

Survival analysis of breast cancer patients in Yogyakarta

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Submission date: 19-Aug-2023 12:41PM (UTC+0700)

Submission ID: 2147867595

File name: Survival_analysis_of_breast_cancer_patients_in_Yogyakarta.pdf (834.62K)

Word count: 5272

Character count: 25782

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To cite this article: M. Ivan Ariful Fathoni *et al* 2021 *J. Phys.: Conf. Ser.* **1722** 012060

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Survival analysis of breast cancer patients in Yogyakarta

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Abstract. A WHO survey conducted revealed that 8-9 percent of women in the world have breast cancer. The highest cancer incidence in Indonesia is breast cancer. The highest prevalence of cancer is in Yogyakarta (4.1 / mile). This research is vital to aim to assess the length of life of patients and prognostic factors associated with survival of breast cancer patients. Research subjects were breast cancer patients who went to dr. Sardjito hospital. Subject data were taken from patient medical records from July 2018 - July 2020. This study used a survival analysis (Cox proportional hazard method), with variables used including neutrophils, lymphocytes, SGOT, albumin, chemotherapy regimens, radiotherapy, hormone therapy, karnofsky index, and stadium are independent variables that will be tested on patient survival as the dependent variable. Using kaplan meier, the $-\ln[-\ln S(t)]$ curve, and the global test, it is found that all variables meet the proportional hazard assumption. Cox regression analysis used there are two stages, namely bivariate and multivariate analysis. All variables by bivariate analyzed were performed to multivariate analysis. The most significant factors based on multivariate analysis are chemotherapy regimen, hormonal therapy, and stages. This result is expected to provide medical advice regarding the proper treatment of breast cancer patients.

1. Introduction

Breast Cancer is a malignant tumor that attacks breast tissue. Breast cancer causes breast cells and tissue to change into abnormal shapes and grow out of control. The World Health Organization (WHO) in 2018 stated that breast cancer is the second largest cancer after lung cancer. The WHO estimates there are 2.088.849 new cases and 626.679 people died of breast cancer in 2018. A survey conducted by WHO reveals that approximately 2 million new breast cancer cases are found each year. It makes breast cancer the most common type of cancer in women after cervical cancer [1].

Indonesia's highest cancer incidence is breast cancer, with approximately 60 thousand new cases for each year [2]. Riskesdas [3] showed a cancer prevalence of 1.4 per mile in Indonesia. The highest prevalence of cancer is in Yogyakarta (4.1 / mile), followed by Central Java (2.1 / mile), Bali (2 / mile), Bengkulu, and Jakarta respectively 1.9 / mile [4]. Research in Indonesia found that breast cancer patients were late visiting the hospital and were diagnosed too late [5].

RSUP Dr. Sardjito as one of the leading referral hospitals in Yogyakarta that provides



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a special place for cancer patients, especially breast cancer, in the Integrated Cancer Center "TULIP". Most patients who come for treatment at the TULIP installation have entered an advanced stage. If breast cancer is found at an advanced stage, treatment becomes more difficult, expensive, and the results of treatment are unsatisfactory, and even tends to accelerate death [6]. According to Gayatri [7], one of the parameters that can be used to assess cancer treatment's success is the probability of patient survival. Besides, medical experts also use the probability of survival to estimate the length of life of patients after being diagnosed with cancer. In this study, the data used is the examination of patients during treatment at the hospital.

2. Method

The statistical analysis used in this study is survival analysis. Survival analysis is an analysis of data obtained from the record of the time achieved by an object until certain events are called failure events. One method often used in survival analysis is the cox proportional hazard model [8]. Cox first introduced this method, and the response used was data obtained from the calculation of the survival time of an event. In the cox proportional hazard model, the independent variables used must meet the proportional hazard assumption, meaning that all independent variables must be constant over time.

