

Proliferative, Cell Regulatory and Angiogenic Patterns of Uterine Fibroid in the Oil Rich Region of Nigeria

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Abstract

Background: Uterine leiomyomas (fibroids) are the most common benign tumours originating from the smooth muscle layer of the uterus.

Aim: This study evaluated the expression of CD34, Ki-67, and P16 tumour markers in uterine leiomyoma using immunohistochemistry (IHC).

Methods: The study was conducted at Niger Delta University Teaching Hospital, Okolobiri, and Federal Medical Centre, Yenagoa, Bayelsa State, Nigeria. One hundred formalin-fixed paraffin-embedded uterine leiomyoma tissues from patients who underwent myomectomy between January 2019 and December 2023 were randomly selected for IHC. Data were analysed using IBM SPSS version 25, with statistical significance set at $p < 0.05$.

Results: Uterine fibroids were most common in women aged 30–39 years (33.0%). IHC showed positive expression rates of 100% for CD34, 60% for Ki-67, and 10% for P16. Correlation analysis demonstrated a moderate positive association between Ki-67 and CD34 ($p = 0.002$), suggesting a link between tumour proliferative activity and vascularity. A weak but significant correlation was also found between Ki-67 and P16 ($p = 0.006$), while the association between CD34 and P16 was not significant ($p = 0.072$). Ki-67 expression varied significantly across age groups ($p = 0.002$), with the highest level in women aged 30–39 years, indicating peak proliferative activity during reproductive age. Women aged 30–39 years had markedly higher odds of Ki-67 positivity (OR = 17.0), whereas those aged 40–49 years and ≥ 50 years had lower odds (OR = 0.25). CD34 expression odds were lower in women aged 30–39 years (OR = 0.28) and 40–49 years (OR = 0.35) than in those aged 20–29 years. P16 positivity was higher in women aged 30–39 years (OR = 4.67), although its association with age was not significant ($p = 0.116$).

Conclusion: Differential expression of CD34, Ki-67, and P16 reflects variations in tumour proliferation, vascularity, and cell-cycle regulation in uterine leiomyoma. The high incidence of fibroids among women of reproductive age highlights the public health burden of fibroids and the need for improved screening, early diagnosis, and effective management. Routine tumour marker

assessment alongside hormonal evaluation may enhance diagnosis, prognosis, and treatment of uterine leiomyoma.

Key words: *Uterine leiomyoma, fibroid, IHC, CD34, Ki-67, P16.*

Introduction

Uterine leiomyomas (UL), commonly referred to as fibroids, are non-malignant tumours arising from smooth muscle cells of the myometrium and are characterized by a monoclonal origin. Based on their position within the uterus, they are classified into intramural (embedded within the myometrial layer), subserosal (located beneath the outer uterine covering), and submucosal (situated just below the endometrial lining)¹. Submucosal fibroids, accounting for approximately 5.5–16.6% of cases, are strongly associated with menstrual irregularities such as heavy bleeding or bleeding between cycles, as well as infertility and repeated miscarriages².

In many healthcare facilities across Nigeria, UL constitute a major cause of gynecological visits and are regarded as the leading benign tumours of the female reproductive system contributing to infertility and early pregnancy loss among women in their reproductive years^{3,4}. The occurrence of UL is significantly higher among women of African descent compared to Caucasian women. In Nigeria, prevalence rates range from 17.9% to 29%, whereas lower rates of 5% to 11% have been documented in Europe and the United States^{5,6,7}. Studies estimate that the lifetime risk of developing fibroids lies between 20% and 40%, with about 35% to 60% of women likely to develop either symptomatic or asymptomatic forms requiring medical attention⁸. These symptoms can adversely affect quality of life, particularly in low- and middle-income countries where delays in seeking healthcare are common⁵. Additionally, UL affect approximately one in every four women of reproductive age, with lifetime prevalence approaching 70% in the general female population, making them the most frequent indication for hysterectomy globally⁹. Around 20% to 40% of affected women exhibit significant symptoms that prompt clinical consultation, including abnormal uterine bleeding, pelvic discomfort, and pressure¹⁰.

