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Application of Proportional Hazard and Additive Models in the Survival Analysis of Breast Cancer Patients

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ABSTRACT

Breast cancer is the most common type of cancer among women and one of the highest causes of death among other types of cancer. This study aims to evaluate the methodological advantages of additive hazard models over the multiplicative Cox model in identifying temporal risk factors for breast cancer survival. Using secondary data from 1458 patients and 10 covariates, applying three methods, Cox proportional hazards model, Lin-Ying additive hazard model, and Aalen additive hazard model. The proportional hazard assumption test indicated that Cox regression model did not fully satisfy the assumption; therefore, the Lin–Ying and Aalen additive models were applied. In the Lin–Ying models, hormonal therapy, radiotherapy, the Nottingham Prognostic Index (NPI), and tumor size were identified as significant predictors of survival, whereas in the Aalen model, significant factors also included age and chemotherapy in addition to those four covariates. These findings highlight that while the Cox model provides efficient estimation and interpretable hazard ratios, the Lin–Ying and Aalen models offer more robust alternatives when the proportional hazard assumption is violated. The Aalen model was selected based on the results of the Aalen plot. Overall, risk control efforts in breast cancer patients should focus on managing NPI scores and tumor size as well as ensuring appropriate therapies, particularly hormonal therapy and radiotherapy, which have been demonstrated to provide protective effects.

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A. INTRODUCTION

Cancer is one of the diseases that causes high mortality rates and poses a massive challenge to human health. (Deo et al., 2022). According to data from the Global Cancer Observatory in 2022, a total of 408,661 new cases of cancer recorded in Indonesia and 242,988 deaths caused by cancer in 2022 (Kristina et al., 2025). Despite significant advances in various therapies such as surgery, chemotherapy, radiotherapy, and hormonal therapy, cancer remains a complex and heterogeneous disease, with high rates of recurrence and resistance to treatment (Zafar et al., 2025).

One type of cancer that commonly occurs, especially in women, is breast cancer. (Siegel et al., 2025). Global Cancer Observatory recorded that, in 2022, there were 66,271 cases of breast cancer. This number represents the highest proportion of cancer cases in Indonesia, accounting for 30.1% of the total 220,266 cancer cases among women, with 22,598 deaths reported in the same year (Tuelah et al., 2025). Breast cancer is the leading cause of cancer-related deaths in women (Sung et al., 2021). The population most vulnerable to breast cancer is older women, especially those with a family history of similar cancers, high exposure to estrogen hormones, and unhealthy lifestyles (Obeagu & Obeagu, 2024). Breast cancer can develop slowly but progressively. If it is not detected or treated early, it can metastasize to other vital organs such as lungs, liver, and bones (Jin et al., 2018). Therefore, understanding the factors that affect patient survival time is very important in mitigating breast cancer (Zhang et al., 2025).

The survival of breast cancer patients is influenced by several classical and well-accepted clinical and pathological prognostic factors, including tumor size, lymph node involvement, clinical stage, and biomarker status such as hormone receptor and HER2 expression (Liu et al., 2021). The analysis of these factors presents statistical challenges due to the unique characteristics of survival data, particularly the presence of censored observations. Censored data is a condition in which the time between an initial and a final event is incompletely measured due to limited follow-up and intermittent observation (Oller & Gómez Melis, 2023). Consequently, conventional statistical methods such as standard linear regression are inadequate, and survival analysis is required to appropriately handle incomplete survival times and complex risk structures throughout the follow-up period (Schober & Vetter, 2018; Turkson et al., 2021).

One of the main advantages of survival analysis is its ability to accommodate censored data (Hazra & Nithya, 2017). The Kaplan Meier method is one of the most widely applied approaches in medical clinical trials for survival analysis (In & Lee, 2018). It provides estimates of the time from treatment initiation to key events, such as death or disease progression, among participants who remain under observation until the event occurs, or the study is completed. Although the Kaplan–Meier method is useful for showing survival over time, it cannot show how big the differences between groups are or take covariates such as age into account (Dudley et al., 2016).

