

Cox Proportional Hazard Model to Examine the Association between Tumour Size and Breast Cancer: Applying on Swedish Breast Cancer Patients

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Abstract

The focus of this research is to study whether the tumour size is one of the vital variables that effect on the overall survival rate of breast cancer cases after stratified by the hormone receptor. A sample of six hundred and sixty-three women cases with breast cancer aged between 23 to 83 years was examined. Cox Proportional Hazard regression model is used. Unadjusted and adjusted model (adjusting by age, menopause status and Lymph node status) are fitted. All analyses are stratified by the hormone receptor status. In conclusion, tumour size is one of the important risk factors that increase the mortality rate for the breast cancer patients.

Keywords

Breast cancer, tumour size, survival analysis

INTRODUCTION

Breast cancer is the vital disease worldwide (developed and developing countries)[1]. One of ten cancer cases were diagnosed each year [2]. Breast cancer is one of the important causes of death in the world [2-7]. Survival rate is used as an indicator of cancer burden [3-5].The survival rate is the survival time from the date of diagnosis breast cancer cases until death.

In breast cancer, many prognostic factors (e.g. tumour size, lymph node status, Hormone receptor status, and tumour grade) have been reported. However, the historical background of each patient (e.g. the stage of breast cancer, age, and the individual therapy intake) differ among patients. Tumour size is reported as one of the essential risk factor in breast cancer and mortality rate[8, 9]. These findings are essentially identified on stage T3 tumours(>5cm). The association between the all stages of the breast cancer (tumour size) and survival time has been investigated[10]. However, in most studies the tumour size is always categorised based on a specific cut-off points[11]. Recently, studies have reported categorizing the continuous prognostic factor might lead to loss of information and yield overestimated results (which due to mislead the decision)[12-14]. Thus, in this study

the continuous scale for tumour size is undertaken. In addition, stratified analyses by hormone receptor possibly yield more specific findings. The focus is on examining the association between the tumour size (in a continuous scale) and survival time per months (after the first breast cancer surgery). Unadjusted and adjusted Cox proportional hazard models are estimated. The adjusted model is controlling by age, menopause status and lymph node status. All analyses are stratified by hormone receptor.

Methods

Study population

Six hundred and sixty-three female breast cancer patients have been provided from Swedish clinical trial which was one of the dataset provided from European Organization for Research and Treatment of Cancer Receptor and Bio-marker Group (EORTC-RBG). In this study the focus is on women aged between 23 to 85 years old. Participants were selected based on the availability of survival time per months and tumour size measurements. The patients were born between November 1891 and September 1969. The primary surgery for the patients was before 1996. It was 18 clinical trials studies the breast cancer disease for 18 European countries; however, the focus in this study was only on the Swedish clinical trial based on the availability of the data.

Variables

Overall Survival Time

For all individuals the overall survival time was measured in months after the first breast cancer operation. The overall survival time ranged between 2 to 85 months.

Tumour size

The stage of the breast cancer can be determined by the tumour size, in this study it is ranged between 1 to 250mm. It is measured in the continuous scale.

Hormone Receptor

Hormone Receptor is a treatment for the breast cancer cells and it might be estrogen or progesterone. It is classified into two categories (i) positive hormone receptor (HR=1) which means that the cells of the breast cancer patients is respond to the

hormone treatment; (ii) Negative hormone receptor(HR=0) which means that the hormone treatment is possibly not working on the breast cancer cells.

Lymph node status

Prognosis of the breast cancer is highly related to Lymph node status. Lymph node status is classified to two categories (i) Positive lymph node status (np=1) which indicates of breast cancer prognosis; (ii) Negative lymph node(np=0) which means that no cancer cells exist.

Menopausal status

One of the important risk factors of breast cancer is menopausal status. It is measured in a binary scale (Premenopausal = 0 and post-menopausal = 1).

Statistical Analysis

In this study Cox proportional model, a semi-parametric model, is used to analyse the breast cancer survival data [15,16]. Mathematically, it is written as follows

$$\lambda(t) = \lambda_0(t) e^{\sum_{i=1}^k \beta_i x_i}$$

Where (t) , as an independent variable, is the hazard at time t of breast cancer patients (independent variables). $\lambda_0(t)$ is the constant hazard for breast cancer participants (when x_i value is zero) . k is the number of the confounding variables (e.g. age, lymph node status, menopausal status). Maximum partial likelihood method (MPLE) has been used to estimate, β_i .