Although the precise mechanism underlying the development of uterine leiomyomas is not fully understood, their development has been strongly associated with genetic alterations, hormonal influences, and dysregulated tumour markers¹¹. Tumour markers are specific proteins that are useful in the detection of diseases in tissues with the aid of immunohistochemistry. P16 as a tumour marker, plays a critical role in cell cycle regulation, specifically acting as a crucial tumour suppressor protein¹². *Ki-67* serves as a surrogate marker for cellular proliferation, with higher expression levels indicative of increased proliferative activity while CD 34 is known for its angiogenic activities in tumours¹³. The categorization of uterine leiomyomas is predicated upon diverse frameworks that consider attributes such as their anatomical localization, proliferative characteristics, and histological properties¹⁴. Given the role of angiogenesis in tumour growth and sustenance, *CD34* derives valuable information regarding the vascular dynamics of leiomyomas, however, research exploring *CD34*, P16 and *Ki-67* expression in African populations is scarce and is a gap in knowledge. Proliferation and angiogenesis are interdependent processes in tumour biology, and the combination of these two features should provide more informative insight into the behaviour of leiomyomas. It is against this background that these researchers wish to assess the proliferative, cell regulatory and angiogenic patterns of uterine fibroid in the oil rich region of Nigeria using immunohistochemistry.

Materials and Methods

Study Area

The study was carried out in Niger Delta University Teaching Hospital (NDUTH), Okolobiri and Federal Medical Centre Yenagoa (FMCY), in Yenagoa Local Government Area, Bayelsa State, Nigeria. Niger Delta University Teaching Hospital (NDUTH), Okolobiri and Federal Medical Centre, Yenagoa are tertiary health institutions and serves as referral centres within and outside the State.

Study Design

The study utilized a cross-sectional design. One hundred (100) formalin-fixed paraffin-embedded (FFPE) archived leiomyoma tissue blocks from patients who had myomectomy were randomly selected from 1st January 2019 to 31st December, 2023.

Inclusion and Exclusion Criteria

Inclusion: uterine fibroid tissue blocks from patients with relevant clinical and demographic data who were diagnosed of uterine leiomyoma and confirmed with haematoxylin and eosin staining technique were included for the study

Exclusion: Non- uterine leiomyoma tissue blocks were excluded from the study.

Microtomy

Tissue sectioning was done with rotary microtome (LEICA RM 2125 RTS). Tissue sections were trimmed at 20 microns and sectioned at 5 microns thickness, floating in and out of water bath and drying on hot plate.

Haematoxylin and Eosin Staining

Haematoxylin and Eosin staining technique was carried out using the protocol described by¹⁵ to confirm uterine leiomyoma tissues.

Immunohistochemical Analysis

Immunohistochemistry evaluation was done at Gwarinpa Medical Diagnostic and Cervical Screening Centre, Abuja, Nigeria. ABC (Avidin Biotin-Complex) method was used to detect tumour markers using the protocol described by¹⁵.

Ethical Consideration

Ethical clearance for the approval of this study was granted by the Research Ethics Committees of the Niger Delta University Teaching Hospital (NDUTH), Okolobiri, with Ref. No: NDUTH/REC/0108/2024 and Federal Medical Centre, Yenagoa, Bayelsa State with Ref. No: FMCY/REC/ECC/2024/DEC/81.

Statistical Analysis

All data obtained from the study were collated, coded, and analyzed using IBM SPSS version 25 software. Data was subjected to appropriate descriptive and inferential statistical methods. Categorical variables are presented as frequencies and percentages, and results are presented in tables and bar charts. The Chi-square test of independence (χ^2) was used to determine associations between categorical variables. A p-value of ≤ 0.05 is considered statistically significant at 95% confidence interval. Furthermore, logistic regression analysis was applied to estimate odds ratios

(ORs) as an assessment of the relative likelihood of marker positivity across different age strata. All statistical analyses were carried out in accordance with standard research procedures, and results interpreted based on statistical significance at the set confidence interval of 95%.

