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### RESEARCH ARTICLE

#### SURVIVAL BAYESIAN ANALYSIS OF CERVICAL CANCER PATIENTS.

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#### Abstract

Cancer is an abnormal growth of a cell or tissue in which the cell or tissue grows and develops out of control, the speed of growth is excessive, and is often accompanied by changes in the fight cells that eventually disrupt other organs. Cervical cancer is cancer that grows and develops in the cervix or cervix, mainly originating from the epithelial layer or the outer layer of the cervical surface. Based on medical record data in RSSA Malang, there are 1487 inpatient / medical treatments for cervical cancer patients during 2017. The high number of people with cervical cancer in Malang is the background of researchers researching this city. This study analyzed the survival of cervical cancer patients in Malang with Survival Bayesian Analysis. The results of this study found significant variables, namely, stage, age, and anemia status. The standard error of the 0.0913 age variable is that for anemia status the standard error of 0.0869 is obtained.

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#### Introduction:-

Cancer is uncontrolled cell growth, can invade and metastasize (Murray, 2014). According to Samadi, cancer is an abnormal growth of a cell or tissue in which the cell or tissue grows and develops out of control, the speed of growth is excessive, and often accompanied by changes in cell combat that ultimately disrupt other organs (Samadi, 2011). According to the American Cancer Society, cancer is a malignant disease in the world that has a high mortality rate with 13% of deaths, or around 7.4 million sufferers died in 2004 worldwide (American Cancer Society, 2016). More than 70% of cancer deaths occur in poor and developing countries. This percentage is expected to increase until it reaches 12 million deaths by 2030. According to Aune et al., among gynecological malignancies, uterine cervical cancer is still ranked first in the world (Aune, Sen, & Vatten, 2017).

Gynecologic cancers are caused by uncontrolled growth and spread of abnormal cells originating in the female reproductive organs, including the cervix, ovaries, uterus, fallopian tubes, vagina and vulva (Bittoni, Fisher, & Weier, 2015). Cervical cancer is a type of malignancy emerging from the cervix (Deverakonda, 2016). Cervical cancer is second only to breast cancer as the most common female malignancy in both incidence and mortality worldwide (Reis, 2011). There is strong evidence that the incident has a close relationship with a number of extrinsic factors, including important ones rarely found in virgins (Virgo), the incidence is higher in those who are married than those who are not married, especially in girls whose first coitus (coitarche) is experienced at a very young age ( <16 years). Cervical cancer has been closely related to low socio-economic status in developed countries (Robinson, Christensen, Ottesen, & Krasnik, 2011). Incidence increases with high parity, especially if the distance of labor is too close; they are from low socioeconomic groups (poor sexual hygiene), social activities that

often change partners (promiscuity). It is rare to find people whose husbands are circumcised (circumcision) — often found in women who have HPV (Human Papilloma Virus) type 16 or 18 infection, and smoking (Mardjikoeno, 1994). Cervical cancer is mainly caused by the sexually-transmitted Human Papilloma Virus (HPV), which is the most common viral infection of the female reproductive tract (Aweke, Ayanto, & Ersado, 2017). Almost all sexually active individuals will be infected with HPV at some point in their lives, and some may be repeatedly infected (WHO, 2014). There are several cases of this HPV virus subsiding on its own, and there are those that do not go away and progress to cervical cancer. About 70% of cervical cancer events are the result of HPV (Human Papilloma Virus) type 16 or 18. New vaccines are available to prevent infection by the HPV types most associated with cervical cancer deaths worldwide. These prophylactic vaccines represent a life-saving development—in particular for girls who have not yet been exposed to the virus through sexual activity (Cervical Cancer Action, 2007).

According to the results of a National Institute of Allergy and Infectious Diseases study, nearly half of women infected with HPV do not have apparent symptoms. Moreover, even more so, infected people also do not know that they can transmit HPV to other healthy people. Symptoms are not very visible at an early stage, in the pre-cancer stage to stage I, practically no complaints are felt. Just stepping on stage 1A-3B there are complaints. However, some symptoms can be observed even though it does not always give a hint of HPV infection, vaginal discharge or a small amount of blood after intercourse (Diananda, 2008).

