Section: Pathology

Original Research Article

LIQUID-BASED CYTOLOGY VERSUS CONVENTIONAL PAP SMEAR FOR DETECTING CIN: A COMPARATIVE STUDY WITH HISTOPATHOLOGY CORRELATION

Manisha Vishnu Badne[1], *Arvind Eknath Rathod*[2]

[1]*Consultant, Department of Pathology, Diagnostica Span PVT Limited, India.*
[2]*Associate Professor, Department of Pathology, Government Medical College, Gondia, India.*

Received *: 21/07/2025*
Received in revised form *: 05/09/2025*
Accepted *: 26/09/2025*

Corresponding Author:
Dr. Arvind Eknath Rathod,
Associate Professor, Department of Pathology Government Medical College, Gondia, India.
Email: manishabadne@gmail.com

DOI: 10.70034/ijmedph.2025.4.14

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (4); 72-77

ABSTRACT

Background: Cervical cancer is a leading cause of morbidity and mortality among women in developing countries. Conventional Pap smear (CPS) has been the cornerstone of screening but is limited by unsatisfactory smears and obscured cellular morphology. Liquid-based cytology (LBC) was developed to address these limitations. This study compares the diagnostic efficacy of LBC and CPS in detecting cervical intraepithelial neoplasia (CIN), with histopathology as the gold standard.

Materials and Methods: A prospective comparative study was conducted on 60 women attending the gynecology outpatient department of a tertiary-care hospital. Each participant underwent both CPS and LBC, followed by colposcopically guided biopsy for histopathological correlation. Cytology was reported using the Bethesda System 2014. Diagnostic efficacy, smear adequacy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Statistical analysis included McNemar's test, Chi-square, and odds ratios with 95% confidence intervals.

Results: LBC detected ≥LSIL in 43.3% compared to 33.3% with CPS (p=0.210). Sensitivity and specificity of LBC were 86.4% and 81.6%, respectively, versus 72.7% and 89.5% for CPS. LBC significantly outperformed CPS in smear adequacy (95.0% vs 81.7%, p=0.021), presence of transformation zone component (76.7% vs 61.7%, p=0.035), and lower unsatisfactory rate (5.0% vs 18.3%, p=0.021). Association with histopathology was highly significant for both LBC (OR=28.05, p<0.000001) and CPS (OR=22.67, p<0.00001).

Conclusion: Both LBC and CPS are effective in detecting CIN; however, LBC provides superior sample adequacy, morphology, and sensitivity. While CPS remains reliable and economical, wider implementation of LBC could enhance the quality of cervical cancer screening programs.

Keywords: Liquid-based cytology, Conventional Pap smear, Cervical intraepithelial neoplasia

INTRODUCTION

Cervical cancer remains one of the most significant public health challenges worldwide, particularly in developing countries where organized screening programs are limited. According to global cancer statistics, cervical cancer is the fourth most common cancer among women, with an estimated 604,000 new cases and 342,000 deaths in 2020 (WHO, 2021). The disease is strongly associated with persistent infection by high-risk human papillomavirus (HPV) subtypes, especially HPV 16 and 18, which are implicated in the pathogenesis of cervical intraepithelial neoplasia (CIN) and invasive carcinoma. Early detection of precancerous lesions and timely intervention is crucial in reducing both incidence and mortality.[1]

Traditionally, the Papanicolaou (Pap) smear, introduced in the 1940s, has served as the cornerstone of cervical cancer screening. The conventional Pap smear (CPS) technique involves spreading exfoliated cervical epithelial cells directly onto a glass slide,

followed by fixation and staining. Although this method has significantly reduced cervical cancer burden in populations with high screening coverage, it is not without limitations. CPS is prone to technical errors such as inadequate sampling, uneven spreading, obscuring by blood, mucus, and inflammatory cells, and variability in interpretation by cytopathologists. Reported sensitivity of CPS for detecting high-grade CIN lesions is only 50-60%, although specificity is higher (65-95%).[2]