Results

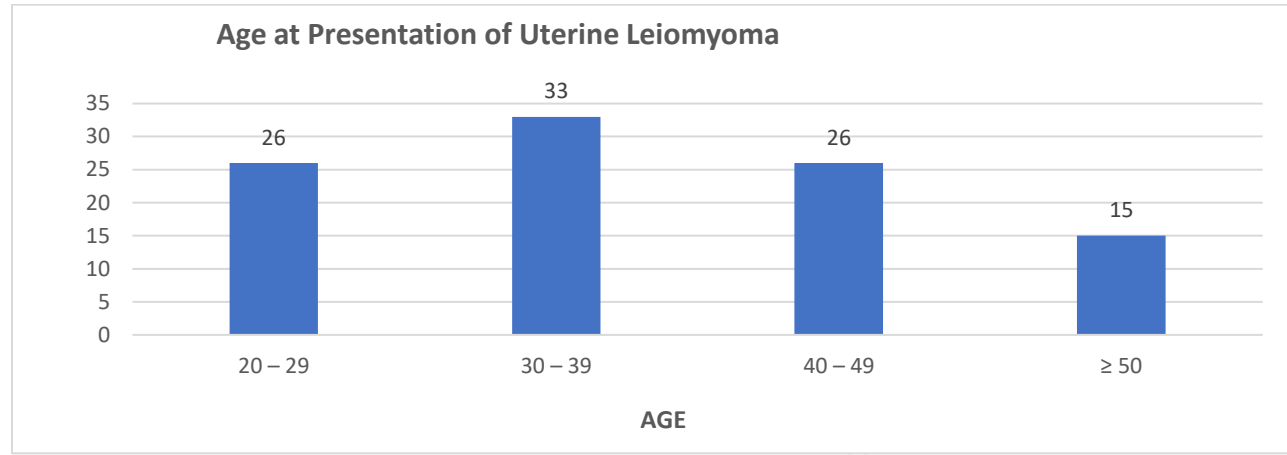


Fig. 1 shows the age at presentation of uterine leiomyoma. The study revealed that the condition is most frequent in individuals aged 30-39 (33.0%), followed by those aged 20-29 and 40-49 (26.0% each). Its occurrence is less common in the ≥ 50 age category (15.0%, 15 cases).

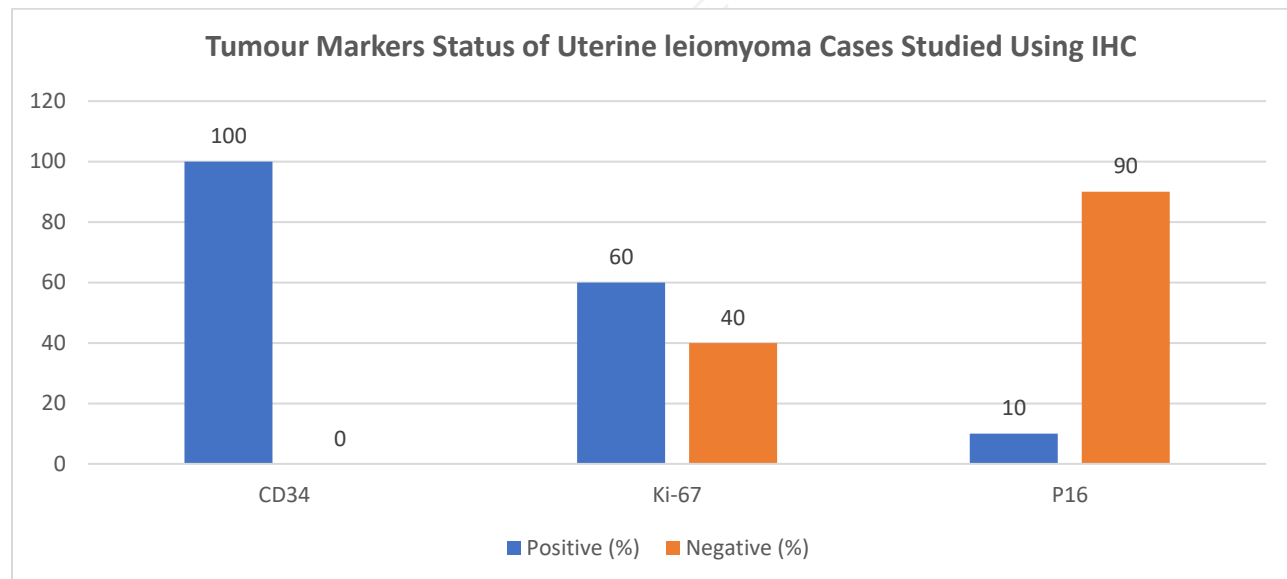
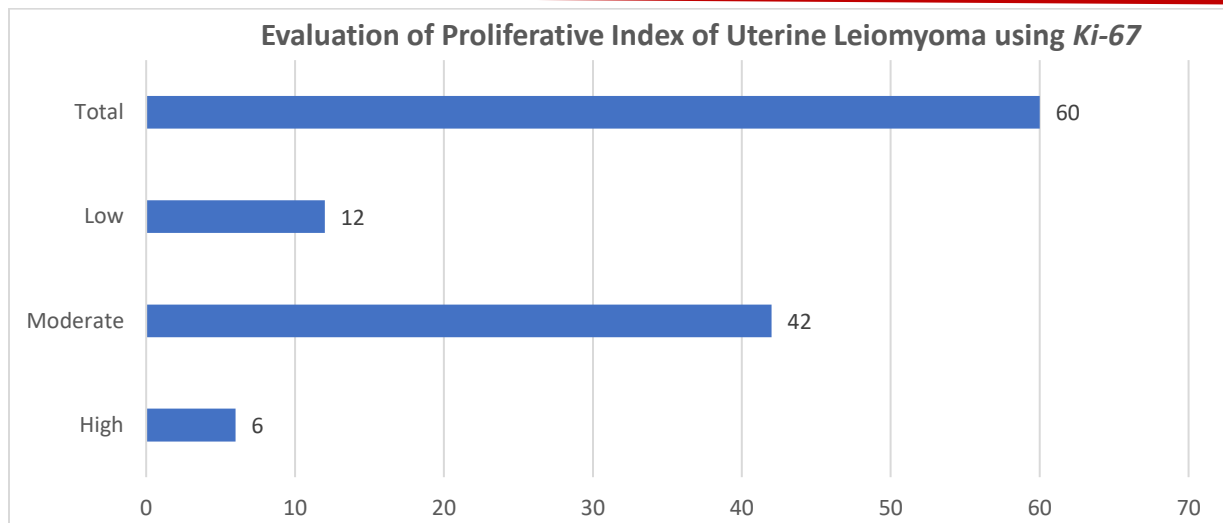


