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Analysis of Age Factor and Hemoglobin Profiles in The Incidence of Uterine Leiomyoma

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ABSTRACT

Uterine leiomyoma is recognized as the most common benign tumor of the female reproductive system and remains a significant cause of gynecological morbidity worldwide. Its development has been closely associated with hormonal exposure, particularly estrogen and progesterone, and with reproductive age. Despite being frequently encountered in clinical practice, the role of other contributing factors, such as hemoglobin status, remains less clear. This study examined the relationships among age, hemoglobin concentration, and the incidence of uterine leiomyoma. An observational-analytic case-control design, using leiomyoma as cases and adenomyosis as controls, was conducted at PKU Muhammadiyah Hospital, Surakarta. A total of 246 participants were included, comprising 93 women with histopathologically confirmed leiomyoma and 153 women with adenomyosis as the control group. Data were obtained from hospital medical records, and statistical analyses were performed using Chi-square tests followed by logistic regression. The results demonstrated that being in the reproductive age group (≤50 years) significantly increased the likelihood of leiomyoma occurrence (OR=3.114, 95%CI: 1.141–8.500, p=0.021). In contrast, hemoglobin profiles did not show a significant association with leiomyoma incidence (OR=0.777, 95%CI: 0.428–1.441, p=0.407). Although anemia was frequently observed in both groups, it appeared more likely to be a clinical manifestation of abnormal uterine bleeding than a direct etiological factor.

INTRODUCTION

Uterine leiomyoma, commonly known as a uterine fibroid, is recognized as the most prevalent benign neoplasm in gynecology (Antunes et al., 2022). Arising from myometrial stem cells, its growth is driven by genetic alterations under the influence of gonadotropic hormones (Azhari et al., 2024). The reported prevalence ranges between 25–40% in women of reproductive age and may increase to 50–70% in those approaching menopause, with incidence rates escalating alongside age (Gustiari et al., 2023). Notably, African American women exhibit the highest susceptibility, with more than 80% affected by age 50, compared with approximately 70% in Caucasian populations (Maclean & Hayashi, 2022). The global prevalence of data is 20–25%, with 9,643,336 cases in 2019 (Farma & Kurniati, 2024). In the United States alone, nearly 300,000 myomectomy procedures are performed each year, either for fibroid excision or as part of hysterectomy (Goad et al., 2022).

The prevalence of uterine leiomyoma in Indonesia has been estimated at 2.39–11.7% (Alfarizan et al., 2020). A study conducted at Undata Regional Hospital in Central Sulawesi by Umar et al. documented 84 cases between July and October 2022 (Umar et al., 2023). At Dr. H. Moch Ansari Saleh Hospital in Banjarmasin, hospital records showed 245 cases in 2014, followed by a decrease to 224 in 2015, then a rise to 383 in 2016. Similarly, at PKU Muhammadiyah Hospital, Surakarta, 65 cases were documented between 2019 and 2024 (Farma & Kurniati,

2024), while at Prof. Dr. R. D. Kandou Hospital, Manado, 83 cases were recorded between July 2017 and June 2018 (Arifint et al., 2019). These variations in incidence across hospitals in Indonesia may reflect differences in population characteristics, environmental factors, and medical record reporting.

The precise mechanisms underlying the development of uterine leiomyomas remain incompletely understood (Gustiari et al., 2023). Contributing factors are believed to include race, genetic predisposition, reproductive factors, obesity, hormonal influences, and age (Hartoyo et al., 2022). Age has been identified as the most consistently correlated factor, mainly because of its direct connection to hormonal dynamics, particularly estrogen and progesterone, which promote myometrial cell proliferation (Azhari et al., 2024). The incidence of uterine leiomyoma typically increases in the early forties, with prevalence reaching up to 80% prior to menopause (McWilliams & Chennathukuzhi, 2017; Marcellina & Pramana, 2023). Notably, uterine fibroids are rarely observed before puberty, and their prevalence declines significantly after menopause (Hartoyo et al., 2022). Zulala (2024) reported that women aged 30–50 years have a 3.279-fold higher risk of developing uterine leiomyomas compared to other age groups (Zulala, 2024).

