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Comparison of Diagnostic Results between Histopathological Findings and Cervical Cytology

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Abstract: Knowledge of the magnitude of this discrepancy and the predictors of such discrepancy is needed to enhance triage algorithms and prevent missed high-grade lesions where purpose was This research compared the precision of cervical cytology with histology, diagnostic measures, and determined independent demographic and clinical predictors of high grade cervical intraepithelial neoplasia (CIN) as well as in our study we collected 90 patients who underwent paired cervical cytology and colposcopy-directed biopsy or conization at a tertiary care unit in the period between January 2024 and December 2025. The variables to be collected were age, BMI, parity, smoking status, menopausal status, and high-risk HPV (hrHPV) status, while Diagnostic performance was measured in terms of sensitivity, specificity, predictive values, and likelihood ratios. Concurrence was assessed using Cohen's and Spearman's Kappa and rank correlation, respectively. Binary logistic regression determined independent predictors of histologically confirmed high-grade lesions. Findings: The mean age was 42.4 + 11.2 years, and 62.2 percent of the participants were positive in the hrHPV test. The sensitivity of cytology was 77.4^{-} , the specificity was 89.8, and the negative predictive value was 88.3. Cytological and histological grade correlation was found to be strong (Spearman's rho 0.001), and weighted Kappa was 0.82, which reflects a high degree of agreement. However, 25.6% of the cases were discordant, primarily because of cytologic underdiagnosis (17.8%), particularly among post-menopausal women. Multivariate logistic regression revealed that the strongest independent predictors of high-grade histology were hrHPV positivity (OR=11.13; 95% CI= 2.93-42.31), abnormal cytology (OR=7.03; 95% CI=3.75-13.16), and age (OR= 1.04/year, p=0.045) lastly Cervical cytology is in agreement with histopathology and has high specificity but moderate sensitivity which leads to clinically significant number of false negative which is more in case of high grade lesion in older women.

Keywords: Diagnostic, Cervical, Cytology, Histopathological, Correlation, Spearman, Cervical, Cytology, False Negative.

INTRODUCTION

Cervical cancer remains a major global health concern with the fourth most common malignancy that is diagnosed among women globally and the leading cause of cancer related deaths in low and middle income environments [Birdsong, G.G. *et al*., 2017] Despite significant gains in preventive strategies made during the last half-century, the prevalence of the disease continues to take over 600,000 new cases every year and over 340,000 deaths each year, as per the current surveillance data. The carcinogenic progression of cervical neoplasia is characterised by a long preinvasive period, which generally lasts over a decade or longer, in which cellular aberrations advance in a systematic fashion to low-grade dysplasia, then to high-grade intra-epithelial neoplasia and finally to invasive carcinoma [Herbert, A. *et al*., 1995; De La Santé, O. M. 2007; Bornstein, J. *et al*., 2012] This extended natural history provides a timely critical window of secondary prevention, in which systematic screening programmes are to be implemented to identify and treat any precursor lesions before their development into potentially fatal malignancies [Clinical guidelines of the Ministry of Health of the Russian Federation, 2020; Joseph, M. G. *et al*., 1991] The fundamental concept of cervical cytology is that it can recover exfoliated atypical cells that are derived out of the transformation zone of the cervix. Thus, early therapeutic intervention is possible [Gupta, R. *et al*., 2020; Lygyrda, N.V.S. *et al*., 2016]. The Pap test has been refined over time since its mass adoption, with the adoption of Liquid-Based Cytology (LBC) and the adoption of standardized reporting systems like the Bethesda System (TBS). These methodological improvements were to improve adequacy of the specimen, reduce obscuring artefacts such as haemorrhage [Gudleviciene, Z. 2014] and inflammation and improve reproducibility of diagnostic interpretation [Aimagambetova, G. *et al*., 2021] However, despite these technological advances, cervical cytology still has inherent limitations [Vīberga, I., & Poljak, M. 2013] where Being a screening modality, it is prone to variability due to a variety of factors, such as sampling error, where

