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RESEARCH ARTICLE

Modeling Annual Parasite Incidence of Malaria in Indonesia of 2017 using Spatial Regime

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Abstract. Malaria is an infectious disease caused by the Plasmodium parasite and transmitted through infected female Anopheles mosquitoes. The morbidity of malaria is determined by Annual Parasite Incidence (API) per year. A region with high malaria cases can spread malaria to other regions. Therefore, the purpose of this study is to determine the spatial regimes and factors that significantly influence the spread of malaria in Indonesia of 2017. Spatial regime is a method obtained by clustering the coefficient values from the well-known method in modeling spatial varying relationship namely geographically weighted regression (GWR). The data used in this study are malaria Passive Case Detection (PCD) from Puskesmas throughout Indonesia in 2017. The results show three groups which can be classified as regencies/cities with low, moderate and high API, while slide positivity rate and annual blood examination are predictors which influent API rates in Indonesia significantly.

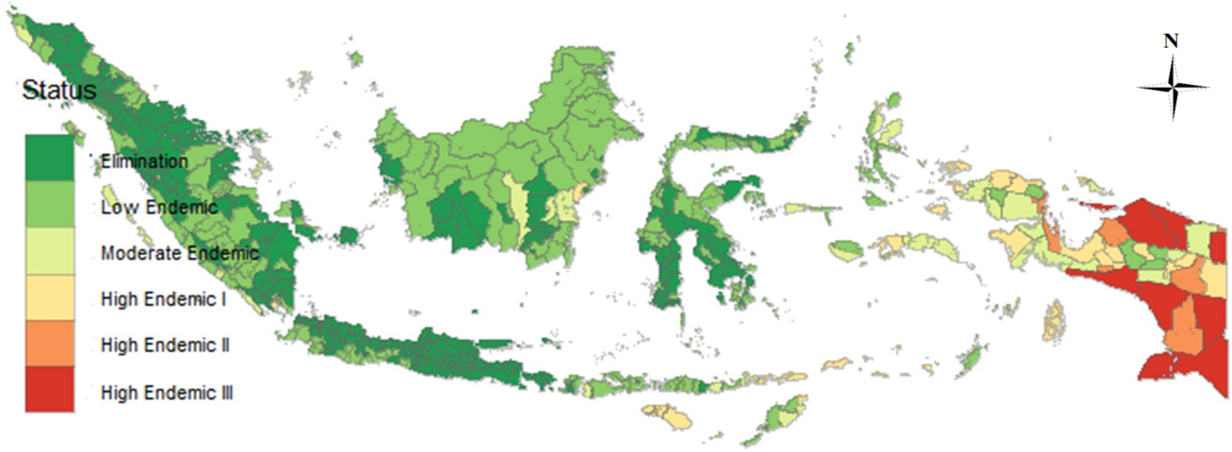
1. Introduction

Malaria is one of the public health problems that can cause death especially in high-risk groups, namely infants, toddlers, and pregnant women. Indonesia is one of the malaria-endemic areas in southeast Asia with high malaria cases (WHO 2018). The disease has been known for a long time, and various efforts have been made to overcome it. However, until now the disease still endemic in some parts of Indonesia (Juhairiyah *et al.*, 2014) and health problems due to malaria are still concerning, especially in rural areas (Departemen Kesehatan RI, 2010).

The malaria morbidity in a certain area is measured by the Annual Parasite Incidence (API) rate, which represents the number of malaria positive cases per 1000 population in one year (PUSDATIN, 2016). Based on the distribution of of malaria endemicity in 514 regencies/cities in Indonesia (Figure 1), the tendency of malaria incidence in eastern Indonesia which was higher than in western Indonesia. KEMENKES (2017) grouped these regencies/cities into four based on the measured API. There are 272 regencies/cities categorized as malaria elimination, i.e. area with rare malaria cases. Meanwhile, there are 166 regencies/cities categorized as low endemic areas (API rate less than 1 per 1000 population), 37 regencies/cities belong to moderate endemic areas (API rate between 1 to 5 per 1000 population), and 39 regencies/cities belong to high endemic areas (API rate more than 5 per 1000 population). The high endemic category is further divided into three groups. High Endemic I is an area with an API rate of 5 to 50 per 1000 population, High Endemic II is an area with an API rate of 50 to 100 per 1000 population, and High Endemic III is an area with an API rate of more than or equal to 100 per 1000 population.