To address these limitations, survival regression models that incorporate covariate effects, like the Cox proportional hazards regression model, can be applied. Introduced by Sir David Cox in 1972, the Cox model has become one of the most commonly used methods in survival analysis (Elhafeez et al., 2021). As a semiparametric approach, it allows for the estimation of hazard ratios for multiple covariates without requiring specification of the baseline hazard function (Stevens et al., 2020). However, in certain situations, the assumption of proportional hazards underlying the Cox model may not hold (Perera & Tsokos, 2018).

As an alternative, additive hazard models can be employed to address this issue. Two prominent models within this framework are the Lin–Ying additive hazard model and the Aalen additive hazard model. The Lin-Ying model was introduced by D.Y. Lin and Z. Ying (Brueckner et al., 2019). This model uses semiparametric estimates of the additive effects of covariates on hazard. This provides an advantage in terms of direct interpretation of risk differences. In contrast, Aalen model allows for the estimation of regression coefficients that can change over time (Başar, 2017). This advantage provides flexibility in handling data with dynamic time effects. Although the Cox model excels in terms of efficiency and hazard ratio interpretation, Lin-Ying model and Aalen model provide more robust alternatives in situations where the proportional hazard assumption in Cox regression is violated (Madadizadeh et al., 2017).

According to Dizaji et al. (2020), a comparative study of 1,025 breast cancer patients applied Cox, Lin–Ying, and Aalen regression models, with the optimal additive model selected based on minimizing the Standard Error (SE), leading to the selection of the Aalen model. However, reliance on SE minimization alone is limited, as it emphasizes numerical precision without explicitly assessing the temporal behavior of regression coefficients. To address this limitation, the present study introduces a methodological novelty by employing the Aalen plot as the primary criterion for model selection. This visual diagnostic directly evaluates whether covariate effects are constant or time-varying by examining the slope of the cumulative regression coefficients, thereby enabling a more accurate distinction between the Lin–Ying and Aalen models without dependence on SE comparisons.

B. METHODS

1. Research Design

This research models the factors that affect the survival time of breast cancer patients using three survival regression models. The three models used are the Cox proportional hazards model, Lin-Ying additive hazard model, and Aalen additive hazard model. The analysis begins with the Cox model, which is widely used due to its efficiency and ease of interpretation but requires the proportional hazards assumption to be satisfied. This assumption is evaluated using the Schoenfeld residual test, and when it is violated, additive hazard models are considered as appropriate alternatives.

Subsequently, the Lin–Ying and Aalen additive hazard models are applied, with the final model selection based on a comparative evaluation using the Aalen plot. This plot illustrates the main theoretical difference between the two models. The Lin–Ying model assumes that the effects of covariates remain constant over time, while the Aalen model allows these effects to change over time. Therefore, the Aalen plot is used to assess whether covariate effects are constant or time-varying, which helps determine whether the Lin–Ying or Aalen model is more suitable.

2. Dataset Description

The data used for analysis are secondary data obtained from the cBioPortal for Cancer Genomics. Clinical data were taken from the BRCA METABRIC study (Bruijn et al., 2023; cBioPortal for Cancer Genomics, 2016; Pereira et al., 2016; Rueda et al., 2019). In this research, records containing missing values were excluded from the analysis. A total of 1458 observations with 10 covariates were used. The summary of Covariates along with their characteristics and categorization is presented in Table 1 below. These covariates are used as predictors in testing the model and identifying factors that affect the survival time of breast cancer patients.

Table 1. Description of covariates

Covariate	Description
Age at Diagnosis	Continous; age in years.
Chemotherapy (Chemo)	Categorical (No, Yes).
ER Status	Categorical (Positive, Negative).
Hormone Therapy (HTherapy)	Categorical (No, Yes).
Inferred Menopausal State (IMS)	Categorical (Pre, Post).
Nottingham Prognostic Index (NPI)	Continous.
PR Status	Categorical (Positive, Negative).
Radiotherapy (RTherapy)	Categorical (No, Yes).
Tumor Size	Continous, tumor size in milimeters.
Tumor Stage	Categorical (0, 1, 2, 3, 4).

The response variables were time and status, where time represents the survival time of patients in months. The patient status variable, based on the source data, consists of three categories, namely Living, Died of Other Causes, and Died of Disease. In this study, patients with the status Died of Disease were defined as events, while patients categorized as Living or Died of Other Causes were considered censored data.