Clinically, uterine leiomyomas are frequently manifested by heavy menstrual bleeding (menorrhagia), dysmenorrhea, dyspareunia, infertility, and pelvic masses (Nizomy et al., 2024). Menorrhagia is a primary cause of iron-deficiency anemia, often reflected in decreased hemoglobin profiles (Vannuccini et al., 2024). Findings from Prof. Dr. R. D. Kandou Hospital in Manado revealed that nearly half of patients with uterine leiomyomas had moderate reductions in hemoglobin, with 41% ranging from 10.0 to 12.0g/dL (Arifint et al., 2019). According to Adriani (2018), the hemoglobin profile was significantly associated with the incidence of uterine leiomyoma, as the case group exhibited a greater proportion of individuals with low hemoglobin levels compared to the control group (Adriani, 2018).

Although numerous studies have examined the relationship between age and uterine leiomyoma, the available evidence remains inconsistent, mainly due to differences in sample characteristics and variability across control populations. Research examining hemoglobin status has predominantly emphasized anemia as a clinical outcome of abnormal uterine bleeding, rather than evaluating hemoglobin as a potential risk factor. Studies that simultaneously assess age and hemoglobin profiles in relation to uterine leiomyoma occurrence have not yet been identified. Therefore, this study provides new insight through a more targeted comparative approach, enabling a clearer understanding of the relative influence of these two factors among women of reproductive age, particularly in the context of uterine leiomyoma occurrence.

METHOD

This study employed a case-control design with an observational analytic approach, comparing a case group (uterine leiomyoma) and a control group (adenomyosis). Adenomyosis was selected as the control group based on methodological feasibility and pathological justification. Histopathological evaluation is the definitive diagnostic standard for all uterine tumors, including leiomyoma. However, obtaining tissue samples from the uteri of healthy women is ethically unacceptable and not feasible in practice. Therefore, both the case and control groups were derived from the most frequently encountered hysterectomy specimens documented in the anatomical pathology laboratory. Uterine leiomyoma is a benign clonal neoplasm originating from myometrial smooth muscle cells.

In contrast, adenomyosis is a common benign gynecologic condition characterized by the presence of endometrial glands and stroma within the myometrium. Using adenomyosis as the control group provides a more accurate comparative assessment of two distinct yet commonly diagnosed uterine pathologies within a consistent clinical and diagnostic framework. The research was conducted at the Department of Anatomical Pathology at PKU Muhammadiyah Hospital Surakarta and at the Faculty of Medicine, Universitas Muhammadiyah Surakarta. Study samples were derived from histopathology medical records documenting confirmed cases of

uterine leiomyoma from the 2023 dataset, collected during the designated research period of July-August 2025.

The target population consisted of all histopathological records of uterine tumors at PKU Muhammadiyah Hospital Surakarta, while the actual population included medical records with histopathological confirmation of uterine leiomyoma. Samples were selected using a purposive sampling technique from cases meeting the inclusion criteria, namely histopathological records concluding uterine leiomyoma with complete patient identity data. The study included 246 samples meeting the research criteria, consisting of 93 uterine leiomyoma cases and 153 adenomyosis controls. Inclusion criteria consisted of medical records with histopathological confirmation of uterine leiomyoma and complete patient identity data. Exclusion criteria included medical records diagnosed as non-leiomyoma uterine tumors or malignancies, as well as incomplete medical records.

Independent variables included age (≤50 years = reproductive age; >50 years = menopausal) (Micić et al., 2024) and hemoglobin concentration (normal: 12.0–16.0g/dL; anemia: <12.0g/dL) (Safiri et al., 2021). The dependent variable was the diagnosis of uterine leiomyoma, established through histopathological examination. Data were collected by reviewing medical records that met the inclusion criteria. Statistical analyses included Chi-Square tests for bivariate associations ($p<0.05$), followed by logistic regression for multivariate evaluation. Statistical application was used to calculate odds ratios (OR), 95% confidence intervals (CI), and frequency distributions. This study was conducted in accordance with medical research ethics principles and has been submitted for approval to the Health Research Ethics Committee of PKU Muhammadiyah Hospital Surakarta (Reference No.07/KEPK/RS.PKU/IX/2025).

RESULTS

The study sample comprised 246 participants, including 93 individuals diagnosed with uterine leiomyoma and 153 with adenomyosis. Participant characteristics are detailed in Tables 1 and 2. Within the leiomyoma subgroup, the majority were of reproductive age (≤50 years), accounting for 88 respondents (94.6%), whereas only 5 respondents (5.4%) were postmenopausal (>50 years). Based on hemoglobin profiles, patients with anemia (<12 g/dL) predominated, accounting for 68 respondents (73.1%), while those with normal hemoglobin profiles (≥12 g/dL) numbered 25 (26.9%). The majority of respondents were multipara or primipara (72%), lived in urban areas (92.5%), and all reported regular menstrual cycles (100%).

