

**Original Research Paper**

## Analysis of Adenomyosis Incidence based on Age and Neutrophil-lymphocyte Ratio Factors

**Yuni Prastyo Kurniati<sup>1,a,\*</sup>, Yusuf Alam Romadhon<sup>2</sup>, Karmila Indar Parawansa<sup>3\*</sup>**

<sup>1</sup> Department of Pathology Anatomy, Medical Faculty, Universitas Muhammadiyah Surakarta, Indonesia

<sup>2</sup> Department of Public Health, Medical Faculty, Universitas Muhammadiyah Surakarta, Indonesia

<sup>3</sup> Medical Faculty, Universitas Muhammadiyah Surakarta, Indonesia

<sup>a</sup>ypk134@ums.ac.id

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### **Abstract**

Adenomyosis is a type of disorder which endometrial glands and stroma grow in the myometrium. This disease causes a very high burden of health care, which 82.0% of patients undergoing hysterectomy and 37.6% on chronic pain medication. The exact number of global incidence of adenomyosis is less known. Studies suggest risk factors include increasing age, parity, and a history of uterine procedures. However, the timing of first appearance and age-related evolution of adenomyotic lesions remains controversial. There is research on the neutrophil-lymphocyte ratio (NLR) which is increased in this disease. However, there is still very limited research on this matter. The study aims to analyze the incidence of adenomyosis based on age and NLR. Analytical observational research method with a cross sectional approach. A total of 135 samples using the consecutive sampling method. Data from Anatomical Pathology medical records from 2018 to 2023. Analysis using univariate, chi square test, and multivariate logistic regression. The results showed that the incidence of adenomyosis was highest in reproductive age (86.8%) and the NLR value at risk was 64.7%. The chi square test and logistic regression obtained the same findings, namely that there was a significant relationship between age and NLR on the incidence of adenomyosis ( $p<0.001$ ). The prevalence ratio of age and NLR factors is 16.17 and 19.01. This means that NLR at risk has a 19.01 times on the incidence of adenomyosis, rather than age. Nagelkerke R-square shows that age and NLR influence the incidence of adenomyosis by 54.9%. In conclusion, there is a significant relationship between the incidence of adenomyosis based on age and NLR. The implications of this study show that NLR can be a simple predictor for the incidence of adenomyosis. This can be done especially in women of reproductive age with a history of dysmenorrhea with complaints of chronic pain.

**Keywords:** Adenomyosis; age; NLR

### **1. Introduction**

Adenomyosis is a condition in which endometrial glands and stroma grow within the uterine muscle layer or myometrium tissue (Protopapas et al., 2020). This can have a serious impact on women's quality of life (Upson & Missmer, 2020). Women who experience this disease can experience abnormal uterine bleeding, dysmenorrhea, dyspareunia, menorrhagia, pelvic pain and infertility (Vannuccini & Petraglia, 2019). Heavy menstrual bleeding is the most common symptom of this disorder (Bruun et al., 2018). Thus, it can be said that the burden of adenomyosis on individuals and the health service system is quite high (Yu et al., 2020). This disease has a very high healthcare burden with 82.0% of patients having to undergo hysterectomy (removal of the uterus) and 37.6% of chronic pain medications (Yu et al., 2020).

The statistical figure of the incidence of adenomyosis globally is not known with certainty, because the diagnosis of this disorder is usually obtained in women who undergo hysterectomy, magnetic resonance imaging (MRI) examination and transvaginal ultrasound or called TVUS (Putra & Anggraini,



2022). In Italy, 89% of patients are diagnosed with adenomyosis from all uterine tissue surgery performed (Morassutto et al., 2016). Based on research in the United States, it is explained that the incidence of adenomyosis is the highest at 69.1 per 10,000 women/year. Black women have a higher prevalence of 44.6 per 10,000/year compared to white women at 27.9 per 10,000/year (Yu et al., 2020). Meanwhile, in Indonesia, the exact number of adenomyosis incidences is not yet known.