3. Cox Proportional Hazards Regression Model

Cox Proportional Hazards regression model is a semiparametric survival regression model in survival analysis (Zhang, 2016). Cox regression analyzes the impact of covariates on the hazard rate, which represents the instantaneous risk of an event occurring at a specific time. One advantage of Cox regression is that it does not require explicit assumptions regarding the shape of the baseline hazard (Lefebvre & Giorgi, 2021). The regression coefficients in the Cox model are estimated using the partial likelihood method, and statistical inference is conducted using the Wald Z test. Cox regression relies on a strict assumption known as the proportional hazard assumption. The proportional hazard assumption states that the hazard ratio between two individuals with different characteristics is constant over time (Kuitunen et al., 2021). The Cox regression model is represented by the formula.

$$\lambda\big(t\big|Z(t)\big) = \lambda_0(t) exp\left(\sum_{j=1}^{p} \beta_j Z_j(t)\right) \quad (1)$$

where:

$\lambda\big(t\big|Z(t)\big)$: hazard function at time t given the covariate vector $Z(t)$

$\lambda_0(t)$: baseline hazard function

β_j : regression coefficients for the j-th covariate

$Z_j(t)$: value of the j-th covariate at time t

p : total number of covariates in model.

In Cox regression, the proportional hazard assumption is an important assumption that must be satisfied. If this assumption is violated, it could result in an incorrect interpretation of the hazard ratio. (Dumas & Stensrud, 2025). The proportional hazards assumption can be tested using the Schoenfeld residual test (In & Lee, 2019).

4. Lin-Ying Additive Hazard Model

Lin-Ying additive hazard model is a semiparametric approach in survival analysis that models the effect of covariates on the hazard function additively, assuming that the covariate effects remain constant over time. The regression coefficients in the Lin–Ying model are estimated using the likelihood-based method, with statistical inference performed using the Wald Z test. In the Lin–Ying model, the regression coefficients are assumed to be constant over time (Lefebvre & Giorgi, 2021).

$$\lambda\big(t\big|Z(t)\big) = \lambda_0(t) + \sum_{j=1}^{p} \beta_j Z_j(t) \quad (2)$$

5. Aalen Additive Hazard Model

Aalen additive hazard model is an additive hazards regression approach that estimates the additive contribution of covariates to the baseline hazard through time-varying nonparametric regression functions. The regression coefficients in the Aalen model are estimated using the least squares method, and statistical inference is conducted using the Wald Z test. In the Aalen regression, the regression coefficients are allowed to vary over time (time-varying coefficients) (Lefebvre & Giorgi, 2021). The main difference between Aalen and Lin-Ying additive hazard models is the ability of the Aalen model to accommodate covariate contributions to the hazard function that may change over time. This property is commonly known as time-varying covariates, that allows regression coefficients to depend on time, making it more flexible in capturing changes in hazard over time (Başar, 2017). The Aalen additive hazard model is represented by the formula.

$$\lambda\big(t\big|Z(t)\big) = \lambda_0(t) + \sum_{j=1}^{p} \beta_j(t) Z_j(t) \quad (3)$$

where:

$\beta_j(t)$: regression coefficient for the j-th covariate at time t

C. RESULT AND DISCUSSION

1. Descriptive Statistics

Descriptive statistics are used to provide an overview of the patient characteristics and the covariates. Table 2 presents the frequency distribution for categorical covariates, whereas Table 3 displays the mean values for continuous covariates.

Table 2. Frequency Distribution of Categorical Covariates

Covariate	Category	N
Chemo	No	1,143
	Yes	315
ER	Negative	340
	Positive	1,118
HTherapy	No	570
	Yes	888
IMS	Pre	325
	Post	1,133
PR	Negative	695
	Positive	763
RTherapy	No	503
	Yes	955
Stage	0	9
	1	498
	2	825
	3	116
	4	10

Table 3. Descriptive Statistics of Continuous Covariates

Covariate	Mean
Age	60.70
NPI	4.03
Size	22.85

2. Kaplan-Meier Plot

The Kaplan-Meier curve is a key tool in survival analysis for describing the probability of survival over time in a group of patients. The Kaplan-Meier curve for the survival time of breast cancer patients is shown in Figure 1.