One of the most important assumptions of Cox PH model is the hazard ratio is constant over time. To check this assumption, two methods have been used (i) Graphical method: (-ln(-ln) survival curves over different categories (e.g. hormone receptor for unadjusted and adjusted model)have been undertaken; the assumption is achieved when there is no intersection between the curves. (ii) The goodness of fit test by using Schoenfeld residuals, if the p-value >0.05 this indicates that the assumption is achieved, for more details see Schoenfeld et al. [13].

Kaplan-Meier method has been used to illustrate the survival of the breast cancer patient over time[15]. It can be used to compare the survival over time between two or more groups such as hormone receptor, menopausal status, or Lymph node status.

RESULTS

Descriptive Statistics

A sample of Sixty hundred sixty-three breast cancer patients was used in the analysis. Five hundred eighty six women breast cancer patients with percentage of 88.54% were censored (alive until the end of the follow up). The average mean of participants with the standard deviation was 58.42 ± 11.50 and 55.58 ± 9.97 for positive and negative hormone receptor, respectively.

The average tumour size for positive hormone receptor was 25.57 which is smaller than the negative hormone receptor, see Table1. Log transformation has been undertaken to tumor size to avoid the right skewness. The prevalence of the post-menopausal status is 61% and 6% for positive and negative hormone receptor respectively. The prevalence of post-menopause breast cancer patient who received hormone receptor are more than the pre-menopause group. The percentage of lymph node positive is 41% for breast cancer who received hormone receptor, see table 1.

Table 1: The descriptive statistics of breast cancer patients (n=663)for survival rate, tumour size, age, pre-menopausal and post-menopausal status classified by hormone receptor for swedish dataset

	Positive Hormone receptor	Negative hormone receptor
Survival Rate: <i>mean</i> \pm <i>SD</i>	45.638 \pm 15.735	39.716 \pm 16.563
Tumour size: <i>mean</i> \pm <i>SD</i>	25.57 \pm 42.672	26.96 \pm 16.87
Age: <i>mean</i> \pm <i>SD</i>	58.42 \pm 11.50	55.58 \pm 9.97
Pre-menopause: <i>n</i> (%)	200(30%)	20(3%)
Post-menopause: <i>n</i> (%)	407(61%)	36(6%)
Lymph node positive: <i>n</i> (%)	273(41%)	21(3%)
Lymph node negative: <i>n</i> (%)	334(51%)	35(5%)

Univariate analyses (Unadjusted Model)

Unadjusted Cox PH model was used to estimate the probability of the risk factor between tumour size and mortality rate for the women breast cancer. The findings suggest that the tumour size increase the risk of mortality for all participants who were classified as positive or negative hormone receptor. While the risk probability of the participants who received positive hormone treatment (HR=2.50) is smaller than the other patients who did not receive hormone treatment (HR=3.45), see Table 2 and 3. For example, patients with positive hormone receptor have 2.5-fold higher risk of dying for increasing one unit of tumour size. While, negative hormone receptor patients' have almost 3.5-fold higher risk of dying for increasing one unit of tumour. This means that receiving hormone treatment decrease the risk of mortality rate.

Multivariate Analysis (Adjusted Model)

There is no multi-collinearity reported among the variables. Thus, all variables are included in the analysis. Adjusted cox PH model is fitted. The model is controlling by age, Lymph node status, and menopausal status. The model is stratified by hormone receptor. Table 2 and 3 shows the findings of the Cox PH model. The adjusted model reveal that the tumour size is still have a positive significant association with the mortality rate. However, in the positive hormone receptor group, the adjusted model yielded less risk of tumour size (with hazard ratio equal 1.93) compared to the unadjusted model. Positive Lymph node variable has been shown positive significant results with (HR=5.19). This indicates perhaps there are other factors that might influence on the mortality rate for breast cancer patients. Age and post-menopause status does not show any significant association with the mortality rate. In the negative hormone receptor group (adjusted model), The effect of tumour size risk is greater than the unadjusted model. Patients have 4.29fold higher risk of dying for one-unit increase of tumour compared to an unadjusted model (HR=3.45). Age, Positive Lymph node, and pre-menopause status does not show any significant findings.

