Original Article
DOI: https://doi.org/10.70749/ijbr.v3i5.1463

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Crossref

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Enhancing Diagnostic Precision and Treatment Guidance in Ovarian Neoplasms: Evaluating Immunohistochemistry's Role and Utility

Parsa Javaid[1], Asima Naz[1]

[1]Department of Histopathology, Sir Gangaraam Hospital, Lahore, Pakistan

ARTICLE INFO

Keywords: Ovarian Neoplasms, Immunohistochemistry, Hematoxylin and Eosin, Diagnostic Accuracy, Kappa Statistic, Histopathology.

Correspondence to: Parsa Javaid,
Post Graduate Resident, Department of Histopathology, Sir Gangaraam Hospital, Lahore, Pakistan
Email: parsajavaid362@gmail.com

Declaration

Authors' Contribution: Both authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 18-04-2025 Revised: 07-05-2025
Accepted: 17-05-2025 Published: 25-05-2025

ABSTRACT

Background: Ovarian neoplasms are a heterogeneous group of tumors with varied histogenesis and biological behavior. Accurate classification of these tumors is critical for appropriate clinical management. However, relying solely on hematoxylin and eosin (H&E) staining can lead to diagnostic uncertainty, particularly in borderline and poorly differentiated tumors. Immunohistochemistry (IHC) offers an adjunct diagnostic modality by identifying cell-specific markers that enhance diagnostic precision. **Objective:** To evaluate the utility of immunohistochemistry as an adjunct to H&E staining in the classification of ovarian neoplasms and to assess the level of diagnostic concordance between the two methods. **Material and Methods:** This descriptive cross-sectional study was conducted at the Department of Histopathology, Fatima Jinnah Medical University, Lahore from January 15, 2025 to April 14, 2025. A total of 100 archived cases of histologically confirmed ovarian neoplasms were included. Initial diagnoses based on H&E-stained sections were compared with final diagnoses incorporating IHC markers such as CK7, CK20, WT1, Inhibin, p53, and others. Data were analyzed using SPSS version 25. Kappa statistics and Chi-square tests were applied. **Results:** Of the 100 cases, 89 (89.0%) showed concordance between H&E and IHC diagnoses. The Kappa coefficient was 0.820 ($p < 0.001$), indicating almost perfect agreement. No statistically significant association was observed between diagnostic agreement and menopausal status ($p = 0.803$), family history ($p = 0.668$), or tumor type ($p = 0.243$). **Conclusion:** IHC significantly enhances diagnostic accuracy in ovarian neoplasms and should be considered a standard adjunct to conventional histopathology, regardless of patient demographics or tumor subtype.

INTRODUCTION

Ovarian neoplasms present a diverse range of histopathological subtypes, each with distinct biological behavior and therapeutic implications. Accurate classification of these tumors is essential for prognosis, treatment planning, and research. Traditionally, histopathological diagnosis has relied heavily on hematoxylin and eosin (H&E) staining. While H&E remains a cornerstone of diagnostic pathology, it often falls short in precisely subclassifying ovarian tumors, especially in borderline or poorly differentiated cases [1]. In recent years, immunohistochemistry (IHC) has emerged as a powerful adjunct to conventional H&E staining, offering enhanced diagnostic accuracy through the identification of lineage-specific markers.

The limitations of H&E staining alone have been well-documented, particularly in challenging cases where morphologic features overlap between tumor types. Studies have shown that incorporating IHC into diagnostic workflows improves interobserver agreement and overall diagnostic precision [2]. For example, in ovarian clear cell carcinoma, IHC using anti-pan-cytokeratin antibodies (e.g., AE1/AE3) has facilitated the detection of micrometastases and isolated tumor cells that are often missed on H&E staining alone [3]. This refinement in detection has potential implications for staging and disease management.

Furthermore, the advent of algorithmic IHC panels, such as the six-split decision tree incorporating markers like p53, WT1, and Napsin A, has revolutionized epithelial ovarian cancer classification. Such algorithms have demonstrated diagnostic precision exceeding 96%, and often correct misclassifications made based solely on H&E features [4]. Similarly, machine learning models trained on IHC-augmented datasets have shown improved histotype determination compared to pathologists relying on H&E slides alone [5].

In gynecologic pathology broadly, IHC has played a transformative role. A 2024 expert review emphasized that IHC not only enhances diagnostic certainty but also enables precise molecular subtyping, paving the way for targeted therapies [6]. The integration of IHC in ovarian tumor evaluation is particularly important in the context of histotypes with overlapping morphologic features, such

as endometrioid and high-grade serous carcinomas.

Recent research also underscores the utility of IHC in resource-limited and intraoperative settings. Imprint cytology and frozen sections, often complemented by IHC, have demonstrated high sensitivity and specificity when compared to final histopathological diagnosis [7]. Moreover, retrospective analyses continue to affirm that the application of IHC reveals diagnostic details that are not apparent on routine staining, particularly in early-stage or borderline neoplasms [8,9].