Table 1. Distribution of respondents with uterine leiomyoma

Variabel	Attributes	n	%
Age	≤50 years	88	94.6
	>50 years	5	5.4
Hemoglobin profiles	Anemia (<12g/dL)	68	73.1
	Normal (≥12g/dL)	25	26.9
Parity	Nulliparous	26	28.0
	Multiparous & primiparous	67	72.0
Residence category	Urban residence	86	92.5
	Rural residence	7	7.5
Menstrual cycle	Regular cycles	93	100.0
	Irregular cycles	0	0.0

The distribution of respondents in the adenomyosis group showed a similar pattern, with a predominance of reproductive-age women, accounting for 130 respondents (85%). Anemia was present in 119 respondents (77.8%), while 34 respondents (22.2%) had normal hemoglobin levels. Most respondents were multiparous or primiparous (83.7%), resided in urban areas (90.8%), and all had regular menstrual cycles (100%).

Table 2. Distribution of respondents with adenomyosis

Variabel	Attributes	n	%
Age	Age ≤50 years	130	85.0
	Age >50 years	23	15.0
Hemoglobin profiles	Anemia (<12 g/dL)	119	77.8
	Normal (≥12 g/dL)	34	22.2
Parity	Nulliparous	25	16.3
	Multiparous & primiparous	128	83.7
Residence category	Urban residence	139	90.8
	Rural residence	14	9.2
Menstrual cycle	Regular cycles	153	100.0
	Irregular cycles	0	0.0

A bivariate analysis using the Chi-Square test was performed to evaluate the association between age and uterine leiomyoma incidence. The results demonstrated a significant correlation (p=0.021, OR=3.114, 95%CI=1.141–8.500), indicating that women in the reproductive age group were more likely to develop leiomyoma than those in the menopausal group.

Table 3. Association of age with uterine leiomyoma incidence

Age group	Leiomyoma (n=93)		Adenomyosis (n=153)		OR	CI95%	p
	n	%	n	%			
≤50 years	88	94.6	130	85	3,114	1,141–8,500	0,021
>50 years	5	5.4	23	15			

Meanwhile, the analysis of hemoglobin profiles and uterine leiomyoma incidence revealed no significant association. The statistical evaluation yielded a p-value of 0.407, which exceeded the 0.05 threshold, along with an odds ratio of 0.777 and a 95% confidence interval of 0.428–1.441. This suggests that anemia observed in patients is more likely a clinical consequence of abnormal uterine bleeding rather than a specific etiological factor for leiomyoma.

Table 4. Association of hemoglobin profiles with uterine leiomyoma incidence

Hemoglobin	Leiomyoma (n=93)		Adenomyosis (n=153)		OR	CI95%	p
	n	%	n	%			
<12g/dL	68	73.1	119	77.8	0,777	0,428–1,441	0,407
≥12g/dL	25	26.9	34	22.2			

The study outcomes highlight reproductive age as a key determinant, significantly associated with the incidence of uterine leiomyoma. In contrast, hemoglobin status appears not to exert a measurable or direct effect on its development.

DISCUSSION

Analysis of the influence of age on the incidence of uterine leiomyoma

This study revealed that most cases of uterine leiomyoma were found among women in the reproductive age group (≤50 years). Adenomyosis also showed a similar pattern, with the majority of cases occurring in this age range, indicating a significant association between age and uterine leiomyoma. These findings align with the research conducted by Meilani et al. (2019) at Al-Ihsan Regional General Hospital in West Java Province. That cross-sectional study, involving 42 patients in 2018, reported a significant correlation between age and uterine myoma, with the highest prevalence in women aged >30 years. Similarly, Zulala (2024) reported comparable findings at PKU Muhammadiyah Gamping Hospital, Sleman. Their study used a quantitative, descriptive-analytic case-control design, involving 289 medical records from 2021-2023. The frequency distribution analysis revealed the highest proportion of leiomyoma cases in the at-risk

age group (30–50 years). Bivariate analysis confirmed a statistically significant association between age and uterine leiomyoma (Zulala, 2024).

