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# Mast Cell Density Across Non-neoplastic, Premalignant, and Malignant Cervical Lesions: A Prospective Observational Histopathological Study

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## Abstract

Background: Mast cells participate in inflammation, tissue remodeling, angiogenesis, and tumor-stroma interactions, but their density across cervical lesions has been reported inconsistently. This study compared mast cell counts across non-neoplastic, premalignant, and malignant cervical lesions using 1% toluidine blue.

Materials and methods: In this prospective observational study, 160 consecutive cervical specimens were examined at Gandhi Medical College, Bhopal, India. Diagnoses were established on hematoxylin and eosin-stained sections. Mast cells were counted in 10 consecutive high-power fields incorporating areas of maximum concentration by three observers blinded to diagnosis; consensus counts were analyzed. The groups comprised 100 non-neoplastic, 18 premalignant, and 42 malignant lesions. Comparisons used Kruskal-Wallis tests and Holm-adjusted pairwise Mann-Whitney U tests.

Results: Mean counts per 10 high-power fields were 94.7 ± 21.0, 64.3 ± 18.5, and 22.5 ± 7.0 in the non-neoplastic, premalignant, and malignant groups, respectively (Kruskal-Wallis $H = 103.92$; degrees of freedom = 2; $p < 0.001$; eta-squared based on $H = 0.649$). All pairwise comparisons were significant after Holm correction ($p < 0.001$). Chronic cervicitis had the highest mean count (98.6 ± 20.7). The non-neoplastic group comprised 76 chronic cervicitis cases, 21 polyps, and only three normal/unremarkable specimens. Whole-cohort inverse correlations with age and parity were not statistically significant within the individual disease groups.

Conclusions: Mast cell counts were lower in malignant than in non-neoplastic and premalignant cervical lesions in this cohort. The inflammatory and polypoid composition of the comparator group and the cross-sectional comparison limit causal, temporal, and diagnostic interpretation. Standardized sampling, immunohistochemical confirmation, and external validation are needed before clinical application.

**Categories:** Obstetrics/Gynecology, Pathology, Oncology
**Keywords:** cervical carcinogenesis, cervical dysplasia, cervical lesions, histopathology, mast cells, squamous cell carcinoma, toluidine blue staining, tumor microenvironment

## Introduction

Persistent infection with oncogenic human papillomavirus (HPV) is central to cervical carcinogenesis, but epithelial, stromal, and host immune factors also influence the disease process. The cervical stromal microenvironment contains immune cells that can affect inflammation, tissue remodeling, angiogenesis, and tumor progression [1-3].

Mast cells are tissue-resident immune cells containing metachromatic cytoplasmic granules and mediators, such as histamine, proteases, cytokines, and growth factors. Their effects depend on the tissue context and activation state. Mast-cell responses may contribute to inflammation and tissue repair, while their mediators can also influence angiogenesis, matrix remodeling, and tumor immunity [2,3].

Previous cervical studies have reported divergent findings. Gousuddin et al., Kalyani et al., and Singh et al. described higher counts in inflammatory or premalignant lesions than in invasive malignancy [4-6]. Foukas et al. found increasing stromal mast-cell density with lesion severity, and Mondal et al. linked mast-cell accumulation with angiogenesis in cervical carcinoma [7,8]. Afrin et al. reported higher counts in invasive carcinoma than in carcinoma in situ, with lower counts in higher histological grades of invasive carcinoma [9]. More recent studies have examined survival associations within cervical cancer and the functional heterogeneity of tumor-associated mast cells [10,11].

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The primary objective of this study was to compare mast cell counts per 10 high-power fields (HPFs) across non-neoplastic, premalignant, and malignant cervical lesions in a prospectively enrolled institutional cohort. Secondary objectives were to compare individual histopathological diagnoses and assess correlations with age and parity, both overall and within disease groups.

# Materials And Methods

## Study design and setting

This prospective, institution-based observational histopathological study was conducted in the Department of Pathology, Gandhi Medical College, Bhopal, Madhya Pradesh, India. Specimen accession records for the cohort spanned 2024-2026. Cases were enrolled consecutively, and the analysis compared diagnostic groups at a single assessment rather than following lesions longitudinally.

