International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

Endurance of Endometriosis Patients after Surgery Using Survival Analysis

Citra Komang Sari[a]*, Hari Wijayanto[b], I Made Sumertajaya[c]

[a,b,c]*Department of Statistics, Faculty of Mathematics and Natural Science, IPB University, Raya Dramaga street, 16680 Bogor, Indonesia*

[a]*Email: citrakomangsari@gmail.com*

[b]*Email: hari@apps.ipb.ac.id*

[c]*Email: imsjaya@apps.ipb.ac.id*

Abstract

Endometriosis is a disease that affects reproductive-aged women. Endometriosis is not a deadly disease but can cause severe pain and infertility. The delay in diagnosis caused the lesion was already quite large by the time it was discovered. One of reasons for the delay in diagnosis is assumption that pain during menstruation is normal. Nowadays, solution for this disease is surgery because cure has not been found yet. However, it does not guarantee recurrence of endometriosis. Therefore, this study aims to look for factors that affect the resilience of endometriosis patients since surgery using extended cox models. Results showed that age, surgical history, die, the largest lesion, endometriosis type, and type of surgery significantly affect on recurrence. Patients who have history of surgery, will have a risk of relapse 2.45 times compared to not have surgical history. Someone who has grade III or IV is 2.34 times as likely to relapse as someone who has grade I or II. Laparoscopic patients have 2.27 times more likely to experience recurrence than laparotomy. Someone who has higher age has lower risk of recurrence assuming other covariates are constant.

Keywords: Deep Infiltrating Endometriosis; Endometriosis; Extended Cox Model.

---

* Corresponding author.

1. Introduction

Endometriosis is a disease that commonly affects reproductive-aged women (15 years-49 years). This disease is not as popular as cancer, diabetes, coronary heart disease or other degenerative diseases and does not belong to the deadly disease. Despite that, the sufferer of this is quite numerous, it occurs at 1 in 10 (10%) reproductive-age women [1]. Case of endometriosis were also detected in 50 percent of infertility women [1], 40-80 percent were discovered in women with menstruation pain, and 60 percent in women with pelvic pain [2]. Moreover, some women with endometriosis have vague or unclear symptoms, hence it is estimated that the number of patients is more than that. Although endometriosis is said to be a disease of reproductive-age women, progress of endometriosis is having high trend since it is also found in adolescent and menopausal women. Endometriosis is a lesion that resembles endometrium but located outside the uterine cavity and induces chronic inflammation [2]. It causes many problems that interfere with a woman quality of life either physically, psychologically, or socially. Physically, this condition causes pain that varies from mild to severe on certain organ such as abdominal pain, pelvic, back, bladder, rectum, legs and thighs, pain during intercourse, pain during defecation. The disease also causes nausea, bloating, diarrhea, dizziness, long menstrual cycles, excessive menstrual volume and infertility. Psychologically, it causes feeling of stress, depression, despair due to the pain and feeling of worthlessness. This is because they could not take care their family normally or because of infertility hence could not give a descendant. Pain is felt at the time before menstruation, during menstruation or after menstruation. The pain can even be sedentary before, during or after menstruation. It leads to reduced productivity of women due to frequent absent from school or work for several days and having to only lie down at home or in hospital. Socially, women with endometriosis experience feelings of distress due to lack of empathy from those around them who do not understand the pain, demands to have children, and it would cause family problems that lead to divorce. Until now, no cure has been found to treat endometriosis. The solution to endometriosis sufferers is to remove endometriosis lesions through surgery. Yet it does not guarantee recurrence, consequently women who want to get pregnant seem to race against time to get pregnant as quickly as possible before the new lesions appear. In the data of endometriosis patients, there are observation that could not be observed completely such as patients who is not doing routine check-up in the hospital anymore, hence the data is censored. The effect of time is measured in data processing because focus of this study is looking for the patient endurance. Therefore, the appropriate analysis is survival analysis. Survival analysis is a statistical technique used to analyze data which response variable is the time until the occurrence of an event in which the data could not be observed completely. The study of survival analysis for cancer patients with stage 3A endometrial cancer in [3] showed that the patient has a longer percentage of life if performed surgery followed by radiotherapy and chemotherapy. The study used Kaplan-Meier method and Cox Proportional Hazards model. If proportional hazard is not satisfied then the predictor variable could be discarded, but if the variable is an important covariate and will be maintained, then another method is the right solution. Other method that could be used is extended cox model that covariate, which not satisfy the proportional hazard, is multiplied by the function of time so the covariate could be maintained and hazard ratio is obtained [4,5]. Moreover, there is no need to divide the model into several strata that would be inefficient and complicate researchers. On the study conducted by author in [6] showed increasing in hazards ratio through cox regression model compared to cox extended model and somehow hazards ratio of both models gives significant results so evaluating proportional

