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Comorbid of Chronic Kidney Disease (CKD) Patients who Undergoing Dialysis in Indonesia Using Firth Logistic Regression

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Abstract. Cases of non-communicable diseases (NCD) in Indonesia tend to increase, one of which is Chronic Kidney Disease (CKD). CKD has become a global health problem because of the difficulty of treatment and expensive medical costs. CKD often refers to a a silent killer disease that develops without providing previous symptoms. One of the alternative treatments is dialysis. According to the 2018 Riskesdas, more than fifty percent of CKD patients who are undergoing dialysis is the productive age people. Ten percent to forty percent of these patients also have comorbid CKD like diabetes mellitus and hypertension. The study aims to analyze the determinant of CKD patients who undergo dialysis in Indonesia. Based on the 2018 Riskesdas, 17 percent of CKD patients undergo dialysis. Because of this condition, logistic regression modeling with an imbalance of the binary response (success and failure categories) could create a bias in the predicted probabilities. The stronger the imbalance of the response variable is, the more severe is the bias in the predicted probabilities; therefore, the firth logistic regression method is used to avoid bias. Based on the results, diabetes mellitus status, hypertension status, age, and the lack of fruits and vegetable consumption significantly affect the dialysis status of CKD patients. Thus, the community is always expected to adopt a healthy lifestyle and increase awareness of personal health by regularly checking their health at the health facility.

INTRODUCTION

Health is essential so that humans can move and survive. Healthy individuals are expected to become quality human resources who play a role in development to realize the welfare of society. This is under the third goal of the Sustainable Development Goals (SDGs), which is to ensure a healthy life and support the welfare of all. However, the facts in the world of health show that there are new challenges, namely the occurrence of changes in disease patterns that becomes increasingly complex due to the impact of social and economic changes. The non-communicable disease (NCD) cases tend to increase significantly over time. Indonesia is also in a phase of epidemiological transition where mortality due to NCD continues to increase, while deaths from infectious diseases are declining. The phenomenon is predicted to continue [1]. According to the results of Riskesdas 2018, NCD prevalence increases compared to the results of Riskesdas 2013, including cancer, stroke, chronic kidney failure, diabetes mellitus, and hypertension. Based on FIGURE 1, there was an increase in cancer prevalence from 0.14% in 2013 to 0.18% in 2018. Strokes increased from 0.7% to 1.09%, and chronic kidney failure (CKD) increased from 0.2% to 0.38%. According to the results of blood sugar tests, diabetes mellitus rose from 0.69% to 0.85%, and the results of blood pressure measurements, hypertension rose from 2.58% to 3.41%.

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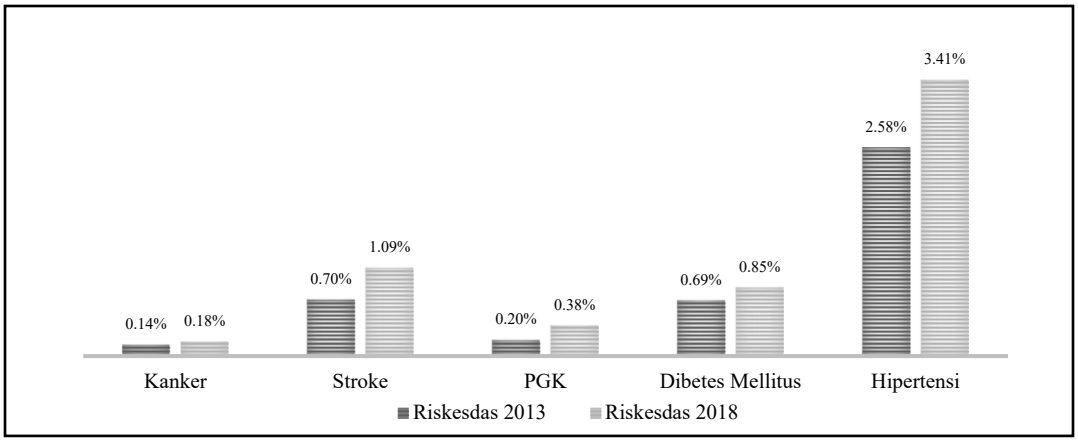

FIGURE 1. Increase in NCD prevalence in Indonesia

The ever-increasing number of CKD can cause a problem seeing that the CKD itself is a dangerous and hazardous disease. CKD is a failure of kidney function that occurs slowly over a long period and results in the accumulation of metabolic waste (uremic toxins). This causes a decreased in kidney function and an experience symptoms of illness [2]. CKD is characterized by a gradual loss of kidney function over time, for months or years. Most people are not aware of experiencing this condition. When symptoms begin to appear, kidney function has been significantly impaired. The signs of kidney damage or pathological disorders can be seen in blood and urine disorders [3].