Some research related to the method of survival and analysis of breast cancer includes the following. Prentice and Gloeckler [9] use the Cox proportional hazard regression model to liberalize the analysis of covariate survival data substantially. Asymptotic likelihood results are given for the estimation of regression coefficients and survivor function. Siegel et al. [10] provided an analysis of cancer events' survival and all causes of death. Incidence and survival modeled by cancer type, patient sex, and age group based on malignancy cases diagnosed from 1975 to 2007. Chao, et al., [11] constructed a model of breast cancer survival analysis using SVM, Logical Regression, and Decision Trees. The data in this study are used to establish a classification of breast cancer survival patterns and offer reference decision-making treatment for the survival abilities of women diagnosed with breast cancer in Taiwan.

With the number of breast cancer events and the relationship between early detection and the length of life of patients, this research is vital to aim to assess the length of life of patients and prognostic factors associated with survival of breast cancer patients. Sinaga et al. [12] analyzed 5-year survival in breast cancer patients at Sardjito Hospital Yogyakarta. The variables examined in this study include age, marital status, occupation, education, family history, stage, tumor size, histology type, tumor location, comorbidities, and surgery. This study's results indicate that the survival rate of women with breast cancer less than 50 years old is lower. Young women with breast cancer tend to have more aggressive breast cancer growth and a higher risk of recurrence.

Based on the above problems, the researcher discusses the cox proportional hazard model in breast cancer cases with a case study of breast cancer patients undergoing treatment at Dr. Sardjito General Hospital, Yogyakarta. In contrast to the study of Sinaga et al., [12], there are laboratory outcome variables from breast cancer patient examinations in this study. This laboratory examination variable is critical to know before the patient begins to undergo periodic treatment at the hospital. This variable also affects the appropriate treatment for cancer patients.

2. Result and Discussion

Research subjects were breast cancer patients who went to Dr. Sardjito hospital. Subject data were taken from patient medical records from July 2018 - March 2020. This study used a survival analysis (Cox proportional hazard method), with variables used including neutrophils, lymphocytes, SGOT, albumin, chemotherapy regimens, radiotherapy, hormonal therapy, karnofsky index, and stadium are independent variables that will be tested on patient survival as the dependent variable.

The stages in data analysis in this study are as follows. The first step is data analysis that correlates with patient survival time. Draw a survival curve for breast cancer patients based on factors thought to influence patient survival with Kaplan Meier analysis. Test differences in the survival curves of breast cancer patients in various categories. Check proportional hazard assumptions on selected factors. Perform bivariate and multivariate analysis. It creates a stratification cox model. It determines differences in the probability of survival of breast cancer patients based on stratification variables.

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3.1. *Dependent and Independent Variables*

The dependent variable in this study is the survival time data (T) of patients with breast cancer. Survival time (T) is when patients who have breast cancer undergo treatment at Dr.Sardjito General Hospital Yogyakarta until the patient is declared dead, stopped or moved on treatment, survives, or lives in units of the day. The provisions of the survival time (T) are as follows.

- The time origin is when the initial patient enters the RSUP Dr. Sardjito for hospitalization due to breast cancer.
- Failure (failure event) is a condition when a patient with breast cancer is declared dead.
- The measurement scale of this study is in units of days.

Patient status (d) is the occurrence or failure of a failure event that is dead during the study period.

- Patient status $d = 1$, is event or uncensored data. It happens if a breast cancer patient experiences a failure event, which is death.
- Patient status $d = 0$, is censored data. It happens if the patient has not experienced a failure event until the study ends, stops, or changes treatment. Patient status (d) is the occurrence or failure of a failure event that is dead during the study period.

The amount of patient data and censored data is shown in table 1.

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Table 1: Case Processing Summary

Total N	N of Events	Censored	
		N	Percent
94	22	72	76.6

30
The independent variables used in this study are the factors that are thought to influence the survival of patients with breast cancer, which are presented in Table 2. The following is the structure of the research data presented in Table 8.

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3.2. *Kaplan Meier survival curves and log rank*

Kaplan Meier survival curves are used to determine the characteristics of the survival curve of breast cancer patients based on factors that are thought to affect the survival of breast cancer patients. The Kaplan Meier curve for the survival probability of breast cancer patients in Yogyakarta is shown in Figure 1. Figure 1 shows the survival rate of breast cancer patients in Dr. Sardjito General Hospital ranges from 0.15 to 1.