Fig. 2 presents tumour markers status of the uterine leiomyoma tissues analyzed in this study. The result revealed that all subjects expressed *CD34* (100%), 60% of subjects expressed *Ki-67* while 40% of subjects did not express *Ki-67*, whereas, 10% of subjects expressed *P16* while 90% did not express *P16* receptor.



KEY: Allred scoring system: Low expression; Moderate expression; High expression. Scoring method: summation of staining intensity plus proportion of stained cells. Where the maximum intensity score is 3 and maximum proportion score is 5, the summation is 8/8. Low expression: 1/8; 2/8 and 3/8. Moderate expression: 4/8 and 5/8. High or marked expression: 6/8, 7/8 and 8/8. Fig. 3 presents the proliferative index of Ki-67 in uterine leiomyoma (UL) across different age groups in the study. The expression of Ki-67 was categorized into low, moderate, and high levels based on the staining intensity observed in the tissue sections. Moderate immunohistochemical expression of Ki-67 was observed in age groups 20-29(10.0%), 30-39 (24.0%) and ≥ 50 (8.0%). Low expressions were observed in age groups 30-39 (4.0%) and ≥ 50 (8.0%) while high expression (6.0%) was observed in 30-39 age group.

Table 1: Trend Analysis of Ki-67 Expression Across Age Groups Using Chi-Square for Trend Test. Chi-square for trend analysis was used to evaluate the presence of a linear trend in Ki-67 expression across ordered age groups.

Age group	Ki-67 Positive N (%)	Chi-square value	P-value
20 – 29	10 (16.7)	9.72	0.002*
30 – 39	30 (50.0)		
40 – 49	11 (18.3)		
≥ 50	09 (15.0)		

Significant: 0.002

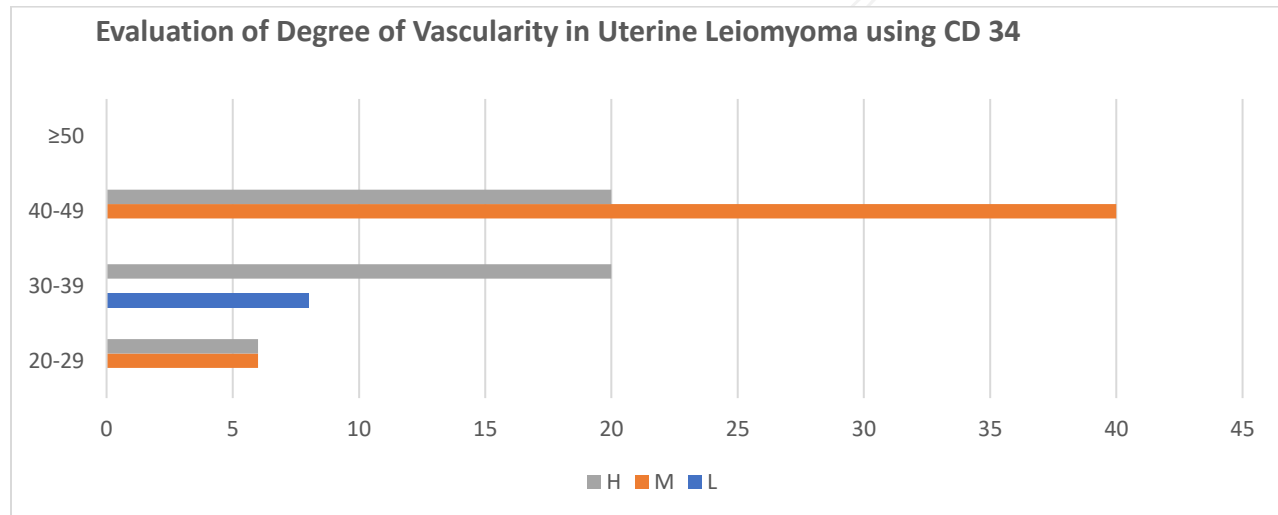
Table 1. presents trend analysis of Ki-67 expression across age groups. The analysis revealed a statistically significant trend in Ki-67 expression across age groups, with the highest proportion observed among women aged 30–39 years. This suggests that tumour proliferative activity varies with age, having its peak within the reproductive age group.