hazards assumption is essential because it raises questions about the validity of cox model and could give incorrect results. Extended cox model research has also been conducted by author in [7] where the results indicated the extended cox model is better than cox proportional hazard regression at the time of drug user resilience. Therefore, this study aims to apply extended cox models on identifying factors that affect the endurance of endometriosis patients after surgery.

2. Data and Methodology

2.1. Data

The data used in this study is a medical record of endometriosis patients who had surgery (removal of endometriosis lesions) and taken from the Endometriosis Center of Fatmawati General Hospital in Jakarta for a month. Response variable is the patient endurance time from surgery until it is declared relapsed. Overall, the number of endometriosis patients is 174 medical records and after cleaning it because the independent variables is incomplete, there are 133 observations that can be processed which consisting of 27 patients experiencing recurrence and 106 patients until the end of the research time do not relapse. Recurrence is stated from the results of ultrasound or MRI examination. The study identified the effect of twelve covariates on the endurance of endometriosis patients who had undergo surgery.

The covariates are age of the patient during surgery (age), menstrual status(mens), surgical history (rb), type of surgery (type), endometriosis type (grade), endometriosis location (location), post-operation medicine (treatment), the largest lesions (size), pain scale (vas), adenomyosis, deep infiltrating endometriosis (die), and removal of reproductive organs (out). In addition, the censored status (status) is also included on the model as incomplete information in the observation.

2.2. Data Analysis Procedure

Endometriosis patient data from the Endometriosis Center of Fatmawati General Hospital located in Indonesia particularly in Jakarta will be analyzed to see the endurance until endometriosis relapse using survival analysis. The steps in this study are

1. Describe the characteristics of patients having endometriosis.
2. Create a kaplan-meier curve and perform a log-rank test for the covariates.
3. Evaluating the proportional hazards assumption using Schoenfeld residual that is obtained from cox proportional hazards modeling.
4. Form a time function that will be interacted with non-proportional hazard variables.
5. Modeling extended cox by adding interactions between time functions and non-proportional hazard variables, which is called time-dependent variable.
6. Testing parameters simultaneously and partially to see statistically significant covariates
7. Create a new equation with covariates that significantly affects the model.
8. Interpretation of the model.

3. Results and Discussion

3.1. Data Exploration

Figure 1 illustrates the age of endometriosis patients at the time of surgery in boxplot form, whereas pie chart depicts infertility.

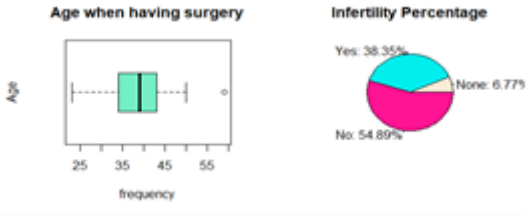

Figure 1: Characteristics of patients based on age and infertility

Based on the boxplot in Figure 1, it shows that the age of endometriosis patients undergoing surgery is not symmetrical and there is an outlier at the age of 59 years. The age of patient has diversity, which the youngest undergoing surgery at the age of 23 years and the oldest at the age of 59 years. Mostly, patients are around 35-45 years. Also, infertility patients are less than those who already have at least one child.

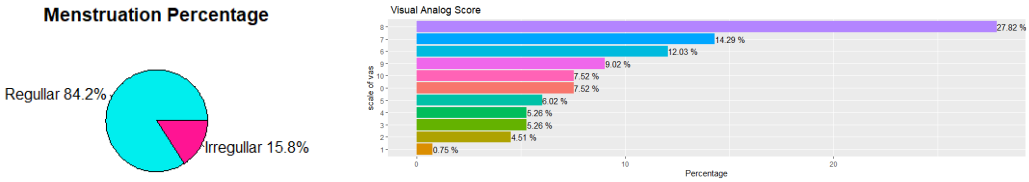

Figure 2: Characteristics of patients based on menstruation and visual analog score

