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Spatial Survival Approach Bayesian Duration of Dengue Hemorrhagic Fever Treatment

Sisvia Cahya Kurniawati[1], Arief Wibowo[2], Windhu Purnomo[3]
[1]Master Student at Faculty of Public Health, Airlangga University, Indonesia
[1&2]Lecturer at Department Biostatistics and Population, Faculty of Public Health, Airlangga University, Indonesia

Abstract
The spread of dengue disease is very fast and can result in death in a short time. Efforts that can be done to suppress the spread of dengue disease is to know the cause. One method used to determine the factors that affect the healing of patients with DHF disease is survival analysis. Survival analysis is a method to determine the factors that affect the healing of patients with DHF disease. The influence of these location factors is known as the spatial factor. Bayesian approach is a method that can be used to provide spatial effects in survival models. The purpose of this research is to get spatial survival model on DHF incidence in Balikpapan. This study is a non-reactive or unobtrusive method. Population in this research refers to population area, that is a segment of region containing amount of research unit (the whole existing sub-district in Balikpapan) and all dengue case in hospital located in Balikpapan city. Subjects in this study were DHF patients who underwent inpatient at a hospital located in Balikpapan in April-May 2016. This study shows significant factors that affect the rate of healing of DBD in Balikpapan City, hematocrit level, Long fever before hospitalization and the CAR (λ) frailty.
Key words: *Spatial Survival, Bayesian, Dengue Hemorrhagic Fever*

I. INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is one of the diseases frequently contributes on public health problems, and the number tends to increase. Dengue s caused by Dengue virus spread by Aides Egypt mosquito. The spread is very rapid and can lead to death (Darmowandowo, 2006).

The incident rate (IR) of DHF case in Balikpapan City in 2014 is 343,64 per 100.00, by 2015 it has increased to 348,46 per 100,000. Case Fertility Rate (CFR) of DHF in Balikpapan City in 2014 is 0.64%, while in 2015 CFR DHF has increased to 1.17% (Dinkes Kota Balikpapan, 2016). Based on the medical record report of Kanujoso Djatiwibowo Hospital, Disease in January 2016 ranks 2 in 10 inpatient diseases after Dengue Fever, and occupies the first position on 10 outpatient diseases.

Various efforts are made to reduce the number of morbidity and mortality rate due to DHF but have not produced results. Therefore, it needs vigilance and cooperation of all related sectors and elements of society (Dinkes Kota Balikpapan, 2016). Survival analysis (Dohoo,2008) are not only used to see whether an event occurs or not as is the case with logistic regression models, but can also be used to identify risk factors for events as well as handle situations where risk factors change over time. Based on the description then to determine the factors that influence the occurrence of an event based on the risk factors of events on time, the survival model is a more adequate tool.

The rate of recovery of dengue disease has a vary pattern in each region. Thus, spatial analysis is needed which can be used to explain the relationship between the rates of recovery in each region and its influencing factors. The inclusion of spatial correlations in survival analysis, by some researchers added a random effect model to address heterogeneity or unexplained variance sources in the model (Darmofal, 2008). Bayesian approach is a method that can be used to provide spatial influence in survival models. Bayesians (Banerjee et,al, 2003) are used to generate spatial dependencies on the random / error effects of adjacent areas. Spatial dependency is then expressed through prior Conditionally Autoregressive (CAR) previously developed by Besag, York and Mollie. Through CAR, the initial autocorrelation should not have any random effects of survival models. The spatial autocorrelation suggests a relationship between adjacent regions expressed by an adjacent matrix.

II. METHODS

A. Design and sample

The purpose of this research was to get spatial survival model on DHF in Balikpapan City. This study used medical record data of hospitalized DHF patients that has been reported to the Balikpapan City Health Office involving spatial factors area/*lattice*. Response variable used in this study is length of stay (t) and the predictor variable are: sex (X_1)(category as $0 = man, 1 = women$, level of hematocrit (Category as 0= ≤40%, 1> 40%)(X_2), and long fever before hospitalization (day)(X_3).

The steps of spatial survival analysis are as follows (1) Determine the spatial weights by using the Queen Contiguity, (2) hazard assumptions using curves ln[ln (S(t)] and predicted Weibull 2-Parameter distribution with MCMC process and Gibb's sampling (4) calculate hazard function and survival function, (5) estimation of spatial parameter of survival Weibull 2-Parameter with frailty CAR

B. Dengue Hemorrhagic Fever (DHF)

Dengue hemorrhagic fever is a severe, acute, severe infection of acute thrombocytopenia, often fatal. In dengue, plasma enlargement is characterized by hemoconcentration (increased hematocrit) or accumulation of body fluids, hemostasis abnormalities, and in severe cases, a syndrome of dengue shock syndrome, thought to be an immunopathologic process (Halstead, 2007) .