Median survival time is the mean survival time value for each group. The main reason why the median is a measure of mean survival time is that the survival time picture is not always normally distributed. The median amount of resistance time can be seen on the Y-axis at point

Table 2: Independent Variables

Symbol	Variables	Description	Value	Scale
X_1	Neutrophils	1 = abnormal	1	Nominal
		2 = normal (40-60)	0	
X_2	Lymphocytes	1 = abnormal	1	Nominal
		2 = normal (20-40)	0	
X_3	SGOT	1 = abnormal	1	Nominal
		2 = normal (5-40)	0	
X_4	Albumin	1 = abnormal	1	Nominal
		2 = normal (3,4-5,4)	0	
X_5	Chemotherapy Regimen	1 = high regimen	1	Ordinal
		2 = low regimen	0	
X_6	Radiotherapy	1 = yes	1	Nominal
		2 = no	0	
X_7	Hormonal Therapy	1 = yes	1	Nominal
		2 = no	0	
X_8	Karnofsky Index	1 = abnormal	1	Nominal
		2 = normal (0,8-1)	0	
X_9	Stages	1 = Advanced Stage (4)	1	Ordinal
		2 = Early Stage (0-3)	0	

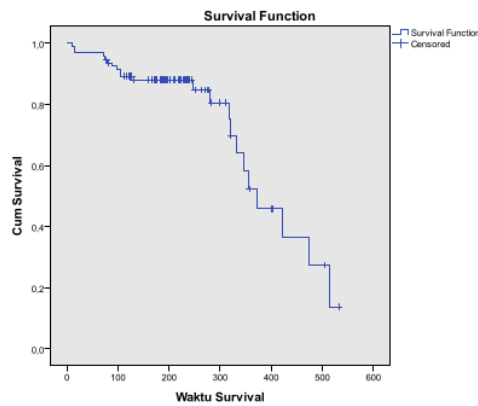


Figure 1: Survival probability curve for breast cancer patients

0.5, then draw a horizontal line to the resistance curve down to the horizontal line on the X-axis. Median survival in all subjects was 373 days, meaning that as many as 50% of subjects had died within 373 days. Based on the Kaplan Meier curve, we can also see the survival rate for a specific time.

The survival curve characteristics presented by Kaplan Meier survival curve in Figure 1 illustrate a survival curve's characteristics in general. Next, we will describe the survival curve characteristics of breast cancer patients based on factors that are thought to influence patient survival. From the nine Kaplan Meier (KM) curves in Figure 2, we can know the survival time and median survival for each group of variables survival probability curve for breast cancer patients.

The normal neutrophil group had a median survival of 422 days on the neutrophil curve, compared to 347 days for abnormal. The normal lymphocyte group curve had a median survival of 373 days, and abnormal lymphocytes 473 days. The normal SGOT group had a median survival of 422 days, while the abnormal SGOT had a median survival of 321. The group with the low chemotherapy regimen had a median survival of 473 days, while the group with the high chemotherapy regimen had 422 days. Significant differences were seen on the albumin curve, where the normal albumin group had a median survival of 355 days, while the abnormal albumin group was only 79 days.

On the radiotherapy curve, the median survival was only obtained in the patients without radiotherapy of 332 days; this is because the number of deaths in the radiotherapy group did not reach 50% of cases. The same case also occurred in the hormonal therapy and stages curve. Only the median survival in the group without hormonal therapy and the advanced stage was 332 and 321 days, respectively. The Karnofsky index group, who had the highest median survival was in the normal group at 422 days, while the abnormal group was 130 days. Karnofsky is a performance status assessment system used in cancer patients; the results of measuring the Karnofsky score are strictly related to the quality of life and the physical functional state of the patient.

Log-Rank and Breslow test is used to find out the survival curves differences between categories in one variable. Table 10 shows the log-rank and breslow test results for the nine variables that influence cancer patients' survival. Based on the table, a neutrophil p-value of 0.085/0.083 is obtained. When compared with the α value of 0.01, the p-value is more than α , so this test results in a decision rejecting H_0 . It means that there is no difference in the survival curve between normal neutrophils and abnormal neutrophils. Different results between the two tests occurred in lymphocytes and albumin, where the log-rank test results showed the p-value was more than α . On the other hand, the Breslow test result showed that the p-value was less than α . The other six variables have a p-value greater than α , there is at least one difference in the survival curve in the group. This conclusion is following the expectations based on the Kaplan Meier survival curve in Figure 2.