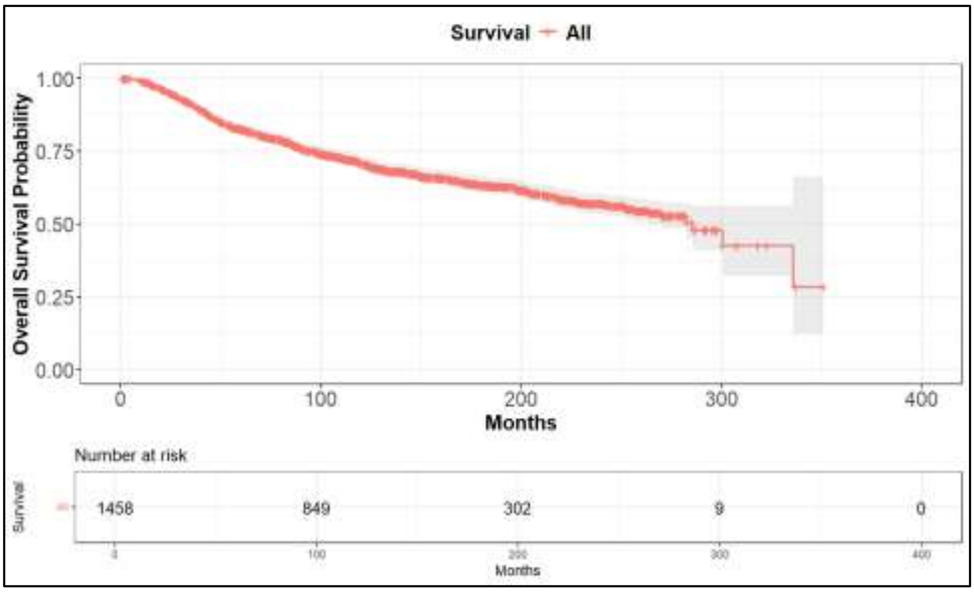

Figure 1. Kaplan-Meier Curve for the Survival Time of Breast Cancer Patients

The curve shows a fairly long survival time with a median survival of around 250 months. Towards the end of the observation period between the 300th and 400th months, the survival rate for breast cancer patients was around 0.25, which means that by the end of the observation period, around 25% of patients were still survived.

3. Model estimation of Cox regression

The best Cox regression model based on the significance test of the regression coefficient parameters is presented in Table 4 below.

Table 4. Estimates Coefficient of Cox Regression Model

No	Covariates	coef	exp(coef)	se(coef)	p-value
1	HTherapyYES	-0.23900	0.787412	0.09525	0.01210
2	NPI	0.51641	1.676002	0.04711	< 2e-16
3	RTherapyYES	-0.26753	0.765268	0.10051	0.00777
4	Size	0.01147	1.011532	0.00219	1.75e-07

Based on the Cox regression analysis results in Table 4, all covariates examined had a significant effect on mortality risk (p-value < 0.05). Hormonal and radiotherapy reduced the risk of death by 21.3% (hazard ratio 0.787412) and 23.5% (hazard ratio 0.765268), respectively. In contrast, a higher NPI score and larger tumor size increased mortality risk. An increase of one unit in the NPI score is associated with a 67.6% increase in the risk of death. (hazard ratio 1.676002), and each 1 mm increase in tumor size raised the risk by 1.15% (hazard ratio 1.011532). A proportional hazard assumption test was conducted. The purpose of this test was to verify whether the data met the requirements of the Cox regression model, as shown in Figure 2.