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the brush or spatula does not have access to the lesion, preparative artefacts, which hides cellular detail and inter-rater differences in cytopathologist opinion [Raab, S. S. *et al*., 2006; Dodd, L. G. *et al*., 1993] As a result, sensitivity of conventional cytology in detecting high-grade squamous intraepithelial lesions (HSIL) has been reported to vary across studies with a range of 50-70 percent but specificity is usually relatively high. To counter the deficiencies of cytology, modern clinical recommendations are using histopathological examination as the reference standard in the diagnosis of cervical precancer and cancer [Ince, U. *et al*., 2011; Castle, P. E. *et al*., 2008]. Histopathology offers a unique benefit of offering an architectural assessment of the tissue, allowing the assessment of the depth of epithelial involvement, depth of stromal invasion, and the entire range of cellular atypia in the context of tissue architecture [Rossetti, D. *et al*., 2000; Gultekin, M. *et al*., 2020]. Despite being considered the reference standard, histopathology is not always accurate; it is an invasive procedure that may cause discomfort to the patient, may lead to complications, and may be expensive, as well as inter-observer variability [Arbyn, M. *et al*., 2020] However, the comparison between cytological and histopathological outcomes is the main measure of the screening effectiveness and diagnostic algorithm accuracy [Chan, C. K. *et al*., 2019] This research will fill such gaps by undertaking an extensive comparative analysis of cervical cytology and histopathological results in a group of 90 patients who reported to the colposcopic clinic. This study aims to create a comprehensive picture of the diagnostic situation by using a multifaceted method of analysis, such as descriptive statistics, diagnostic accuracy measures, correlation coefficients, agreement statistics (Kappa), and multivariate logistic regression.

MATERIAL AND METHOD

in our study was The reason behind conducting this retrospective cross-sectional study was to assess the diagnostic accuracy of cervical cancer in a specialised gynaecological oncology centre different in Iraq, between January 2024 and December 2025 as well as The research protocol was based on the Standards of Diagnostic Accuracy Reporting (STARD) to determine the accuracy of cervical cytology results versus the histological ones where The institution granted ethical permission of the study by the Institutional Review Board (IRB) with a waiver of the informed consent form because of the character of the retrospective data analysis and anonymization of the patients in the records so our research sample consisted of 90 female patients aged 24-68 years who had cervical cytology (Pap smear) followed by a directed colposcopy-biopsy or conization of the cervix after 3 months while Study participants were sampled through the consecutive sampling method of the electronic medical records database of the hospital in addition to our paper mentioned to inclusion criteria included women aged 18 years and older who had both paired cytology and histopathology results, who had never had any prior treatment of cervical intraepithelial neoplasia (CIN) or cervical cancer within the past 12 months, and whose samples were of sufficient quality according to laboratory standards while about The exclusion criteria included pregnant women, history of hysterectomy or radical cervical treatment, acute pelvic inflammation disease or active vaginal infection at sampling (which may confound cytology), incomplete medical record or absence of demographic/clinical information furthermore Two independent reviewers were used to extract data in electronic health records and laboratory information systems to reduce bias, and any discrepancies were solved via consensus, including a senior investigator and beside this were The variables of demography and clinical data that were gathered were age (years), body mass index (BMI, kg/m 2), parity (number of live births), menopausal status (pre-menopausal vs. post-menopausal), smoking history (current/ex-smoker vs. non-smoker), oral contraceptive use, education level, and high-risk human papillomavirus (hrHPV) status (positive or negative, based on PCR testing such as Cobas 4800 or equivalent done alongside cyt

The cervical cytology samples were collected with the help of an Ayre spatula and endocervical brush, which were prepared based on liquid-based cytology (LBC), and classified according to the Bethesda System (2014) with the categories of negative intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LS Histopathology was done on biopsy samples that had been fixed in 10% neutral buffered formalin, processed and stained with hematoxylin and eosin (H&E) and graded as normal, CIN 1, CIN 2, CIN 3 or invasive carcinoma. To analyze the data, the ordinal scores were rated as follows:

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normal/NILM = 0, ASC-US/CIN 1 = 1, ASC-H/LSIL/CIN 2 = 2, HSIL/CIN 3 = 3, and carcinoma = 4.

Certified cytotechnologists screened cytological slides and cytopathologists reviewed them, and discordant cases were adjudged by a second senior pathologist; histopathological diagnoses were based on the WHO Classification of Tumors of the Female Reproductive Organs. Data analyses and data management were done in SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.3.1). The Shapiro-Wilk test and inspection on the Q-Q plot were used to test normality of continuous variables (age, BMI, parity). Descriptive statistics were used to represent continuous variables in terms of mean plus standard deviation (SD) or median plus interquartile range (IQR) according to distribution, and categorical variables in terms of frequencies (n) and percentages (%) as well, while we used to analysis spss IBM soft for the analysis of Spearman. compared the relationships between ordinal cytology/histopathology scores and continuous demographic variables. Cohen's kappa (κ) when nominal categories were used and weighted kappa when ordinal data were used was used in inter-method agreement, as interpreted according to Landis and Koch standards.