## Ethical considerations

The Institutional Ethics Committee, Gandhi Medical College, Bhopal, approved the study (Protocol No. 194/IEC/2024; Letter No. 16306/MC/IEC/2024, dated May 6, 2024). Written informed consent was obtained from all participants before inclusion.

## Case selection and diagnostic classification

All consecutively received cervical biopsies, hysterectomy specimens, and cervical/endocervical polyps meeting the predefined tissue-quality criteria during the study period were eligible. Specimens that were inadequate, poorly preserved, or autolyzed and therefore unsuitable for histopathological assessment or reliable mast-cell identification were excluded. Cases were not selected to achieve predetermined or balanced diagnostic-group sizes; consequently, the final distribution of the 160 cases reflected routine case availability at this institution. Two pairs of specimens had identical accession-number formats but were confirmed from age and clinical details to represent different patients and were retained as independent observations. Because all eligible specimens were enrolled consecutively during the prespecified study period, discretionary case selection was minimized. However, the cohort included only specimens submitted for histopathological examination at a single institution; therefore, institutional selection and diagnostic-spectrum bias could not be eliminated. No matching or balancing of the diagnostic groups was performed.

Case-level diagnoses and mast cell counts were reconciled against the institutional master chart. Spelling variants were standardized without changing diagnoses. Three cases with coexisting chronic cervicitis and mild dysplasia were classified according to the dysplastic component. Chronic cervicitis, endocervical polyps, and normal/unremarkable cervix formed the non-neoplastic group (n = 100). Cervical dysplasia and cervical intraepithelial neoplasia (CIN) III/carcinoma in situ formed the premalignant group (n = 18). Invasive squamous cell carcinoma (SCC) and adenocarcinoma formed the malignant group (n = 42). Mast-cell counts and clinicopathological variables were entered manually on a structured case-record sheet; no dedicated electronic data-capture or image-analysis software was used.

## Sample size rationale

Because this was a consecutive, fixed-period study, no formal sample-size calculation was performed before enrollment. All eligible specimens received during the prespecified 2024-2026 study period were included, and the final sample size of 160 was therefore determined by the number of eligible cases available. An approximate sensitivity analysis based on the achieved sample size indicated that the three-group Kruskal-Wallis test had 80% power, at an alpha level of 0.05, to detect a moderate overall difference among the groups (approximately Cohen's w = 0.25). This calculation applies only to the overall three-group comparison and does not establish adequate statistical power or precision for the smaller diagnosis-specific subgroups.

## Histopathological examination and mast-cell counting

Histopathological diagnoses were assigned from H&E morphology using the 2020 WHO Classification of Female Genital Tumours and the Lower Anogenital Squamous Terminology recommendations for HPV-associated squamous lesions [12,13]. Legacy institutional labels, including mild dysplasia and CIN III/carcinoma in situ, were retained in the tables to match the source records. Tissues were fixed in 10% formalin, routinely processed, paraffin-embedded, and sectioned at approximately 4-5 µm. Hematoxylin and eosin (H&E)-stained sections were used for diagnosis, and a parallel section was stained with 1% toluidine blue. Mast cells were identified by violet-to-purple metachromatic cytoplasmic granules against the blue background. Slides were screened at low power, followed by counting under a 40× objective in 10 consecutive HPFs incorporating areas of maximum mast-cell concentration. Three observers blinded to the histopathological diagnosis counted independently, and an agreed consensus count was recorded for each case. Mast cell density was operationally expressed as the count per 10 HPFs rather than as an area-normalized measure. The toluidine blue staining and hotspot-based counting approach was adapted from prior cervical mast-cell studies [4-6].

Representative H&E sections illustrate chronic cervicitis, mild dysplasia, and poorly differentiated SCC (Figures 1A-1C). Toluidine blue-stained fields illustrate metachromatic cells in the corresponding diagnostic categories (Figures 1D-1F). These selected fields are illustrative; group comparisons were based on the case-level counts obtained using the counting protocol.