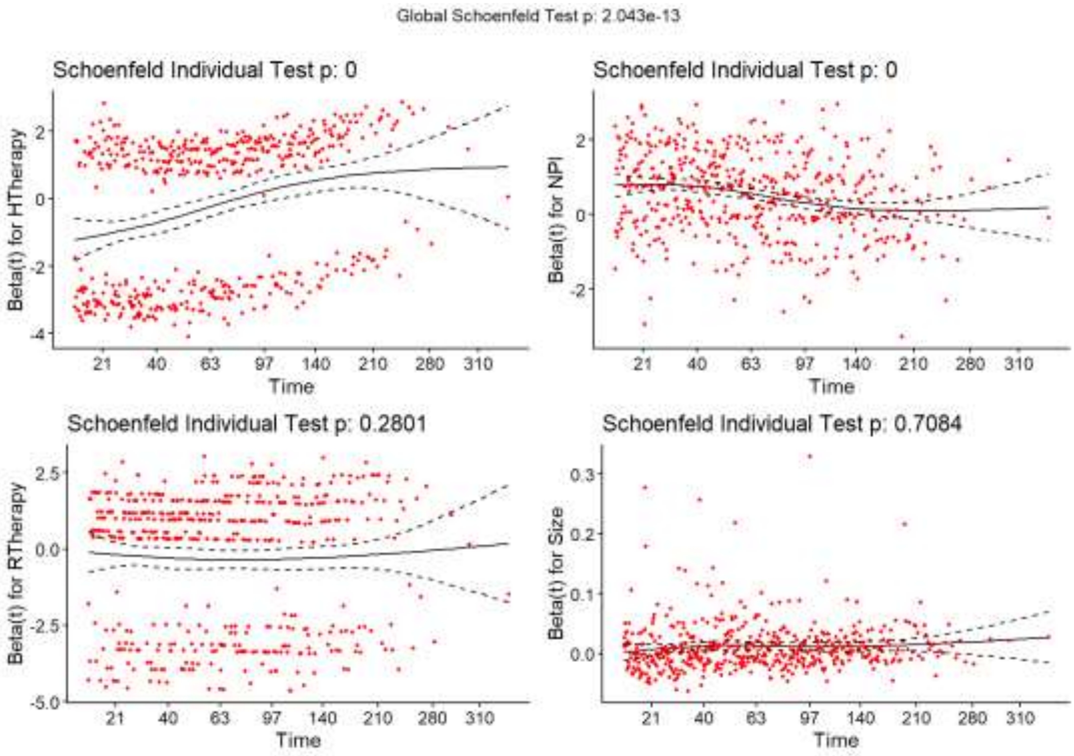

Figure 2. Schoenfeld Residual Plot

According to the Schoenfeld residual plot presented in Figure 2, it is shown that the Schoenfeld residuals for the RTherapy and Size covariates are around zero and do not form a specific trend pattern. This indicates that the RTherapy and Size covariates satisfy the proportional hazard assumption. Meanwhile, for the HTherapy and NPI covariates, the Schoenfeld residuals form a specific pattern that indicates the influence of time on these covariates, meaning that there is a violation of the proportional hazard assumption. Hypothesis testing for Schoenfeld residuals also confirms these results, as shown in Table 5.

Table 5. Proportional Hazard Assumption Test

No	Covariates	p-value
1	HTherapyYES	9.7e-09
2	NPI	8.5e-06
3	RTherapyYES	0.28
4	Size	0.71

The results of the proportional hazard assumption test in Table 5 show that hormonal therapy ($p \leq 0.05$) and NPI ($p \leq 0.05$) violate the proportional hazard assumption, while radiotherapy ($p = 0.28$) and tumor size ($p = 0.71$) satisfy this assumption. However, the global test results produced a p-value ≤ 0.05, indicating that overall, the proportional hazard assumption in the Cox regression model is violated. Therefore, as alternatives, analysis was performed using additive hazard regression models, specifically the Lin-Ying model and the Aalen model, which are specified independently of the proportional hazard assumption.

4. Model estimation of Lin-Ying additive hazard

The best Lin–Ying additive hazard model based on the significance test of the regression coefficient parameters is presented in Table 6 below.

Table 6. Estimates Coefficient of Additive Hazard Model

No	Covariates	coef	se(coef)	p-value
1	HTherapyYES	-8.049e-04	2.695e-04	0.00282
2	NPI	1.309e-03	1.325e-04	< 2e-16
3	RTherapyYES	-5.655e-04	2.543e-04	0.02614
4	Size	6.824e-05	1.376e-05	7.11e-07

The output of the Lin-Ying additive hazard analysis presented in Table 6 shows that all covariates have a significant effect on the event of death (p-value < 0.05). Hormone therapy reduced the hazard by 8.049e-04, while radiotherapy reduced the hazard by 5.655e-04. Conversely, each 1-unit increase in NPI score increased the hazard by 0.001309, and each 1 mm increase in tumor size increased the hazard by 6.824e-05.

5. Model estimation of Aalen additive hazard

The best Aalen additive hazard model based on the significance test of the regression coefficient parameters is presented in

Table 7 below.