The risk factors of Malaria malaria risk factors are can be classified into environmental factors and behavioral factors. Environmental factors are related to the propagation media of malaria vector around the residence. Whereas, behavioral factors are identified with people's habits, such as the use of anti-mosquito repellent, nighttime habits, use of insecticide-treated bed nets, and activities to malaria-endemic areas (Sunarsih *et al.*, 2009). Miranti, *et al.* (2015) performed malaria modeling using geographically weighted lasso regression with influential factors such as treatment with ACT (Artemisinin-based Combination Therapy) and the behavior of preventing mosquito bites (mosquito net, insecticides, mosquito coils, repellent, and taking malaria-preventing drugs). Meanwhile, according to Lestari & Salamah (2014), factors that significantly influence malaria are the area of residence, the habit of using nets, water sources for drinking/cooking needs, and the disposal of feces. Modeling the prevalence of malaria was also carried out by Muharom (2016) using Cox regression, and Siswanto *et al.* (2017) conducted a conditional autoregressive regression. Nababan & Umniyati (2018) also carried out malaria modeling using geographical information system (GIS).

Several studies on malaria were also conducted in malaria-endemic countries using spatial analysis. Yeshiwondim *et al.* (2009) described the global and local distribution pattern of malaria in central Ethiopia using the Moran's Index. Zhang *et al.* (2008) and Gwitira *et al.* (2020) used GIS to detect the existence of spatial clusters in China and Zimbabwe, respectively. Research using GIS was also conducted by Zhao *et al.* (2020) by integrating satellite remote-sensing data with surveillance data from 18 countries of Yunnan Province along the China–Myanmar border to create a spatial model and risk maps.



Source: Malaria Sub-Directorate, Indonesian Ministry of Health, 2017
Note: non-scale map

Figure 1. The malaria endemic map in Indonesia in 2017

In this research, malaria was modeled using geographically weighted regression (GWR). The GWR coefficients were grouped using the K-means method to simplify the interpretation of the GWR model. The groups formed are called spatial regimes. In each subsequent regime, a regression model was formed to determine the factors that influence the spread of malaria in Indonesia in 2017.

2. Methods

The data used in this research were the results of malaria Passive Case Detection (PCD) from Puskesmas throughout Indonesia in 2017 obtained from the Malaria Sub-Directorate of the Indonesian Ministry of Health. Malaria endemicity data consists of 514 regencies/cities in Indonesia. A total of 213 regencies/cities were analyzed using the spatial regime. Regencies/cities which are malaria elimination areas and have zero API rate were not included in the model. The API rate was used as a response variable.

According to KEMENKES (2019), one of the efforts to prevent malaria in Indonesia is through diagnosis, namely microscopic examination of blood preparations and rapid diagnostic tests. In this study, the selected predictors that are associated with the diagnosis were slide positivity rate (SPR), annual blood examination (ABER), the proportion of malaria cases caused by Plasmodium falciparum (PF), and the proportion of malaria cases caused by Plasmodium vivax (PV). SPR is the proportion of positive cases from the tested blood sample, and ABER is the proportion of the population from which the blood sample is taken. Moreover, the number of cases in children aged 2-14 years (CC) was also selected as a predictor. The determination of CC as a predictor was based on the results from Sopi and Patanduk (2015), stating that severe malaria was observed in children under the age of five due to the lack of immunity, which eventually can lead to death. This observation is also supported by the publication from the WHO in 2015, which estimated that there were around 214 million new cases of malaria with the death of around 438,000 people worldwide, of which about a third (306,000) occurred in children under five (KEMENKES, 2016). In 2019, it was estimated that 39% (96,659) of malaria cases in Indonesia occurred in children under 15 years old (Ellyvon, 2020).

