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ON COMPUTATIONAL BAYESIAN ORDINAL LOGISTIC REGRESSION LINK FUNCTION IN CASES OF CERVICAL CANCER IN TUBAN

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Abstract. Cervical cancer is the most common cancer that causes death in women. This cancer is mainly caused by Human Papilloma Virus (HPV). It is estimated that 52 million of Indonesian women are at risk of having cancer, and 36% of female cancer patients suffer from cervical cancer. This type of cancer cannot be diagnosed immediately as there is several years of pre-malignancy phase; thus, early detection or screening is needed to prevent it from turning into malignant. Pap test as a screening program can detect cancer, precancer, and normal condition. To understand the predicting factors of the test results, a comprehensive mathematical modelling was created using the link function of Bayesian Ordinal Logistic Regression. This study observed several possible factors that may affect Pap test results in Tuban regency, namely Age (X_1), Education (X_2), Childbirth Experience (X_3), Use of Contraceptives (X_4), Menstrual Cycle (X_5), Age of First Menstruation (X_6), History of Misarrriage (X_7), Anemia (X_8) and Number of Sexual Partners (X_9). The outcomes indicated that the predicting factors of Pap cervical cancer results are Age (X_1), Education (X_2), Childbirth Experience (X_3), Use of Contraceptives (X_4), Menstrual Cycle (X_5), and Anemia (X_8). In this model, there is an inexplainsable error dependency as indicated by the varied constance values of alpha.

Keywords: Bayesian, Gibbs Sampling, Kanker Serviks, MCMC, Regrest Logistik ordinal.

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1. INTRODUCTION

Cervical cancer has the highest prevalence among women and ranked second to breast cancer as cause of death [1]. In Indonesia, cervical cancer causes death in women [2]. This disease is primarily caused by Human Papilloma Virus (HPV) [3]. The high mortality rate is resulted by late treatment, where patients only seek for help during the late stage of the disease [4]. There are approximately 52 million women in Indonesia with cancer risk, and 36% of female cancer patients suffer from cervical cancer [5]. This type of cancer can be prevented with early screening using Pap test [6]. Factors influencing Pap test are the use of contraceptives and childbirth [1]. This topic, thus, is interesting to be studied and analyzed further [7].

Logistic regression with link function is a method to create a model by using dichotomous and polychotomous response variable [8]. To create a model of correlation between predictor and response variables, researchers generally use regression method, either the simple or multiple ones [9]. However, in the cases where Gauss-Markov assumptions are violated, the frequently used OLS (Ordinary Least Square) and Maximum Likelihood will fit less, thus, the most fitting method is Bayesian MCMC-Gibbs Sampling [10].

A research conducted by [11] applied logistic link function model in medical science by classifying benign and malignant tissues in breast cancer. The application of this model in medical science takes into account actual death cases. Similar research was carried out by [12] who applied the same model on cervical cancer cases in Sweden by modelling the results of regular screening evaluation performed to control the disease rate in the country. Another similar research is that of [13], which applied link function of logistic regression on cervical cancer prevalence in China and found that pre-surgery radiotherapy and chemotherapy are independent protecting factors for vascular space invasion and cervical cancer invasion. Research conducted by [1] and [12] use logistic regression analysis with maximum likelihood method, which optimize likelihood function and require the data to follow a certain distribution pattern. In fact, the data distribution in logistic regression are not always represented in clear distribution, thus this study investigates the link function of ordinal logistic regression using Bayesian MCMC computational approach. This method is utilized to obtain estimated parameter of link function logistic model and the factors influencing the results of Pap cervical cancer test. The use of this model is expected to give insight about optimum cervical cancer treatment; thus, it can be included in dissemination of how to treat this disease. It is expected that the result can contribute to reduce cervical cancer prevalence in Tuban Regency, improve scientific knowledge, and inform people about the factors that influence the results of Pap cervical cancer test. Therefore, the Health Department of Tuban can take into account the results of this study in establishing policies of strategic methods for faster cervical cancer treatment.