Table 7. Estimates Coefficient of Aalen Additive Hazard Model

No	Covariates	coef	se(coef)	p-value
1	Intercept	-1.57e-03	3.07e-04	3.18e-07
2	Age	1.02e-05	4.50e-06	2.38e-02
3	ChemoYES	3.28e-04	1.66e-04	4.79e-02
4	HTherapyYES	-3.04e-04	9.91e-05	2.17e-03
5	NPI	4.42e-04	5.20e-05	1.94e-17
6	RTherapyYES	-2.11e-04	9.79e-05	3.10e-02
7	Size	2.07e-05	4.96e-06	2.86e-05

The output of Aalen additive hazard analysis in

Table 7 shows that all covariates have a significant effect on the event of death (p-value < 0.05). Patient age has an effect with an increase in hazard of 1.02e-05 per year. Chemotherapy increases the hazard by 3.28e-04, while hormonal therapy decreases the hazard by 3.04e-04. An increase of 1 NPI score contributes to an increase in hazard of 4.42e-04, while radiotherapy decreases the hazard by 2.11e-04. In addition, each 1 mm increase in tumor size adds to the hazard by 2.07e-05.

6. Discussion

Cox regression interprets the effects of covariates as relative changes in risk, expressed as hazard ratios between individuals or groups, where covariate effects are multiplicative with respect to the baseline hazard. These effects are interpreted through the hazard ratio values indicated by exp(coef). For example, an exp(coef) value of 1.676 for the NPI covariate indicates that each one-unit increase in the NPI score multiplies the patient's risk of death by 1.676 times relative to the baseline risk. In contrast, additive models such as the Lin–Ying and Aalen models quantify covariate effects as absolute increases in risk per unit of time. For example, the coefficient (coef) values are interpreted directly, indicating that each one-unit increase in the NPI score contributes an additional risk of 0.001309 in the Lin–Ying model and 0.000442 in the Aalen model. Given that the proportional hazards assumption is not satisfied, additive models are more appropriate for this analysis. The distinction between the Lin–Ying and Aalen models can be determined using the Aalen plot, as shown in Figure 3.