In an attempt to overcome these shortcomings, liquid-based cytology (LBC) was introduced in the late 1990s as an alternative method for cytological evaluation. In LBC, cervical samples are collected using a broom-type brush or spatula, which is then rinsed into a preservative fluid. This suspension undergoes laboratory processing to produce a thin, uniform monolayer of cells free from obscuring materials. The advantages of LBC include reduced rates of unsatisfactory smears, better cell preservation, improved morphology, and the possibility of using residual samples for ancillary testing such as HPV DNA, p16INK4a immunostaining, and other molecular assays. Several studies have suggested that LBC has a higher sensitivity than CPS for detecting CIN, though specificity remains comparable.[3]

Despite these advantages, the adoption of LBC has been limited in low-resource settings due to its higher cost compared to CPS. However, as the burden of cervical cancer is disproportionately higher in such regions, there is a strong need to evaluate the diagnostic performance of LBC in comparison to CPS with histopathology serving as the gold standard. Histopathological correlation is essential because cytology is inherently a screening tool rather than a definitive diagnostic modality. CIN, which ranges from CIN I (mild dysplasia) to CIN III (severe dysplasia and carcinoma in situ), provides an important pre-invasive window where intervention can prevent progression to invasive carcinoma.[4]

In India, where cervical cancer contributes substantially to cancer morbidity and mortality, the choice of screening method has important implications. CPS continues to be widely used in public health screening programs due to its affordability, whereas LBC is more frequently employed in tertiary care hospitals and private diagnostic centers. Given the high burden of disease, evaluating these two techniques in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) against histopathological diagnosis of CIN is of both academic and clinical significance.[5]

Aim: To compare the diagnostic efficacy of liquid-based cytology and conventional Pap smear in detecting cervical intraepithelial neoplasia (CIN) with histopathology correlation.

Objectives

1. To evaluate the diagnostic performance of liquid-based cytology (LBC) versus conventional Pap smear (CPS) for the detection of CIN using histopathology as the gold standard.
2. To compare the adequacy, cellular morphology, and unsatisfactory smear rates between LBC and CPS.
3. To assess the sensitivity, specificity, PPV, and NPV of both methods in the detection of CIN.

MATERIALS AND METHODS

Source of Data: The study population consisted of women attending the Diagnostica Span PVT Limited who presented with complaints such as abnormal vaginal bleeding, vaginal discharge, post-coital bleeding, or those undergoing routine cervical cancer screening.

Study Design: This was a prospective, comparative observational study.

Study Location: The study was conducted in the Diagnostica Span PVT Limited.

Study Duration: The study was carried out over a period of 18 months (September 2022-March2024).

Sample Size: A total of 60 women were included in the study based on inclusion and exclusion criteria.

Inclusion Criteria

1. Women aged 21-65 years presenting with gynecological complaints or attending for routine cervical screening.
2. Women willing to undergo Pap smear and colposcopically guided biopsy for histopathological correlation.
3. Women providing written informed consent.

Exclusion Criteria

1. Women with a history of prior treatment for cervical intraepithelial lesions or carcinoma.
2. Women with active vaginal bleeding at the time of examination.
3. Pregnant women and those within 6 weeks postpartum.
4. Women unwilling to participate in the study.

Procedure and Methodology: Each participant underwent a detailed clinical history and gynecological examination. After proper counseling and informed consent, samples were collected as follows:

- Conventional Pap Smear (CPS): Using an Ayre's spatula and endocervical brush, the cervical sample was obtained and immediately smeared onto a clean glass slide. The smear was fixed with 95% ethanol and subsequently stained by the Papanicolaou staining method.
- Liquid-Based Cytology (LBC): Using a cervical broom-type brush, samples were obtained from the ectocervix and endocervix. The brush head was then detached and rinsed into a vial containing preservative solution. The vial was processed using an automated LBC system to produce a thin, uniform cellular monolayer on slides, followed by Papanicolaou staining.

Both CPS and LBC samples were prepared for each patient.

Sample Processing: Slides prepared by both methods were examined under light microscopy by two independent cytopathologists blinded to each other's results. Cytological diagnoses were categorized according to the Bethesda System 2014. For histopathology, colposcopically directed cervical biopsies were obtained from the same patients, fixed in 10% buffered formalin, processed, and stained with hematoxylin and eosin (H&E). Histopathological findings were classified as chronic cervicitis, CIN I, CIN II, CIN III, or invasive carcinoma.