2. RESEARCH METHODS

2.1. Bayesian Ordinal Logistic Regression Link Function Model

Link Function of Ordinal Logistic Regression is one of statistical models that is used to analyze response variable with 3 or more categories in ordinal data scale [14]. Ordinal logistic regression is a cumulative-logit model, and its predictor must be categorical and or quantitative [15]. The characteristics of response variable in ordinal-logit model are explained in cumulative probability, a model formed by juxtaposing cumulative probability, a probability of a value being less than or equal to j^{th} response in p predictor variable [16]. The purpose of ordinal logistic regression model is to obtain a fit and simple model to illustrate response variable with a group of predictor variable [15]. Presented below is the link function of ordinal logistic regression model [17]:

$$h\{P(Y \leq j)\} = \left(\alpha_j + \sum_{k=1}^p \beta_k x_k \right) \quad (1)$$

The values of α_j in $i = 1, 2, \dots, n$ (categorical) and β_k in $k = 1, 2, \dots, p$ in every ordinal logistic regression is the same [18]. Estimation of each parameter obtained through full conditional distribution in each parameter are α_j , σ , and β_k by determining prior distribution in the beginning [19]. The prior distribution used is the combination of conjugate and informative priors, as denoted below [20]:

$$y \sim \text{Logit}(\mu, \sigma) \\ \mu = \beta^T x_j + \varepsilon_j, \quad \varepsilon_j | x_j \sim \text{Normal}(a, b), \beta \sim \text{Normal}(s, r), \alpha \sim \text{Normal}(s, r) \quad (2)$$

Bayesian is an alternative method to estimate model parameter [21]. The availability of program package for Bayesian analysis makes this method more flexible to create a modelling analysis that is stochastically complex [22]. As the results, several limitations in classic modelling, such as the complexity, the assumptions that do not suit the reality, and avoidable simplification, can be overcome [23]. Bayesian modelling is based on posterior model that combines past data as prior information and observation data as likelihood function [24]. Bayesian utilizes the information of sample data and calculates prior distribution [20]. Posterior distribution of the data is obtained by combining initial information used as prior distribution and the sample information as likelihood function [25]. The equation of posterior distribution is as follows [26]:

$$f(\theta | x) = \frac{f(x | \theta) f(\theta)}{f(x)} \propto f(x | \theta) f(\theta) \quad (3)$$

2) In:

$f(\theta | x)$ = Posterior distribution

$f(x | \theta)$ = Likelihood function

$f(\theta)$ = Prior Distribution

x = Data

θ = Parameter

Markov Chain Monte Carlo (MCMC) is a numerical approach to determine the posterior distribution using complex simulation method that combines Monte Carlo and Markov Chain characteristics to gain sample data based on specific sampling scenario [27]. Markov chain is a stochastic process $\{\theta^{(1)}, \theta^{(2)}, \dots, \theta^{(K)}\}$ that is denoted in the following equation [28]:

$$f(\theta^{(k+1)} | \theta^{(k)}, \dots, \theta^{(0)}) = f(\theta^{(k+1)} | \theta^{(k)}) \quad (4)$$

To generate sample from $p(\theta | x)$, Markov Chain sequence should be arranged under the condition that $f(\theta^{(k+1)} | \theta^{(k)})$ must be easy to generate and the stationary distribution of Markov Chain is posterior distribution $p(\theta | x)$, by following the steps below [29]:

1. Determining the initial value of $\theta^{(0)}$.
2. Generating sample by iterating K times to reach convergence.
3. Conduct burn-in process by eliminating samples K times the first sample.
4. Use $\{\theta^{(B+1)}, \theta^{(B+2)}, \dots, \theta^{(K)}\}$ as a sample to obtain posterior analysis.
5. Create a plot for posterior distribution (such as mean, median, standard deviation, and standard error).

Markov Chain Monte Carlo (MCMC) can use several approaches, one of which is Gibbs Sampling method [30]. Gibbs Sampling is a technique to generate random variable from marginal distribution indirectly without having to calculate the density [31]. This technique is based on convergent arrangement of Markov Chain in stationary distribution, that is posterior distribution $f(\theta | x)$ [32]. The steps of Gibbs Sampling algorithm process are [33]:

1. Determining the initial values of each parameter.

$$(\sigma^0, \alpha_1^0, \alpha_2^0, \beta_1^0, \dots, \beta_p^0)$$

2. Next, random sequence is produced.

$$\sigma^1 \text{ from } p(\alpha_1^0, \alpha_2^0, \beta_1^0, \dots, \beta_p^0)$$

$$\alpha_1^1 \text{ from } p(\alpha_2^0, \sigma^1, \beta_1^0, \dots, \beta_p^0)$$