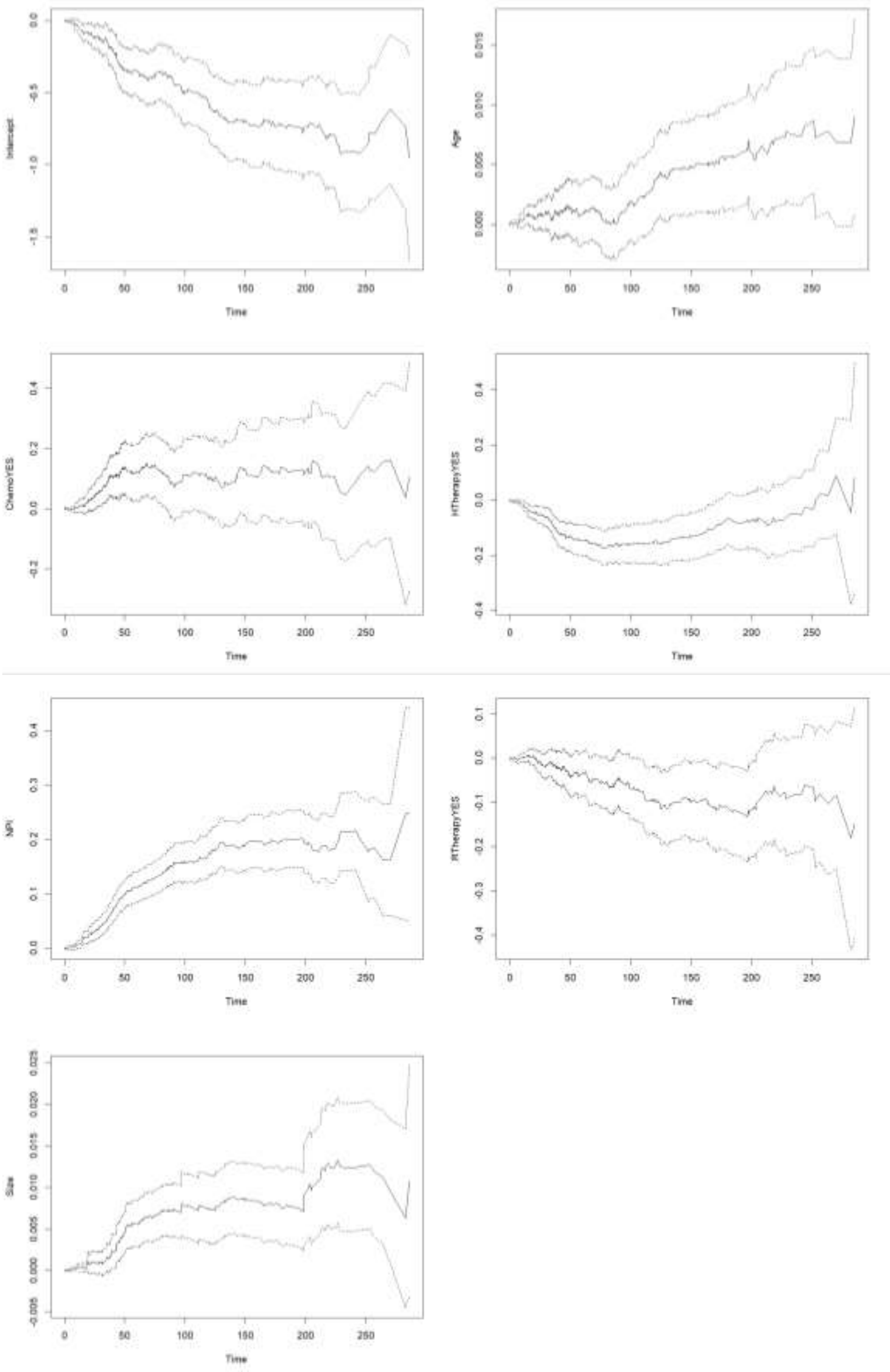

Figure 3. Aalen Plot

Figure 3 shows that the cumulative coefficient curves for all covariates do not fluctuate around zero, indicating that the covariate effects are time-dependent. Therefore, the Aalen model is preferred over the Lin–Ying model. Based on the results of the Aalen Additive Hazard analysis, it can be concluded that chemotherapy increases the risk of patient mortality. This result contradicts most of the clinical literature, which generally reports that chemotherapy reduces mortality risk. However, there is evidence supporting the possibility that chemotherapy may increase the risk of death. Chemotherapy can caused serious side effects (e.g., infections, cardiotoxicity, lymphedema), which may contribute to increased short-term mortality, especially in frail or comorbid patients (Ayodele et al., 2024; Cho et al., 2020; Jeong et al., 2025). In addition, if survival models do not fully adjust for all confounding factors (e.g., stage, comorbidities, molecular subtype), the hazard associated with chemotherapy may be overestimated (Fathoni et al., 2022; Tamirisa et al., 2020; Zhu et al., 2021).

D. CONCLUSION AND SUGGESTIONS

The analysis showed that all covariates had a significant effect on survival outcomes in breast cancer patients. Hormonal therapy and radiotherapy acted as protective factors by reducing the risk of death, while higher NPI scores, larger tumor sizes, older age, and chemotherapy were associated with higher risk. Although the Cox regression initially produced results that supported these relationships, testing of the proportional hazards assumption indicated clear violations, especially for hormone therapy and NPI score. For this reason, the Lin–Ying and Aalen additive hazard models were applied to obtain more appropriate risk estimates. While both additive models produced similar results, the Aalen plot provided clearer and more informative insights by allowing direct observation of changes in absolute risk over time through the cumulative slope. As a result, this visual approach was used as the main basis for selecting the most suitable model, rather than relying only on standard error comparisons.

Nevertheless, the findings should be interpreted carefully because the study was conducted in a single center and relied on historical medical records. Possible information bias and the lack of detailed lifestyle data may have affected the estimation of absolute risks, which limits the applicability of the results to other populations with different clinical or demographic characteristics. Future studies should aim to improve additive hazard models by addressing these limitations. In particular, developing methods for interpreting Aalen plots could reduce subjectivity in deciding whether covariate effects are constant or change over time. In addition, applying penalized regression methods to the Lin–Ying and Aalen models may help manage high-dimensional clinical data and improve the reliability of results in broader clinical settings.

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