Table 2: Hazard ratio of overall survival after 5 years of breast cancer surgery (for positive hormone receptor)

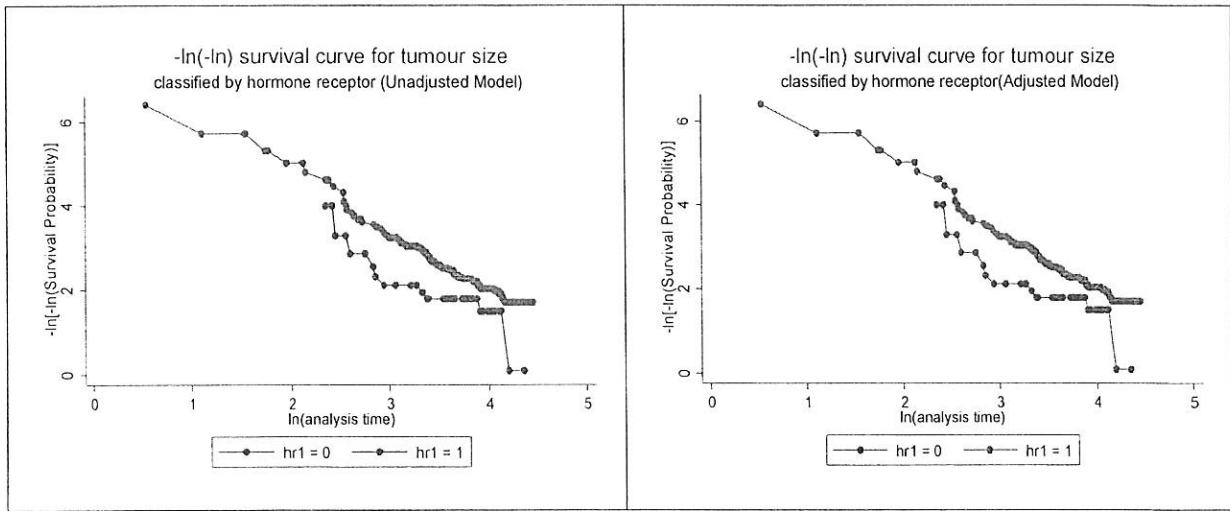
	Univariate		Multivariate	
	HR: 95% CI	P-value	HR: 95% CI	P-value
Tumour size	2.50 (1.82:3.42)	<0.0001	1.93 (1.355: 2.776)	<0.0001
Age	-----	-----	1.003 (.971:1.04)	>0.05
Post-menopause	-----	-----	1.20 (.52: 2.74)	>0.05
Lymph node positive	-----	-----	5.19 (2.74:9.85)	<0.0001

Table 3: Hazard ratio of overall survival after 5 years of breast cancer surgery (for negative hormone receptor)

	Univariate		Multivariate	
	HR: 95% CI	P-value	HR: 95% CI	P-value
Tumour size	3.45 (1.10: 10.78)	0.033	4.29 (1.161:15.87)	0.029
Age	-----	-----	1.055 (.96:1.15)	>0.05
Post-menopause	-----	-----	.30 (.03:2.82)	>0.05
Lymph node positive	-----	-----	1.84 (.50:6.73)	>0.05