Menstrual variable consists of two categories that are regular and irregular. Regular is a period that occurs every month, whether a little or a lot of blood volume and whether a period of 3 days or more than 7 days. Irregular category is menstruation that does not steady or does not occur every month, for example once every three months. According to figure 2, the number of patients who have irregular menstruation was lower than those who have menstruation every month, based on the data collected. Pain during menstruation is measured using a visual analog score (vas). The scale runs from zero to ten, which zero indicating no pain and ten indicating severe and uncontrollable agony that requires medication to reduce the pain. Endometriosis patients with a scale of 6 to 10 are rated highest in figure 2, while those with the light scale were at the lowest. Accordingly, it is possible to infer that one of the reasons the patient is having surgery due to the pain that is already severe so that surgery is needed to reduce the pain. It is cohorent to what author in [8] stated.

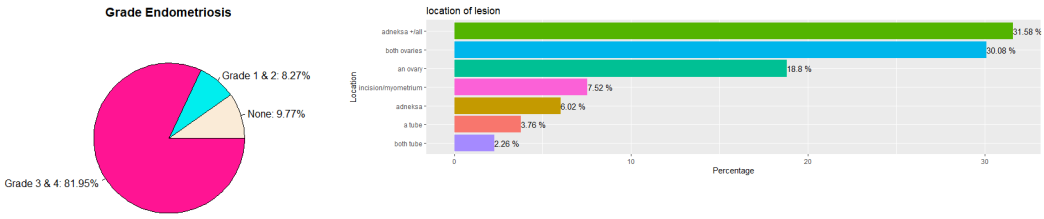

Figure 3: Characteristics of patients by grade and location of endometriosis lesions

Figure 3 shows that the number of patients undergoing endometriosis surgery is dominated by late-stage (grade III or IV) patients rather than individuals with early-stage (grade I or II). Endometriosis is frequently discovered in multiple locations or more than one at the same time. Based on Figure 3, endometriosis lesions could be detected in more than three locations (adneksa+/all). These are partial ovary and fallopian tube plus the other ovary/ fallopian tube or found in both ovary as well as fallopian tube. The second most common site is in both ovaries, with a percentage difference of only 1.5%. With a ratio of 2.26 percent, the rarest areas were detected in both fallopian tubes. Delays in diagnosis results in lesions already being discovered in several locations at the same time. This occurs due to the patient's lack of awareness and knowledge about endometriosis. Diagnosis is difficult to identify since endometriosis does not have typical symptoms so necessitating the collaboration of doctors from various specialists and also lack of government involvement in educating the public about this disease causes delays in diagnosis.

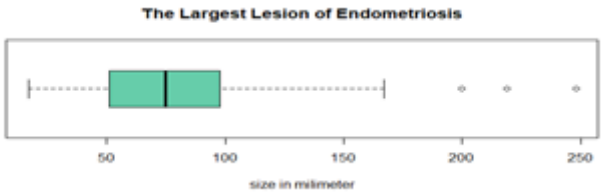

Figure 4: Characteristics of patients by the largest lesion

Based on the boxplot in Figure 4, the largest endometriosis lesions indentified during surgery is not symmetrical and there are several outliers that cause the data to be skewed to the right. The size of the lesion varies, with the biggest size being less than 250mm. Mostly, the largest of lession were reported to be 5cm to 10cm in size.

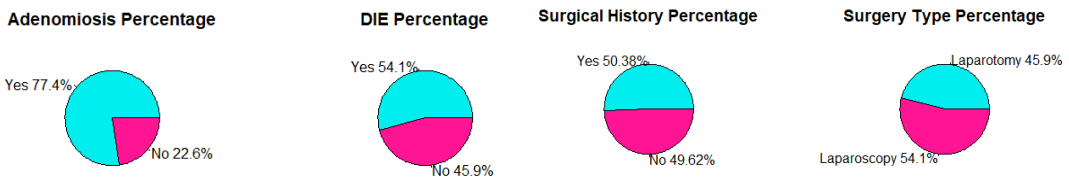

Figure 5: Patient characteristics based on adenomyosis, die, surgical history, and type of surgery