Table 2. Logistic Regression of Ki-67 Expression

Age Group (Years)	Odds Ratio (OR)	Interpretation
20 -29	1.00	-
30 – 39	17.0	17 times higher odds of Ki-67 positivity
40 – 49	0.25	75% lower odds of Ki-67 positivity
≥ 50	0.25	75% lower odds of Ki-67 positivity

KEY: OR=Odds Ratio; NA: Not applicable (Because all cases in that category were negative for the marker).

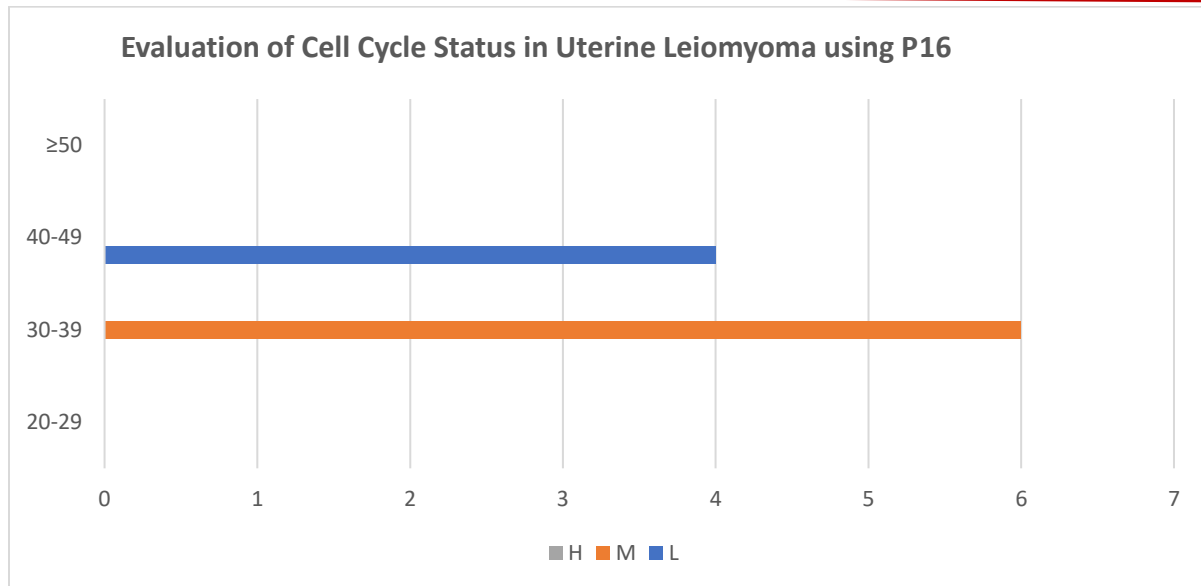
Table 2: presents the likelihood of Ki-67 positivity across age groups, benchmarked against the 20–29-year-old category. Women aged 30–39 demonstrated a substantially greater chance of Ki-67 positivity, with odds 17 times higher (OR = 17.0), indicating heightened tumour cell activity. In contrast, those aged 40–49, and 50 and above both showed significantly reduced odds, approximately 75% lower (OR = 0.25), compared to the youngest group.



*L=low expression; M=moderate expression; H=high expression

KEY: Allred Scoring method: summation of staining intensity plus proportion of stained cells. Where the maximum intensity score is 3 and maximum proportion score is 5, the summation is 8/8. Low expression: 1/8; 2/8 and 3/8. Moderate expression: 4/8 and 5/8. High or marked expression: 6/8, 7/8 and 8/8.

Fig 4: shows the immunohistochemical expression of CD34 in uterine leiomyoma, categorized into low, moderate, and high levels. Low expression of CD34 was observed in 8.0% of subjects in the 30-39 age category, moderate expression of 6.0% and 40.0% were recorded in the 20-29 and 40-49 age categories respectively; while high expression was predominant within the 30-39 and 40-49 age ranges.



*L=low expression; M=moderate expression; H=high expression

KEY: Allred Scoring method: summation of staining intensity plus proportion of stained cells. Where the maximum intensity score is 3 and maximum proportion score is 5, the summation is 8/8. Low expression: 1/8; 2/8 and 3/8. Moderate expression: 4/8 and 5/8. High or marked expression: 6/8, 7/8 and 8/8.

