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Math Model Can Predict Severity of Heart Complication in Diphtheria

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Abstract

Background: *Diphtheria is still fatal disease even in the era of universal immunization., Heart complication (HC) ones of the serious complications, have historically had a large impact on morbidity and mortality, which probably led predictions about the evolution of epidemics have been made for centuries. Many factors may affect severity of HC and needed mentoring by clinician The objective is to identify the most-frequently used mathematical models and the diseases to which they are applied.*
Objective: *To identify the most-frequently used mathematical models and the diseases to which they are applied.*
Methods: *A cross-sectional study was conducted from January to December 2017 at Zainoel Abidin Hospital Banda Aceh, Indonesia. The type of HC, the mathematical model applied, the statistical technique used, were collected. The predictors variable Nutritional status, Immunization, Pain swallow, White membrane, Fever, Stridor, Hemoglobin and Potassium were analyzed, finaly, predictor variables in the multivariate ordinal logistic regression model have $p < 0.1$. The analyzed using SPSS program.*
Results: *Three predictor variables final model have p–value < 0.1 were, Stridor p=0,005, Hb p = 0,076 and K p = 0,075. The present of stridor, increase the probability severe HC as 0.961. Patient with absent in Stridor, abnormal Hb and K,highest probability moderate HC as 0.653 and absent stridor, normal Hb and K, highest probability mild HC as 0.829. The value of Pearson statistics is 4.242, p = 0.515 and Deviance is 5.177, p = 0.395, the final model is suitable with the empirical data can be used to evaluate the relationship between HC categories and Stridor, Hb and K are predictor variables. . According to Nagelkerke criteria, it can be concluded that 39.6% of variability in HC categories can be explained by the predictor variables Stridor, Hb and K.*
Conclusion: *stridor, Hb and K can be used as predictors of HC categories in diphtheria patients .*
Keywords: *diphtheria, predict of heart complication, mathematical models*

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I. Introduction

Diphtheria is still endemic in many developing countries and is responsible for high case fatality. The case-fatality rate for diphtheria is 5%–10% but it could be higher (approximately 20%) among children younger than five years old and elderly[1]. The incidence of diphtheria has steadily declined following effective immunization program, but in Indonesia, between January and November 2017, the government has recorded 593 diphtheria cases, spread across 95 regencies in 20 provinces. Aceh is once of provinces in Indonesia, diphtheria still remains endemic with fulminant complications and mortality especially in children above 5 years.[2] The World Health Organization data on diphtheria shows that the number of cases in Indonesia has fluctuated since the 1980s.[3]

Several factors like inadequate vaccine coverage, poor socio-economic status, delayed reporting, and non-availability/delayed administration of diphtheria antitoxin further contribute to high mortality. The level of immunity declines in late childhood and adolescence due to lack of booster doses, and decreased reservoir of C. Diphtheria in the community leading to gap in the immunity and outbreaks of diphtheria. Only about 75% of Indonesian children have been vaccinated against diphtheria.[2]

Myocarditis is heart complication (HC) may occur in about 10-25% of patients with respiratory diphtheria and was reported to cause high mortality is 50%.[4,5] Many variables to predict of myocarditis such us, Nutritional status (NS), Immunization, Pain swallow (PS), White membrane (WM), Fever, Stridor, Hemoglobin (Hb) and Potassium (K). Diphtheria myocarditis is frequently complicated by arrhythmias that can cause sudden death if not managed properly. The patients with cardiac involvement may be asymptomatic (ECG change and/or raised SGOT) or symptomatic (features of heart failure).[4,5,6,7,8]

The accurate prediction of HC in diphtheria patients is an important challenge in personalized medicine and population health management.[4,5] However, many predictors can take effect to quantity of HC severity. Even when such a clinical variable exists, there are often additional related of blood values that may help improve prediction of future disease state.[7,8,9] To this end, we propose a novel probabilistic model for multivariate longitudinal data that captures dependencies between multivariate trajectories of clinical variables.

We focused our efforts on developing models for HC with is characterized by mild to severe heart problem. A person's HC can be approximated by 12-lead electrocardiography, laboratory values and clinical finding.