Endometriosis cysts commonly found in parallel with adenomyosis and deep infiltrating endometriosis (die). Adenomyosis is endometriosis that grows in myometrium, while die is an infiltration endometriosis that is more

than 5mm below the peritoneal surface [2,9]. Based on Figure 5, it shows that 77.4 percent of patients who undergo endometriosis cyst incision also had adenomyosis and 54.1 percent of patients were also found to have die. Endometriosis lesions can grow in surgical incisions even though this is rare, for instance, on scar of caesarean surgery. If lesions are not detected in the reproductive organs, then the scars of previous surgical incisions will be examined further. It can be noted that 50.38% of endometriosis patients had surgical history and 54.1% of patients had laparoscopic surgery at the time of surgical of removal the endometriosis lesions. Laparoscopy has been done a lot because endometriosis center has been established with competent doctor and many doctors have updated their skill for implementation of the right treatment. Nowadays, Laparoscopy is the standard gold treatment for endometriosis because it allows doctors to identify lesions more easily by utilizing camera that can be magnified.

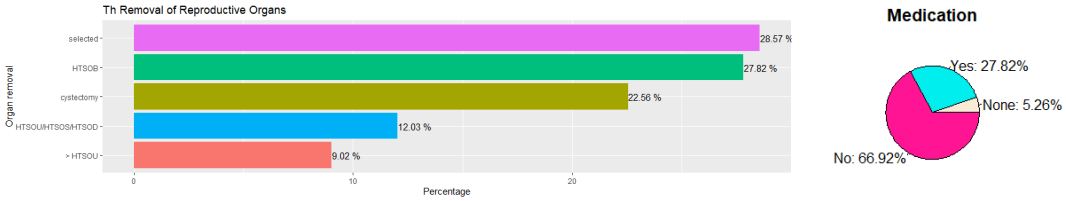

Figure 6: Characteristics of patients based on the organ removal and the consumption of medicine

Endometriosis with a large size will disrupt and damaged reproductive organs, consequently it needs to be removed. Based on the bar plot in Figure 6, it can be seen that the removal of certain organs and removal of all reproductive organs (HTSOB) are prevalent among endometriosis patients, contributing for 28.57 percent and 27.82 percent respectively. Followed by cystectomy (only endometriosis lesions removed) that has percentage of 22.56 percent. Endometriosis treatment is a long-term treatment because it associates with the estrogen hormone in women [2,10]. As the woman has menstruation, endometriosis lesions will develop. Therefore, the doctor will advise HTSOB for women who have several lesions, huge lesions, adhesion, have enough children or toward menopause. Patients who have had surgery and do not intend to have children, are advised to take medication regularly to prevent recurrence and suppress growth of endometriosis. According to the pie chart in Figure 6, the number of patients who take medicine is less than those who do not take it. This case can be caused by a lot of patients assume that after surgery, there is no need to check-up anymore or already had hysterectomy surgery.

3.2. Survival Analysis

3.2.1. Kaplan-Meier and Log-Rank test

Kaplan-Meier (KM) survival is used to determined probability of endometriosis patient endurance after surgery based on potential factors and the log-rank test is a test to distinguish between survival curves from the same factor. This test is only applicable for categorical type covariate [11]. KM survival curve for endometriosis patients can be seen in figure 7.

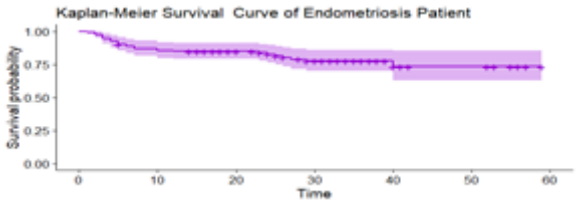

Figure 7: Kaplan-meier survival curve of endometriosis patient endurance

The curve in Figure 7 depicts a slow decline in 60 months. It is due to the large number of patients who have been censored, either because they have not experience relapse or not doing a regular check-up. Based on the curve it is concluded that the probability of the patient endurance not to relapse is still relatively high with a chance of 0.75 to one. Generally, endometriosis will grow and develop while a woman is menstruating since endometriosis obtains food during the woman menstrual cycle. A slow decrease in the curve indicates that many patients do not relapses. According to tabulation of removal of reproductive organs, almost half of the data showed that the patient had undergo removal of uterus. Furthermore, the woman will no longer have menstruation again or in other words menopause so the possibility of recurrence will be relatively low. The curve declines slowly as a result of over half of the data being classified as menopausal women.