CKD is still a global health problem, aside from being difficult to cure; the cost of treatment and care is also expensive. The treatment also varies based on the level of kidney damage experienced. It is necessary to know the level of kidney damage as a reference for carrying out appropriate treatment [4]. The number of patients undergoing hemodialysis tends to increase yearly. There has been an increase in number over the past decade. In 2007, the number of active patients was 1,885 people, and in 2017 reached 77,892 people. It means that the increase reached 70 times in 2017. The increase in the number of new or active patients undergoing dialysis is in line with the increasing prevalence of CKD events in Indonesia. According to the results of Riskesdas 2013, the prevalence of CKD in Indonesia reached 0.2% and increased to 0.38% in 2018.

CKD is a dangerous disease that can be experienced by anyone, not only the teens, but also the adults, or the elderly. CKD is a silent killer that develops without giving symptoms and warning signs. Most people realize that they suffer CKD after this disease is already at a severe stage [5]. According to Riskesdas 2018, many of the CKD sufferers are the productive age. If it was not anticipated, it could have an impact on the reduction in human resources. Productive age should be able to be the main capital in a country's development. CKD is not an easy disease to cure in a short time. Therefore, a precautionary measure is needed, so that the prevalence of CKD can decrease, and the death due to CKD will also reduce and even be eliminated.

Several studies examine factors related to CKD. Sutopo's [6] research concluded that predisposing factors, biomedical factors, and behavioral risk factors are associated with CKD events. CKD can be recognized early on by knowing the factors that influence the incidence of CKD. It can prevent complications due to this disease [8]. Labov et al. [8] used a large population-based cross-sectional study to estimate the prevalence of CKD in León, Nicaragua. The study evaluated the relationship between risk factors previously investigated with CKD. The results using logistic regression found that gender, age, place of residence, education level, hypertension, occupation, alcohol consumption, daily water consumption level, and diabetes significantly influence CKD. The research is comparable with findings in regional studies and supports the Mesoamerican Nephropathy hypothesis.

Arifa et al. [9] concluded that there was a significant relationship between the variables of age, sex, history of diabetes mellitus, and history of kidney stones with the incidence of CKD in patients with hypertension in Indonesia. History of diabetes mellitus, history of kidney stones, and total cholesterol levels are the dominant variables in the incidence of CKD in patients with hypertension in Indonesia. Peng et al. [10] identified lifestyle risk factors for CKD with chronic comorbidity and demonstrated the potential effectiveness of the Association Rule Mining (ARM) analysis of CKD. The result can be generalized with other non-communicable diseases and indicate that lifestyle modification for CKD varies among various comorbidities. Simamora & Permana [11] used medical records data of

the UKI Jakarta Public Hospital in 2011-2015. Using the survival analysis of the Cox PH model, they found that diabetes status, education, sources of HD costs, vascular access, and hypertension affect the survival of hemodialysis patients.

CKD cases are included in rare events. The proportion of CKD sufferers to the total population aged 15 years and over is very small. This study focuses on the case of CKD sufferers, who experience dialysis. This study aims to analyze the determinants of CKD sufferers who undergo dialysis. Binary Logistics is a statistical method used to explain the relationship between categorical dependent variables consisting of two categories (binary) with independent variables in the form of numerical or categorical data. There is a special statistical method that can be used to analyze cases with an imbalance proportion of success and failure categories, namely the firth logistic regression method. This method is considered to be able to overcome the problem that occurs where the possibility of the maximum likelihood estimation results being biased. Heinze [12] revealed the use of this method is more suitable for conducting analysiss, because it is more specific to epidemiologic studies of rare diseases or cases of epidemiological diseases in the health field.

METHOD

Data Collection

This research is a quantitative study using secondary data from the 2018 Riskesdas survey. CKD patients aged 15 years and over in Indonesia are the unit of analysis in this study. Based on secondary data from Riskesdas 2018, as many as 2850 were identified as CKD sufferers, only 2141 were used as samples, because 24.7 percent contained blank records in important data. Furthermore, the research variables in this study were divided into two, namely the dependent variable and the independent variable. The status of undergoing dialysis in CKD patients is the dependent variable. Furthermore, several characteristics become the independent variables in this study, including diabetes mellitus status, hypertension status, heart disease status, gender, age, consumption of fruits and vegetables, and consumption of salty foods.

