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APPLICATION OF COX PROPORTIONAL HAZARD REGRESSION FOR ANALYZING FACTORS INFLUENCING THE RECOVERY RATE OF PULMONARY TUBERCULOSIS PATIENTS

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ABSTRACT

Pulmonary tuberculosis is a serious disease that requires special attention from the community and the Government of Indonesia, especially the Maluku Province. One commonly used analytical method in the health field is survival analysis. Survival analysis is a statistical method related to observing the period until the occurrence of an event or events. This study aims to model and identify factors that affect the recovery rate of patients with pulmonary tuberculosis in Ambon City using Cox Proportional Hazard regression. The results of the Hazard Ratio interpretation show that the variables that have a significant influence are chest pain and night sweats. Specifically, patients experiencing chest pain exhibit a recovery rate 0.487264 times faster than those devoid of such symptoms. Similarly, patients experiencing night sweats demonstrate a recovery rate of 0.619839 times faster than their counterparts not experiencing this symptom. This study highlights the imperative of recognizing and addressing symptoms like chest pain and night sweats in managing pulmonary tuberculosis in Ambon City.

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1. INTRODUCTION

Survival analysis is a statistical method related to observing the period until an event or event occurs. Furthermore [1], this analysis involves observing or observing the length of time it takes from a starting point of research to reaching an event that is in focus research. Generally, this method is used to analyze data collected prospectively in a certain period [2].

In medical-related research, the event assigned as the end point of the study is often related to mortality parameters or survival time. However, this analysis method can also be applied to endpoints that are less fatal or do not indicate death, such as observation of the time of return symptoms of a disease or duration of time decrease in symptoms of a particular disease [3]. Therefore, the application of this method can allow a deeper understanding of temporal changes in the health phenomena of the patient being observed, in particular, patients who have certain diseases. Diseases studied using this approach often highlight fatal conditions, such as leukemia, cancer, diabetes, tuberculosis, or other serious diseases.

In the context of health in Indonesia, tuberculosis is one of the serious diseases that require special attention by the public and the government, and survival analysis can be one method that is used to provide understanding and treatment of the disease [4]. Pulmonary tuberculosis (TB) is an infectious disease primarily affecting the lungs, with extrapulmonary manifestations also falling under its classification when concurrent. Historically, TB has been a significant global health concern, often referred to as "consumption" due to its debilitating effects. Characterized by a persistent productive cough lasting over two weeks, accompanied by symptoms like hemoptysis, chest pain, night sweats, and systemic manifestations such as fatigue and weight loss, TB remains a challenge despite medical advancements, necessitating a comprehensive understanding of effective management and control [5].

Previous research on pulmonary tuberculosis and it's influencing factors using chi-square analysis and binary logistic regression methods established that factors such as chronic cough, appetite and weight loss, fever, night sweats, dyspnea, and hemoptysis [6] [7] exhibit notable influence on pulmonary tuberculosis in patients. Additionally, other variables such as comorbidities [8] and age [9] have been identified as additional factors affecting the occurrence of pulmonary tuberculosis in patients as well. Based on the report of the Ministry of Health of the Republic of Indonesia, Indonesia [10] is a country that ranks second highest in the world after India in terms of the number of pulmonary tuberculosis sufferers, with 969 thousand cases and 93 thousand deaths per year. The information indicates that an average of 11 people die every hour from this disease.

Maluku Province is a province that is in the spotlight of the government because the success rate of pulmonary tuberculosis treatment only reaches 78.7%, making Maluku one of the provinces with the success rate lowest treatment in Indonesia. In addition, the Ministry of Health of the Republic of Indonesia identified [11] Maluku as one of eight provinces that have treatment coverage (TC) and success rate (SR) that do not reach the target (TC<90% and SR< 90%). With an estimated 7584 cases of tuberculosis and 4787 confirmed cases of tuberculosis, this problem is a serious issue that is urgent for the government to address.