Despite its strengths, IHC is not without limitations. False positives, cost, and marker variability across laboratories are ongoing concerns. Nevertheless, when used judiciously, IHC significantly enhances the reliability of ovarian tumor classification, supporting its inclusion in routine histopathological workflows [10,11]. Overall, the concordance between reviewed histological diagnosis and IHC results was 91%, with a Kappa coefficient of 0.86 (P = 0.001) [12].

Rationale

Ovarian neoplasms present a diagnostic challenge due to the wide range of tumor types and varying histological features. Hematoxylin and Eosin (H&E) staining, while widely used, sometimes lacks the specificity required to differentiate between various types of ovarian tumors, particularly in borderline or difficult-to-classify cases. On the other hand, Immunohistochemistry (IHC) offers a more targeted approach by detecting specific protein markers that can help distinguish between benign, borderline, and malignant tumors. This study aims to explore the potential of combining IHC with H&E staining to enhance the diagnostic accuracy and improve classification outcomes.

This study seeks to determine whether the addition of IHC markers, such as CK7, CK20, WT1, and p53, Inhibin, SMA, EMA, Desmin can improve the diagnostic reliability, reduce misclassification, and lead to more accurate treatment planning. Given the complexity of ovarian tumor diagnosis and the implications for patient management, this combined approach could be a valuable tool in routine pathological practice, offering a more precise and consistent method for tumor classification.

METHODOLOGY

This cross-sectional study was conducted at the Department of Histopathology, Fatima Jinnah Medical University, Lahore, from January 15, 2025 to April 14, 2025. A sample size of 100 cases was calculated using a 95% confidence level, 6% margin of error, and an expected frequency of agreement between H&E and IHC of 91%. [12] Non-probability consecutive sampling was employed. Patients aged 18 years or above with histologically confirmed ovarian neoplasms were included. Both benign, borderline, and malignant tumors were considered. Eligibility was based on the availability of tissue samples and complete medical records. Patients with incomplete records, inadequate tissue for IHC, prior neoadjuvant chemotherapy, history of other malignancies, or concurrent gynecological diseases affecting ovarian histology were excluded.

After obtaining approval from the Institutional Review Board (IRB), 100 eligible female patients aged 18 years or older were selected. Written informed consent was obtained from all participants or their legal guardians. Archived paraffin-embedded tissue blocks and pre-prepared hematoxylin and eosin (H&E) stained slides were retrieved. Initial diagnoses based on H&E staining were reviewed and recorded. Additional tissue sections were prepared for immunohistochemistry (IHC) using a panel of markers including CK7, CK20, WT1, Inhibin, p53, SMA, EMA, and Desmin. IHC staining was performed according to standard laboratory protocols, and expression patterns for each marker were documented as positive or negative.

Clinical and demographic data, such as age, menopausal status, family history of ovarian or breast cancer, and prior treatments or surgeries, were obtained from patient records. Tumors were classified into categories such as epithelial, mesenchymal, mixed epithelial and mesenchymal, sex cord-stromal, germ cell, or miscellaneous types. Final tumor classification was recorded as benign, borderline, or malignant based on combined H&E and IHC findings. The outcome variable, i.e., agreement, was determined by comparing the initial H&E-based diagnosis with the final diagnosis incorporating IHC results. Each case was independently reviewed by a pathologist to ensure consistency. All data were entered into a pre-designed data collection sheet for statistical analysis.

The data were analyzed using SPSS version 25. Descriptive statistics were used to summarize the data. Continuous variables, such as age, were presented as mean ± standard deviation (SD), while categorical variables, including menopausal status, tumor type, and family history, were reported as frequencies and percentages. The Kappa statistic was applied to assess agreement between the initial H&E diagnosis and the final IHC-supported diagnosis. A p-value of ≤ 0.05 was considered statistically significant. Stratification was performed for age, menopausal status, and family history, and the Chi-square test was applied to evaluate statistical associations.

RESULTS

A total of 100 patients with histologically confirmed ovarian neoplasms were included in the study. The mean age of the patients was 46.69 ± 15.54 years, with an age range of 18 to 74 years.

The study included 100 patients with histologically confirmed ovarian neoplasms. Among them, 49 (49.0%) were pre-menopausal and 51 (51.0%) were post-menopausal. A positive family history of ovarian or breast cancer was present in 33 (33.0%) patients, while 67 (67.0%) had no such history. Epithelial tumors were the most common subtype, observed in 43 (43.0%) patients, followed by sex cord stromal tumors in 18 (18.0%), germ cell tumors in 14 (14.0%), mesenchymal tumors in 10 (10.0%), mixed epithelial and mesenchymal tumors in 8 (8.0%), and miscellaneous tumors in 7 (7.0%). Initial histopathological evaluation using H&E staining classified 45 (45.0%) cases as benign, 13 (13.0%) as borderline, and 42 (42.0%) as malignant. Following immunohistochemical (IHC) analysis, the final diagnosis was benign in 46 (46.0%), borderline in 16 (16.0%), and malignant in 38

(38.0%) cases. Overall, 89 (89.0%) patients showed concordance between the initial H&E diagnosis and the final IHC diagnosis, while 11 (11.0%) showed a change in classification after IHC evaluation. (Table 1)