Fig 5: outlines the immunohistochemical expression of P16 in uterine leiomyoma, categorized into low, moderate, and high levels. Low immunohistochemical expression of P16 was recorded in the 40-49 age group (40.0%) while moderate expression constituted 60.0% of P16-positive cases, observed in the 30–39 age group.

Table 3: Correlation Analysis of Tumour Markers (Ki-67, P16, and CD34) in Uterine Leiomyoma. Correlation analysis using Pearson/Spearman correlation coefficients was performed to assess the relationships between immunohistochemical markers.

Variable	Ki-67 (p-value)	P16 (p-value)	CD34 (p-value)
Ki-67	1.00	0.28 (0.006*)	0.34(0.002*)
P16	0.28(0.006*)	1.00	0.18(0.072)
CD34	0.34 (0.002*)	0.18 (0.072)	1.00

Significant: 0.006, 0.002*

Table 3: presents correlation analysis of immunohistochemical markers (Ki-67, P16, and CD34). The results show a moderate positive correlation between Ki-67 and CD34 expression, suggesting a relationship between tumour proliferative activity and vascularity. A weak but statistically significant correlation was observed between Ki-67 and P16. However, the association between CD34 and P16 was weak and not statistically significant.

Table 4 Logistic Regression of *P16* Expression

Age Group (Years)	Odds Ratio (OR)	Interpretation
20 -29	1.00 -	
30 – 39	4.67	Higher odds of <i>P16</i> positivity
40 – 49	0.10	90% lower odds of <i>P16</i> positivity
≥ 50	0	NA

KEY: OR=Odds Ratio NA: Not applicable (Because all cases in that category were negative for the marker).

Table 4: presents the likelihood of P16 expression across age groups compared with the 20–29 age group as a reference category. Women aged 30–39 had nearly five times higher odds of *P16* positivity (OR = 4.67). While women aged 40–49 exhibited reduced odds, no positive P16 cases were found in those aged 50 and older, making an odds ratio calculation impossible for that group. Despite these variations in odds, the overall statistical analysis revealed no significant association between P16 expression and age ($\chi^2 = 4.25$, $p = 0.116$).

Table 5: Logistic Regression of CD34 Expression on Age Group

Age Group (Years)	Odds Ratio (OR)	Interpretation
20 -29	1.00 -	
30 – 39	0.28	72% lower odds of positivity
40 – 49	0.35	65% lower odds of positivity
≥ 50	0.00	No CD34 positivity observed

Table 5: presents the odds ratios (OR) for CD34 positivity across age groups compared with the 20–29 age category as a reference category. Logistic regression analysis revealed that women aged 30–39 years (OR = 0.28) and 40–49 years (OR = 0.35) had substantially lower odds of CD34 expression compared to those aged 20–29 years. No CD34 expression was detected in women ≥50 years.

Immunohistochemistry Photomicrographs

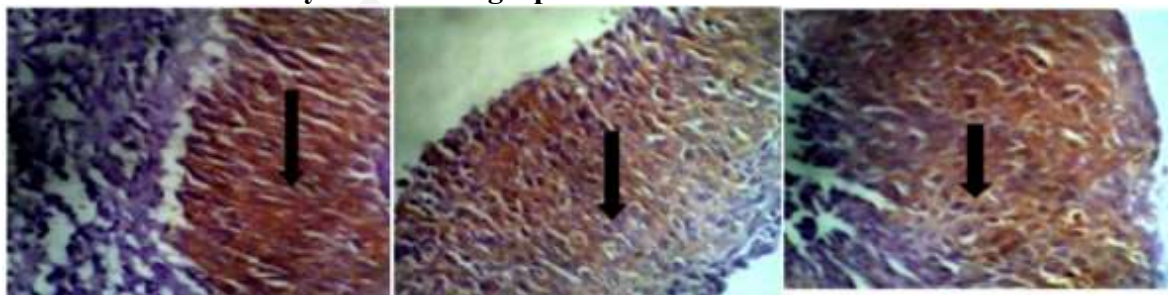


Plate 1 (Control): arrows (brownish deposits) show high (marked) expression of antibodies in the uterine leiomyoma (x400 magnification).