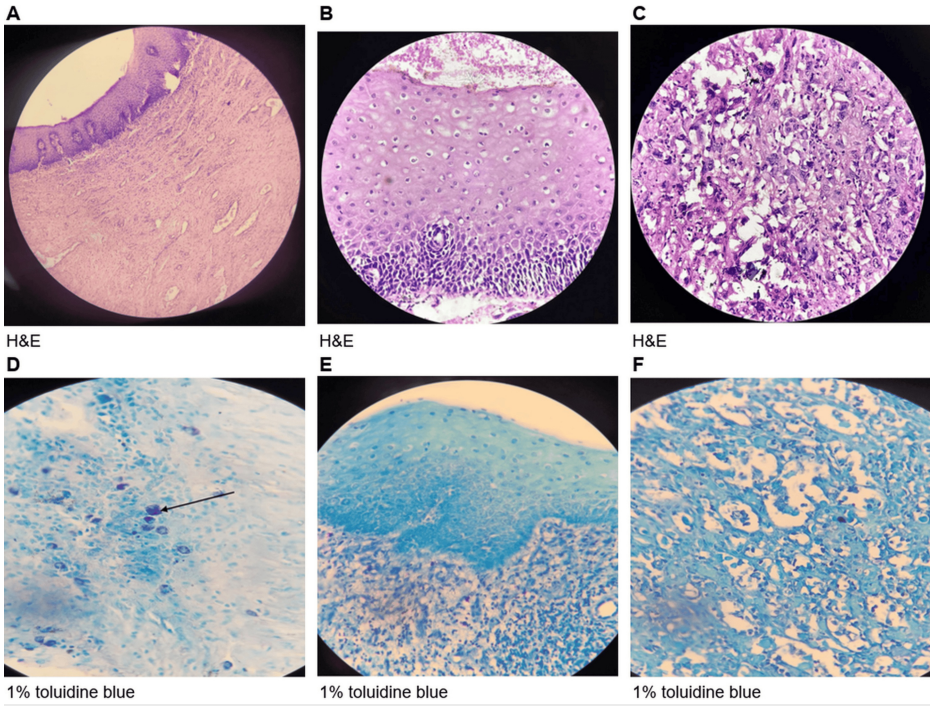



**FIGURE 1: Representative original photomicrographs across the cervical lesion spectrum**

Panels A-C show original hematoxylin and eosin (H&E)-stained photomicrographs of chronic cervicitis, mild dysplasia, and poorly differentiated squamous cell carcinoma, respectively. Panels D-F show original 1% toluidine blue-stained photomicrographs from the corresponding diagnostic categories. The arrow in panel D indicates a metachromatic mast cell. These images are representative of the respective histopathological categories; quantitative analyses were based on case-level mast cell counts obtained over 10 high-power fields. All six panels were standardized to identical dimensions and aligned in a two-row, three-column grid.

### Statistical analysis

Statistical analysis was performed using the jamovi desktop application (version 2.6.44). Counts were summarized using the mean and standard deviation (SD), median and interquartile range (IQR), and range. Nonparametric comparisons were used because distributional shape and variance differed across groups. The Kruskal-Wallis test compared the three principal groups and, separately, the seven individual diagnoses. The three-group effect size was expressed as eta-squared based on H, calculated as $(H - k + 1)/(N - k)$, where k is the number of groups and N is the total sample size. Pairwise Mann-Whitney U tests were adjusted using the Holm method. The U statistic refers to the first-listed group, and absolute rank-biserial correlations were reported as effect sizes.

Spearman correlations between mast cell count and age or parity were calculated for the whole cohort and within each disease group. Two-sided $p < 0.05$ was considered statistically significant. An exploratory receiver operating characteristic (ROC) analysis assessed lower mast cell count as an in-sample discriminator of invasive malignancy (SCC or adenocarcinoma) versus all other lesions. The apparent area under the curve (AUC) and bootstrap 95% confidence interval (CI) were reported without independent validation. This analysis was treated as hypothesis-generating.