One popular method often used in survival analysis is the Cox Proportional Hazard. This model is popular in various fields of research, including in medical research, because it can provide flexibility in dealing with varied data situations without requiring specific time distribution specifications. Some previous studies that applied the Cox Proportional Hazard model were researched by Faisal et al (2020) who applied the Cox Proportional Hazard model to analyze factors affecting hospitalized patients with typhoid fever at RSUD Haji Makassar [12]. Then research by Modeong et al. (2023) uses the Cox Proportional Hazard model to analyze pulmonary tuberculosis patient survival rate [8], and research by Li et al. (2020) compares the Cox Proportional Hazard model with the Proportional Baselines Landmark Supermodel (PBLS) in analyzing cervical cancer patient survival [13].

In other words, this model can provide a solution to overcome the complexity of survival data often encountered in studies with complex medical data where the timing of events can differ among patients after conducting research [1]. Therefore, the Cox Proportional Hazard model can be used to facilitate understanding of the factors that affect the recovery rate of pulmonary tuberculosis hospitalized patients in Ambon City.

2. RESEARCH METHODS

2.1 Survival Function and Hazard Function

Kleinbaum & Klein (2012) define survival function S(t) as a function that can explain the probability or chance that a person can survive longer than a t predetermined time [1]. In other words, it can describe the probability that a random variable (patient survival time) will exceed a certain time value. Mathematically, the survival function can be expressed as follows:

$$S(t) = P(T > t), 0 \leq t \leq \infty \quad (1)$$

Then, the survival function can be described by utilizing the cumulative function definition $F(t) = P(t \leq T)$ as follows:

$$S(t) = P(T > t) = 1 - P(T \leq t) = 1 - F(t) \quad (2)$$

Furthermore, Kleinbaum & Klein (2012) describe the hazard function as a function that can be considered as a concept that provides different information when compared to the survival function [1]. The hazard function is defined as the probability for an event to fail instantly per unit of time, focusing on the failure of an event. Where the concept is a concept that conflicts with the concept of the survival function which highlights the "not" failing of an event.

The hazard function h(t) is the probability that an individual will experience a failed event in a time interval Δt. This function helps in understanding the degree of failure risk at any point in time and evaluating potential changes in survival behavior as time changes. So that the hazard function can be defined as follows:

$$h(t) = \lim_{\Delta t \to 0} \frac{p(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \quad (3)$$

Then, using the conditional probability theorem obtained the relationship of hazard functions which can be expressed as follows [14]:

$$h(t) = \frac{f(t)}{S(t)} = -\left[\frac{dS(t)/dt}{S(t)}\right] = -\frac{d}{dt} \ln S(t) \quad (4)$$

2.2 Cox Proportional Hazard Model

The Cox Proportional Hazard model was invented by Cox in 1972 and is called the Cox model because it is based on the assumption of proportional hazard, where the hazard function of different individuals is considered constant or proportional [15]. This model falls into the category of semi-parametric distribution because it does not require specific information about the distribution of survival time used in the study. In addition, the basic hazard functions used do not have to be specified to estimate regression parameters from the model [16].

The Cox Proportional Hazard model presents an expression that for hazard at times t for individuals with certain characteristics of a set of predictor variables denoted by **X**. Cox's model formula states that the hazard function at t time is based on two quantities, namely the basic hazard function $h_0(t)$ and the exponential e for linear sum of $\beta_i X_i$, where the sum involves a p number of predictor variables **X** [1].

Formally and theoretically, the Cox Proportional Hazard model is generally formulated with the following hazard model formula:

$$h(t, \boldsymbol{X}) = h_0(t) e^{\sum_{i=1}^{p} \beta_i \boldsymbol{X}_i} \quad (5)$$

with $h(t, \mathbf{X})$ as hazard with t times and vector predictor variables **X**, $h_0(t)$ as basic hazard functions, β_i as regression parameters for variables X_i and $\sum_{i=1}^{p} \beta_i X_i$ as linear sums of the product of regression parameters and predictor variables.