C. Survival Analysis

According Kleinbaum in Aksioma (2012) survival model is a statistical procedure used to analyze the time of survival data that is time data until a certain event / event occurs and is often called failure event

D. Model Spatial Survival

Time-to-event data or time data up to the occurrence of an event according to Banerjee, et al (2003) are often grouped in strata / groups such as geographic areas or disaster areas. In such circumstances, the hierarchical approach through the stratum-specific frailties is often appropriate. Weibull-2 parametric model, hazard rate is given by the following equation:

$$h(t_{ij}; x_{ij}) = \rho t_{ij}^{\rho-1} exp(\beta^T x_{ij}) \quad (1)$$

Then if the model captures the frailty, the proportional hazard $h(t_{ij}; x_{ij})$ can be expanded into:

$$h(t_{ij}; x_{ij}) = \rho t_{ij}^{\rho-1} exp(\beta^T x_{ij} + W_i) \quad (2)$$

Where $j(j = 1,2, \dots, n_j)$is the time until the event occurs, $i(i = 1,2, \dots, I)$is the number of strata / group, t_{ij} is the event time, x_{ij} denotes the covariate vector , P is a baseline hazard parameter and β has an intercept. ρ is the shape parameter of the baseline is hazard and β contains the intercept for the baseline hazard. Parameter ρ represent monotonicity of hazard rate in the Weibull model. When $\rho > 1$, then the hazard rate will be monotonic increasing, and inversely, $\rho < 1$ gives a decreasing monotone, while $\rho = 0$ states a constant hazard rate(Box and Tiao, 1973). In the spatial survival approach, the model is formed through survival data arranged by adjacent areas which means that W_i frailties from adjacent areas illustrate the possibility that these areas have similar characteristics(Darmofal, 2008). As a result, the distribution of random effect W is defined as,

$$W|\lambda \sim CAR\ (\lambda) \quad (3)$$

The notation λ is the CAR parameter distribution stating precision or variance inverse of its random effect distribution (θ).

$$p(\theta \mid x) \propto l(x \mid \theta) p(\theta) \quad (4)$$

In generating a sample of $p(\theta|x)$, a Markov Chain must first be constructed provided that $f(\theta^{(t+1)} \mid \theta^{(t)})$should be easily generated and stationary distribution of Markov Chain is Posterior distribution $p(\theta|x)$, with the following steps:

1. Specifies initial iteration $p(\theta|x)$.
2. Generate T samples $\theta^{(1)}, \theta^{(2)}, \dots, \theta^{(T)}$ from the posterior distribution $p(\theta|x)$. until the stationary distribution is reached
3. Performing algorithms until convergent. If it does not converge then it needs to generate more observation data
4. Dispose of the first observation to avoid the effect of the initial iteration
5. Assume $\{\theta^{(B+1)}, \theta^{(B+2)}, \dots, \theta^{(T)}\}$ as the sample for posterior analysis with B is the initial iteration
6. Create a posterior distribution plot
7. Obtain the summaries of the posterior distribution (mean, median, standard deviation and correlation) [10].

Markov Chain Monte Carlo (MCMC) provides a random sample, $\theta^{(1)}, \theta^{(2)}, \dots\ \theta^{(t)}, \dots, \theta^{(T)}$. From the sample, for each function $G(\theta)$ and parameter θ can be obtained:

1. The sample of the desired parameter is $G(\theta^{(1)}), G(\theta^{(2)}), .., G(\theta^{(t)}), G(\theta^{(T')})$
2. The posterior summary $G(\theta)$of the sample using a simple sample estimate, for example, can be obtained from the posterior mean by the following formula:
$$\hat{E}(G(\theta)\backslash x) = \frac{1}{T'}\sum_i^T G\left(\theta^{(t)}\right) \quad (5)$$
3. Summary MC error, ie a measurement scale that uses the variability of each estimate during simulation. MC error must be of little value to calculate the desired parameters with increased precision.
4. Correlation of among parameters
5. Plot of the posterior marginal distribution.

III. RESULTS

The first step simulation in spatial survival model was defining a matrix of spatial weights. Spatial factors were elaborated by the neighborhood between the locations of another(adjacent matrix). The map of Balikpapan is shown in Figure 1.