## Results

### Study population

The study included 160 women with a mean age of 47.58 ± 10.62 years (range: 25-76 years). Forty-eight patients (30.0%) were postmenopausal. Chronic cervicitis was the most frequent diagnosis (47.5%), followed by SCC (24.4%), endocervical polyp (13.1%), and cervical dysplasia (10.6%) (Table 1).

| Histopathological diagnosis | n | Percentage |
|---|---|---|
| Chronic cervicitis | 76 | 47.5 |
| Squamous cell carcinoma | 39 | 24.4 |
| Endocervical polyp | 21 | 13.1 |
| Cervical dysplasia | 17 | 10.6 |
| Adenocarcinoma | 3 | 1.9 |
| Normal/unremarkable cervix | 3 | 1.9 |
| CIN III/carcinoma in situ | 1 | 0.6 |
| Total | 160 | 100 |

**TABLE 1: Histopathological spectrum of the cervical specimens**

Percentages use the total cohort of 160 specimens as the denominator.

n: number of specimens; CIN: cervical intraepithelial neoplasia

## Mast cell counts across the principal disease groups

Mean counts per 10 HPFs were 94.7 ± 21.0 in non-neoplastic lesions, 64.3 ± 18.5 in premalignant lesions, and 22.5 ± 7.0 in malignant lesions. Median counts were 97.0, 67.0, and 23.5, respectively. The distributions differed significantly (Kruskal-Wallis H = 103.92; degrees of freedom (df) = 2; $p < 0.001$), with eta-squared based on H = 0.649 (Table 2).

| Disease group | n | Mean ± SD | Median (IQR) | Range |
|---|---|---|---|---|
| Non-neoplastic | 100 | 94.7 ± 21.0 | 97.0 (79.8-112.0) | 52-142 |
| Premalignant | 18 | 64.3 ± 18.5 | 67.0 (55.2-77.2) | 10-85 |
| Malignant | 42 | 22.5 ± 7.0 | 23.5 (18.0-27.0) | 9-36 |

**TABLE 2: Mast cell counts by principal disease group**

Counts are expressed per 10 high-power fields.

n: number of specimens; SD: standard deviation; IQR: interquartile range. Kruskal-Wallis H = 103.92; degrees of freedom = 2; $p < 0.001$; eta-squared based on H = 0.649

Each pairwise comparison remained statistically significant after Holm adjustment. The non-neoplastic group had higher counts than the premalignant and malignant groups, and the premalignant group had higher counts than the malignant group (Table 3).

| Comparison | U | Adjusted p | Absolute rank-biserial r |
|---|---|---|---|
| Non-neoplastic vs Premalignant | 1555 | <0.001 | 0.728 |
| Non-neoplastic vs Malignant | 4200 | <0.001 | 1 |
| Premalignant vs Malignant | 715.5 | <0.001 | 0.893 |

**TABLE 3: Pairwise comparisons of mast cell counts**

U: Mann-Whitney U statistic for the first-listed group; p values are Holm-adjusted. Absolute rank-biserial r = |2U/(n1 × n2) - 1|, where n1 and n2 are the group sizes. The first-listed group had higher counts in each comparison.

The distributions show complete separation between the observed non-neoplastic and malignant count ranges, with some overlap involving the premalignant group (Figure 2).