Table 1: Log-rank test results

Covariate	*Chisq*	*Df*	*P-value*	Decision
Menstruation	0.8	1	0.37	Not reject H_0
Grade	2.3	2	0.31	Not reject H_0
Location	10.4	6	0.11	Not reject H_0
Adenomyosis	3.4	1	0.067	Not reject H_0
Die	2.7	1	0.1	Not reject H_0
Surgical history	0.3	1	0.6	Not reject H_0
Surgery type	0.3	1	0.56	Not reject H_0
Removal Organs	11.3	4	0.024	Reject H_0
Treatment	3.1	2	0.21	Not reject H_0

Table 1 shows that all covariates except out (removal of reproductive organs) have *p-value* greater than $\alpha = 0.05$ level. This indicates that there is no difference on survival curves in the same group. Whereas the removal of reproductive organs has a smaller *p-value* than significant level of $\alpha = 0.05$, thus there is at least one difference in endometriosis patient endurance between the types of organ removal.

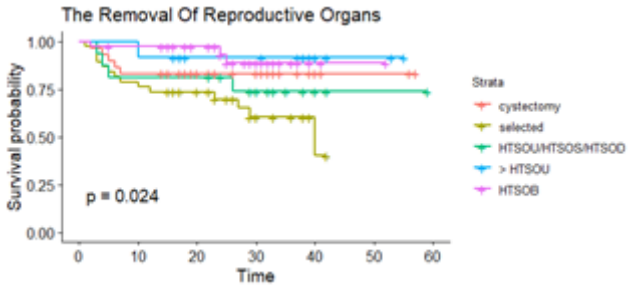

Figure 8: Kaplan-meier survival curve based on organ removal factor

Figure 8 depicts the curve indicating that removal of specific reproductive organs has the lowest chance of survival than others. The highest chance of survival is patients who undergo HTSOU and HTSOB. According to the curve, it is suspected there is a difference between the patient on the removal of selected organs and other types of reproductive organ removal.

3.2.2. Evaluating Hazard Proportional Assumption

Cox regression modeling must be done first to obtain schoenfeld residuals which is useful to determine whether the covariates satisfy hazard proportional assumptions. The number of variables in the model is 12 covariates and after the model is obtained and simultaneous tests are satisfied, then each of predictor is selected using stepwise procedure. As the result, given the significant level of 10%, there are six covariates that significantly affects the recurrence of endometriosis. These covariates are age, surgical history, deep infiltrating endometriosis (die), endometriosis type, type of surgery, and the largest of endometriosis lesions. The next step is to evaluate hazard proportional assumptions. The test is known as goodness of fit using schoenfeld residuals acquired from cox regression modeling [5]. The test results are presented in Table 2.

Table 2: Hazard proportional evaluation results

Covariate	Chisq	Df	*P-value*
Age	0.3834	1	0.536
Rb	0.3479	1	0.555
Die	0.0858	1	0.770
Grade	0.7379	2	0.691
Size	4.7969	1	0.029
Tipe	0.1710	1	0.679
Global	8.6968	7	0.275

Table 2 shows p- value of size is significant below the 5% level, indicating the assumption of proportional hazard is not satisfied. Therefore, the analysis process is continued by performing extended cox model.

3.2.3. Extended Cox Model

In this modelling, the first stage of analysis is to create a new covariate that is an interaction between the

function of time and a non-proportional hazards covariate [4,5]. The time function used is the log(t) of endurance time of endometriosis patients. The new covariate is named as logsize. After that, cox regression modeling is performed by inserting the original covariates from stepwise and logsize covariate. The results of the estimated extended cox parameters and covariate testing can be seen in Table 3.

Table 3: Estimated Extended *Cox* Parameters

Covariate	coef	exp(coef)	se(coef)	Z	P-value
age	-0.0702	0.93221	0.028461	-2.699	0.00695
rb1	0.894817	2.446889	0.439105	1.901	0.05733
die1	-1.14267	0.318968	0.479065	-2.458	0.01398
grade2	0.851181	2.342411	1.038765	0.842	0.39982
grade3	2.071161	7.93403	1.146102	2.043	0.04106
size	0.031494	1.031996	0.00981	3.996	6.45e-05
tipe1	-0.82157	0.43974	0.470265	-1.882	0.05982
logsize	-0.01161	0.988453	0.005592	-2.374	0.01759
Likelihood Ratio = 24.64			df = 8		P = 0.002