2.3 Proportional Hazard Assumption

The PH assumption implies that the relative hazard function between individuals remains constant over time [17]. In other words, the ratio between the hazard of two particular individuals is fixed and does not change over time. This concept reflects that the effect of predictor variables on hazard remains proportional

throughout the observation period, ensuring consistency of association between variables and survival risk levels.

A common approach to estimating proportional hazard assumptions is through chart analysis and the Goodness of Fit (GOF) test. The graph approach is carried out with log-minus-log survival plots or hazard cumulative log plots, where it is assumed that the proportional hazard assumption will be met if the survival time between each category of predictor variables is parallel and/or graphs of survival function estimates of the time between observation curves are parallel. The disadvantage of using a graph/plot approach is that it is subjective; Whether it is parallel or not depends on the perspective of the researcher **[18]**.

2.4 Hazard Ratio

The Cox model is a regression model in survival analysis that provides hazard ratio estimates along with confidence estimates. The hazard ratio is an estimate of the hazard rate ratio of the treatment group and the control group. The hazard rate, in this context, describes the probability that if an event has not occurred in a time interval, then it will occur in the next time interval, divided by the length of that interval **[19]**.

The hazard ratio indicates the increased or decreased risk of an individual with certain characteristics and can be used to interpret cox regression models. The cox regression equation $h(t, X_j) = h_0(t)e^{\beta \boldsymbol{X_j}}$ for the set of covariates x_0 and x_1 of two individuals, then obtained

$$\left[\frac{h(t,\boldsymbol{X}_1)}{h(t,\boldsymbol{X}_0)}\right] = \frac{h_0(t)e^{\beta \boldsymbol{X_1}}}{h_0(t)e^{\beta \boldsymbol{X_0}}} = \frac{e^{\beta \boldsymbol{X_1}}}{e^{\beta \boldsymbol{X_0}}} = e^{(\boldsymbol{X}_1 - \boldsymbol{X}_0)\beta}, \forall t > 0 \qquad (6)$$

The equation shows the magnitude of the relative ratio of individuals to risk factors X_1 compared to risk factors X_0 of other individuals. Then, the value of $e^{\beta j}$ is the hazard ratio that can be related to the value of X_j **[15]**.

$$\left[\frac{h(t,\boldsymbol{X}_{j+1})}{h(t,\boldsymbol{X}_0)}\right] = e^{\beta_j}, \forall t > 0 \qquad (7)$$

This equimplifies the comparison of hazard for individuals with covariate X_{j+1} relative ti X_0. If β_j is greater than 1, it indicates an increased hazard for X_{j+1} compared to X_0 and vice versa.

The equation is equivalent to

$$\left[\frac{h(t,\boldsymbol{X}_{j+1}) - h(t,\boldsymbol{X}_j)}{h(t,\boldsymbol{X}_j)}\right] = e^{\beta_j} - 1, \forall t > 0 \qquad (8)$$

So, $e^{\beta_j} - 1$ can be interpreted as the percentage change in hazard value for each rise and fall of $\mathbf{X}_j$ by assuming other covariates are fixed. The β_j parameter conjecture value can be used for hazard values with three (3) categories, as follows **[20]**:

1. $\beta_j > 0$ shows that an increase in X_j value will increase the hazard value or risk of an individual experiencing failure.
2. $\beta_j < 0$ shows that an increase in X_j value will decrease the hazard value or risk of an individual experiencing failure.
3. $\beta_j = 0$ shows that the risk of an individual experiencing failure is as great as the risk of the individual not failing.

2.5 Data Analysis

This type of research is a case study, which models the duration of the patient's hospitalization based on factors that are thought to be influential using Cox Proportional Hazard regression. The data used in this study was sourced from Tuanaya (2023) with 95 patients data that are obtained from the archives library of the Department of Mathematics, Faculty of Mathematics and Natural Sciences, Pattimura University **[21]**.