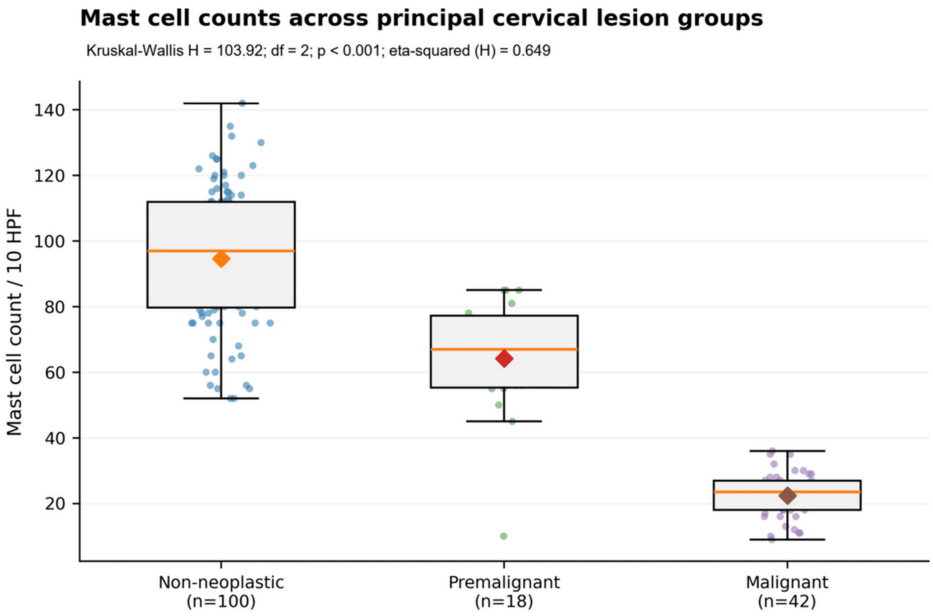



**FIGURE 2: Distribution of mast cell counts across the principal disease groups**

Counts are expressed per 10 high-power fields (HPFs). Boxes indicate the interquartile range, horizontal lines indicate medians, diamonds indicate means, and points indicate individual observations.

n: group size; df: degrees of freedom; H: Kruskal-Wallis statistic; $\eta H^2$: eta-squared based on H

## Mast cell counts across individual diagnoses

Counts differed across the seven histopathological diagnoses (Kruskal-Wallis H = 112.76; df = 6; p < 0.001). Chronic cervicitis had the highest mean count (98.6 ± 20.7), followed by endocervical polyp (85.8 ± 15.1) and dysplasia (67.5 ± 13.0). SCC and adenocarcinoma had lower mean counts (22.9 ± 6.9 and 16.7 ± 7.1, respectively). The single CIN III/carcinoma-in-situ case had a count of 10 (Table 4).

| Diagnosis | n | Mean ± SD | Median | IQR | Range |
|---|---|---|---|---|---|
| Chronic cervicitis | 76 | 98.6 ± 20.7 | 101.5 | 82.0-114.0 | 52-142 |
| Endocervical polyp | 21 | 85.8 ± 15.1 | 87 | 77.0-92.0 | 52-119 |
| Dysplasia | 17 | 67.5 ± 13.0 | 67 | 56.0-78.0 | 45-85 |
| Normal/unremarkable | 3 | 57.3 ± 2.3 | 56 | 56.0-58.0 | 56-60 |
| Squamous cell carcinoma | 39 | 22.9 ± 6.9 | 25 | 18.0-27.5 | 10-36 |
| Adenocarcinoma | 3 | 16.7 ± 7.1 | 18 | 13.5-20.5 | 9-23 |
| CIN III/carcinoma in situ | 1 | 10 | 10 | Not applicable | 10-10 |

**TABLE 4: Mast cell counts across individual histopathological diagnoses**

Counts are expressed per 10 high-power fields. SD and IQR cannot be estimated for the single CIN III/carcinoma-in-situ case. The normal/unremarkable and adenocarcinoma subgroups contain three specimens each and should be interpreted descriptively.

n: number of specimens; SD: standard deviation; IQR: interquartile range; CIN: cervical intraepithelial neoplasia

The non-neoplastic group comprised 76 chronic cervicitis cases and 21 polyps, with only three normal/unremarkable specimens. The mean count in normal/unremarkable cervix (57.3 ± 2.3) was lower than that in dysplasia. Thus, the principal group comparison does not demonstrate a monotonic decline from histologically normal cervix through dysplasia to carcinoma. The diagnosis-specific distributions are shown in Figure 3.