The statistical methods used in this study are geographically weighted regression (GWR), cluster analysis, and multiple regression. The GWR was used to determine the coefficients of the predictors in each regency/city. The K-means clustering method is used to classify the coefficients of the GWR. Multiple regression analysis is used to estimate the coefficients of the predictors in each cluster (regime). The stages of the analysis in this research are listed below:

1. Identify the relationship trend between predictors and API rate (response variable) and make thematic maps of malaria data in Indonesian regencies/cities.
2. Test the spatial heterogeneity using the Breusch-Pagan (BP) test (Anselin, 1988).
3. Calculate the value of the variance inflation factor (VIF) to determine the multicollinearity between predictors.
4. Estimate GWR parameters. The formula of GWR model is written as follows:

$$y_i = \beta_0(u_i, v_i) + \sum_{k=1}^{p} \beta_k (u_i, v_i) x_{ki} + \varepsilon_i$$
$$i = 1, 2, \cdots, n \text{ and } k = 1, 2, \cdots, p \quad (1)$$

Where y_1 is response variable at i-th location, x_{ki} is the k-th explanatory variable at i-th location, $\beta_0(u_i,v_i)$ is intercept at i-th location, $\beta_k(u_i,v_i)$ is parameter of the k-th explanatory variable at i-th location, (u_i,v_i) is coordinate at i-th location (latitude, longitude), and ε_i is residual at i-th location.

The parameter estimation method of GWR is weighted Least least Squaresquare. (WLS). WLS produces the parameters of each location. The formula for of the parameter estimation of GWR in each location estimation is defined as:

$$\hat{\boldsymbol{\beta}}(u_i, v_i) = (\boldsymbol{X}'\boldsymbol{W}(u_i, v_i)\boldsymbol{X})^{-1}\boldsymbol{X}'\boldsymbol{W}(u_i, v_i)\boldsymbol{y} \quad (2)$$

Where Beta is $\hat{\boldsymbol{\beta}}(u_i, v_i)$ is a vector of parameter estimate of $\beta(u_i,v_i)$ and $\boldsymbol{W}(u_i,v_i)$ spatial weight matrix at i-th location and its diagonal elements are determined by the proximity of i-th location to other locations.

In GWR model, the accuracy in determining the bandwidth is required. The optimum bandwidth is obtained when the cross-validation (***CV***) has a minimum value which is obtained through an iterative process (Fotheringham *et al.*, 2002). The formula of ***CV*** is written below:

$$CV = \sum_{i=1}^{n}\left(y_i - \hat{y}_{\neq i}(h)\right)^2 \quad (3)$$

where $y_{\neq i}^{(h)}$ is the estimation value of y_i without the *i-th* observation.

The approximate relationship between locations is expressed by the spatial weight matrix (***W***). This matrix has a size of n x n, with n is the number of location, and its diagonal equals zero. The spatial weight matrix has a function to determine different parameter in each point of observation locations. In this research, the weighted function between *i*-th location and *i-th* location (w_{ij}) is the gaussian adaptive and the formula is shown in Equation (4).

$$w_{ij} = \begin{cases} \exp\left[-\frac{1}{2}\left(\frac{d_{ij}}{h_i}\right)^2\right] & \text{if } d_{ij} < h_i \\ 0 & \text{otherwise} \end{cases} \quad (4)$$

where d_{ij} is Euclidean distance between *i-th* location and *j* th location, and h_i is the bandwidth at *i*-th location.

