

Research Article

Postoperative Pain Survival and Correlating Factors in Endometriosis Patients

Kesintasan Keluhan Nyeri Pascapembedahan pada Pasien Endometriosis serta Faktor-Faktor yang Mempengaruhi

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Abstract

Objective : To determine the survival of pain complaints at 3, 6, 9 and 12 months and the correlation between age at diagnosis, age of menarche, parity, stage of disease and post-operative medication in endometriosis patient at RSUPN Dr. Cipto Mangunkusumo.

Methods : This was a prospective cohort study with survival analysis method of 139 women of productive age with endometriosis who came to gynecology outpatient clinic in Dr. CiptoMangunkusumo Hospital from January 2015 to January 2017. The patients were observed at 3 months, 6 months, 9 months and 12 months after the surgery.

Results : Survival of pain complaints at 3, 6, 9 and 12 months after endometriosis operation was 99.2%, 96.6%, 93% and 88.4% respectively. There was no significant correlation between post-operative pain survival and age of diagnosis ($p=0.138$), age of menarche ($p=0.492$), parity ($p=0.110$) and stage of disease ($p=0.908$). There was a significant correlation between post-operative medical therapy and pain complaints survival. Subjects who were given medication had a risk of 0.26 times (CI 95% 0.081-0.857) pain recurrence compared to those who were not.

Conclusions : Pain complaints survival were significantly associated with post-operative medical therapy, but not associated with age, age of menarche, parity and stage of disease.

Keywords : endometriosis, postoperative medical therapy, postoperative pain, survival.

Abstrak

Tujuan : Mengetahui kesintasan keluhan nyeri pada 3, 6, 9 dan 12 bulan dan hubungan antara usia saat diagnosis, usia menarke, paritas, stadium penyakit dan terapi medisinalis pascapembedahan pada pasien endometriosis di RSUPN Dr. CiptoMangunkusumo.

Metode : Penelitian kohort prospektif pada 139 perempuan usia produktif dengan metode analisis kesintasan pada pasien endometriosis yang datang ke poliklinik ginekologi RSUPN Cipto Mangunkusumo pada bulan Januari 2015 hingga Januari 2017. Pasien kemudian diobservasi pada bulan ke 3, 6, 9 dan 12 setelah operasi.

Hasil : Kesintasan keluhan nyeri pada bulan ke 3, 6, 9 dan 12 berturut-turut adalah 99,2%, 96,6%, 93% dan 88,4%. Tidak ada hubungan yang bermakna antara kesintasan nyeri pascapembedahan dengan usia saat diagnosis ($p=0,138$), usia saat menarke ($p=0,492$), paritas ($p=0,110$) dan stadium penyakit ($p=0,908$). Terdapat hubungan yang bermakna antara terapi medisinalis pascapembedahan dan kesintasan keluhan nyeri. Subyek yang mendapatkan terapi medisinalis pascapembedahan memiliki risiko 0,26 kali mengalami kekambuhan nyeri dibandingkan dengan yang tidak.

Kesimpulan : Kesintasan keluhan nyeri memiliki hubungan yang bermakna dengan terapi medisinalis pascapembedahan namun tidak memiliki hubungan dengan usia saat diagnosis, usia menarke, paritas dan stadium penyakit.

Kata kunci : endometriosis, kesintasan, nyeri pascapembedahan, terapi medisinalis pascapembedahan.

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INTRODUCTION

Endometriosis is defined as abnormal implantation of endometrial tissue outside the uterine cavity. This ectopic tissue may lead to chronic inflammation process that depends on estrogen hormone.¹⁻⁷ Endometriosis is found in up to 176 million people all over the world.

It affects around 5-10% women of reproductive age.^{5,7,8} This disease is one of the leading causes of pain complaints; which includes dysmenorrhea, dyspareunia, chronic pelvic pain, dysuria and dyschezia.⁴ In Dr. Cipto Mangunkusumo Hospital, most endometriosis patients came with the complaint of pelvic pain (82.5%), followed by dysmenorrhea (81%), low back pain (32.5%),

dyspareunia (20,9%) and dyschezia (4.6%). These pain complaints lead to low quality of life; therefore, treatment is required.^{7,9,10}

There are two modalities in treating endometriosis patients which are conservative and surgical therapy. Until today, the treatment of choice to treat endometriosis is laparoscopy. This treatment has several purposes such as to lessen the pain, recurrence rate and to maintain fertility.^{11,12}

Endometriosis has a high recurrence rate of 21.5%, 46.7% and 55.4% at the second, fifth and seventh year after surgery.¹³ A study 23 studies, the recurrence rate of endometriosis after surgery is as high as 40-50% at the fifth year.^{14,15} This study also stated that the risk factors of this high recurrence include age when diagnosed, stage of disease and history of previous treatment.