II. Methods

A cross-sectional study was conducted on January to December 2017 in Zainoel Abidin Hospital, Banda Aceh, Indonesia. Subject were collected by total sampling, with blood values (Routine blood values and electrolyte) and clinical finding complete data by medical record. The mathematical model was used to fit the observed numbers of cases diphtheria, the predictor of HC and level of HC posted,.This study was approved by Ethics Committee of Syiah Kuala University Medical School, Banda Aceh. The collected data were processed, analyzed, and presented using SPSS 16 version software

III. Results

A total of 43 diphtheria children had complete data to the study. There were 23 (53.5%) males and 20 (46.5%) females, and ranged in age from 20 to 211 month The 36 diphtheria patients (83.7%) never received DPT vaccination while 5 (11.6%) had not completed the full DPT vaccine series, only 2 (4.7%) had completed the full DPT vaccine series.

The 22 (51.2%) patients had mild asymptomatic HC were AV Block-1 or inappropriate tachycardia. As many as 3 (7%) patients diphtheria had "Bullneck", died with severe HC is Total AV block (AV Block-3), the other, there are 12 patients (27.8%) with HC moderate i.e AV Block-2 or T invers or ST elevation with inappropriate tachycardia. Only 6 (14%) patients without HC (characteristic diphtheria patients in table 1)

Table 1. Characteristics of Diphtheria Subjects

Characteristics	**N (%)**	
Sex		
Female	20 (46.5)	
Male	23 (53.5)	
Range of age	20 - 211	
(month)		
DPT Vaccination		
No	36 (83.7)	
Not completed	5 (11.6)	
Completed	2 (4.7)	
Heart Complication (HC) Mild Moderate Severe	 22 (51.2) 12 (27.8) 3 (7)	
No Heart Complication	6 (14)	

In order to evaluate the relationship between response variable i.e. heart complication (HC) categories and its predictor variables (Nutritional status (NS), Immunization, Pain swallow (PS), White membrane (WM), Fever, Stridor, Hemoglobin (Hb) and Potassium (K)) we employ the ordinal logistic regression analysis due to its predictor variable data type. We perform multivariate ordinal logistic regression analysis with backward elimination to eliminate the insignificant predictor variables from the model. Each predictor variable that have p-value > 0.25 in each step elimination of multivariate model is removed from the model until all predictor variables are significant at level 0.1. In the first step of multivariate model, we include all predictor variables as baseline model. The results are shown in the Table 2.

Table 2. Multivariate ordinal logistic regression baseline model

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Upper Bound	Lower Bound
Threshold	[HC = 1.00]	-5.183	3.081	2.831	1	0.092	-11.221	0.855
	[HC = 2.00]	-1.447	2.648	0.299	1	0.585	-6.636	3.743
Location	[NS =1.00]	-1.420	1.486	0.913	1	0.339	-4.332	1.493
	[NS =2.00]	0.818	0.985	0.690	1	0.406	-1.112	2.748
	[NS =3.00]	-0.153	1.541	0.010	1	0.921	-3.173	2.868
	[NS =4.00]	-20.141	0.000	.	1	.	-20.141	-20.141
	[NS =5.00]	0[a]	.	.	0	.	.	.
	[Immunization =1.00]	-2.135	1.976	1.167	1	0.280	-6.009	1.739
	[Immunization =2.00]	-1.105	2.205	0.251	1	0.616	-5.427	3.216
	[Immunization =3.00]	0[a]	.	.	0	.	.	.
	[PS =1.00]	0.565	1.176	0.231	1	0.631	-1.740	2.871
	[PS =2.00]	0[a]	.	.	0	.	.	.
	[WM =2.00]	0[a]	.	.	0	.	.	.
	[Fever =2.00]	0[a]	.	.	0	.	.	.
	[Stridor =1.00]	-5.296	1.904	7.735	1	0.005	-9.028	-1.564
	[Stridor =2.00]	0[a]	.	.	0	.	.	.
	[Hb =1.00]	3.129	1.324	5.583	1	0.018	0.534	5.724
	[Hb =2.00]	0[a]	.	.	0	.	.	.
	[K =1.00]	1.648	0.984	2.803	1	0.094	-0.281	3.578
	[K =2.00]	0[a]	.	.	0	.	.	.

Link function: Logit.
[a] This parameter is set to zero because it is redundant.
Model fitting information: Chi-square = 22.961 (p-value = 0.011).
Goodness of fit: Pearson = 38.273 (p-value = 0.367); Deviance = 28.966 (p-value = 0.791).
Pseudo R^2: Nagelkerke = 0.559.