According to research, risk factors for the occurrence of adenomyosis include increased age, parity, and history of uterine procedures (Bruun et al., 2018). However, the timing of the first appearance and evolution of age-related adenomyotic lesions is still controversial (Protopapas et al., 2020). There is a difference of opinion about the age factor and the incidence of adenomyosis. The average age of patients diagnosed with adenomyosis in the Taran et al study was more than 50 years old (Taran et al., 2013). In the United States, the incidence is highest in women aged 41-45 years (Yu et al., 2020). Most patients are diagnosed aged 40 to 50 years (Bruun et al., 2018).

In terms of age, a study in Italy found that the median age is 24 years old with an age range of 23 – 27 years. In the study, the most common age of women with this disorder was 26 years old (Pinzauti et al., 2015). Another study conducted in Italy provided another finding that the highest adenomyosis occurred in the age group of 46-50 years (Morassutto et al., 2016). The available information on the incidence of adenomyosis in adolescents is still very limited (Benagiano et al., 2015). In Indonesia, research conducted by Fitriana at Hasan Sadikin Hospital, Bandung, found that the average age of adenomyosis patients is 39 years old (Fitriana et al., 2018).

Some recent studies have shown the importance of chronic inflammatory processes and biomarkers in the development of this disorder (Bodur et al., 2015). Adenomyosis is a chronic inflammation that causes the size of the uterus to continue to increase (Ilgen et al., 2023). The disease causes hyperplasia and myometrium hypertrophy, resulting in an enlarged uterus (Güzel et al., 2015). Study of Bodur et al. (2015) stated that the neutrophil-lymphocyte ratio (NLR) is acceptable as an effective and simple inflammatory parameter. The calculation of complete blood count components is very important and easy to do and saves costs (Bodur et al., 2015). Although there are other immuno-inflammatory indicators or indexes, namely using the platelet-lymphocyte ratio (PLR) (Dong et al., 2024), however, in other literature, it is stated that these two indicators, PLR and NLR, also have a correlation with the size of uterine leiomyoma tumors (Duan et al., 2022). The use of NLR is also used in assessing the severity of endometriosis cases (Tabatabaei et al., 2023). On the other hand, there is research on NLR which has increased quite a lot in this disease. This occurs due to inflammation caused by the tissue injury and repair (TIAR) mechanism. This mechanism causes a high number of neutrophils and a low number of lymphocytes (Madendag et al., 2018). The mechanism of TIAR in adenomyosis occurs through the local microtrauma effect of uterine peristaltic activity on the border of the myometrium and endometrial area (Bodur et al., 2015).

However, research on the relationship of NLR has only been conducted by Madendag et al (2018) which stated that an increase in the number of neutrophils and a decrease in the number of lymphocytes in adenomyosis have been detected (Madendag et al., 2018). The simple bibliometric analysis carried out by the authors, using the Scopus database with the keywords "adenomyosis" AND "NLR" without limitations, only obtained 10 documents, which only began to exist in the database in 2010. Searches using Pubmed only get 1 (one) document, searches with google scholar devices from 2004 – 2024 get 355 documents, with only 1 (one) research conducted in Indonesia. From this description, studies on age risk factors and NLR on the incidence of adenomyosis in Indonesia, are still very limited. Therefore, the purpose of this study is to analyze the incidence of adenomyosis based on age factors and NLR.

## 2. Research Method

This study operates a type of analytical observational research with a cross sectional approach. Sampling was carried out at PKU Muhammadiyah Hospital Surakarta in November – December 2023.

The type of data used is secondary data from the medical records of Anatomical Pathology of female patients. The sample in this study is a histopathological preparation with a final diagnosis of adenomyosis from 2018 to 2023. A total of 135 samples were obtained using the non-probability technique of consecutive sampling. The variables obtained in this study were age, NLR, parity status, place of residence, and incidence of adenomyosis.

Age variables were categorized into reproductive age (11-49 years) and menopausal age ( $\geq 50$  years). The NLR value was divided into risk ( $>3.53$ ) and non-risk ( $\leq 3.53$ ) groups. Parity status is categorized as risky (multipara) and non-risky parity (nullipara, primipara). The residential category is divided into urban/urban and rural/rural.

Data from the medical records that have been obtained are then selected according to the restriction criteria that have been set in the study. Samples with a final diagnosis of anatomical pathology of adenomyosis, but accompanied by other malignancies, were not included as respondents (exclusion criteria). Data analysis in this study uses bivariate and multivariate. Chi square test on bivariate analysis. The data obtained then, if significant, will be followed by multivariate analysis using logistic regression tests.