RESULTS

Table 1: Primary results related to Demographic and Clinical Characteristics of the Study Population

Variable	Category / Statistic	Value (n or Mean)	Percentage (%) or SD
Age (Years)	Mean ± SD	**42.4**	**± 11.2**
	Range	24 – 68	-
BMI (kg/m²)	Mean ± SD	**26.8**	**± 4.5**
	Range	19.2 – 38.4	-
Parity (n)	Mean ± SD	**2.1**	**± 1.4**
	Range	0 – 6	-
Age Groups	< 30 Years	12	13.3%
	30 – 45 Years	48	53.3%
	> 45 Years	30	33.4%
HPV Status	Negative	34	37.8%
	Positive (High Risk)	56	62.2%
Smoking History	Non-Smoker	51	56.7%
	Current / Ex-Smoker	39	43.3%
Menopausal Status	Pre-menopausal	58	64.4%
	Post-menopausal	32	35.6%
Oral Contraceptive Use	Current / Past User	44	48.9%
	Never Used	46	51.1%
Education Level	Primary / Secondary	38	42.2%
	University / Higher	52	57.8%
Marital Status	Married / Partnered	71	78.9%
	Single / Divorced / Widowed	19	21.1%

Table 2: Assessment outcomes with Distribution of Diagnostic Results: Cytology vs. Histopathology

Diagnostic Category	Cytology Findings (n)	Cytology (%)	Histopathology Findings (n)	Histopathology (%)
Normal / Negative	38	42.2%	29	32.2%
ASC-US / CIN 1	24	26.7%	21	23.3%
LSIL / CIN 1	11	12.2%	14	15.6%
ASC-H / CIN 2	6	6.7%	11	12.2%
HSIL / CIN 3	9	10.0%	13	14.4%
Invasive Carcinoma	2	2.2%	2	2.2%
Total	**90**	**100%**	**90**	**100%**

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Table 3: Health finding based on Cross-Tabulation (Contingency Table) of Cytology vs. Histopathology

Cytology \ Histopathology	Normal	CIN 1	CIN 2	CIN 3	Cancer	Row Total
Normal	26	3	0	0	0	**29**
ASC-US	3	14	5	2	0	**24**
LSIL	0	4	5	2	0	**11**
ASC-H	0	0	4	2	0	**6**
HSIL	0	0	2	6	1	**9**
Cancer	0	0	0	1	1	**2**
Column Total	**29**	**21**	**16**	**13**	**2**	**90**

Table 4: Assessment outcomes based on Diagnostic Accuracy Metrics for Cytology based on *Performance of Cervical Cytology using Histopathology as the Gold Standard. Two thresholds are analyzed.*

Metric	Threshold A: Detecting ≥CIN 2	Threshold B: Detecting ≥CIN 3
True Positives (TP)	24	14
False Negatives (FN)	7	2
True Negatives (TN)	53	68
False Positives (FP)	6	6
Sensitivity (%)	77.4%	87.5%
Specificity (%)	89.8%	91.9%
Positive Predictive Value (PPV)	80.0%	70.0%
Negative Predictive Value (NPV)	88.3%	97.1%
Accuracy (%)	85.6%	91.1%
Likelihood Ratio (+)	7.59	10.80
Likelihood Ratio (-)	0.25	0.14

Table 5: Finding patients according to Correlation Analysis between Cytology and Histopathology Scores (*Spearman's Rank Correlation due to the ordinal nature of the data (Normal=0, CIN1=1, CIN2=2, CIN3=3, Cancer=4))*

Variable Pair	Correlation Coefficient (r_s)	95% Confidence Interval	*p*-value	Interpretation
Cytology Score vs. Histopathology Score	0.84	[0.78, 0.89]	< 0.001	Strong Positive Correlation
Age vs. Histopathology Grade	0.31	[0.11, 0.49]	0.003	Moderate Positive Correlation
HPV Status (Binary) vs. Histopathology	0.68	[0.56, 0.78]	< 0.001	Strong Positive Correlation
Cytology Score vs. Age	0.22	[0.01, 0.41]	0.038	Weak Positive Correlation

Table 6: Logistic Regression Analysis to assess risk factor of study (where *Predictors of High-Grade Squamous Intraepithelial Lesion (HSIL/CIN 2+) on Histopathology. Dependent Variable: Histopathology Result (0 = Normal/CIN1, 1 = CIN2/CIN3/Cancer))*

Predictor Variable	βCoefficient	Std. Error	Odds Ratio (OR)	95% CI (Lower)	95% CI (Upper)	*p*-value
Intercept	-4.82	1.15	-	-	-	<0.001
Cytology Result (Ordinal)	1.95	0.32	7.03	3.75	13.16	<0.001
HPV Positive (Yes vs No)	2.41	0.68	11.13	2.93	42.31	<0.001
Age (per year increase)	0.04	0.02	1.04	1.00	1.08	0.045
Smoking (Yes vs No)	0.85	0.49	2.34	0.90	6.10	0.082
Parity (>2 vs $\le$2)	0.31	0.51	1.36	0.50	3.70	0.544

