.98e-04)	-	4.11 (<0.001)
No_ L Node	2.65e-4 (2.83e-05, 4.64e-04)	-	2.21 (0.027)
Tumor size	4.54e-4 (2.82e-06, 9.05e-04)	-	1.97 (0.049)
History of disease	−2.54e-3 (−3.89e-03, −1.19e-03)	-	−3.70 (<0.001)
Metastasis	1.07e-2 (6.01e-03, 1.54e-02)	-	4.47 (<0.001)
Hormonal therapy	−3.21e-3 (−5.31e-03, −1.10e-03)	-	−2.99 (0.003)
Excapsular	3.06e-3 (−8.06e-04, 6.92e-03)	-	1.55 (0.121)
Surgery breast saving	−9.26e-4 (−2.25e-03, 4.02e-04)	-	−1.37 (0.172)
Evacuation_ L node	−1.23e-4 (−2.19e-04, −2.62e-05)	-	−2.49 (0.013)

*HR for Aalen's and Lin and Ying's models is not applicable. AH=Additive hazards; CI=Confidence interval; HR=Hazard ratio

regression function was positive. This shows that the risk of BC increases over time for these patients.

DISCUSSION

As we know, statistical models can describe the nature of data from any scientific field such as medicine, clinical studies, and health care. In this sense, one can make statistical inferences about the parameters in order to predict goals and also decision-making for some interventions in human health.[21,22] Survival analysis is used to model the relationship between the risk factors in time-to-death cancer studies.[14-16] In this field, the use of the Cox PH model is more popular. In this model, hazard ratios are estimated which are useful in understanding the magnitude of association between exposure and survival. Comparing to this model, AH models provide the difference in hazards, i.e., the change in the event rate due to the exposure variable (Xie, 2013).[23]

Many studies were made on survival of Iranian BC patients.[12,13,18,24,25] The overall relative survival in Iranian BC patients was reported higher than some Asian and eastern European countries and was lower than the U.S. and western European countries.[25]

In this study, the Cox PH, the Lin and Ying's AH, and the Aalen's AH models were applied to BC data. The interpretation of additive models and Cox proportional hazards model is very different, so that the exponential of coefficients in Cox proportional hazards model is relative hazards, but those in additive models are the attributable risk.[12]

Results of fitting the BC data with these models were similar with little difference in Lin and Ying's AH model. The Standard Error (SE) in Aalen's additive model was better than the Cox model and Lin and Ying's AH model, so Aalen's AH model is better than to two other mentioned models. Based on Aalen's AH model, age at diagnosis, number of lymph nodes, and evacuation lymph nodes had a significant effect on the hazard of the event. In addition, history of disease, hormonal therapy, and metastasis had a significant effect on the hazard of the event.

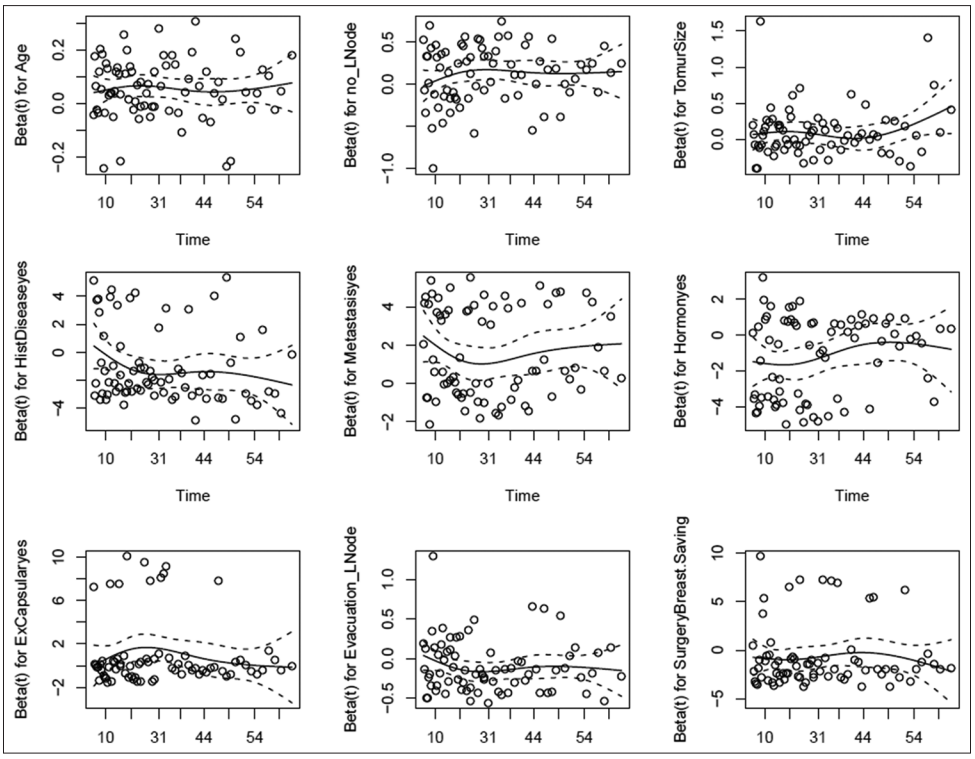

Figure 1: Smoothed scaled Schoenfeld residual plots with 95% pointwise confidence intervals for covariates