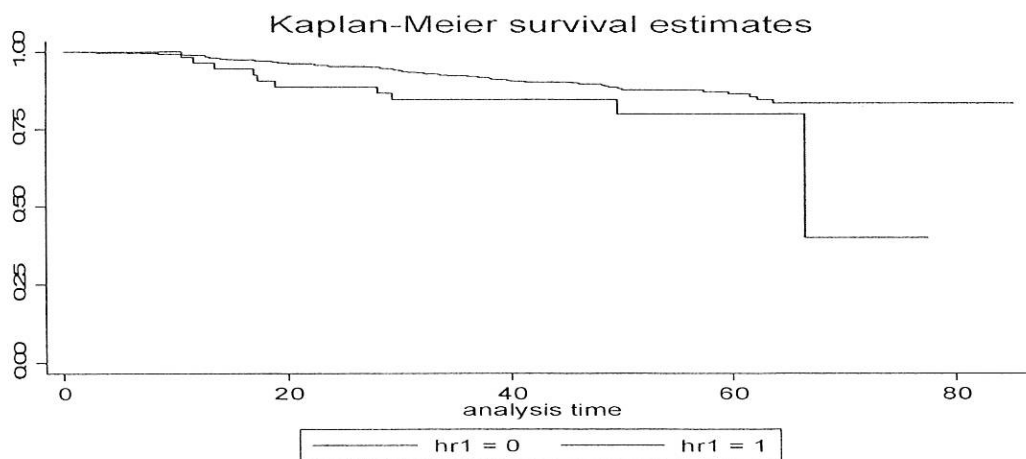
Figure 1 shows $-\ln(-\ln)$ survival curve of the tumour size stratified by the hormone receptor for unadjusted and adjusted model (by age, menopause status, and lymph node status) to test the assumption of cox PH model. The parallel lines indicate that the assumption is achieved. In addition, it is noticed that the survival rate for patients who received hormone treatment (positive hormone receptor) is greater than the other group (negative hormone receptor). These findings are matched with the results which obtained from the unadjusted and adjusted model [Table 2, and 3].

Figure 1: Shows $-\ln(-\ln)$ survival curve for tumour size classified by hormone receptor for unadjusted and adjusted model to test the assumption of the cox PH model



The Cox PH model assumption has also been tested by using the goodness of fit test (Schoenfeld residuals), the test shows that the assumption is achieved for all variables with P-value > 0.05. Figure 2 shows the Kaplan-Meier Survival curves for breast cancer patients stratified by the hormone receptor. It can be seen from the graph that the survival time for the patients who received the hormone treatment much more than who received negative hormone receptor.

Figure 2: Kaplan-Meier Survival curves to estimate the survival time for breast cancer patients classified by the hormone receptor. (Negative hormone receptor (hr1=0), Positive hormone receptor (hr1=1))



DISCUSSIONS

In this study, we found that the breast cancer tumour size is associated with the mortality rate either for positive or negative hormone receptor. However, the probability of the risk is more likely at negative hormone receptor compared to positive hormone receptor in an unadjusted and adjusted model. In the positive hormone receptor, the risk probability of the tumour size is more in an unadjusted model compared to adjusted model. The probability of the risk was smaller in the adjusted model because the positive lymph node status shows a significant association with mortality rate.

Previous studies reported the same findings[9, 16-24]. For example, in Rosenberget al. [9]The authors found that the large tumour size and tumour grade have adverse effect on survival rate. In Narod et al.[21]study, the author concludes that there is a negative association between the tumour size and breast cancer survival rate in a prospective study for almost 220 breast cancer patients in Toronto, Canada. The author also concludes that the early detect of the tumour size reduce the death in young women. In Michaelson et al[22]The author found that both of the tumour size and Positive hormone status yielded negative association with the survival rate in breast carcinoma .In Stankov et al.[23], the authors found that the lymph node status (positive or negative, and the neoadjuvant chemotherapy (yes or no) are primary prognostic factors for recurrence breast cancer at the National Cancer Institute of Mexico. In Hedeem[24] et al. The authors investigate the association between tumour size (greater than 1 cm) and survival rate stratified by race, the paper reported that the breast cancer tumour size is a prognostic factor for all Asian American, Chinese, Filipino and Korean American.

The strength points in this study are(i) the analysis was stratified by the hormone receptor (negative or positive) to examine the association between breast cancer and mortality rate for each group and examine whether there is difference findings for the negative and positive hormone receptor. (ii) unadjusted and adjusted model (controlling by age, lymph node status and menopausal status) have been fitted to examine whether the different findings were obtained. (iii) A semi-parametric cox PH model was fitted, and the model assumptions was achieved. (iv) Kaplan Meier curve is used to compare the survival over time between two groups (positive and negative hormone receptor of breast cancer patients).

The weakness in this study are(i) small data has been used for the analysis. (ii) controlling the model by other biochemical variables such as Urokinase-Type Plasminogen Activator and Its Inhibitor PAI-1 might yield different findings. (iii) race differences might yield interest findings, however, the analysis was restricted due to the availability of the data.

CONCLUSION

Tumour size is an important prognostic factor for female breast cancer patients. The patients who received hormone receptor yielded less risk compared to other patients (who received negative hormone receptor).

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