The variables used in this study amounted to 7 variables with the following details

Table 1. Research Variables

Variable	Variable Name	Category	Scale	Unit
Y	Survival time	-	Ratio	Day
d	Patient status	0 : Censored 1: Uncensored	Nominal	-
X_1	Age	-	Ratio	Year
X_2	Gender	0: Male 1: Female	Nominal	-
X_3	Hemoptysis	0: No 1: Yes	Nominal	-
X_4	Chest pain	0: No 1: Yes	Nominal	-
X_5	Night Sweats	0: No 1: Yes	Nominal	-

Data analysis will be carried out with the help of R software, with the following stages:

a. Descriptive analysis of research variables
b. Proportional Hazard assumption testing
c. Cox Proportional Hazard Regression Parameter Estimation
d. Significance Test of Cox Regression Proportional Hazard Parameters
e. Hazard Ratio Value Interpretation

3. RESULTS AND DISCUSSION

3.1 Descriptive Analysis

Descriptive statistics are used to describe the characteristics of survival time of patients with pulmonary tuberculosis and identify factors that are thought to affect the recovery rate of patients with pulmonary tuberculosis. Factors to be identified include age, sex, hemoptysis, chest pain, and night sweats. Descriptive information in this study will be displayed in the form of average tabulation, standard deviation, maximum, minimum, and pie chart values.

Table 2. Descriptive Analysis of Survival Time and Age

Variable	Average	At least	Maximum	Standard Deviation
Survival Time	7.353	1.000	25.000	4.253
Age	37.284	13.000	75.000	15.310

Within the scope of this study, the survival time of tuberculosis patients refers to the time when a person receives a diagnosis of pulmonary tuberculosis and is hospitalized at Dr. M. Haullusy Hospital and Al Fatah Hospital until the patient is declared to have improved clinical condition. The average survival time of pulmonary tuberculosis patients in this study was about 7 to 8 days, with the shortest time span being 1 day and the highest being 25 days. A survival time standard deviation of 4.253 indicates the degree of variation or dispersion within the study group. In addition, the age of patients at the time of receiving a diagnosis of pulmonary tuberculosis had an average of between 37 and 38 years, with the youngest patient aged 13 years and the oldest patient aged 75 years. The standard deviation of patient age of 15.310 indicates significant variation in the age of pulmonary tuberculosis patients in the context of this study.

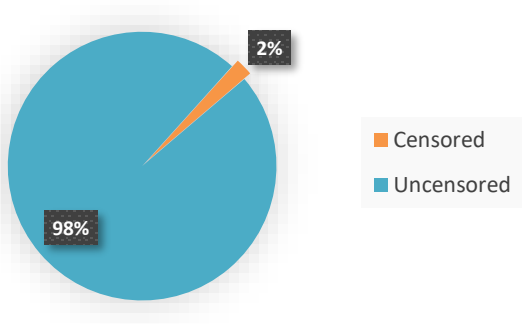

Figure 1. Patient Censorship Status

Based on **Figure 1**, it can be seen that out of the total 95 data points of patients in this study, a minimal proportion, specifically 2%, equivalent to 2 data points, is identified as censored data. In contrast, the majority, constituting 98% or 93 data points, is categorized as uncensored data. The presence of censored data in the dataset implies instances where information about the survival time of pulmonary tuberculosis patients is limited or incomplete.

Furthermore, descriptive analysis will be displayed for other categorical factors that are also considered to affect the cure rate of pulmonary tuberculosis patients.