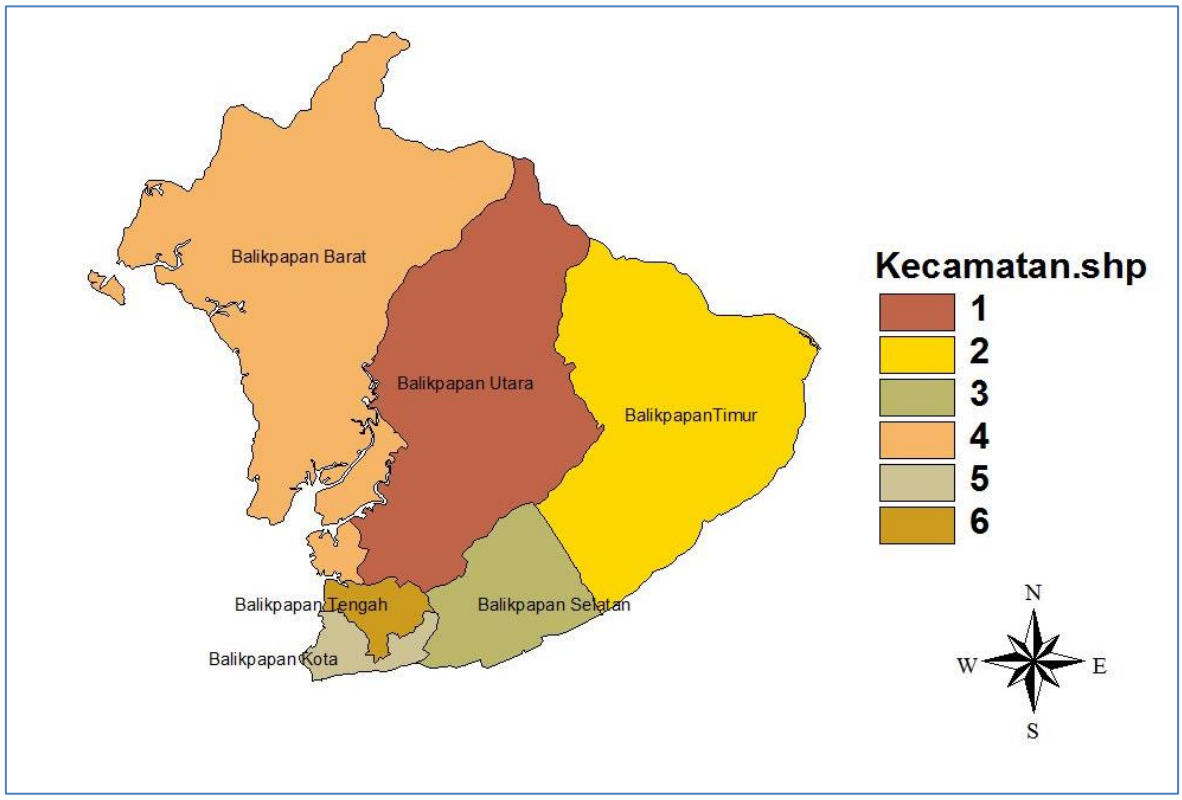
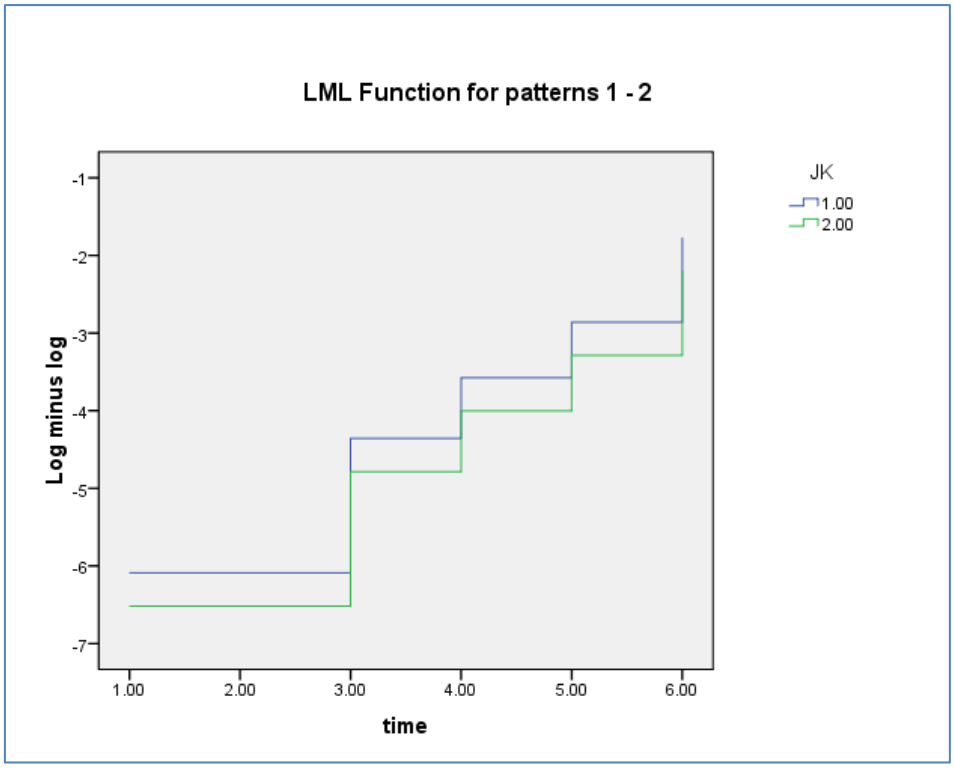