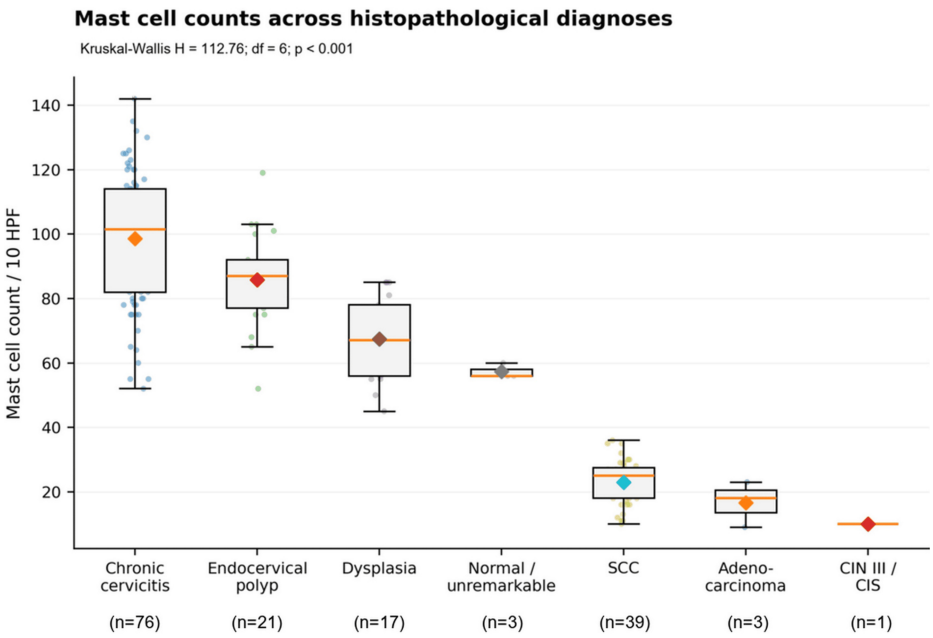



**FIGURE 3: Mast cell counts across individual histopathological diagnoses**

Counts are expressed per 10 high-power fields (HPFs). Boxes indicate the interquartile range, horizontal lines indicate medians, diamonds indicate means, and points indicate individual observations. The normal/unremarkable, adenocarcinoma, and CIN III/carcinoma-in-situ subgroups contain three, three, and one specimen, respectively, and do not provide stable subgroup estimates. The sample size for every diagnostic category is shown below its x-axis label.

SCC: squamous cell carcinoma; CIN: cervical intraepithelial neoplasia; CIS: carcinoma in situ; df: degrees of freedom; H: Kruskal-Wallis statistic

## Associations with age and parity

Across the whole cohort, mast cell count correlated inversely with age (Spearman rho = -0.457; p < 0.001) and parity (rho = -0.440; p < 0.001). Neither correlation was statistically significant within any of the three disease groups (Table 5). This attenuation is compatible with differences in case composition across the groups; however, stratified nonsignificance does not exclude an independent association, particularly in the smaller groups.

| Group | n | Age rho (p) | Parity rho (p) |
|---|---|---|---|
| Whole cohort | 160 | -0.457 (<0.001) | -0.440 (<0.001) |
| Non-neoplastic | 100 | -0.172 (0.087) | -0.147 (0.146) |
| Premalignant | 18 | -0.313 (0.207) | -0.001 (0.997) |
| Malignant | 42 | 0.078 (0.625) | -0.088 (0.581) |

**TABLE 5: Correlations of mast cell counts with age and parity**

Within-group analyses are descriptive and do not establish the absence of an independent association.

rho: Spearman correlation coefficient; n: group size; p: two-sided p value

## Exploratory discrimination analysis

The exploratory ROC analysis yielded an apparent AUC of 0.992 (bootstrap 95% CI: 0.974-1.000) for lower mast cell counts as a discriminator of invasive malignancy. The same cohort was used to assess discrimination, and no independent validation cohort was available. The curve is provided in the appendix (Figure 4).