CD34 Receptor

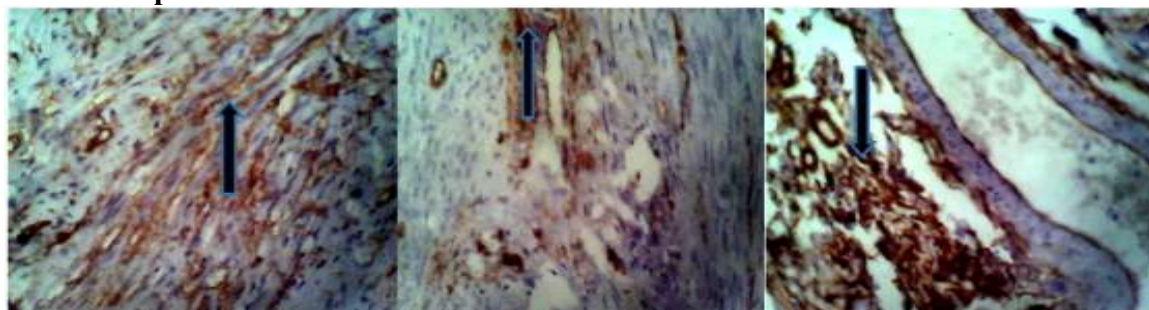


Plate 2: Positive expression of *CD 34* protein in uterine leiomyoma (x 400 magnification).

Ki67 (Positive)

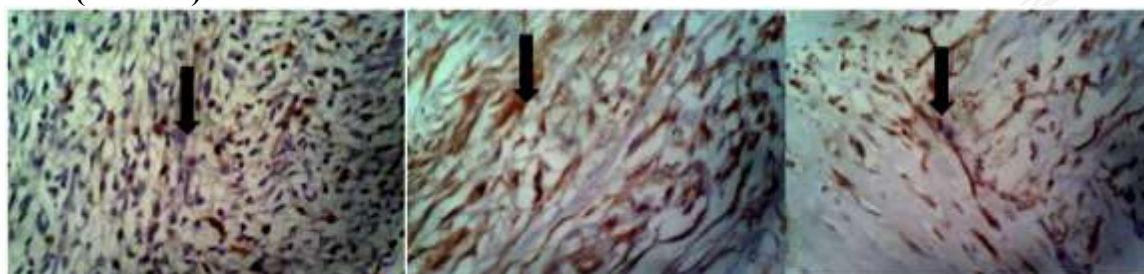


Plate 3: Positive expression of *Ki 67* protein in uterine leiomyoma (x 400 magnification)

Ki 67 (Negative)



Plate 4: Negative expression of *Ki 67* protein in uterine leiomyoma (x 400 magnification).

P16 (Mildly Positive)



Plate 5: Mild positive expression of *P 16* protein in uterine leiomyoma (x 400 magnification)

***P16* (Negative)**



Plate 6: Negative expression of *P 16* protein in uterine leiomyoma (x 400 magnification)

Discussion

Age is considered a primary determinant in the onset of fibroids⁹. In this present study the overarching trend indicated that uterine leiomyoma manifested predominantly among women during their reproductive years. The highest frequency of cases was identified within the 30–39 years age bracket, representing 33.0% of the total recorded occurrences throughout the study interval. This was succeeded by the 20–29 years and 40–49 years age categories, whereas the lowest incidence was noted among individuals aged 50 years and above (Fig 1). The observed distribution in this study suggests that uterine leiomyoma primarily affects women between 30 and 49 years of age, a period characterized by heightened hormonal activity. The comparatively reduced occurrence in women aged 50 years and older can be linked to the decrease in ovarian hormonal function associated with menopause, a physiological alteration known to influence fibroid progression and clinical presentation. These findings underscore that uterine leiomyoma remains largely confined to reproductive age groups within the study population, a pattern also reported by⁷. According to a study,¹⁶ fibroid growth reached its peak in the 35–39 age range among women, subsequently experiencing a marked deceleration in those aged 40–44 years and in subsequent age cohorts. The outcomes of this study are consistent with that of Iwuoha et al¹⁷ in the same geographical area, whose research indicated that the majority of participants diagnosed with uterine fibroids were within the 31–40-year age group.

This study evaluated the immunohistochemical expression pattern of tumour markers-Ki-67, P16 and CD34 with the aim to ascertain their proliferative, cell regulatory and angiogenic role in uterine leiomyoma (Fig. 2; Plates 2-6). *Ki-67* serves as a surrogate marker for cellular proliferation, with higher expression levels indicative of increased proliferative activity¹⁸. The low to moderate cell proliferation typical of the benign leiomyomas compared with malignant smooth muscle neoplasms is evidenced by the positive expression of the *Ki-67* in 60% of the cases observed in this study. *Ki-67* expression showed significant associations with age group ($p = 0.002$) which suggests that tumour proliferative activity varies with age (Fig.2; Table 1 & 2). It was more expressed in age group 30–39 and 40–49. Eulálio Filho et al¹⁹ reported similar results, demonstrating that *Ki-67* expression in leiomyomas was higher in normal myometrium but significantly lower in malignant smooth muscle tumours. These results suggest that while most of the leiomyomas are indolent, subgroups with the high expression of the *Ki-67* protein would grow more rapidly with more severe symptoms. High *Ki-67* indicated increased cellular proliferation and is often associated with more aggressive tumour behavior and poorer clinical outcomes.