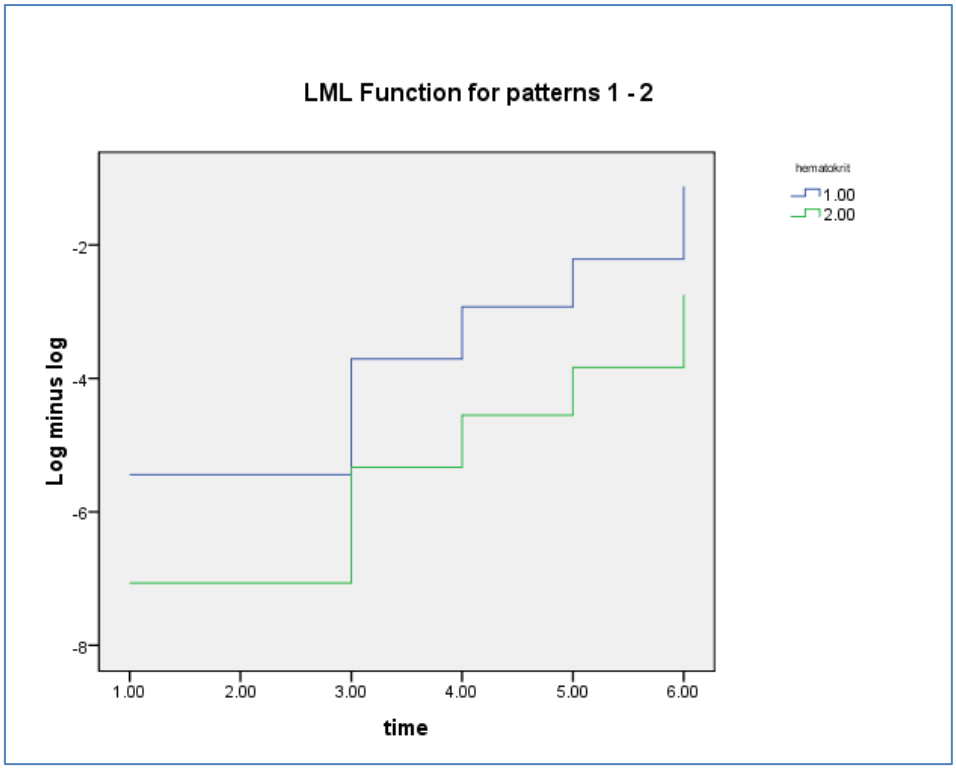