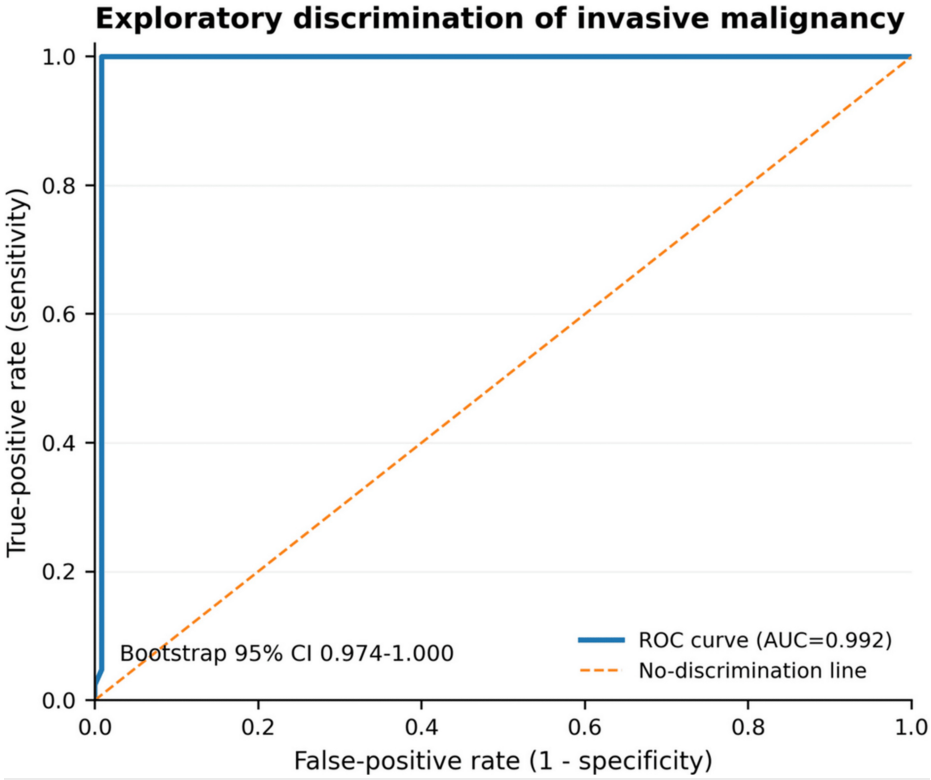



**FIGURE 4: Exploratory receiver operating characteristic curve**

Exploratory receiver operating characteristic (ROC) curve evaluating lower mast cell counts as an in-sample discriminator of invasive cervical malignancy, defined as squamous cell carcinoma or adenocarcinoma, versus all other lesions. The apparent area under the curve (AUC) was 0.992, with a bootstrap 95% confidence interval of 0.974-1.000. This analysis was performed in the same cohort and was not independently validated; therefore, the result should be considered exploratory and does not establish a clinically applicable diagnostic cutoff.

## Discussion

Mast cell counts were the highest in non-neoplastic lesions, intermediate in premalignant lesions, and the lowest in malignant lesions in this cohort. The omnibus effect size and pairwise rank-biserial correlations indicate substantial separation of the observed distributions. Nevertheless, the study compared different patients at a single assessment and cannot establish whether mast-cell depletion precedes or contributes to malignant transformation.

The composition of the non-neoplastic comparator is central to interpretation. Chronic cervicitis and endocervical polyps accounted for 97 of its 100 specimens. Their higher counts may reflect the participation of mast cells in inflammatory responses, vascular permeability, tissue repair, and stromal remodeling [2,3]. Only three specimens were normal/unremarkable, and their mean count was below that of the dysplasia group. The results therefore describe differences between the sampled lesion categories rather than a uniform normal-to-cancer continuum.

The lower counts in invasive carcinoma are consistent with previous reports by Gousuddin et al., Kalyani et al., and Singh et al. [4-6]. Other studies have produced different patterns. Foukas et al. found greater stromal mast-cell density with increasing lesion severity using CD117 immunohistochemistry, while Mondal et al. reported mast-cell accumulation accompanying angiogenesis in cervical carcinoma [7,8]. Afrin et al. observed higher counts in invasive SCC than in carcinoma in situ, followed by a reduction between well-differentiated and higher-grade invasive tumors [9]. Differences in stains, sampled compartments, counting strategies, and diagnostic composition may contribute to the divergent findings; the present study does not establish which explanation predominates.

Lesion-category comparisons also address a different question from prognosis within established cervical cancer. Guo et al. associated lower tumor-infiltrating mast-cell density with better overall survival [10]. Zhao et al. identified an ALOX5-positive mast-cell subset using single-cell RNA sequencing, supporting functional heterogeneity within the cervical tumor microenvironment [11]. Total toluidine-blue-positive counts cannot distinguish protective from tumor-promoting mast-cell phenotypes or determine activation state. The observed lower counts in invasive lesions should therefore not be interpreted as evidence of an antitumoral role for all mast cells.