Accordingly on Table 3, the equation of extended cox can be written as follows

$$h(t|X) = h_o(t)\exp(-0.0702age + 0.8948rb1 - 1.1427die1 + 0.8512grade2 + 2.0712grade3 + 0.0315size - 0.8216tipe1 - 0.01161logsize)$$

Based on Table 3, the likelihood ratio yields p-value of 0.002 for simultaneous test. This indicates that H_0 is rejected at $\alpha = 0.05$ level. Therefore, it can be concluded that there is at least one significant factor affecting the recurrence of endometriosis patients. Furthermore, a partial test was conducted to determine which covariate statistically influences the patient endurance. Table 4 also showed factors that significantly affect the recurrence. At $\alpha = 0.05$ level, there are age, deep infiltrating endometriosis (die), the largest lesion (size), and endometriosis type (grade), whereas the type of surgery and surgical history (rb) significantly affect at 0.1 level.

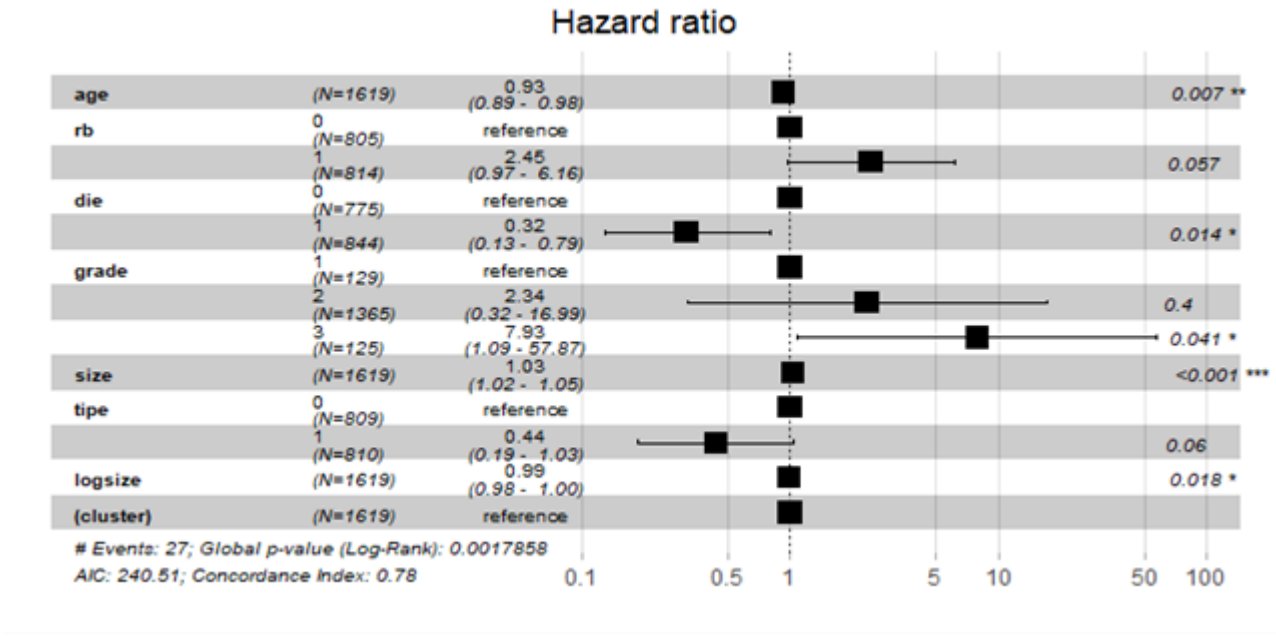

Figure 9: Hazard ratio extended cox

According to Figure 9,

- Patients who had surgical history have 2.45 times greater probability of relapse than those who never had history of surgery assuming other covariates constant.
- Deep infiltrating endometriosis (die) patients have a 0.32 lower probability of resilience compared patients who did not have die. This could happen because

1. The number of patients who had die and censorship was more dominant than those who relapse. According to cross tabulation, percentage of die patients who did not relapse (censored) was 86.1 percent, whereas the relapsed one was only 13.9%. Censorship occurs because many patients do not check up regularly to see possibility of recurrence. This is due to many patients believe that if they have had surgery, they are cured and do not need to check up regularly. In fact, endometriosis is a lifelong disease until menopause.
2. Most patients undergo the removal of reproductive organs such as the removal of ovaries, uterus, tuba, or removal of all organs (HTSOB). Cross tabulation indicates that a lot of patients undergo reproductive organ removal rather than only removing endometriosis lesions.
3. If the lesion die has been excluded, the patient has a probability for a spontaneous pregnancy which prevent the lesion from growing again since pregnancy and breastfeeding suppresses the hormone estrogen. This is supported by [2] which states severe pain complaints were found in 95 percent of die cases and after performing surgery, spontaneous pregnancy success increased by 50 percent. Therefore, there is a correlation between infertility and die

- Someone who had grade2 (grade III or IV) is 2.34 times as likely to relapse as someone who had grade1 (grade I or II) assuming other covariates constant. It can be inferred that high grade has higher risk of recurrence compared to light grade.