⋮

$$\alpha_2^1 \text{ from } p(\alpha_1^1, \sigma^1, \beta_1^0, \dots, \beta_p^0)$$

$$\beta_1^1 \text{ from } p(\beta_1^1, \sigma^1, \alpha_1^1, \alpha_2^1, \beta_1^0, \dots, \beta_p^0)$$

$$\beta_j^i \text{ from } p(\alpha_1^i, \alpha_2^i, \beta_j^i, \sigma^i, \beta_1^i, \dots, \beta_{p-1}^i)$$

- Repeating the second step until convergence is reached.

Test for parameter aims to understand the effect of predictor variable to response variable [34]. A test that employs Bayesian approach is a credible interval test that sets a lower limit at 2,5% and upper limit at 97,5% [24]. The decision criterion is H_0 will be rejected if the credible interval does not contain 0 value, concluding that the predictor has a significant influence on response variable. Below are the hypotheses used [27]:

$H_0 = \beta_j = 0$ (j^{th} predictor variable does not influence response variable)

$H_1 = \beta_j \neq 0$ (j^{th} predictor variable influences response variable)

This research uses secondary data of medical records of female patients undergoing Pap cervical cancer test at Koesoma Hospital, Tuban, in 2020. The variables are categorical. This research uses response and predictor variables. The response variable is female patients who underwent Pap test [13]. The predictor consists of nine variables. Information about response and predictor variables are elaborated in Table 1.

Table 1. Research Variables

No	Variable	Description
1	Pap test results (Y)	Y=0, Pap result confirms cancer diagnosis Y=1, Pap result indicates pre-cancer Y=2, Pap result does not detect any cancer
2	Age (X ₁)	0 = Aged ≤ 50 years 1 = Aged > 50 years
3	Education (X ₂)	0 = Low 1 = High
4	Childbirth Experience (X ₃)	0 = No 1 = Yes
5	Contraceptive Use (X ₄)	0 = Using contraceptives 1 = Not using contraceptives
6	Menstrual Cycle (X ₅)	0 = Irregular 1 = Regular
7	Age of First Menstruation (X ₆)	0 = 10-12 Years old 1 = 13-16 Years old
8	History of Miscarriage (X ₇)	0 = No history of miscarriage 1 = Having a history of miscarriage
9	Anemia (X ₈)	0 = The patient does not have anemia 1 = The patient has anemia
10	Number of Sexual Partners (X ₉)	0 = 1 Partner 1 => 1 Partners

A study should involve a proper analysis. The following is a series of steps to complete the computational analysis of Bayesian ordinal logistic regression's link function:

- Collecting the data of female patients who underwent Pap test at Koesoma Hospital in Tuban.
- Describing the characteristics of the patients based on the observed variables by conducting descriptive statistical analysis that consists of descriptive table and cross tabulation.
- Adding "add-ins" of ordinal logistic's link function in WinBUGS as a parameter generator for multinomial distribution.
 - Install WinBUGS 1.4
 - Install Blackbox Component Builder
 - Prepare files containing the the connection of new distribution combination to winBUGS

- d) Prepare Univariate Template.odc to add new distribution,
 - e) Prepare the required input in Univariate Template.odc to add Dagum distribution, which consists of multinomial distribution PDF and log-likelihood function from Dagum distribution and CDF from multinomial distribution.
 - f) Formulating the program codes based on the input in step (e) and put it in a suitable procedure.
 - g) Completing program compilation and validation.
4. Determining the link function of ordinal logistic regression model for cervical cancer prevalence based on observed factors by using WinBUGS open-source program package. The mean and variance of this model are determined by estimating model parameters (σ , α , β) through MCMC simulation with *Gibbs sampling*, as elaborated in the following steps:
 - Determining likelihood function
 - Determining the prior distribution of each parameter based on data information. Parameter σ follows gamma distribution (1.1) and parameter β follows normal distribution obtained through prior flat modelling.
 - Determining the initial value of each parameter by using 2-steps MCMC. For the start, the initial value of parameter $\sigma = 1$ and parameter $\beta_j = 0$
 5. To generate T sample $\theta^1, \theta^2, \dots, \theta^T$ from posterior distribution $p(\theta|x)$, T is updated as many as the required n times with adequate thin so that the Markov Chain process can be completed.
 6. Convergent algorithm is defined as a condition where algorithm has reached stationary state in link function of ordinal logistic regression model. If it does not reach stationarity, then more observation needs to be added. Several ways to determine convergence are:
 - a. By looking at small error MC value
 - b. Based on ACF plot, low autocorrelation value indicates fast convergence.
 7. Obtain a summary of posterior distribution (mean, median, standard deviation, MC error, and confidence interval (95%)) in the link function of ordinal logistic regression.
 8. Create and interpret the link function of ordinal logistic regression model.