5. Perform cluster analysis.

a. Cluster analysis is based on the GWR parameter estimators. Suppose $\hat{\boldsymbol{\beta}}_i = (\hat{\beta}_{1i}, \hat{\beta}_{2i}, \ldots, \hat{\beta}_{pi})^T$ is a estimators vector of GWR parameters estimates for *i*-th location with. Furthermore, the value of $\hat{\boldsymbol{\beta}}_i$ is clustered using the K-means method (Johnson & Wichern, 2007). The resulting cluster is $G = (G_1, \ldots, G_K)^T$ which is a group of regencies/cities in Indonesia.

b. Determination of the number of groups by the elbow method, namely by making a plot between the value of the sum of square error (SSE) with the number of clusters (*K*). The formula used to determine SSE is as follows (Madhulatha, 2012):

$$SSE = \sum_{l=1}^{K}\sum_{i\in G_l}\left\|\hat{\boldsymbol{\beta}}_i - C_l\right\|^2 \quad (5)$$

with G_l is *l*-th cluster, and C_l is a vector of the centroid center for *l*-th cluster. The optimal group cluster is determined based on a significant decrease in SSE.

6. Estimate the multiple linear regression parameters in each cluster (regime).

3. Result and Discussion

Data Exploration

The distribution plots and box-plot for API rate are presented in Figure 2. The distribution pattern of API in Figure 2a is not clearly visible due to many zero values. Therefore, an API distribution plot with a value of more than three was added (Figure 2b), and it is apparent that the API rates have a right-skewed distribution.In the box-plot (Figure 2c). It can be seen that there are many outliers (outliers symbolized circle), which are mostly data from regencies/cities of Papua and West Papua Provinces. To overcome the right skew, the data is were transformed to logarithmic (ln). The distribution plot and box-plot of the transformaed data are shown in Figure 3, and the results now suggest symmetric distribution.

The box-plot of the square root the predictors (Figure 4) shows there are many outliers. Regencies/cities in Papua and West Papua Provinces and some regions in East Nusa Tenggara Province, such as East Sumba and North Central Timor are regions that have high of SPR, ABER, PF, and PV. Meanwhile, Pandeglang, Sukabumi, Tasikmalaya and Pangandaran Regencies in West Java Province and Kulonprogo Regency in Yogyakarta Province also only have high SPR.