Analysis Method

The analytical method used in this study is the firth logistic regression (firth method). The method is used because the distribution of the response variable is an imbalance. Imbalance data will produce inaccurate estimates if it is still forced to be analyzed using conventional binary logistic regression methods. Conventional logistic regression uses the maximum likelihood estimation method to estimate its parameters. The maximum likelihood estimation method is not appropriate for imbalance data (rare events). It will cause biased estimation. The imbalance data on the response variable exists when the event of failure more than the successful event. This condition makes P (Y = 1) to underestimates while P (Y = 0) overestimates. Some methods can overcome the problem of estimation bias in rare event data [13]. These methods can reduce the bias resulting from a small sample of maximum likelihood estimates in rare event data. One of these methods was found by Firth [14] and known as the Firth method. This firth method uses the penalized likelihood equation to estimate parameters. The equation is $L^*(\theta) = L(\theta)\det(I(\theta))^{1/2}$.

The steps for analyzing with Firth Logistic Regression are:

1. Estimating parameters with penalized likelihood ratio

The likelihood equation based on maximum likelihood estimation is:

$$\frac{\partial L(\boldsymbol{\beta})}{\partial(\beta_j)} = \sum_{i=1}^{n} y_i x_{ji} - \sum_{i=1}^{n} x_{ji}\left\{\frac{\exp\left(\sum_{j=0}^{k}\beta_j x_{ji}\right)}{1+exp(\sum_{j=0}^{k}\beta_j x_{ji})}\right\} = 0$$

$$\left\{\frac{\exp\left(\sum_{j=0}^{k}\beta_j x_{ji}\right)}{1+exp(\sum_{j=0}^{k}\beta_j x_{ji})}\right\} = \widehat{y_i}$$

If $U(\boldsymbol{\beta})$is the first derivative vector of log-likelihood β and $I(\boldsymbol{\beta})$is the second derivative matrix, so that:

$$U(\boldsymbol{\beta}) = \frac{\partial L(\boldsymbol{\beta})}{\partial(\beta)} = \sum_{i=1}^{n} x_i y_i - \sum_{i=1}^{n} x_i \widehat{y_i}$$

$$I(\boldsymbol{\beta}) = \frac{\partial^2 L(\boldsymbol{\beta})}{\partial(\beta)\partial(\beta)'} = -\sum_{i=1}^{n} x_i x_i' \, \widehat{y_i}(1-\widehat{y_i})$$

The first derivative vector of $U(\boldsymbol{\beta})$is gradient, and the second derivative matrix $I(\boldsymbol{\beta})$is Hessian.

Penalized Maximum Likelihood estimates will be obtained by dividing or selecting the number of observations i into two new observations that have a response value of y_i and $1 - y_i$ with weights of $1 + \frac{h_i}{2}$and $\frac{h_i}{2}$respectively. So that will produce the equation $U(\boldsymbol{\beta}^*) = \sum_{i=1}^{n} \boldsymbol{x}_i y_i - \sum_{i=1}^{n} \boldsymbol{x}_i \hat{y}_i - \sum_{i=1}^{n} h_i \boldsymbol{x}_i (0.5 - \hat{y}_i) = 0$. Penalized Maximum Likelihood in estimating β can be obtained from the iteration process until convergence. In this study, iteration is carried out using statistical software to estimate the value of the parameter.

2. Testing the significance of parameters simultaneously

Simultaneous parameter testing is useful to test the effect of all the independent variables used in this study. The independent variables are the status of diabetes mellitus, hypertension status, heart disease status, gender, age, fruit and vegetable consumption; and consumption of salty foods tested together on the dependent variable (the status of undergoing dialysis in patients with CKD) by using the likelihood ratio test using G statistics.

$$G = -2 \ln \left(\frac{L_0}{L_1} \right) = -2[ln(L_0) - \ln (L_1)] \sim \chi_k^2$$

The decision will reject H_0 if $G > \chi^2_{(0,1;7)}$ or p-value <0.1.

3. Partial significance testing of parameters

The partial test is useful to find out the independent variables that significantly affect the status of undergoing dialysis in patients with CKD in Indonesia. Partial test using the results obtained from the Wald test.

$$W_j = \left(\frac{\widehat{\beta}_j}{SE(\widehat{\beta}_j)} \right)^2 \sim \chi_1^2$$

The decision is to reject H_0 if $W > \chi^2_{(0,1;1)}$ or p-value <0.1.