3.3. Proportional Hazard

Before making a model, testing the proportional hazard assumption is first tested on factors that are thought to affect the probability of survival of the patient. Melan Kaplan curves in Figure in almost every variable occur time-dependent conditions due to changes in speed, so the assumption of proportional hazard cannot be obtained only from the Kaplan Meier curve. Another way to find out proportional hazard (PH) assumptions is by the $-\ln[-\ln S(t)]$ graph method of time and the global statistical test. If each category of the variables in the plot $-\ln[-\ln S(t)]$ shows a parallel pattern, then the related variable meets the proportional hazard assumption. The graph image of $-\ln[-\ln S(t)]$ is shown in Figure 3.

The number of points or circles in the plot depends on the number of patients who experienced the event. So that if the plot does not experience the event, the plot results are not drawn. Based on the $-\ln[-\ln S(t)]$ graph by SGOT, Albumin, Chemotherapy Regimen, Radiotherapy, Hormonal Therapy, Karnofsky Index, and Stages, there are no intersection between groups of patients in each variable. However, many variables do not meet the proportional hazard assumption because the graphs appear to intersect each other, that is

Neutrophils and Lymphocytes. These results need further verification with a statistical test (global test). Statistical test results are shown in Table 9.

In Table 9, the p-value in the global test is displayed in the rightmost column. The p-value condition is higher than 0.05 states that the PH assumption is fulfilled. In Table 9, the p-value in the global test is displayed in the rightmost column. The p-value condition is higher than 0.05 states that the PH assumption is fulfilled.

Table 3: Conclusion of proportional hazard

Variables	The Kaplan Meier Curve	The $-\ln[-\ln S(t)]$ Curve	Global Test	Conclusion
Neutrophils	There are line intersections	There are line intersection	$p > 0.05$	PH assumption is fulfilled
Lymphocytes	There are line intersections	There are line intersection	$p > 0.05$	PH assumption is fulfilled
SGOT	No line intersections	No line intersection	$p > 0.05$	PH assumption is fulfilled
Albumin	No line intersections	No line intersection	$p > 0.05$	PH assumption is fulfilled
Chemotherapy Regimen	There are line intersections	No line intersection	$p > 0.05$	PH assumption is fulfilled
Radiotherapy	No line intersections	No line intersection	$p > 0.05$	PH assumption is fulfilled
Hormonal Therapy	No line intersections	No line intersection	$p > 0.05$	PH assumption is fulfilled
Karnofsky Index	There are line intersections	No line intersection	$p > 0.05$	PH assumption is fulfilled
Stages	No line intersections	No line intersection	$p > 0.05$	PH assumption is fulfilled

Based on Table 3, it can be concluded that all variables from the three examinations meet the proportional hazard assumption. The Cox regression model was used to model the survival data for breast cancer patients in Yogyakarta. There are two stages of Cox regression analysis, namely bivariate and multivariate analysis.

3.3.1. Bivariate Analysis Bivariate analysis was performed with Cox regression analysis for all variables that fulfilled the PH assumptions. Cox regression results of eight variables that meet the PH assumptions are as follows.

Based on the Table 4, the hazard ratio for neutrophils is 2,260. It can be interpreted that at any time, the abnormal neutrophils group is 2,260 times more likely to die than the normal neutrophils group. Likewise with the other hazard ratio variables. All variables by bivariate analyzed in Table 4 have a condition of p-value < 0.1 . Based on that, then all variables were performed multivariate analysis.