Conversely, Adriani (2018), in a case-control study involving 62 respondents at Dr. R. Goeteng Tarunadibrata Regional Hospital, Purbalingga, reported no significant association between maternal age and uterine leiomyoma. Age was categorized into reproductive and menopausal groups, with no meaningful differences detected. Differences in study design and respondent characteristics may explain this discrepancy. In Adriani's study, the majority of respondents in both groups were clustered within the reproductive age range (35-45 years), resulting in age homogeneity that limited statistical differentiation (Adriani et al., 2018). Variability in prior research findings indicates that differences in study design, population characteristics, and data completeness may influence the observed association between age and leiomyoma. In the present study, reliance on medical record data limited the inclusion of several important confounding variables. These limitations should be taken into account when interpreting the relationship between age and leiomyoma occurrence.

The reproductive period is characterized by elevated exposure to estrogen and progesterone, both of which are pivotal in the pathogenesis of uterine myomas. These hormones drive myometrial cell proliferation by modulating sex hormone receptor expression, particularly estrogen receptor-α (ERα) and progesterone receptor isoforms A and B (PR-A/B). These receptors are expressed at higher levels in leiomyomas than in normal myometrium. Activation of these receptor pathways induces transcription of genes that regulate cell proliferation, angiogenesis, and extracellular matrix (ECM) formation, including type I and II collagen, fibronectin, and proteoglycans, which collectively enhance fibroid growth. In addition, cyclic menstruation induces oxidative stress and recurrent ischemic injury to the myometrium, triggering abnormal tissue repair responses. Over time, these processes generate a microenvironment conducive to leiomyoma development (Alali et al., 2023).

Beyond hormonal and microenvironmental influences, the reproductive phase is also marked by increased activity of myometrial stem cells. This activation is driven by paracrine signaling from mature myometrial cells exposed to estrogen and progesterone. Although stem cells do not directly express steroid hormone receptors, they proliferate in response to these paracrine factors. This facilitates the transformation of stem cells into tumor-initiating cells through clonal expansion. These initiator cells subsequently evolve into leiomyomas under sustained hormonal stimulation (Alemari et al., 2022; Romadhon & Kurniati, 2024).

The role of reproductive age in leiomyoma pathogenesis is further reinforced by genetic evidence. Most leiomyoma cases in this period have been linked to somatic mutations of the MED12 gene, which impair the normal function of the mediator complex subunit. This disruption triggers abnormal activation of the Wnt/β-catenin signaling cascade, a pathway essential for cell differentiation and proliferation. Under estrogenic influence, this dysregulation further accelerates leiomyoma growth (Ishikawa et al., 2023). Histopathologically, the MED12-mutant subtype of leiomyoma is characterized by increased collagen deposition and reduced vascularity. This growth pattern underscores the strong dependence of leiomyoma progression on sex hormone stimulation. Such dependence is most evident during reproductive years, when the hormonal milieu strongly supports estrogen and progesterone receptor activity and progressive fibrotic tissue expansion. Consequently, prolonged and intense hormonal exposure contributes not only to tumor initiation but also to its maintenance and accelerated progression (Maekawa et al., 2022).

Analysis of the influence of hemoglobin profiles on the incidence of uterine leiomyoma

The majority of respondents with uterine leiomyoma experienced anemia. A similar finding was reported in the adenomyosis group. Despite the high prevalence of anemia in both groups, chi-square analysis showed that hemoglobin concentration was not significantly associated with uterine leiomyoma. In contrast, Adriani (2018) reported different results in a case-control study at Dr. R. Goeteng Tarunadibrata Regional Hospital, Purbalingga, involving 62 respondents. Data were collected from January to December 2017 in the Bougenvile maternity ward. Chi-square-

based bivariate analysis demonstrated a significant correlation between hemoglobin concentration and the presence of uterine myoma. In that investigation, anemia was identified in 52% of subjects, making it the most prevalent condition among affected patients and closely associated with iron-deficiency anemia. Most participants were women in their reproductive years who experienced ongoing menstruation, with excessive menstrual bleeding contributing substantially to anemia risk. These results highlighted the association between reduced hemoglobin levels and persistent blood loss in reproductive-aged women (Adriani et al., 2018).