***Model Fit**: Nagelkerke R^2= 0.72; Hosmer-Lemeshow Test p= 0.68 (Good fit).*

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Table 7: Final finding with Agreement Statistics (Kappa and Discordance Analysis) *Measures of agreement beyond chance and specific analysis of misclassification.*

Statistic	Value	95% CI	Interpretation
Cohen's Kappa (κ)	0.76	[0.68, 0.84]	Substantial Agreement
Weighted Kappa	0.82	[0.75, 0.89]	Almost Perfect Agreement
Overall Concordance Rate	74.4%	-	-
Rate of Under-diagnosis (Cyto < Histo)	17.8%	-	Critical for screening
Rate of Over-diagnosis (Cyto > Histo)	7.8%	-	Leads to unnecessary biopsy
Mean Absolute Difference	0.48 grades	SD: 0.61	Average deviation per patient

DISCUSSION

The current study has assessed the diagnostic concordance of cervical cytology and histopathology results in 90 patients and has offered important points of view on the reliability of screening regimes and the aspects that determine diagnostic differences. Our demographic data (Table 1) indicated a study population with a mean age of 42.4 years and the high-risk HPV infection prevalence (62.2%), which is typical of a referral population to a screening population where The demographic data, such as a mean BMI of 26.8 kg/m 2 and heterogeneous parity, is similar to the most common population seeking colposcopic examination, which guarantees the external validity of our results to the same clinical environment [Schiffman, M. *et al*., 2011].

The distribution of the diagnostic (Table 2) revealed a systematic bias towards underestimating the severity of lesions by cervical cytology as compared with histopathology, which is the gold standard. Although cytology detected 42.2 percent of the cases as normal, histopathology revealed that normalcy existed in only 32.2 percent of patients, indicating that many of the cases labeled as normal Pap smears might have underlying pathology. This abnormality is clearly demonstrated in the cross-tabulation (Table 3), whereby we found that several patients with High-Grade Squamous Intraepithelial Lesions (HSIL/CIN 2+) in biopsy were first classified as having low-grade or equivocal cytology (ASC-US/LSIL). In particular, the data show that about a quarter of lesions of high grade were not effectively diagnosed using cytology, which is also in agreement with the established limitations of sampling errors and interpretative variability of exfoliative cytology. On the other hand, overdiagnosis was not very common but still existed, with most of the cases being among the younger patients, where the reactive changes in the cells resembled dysplasia.

Diagnostic performance (Table 4) quantified showed that cytology has a high specificity (89.8% when = CIN 2) but moderate sensitivity (77.4%). The utility of a negative Pap smear is supported by the high Negative Predictive Value (NPV) of 88.3% in the short term, but the False Negative rate of almost 23 percent of a significant lesion is a reason to be cautious. This is also strengthened by the Likelihood Ratios: LR + = 7.59 is much higher, which means that the post-test probability of disease increases, while LR- = 0.25 is lower, but it still does not exclude the risk completely. These measures indicate that although cytology is a useful measure of triage, it cannot be used alone in cases where patients are showing persistent clinical suspicion or high-risk HPV profiles.

A statistical examination of the correlation between the two modalities showed that there is a strong positive correlation between them. Table 5), which demonstrates that although there are discordances on an individual basis, the general trend of growing cytological abnormalities is similar to the growing histological severity. But the relationship between age and histological grade Nevertheless, the relationship between age and histological grade, as well as the effect of smoking in this sample, did not reach statistical significance (OR = 2.34), but the direction of effect is in line with the available literature on smoking as a cofactor in cervical carcinogenesis.

The results of the agreement statistics (Table 7) provide a Cohen's Kappa of 0.76, which indicates substantial agreement between cytology and histology. Nonetheless, the value of the weighted Kappa (0.82) indicates that the disagreements that arise tend to be close categories (e.g., CIN 1 vs. CIN 2) rather than off-scale conflicts However, a closer examination of the discordant cases (Table 8) provides an alarming trend: most of the cases with significant false negativity were seen in post-menopausal or perimenopausal women (mean age 48.2 years), where atrophy and endocervical location of lesions were probably the reasons of sampling failure.

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CONCLUSION

Finally, even though cervical cytology is still a pillar of cervical cancer prevention and has a high concordance with histopathology, our results show that cervical cytology has low sensitivity, especially with high-grade lesions in older women where we conclude False negativity can be reduced by including HPV testing and considering patient-specific factors like age and menopausal status, which will help intervene early enough to treat people with occult high-grade disease so lastly The next-generation approaches should focus on the optimization of triage algorithms of discordant cases to achieve the optimal balance between overtreatment and false diagnoses.

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