Conversely, low levels of *Ki-67* expression (Table 3) suggest decreased cellular proliferation and may indicate a less aggressive disease course^{18,20}.

Studies investigating the clinicopathological correlates of *Ki-67* expression in uterine leiomyoma have identified several associations with tumour characteristics and patient demographics¹⁹. Higher *Ki-67* expression levels have been linked to larger tumour size, higher histological grade, and increased cellular atypia, suggesting a potential role in tumour aggressiveness²¹. Additionally, *Ki-67* expression has been found to vary according to histological subtype, with certain subtypes exhibiting higher proliferation rates than others. Age, parity, hormonal status, and race/ethnicity have also been implicated as potential factors influencing *Ki-67* expression in uterine leiomyoma, although findings have been inconsistent across studies²¹. This study observed mild, moderate and marked expression of *Ki-67* (Plates 3 & 4) which is in agreement with¹⁹; and at variance with²³ who reported no expression of *Ki-67* in uterine leiomyoma. Clinically, the evaluation of *Ki-67* expression in uterine leiomyomas plays a significant role in risk stratification and treatment planning. Patients with tumours exhibiting high *Ki-67* expression levels may require more aggressive treatment strategies, such as surgical intervention or adjuvant therapy, to effectively manage their condition and reduce the risk of disease recurrence. On the other hand, patients with tumours displaying low *Ki-67* expression levels may have a better prognosis and may benefit from less aggressive treatment approaches²⁴.

The p16 protein is a tumour-suppressor gene that acts as a negative cell cycle regulator. It functions by inhibiting cyclin-dependent kinases 4 and 6 (CDK4/6), which are essential for cell cycle progression from the G₁ to S phase^{25,26}. When activated, P16 effectively halts cell division by preventing the phosphorylation of retinoblastoma protein, thereby maintaining cell cycle checkpoint integrity²⁷. This mechanism is particularly important in preventing uncontrolled cell proliferation, which could lead to tumour formation. By sensing cellular stress, DNA damage, or oncogenic signals, *P16* can trigger cell cycle arrest, giving cells an opportunity to repair potential genetic errors or initiate programmed cell death if damage is irreparable²⁸. In this study, only 10% of the cases demonstrated positive immunohistochemical expression of P16, whereas the majority of cases (90%) showed no detectable P16 expression (Figs. 4&5). The low level of P16 (Table 4) expression observed in this study may suggest limited activation of cell cycle inhibitory pathways within the tumour tissues. This pattern is consistent with the benign biological behavior of uterine leiomyomas, where dysregulation of cell cycle control is less pronounced compared with malignant uterine tumours as posited by^{29, 30}.

CD34 is commonly used as a marker of endothelial cells and is associated with angiogenic activity within tissues³¹. In this study, all the subjects expressed CD34 (Table 3 & Plate 2). This 100% expression of CD34 in the present study indicates a prominent vascular component within the leiomyoma tissues, reflecting the presence of well-developed microvascular networks that support tumour growth and maintenance. This finding is consistent with the vascular nature of uterine leiomyomas, where angiogenesis contributes to tumour nourishment and structural organization³². The findings of this study indicate that *CD34* expression was prevalent across all age groups, with the highest expression in the 30-39 and 40-49 age ranges. which attest to the fact that the growth of uterine leiomyoma increases with age³³. The higher proportion of CD34 expression observed among individuals aged 40–49 years (Table 5) may therefore indicate increased vascularization within leiomyoma tissues in this age group, suggesting that angiogenic processes may contribute to tumour growth and maintenance during the reproductive years³⁴. The findings of this study support the propositions that *CD34* expression is a significant feature of uterine leiomyomas

development³² and aligns with ³⁵ which reported the expression of CD34 in all the uterine leiomyoma tissues.

This study was limited to two hospitals in Bayelsa State, which may not reflect the broader Nigerian population; and is considered a limitation.

Conclusion

The study observed that CD34, Ki-67 and P16 were expressed at varying levels in different age categories, reflecting proliferative activity, vascular characteristics, and cell cycle regulatory mechanisms in uterine fibroid pathogenesis within the study population.

Acknowledgement

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Competing Interest

The authors declare that there is no competing interest.

Author's Contribution

All authors contributed reasonably to this work.

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