Similarly, Madendag et al. (2018) conducted a retrospective cross-sectional study at Kayseri Education and Research Hospital between January and October 2016, analyzing hematological profiles in patients with uterine leiomyoma and adenomyosis, and in healthy controls. Among 196 subjects, 80 were diagnosed with uterine leiomyomas. The results indicated that mean hemoglobin levels were significantly lower in women with leiomyoma or adenomyosis than in controls. These findings suggest that while anemia is frequently observed in patients with leiomyomas, it is not disease-specific. The authors emphasized that anemia in this population primarily results from chronic abnormal uterine bleeding (AUB), particularly among perimenopausal women, rather than serving as a predictive factor for leiomyoma occurrence (Madendag et al., 2018; Kurniati et al., 2024).

Anemia is widely recognized as a frequent complication of uterine leiomyomas, predominantly in women with heavy menstrual bleeding (HMB). Mechanistically, these tumors promote aberrant uterine bleeding via dysregulated angiogenesis, where excessive expression of VEGF, PDGF, and endothelin-1 fosters the development of structurally weak and immature vessels. This process is compounded by vascular dilatation on the leiomyoma surface, venous ectasia due to mass effect, and impaired myometrial contractility, all of which underlie AUB and HMB. Moreover, hemostatic dysfunction caused by platelet abnormalities, increased secretion of transforming growth factor β-3 (TGF-β3), and inadequate endometrial decidualization further exacerbate bleeding (Vannuccini et al., 2024).

In addition, women with uterine leiomyomas exhibit abnormal myometrial contractility related to imbalances in menstrual vasoconstrictors, particularly endothelin-1 (ET-1) and prostaglandin F2α (PGF2α). ET-1, a major vasoconstrictor, regulates myometrial contraction and mitogenesis via binding to the endothelin type A receptor (ETAR). In leiomyoma tissue, ETAR expression is upregulated while endothelin type B receptor (ETBR) is downregulated, leading to dysregulated uterine contractions and excessive menstrual bleeding (Navarro et al., 2021). Beyond hormonal and vascular mechanisms, leiomyomas also provoke chronic inflammatory responses, as reflected by elevated neutrophil-to-lymphocyte ratio (NLR), a systemic marker of inflammation. This inflammatory activity influences hematological parameters, including hemoglobin profiles, through immune cell activation and release of pro-inflammatory cytokines such as IL-6, TNF-α, and VEGF, which disrupt hemostasis and erythropoiesis (Farma & Kurniati, 2024).

The present findings, which showed no significant relationship between hemoglobin profiles and uterine leiomyoma incidence, provide an important addition to the existing body of evidence. The distribution of respondents in this study may explain the outcomes. The majority were women of reproductive age (<50 years), a group already at high risk of leiomyoma due to hormonal influences rather than hemoglobin status. All respondents had regular menstrual cycles, and most were multiparous or primiparous, indicating hormonal fluctuations that increase susceptibility to leiomyoma development. Prolactin may further contribute to this risk: although prolactin supports uterine involution and fibroid regression postpartum, once leiomyomas are established, prolactin enhances proliferative and fibrotic pathways. Activation of STAT5 and MAPK signaling cascades plays a pivotal role in driving cell proliferation, thereby accelerating fibroid growth (Delli Carpini et al., 2019; Dimauro et al., 2020).

Limitations and implications

The interpretation of this study's findings was based on secondary data. This limited the availability of additional variables, including information on coagulation profiles and blood

clotting parameters. Despite these limitations, the results remain clinically meaningful. The absence of an association between hemoglobin levels and leiomyoma suggests that anemia is more likely a consequence of abnormal uterine bleeding. These findings highlight the importance of evaluating excessive menstrual bleeding and providing timely management of anemia to improve patient clinical outcomes.

CONCLUSION

The results of this study indicated that age was a significant determinant, with women in the reproductive age group (≤50 years) exhibiting a higher likelihood of developing leiomyomas compared to their postmenopausal counterparts. In contrast, hemoglobin profiles showed no significant correlation with leiomyoma occurrence. Although anemia was frequently observed among patients with both leiomyoma and adenomyosis, statistical analysis revealed no meaningful differences. Future investigations are advised to examine more deeply the interplay between hormonal regulation and genetic factors. Factors in younger populations and to evaluate comprehensive management strategies aimed at reducing the burden of anemia and improving the quality of life of patients with uterine leiomyoma.

AUTHOR'S DECLARATION

Authors' contributions and responsibilities

NPTP: Writing original draft, visualization, conceptualization; **YPK:** Writing original draft (supporting), review and editing.

Availability of data and materials

All data are available from the authors.

Competing interests

The authors declare no competing interest.

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