Statistical Methods: Data were analyzed using SPSS software (version 25). Descriptive statistics were applied to summarize demographic and clinical characteristics. The diagnostic accuracy of CPS and LBC was evaluated by calculating sensitivity, specificity, PPV, NPV, and overall diagnostic accuracy with histopathology as the reference standard. McNemar's test and Chi-square test were used to compare proportions. A p-value <0.05 was considered statistically significant.

Data Collection: Data were recorded in a predesigned proforma including patient demographics, clinical presentation, cytological findings from CPS and LBC, and histopathological diagnosis. The results of cytology were correlated with biopsy findings to determine diagnostic performance.

RESULTS

[Table 1] compares the head-to-head detection of cervical intraepithelial neoplasia (CIN) at or above the LSIL threshold between liquid-based cytology (LBC) and conventional Pap smear (CPS) among 60 women. LBC identified 26 cases as positive (43.3%, 95% CI: 31.6-55.9%), whereas CPS detected 20 positives (33.3%, 95% CI: 22.7-45.9%). Although LBC yielded a higher detection rate, the difference between the two methods was not statistically significant on McNemar's test (χ^2=1.56, p=0.210). Negative cytology results were correspondingly more frequent with CPS (66.7%) than LBC (56.7%), suggesting that LBC tended to flag more abnormal cases, though without clear statistical superiority in this dataset.

Table 1: Head-to-head detection of CIN (≥LSIL) by cytology method (N=60)

Outcome	LBC n (%) [95% CI]	CPS n (%) [95% CI]	Test of significance
Cytology positive (≥LSIL)	26 (43.3%) [31.6-55.9%]	20 (33.3%) [22.7-45.9%]	McNemar χ^2=1.56; exact p=0.210
Cytology negative	34 (56.7%)	40 (66.7%)	-

Notes: Same-patient paired comparison. Exact McNemar p shown; continuity-corrected χ^2 also reported.

Table 2: Diagnostic cross-tabs versus histopathology (gold standard)

2A. LBC vs histopathology (N=60)			
Cytology (LBC)	**Histopath CIN+**	**Histopath CIN−**	**Row total**
Positive	19 (31.7%)	7 (11.7%)	26 (43.3%)
Negative	3 (5.0%)	31 (51.7%)	34 (56.7%)
Column total	22 (36.7%)	38 (63.3%)	60 (100%)
Association: χ^2 (Yates) = 23.50, p=1.25×10⁻⁶; Odds Ratio = 28.05 (95% CI 6.46-121.76).			
2B. CPS vs histopathology (N=60)			
Cytology (CPS)	**Histopath CIN+**	**Histopath CIN−**	**Row total**
Positive	16 (26.7%)	4 (6.7%)	20 (33.3%)
Negative	6 (10.0%)	34 (56.7%)	40 (66.7%)
Column total	22 (36.7%)	38 (63.3%)	60 (100%)
Association: χ^2 (Yates) = 21.54, p=3.47×10⁻⁶; Odds Ratio = 22.67 (95% CI 5.60-91.71).			