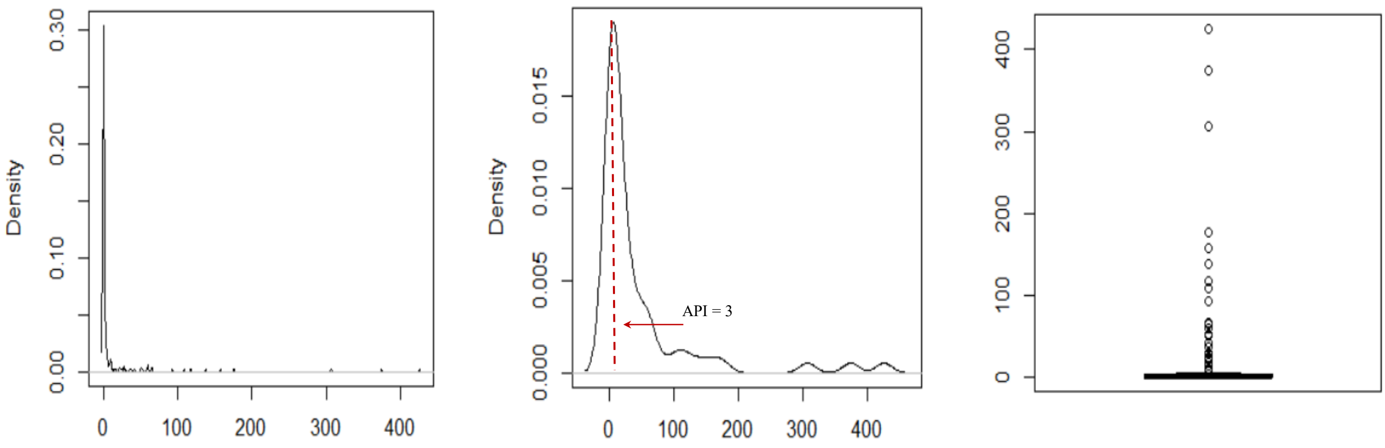


Figure 2 The distribution plot and box-plot of API

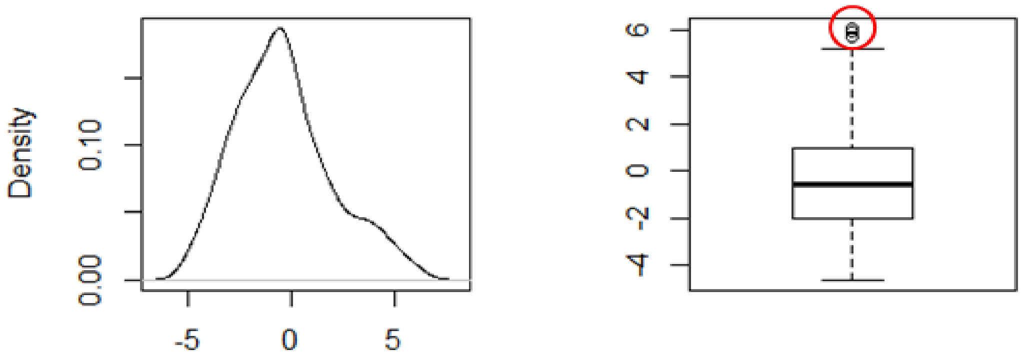


Figure 3. The distribution plot and box-plot of ln(API)

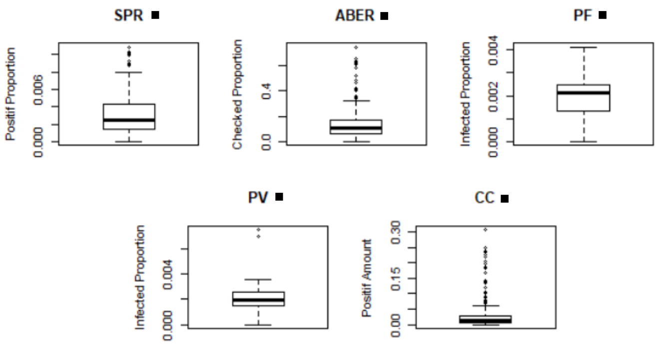


Figure 4. The box-plots of the the square root of predictor (▪)

The GWR requires that the trend of the relationship between the response variable (y) and predictor (X) to be linear (Fotheringham *et al.*, 2002). Thus, the correlation was implemented to measure the closeness of the linear relationship between the two variables. The greater the correlation value, the stronger the linear relationship between the two variables (Mendenhall & Sincich, 2014). Table 1 presents the correlation coefficient between API and predictors for several types of transformations, and the highest correlation value was observed for the relationship of ln(y) and the square root of X. All square roots of predictors have a positive trend with ln(API), and the predictors of CC and ABER have the highest correlations. The scatter plot between ln(API) and the predictor that has been transformed by the square root can be seen in Figure 5.

Table 1. The Correlation coefficient between API (y) and predictor (X) in various transformation combinations

Predictor (X)	Correlation Coefficient between			
	y and X	ln(y) and X	ln(y) and X^2	Ln (y) and $\sqrt{X}$
SPR	0.43	0.43	0.34	0.53
ABER	0.69	0.64	0.49	0.73
PF	0.13	0.13	0.01	0.23
PV	-0.07	-0.06	-0.07	0.05
CC	0.79	0.63	0.45	0.79

Geographically Weighted Regression

Multicollinearity between predictors is one of the assumptions of multiple linear regression analysis. Values of variance inflation factors (VIF) greater than 10 indicate the presence of multicollinearity. Based on Table 2, there are no VIF values of more than 10, and hence the assumption of the absence of multicollinearity has been fulfilled.