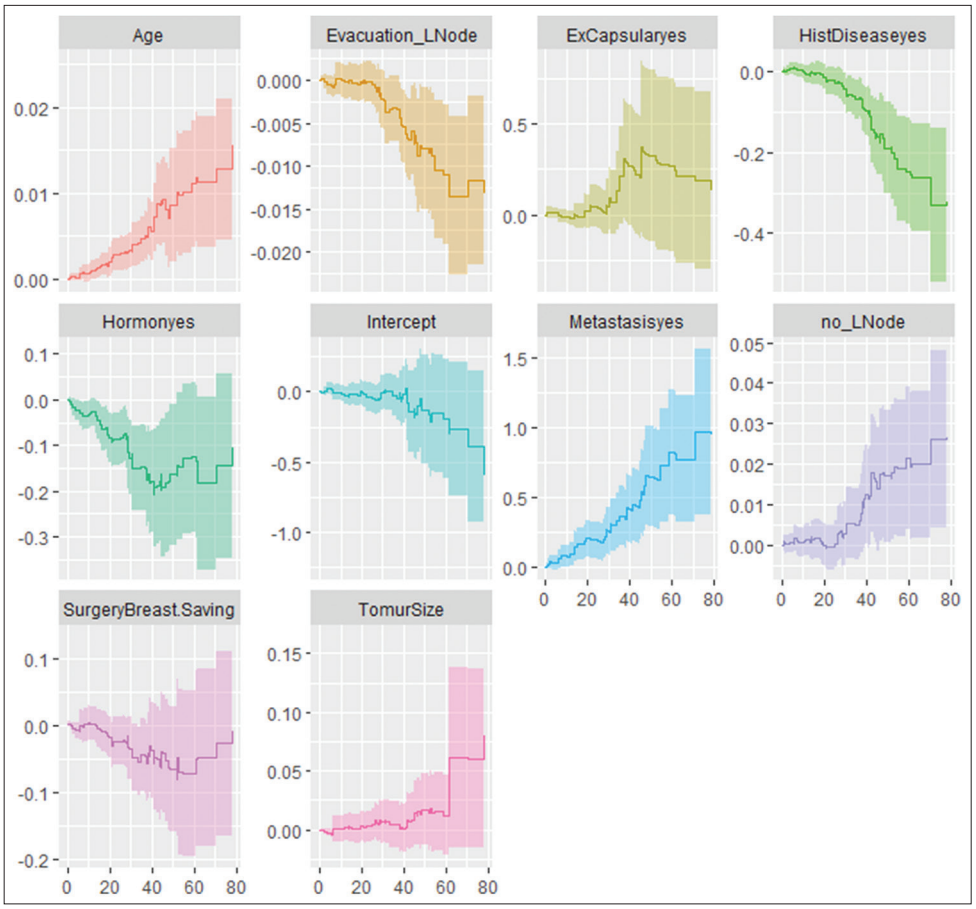

Figure 2: Estimated cumulative regression functions with 95% pointwise confidence intervals based on Aalen's additive model; which x label is time in month and y label is cumulative coefficients (i.e., risk at time)

In the present study, age at diagnosis of BC was an important factor affecting the survival of patients. Some researches demonstrate that a relationship exists between age and the proportion of BC. Wei *et al*. showed that in the group of very young patients (age < 35 years), there were more triple-negative tumors than older patients.[26] Largillier *et al*. reported a poor prognosis for BC patients over 50 years of age.[27] In China, the prognostic mathematical model of lymph node-negative BC was firstly established in 2003.[28] Compared with them, our study showed that the number of lymph nodes was a risk factor of BC. Our results showed that the patients who had not history of disease, the risk of disease decreases for them as the time goes on. This is close to results of some studies in Iran which they showed that history of disease was a significant factor of BC.[12,18,24,25] Metastasis was the significant risk factor in Aalen's AH model which we used in this study. This factor was also reported as a significant factor in other studies.[24] The overall survival of BC after metastasis was shorter reported[29] and also was reported as a factor which increases the hazard of the event of death.[24]

Some studies suggested a linear and others suggested a nonlinear effect of tumor size. It is mentioned that some studies reported that tumor size increased the risk of metastasis in patients with BC,[30,31] but in our study, the relationship between tumor size and survival of BC patients only in Aalen's AH model has been controversial.

One of the limitations of this study was missingness in some clinical information such as grade and nodal involvement. In addition, there was not the survival time of some patients because of changing in contact information. So some samples be excluded from the analysis because of this missingness. Moreover, it was assumed that the patient censoring was not informative and thus was independent of the BC death. Another limitation of this study was the lack of time-varying scheme data, and hence, the extended Cox model was not used. On the other hand, our data could not support the use of the extended Cox model. It is suggested that future studies be conducted longitudinally to allow for data collection over time which makes a useful data source.

CONCLUSION

The current study showed that the age at diagnosis, number of lymph nodes, and evacuation lymph nodes had increased the effect on the hazard of the event. In addition, history of disease, hormonal therapy, and metastasis also increased the effects on the hazard of the event. For patients who had history of disease, or gave hormonal therapy, or evacuation Lymph node; the risk decreases as the time goes on, i.e., the slope of the graph is negative for this patient during 80 month. For patients with metastasis, patients with higher age, and patients with high number of lymph nodes, the slope of an estimated cumulative regression function was positive. This shows that the risk of BC increases over time for these patients. This study applied Aalen's AH and Lin and Ying's models beside Cox proportional hazards model to analyze BC patients. The results of these models were similar. The Aalen's AH model has a similar fit than other models but gives information about covariate effect when time goes on. This aspect of the association between the survival time and covariates is a useful and helpful interpreter for therapists and clinical researchers.

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Conflicts of interest

There are no conflicts of interest.

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