Based on data from the Saiful Anwar Hospital (RSSA) Malang per month on average, it handles the care of around 450 cervical cancer patients. Throughout 2017, there were 1,468 patients in the house. Referring to 2015, there were 5,564 patients and increased to 6,099 patients in 2016. Meanwhile, based on medical record data, there were 1487 hospitalizations / medical treatments for cervical cancer patients during 2017. The high number of cervical cancer patients in Malang was the background of researchers researching this city. This study analyzed the survival of cervical cancer patients in Malang City with Bayesian Survival Analysis. Survival analysis is the analysis of time-to-event data. Such data describe the length of time from a time origin to an endpoint of interest (Kartsonaki, 2016).

Kneib and Fahrmeir compare the maximum likelihood and Bayesian approaches in parameter estimation in the hazard model with some variation in the amount of censored data and the results are not much different from the estimation accuracy, but in terms of the average probability of coverage the Bayesian approach is better than the maximum likelihood, especially for high censored data (Kneib & Fahrmeir, 2007). Another advantage of the Bayesian approach is the inference of unknown parameters directly from its posterior distribution and accommodating prior research information in the form of priors (Marin, Mengersen, & Robert, 2005).

Based on several studies above that have developed previously found several factors, it can affect the survival of cervical cancer patients. Including age, stage and anemia and completeness of treatment as well as a factor that affects the survival of people with cervical cancer (Benedet, 2000; Crowder, Lee, & Santoso, 2001; Franco, 1995). This study uses variables of age, stage and anemia status. The data used in this study were cervical cancer sufferers who had undergone treatment at the Saiful Anwar Hospital (RSSA) period 2017. The data were obtained from hospital medical records.

## Method:-

In estimation theory, there are two approaches, namely the classical statistical approach and the global statistical approach (Bayesian). Classical statistics are statistics in which decision-making procedures are based only on sample data taken from the population. Whereas Bayesian statistics in decision making is based on new information from observed data (samples) and prior knowledge (Wong, Lam, & Lo, 2005). Statistical inference with the Bayesian statistical approach is different from the classical statistical approach. The classical statistical approach views the  $\beta$  parameter as a fixed value parameter. Whereas the Bayesian statistical approach views the  $\beta$  parameter as a random variable that has a distribution, called the prior distribution. From the prior distribution, the posterior distribution can be determined so that the Bayesian estimator is obtained, which is the mean or mode of the posterior distribution. If the observation data is stated as the parameter data is stated as  $\beta$ . The  $\beta$  distribution with conditions is given through the Bayes theorem as follows,

$$p(\beta | x) = \frac{l(x | \beta) p(\beta)}{p(x)} \dots\dots(1)$$

Also called a method that updates prior parameter information  $\beta$  ( $p(\beta)$ ) from the data before the observations were made using sample information in the likelihood data to get posterior information used in decision making is a normalized constant. The posterior distribution is a likelihood of a prior distribution so that it can be written as  $p(\beta | x) \propto l(x | \beta)p(\beta)$  .....(2)

The prior distribution is the initial information needed in forming the posterior distribution. Also, information is needed from the sample stated through likelihood.

The variables used in this study are as follows:

#### **Survival time/survival time (t)**

The time during which cervical cancer patients undergo treatment at RSUD Dr. Saiful Anwar until the patient was declared dead, stopped/moved treatment, survived/lived in units of days that occurred during the study period. The period of this research is the January 2017 start point and the December 2017 endpoint.

#### **Patient Status**

Patient status is the occurrence or failure of a failure event that is during the study period.

Patient status = 1, is uncensored data. This happens if a cervical cancer patient experiences a failure event that is dead.

Patient status = 0, is censored data. This happens if cervical cancer patients have not experienced a failure event until the time the study ends, stop/switch treatment (lost to follow up).

#### **Stadium (X1)**

Clinical stadium when patients undergo treatment at RSUD Dr. Saiful Anwar, starting from stage 1- IV. Staging variables include.

1. Stage I, namely IA and IB
2. Stage II, namely IIA and IIB
3. Stage III, namely IIIA and IIIB
4. Stage IV, namely IVA and IVB

#### **Age (X2)**

The age variable is the age at which cervical cancer patients undergo treatment at RSUD Dr. Saiful Anwar.