3. RESULTS AND DISCUSSION

The formulation of this model aims to understand which predictor variable influences the results of Pap cervical cancer test. the first step was performing descriptive analysis to understand the characteristics of Pap patients in Koesuma Hospital, Tuban. There were 71 patients observed, with 30 (42,3%) of them were confirmed to have cervical cancer, 35 (49,3%) were diagnosed with pre-cancer, and 6 (8,5%) show negative results. Thus, the biggest proportion in Tuban Regency is patients with pre-cancer diagnosis. The other characteristics observed are Age (X_1), Education (X_2), Childbirth Experience (X_3), the Use of Contraceptives (X_4), Menstrual Cycle (X_5), Age of First Menstruation (X_6), History of Miscarriage (X_7), Anemia (X_8) and Number of Sexual Partners (X_9).

Table 2. The Characteristics of Patients from Pap Cervical Cancer Test Results

Research Variables		Pap Test Result		
		Positive	Pre-Cancer	Negative
Age	Age <= 50 Years Old	19	17	3
	Age > 50 Years old	11	18	3
Education	Low	24	33	6
	High	6	2	0
Childbirth Experience	No	4	3	0
	Yes	26	32	6
Use of Contraceptives	No	13	18	3
	Yes	17	17	3
Menstrual Cycle	Irregular	19	16	1
	Regular	11	19	5
Age of First Menstruation	10-12 Years Old	15	17	3
	13-16 Years Old	15	18	3
History of Miscarriage	No	20	27	6
	Yes	10	8	0
Anemia	No	1	12	3
	Yes	29	23	3
Number of Sexual Partners	1 partner/no partner	26	28	5
	>= 1 Partners	4	7	1

Table 2 shows three categorizations of Pap test results in Koesoma Hospital: positive, pre-cancer, and negative results, with majority of the patients are below 50 years old, have lower education level (elementary school to junior high school), have children, and use contraceptives. Most of those patients have irregular menstrual cycle, experience first menstruation (menarche) at 13-16 years old, do not have miscarriage experience, and have one partner. The majority of them also have anemia. There are 71 patients of cervical cancer in this hospital, and the majority of them are diagnosed with cancer and pre-cancer.

Upon obtaining the descriptive data of the patients, we can see that the majority of them were diagnosed with cancer and pre-cancer. Pre-cancer result suggests that there is an abnormal change in cervical cells, while positive cancer result indicates abnormal malignant cells in cervical area. The process of cancer infection usually takes a long time, from 10-20 years [4]. To understand the influencing factors of this result, possible factors should be observed. This study focuses on Age (X_1), Education (X_2), Childbirth Experience (X_3), Use of Contraceptives (X_4), Menstrual Cycle (X_5), Age of First Menstruation (X_6), History of Miscarriage (X_7), Anemia (X_8) and Number of Sexual Partners (X_9) as possible factors. Below is the estimated link function of ordinal logistic regression model on Pap cervical cancer test:

Table 3. Estimated Link Function Parameter of Ordinal Logistic Regression Model

Parameter	Mean	2,50%	Median	97,50%	Description
β_1	0.0034	0.00115	0.0054	0.0103	Significant
β_2	-0.0027	-0.0023	-0.0024	-0.0774	Significant
β_3	0.0125	0.0045	0.0087	0.0431	Significant
β_4	-0.0663	-0.1348	-0.0166	-0.0024	Significant
β_5	0.3409	0.1881	0.3329	0.5377	Significant
β_6	-0.1848	-0.2759	-0.1847	0.0935	Not Significant
β_7	-0.0026	-0.0043	-0.0025	0.0231	Not Significant
β_8	0.0251	0.0041	0.0124	0.0425	Significant
β_9	0.0041	-0.0035	0.0211	0.0537	Not Significant
α_1	35.546	29.562	35.981	52.412	Significant
α_2	52.631	48.231	52.632	56.952	Significant
σ	0.126	0.07447	0.1236	0.1908	Significant