These data imply that pain recurrence in endometriosis patients is an essential aspect. Therefore, it is important to know what factors could affect pain survival. Considering that, we are interested to know the recurrence rate of pain in endometriosis patients through survival analysis and its correlating factors in Dr. Cipto Mangunkusumo Hospital.

METHODS

This research was a prospective cohort study. Subjects were women 18-49 years old who came to Gynecology Outpatient Clinic from January 2015 to January 2017. A total of 154 patients obtained consecutively who were diagnosed with endometriosis underwent surgery in Dr. Cipto Mangunkusumo Hospital at that time. Only 139 out of 154 patients met the inclusion criteria of this research. Inclusion criteria were endometriosis patients who had a psychosocial activity limitation, use of analgesic medication, and visual analogue scale (VAS) of 4 or more. The VAS was 4 or more on dysmenorrhea, dyspareunia, pelvic pain, dysuria or dyschezia symptoms with a minimum of once at the measurement period. Exclusion criteria were patients who had a history of abdominal surgery (except appendectomy), who had other diseases than endometriosis which could lead to pelvic pain, diagnosed with neurotic disease and/or psychiatric diseases and had a history of tubectomy.

Data were analyzed using SPSS® software for IOS version 22.0. The survival rate of pain complaints was analyzed using Kaplan-Meier analysis. All variables meet the proportional hazard assumption, therefore the analysis was done using cox regression. Patients were followed up to 12 months.

RESULT

Table 1. Characteristics of Postoperative Endometriosis Patients in Cipto Mangunkusumo from January 2015 to January 2017

Characteristics	Description (n=139)	
Age (years)		40 (17 – 49)
Age category	<30	18 (12.9%)
	≥30	121 (87.1%)
Age of menarche	<11	4 (2.9%)
	≥11	135 (97.1%)
Parity	0	66 (47.5%)
	1	23 (16.5%)
	2	29 (20.9%)
	3	19 (13.7%)
	4	2 (1.4%)
Parity category	0	66 (47.5%)
	1-2	53 (38.1%)
	≥3	20 (14.4%)
Stage of disease	Minimal	1 (0.7%)
	Mild	24 (17.8%)
	Moderate	47 (37.8%)
	Severe	67 (48.2%)
Stage of disease category	Minimal and mild	25 (18%)
	Moderate and severe	114 (82%)
Medical therapy	No	91 (65.5%)
	Yes	48 (34.5%)
Post-operative medical therapy	No medicinal therapy	91 (65.5%)
	Progestin	28 (20.1%)
	GnRH agonist	11 (7.9%)
	Progestin + GnRH agonist	2 (1.4%)
	COC	6 (4.3%)
	COC + progestin	1 (0.7%)
	Did not	
Pain after surgery	recur (<i>sensor</i>)	126 (90.6%)
	Recur (<i>event</i>)	13 (9.4%)

In this study, the age of subject ranges from 17-49 years old with the median of 40 years old. Most subjects (87.1%) are 30 years and above. One hundred and thirty-five subjects (97.1%) had menarche at the age of 11 or more. Most subjects (66 patients) were nullipara, 23 subjects (16.5%) were primipara, 29 subjects (20.9%) had 2 parity, 19 subjects (13.7%) 3 parity and only 2 subjects had 4 parity.

Endometriosis degree of patients in this study was assessed into four stage. One subject (0.7%) had minimal disease, 24 subjects (17.8%) had mild disease, 47 subjects (37.8%) had moderate disease and 67 patients (48.2%) had severe disease. Forty-eight subjects (34.5%) were given medical therapy after the surgery. Most of them (20.1%) were given progestin medication. After a 3 months regular follow-up up to a year, 126 patients (90.6%) stated the pain did not recur.

Survival Rate

The pain survival rate were acknowledged every three months. On the third months, the pain survival rate were 99.2%. However this percentage were decreased to 96.6% after 6-month follow-up and 93% after 9 months follow up. After 12 months of follow-up, the pain survival rate was 88.4%. From the Kaplan-Meier curve, the survival rate decreased over time. However, this research did not reach the median time because the observation is limited to 12 months.