Table 4: Bivariate Analysis Results

Variables	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Neutrophils	0,815	0,487	2,806	1	0,094	2,260	0,871	5,864
Lymphocytes	0,879	0,453	3,761	1	0,052	2,408	0,991	5,852
SGOT	1,192	0,448	7,098	1	0,008	3,295	1,371	7,922
Albumin	1,191	0,573	4,318	1	0,038	3,291	1,070	10,121
Chemotherapy Regimen	-0,271	0,462	7,559	1	0,006	0,280	0,113	0,694
Radiotherapy	-2,627	1,025	6,573	1	0,010	0,072	0,010	0,539
Hormonal Therapy	-2,718	1,024	7,041	1	0,008	0,066	0,009	0,492
Karnofsky Index	2,209	0,530	17,364	1	0,000	9,110	3,223	25,754
Stages	2,272	0,566	16,093	1	0,000	9,702	3,197	29,448

3.3.2. *Multivariate Analysis* The variables included in the multivariate analysis were the variables in the bivariate analysis with a p-value < 0.1, that is all variables. In multivariate analysis, the analysis of the relationship between variables is carried out. The analysis results were obtained using the Backward Stepwise (Likelihood Ratio) method. The variable with the largest p-value in each step will be removed for the next stage of analysis. The results of this analysis were reviewed from the p-value < 0.3 and p-value < 0.1.

Table 5: Multivariate Analysis Results in Step 4

Variables	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Albumin	-1,213	0,890	1,860	1	0,173	0,297	0,052	1,700
Karnofsky Index	1,023	0,735	1,935	1	0,164	2,782	0,658	11,757
Neutrophil	0,973	0,878	1,228	1	0,268	2,645	0,473	14,772
Chemotherapy Regimen	-1,122	0,808	1,931	1	0,165	0,325	0,067	1,585
Hormonal Therapy	-1,780	1,127	2,494	1	0,114	0,169	0,019	1,536
Stages	1,565	0,947	2,730	1	0,098	4,783	0,747	30,614

Table 5 displays the results of the analysis using p-value < 0.3. The results of the analysis stop at step 4 with 6 significant variables, i.e. albumin, hormonal therapy, karnofsky index, neutrophil, stages, and chemotherapy. If specifying p-value < 0.1, then the analysis stopped at step 7 where there were only three significant variables, i.e. Stages, Chemotherapy regimen, and Hormonal Therapy, see Table 6.

Table 6: Multivariate Analysis Results in Step 7

Variables	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Chemotherapy Regimen	-1,401	0,751	3,477	1	0,062	0,246	0,057	1,074
Hormonal Therapy	-1,584	1,085	2,132	1	0,144	0,205	0,024	1,720
Stages	2,018	0,803	6,308	1	0,012	7,522	1,558	36,327

Based on Table 6, there are three variables affect the survival of breast cancer patients in Yogyakarta. The variables from Table 5 that were eliminated successively include Neutrophil, Albumin, and Karnofsky Index. Based on the parameter estimation results in Table 6, the Cox Proportional Hazard (Hazard Function) regression model is obtained in equation (1). As for the survival function, the formula obtained in equation (2).

$$\begin{aligned}
 H(t) &= H_0(t) \exp(y) \\
 &= H_0(t) \exp(-1,401X_5 - 1,584X_7 + 2,018X_9)
 \end{aligned} \tag{1}$$

$$\begin{aligned}
 S(t) &= S_0(t)^{\exp(y)} \\
 &= S_0(t)^{\exp(-1,401X_5 - 1,584X_7 + 2,018X_9)}
 \end{aligned} \tag{2}$$

where $H(t)$ is hazard at a certain time, $H_0(t)$ is baseline hazard at a certain time, $S(t)$ is survival at a certain time, and $S_0(t)$ is baseline survival at a certain time.

3.4. Recommendation

The hazard function and survival function model based on equations 1 and 2 can be applied to calculate the patient's hazard and the probability of survival at any given time. The $X_5, X_7,$ and X_9 values adjust the conditions in Table 2. The $H_0(t)$ and $S_0(t)$ values can be obtained from the Table 7. In survival tables, we get information about the baseline hazard and baseline survival.