Table 2. The VIF values of predictors

Predictor	VIF
Slide positivity rate/SPR ▪	1.70
Annual blood examination/ABER ▪	2.81
The Proportion of *Plasmodium falciparum*/PF▪	1.26
The Proportion of *Plasmodium vivax*/PV▪	1.17
Number of cases in children aged 2-14 years/CC ▪	3.71

▪square root transformation

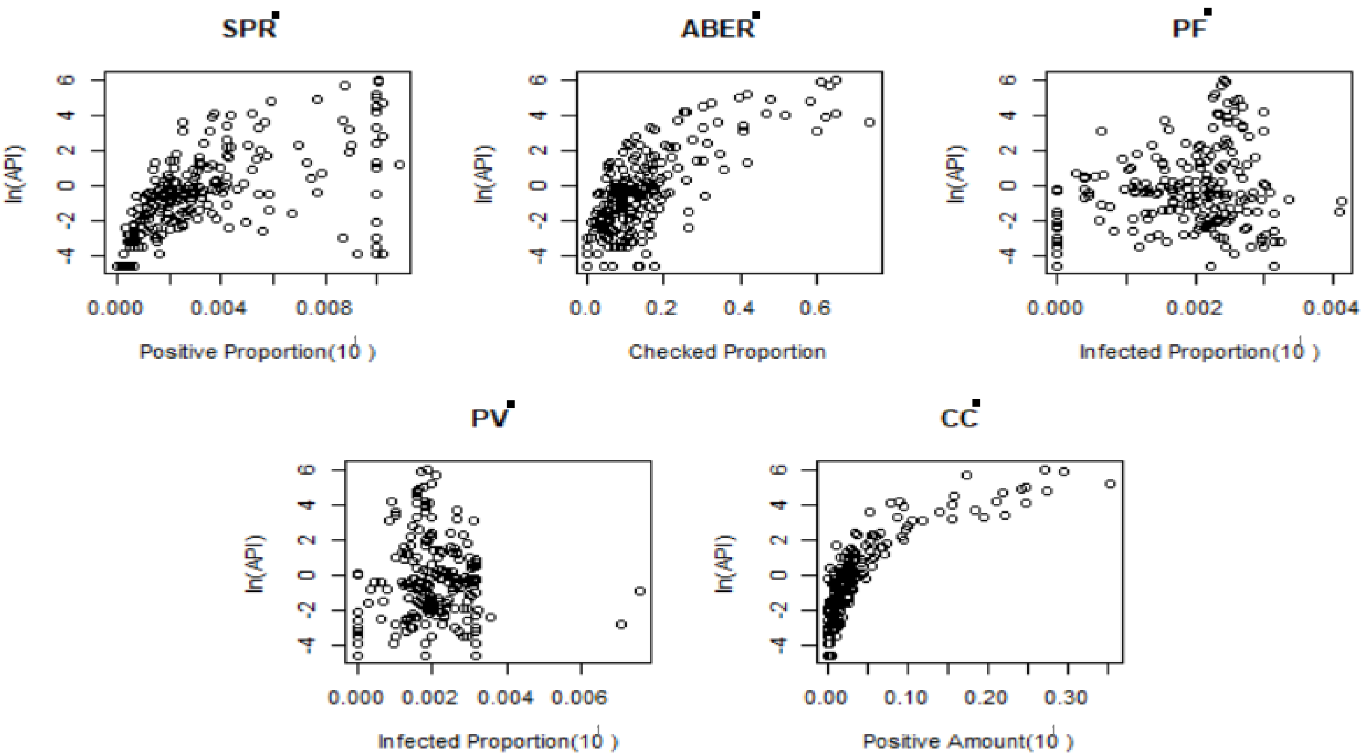


Figure 5. Scatter plots of the square root of predictors (▪) and ln(API)

In order to test spatial heterogeneity, BP test was performed. The results show the BP test value is 15.96 (p-value= 0.007) less than the significance level of 0.05, and thus we concluded that there was heterogeneity among regencies/cities. It This also means that local analysis was required to determine the characteristic of each regency/city. The result confirmed that the GWR model should be used for this case.

The estimator values of the GWR parameters are summarized by the Table 3. The estimated parameter of all the predictors has a positive relationship to the API rates for all observation sites. This finding suggests shows that the API rate in a certain region will increase when the value of the predictor increases. The magnitude of the effect of increasing the API rate at each observation location is different. Moving towards the western region of Indonesia, the effect of SPR on API rate is more significant, as indicated by the increase in coefficient value. Meanwhile, the effect of PF, PV, ABER, and CC on the API rate is more significant towards the eastern region of Indonesia. The pseudo-R^2 value of the GWR model is 77.77% which means that the diversity of API rates that can be explained by predictors is 77.77%.