4. Testing the suitability of the model with the Hosmer-Lemeshow test and classification table

The suitability test of the model used in this study is the Hosmer-Lemeshow test and classification table. The Hosmer-Lemeshow test is performed using the following hypothesis:

H_0: Model Fit (the model used is sufficient to explain the data)

H1: Model is not fit (the model used is not enough to be able to explain data).

$$\hat{C} = \sum_{k=1}^{g} \frac{(o_k - n'_k \bar{\pi}_k)^2}{n'_k \bar{\pi}_k (1 - \bar{\pi}_k)} \sim \chi^2_{(g-2)}$$

The decision isto reject H_0 if $\hat{C} > \chi^2_{(10-2)}$ or p-value <0.1.

In the classification table, the value of sensitivity and specificity required cut-point value (*c*). The value of *c* is used to compare the estimated probability for the logistic model to create a classification table, usually using *c* of 0.5. In this study, the *c* value of 0.176085 will be used. If the estimated value is less than 0.176085, then the value of the response variable is 0. Conversely, if the estimated value of the opportunity is more than or equal to 0.176085, then the value of the response variable is 1[15]. The greater the percentage value of the total classification accuracy, sensitivity, and specificity is, then the better the model is. Sensitivity shows that the percentage of patients with CKD who have had dialysis is correctly predicted in the group that has had dialysis. Specificity shows the percentage of CKD patients who have never undergone dialysis is correctly predicted to return to the group who never had dialysis.

RESULT AND DISCUSSION

TABLE 1 presents the Wald statistic values that can be used to determine the significance of variables partially. When the p-value is smaller than the significance level used that is 0.1, then it can be concluded that the variable significantly influences the status of undergoing dialysis in patients with CKD. Based on TABLE 1, it can be concluded that there are 5 out of 7 independent variables that significantly affect the status of undergoing dialysis in patients with CKD, which is diabetes mellitus status, hypertension status, gender, age, and adequacy of fruit and vegetable consumption. The heart disease status and consumption of salty foods do not significantly affect the status of undergoing dialysis in patients with CKD.

Firth model that is formed is as follows:

$$\hat{g}(x) = -2.213 + 0.444x_1 + 0.433x_2 - 0.081x_3 - 0.234x_4 - 0.007x_5 + 0.906x_6 + 0.059x_7$$

where:
(x_1) : Diabetes mellitus status (1:Yes, 0:No)
(x_2) : Hypertension status (1:Yes, 0:No)
(x_3) : Heart disease status (1:Yes, 0:No)
(x_4) : Sex variable (1:Male, 0:Female)
(x_5) : Age (Single age of CKD suffers)
(x_6) : Consumption of fruits and vegetables (1:less consumption, 0:Enough)
(x_7) : Consumption of salty foods (1:high risk, 0:low risk)

TABLE 1. Summary of the results of processing partial test using firth logistic regression

Variable	$\widehat{\boldsymbol{\beta}}$	*p-value*	*Odds Ratio*
Intercept	-2.213	0.000	0.109
Diabetes Mellitus Status (x_1)	0.444	0.006	1.559
Hypertension Status(x_2)	0.433	0.000	1.543
Heart Disease Status (x_3)	-0.081	0.647	0.992
Sex (x_4)	-0.234	0.044	0.791
Age (x_5)	-0.007	0.098	0.993
Consumption of Fruits and Vegetables (x_6)	0.906	0.045	2.474
Consumption of Salty Foods (x_7)	0.059	0.623	1.061

TABLE 1 also presents odds ratios that indicate the tendency of patients with CKD who have certain characteristics to undergo dialysis compared to those with CKD who have the characteristics of the reference category. The odds ratio value greater than one states that CKD sufferers undergoing dialysis are greater than the reference category, assuming other variables are constant. Conversely, when the odds ratio is less than 1, it means that the tendency of patients with CKD who undergo dialysis is smaller than the reference category, assuming other variables are constant.

The odds ratio value of the diabetes mellitus status variable is 1.559. It means, CKD sufferers who suffer diabetes mellitus tend to dialysis and have a tendency of 1.559 times greater than CKD sufferers who do not suffer from diabetes mellitus, assuming other variables are constant. CKD patients who undergo dialysis with comorbid diabetes mellitus have a risk of death of 1.38 times faster than those without comorbid diabetes mellitus [16]. There was a significant relationship between diabetes mellitus and the incidence of CKD in hemodialysis patients at Tugurejo District Hospital SemaranG [17]. There is a relationship between the duration of diabetes mellitus and the incidence of CKD in patients at Moewardi Hospital Surakarta, and the relationship obtained is positive, which means the longer the patient has diabetes mellitus, the higher the risk for CKD[18].