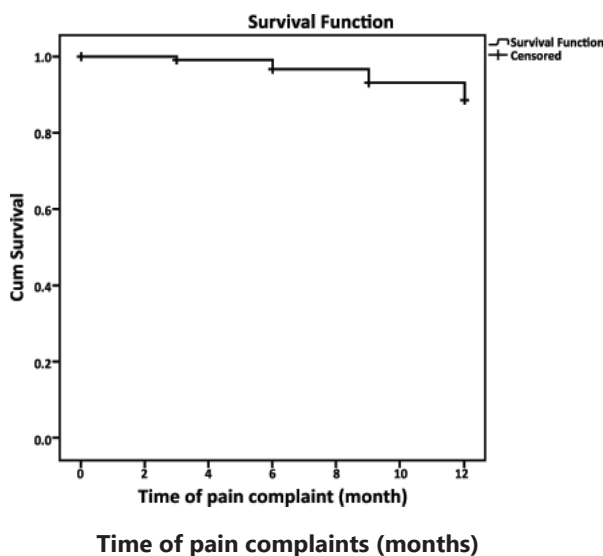


Figure 1. Kaplan Meier Curve of Overall Pain Survival in Endometriosis Patients

Subjects who were under 30 years old and 30 years above had the pain survival rate at 12 months follow-up of 63% and 87%, respectively. However, the log-rank test analysis showed there was no significant association between pain survival and the age category ($p=0.152$). In this study, subjects who had menarche on the age of 11 years old and above had the pain survival rate of 86% after 12 months follow-up. Below 11 years old, the pain survival was 50% after 12 months follow up, while 11 years old has pain

survival for 86% after 12 months follow-up, This study also analyzed the association between age of menarche and pain survival and it is found that there was no significant association between both variables ($p=0.286$). Subjects with 0, 1-2, and 3 or more parity had the pain survival rate after 12 months follow-up of 83%, 93% and 68%, respectively. However, both groups were statistically insignificant, with the p value= 0.061. At 3 months follow up, subjects with 0, 1-2, and 3 or more parity had an almost similar percentage of survival 98%, 100%, and 100% respectively, however, significant decrease after six months follow up were subjects with three or more parity (87%).

In this study, subjects with a minimal-mild stage of endometriosis experienced pain survival of 90% and subjects with moderate-severe stage's pain survival were 83%. Nevertheless, this result is statistically insignificant ($p=0.908$).

The pain survival rate of patients who received postoperative medical therapy was started from 100% on 3 months follow up to 73% after 12 months follow-up, and those who did not receive had the pain survival rate was started from 99% on the first 3-month follow-up to 91%. From the analysis, the post-operative medical therapy category and pain survival had no significant association.

Variables were also analyzed using bivariate analysis to find the hazard ratio. The hazard ratio (HR) of age when diagnosed, age of menarche, parity, stage of the disease and post-operative medical therapy were 2.46, 2.85, 0.44 and 0.03, 0.92 and 0.26, respectively. Variables who had the p -value < 0.25, which were age, age of menarche, parity and post-operative medical therapy, were then included in the multivariate analysis. From the multivariate analysis, it was found that post-operative medical therapy had the p -value of 0.027 and HR of 0.26 (CI 95% 0.081-0.857).

Table 2. Multivariate Analysis Result

Variables	HR			
	Model 1	Model 2	Model 3	Model 4 (last)
Age category	3.31	3.83	2.39	3.31
Age of menarche category	2.22	-	-	2.22
Parity category	1.92	1.89	-	1.92
Post-operative medical therapy	0.25	0.24	0.27	0.25

DISCUSSION

From 139 subjects, 13 subjects had censor (loss to follow up). Overall, the pain survival rate reduces over time from 99.2% at three months to 88.4% at 12 months. The median time of pain survival was 24 months. Therefore, this study needed a longer follow-up time.¹⁶

Pain Survival and Age when Diagnosed

Pain survival in postoperative endometriosis patients with the age < 30 years old when diagnosed at 3, 6, 9 and 12 months were 100%, 100%, 92% and 63%. While the group of age 30 and above had the pain survival of 98%, 96%, 92% and 87%. This showed that pain recurrence was found more in patients age 30 and above. Though statistically insignificant, this variable was included in the multivariate analysis because it was clinically significant. However, at the third model, this variable did not affect the pain complaints.