The researcher has obtained a research permit from the Faculty of Medicine, University of Muhammadiyah Surakarta with the issuance of letter No.0214/B.6-III/FK-BS/X/2023, as well as the approval of the health code of ethics through the Health Research Ethics Committee (KEPK) of PKU Muhammadiyah Surakarta Hospital No.04/KEPK/RS. PKU/XI/2023.

### 3. Results and Discussion

#### 3.1. Results

A total of 135 subjects were obtained in this study. The characteristics of the subjects were then analyzed based on the age factor, NLR score, parity status and residence factor of the respondents. The following Table 1 below will describe the characteristics of the respondents.

**Table 1. Characteristics of Univariate Respondents**

Variable	Group			
	Adenomiosis		Other benign tumors (non Adenomiosis)	
	(n)	(%)	(n)	(%)
<b>Age</b>				
Reproductive	59	86,8	27	40,3
Menopause	9	13,2	40	59,7
<b>NLR (<math>&gt;3,53</math>)</b>				
Risk	44	64,7	9	13,4
No Risk	24	35,3	58	86,6
<b>Paritas</b>				
Risk (multipara)	48	70,6	45	67,2
No Risk	20	29,4	22	32,8
<b>Residence</b>				
Urban	49	72,1	38	56,7
Rural	19	27,9	29	43,3

The results shown in Table 1 explain that the group that experienced adenomyosis mostly occurred at reproductive age, namely 59 respondents (86.8%). Then, subjects who experienced adenomyosis were more likely to have a risky NLR value, with a total of 44 respondents (64.7%). Meanwhile, judging from the parity status and residence of the two diagnosis groups, they gave the same findings. The

adenomyosis group and other benign tumors that are not adenomyosis, are both more commonly found in risky parity status and most of them live in urban/urban areas.

**Table 2.** Analysis of the relationship between age and incidence of adenomyosis

Age	Group				CI 95%			p	
	Adenomyosis		Other benign Tumors (Non Adenomyosis)		RP				
	n	%	n	%		Lower	Upper		
Reproductive	59	86,8	27	40,3	9,71	4,13	22,82	<0,001	
Menopause	9	13,2	40	59,7					
Total	68	100	67	100					

RP = prevalence of risk, CI=confidence interval

Table 2 explains that the incidence of adenomyosis occurred in 86.8% of respondents of reproductive age. In contrast, the incidence of benign tumors with non-adenomyosis is more common at menopausal age (59.7%). There is a relationship between age and the incidence of adenomyosis in this study. The results of bivariate analysis using the Chi-square t test showed a significant relationship with a p-value of 0.001 and a prevalence ratio (RP) of 9.71. This indicates that women of reproductive age are 9.71 times more likely to develop adenomyosis, compared to menopausal women.

**Table 3.** Analysis of the relationship between NLR values and the incidence of adenomyosis

NLR	Group				CI 95%			P	
	Adenomyosis		Other Benign Tumors (non Adenomyosis)		RP				
	n	%	n	%		Lower	Upper		
Risk (>3,53)	44	64,7	9	13,4	11,81	4,99	27,93	<0,001	
No Risk ( $\leq 3,53$ )	24	35,3	58	86,6					
Total	68	100	67	100					

Table 3 explains that as many as 64.7% of respondents with adenomyosis have a risky NLR value. Meanwhile, a total of 86.6% of respondents with other benign tumors that are not adenomyosis have NLR values that are not at risk. There is a relationship between NLR and the incidence of adenomyosis in this study. The results of bivariate analysis using the Chi-square test showed a significant relationship with a p-value of 0.001 and a Prevalence Ratio (RP) of 11.81. This shows that women who have a risky NLR value have an 11.81 times higher chance of developing adenomyosis than women who do not have a risky NLR.