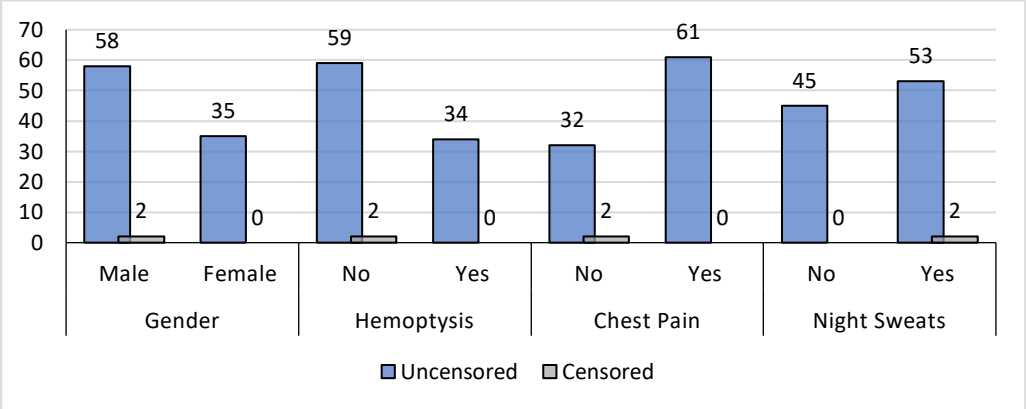

Figure 2. Distribution of Other Categorical Factors

Figure 2 presents the distribution of categorical variables, including gender, hemoptysis, chest pain, and night sweats within the dataset. A consistent trend is observed across uncensored patients, primarily comprising male patients without hemoptysis or chest pain but experiencing night sweats. Similarly, the majority of the censored patients consist of male patients who didn't experience hemoptysis but experienced chest pain and night sweats. Among these variables, chest pain emerges as the most prevalent symptom, affecting 61 patients. Notably, night sweats exhibit a balanced distribution, with 55% of patients experiencing them and 45% not.

3.2 Proportional Hazard Assumption Test

Proportional Hazard assumptions test in cox regression modeling can be done in several ways such as the graph method and through the Goodness of Fit Test. The hypotesis used for the test is:

H_0 : The proportional hazard assumption is met

H_a : The proportional hazard assumption is not met

In this study, the Goodness OF Fit Test will be used to test the assumption of Proportional Hazard as seen in **Table 3**.

Table 3. Goodness of Fit Test Results

Variable	Chisq	p − value	Decision
X_1	2.440	0.12	Failed to reject H_0
X_2	0.083	0.77	Failed to reject H_0
X_3	1.060	0.30	Failed to reject H_0
X_4	0.137	0.71	Failed to reject H_0
X_5	0.451	0.50	Failed to reject H_0

Based on **Table 3**, it appears that the $p-$value for all independent variables are greater than the significant level $\alpha = 0.05$.so that the resulting decision is a failure to reject H_0. This means that all variables have met the Proportional Hazard assumption so that cox Prortional Hazard regression modeling can be performed.

3.3 Parameter Estimation

Cox Proportional Hazard regression is one of the regression models that can be used to model survival time. This regression can be done after meeting the proportional hazard assumption. The following is given an estimate of the Cox Proportional Hazard Regression parameter.

Table 4. Cox Proportional Hazard Regression Parameter Estimation

Variable	COEF	Exp(coef)	Se(coef)	p − value	Decision
X_1	-0.004171	0.995838	0.007994	0.60183	Failed to reject H_0
X_2	0.385390	1.470187	0.230151	0.09403	Failed to reject H_0
X_3	0.049254	1.050487	0.224017	0.82598	Failed to reject H_0
X_4	-0.718948	0.487264	0.243647	0.00317	Reject H_0
X_5	-0.478295	0.619839	0.224341	0.03301	Reject H_0

Based on **Table 4**, parameter estimation for Cox Proportional Hazard regression are obtained, taking into account column 2 (coef), a temporary Cox Proportional Hazard regression model can be formed for all independent variables as follows:

$$h(t, \boldsymbol{X}) = h_0(t) exp\ (-0.004171X_1 + 0.385390X_2 + 0.049254X_3 - 0.718948X_4 - 0.478295X_5)$$

3.4 Parameter Significance Test

A parameter significance test has been conducted to assess the collective and individual impact of independent variables on the dependent variable. The Likelihood Ratio test statistics were employed for a simultaneous examination of the independent variables' significance, while the Wald test statistics were used for a partial assessment, analyzing the individual influence of each independent variable on the dependent variable. Hypotesis used for likelihood ratio test is:

H_0 : All independent variables have no significant effect on the duration of the patient's hospitalization.

$(\beta_1 = \beta_2 = \cdots = \beta_5)$

H_a : At least one independent variable has a significant effect on the the duration of the patient's hospitalization.