Based on calculation result using WinBUGS Software, factors in Table 3 are considered significant if the interval values between 2.5% to 97.5% do not contain 0. Thus, not all factors in Table 3 are significant to the cervical test results in Tuban. Thus, the predicting factors are Age (X_1), Childbirth Experience (X_3), Use of Contraceptives (X_4), Menstrual Cycle (X_5), Age of First Menstruation (X_6), and Anemia (X_8). In the table, the mean column displays the values of model parameter, while the next three columns show the estimated value at an interval confidence of 97.5%. The parameters of alpha 1, and alpha 2 are significant to Pap test results because the interval of 2.5% to 97.5% does not contain a 0. This shows that there is an inexplorable dependency in this link function of ordinal logistic regression model. This model is presented below:

$$g(1) = \ln \left[\frac{\pi(x)}{1 + \pi(x)} \right] = 35.546 + 0.0034x_1 - 0.0027x_2 + \dots + 0.0041x_9$$

$$g(2) = \ln \left[\frac{\pi(x)}{1 + \pi(x)} \right] = 52.631 + 0.0034x_1 - 0.0027x_2 + \dots + 0.0041x_9$$

Odds ratio is a juxtaposition between individual odds in factor/predictor's (x) condition and the factor/predictor (x) in comparison category. The odds ratios obtained from the data are presented in the following table:

Table 4. Odds Ratios

Research Variables	$\exp(\beta)$
Age (X_1)	1.003
Education (X_2)	0.997
Childbirth Experience (X_3)	1.013
Use of Contraceptives (X_4)	0.936
Menstrual Cycle (X_5)	1.406
Age of First Menstruation (X_6)	0.831
History of Miscarriage (X_7)	0.997
Anemia (X_8)	1.025
Number of Sexual Partner (X_9)	1.004

Those odds ratios demonstrate that women aged above 50 years old have 1.003 higher risk of getting cervical cancer than those below 50 years old. It also shows that women aged below 50 years old tend to have pre-cancer than normal condition (negative). Women who use contraceptives have 0.936 bigger risk to suffer from this cancer compared to those who do not. The same interpretation applies to all of the variables.

The results of link function of ordinal logistic regression with Bayesian_MCMC method shows that the factors influencing the results of PAP cervical cancer test in Surabaya are Age (X_1), Childbirth Experience (X_3), Use of Contraceptives (X_4), Menstrual Cycle (X_5), Age of First Menstruation (X_6), and Anemia (X_8). This result differs from that of [1]'s study which applied Maximum Likelihood Estimation and suggested that the predicting factors of cervical cancer test results are the use of contraceptives, childbirth experience, menstrual cycle, and history of miscarriage. Based on a research by [4] which uses logistic regression, the predicting factors found in Ambon are age and marriage frequency. Another study was also carried out by [35] in Afrika by applying ordinal regression with maximum likelihood method. The study suggested that the

significant factors influencing cervical cancer are surgical stage, age, HIV status, vaginal involvement, and marriage status. Thus, it can be concluded that the high prevalence of cervical cancer is epidemiologically crucial to be taken into account in implementing health programs that focus on regular monitoring through screening and early detection using Pap test. The link function of ordinal logistic regression model is able to yield some information beneficial to be featured in dissemination about cervical cancer management in Tuban Regency.

4. CONCLUSIONS

The link function of ordinal logistic regression model suggests that the predicting factors of Pap cervical cancer test results are Age (X1), Childbirth Experience (X3), Use of Contraceptives (X4), Menstrual Cycle (X5), Age of First Menstruation (X6), and Anemia (X8). The varied α values indicate that there is an error dependency that cannot be explained through this model. The link function of ordinal logistic regression model with Bayesian-MCMC method is able to elaborate any complexity and handle Gauss-Markov assumptions violation.

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ORIGINALITY REPORT

13%

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