Figure 1. Map of Balikpapan City

The following matrix was used as parameters of the CAR prior distribution in the formation of spatial survival model. Queen Contiguity could be used for determining the spatial weight matrix by employing the neighborhood of their respective areas of the so-called contiguity/adjacent. Adjacent matrix of Balikpapan City is as follows:

list(num = c(4, 2, 2, 2, 4, 4),
adj = c(
6, 5, 3, 2,
5, 1,
6, 1,
6, 5,
6, 4, 2, 1,
5, 4, 3, 1),
sumNumNeigh = 18)





(a)Hematocrit (b)Sex

Figure 2: Proportional Hazard Assumption

The next step was modeling assumptions that must be met in the proportional hazard modeling, that is the hazard function of the categorical predictor variables have to be proportional at all times. Proportional testing was applied by plotting $-ln[-ln\,S(t)]$ descriptively. Figure 2 shows the lines among categories hematocrit (≤40% and > 40%) and sex were paralel, and the proportional hazard assumption, therefore, could be fulfilled.

It means that the predictor variables were independent of time and the relationship between the cumulative hazard was proportional/ every time.

The next step was determining the distribution of the length of stay as its survival time (t). From the goodness of fit test, all of 6 districts in Balikpapan, statistically could be modeled as Weibull distributions. This study, therefore, will employ the Weibull 2 Parameter proportional hazard to estimate the spatial survival model with CAR frailty.

Table 1. Estimated Parameter Survival Weibull 2 Parameters with CAR Frailty

Node	Mean	MC error	2.5%	median	97.5%
Sex	0,010	-0,238	0,010	0,259	0,010
Hematocrit	0,279	0,032	0,279	0,524	0,279
Fever	0,225	0,103	0,225	0,348	0,225
b0	-5,159	-5,906	-5,15	-4,416	-5,159
λ	0,834	0,454	0,774	1,57	0,834
ρ	3,082	2,813	3,081	3,356	3,082

According to table 1, it can be inferred that the Survival model with Frailty CAR Weibull 2 Parameter gives:

$$\hat{h}(t_{ij}; x_{ij}) = 3.082\, t^{2.082} exp(-5{,}159 + 0{,}010x_1 + 0{,}279x_2 + 0.225x_3 + W_i^* \quad (6)$$

Based on the model (6), sex was not significantly affect DHF. The hematocrit (X_1) with value ($\hat{\beta}$= 0,279) significantly affected the healing rate of dengue patients by exp $(0.279 = 1.321$. Based on table 1 that patients with hematocrit more than 40% were more likely to be slow to recover or a recovery rate of 1,321 times than patients with hematocrit levels of less than 40%.

Factor of fever before hospitalization (X_3) with value $\hat{\beta} = 0{,}225)$ significantly affect the healing rate of DHF patients by exp $(0.225) = 1.252$. This indicated that with the increase of one unit of febrile complaints before the hospital then the patient tends to be slower to recover by 1.252 times.

Table 2. Estimation of Random Spatial Effect

Node	Mean	MC error	2.5%	median	97.5%
B. Utara $(\boldsymbol{W_1^*})$	-0.1428	8.546E-4	-0.3852	-0.1414	0.09026
B. Timur $(\boldsymbol{W_2^*})$	-0.05403	8.288E-4	-0.373	-0.04947	0.2427
B. Selatan $(\boldsymbol{W_3^*})$	-0.2365	9.755E-4	-0.4837	-0.2353	-0.004354
B. Barat $(\boldsymbol{W_4^*})$	-0.1739	9.459E-4	-0.4566	-0.1708	0.09232
B. Kota$(\boldsymbol{W_5^*})$	0.3595	0.001442	0.001784	0.3578	0.7199
B. Tengah $(\boldsymbol{W_6^*})$	0.2478	8.864E-4	-0.04646	0.2493	0.5383

Table 2 shows that CAR random effects (λ) with value (0.83) significantly affected the rate of recovery, it could be said that there were spatial dependencies. The 6 observed regions were two region significantly affect of DHF. Sub-districts in Balikpapan that affected the survival rate at the healing rate of Dengue Fever are Balikpapan Selatan Selatan and Balikpapan. This indicated that regions with the same characteristics generally have nearly the same parameter estimation results. Others Sub-district not significant, this means that DHF patients in all districts had the same rate of recovery. Parameter of on the components of variance, but spatial dependencies did not occur in the mean component. Differences in the variance values of spatial random effected in each sub-district resulted in a confidence interval width for estimation of the healing rate of DHF patients to be different in each sub-district.

IV. DISCUSSION

Levels of hematocrit in this study showed that the higher the hematocrit level then the longer undergoing hospitalization in the hospital. Based on the research conducted by Amalia (2010), there is a significant relationship between hematocrit level of dengue hemorrhagic patients and the rate of cure, whereas the greater

the hematocrit level of patients with the increase of one unit tends to be longer. Increased hematocrit is usually preceded by a decrease in platelets, this increase reflects increased capillary permeability and plasma permeability. Hematocrit levels will continue to increase if there is always bleeding and will decrease after administration of fluid in patients.

Another variable that has significant effect on the rate of healing of dengue fever is the duration of fever before hospitalization. The speed at referral to the hospital is indicated by the duration of fever at home. Fever is a major complaint in all patients with DHF. The length of fever before being referred to the hospital is an indicator of the speed of referral to the hospital, thus obtaining rapid and appropriate treatment.

V. CONCLUSION

Factors that significantly influence the rate of recovery of Dengue Hemorrhagic Fever (DHF) are hematocrit (X_2), and fever (X_3) and the resulting model is:

$$\hat{h}(t_{ij}; x_{ij}) = 3.082\, t^{2.082} exp(-5{,}159 + 0{,}010x_1 + 0{,}279x_2 + 0.225x_3 + W_i^*$$

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