(There's at least one $\beta_j \neq 0, j = 1, 2, \ldots, 5$)

The following are given the results of parameter significance test.

Table 5. Simultaneous significance test using likelihood ratio test

Test	Chi Square	Df	p − value	Decision
Likelihood Ratio	12.05	5	0.03414	Reject H_0

Table 5 shows the results of the Likelihood Ratio test used to test the significance of the parameters simultaneously. Based on Table 5, it can be seen that the Likelihood Ratio value is 12.05 with degree of

freedom 5 and p − value 0.00314 which is smaller than the significant level $\alpha = 0.05$ so that the resulting decision is rejected H_0. This implies that there is at least one independent variable significantly affecting the duration of the patient's hospitalization.

After conducting simultaneous parameter significance tests, then partial parameter significance test is carried out to find out what variables have a significant influence on the duration of the patient's hospitalization. Hypothesis used for the test is :

H_0 : The independent variables have no significant effect on the duration of the patient's hospitalization.

$(\beta_j = 0, j = 1, 2, \dots, 5)$

H_a : The independent variable has a significant effect on the the duration of the patient's hospitalization.

$(\beta_j \neq 0, j = 1, 2, \dots, 5)$

Based on **Table 4**, the p − value for the variables X_1, X_2, X_3 successively are 0.60183, 0.09403, and 0.82598 which are greater than the significant level $\alpha = 0.05$ so that the resulting decision is a failure to reject H_0. This means, it is partially X_1, X_2, X_3 variable does not have a significant influence on the duration of the patient's hospitalization. As for X_4 and X_5 variables are having p − value respectively as 0.00317 and 0.03301 which are smaller than the significant level $\alpha = 0.05$ so that the resulting decision is rejected H_0. This means that partially, X_4 and X_5 variables have a significant influence on the duration of the patient's hospitalization

After carrying out significance testing both simultaneously and partially, a Cox Proportional Hazard regression model can be formed based on variables that have a significant effect as follows.

$$h(t, \boldsymbol{X}) = h_0(t) exp\ (-0.718948X_4 - 0.478295X_5)$$

3.5 Interpretation of Hazard Ratio Values

Interpretation of the Cox Proportional Hazard regression model can be done by looking at the the Hazard ratio value based on variables that have a significant effect. Below are given the Hazard ratio value for the independent variable that has a significant effect as follows.

Table 6. Hazard Ratio Value

Variable	Hazard Ratio
Chest pain (X_4)	0.487264
Night Sweats (X_5)	0.619839

According to the findings presented in **Table 6**, it can be inferred that pulmonary tuberculosis patients who exhibit symptoms of chest pain demonstrate a faster recovery rate, approximately 0.487264 times higher than that of patients who do not experience chest pain. Similarly, patients with pulmonary tuberculosis who report experiencing night sweats exhibit an accelerated cure rate, approximately 0.619839 times higher than patients who do not manifest symptoms of night sweats.

4. CONCLUSIONS

Based on the comprehensive analysis presented in the results and discussion, a compelling conclusion can be drawn. It is evident that the factors of chest pain and night sweats exert a notable and statistically significant influence on the recovery rate of pulmonary tuberculosis patients in Ambon City in the year 2021. In simpler terms, patients who are experiencing chest pain and night sweats are more likely to recover from pulmonary tuberculosis within the observed timeframe. The resulting Cox Proportional Hazard regression model is

$$h(t, \boldsymbol{X}) = h_0(t) exp\ (-0.718948X_4 - 0.478295X_5)$$

The results of the Hazard Ratio interpretation show that the variables that have a significant influence are chest pain (X_4) and night sweats (X_5). Therefore, patients with chest pain and night sweats might require

closer observation to evaluate disease advancement. This is because the strong medical link between these symptoms and higher recovery rates indicating a potentially better response to therapy. If there are indications of progress, doctors may continue their treatment as planned. However, if symptoms worsen or other complications arise, more aggressive actions or changes in treatment plans can be initiated promptly.

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