This result was similar that age and pain survival is statistically insignificant but patients with younger age (29,9±5,4 years old vs 32.6±6.1 years old) had clinically significant pain survival and recurrence of endometriosis with the HR = 0.935 (CI 0.895-0.977).^{16,17} Endometriosis patients who were diagnosed at a younger age were linked with lesser estrogen and therefore may reduce the recurrence rate. The low survival rate of 63% at subjects <30 years old may be due to limited number of samples in this category.

Pain Survival and Age of Menarche

Patients who had menarche at the age of <11 years old had pain survival at 3, 6, 9 and 12 months of 100%, 100%, 100% and 50%. While the other group had the pain survival of 99%, 96%, 93% and 86%. However, this variable is clinically insignificant after the Log rank test. This variable

was included in the multivariate analysis because its p value=0.315 but at the end of the analysis, this variable showed no effect in pain complaints. This result showed that patients who had menarche at a younger age had a higher risk of pain complaints recurrence. This was supported by other literature that stated patients who had menarche at an earlier age is at higher risk of pain recurrence in endometriosis.¹⁶

Pain Survival and Parity

Subjects with 0-1 parity had the highest pain survival rate at 3, 6, 9 and 12 months among the group, which were 100%, 100%, 98% and 93%. From the log-rank test, parity was not significantly associated with pain survival. However, this variable was found to be clinically significant and was included in the multivariate analysis. This result was different from several studies that found pregnancy before endometriosis surgery as a protective factor of pain survival with the OR=0.759 (p<0.05).^{12,18-20} Infertility was found to have a linked with more prolonged estrogen exposure and therefore could trigger the occurrence of endometriosis. In contrast, pregnancy could cause regression of endometriosis lesion.^{21,22}

Pain Survival and Stage of Disease

In this study, the stage of disease was categorized into minimal-mild and moderate-severe. Patients with minimal-mild disease had the pain survival after 3, 6, 9 and 12 months of 95%, 95%, 90% and 90%. While patients with the moderate-severe disease had the pain survival of 100%, 97%, 94% and 83%. From the log-rank test, this variable was found to be statistically unassociated with the pain survival rate. Bivariate analysis showed that this variable is clinically insignificant, so this variable was not included in the multivariate analysis.

From other literature, high recurrence rate was found in subjects with moderate to severe stage of endometriosis. Besides the stage, the surgery technique was also associated with the recurrence rate. Conservative operations could lead to progressive growing of endometriosis and therefore subjects can experience chronic pelvic pain.^{13,16,23-27}

Pain Survival and Medical Therapy

Forty-eight subjects received medical therapy after the surgical procedure in this study. From the 48 subjects, 20.1% received progestin, 7.9% received Gn-RH agonist, 1.4% received progestin and Gn-RH agonist, 4.3% received combined oral contraceptives (COC); 0.7% received COC and progestin. The pain survival of subjects receiving medical therapy was 100%, 93%, 86% and 73% at 3, 6, 9 and 12 months follow-up. From the bivariate analysis, this variable was found to have a significant association with pain survival (HR=0.26, CI 95% 0.08-0.86; p=0.027).

From a systematic review, though still inconsistent, it was found that hormonal therapy suppression after surgery compared to surgery alone reduced pain complaints after 12 months.²⁸ Some studies showed that patients who were treated with laparoscopic excision and cyclic oral contraceptives (such as desogestrel, gestodene and dianogest) had significant reduction of pain than those treated with laparoscopic excision alone. Progestin prevented implantation and endometriosis growth by inhibiting the expression of metalloproteinase matrix and angiogenesis thus reducing inflammation.²⁹⁻³¹

Besides progestin, COC could also be used. COC worked by reducing the frequency of menstrual period, inducing endometriosis to become atrophy, reducing prostaglandin production that plays a role in pain and reducing cell proliferation.^{29,32} Gn-RH agonist is another treatment method of endometriosis; however, it should not be used for longer than 6 months due to its effect of estrogen deficit.³³

CONCLUSIONS

In conclusion, the 3, 6, 9 and 12 months follow-up of post-operative endometriosis patients showed a pain survival of 99.2%, 96.6%, 93% and

88.4%, respectively. Age, age of menarche, parity and stage of the disease have no significant association with the pain survival of post-operative endometriosis patients. However, postoperative medical therapy was significantly associated with reduction of pain. Longer study and *randomized controlled trial* (RCT) study is needed to reduce selection bias and indication bias.

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