#### **Anemia Status (X3)**

Anemia is one of the instructions. The further and the worse the patient's disease tends to experience anemia, this is due to the bleeding experienced by the patient. Anemia status includes,

0 = patient has no anemia

1 = patient has anemia

The steps used are (1) Collecting data in a table; (2) Review the parameter estimator from Bayesian Survival Analysis; (3) Determine / estimate the density function of the opportunity of the survival time of patients with cervical cancer. The survival time of people with cervical cancer is assumed to follow the Weibull Distribution with

the following opportunity density function  $f(t|\lambda, k) = \frac{k}{\lambda} \left(\frac{t}{\lambda}\right)^{k-1} \exp\left[-\left(\frac{t}{\lambda}\right)^k\right]$  ..... (3)

where  $t \geq 0$ ,  $\lambda > 0$ ,  $k > 0$ .  $\lambda$  is a scale parameter, and  $k$  is the form parameter and  $\lambda$ ,  $k$  considered a random variable.

(4) Determine the likelihood function of survival time/survival of people with cervical cancer. The distribution of the survival time of cervical cancer patients is thought to follow the Weibull Distribution 2 parameter, where  $k$  is the shape parameter and  $\lambda$  scale parameter. Then the likelihood function is

$$L(t_1, t_2, \dots, t_n | \lambda, k) = \prod_{i=1}^n f(t_i | \lambda, k) \dots (4)$$

(5) Determine the prior distribution; (6) Look for posterior functions with MCMC and Gibbs sampling; (7) Establish a survival function from the estimated parameter results; (8) Put together a WinBUGS program; and (8) Knowing whether there is a difference in survival of patients with cervical cancer in the stage, the action/treatment, age, complications, and anemia status are different.

### Results and Discussion:-

This study uses a prior distribution of the normal distribution ( $g(\mu, \sigma)$ ), so the joint probability robust function obtained is

$$H(t_1, t_2, \dots, t_n, \lambda, k, \mu, \sigma) = \prod_{i=1}^n f(t_i | \lambda, k) g(\mu, \sigma) = L(t_1, t_2, \dots, t_n | \lambda, k) g(\mu, \sigma) \dots (5)$$

Whereas the following function is determined by MCMC and Gibbs sampling. Gibbs sampling is an MCMC algorithm that includes an iterative sampling of each conditional distribution, where parameters are  $\beta$  partitioned into sections,  $\beta = (\beta_1, \beta_2, \dots, \beta_p)$  and the wholly conditional posterior distribution is  $p(\beta_1 | x, \beta_2, \dots, \beta_p), \dots, p(\beta_p | x, \beta_1, \dots, \beta_{p-1})$  or with the simple one is  $\beta^{(1)}, \beta^{(2)}, \dots, \beta^{(p)}$  (Congdon, 2003). Gibbs sampling works with the following steps.

Take the value of  $m = 0$  and determine the initial value (initial value) of

$$\beta^{(0)} = \{\beta_1^{(0)}, \beta_2^{(0)}, \dots, \beta_p^{(0)}\}$$

Generating each component from

$$\beta^{(m+1)} = \{\beta_1^{(m+1)}, \beta_2^{(m+1)}, \dots, \beta_p^{(m+1)}\}$$

Where

Value  $\beta_1^{(m+1)}$  came from  $p(\beta_1 | x, \beta_2^{(m)}, \dots, \beta_p^{(m)})$

Value  $\beta_2^{(m+1)}$  came from  $p(\beta_2 | x, \beta_1^{(m+1)}, \beta_3^{(m)}, \dots, \beta_p^{(m)})$

$\vdots$

Value  $\beta_p^{(m+1)}$  came from  $p(\beta_p | x, \beta_1^{(m+1)}, \beta_2^{(m+1)}, \dots, \beta_{p-1}^{(m+1)})$

1. Take value  $m_1 = m + 1, m_2 = m + 2, \dots, m_x = m + x$  and repeat step 1 and 2
2. Consider  $\{\beta^{(1)}, \beta^{(2)}, \dots, \beta^{(x)}\}$  as a sample for posterior analysis
3. Get the mean, median, standard deviation of the posterior distribution
4. Establish a survival function from the estimated parameter results

$$h(t) = h_0(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p)$$

Data retrieval process at RSUD Dr. Saiful Anwar began when researchers permitted since March 5, 2019, with a request from the agency of origin and proposal. On May 31, 2019 researchers conducted further licensing by filling out an ethical form from the Hospital, and on July 10, 2019, the study entitled, "Analysis of Survival Bayesian in the Survival of Cervical Cancer Patients in Malang City" was declared ethical as ethical by the research ethics committee of Dr. RSUD research. Saiful Anwar Malang. Furthermore, starting on July 15, 2019, researchers were able to retrieve medical record data at RSUD Dr. Saiful Anwar.