For example, we want to know the hazard and the survival probability of advanced stage breast cancer patients who underwent chemotherapy on day 104 with a low regimen and hormonal therapy. In that case, we have

$$\begin{aligned}
 H(t) &= H_0(t) \exp(-1,401X_5 - 1,584X_7 + 2,018X_9) \\
 H(104) &= (0,088) \exp(-1,401(0) - 1,584(1) + 2,018(1)) \\
 &= 0,1
 \end{aligned}$$

Hazard is the speed at which an event occurs, which is mathematically a comparison between incidents and time. In this case example, a hazard value 0,1 was obtained.

$$\begin{aligned}
 S(t) &= S_0(t)^{\exp(-1,401X_5 - 1,584X_7 + 2,018X_9)} \\
 S(104) &= (0,971)^{\exp(-1,401(0) - 1,584(1) + 2,018(1))} \\
 &= 0,4
 \end{aligned}$$

The probability of survival of patients until day 104 in this case sample is obtained 0.4.

Table 7: ²⁴Survival Table

Time	Baseline	At mean of covariates		
	Cum Hazard	Survival	SE	Cum Hazard
14	0,014	0,995	0,005	0,005
71	0,030	0,990	0,009	0,010
74	0,048	0,984	0,012	0,016
97	0,068	0,977	0,016	0,023
104	0,088	0,971	0,020	0,030
105	0,111	0,963	0,024	0,037
130	0,138	0,955	0,029	0,047
280	0,219	0,929	0,042	0,074
321	0,351	0,889	0,067	0,118
332	0,527	0,838	0,093	0,177
347	0,743	0,779	0,124	0,250

4. Conclusion

Several factors influence ¹³the survival ³of breast cancer patients in Yogyakarta. The most significant factors based on this study were the chemotherapy regimen, hormonal therapy, and stage. The stage of cancer had the most significant impact on decreasing patient survival. Early detection of the stage of ³cancer by laboratory tests is crucial to prevent worse effects and increase the chances of recovery. The higher the stage, the more difficult it is to treat, and the smaller the patient's life expectancy. Chemotherapy treatment with the right regimen and hormonal therapy ²as a follow-up treatment also dramatically determines the patient's survival. This research is expected to provide medical advice regarding the proper handling of breast cancer patients.

Acknowledgments

The author thanks the Deputy for Research and Strengthening Development of the Ministry of Research and Technology Indonesia (The National Research and Innovation Agency) which has provided research funding based on decree number 27/E1/KPT/2020 and contract number agreements 6/AMD/E1/KP.PTNBH/2020 and 3068/UN1.DITLIT/DIT-LIT/PT/2020 as well as Jogja Cancer Registry for data availability and discussion of research results.

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Appendix

Table 8: Research Data Structure

Patients	T	d	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9
1	t_1	0/1	x_{11}	x_{12}	x_{13}	x_{14}	x_{15}	x_{16}	x_{17}	x_{18}	x_{19}
2	t_2	0/1	x_{21}	x_{22}	x_{23}	x_{24}	x_{25}	x_{26}	x_{27}	x_{28}	x_{29}
3	t_3	0/1	x_{31}	x_{32}	x_{33}	x_{34}	x_{35}	x_{36}	x_{37}	x_{38}	x_{39}
:	:	:	:	:	:	:	:	:	:	:	:
i	T_i	0/1	x_{i1}	x_{i2}	x_{i3}	x_{i4}	x_{i5}	x_{i6}	x_{i7}	x_{i8}	x_{i9}

where

$i : 1, 2, 3, \dots, n$

T_i : survival time for patient i

d_i : patient status i

X_{i1} : neutrophil variable value for patient i

X_{i2} : lymphocyte variable value for patient i

X_{i3} : SGOT variable value for patient i

X_{i4} : albumin variable value for patient i

X_{i5} : regimen chemotherapy variable value for patient i

X_{i6} : radiotherapy variable value for patient i

X_{i7} : hormonotherapy variable value for patient i

X_{i8} : karnofsky index variable value for patient i

X_{i9} : stage variable value for patient i

Table 9: Conclusion of Global Test

Variable (Global Test)	Chi2	df	Prob>Chi2
Neutrophils	0.47	1	0.4917
Lymphocytes	1.69	1	0.1941
SGOT	1.70	1	0.1922
Albumin	3.11	1	0.0779
Chemotherapy Regimen	1.50	1	0.2214
Radiotherapy	0.46	1	0.4971
Hormonal Therapy	0.68	1	0.4086
Karnofsky Index	0.59	1	0.4437
Stages	1.25	1	0.2635