**Table 4.** Multivariate analysis of age variables and RNL in the incidence of adenomyosis

Variable	Coefficient	Value p	Exp B	CI 95%		Negelkerke R-square
				Lower	Upper	
Usia	2,75	0,000	16,176	5,017	52,154	0,549
NLR	2,94	0,000	19,016	6,020	60,073	
Constant	-8,56	0,000	0,000			

The multivariate analysis in table 4 shows that the age-independent variable and the NLR value both have a relationship with the incidence of adenomyosis with a p value of <0.001. The strength of the relationship can be seen from the largest to the smallest RP value, the largest RP in the NLR variable with the value of RP=19.01. While the smallest RP is in the age variable with a value of RP=16.17. Based on multivariate analysis, the Nagelkerke R-square result was obtained at 0.549. This value shows that age and NLR value can cause an incidence of adenomyosis as much as 54.9%. While a total of 45.1% can be caused by other variables.

### **3.2. Discussion**

Adenomyosis is a gynecological disease, defined as the presence of endometrial tissue that is in a physiologically inappropriate place (Morassutto et al., 2016). Adenomyosis is defined as endometrial cells in the myometrium accompanied by muscular hyperplasia, hypertrophy and fibrosis (Bruun et al., 2018). Bleeding is one of the consequences of the endometrial tissue's response to hormonal stimuli, which causes inflammation and the formation of scarring. This causes complications such as dysmenorrhea, infertility, chronic pelvic pain, and dyspareunia (Morassutto et al., 2016). The etiology of adenomyosis is less known with certainty. This is due to the inability to accurately diagnose using non-invasive diagnostic methods. The pathogenesis of adenomyosis has several theories. The most common theory is that there is an invagination of the basal lining of the endometrium into the myometrium. This condition results in disturbances in the border zone so that it allows the abnormal proliferation of endometrial cells within the myometrium accompanied by hypertrophy and hyperplasia in the smooth muscle cells of the myometrium (Putra & Anggraini, 2022).

#### **3.2.1. Relationship between Age factors and the incidence of adenomyosis**

Adenomyosis has a close relationship with age factors (Yu et al., 2020). The age with a high potential for the incidence of adenomyosis is women of reproductive age. This is associated with increased estrogen levels in women of reproductive age (Putra & Anggraini, 2022). The development of the disease requires a high concentration of estrogen. Another source of estrogen is the production of estrogen 3 sulfate through the conversion process by the enzyme estrogen sulfatase to estrone, especially those found in adenomyosis tissue. This process converts estrone into 17 $\beta$  estradiol, which then increases estrogen activity. The presence of estrogen in this circulation will stimulate the growth of adenomyosis (Rusnaldi & Ayu, 2020).

Referring to the results of the study of respondents diagnosed with adenomyosis listed in table 1, it shows that women of reproductive age experience more of these lesions than women of menopausal age. The median age of women with adenomyosis was  $43.99 \pm 5.28$  years. This is in accordance with Morassutto's findings which stated that the prevalence of adenomyosis most often affects women of reproductive age and tends to decrease after menopause due to reduced estrogen production (Morassutto et al., 2016). The results of the study are also in accordance with the study conducted by Yu, et. AL (2020). The study stated that the age of respondents who suffered from adenomyosis the most was in the age range of 41-45 years. This disease occurs mostly in women of reproductive age. This is because endometrial growth in this disorder is influenced by the stimulation of the hormone estrogen secreted by the ovaries which increases during that period. The hyperestrogenic state plays a role in the process of invagination of the basal layer of the endometrium into the myometrium.

In addition to these conditions, these lesions are not only related to estrogen receptors, but also to aromatase which is an enzyme that facilitates the conversion of androgens into estrogen which will stimulate the growth of adenomyosis (Rusnaldi, 2022). Women of reproductive age mean they still have more chances of getting pregnant and giving birth. Women who are still actively in labor will have a greater chance of experiencing local microtrauma to the endometrial myometrium border as a result of

direct trauma. Such trauma can lead to the activation of the mechanism of injury and tissue repair /TIAR (Bodur et al., 2015). This condition then causes the invasion of the basal layer of the endometrium into the myometrium, thus finally triggering the formation of adenomyosis (Stratopoulou et al., 2021).

### **3.2.2. Relationship between NLR value and incidence of adenomyosis**

NLR can also affect the occurrence of adenomyosis, as well as age factors. This study gave the results that women who suffered from adenomyosis had an average NLR value of  $4.31 \pm 2.14$ . Table 2 shows that there are 44 respondents who have NLR values who are at risk of developing adenomyosis, which is said to be at risk if they have an NLR value of  $>3.53$ . This research is in line with Madendag et al (2018) conducted at Kayseri Hospital in Turkey, the same results were obtained that there is a meaningful correlation between NLR and adenomyosis.