Cluster analysis

In the GWR model, each regency/city has different coefficients. To simplify the interpretation, the GWR coefficients are grouped by the K-Means clustering method. The elbow method was used to determine the number of clusters (Figure 6), and the result showed that there are three optimal clusters.

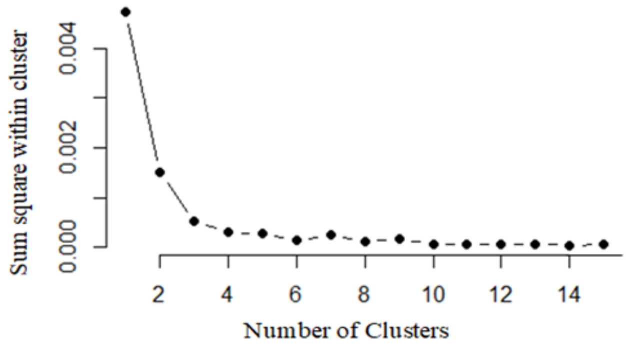
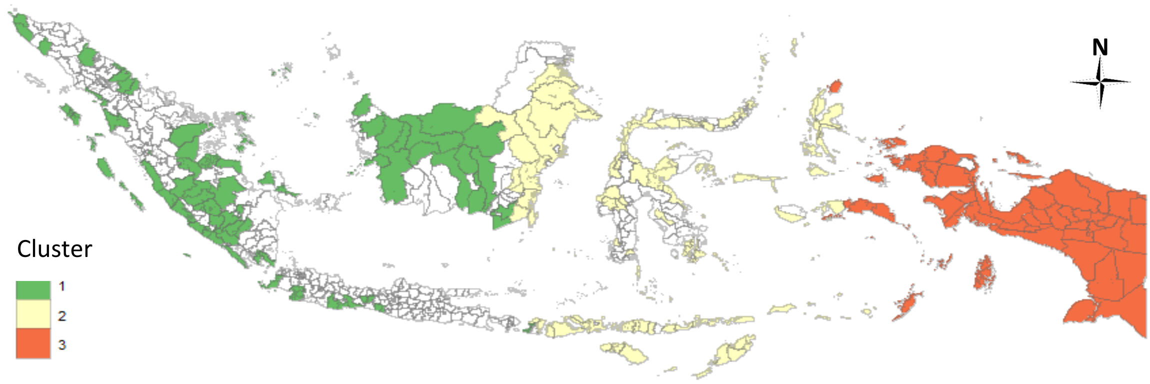


Figure 6. Elbow method of K-means clustering

The map of regencies/cities groups is shown in Figure 7. Cluster 1 shows areas with low API rates covering the western part of Indonesia, namely regencies/cities throughout Sumatra and Java Islands and in West Kalimantan and Central Kalimantan Provinces. Cluster 2 shows moderate areas with API rate covering areas in the central part of Indonesia, namely regencies/cities throughout the provinces of East Kalimantan, North Kalimantan, South Kalimantan, Bali and Nusa Tenggara, and regencies/cities on Sulawesi and Maluku Islands. Cluster 3 shows areas with high API rate covering regencies/cities in the Provinces of West Papua and Papua.