Table 10: Log-Rank (L) and Breslow (B) Test

Variables	L	Chi-Square	df	Sig.
	B			
Neutrophils	L 2,961	1	0,085	
	B 2,997	1	0,083	
Lymphocytes	L 3,976	1	0,046	
	B 7,048	1	0,008	
SGOT	L 7,790	1	0,005	
	B 11,392	1	0,001	
Albumin	L 4,701	1	0,030	
	B 13,264	1	0,000	
Chemotherapy Regimen	L 8,551	1	0,003	
	B 10,885	1	0,001	
Radiotherapy	L 11,273	1	0,001	
	B 7,632	1	0,006	
Hormonal Therapy	L 12,553	1	0,000	
	B 9,539	1	0,002	
Karnofsky Index	L 25,540	1	0,000	
	B 13,488	1	0,000	
Stages	L 22,411	1	0,000	
	B 25,248	1	0,000	

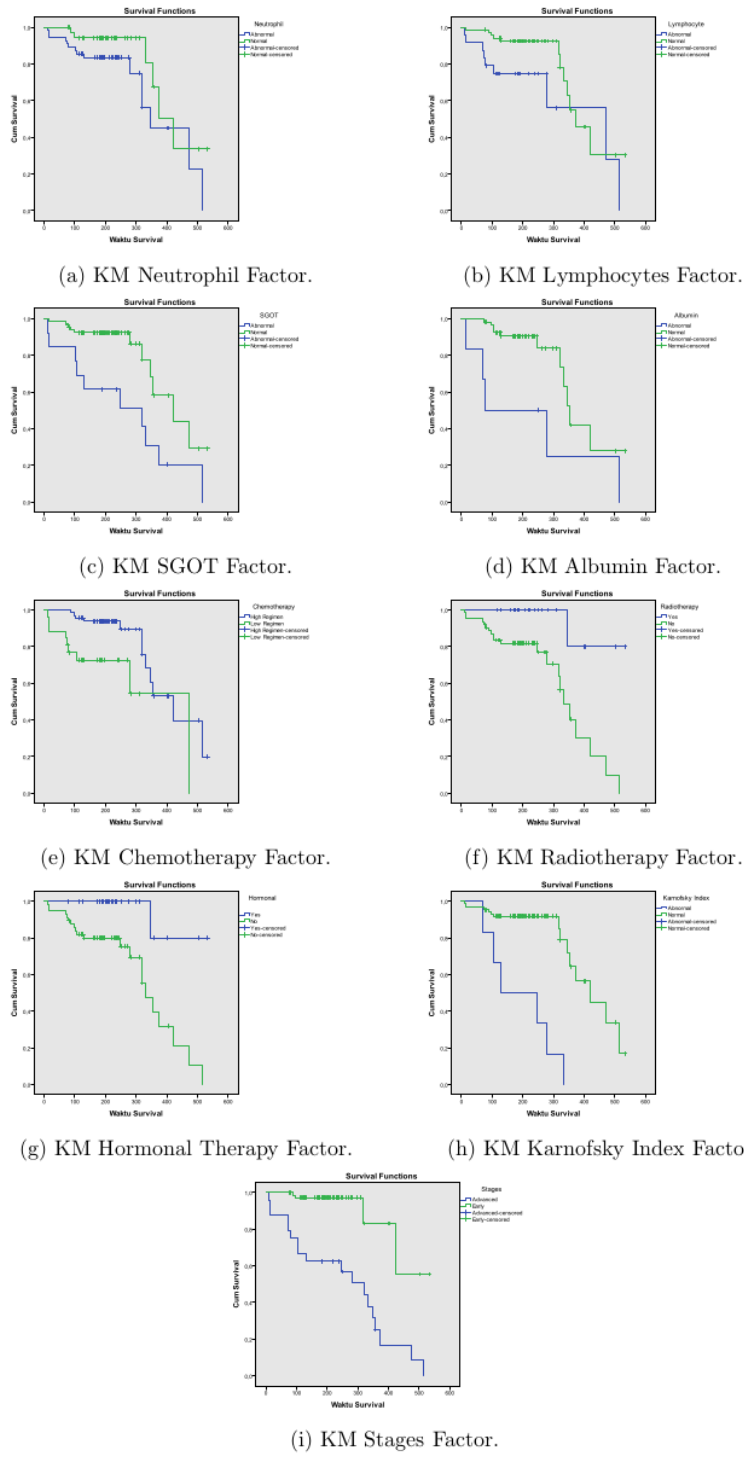


Figure 2: Survival probability curve based on variables.