In the hypertension status variable, the odds ratio is 1.542. The patients with CKD who suffer from hypertension tend to experience dialysis 1.542 times greater than those with CKD who do not suffer from hypertension. Prolonged hypertension results in changes in the structure of the arteries in the body, characterized by fibrosis and hyalinization of blood vessel walls causing glomerular damage and tubular atrophy so that the entire nephron is damaged and causes CKD (19). There is a significant relationship between hypertension and the incidence of CKD in hemodialysis patients at Tugurejo District Hospital Semarang. Patients who were suffering from hypertension have a 5.652 times greater tendency to experience CKD compared to patients who do not suffer from hypertension [17].

The odds ratio value for the gender variable is 0.791. It shows, men tend to experience dialysis 0.791 times smaller than patients with CKD female sex. Because of this, women have a greater tendency to experience dialysis than men. Every disease can affect humans, both men and women, but in some diseases, there are differences in risk between men and women. It is partly due to differences in work, living habits, genetics, or physiological conditions. Yuliaw [20] found that men have a worse quality of life than women. The longer the dialysis (hemodialysis) means the lower the quality of life.

The odds ratio for the age variable is 0.993. It shows that every one year increase in age, the tendency of people with CKD to experience dialysis is 0.993 times. Therefore, young age groups are more likely to experience dialysis. There is a significant relationship between age and quality of life of patients with CKD who undergo hemodialysis at RSUD dr. M. Yunus Bengkulu [21]. The younger a person is, the greater the motivation to recover from CKD. Many of the young population (under 60 years) do dialysis compared with old age (over 60 years). It is also supported by Valdivia et al.[22]. They said that the survival of patients with CKD who undergo hemodialysis for age

over 60 years is zero percent. The survival of patients with old age is very low; the more severe the age decreases kidney function and is associated with worsening of glomerular and tubular excretion function. It is in line with other findings that are known as differences in the survival curve of CKD patients with hemodialysis aged less than 60 years and more than 60 years [23].

In the variable consumption of fruit and vegetables, the odds ratio value is 2.474. It means that the tendency of patients with CKD who are lacking in consuming fruits and vegetables is 2.474 times more likely to experience dialysis compared to those with CKD. They are consuming enough fruits and vegetables. It can be concluded that less consumption of fruits and vegetables can lead to the severity of CKD experienced which also can increase and heighten one's tendency to undergo dialysis. It is in line with the founding of consuming fruits and vegetables that are high in fiber can reduce the risk of increased crystallization of urine and keeps the kidneys in good health [24].

The Goodness of Fit Test

The suitable model to explain the status of undergoing dialysis in patients with CKD should be checked by Hosmer and Lemeshow test and classification table. Based on the results of the Hosmer and Lemeshow test, a p-value is 0.6761. This value is greater than the α=0.1, and the decision failed to reject H_0. It means that the model used is fit or appropriate in explaining the response variable.

TABLE 2. Classification table of the Firth logistic regression

		Predicted		Percentage of Total Accuracy ofClassification
		No Dialysis	Undergoing Dialysis	
Observed	No Dialysis	989	775	56.07%
	Undergoing Dialysis	156	221	58.62%
Total				57.34%

Source: Riskesdas 2018, processed

Based on **TABLE 2**, the percentage of total classification accuracy is 57.34 percent. It means that the overall model can classify all observations correctly by 57.34 percent. The sensitivity of the model obtained was 58.62 percent. There is as many as 58.62 percent of patients with CKD who had dialysis is correctly predicted to the group of people with CKD who had dialysis. The specificity of the model is 56.07 percent. Specificity shows that as many as 56.07 percent of patients with CKD who do not have dialysis are correctly predicted to the group of people with CKD who do not have dialysis.

CONCLUSION

Indonesia is in a phase of epidemiological transition where mortality due to NCD continues to increase, while deaths from infectious diseases are declining. Non-communicable disease cases tend to increase significantly over time. Variables that significantly affect the status of undergoing dialysis in patients with CKD in Indonesia in 2018 are the status of diabetes mellitus, the status of hypertension, sex, age, and consumption of fruits and vegetables. CKD sufferers who have a greater tendency to undergo dialysis are sufferers of CKD with the characteristics of suffering from diabetes mellitus, suffering from hypertension, female, young, and lacking in fruit and vegetable intake.

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