- Patients who undergo laparotomy surgery have a lower chance by 0.44 times over patient who had laparoscopic surgery or in other words patients who had laparoscopic surgery have risk 2.27 times greater than patients who had laparotomy surgery if other covariates constant.
- Someone who is older has lower risk of recurrence or in other words the longer someone live, the less risk they had for experiencing endometriosis recurrence if other covariates are assumed constant. It could be because patients over the age of 39 years have more reproductive organ removals than patients who are less than 39 years old because they do not prioritize having children. Therefore, there are only fewer locations for the growth of new lesion or even none since the uterus has been removed so no menstruation which is the source of the contents of endometriosis lesions (already categorized as menopause).
- Hazard ratio in covariate size depends in time. The bigger size of the lesion, the higher risk for relapse, but the longer individual survives of recurrence, the lower risk for recurrence assuming other covariates constant.

The quality performance of model is rather high which is shown by concordance index (c-index) of 0.78 and model has small Akaike information criterion (AIC) despite a lot of censored data. Although AIC and c-index of extended cox model only has slightly differences from cox regression, the more appropriate model used is extended cox rather than cox regression because there is covariate whose value depends on time in order to achieve the correct conclusion. Thus, it can be concluded that the extended cox model is better at suspecting the recurrence of endometriosis patients. Concordance index of 0.78 indicates that even though the fact that the amount of censored data is a lot more than the number of relapses, extended cox model outperforms the random guessing.

4. Conclusion

The survival curve of endometriosis patients shows the patient still has high probability of survival in 5 years. Log-rank tests on the kaplan-meier survival curve for reproductive organ removal show there is difference in survival curves between categories. The removal of specific organs has the lowest survival probability compared to other categories. HTSOB and HTSOU have the highest probability rather than other categories. Extended cox analysis on endometriosis patients revealed that age, surgical history, die, largest lesion size, grade, and type of surgery significantly affecting the endurance of endometriosis patients. Someone who had surgical history have 2.45 times greater probability of relapse than those who never had history of surgery. Die patients have 0.32 lower chance of resilience compared patients who did not have die. Someone who has grade III or IV is 2.34 times as likely to relapse as someone who has grade I or II. Patients who had laparoscopic surgery have risk 2.27 times greater than patients who had laparotomy surgery. Someone who is older has lower risk of recurrence if other covariates are assumed constant. Hazard ratio on covariate size depends on time. The larger size of the lesion, the higher risk for relapse, but the longer individual survives of recurrence, the lower risk for recurrence assuming other covariates constant.

5. Limitations and Recommendations

Although model is adequate for estimation, there is no method for handling imbalanced data. As we can see, the number of censored data is more than 75 percent. Thus, It would be better to include method for handling the imbalances. In this study, there was no comparison of strategies for handling ties in the data while authors only use breslow for handling it. Therefore, modeling extended cox using other approaches such as efron and exact could be done for further research. According to the research, food intake has an effect on the risk of endometriosis [12,13]. Author in [14] also perfomed a preclinical trial phase research on mice to investigate whether exercise affected the risk of endometriosis. Considering to include non-medical covariates such as exercise and food intakes would be better. Therefore, endometriosis sufferer could implement a healthy lifestyle by consuming appropriate and nutritious food. Endometriosis sufferers are expected to do regular check-up in order to detect any possible recurrence.

Acknowledgement

We would like to convey our gratitude to IPB University as a place to carry out this study and Fatmawati General Hospital for using the data.

References

[1]. A. Elnouri. (2016, May). “Endometriosis and Fertility.” European Journal & Gynecology and Reproductive Biology. [On-line]. 206, pp. 251. Available: https://doi.org/10.1016/j.ejogrb.2016.07.005. [Jan. 20, 2020]

[2]. H. Hendarto. Endometriosis dari Aspek Teori sampai Penanganan Klinis. Surabaya, Indonesia: Airlangga University Press, 2015.