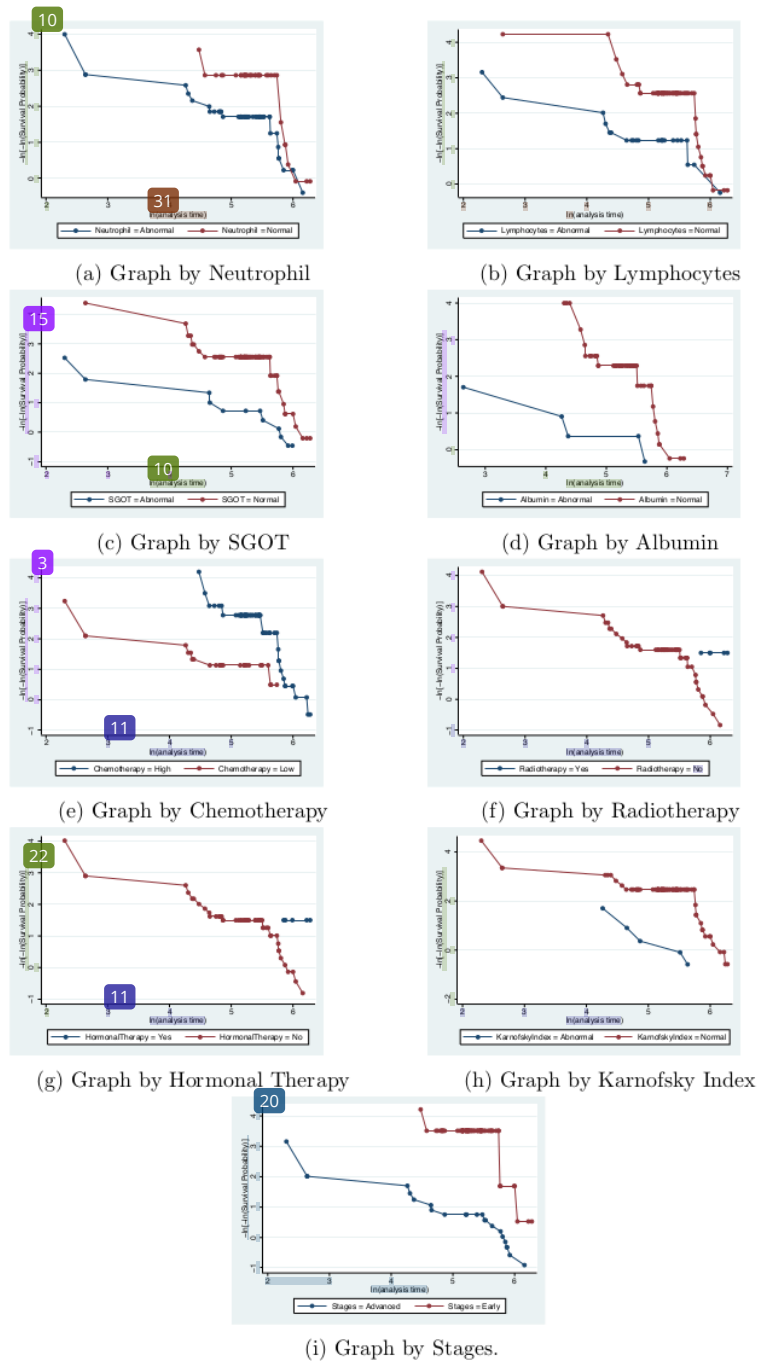


Figure 3: The $-\ln[-\ln S(t)]$ graph based on variables

Survival analysis of breast cancer patients in Yogyakarta

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