Note: non-scale map

Figure 7. Map of regencies/cities in three clusters

Table 3. The five series statistics of GWR parameter estimationestimate of GWR

Parameter Predictor	Minimum	First Quartile	Median	Third Quartile	Maximum
Intercept	-4.58	-4.54	-4.46	-4.40	-4.31
Slide positive rate/SPR ▪	302.78	309.81	318.70	325.36	333.81
Annual blood examination/ABER ▪	8.51	8.58	8.62	8.67	8.75
The Proportion of *Plasmodium* falcifarum/PF ▪	315.59	329.71	342.35	354.73	359.45
The Proportion of *Plasmodium vivax*/PV▪	317.84	338.55	354.84	375.03	385.94
Number of cases in children aged 2-14 years/CC▪	7.24	7.82	8.24	8.88	9.51

▪square root transformation

The characteristics of the clusters that were formed differed depending on the average coefficient of variables at each location. Figure 8 shows that the coefficient of predictors in each cluster is different. Cluster 1 which is a low API rate region is characterized by the high coefficient on the predictors: of ABER, PV, and CC. Cluster 2, which is a moderate API rate region is characterized by the medium coefficient on all predictors. Cluster 3, which is a high API rate region, is characterized by a high coefficient on SPR and the low coefficient on remain predictors.

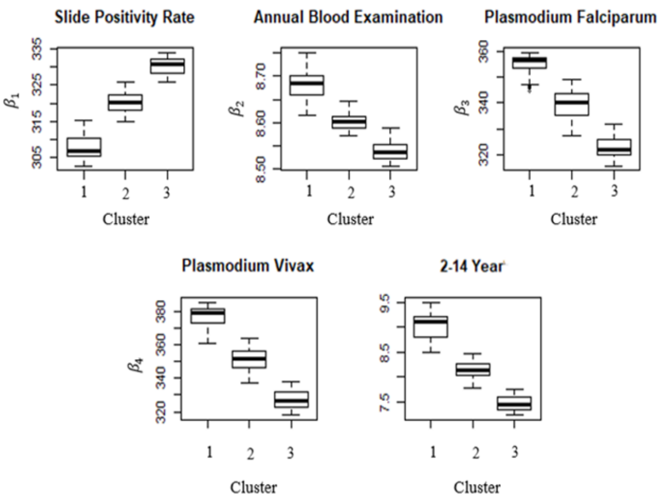


Figure 8. Box-plots of coefficient GWR in each groupcluster

The Regression Model in Cluster

Multiple linear regression analysis was performed to determine the predictors that were affected the API rates in each cluster. Table 4 shows the estimated parameters of the regression model for each cluster. Significant predictors vary by group cluster and all coefficients are positive. Predictor SPR and ABER have significant effects on clusters. Meanwhile, predictor PF and PV have a significant effect on clusters with low API rates, and CC has a significant effect with low and high API rates.

The PF and PV only have a significant effect in areas with low API rates, namely areas located in western Indonesia. The results of this study are in line with research conducted by Hakim (2011) that the dominant Plasmodium species in all regions in Indonesia are *Plasmodium falciparum* and *Plasmodium vivax*. In the eastern part of Indonesia, there are more *Plasmodium ovale* and *Plasmodium malariae* species present.

Table 4. Estimate parameters of the regression model in each cluster

Predictor	Cluster		
	Low API	Medium API	High API
Intercept	-5.58 **	-3.79 **	-2.75
SPR▪	240.14 **	616.73 **	278.79 **
ABER▪	13.48 **	11.37 **	6.01 **
PF▪	374.52 ***	34.34	23.26
PV▪	293.6* **	-120.86	531.55
CC▪	54.60 **	67.16	5.06 *
Pseudo- R^2	68.67%*	76.53%*	89.16%*

▪square root transformation, * significant at α=5%, ** significant at α=1%

Predictors that affect the API rates in each cluster are different. Local governments can utilize in prioritizing special programs as an effort to control malaria in their regions. The government can increase socialization and counseling to prevent malaria through regional health workers.

4. Conclusion

Spatial regimes produce simpler models and provide convenience in determining the predictors that have significant influences on API rates. There are three regimes in the API rates data, identified as groups of regions with low, medium moderate, and high API rates. Variables ofThe slide positivity rate and annual blood examination had significant effects on all groupsclusters. Meanwhile, Variable of the number of children aged 2-14 years also had a significant effect on clusters with low and high API rates. The proportion of *Plasmodium falciparum* and *Plasmodium vivax* variables had a significant effect only on low API rates.

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