[3]. T.W. Belnap, A.P. Brown, M.K. Dodson, J. Frandsen, D.K. Gaffney, M.M. Lum, et al. (2015, Jun.). “Survival Analysis of Cancer Patients with FIGO Stage IIIA Endometrial Cancer.” American Journal of Clinical Oncology. [On-line]. 38 (3), pp. 283-288. Available: https://doi.org/10.1097/coc.0b013e31829c12be [Jan. 17, 2020].

[4]. M. Klein, D.G. Kleinbaum. Survival Analysis: A self-Learning Text. New York, US: Springer, 2012.

[5]. Nurfain, S.W. Purnami. (2017, Mar.). “Analisis Regresi Cox Extended pada Pasien Kusta di Kecamatan Brondong Kabupaten Lamongan.” Jurnal Sains dan Seni ITS. [On-line]. 6(1), pp. 94-100. Available: http://dx.doi.org/10.12962/j23373520.v6i1.22440 [Nov. 22, 2020].

[6]. A. Mathew, J. Krishna, P.S. George. (2017, Jun) “Cancer Survival Estimates Due to Non-Uniform Loss to Follow-Up and Non-proportional Hazards. Asian Pacific Journal of Cancer Prevention. [On-line]. 18(6), pp. 1493-1497. Available: https://dx.doi.org/10.22034/APJCP.2017.18.6.1493 [Jun. 25, 2021]

[7]. N. Lasmini. "Model Regresi Cox dengan Hazard Tak Proporsional dan Aplikasinya pada Waktu Ketahanan Pengguna Narkoba." B.S. Thesis, IPB University, Indonesia, 2013.

[8]. E. Suparman, E. Suparman. (2012, July). "Penatalaksanaan Endometriosis." Jurnal Biomedik. [On-line]. 4 (2), pp. 69-78. Available: https://doi.org/10.35790/jbm.4.2.2012.754 [Jan. 20, 2020].

[9]. L. Kiesel, M. Langhardt, F. Petraglia, T. Rabe, K.W Schweppe, J. Woziwodzki. (2013). "Endometriosis-Pathogenesis, Diagnosis and Therapeutic Options for Clinical and Ambulatory Care." Journal of Reproductive Medicine and Endocrinology. [On-line]. 10(1), pp. 102-119. Available: https://www.kup.at/kup/pdf/11285.pdf [Feb. 9, 2020].

[10]. M.R. Akhoond, M. Ashrafi, S.J. Sadatmahalleh, M. Talebi. (2016, April). "Evaluation of Risk Factor Associated with Endometriosis in Infertile Women." International Journal of Fertility and sterility. [On-line]. 10(1), pp. 11-21. Available: https://dx.doi.org/10.22074%2Fijfs.2016.4763 [Jan. 17, 2020].

[11]. J. Harlan. Analisis Survival. Depok, Indonesia: Gunadarma, 2017.

[12]. A. Kazemnejad, A. Mottagi, Sj. Sadatmahalleh, S. Youseflue. (2019, Sep). "The Association of Food Intake with Endometriosis Risk in Iranian Woman: A case-control study." International Journal of Reproductive Biomedicine. [On-line]. 17(9), pp 661-670. Available: https://doi.org/10.18502/ijrm.v17i9.5102 [Jun, 25. 2021].

[13]. N. Eliyati, S.I. Maiyanti, O. Dwipurwani, S.W. Hamidah. (2021, March). "Model Regresi Cox untuk Menganalisis Pengaruh Faktor Asupan Makanan terhadap Risiko Kekambuhan Endometriosis. Barekeng: Jurnal Imu Matematika dan Terapan. [On-line]. 15(1), pp 103-114. Available: https://doi.org/10.30598/barekengvol15iss1pp103-114 [Jun. 3, 2021].

[14]. A. Ribeiro-Silva, C.M. Bonocher, J. Moela, J.C. Rosa-e-Silva, M.L. Montenegro, M.O. Brunaldi, R.A. Ferriani, R.L. Portella. (2019, Jun). "Efect of Physical Exercise on Endometriosis Experimentallly Induce in Rats." Reproductive Sciences. [On-line]. 26(6), pp 785-793. Available: https://doi.org/10.1177/1933719118799205 [Jun. 25, 2021].