Based on the result of base multivariate model which represent in the Table 2, there are 3 predictor variables that have p-value > 0.25 i.e. Nutritional status (NS), Immunization, Pain swallow (PS) and 2 other variables that have no effect in the model i.e. White membrane (WM) and Fever due to similar data of all patient (sample) in each of these predictor variables. (Note: These two variables consist of the same answer from all respondents in each of it). Therefore, we should exclude those five predictor variables from the final model. The result of multivariate ordinal logistic regression final model with 3 significant variables in first step elimination are shown in the Table 3.

Table 3. Multivariate ordinal logistic regression final model

		Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
							Upper Bound	Lower Bound
Threshold	[HC = 1.00]	-2.998	1.664	3.247	1	0.072	-6.258	0.263
	[HC = 2.00]	0.148	1.383	0.011	1	0.915	-2.564	2.859
Location	[Stridor =1.00]	-4.580	1.649	7.711	1	0.005	-7.812	-1.347
	[Stridor =2.00]	0[a]	.	.	0	.	.	.
	[Hb =1.00]	1.855	1.044	3.156	1	0.076	-0.192	3.902
	[Hb =2.00]	0[a]	.	.	0	.	.	.
	[K =1.00]	1.486	0.834	3.177	1	0.075	-0.148	3.121
	[K =2.00]	0[a]	.	.	0	.	.	.

Link function: Logit.
[a] This parameter is set to zero because it is redundant.
Model fitting information Chi-square: 14.702 (p-valeu = 0.002).
Goodness of fit: Pearson = 4.242 (p-value=0.515); Deviance = 5.177 (p-value=0.395).
Pseudo R^2: Nagelkerke: 0.396.

As can be seen from Table 3, those three predictor variables in the multivariate ordinal logistic regression final model have p–value < 0.1 i.e. Stridor (p-value = 0,005), Hb (p-value = 0,076) and K (p-value = 0,075), indicate that those variables are significant at 0.1. Each coefficient of those predictor variables in the final model is used to calculate the probability value of each HC categories by using following formula:
For = , , then

- (1)

As there are three predictor variables in the final model, then equation (1) becomes equation (2) as follow:

- (2)

Where is response category index, is number of response category, is number of predictor variables and is number of category in each predictor variable.

The logit function in the equation (2) can be used to calculate the probability for each HC categories using following formula:

-
- (3)

Accordingly, for the first category “Mild” :

- (4)

For the second category “Moderate” :

-

= (5)

While for the last category “Severe” :

- (6)

Using formulas in the equation (4), (5), and (6), we calculate the probability of HC categories: “mild”, “moderate” and “severe” of all possible combination of predictor variables as can be seen at Table 4.

Table 4. Probability of heart complication categories

Predictor variable			**Heart complication (HC)**		
Stridor	**Hb**	**K**	**Mild (1)**	**Moderate (2)**	**Severe (3)**
Present	Good	Good	0.048	0.489	0.463
Present	Good	Not Good	0.011	0.197	0.792
Present	Not Good	Good	0.008	0.146	0.846
Present	Not Good	Not Good	0.002	0.038	0.961
Absent	Good	Good	0.829	0.162	0.009
Absent	Good	Not Good	0.524	0.438	0.038
Absent	Not Good	Good	0.432	0.514	0.054
Absent	Not Good	Not Good	0.147	0.653	0.200

Table 4 presents the probability of each HC categories for all possible combination of the predictor variables (Stridor, Hb and K). As an example, a patient (sample) with present in Stridor, good in Hb and K would likely to be classified as HC categories “mild” with probability 0.011, category “moderate” with probability 0.197 and category “severe” with probability 0.792. Table 4 can be also figured as follow:

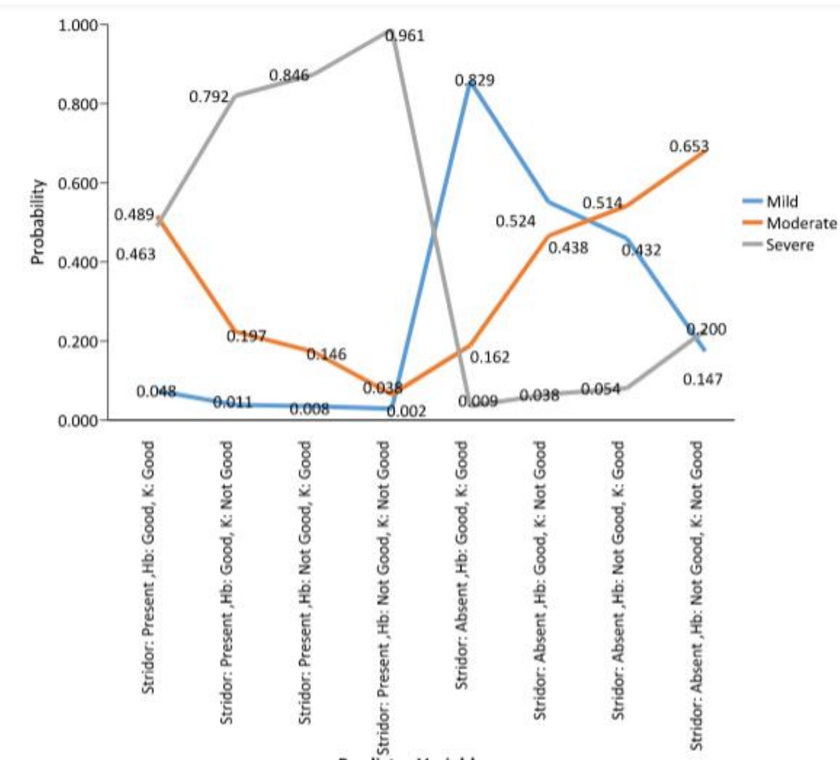

Figure 1. Probability of heart complication categories

IV. Discussion

The method described in this paper is easy to understand and to use. It can be useful in at least two situations. Firstly, a clinician can estimate the HC of an outbreak diphtheria before control the predictor are effectively put into practice. Secondly, it may be useful for public education to illustrate what could happen in a population where no action is taken to stop severity of HC.

As can be seen from Table 4 and Figure 1, the present of stridor will increase the probability of a patient for being classify as category "severe" significantly comparing to others variables. Furthermore, the highest probability of a patient for being classify as category "severe" is 0.961 when Stridor present in the patient and also has not good in Hb and K. Hence we will surely classify that patient into category "severe". On the other hand, patient with absent in Stridor, not good in Hb and K will have the highest probability for being classify as category "moderate" with probability as 0.653. While the patient with absent in stridor, good in Hb and K will have the highest probability for being classify as category "mild" as 0.829. Therefore, the patient with those criteria will surely classify as category "mild". In general, classification can be done by looking at the highest probability in each category for each patient (sample). For example, patient (sample) with the highest probability in category "mild" among all categories will likely to be classified as category "mild". The rule is similar for two other categories.

Beside the model interpretation, we should also check the model fitting, goodness of fit and the Pseudo R^2 of the model. Model fitting information compares the -2log likelihood value of model with intercept only and model with predictor variables. This comparison is evaluated by Chi-square statistic. Model with significant Chi-square means that the model with predictor variable is better than model with intercept only due to significant decreasing of -2log likelihood value. The model fitting information Chi-square of multivariate ordinal logistic regression final model is significant with p-value = 0.002. Hence, the predictor variables Stridor, Hb and K are significantly affect the response variable HC categories.

The goodness of fit statistics indicates the compatibility of model with the empirical data and can be represented by Pearson and Deviance statistics. On the other word, these statistics are intended to test whether the observed data are consistent with the fitted model. The null hypothesis states that the fit is *good*. Therefore, the final model would be good if the statistics have large p-value. The value of Pearson statistics is 4.242 (p-value = 0.515) and Deviance is 5.177 (p-value = 0.395). Those two statistics are insignificant due to its p-value that larger than 0.1. Therefore, the final model is suitable with the empirical data or it fit very well and can be used to evaluate the relationship between HC stage and its predictor variables, Stridor, Hb and K.

Another important statistic in the multivariate ordinal logistic regression model is Pseudo R^2 which summarizes the proportion of variance in the response variable that can be accounted for by the predictor variables. According to Nagelkerke criteria,[10,11,12,13] it can be concluded that 39.6% of variability in heart complication categories can be explained by the predictor variables Stridor, Hb and K, while the rest (60.4%) is affected by other variables outside the model.

V. Conclusion

The final model is suitable with the empirical data or it fit very well and can be used to evaluate the relationship between HC stages categories and its predictor variables, Stridor, Hb and K.

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The authors declare that there is no conflict of interest

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