**Figure 1:-**Ethical clearance from RSSA

Data on medical records of cervical cancer patients who became observers of the researchers are data of patients undergoing action/treatment throughout 2017. The samples observed were patients undergoing treatment in 2017. Data recorded were the patient's age, patient status, time of survival of cervical cancer patients, stage, treatment, complications, and anemia status.

In Bayesian Survival Analysis, we need to know the distribution of survival time data (t) of cervical cancer patients first. The distribution of survival time (t) data is assumed to follow the Weibull distribution.

1.  $H_0$ : Survival time data (t) is an independent random variable that has a Weibull distribution
2.  $H_1$ : Survival time data (t) are independent random variables that do not have Weibull distribution

**As for the test statistics: Kolmogorov Smirnov**

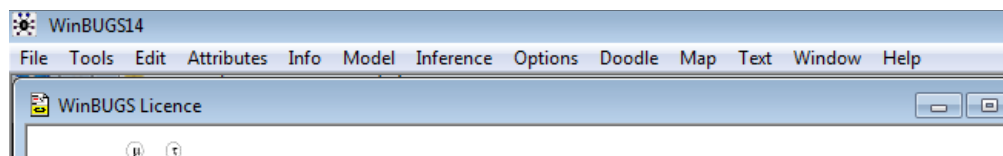
Critical area: Reject  $H_0$  if Kolmogorov Smirnov's calculated value > table value n,  $1-\alpha$

**Table 1:-**Testing the distribution of survival time data (t)

Test Statistics	Sig Value	Decisions
1,031	0.238	failed to reject $H_0$

Based on the results of distribution testing, it can be concluded that the survival time data (t) is an independent random variable that has a Weibull distribution.

Next, determine the estimated parameters of the survival of Bayesian cervical cancer patients using WINBUGS software. WinBUGS (the MS Windows operating system version of BUGS: Bayesian Analysis Using Gibbs Sampling) is a versatile package that has been designed to carry out Markov chain Monte Carlo (MCMC) computations for a wide variety of Bayesian models. The software is currently distributed electronically from the BUGS Project website.



**Figure 2:-**Menu bar in the WINBUGS software

The results of the estimated parameters are presented in table 2.

**Table 2:-Parameter Estimation Using Bayesian**

Parameter	Mean	Error	2.5%	Median	97.5%
Stadium					
Stadium (1)	-13,41	0,158	-9,33	-12,51	-15,69
Stadium (2)	-5,68	0,69	-8,45	-5,995	-3,54
Stadium (3)	-1,23	0,45	-0,74	-1,685	-2,63
Stadium (4)	-0,76	0,29	-1,15	-0,885	2,92
age	-0.0435	0,0913	-0.016	-0,0425	-0.069
anemia	-0.179	0.0869	-0.0381	-0.199	-0.361

Based on table 2 the estimated parameters for stage variable (1) cancer -13.41, stage variable (2) cancer -5.68, stage variable (3) cancer -1.23, patient age variable is -0.0435 and anemia status variable - 0.179. Significant variables are variables whose interval values are 2.5 to 97.5, not past zero. So the insignificant variable is stage (4) and the significant variable is stage (1) cancer, stage (2) cancer, stage (3) cancer, age, and anemia status. So the hazard function model is as follows

$$h(t) = h_0(t) \exp (-13,41 \text{ stadium (1)} - 5,68 \text{ stadium(2)} -1,23 \text{ stadium (3)} -0,0435 \text{ usia} -0,179 \text{ anemia})$$

### Conclusion:-

This study analyzed the survival of cervical cancer patients in Malang City with Bayesian Survival Analysis. This study uses the variable stage, age, and anemia status. The data used in this study were cervical cancer sufferers who had undergone treatment at the Saiful Anwar Hospital (RSSA) Hospital in the 2017 period. The hazard function model is as follows

$$h(t) = h_0(t) \exp (-13,41 \text{ stadium (1)} - 5,68 \text{ stadium (2)} -1,23 \text{ stadium (3)} -0,0435 \text{ usia} -0,179 \text{ anemia})$$

Based on the hazard function model above, it can be interpreted that for the age variable for the addition of 1 year of age, cervical cancer patients will increase the danger failure (death) rate by  $\exp(-0,043)=0,958$  times the initial hazard failure rate if other variables are not included in the model.

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