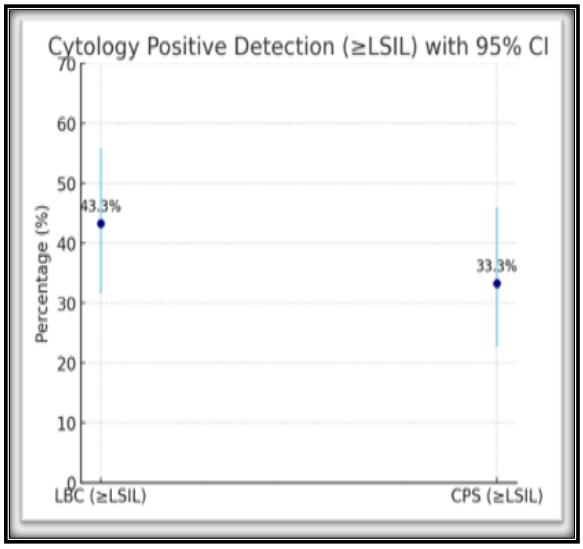

Figure 1

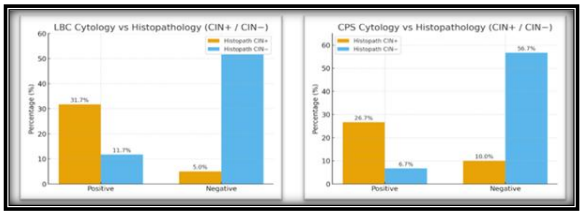

Figure 2: A&B

[Table 2] presents the diagnostic performance of each cytological method against histopathology, the gold standard. For LBC, 19 of 22 histopathologically confirmed CIN cases were correctly identified (sensitivity 86.4%), while 31 of 38 non-CIN cases were negative (specificity 81.6%). Only 3 CIN cases were missed by LBC, and 7 false positives occurred. The association between LBC and histopathology was highly significant (χ^2=23.50, p<0.000001), with an odds ratio of 28.05 (95% CI: 6.46-121.76),

indicating a strong likelihood that positive cytology reflected true CIN. For CPS, 16 of 22 CIN cases were detected (sensitivity 72.7%) and 34 of 38 negatives were correctly classified (specificity 89.5%). Six CIN cases were missed, and 4 false positives occurred. This method also showed a highly significant correlation with histopathology (χ^2=21.54, p<0.00001; OR=22.67, 95% CI: 5.60-91.71). Taken together, both methods demonstrated good diagnostic association with histopathology, but LBC showed slightly better sensitivity, while CPS performed marginally better in specificity.

Table 3: Smear adequacy and morphology/quality (paired; N=60)

Parameter (criterion)	LBC n (%) [95% CI]	CPS n (%) [95% CI]	Paired test
Satisfactory for evaluation	57 (95.0%) [86.3-98.3%]	49 (81.7%) [70.1-89.4%]	McNemar χ^2=4.90; exact p=0.021
EC/TZ component present	46 (76.7%) [64.6-85.6%]	37 (61.7%) [49.0-72.9%]	McNemar χ^2=4.27; exact p=0.035
Obscured by blood/inflammation ≥50% fields (undesirable)	5 (8.3%) [3.6-18.1%]	14 (23.3%) [14.4-35.4%]	McNemar χ^2=4.92; exact p=0.022
Adequate cellularity (≥5,000 cells)	54 (90.0%) [79.9-95.3%]	41 (68.3%) [55.8-78.7%]	McNemar χ^2=8.47; exact p=0.002
Unsatisfactory smear	3 (5.0%) [1.7-13.7%]	11 (18.3%) [10.6-29.9%]	McNemar χ^2=4.90; exact p=0.021

Notes: Exact McNemar p values shown; Wilson 95% CIs for proportions in brackets.

Table 3 highlights differences in smear adequacy and morphology between LBC and CPS in paired samples. LBC significantly outperformed CPS in adequacy, with 95.0% of smears satisfactory versus 81.7% for CPS (p=0.021). Transformation zone/endocervical components were more frequently present in LBC (76.7%) than CPS (61.7%) (p=0.035). Importantly, obscuring factors such as blood or inflammation were far less common in LBC smears (8.3%) than in CPS (23.3%), with this difference being statistically significant (p=0.022). Adequate cellularity (≥5,000 cells) was also more consistently achieved in LBC (90.0%) compared with CPS (68.3%), showing strong significance (p=0.002). The rate of unsatisfactory smears was markedly lower in LBC (5.0%) than CPS (18.3%), again statistically significant (p=0.021). These findings underline the superior quality and interpretability of LBC preparations, which reduce sampling artifacts and enhance diagnostic reliability.

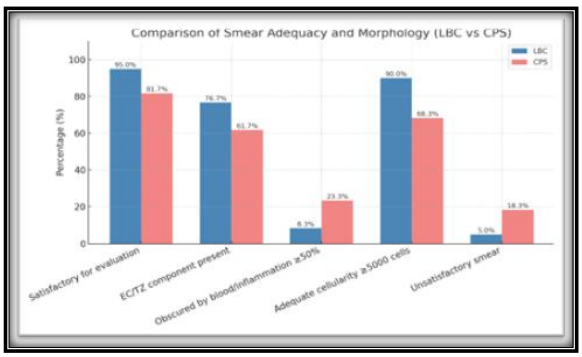

Figure 3:

Table 4: Diagnostic accuracy metrics versus histopathology (with 95% CIs) and between-method tests

Metric	LBC % [95% CI]	CPS % [95% CI]	Between-method comparison
Sensitivity (CIN+)	86.4% [66.7-95.3%]	72.7% [51.8-86.8%]	McNemar χ^2=0.57; exact p=0.453
Specificity (CIN−)	81.6% [66.6-90.8%]	89.5% [75.9-95.8%]	McNemar χ^2=0.44; exact p=0.508
PPV	73.1% [53.9-86.3%]	80.0% [58.4-91.9%]	χ^2 (Yates)=0.04; p=0.844
NPV	91.2% [77.0-97.0%]	85.0% [70.9-92.9%]	χ^2 (Yates)=0.21; p=0.650
Accuracy	83.3% [72.0-90.7%]	83.3% [72.0-90.7%]	McNemar χ^2=0.00; p=1.000

[Table 4] summarizes the diagnostic accuracy of LBC and CPS against histopathology. LBC showed higher sensitivity (86.4%) compared to CPS (72.7%), whereas CPS had slightly higher specificity (89.5% vs 81.6%). The positive predictive value was marginally greater for CPS (80.0%) than LBC (73.1%), while the negative predictive value was higher for LBC (91.2% vs 85.0%). Diagnostic accuracy was identical for both methods at 83.3%. However, none of these differences reached statistical significance (p>0.05), indicating that LBC and CPS performed comparably in terms of overall diagnostic efficacy, with LBC offering better sensitivity and NPV and CPS showing slightly higher specificity and PPV.

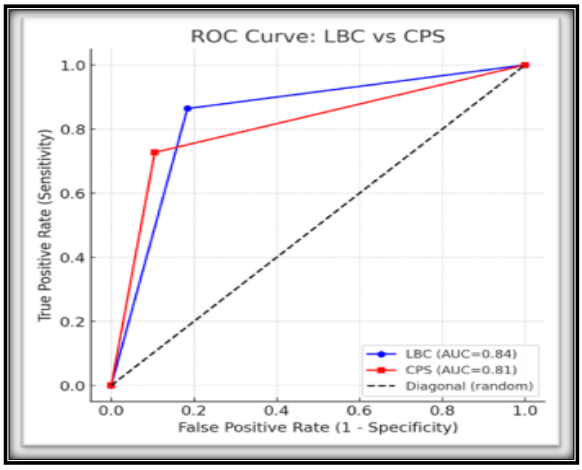

Figure 4

DISCUSSION

In the paired, head-to-head comparison [Table 1], LBC yielded a higher crude detection of ≥LSIL than CPS (43.3% vs 33.3%), but the difference was not statistically significant (McNemar p=0.210). This pattern is consistent with several large evaluations where gains in detection with LBC were modest and often non-significant once study quality and paired design were accounted for. Mwafaq H et al.(2025),[6] randomized assessment reported no statistically significant improvement in sensitivity for CIN2+ with LBC compared with conventional cytology, despite fewer inadequate smears in LBC arms. Likewise, the Netherlands screening study by Hashmi AA et al (2020),[7] found no superiority of LBC over CPS in relative sensitivity or PPV for CIN2+, underscoring that apparent detection differences may be small and sample-size sensitive. Meta-analytic syntheses have also concluded that LBC is neither more sensitive nor more specific than CPS for high-grade disease overall, particularly in high-quality studies. These data collectively mirror Table 1 finding-numerically higher positivity with LBC, but without clear statistical superiority at N=60.

When benchmarked against histopathology [Table 2], LBC showed higher sensitivity (86.4%) and slightly lower specificity (81.6%) than CPS (72.7% and 89.5%, respectively). This "trade-off" has been described previously: some programs adopting LBC reported more cytology-positive calls (raising sensitivity) with a small offset in specificity or PPV. For example, the Swedish program analysis Trzeszcz M et al (2021),[8] reported a higher yield of histologic high-grade lesions after LBC adoption; conversely, randomized and program-level studies such as Maheshwari Y et al (2023),[9] observed broadly comparable sensitivities between methods, with LBC sometimes generating more positives and thus a lower PPV. odds ratios (LBC OR 28.05; CPS OR 22.67) indicate a strong association with true disease for both methods, aligning with the overall literature that both platforms are clinically useful and that any sensitivity advantage for LBC-where present-tends to be incremental rather than transformative.