The attenuation of age and parity correlations after stratification suggests that case composition may contribute to the whole-cohort associations. However, the stratified analyses do not replace multivariable adjustment and have limited precision in the smaller groups. Neither independence from age and parity nor the absence of their effects can be established from these findings.

The apparent ROC performance is exploratory. Hotspot selection, a small normal comparator, and a spectrum of histologically established lesions may limit performance in diagnostically difficult biopsies. The AUC was assessed in the same dataset used to explore discrimination and may overestimate performance in another population. No validated clinical cutoff, prognostic use, or stand-alone diagnostic application follows from this analysis. Accordingly, mast-cell counting is not proposed as a replacement for routine histopathological diagnosis, and the present findings do not support changes in treatment decisions or prognostic assessment.

### Strengths and limitations

Strengths include prospective consecutive enrollment, reconciliation of case-level observations with the institutional master chart, inclusion of a broad lesion spectrum, independent counting by three observers, and a separate premalignant group. Nonparametric comparisons, correction for multiple pairwise testing, and effect-size reporting support interpretation of the group differences.

Although consecutive enrollment reduced discretionary case selection, it did not eliminate the selection and diagnostic-spectrum bias inherent in a single-center, specimen-based cohort. The diagnostic groups were markedly unequal, and the non-neoplastic comparator comprised 76 chronic cervicitis cases, 21 endocervical polyps, and only three normal/unremarkable specimens. Consequently, the observed differences may partly reflect inflammatory or polyp-associated tissue composition rather than neoplastic status alone. Hotspot selection may increase absolute counts and reduce comparability with systematic field sampling. Counts were not normalized to field area, and quantitative interobserver agreement was not reported. Toluidine blue staining was not supplemented by immunohistochemical phenotyping or an analysis of intratumoral and peritumoral compartments. Tumor stage, HPV status, treatment, and clinical outcomes were unavailable. Active menstrual status at the time of tissue sampling and other relevant hormonal exposures were not systematically recorded and therefore could not be analyzed. Although overall postmenopausal status was available, this cannot be considered equivalent to active menstrual status among the remaining participants. Potential menstrual-cycle and hormonal influences on mast-cell counts therefore remain unmeasured confounders. The cross-sectional comparison cannot support causal or temporal inference, and the exploratory discrimination analysis requires external validation.

## Conclusions

Mast cell counts measured using 1% toluidine blue were lower in malignant than in non-neoplastic and premalignant cervical lesions in this institutional cohort. The findings indicate an association with lesion category. The inflammatory and polypoid composition of the non-neoplastic group, the small normal comparator, and the cross-sectional analysis limit interpretation as a sequence of malignant transformation.

Toluidine blue-based enumeration is a technically simple parameter that merits further study alongside routine histopathology. Multicenter investigations should standardize field selection and field area, quantify observer agreement, characterize mast-cell phenotypes, and incorporate relevant clinical variables. Independent validation is needed before diagnostic or prognostic application.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Pooja Nawlakhe

**Acquisition, analysis, or interpretation of data:** Pooja Nawlakhe, Pramila Jain, Ashish Koshti, Maneesh Sulya, Poorva Badkur

**Drafting of the manuscript:** Pooja Nawlakhe, Pramila Jain, Maneesh Sulya

**Critical review of the manuscript for important intellectual content:** Pooja Nawlakhe, Ashish Koshti, Maneesh Sulya, Poorva Badkur

**Supervision:** Ashish Koshti, Maneesh Sulya, Poorva Badkur

### Disclosures

**Human subjects:** Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee, Gandhi Medical College, Bhopal, Madhya Pradesh, India issued approval 16306/MC/IEC/2024. This study was approved by the Institutional Ethics Committee, Gandhi Medical College, Bhopal, Madhya Pradesh, India (Protocol No. 194/IEC/2024; Letter No. 16306/MC/IEC/2024, dated May 6, 2024). Written informed consent was obtained from all participants prior to inclusion in the study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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