Blood count examination is one of the important biomarkers that can be used in adenomyosis which is an inflammatory disease. Blood count tests, especially neutrophils and lymphocytes, can be used to detect the presence of inflammatory processes. Neutrophils play a role in the body's response to inflammation by functioning as part of the immune system by targeting and destroying pathogens or foreign substances that cause inflammation while those that play a protective component against inflammation are lymphocytes (Bourdon et al., 2021; Guo, 2023). The highest number of leukocytes are neutrophils. These cells will first migrate from the blood to the site of inflammation. These cells will destroy pathogens (Khan et al., 2024; Kobayashi, 2023). In adenomyosis, neutrophils are carried to the tissue through a process involving chemotaxis, which is the movement of cells towards chemical stimuli. Chemokine ENA-78 is a neutrophil chemotactic factor. ENA-78 will activate those cells and promote cytosol-free calcium changes, which can lead to neutrophil chemotaxis and angiogenesis of inflammatory tissues. ENA-78 is induced by inflammatory mediators and its production is stimulated by IL-1 and Tumor Necrosis Factor (TNF  $\alpha$ ) (Gardella et al., 2022; Kobayashi, 2023).

Changes in cell death regulation will increase the number of neutrophils and decrease the number of lymphocytes. Delays in the process of neutrophil cell death will result in prolongation during inflammation, while increased lymphocyte cell death results in decreased inflammatory effectors as well as suppression of the immune system. An increase in the number of neutrophils and a decrease in the number of lymphocytes leads to an increase in NLR. So that the NLR value can be used as a marker of inflammation (Abramiuk et al., 2022; Mirantika et al., 2021; Yucel Cicek & Doger, 2022a).

Activation of the TIAR mechanism occurs through the local microtrauma effects of uterine peristaltic activation at the endometrial myometrium border followed by an increase in chronic inflammation. The interaction of macrophages with platelets at the site of inflammation during the injury and repair process can secrete cytokines induced by macrophages and platelets. Macrophages, platelets, and some cytokines are thought to contribute to the development of adenomyosis with mechanisms of neurovascularization, inflammation, and endometrial cell attachment (Bodur et al., 2015).

Patients with adenomyosis are found to have significantly more activity in the endometrial area than in the normal endometrium. Specifically, higher microvessel density (MVD) is found in the ectopic endometrium than that occurs in the eutopic endometrium (Qi et al., 2023; Stratopoulou, Camboni, et al., 2021; Yucel Cicek & Doger, 2022b). A positive correlation was found between the expression of VEGF and MMP-2, as well as MMP-9, in this disease. A similar relationship was also found between MVD expression and MMP-2 or MMP-9. These findings suggest that an increase in MMP-2 and MMP-9 expression may be an important factor in the development of the disease. Thus contributing to the invasion of endometrial tissue into the myometrium as well as angiogenesis in adenomyotic implants (Qi et al., 2023; Stratopoulou, Camboni, et al., 2021; Yucel Cicek & Doger, 2022b). Overexpression of IL-6 in adenomyosis will lead to increased estrogen receptor expression. Increased expression of P450 aromatase in women with adenomyosis will also increase the production of local estrogen within the

endometrium. This condition will result in impaired progesterone receptor function. Changes in the balance between estrogen and progesterone will result in the persistence of estrogen-a receptors. Decreased regulation of these receptors is one of the main functions of progesterone. Overexpression of estrogen receptors in the mid-secretion phase, will reduce the secretion of integrin b-3 which is negatively regulated by estrogen thereby altering the microenvirontment of uterine receptivity (Rusnaidi & Ayu, 2020).

#### **4. Conclusion**

Based on the results of the studies that have been presented, it can be concluded that there is a relationship between the incidence of adenomyosis based on age factors and the neutrophil-lymphocyte ratio. The implications of this study suggest that NLR can be a simple predictor of the incidence of adenomyosis. This can be done especially in women of reproductive age accompanied by a history of dysmenorrhea with chronic pain complaints.

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