Quality and adequacy metrics [Table 3] show the clearest and most consistent edge for LBC: significantly higher rates of satisfactory smears, EC/TZ representation, and adequate cellularity, with fewer samples obscured by blood/inflammation and a markedly lower unsatisfactory rate. This profile closely matches many observational and programmatic reports, where LBC improves slide quality, reduces obscuring elements, and lowers unsatisfactory rates-features long cited as the principal operational advantage of LBC. Aboobacker KK et al (2020),[10] noted improved downstream detection after LBC implementation in Sweden, and multiple hospital-based series (including recent Indian cohorts) confirm better adequacy and cleaner backgrounds with LBC. That said, high-quality systematic reviews Andola SK et al (2024),[11] caution that reductions in unsatisfactory rates and accuracy gains may attenuate when study design and laboratory effects are rigorously controlled; some analyses even suggested no clear reduction in inadequacy in the highest-quality strata. paired, same-patient findings nonetheless align with the practical laboratory experience that LBC provides more interpretable slides with fewer technical pitfalls.

Contextualizing to Indian practice, several institutional studies report that LBC improves adequacy and reduces unsatisfactory smears, often with small improvements in detection-yet overall diagnostic performance relative to CPS may be similar, and cost remains a key determinant. Sutrakar SK et al (2025),[12] found LBC primarily superior in lowering unsatisfactory rates, while arguing that CPS is more feasible economically in many Indian settings. More recent Indian series Bacanakgil BH et al (2021),[13] echo [Table 3] pattern-higher adequacy, cleaner backgrounds, and frequent (though not always statistically significant) upticks in epithelial abnormality detection on LBC-supporting interpretation that LBC's main advantages are operational and quality-related, with diagnostic accuracy broadly comparable to CPS at modest sample sizes.

In [Table 4], LBC demonstrated higher sensitivity (86.4%) and negative predictive value (91.2%) compared to CPS (72.7% and 85.0%, respectively), suggesting that LBC is more effective in identifying true CIN cases and ruling out disease. Conversely, CPS showed slightly better specificity (89.5% vs 81.6%) and PPV (80.0% vs 73.1%), indicating fewer false positives. The overall diagnostic accuracy, however, was identical for both methods (83.3%), and none of the differences were statistically significant. These findings align with Chun JW et al (2020),[14] who reported broadly comparable accuracy between LBC and CPS in a large randomized trial, and with Yu L et al (2022),[15] whose meta-analysis concluded that while LBC may improve smear adequacy, its diagnostic accuracy for CIN2+ is largely equivalent to CPS.

CONCLUSION

The present study demonstrates that both liquid-based cytology (LBC) and conventional Pap smear (CPS) show strong diagnostic association with histopathology for detecting cervical intraepithelial neoplasia (CIN). While LBC exhibited higher sensitivity and improved smear adequacy, CPS showed slightly higher specificity. Importantly, LBC consistently reduced unsatisfactory smears, improved cellular morphology, and minimized obscuring artifacts, thereby enhancing interpretability. Thus, LBC appears to be a superior

cytological technique in terms of quality and sensitivity, although CPS continues to provide reliable results and remains a cost-effective option in resource-constrained settings. Integration of LBC into cervical screening programs may enhance early detection of CIN, provided cost and infrastructure limitations are addressed.

Limitations

1. **Small sample size (N=60):** The modest number of participants may limit the statistical power and generalizability of the findings.
2. **Single-center design:** Results may not fully reflect variations in population characteristics or laboratory practices across different regions.
3. **Short study duration:** Long-term follow-up and repeat cytology/biopsy correlation were not performed, restricting assessment of progression or regression of lesions.
4. **Resource bias:** The study did not include a cost-effectiveness analysis, which is crucial in the Indian healthcare context where affordability influences choice of screening method.
5. **Exclusion criteria:** Pregnant women and those with recent cervical procedures were excluded, potentially limiting applicability to broader populations.

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