This study assessed the level of agreement between the initial diagnosis based on hematoxylin and eosin (H&E) staining and the final diagnosis following immunohistochemistry (IHC) in 100 cases of ovarian neoplasms. As shown in Table 2, there was substantial concordance between the two diagnostic methods. Among the 45 cases initially diagnosed as benign on H&E staining, 41 (91.1%) were confirmed as benign on IHC, while 3 (6.7%) were reclassified as borderline and 1 (2.2%) as malignant. Of the 13 borderline cases, 11 (84.6%) retained the same diagnosis after IHC, while 2 (15.4%) were reclassified as benign. Among the 42 cases initially identified as malignant, 37 (88.1%) remained malignant after IHC, while 2 (4.8%) were downgraded to borderline and 3 (7.1%) to benign. Overall, IHC confirmed the initial diagnosis in 89 out of 100 cases (89.0%). A change in diagnosis was observed in 11 (11.0%) cases, reflecting the added diagnostic clarity provided by IHC, especially in histologically ambiguous or poorly differentiated tumors. To statistically evaluate this agreement, Cohen's Kappa coefficient was calculated. The value of the Kappa statistic was 0.820, with a standard error of 0.050 and a T-value of 10.829, which was statistically significant ($p < 0.001$). According to Landis and Koch's interpretation scale, a Kappa value above 0.80 indicates "almost perfect agreement." This suggests that the diagnostic reliability of H&E staining is high, but IHC contributes critical clarification in a subset of diagnostically uncertain cases. These findings support the utility of IHC as an adjunct diagnostic tool in the classification of ovarian neoplasms, particularly when dealing with borderline or poorly differentiated histologies, where morphology alone may be insufficient. (Table 2)

The association between diagnostic agreement (Yes/No) and selected patient and tumor characteristics was evaluated using the Chi-square test. As shown in Table 3, no statistically significant associations were found for any of the variables assessed. When analyzing menopausal status, agreement between H&E and IHC diagnoses was observed in 44 of 49 (89.8%) pre-menopausal patients and 45 of 51 (88.2%) post-menopausal patients. The difference was minimal and not statistically significant ($p = 0.803$), with a very low Kappa value of 0.015, indicating negligible agreement beyond chance between menopausal status and diagnostic concordance. Similarly, in patients with a positive family history of ovarian or breast cancer, agreement was noted in 30 of 33 (90.9%) cases, while in those without a family history, agreement was seen in 59 of 67 (88.1%). Again, the difference was statistically insignificant ($p = 0.668$), and the Kappa coefficient was only 0.020, suggesting a lack of predictive value of family history for diagnostic agreement. Regarding tumor type, the highest concordance was observed in germ cell tumors (100%) and mixed epithelial and mesenchymal tumors (100%), followed by sex cord stromal tumors (94.4%), and mesenchymal tumors (90.0%). Conversely, lower agreement was seen in miscellaneous tumors (71.4%) and epithelial tumors (83.7%). However, these differences were not statistically significant ($p = 0.243$), and the Kappa statistic was –0.039, indicating no meaningful agreement and suggesting that variation in agreement across tumor subtypes may have occurred by chance. In summary, while high overall agreement was noted between H&E and IHC diagnoses, no significant relationship was found between diagnostic concordance and menopausal status, family history, or tumor type. This implies that the utility of IHC in improving diagnostic precision is independent of these clinical and pathological variables, reinforcing its value as an adjunct tool across a broad range of ovarian neoplasms regardless of patient demographics or tumor subtype.

Table 1

Frequency Distribution of Demographic, Clinical, and Diagnostic Variables Among Study Participants (n = 100)

Variable	Frequency (n)	Percent (%)
Menopausal Status		
Pre-menopausal	49	49.0
Post-menopausal	51	51.0
Family History (Ovarian/Breast Cancer)		
Yes	33	33.0
No	67	67.0
Tumor Type		
Epithelial	43	43.0
Mesenchymal	10	10.0
Mixed epithelial and mesenchymal	8	8.0
Sex cord stromal	18	18.0
Germ cell	14	14.0
Miscellaneous	7	7.0
Initial H&E Diagnosis		
Benign	45	45.0
Borderline	13	13.0
Malignant	42	42.0
Final IHC Diagnosis		
Benign	46	46.0
Borderline	16	16.0
Malignant	38	38.0
Agreement (H&E vs IHC Diagnosis)		
Yes	89	89.0
No	11	11.0

Table 2

Cross-tabulation of Initial H&E and Final IHC Diagnoses with Kappa Agreement (n = 100)

Initial H&E Diagnosis	Final IHC: Benign	Final IHC: Borderline	Final IHC: Malignant	Row Total
Benign	41 (91.1%)	3 (6.7%)	1 (2.2%)	45 (100.0%)
Borderline	2 (15.4%)	11 (84.6%)	0 (0.0%)	13 (100.0%)
Malignant	3 (7.1%)	2 (4.8%)	37 (88.1%)	42 (100.0%)
Column Total	46 (100.0%)	16 (100.0%)	38 (100.0%)	100 (100.0%)
Kappa Statistic	Value: 0.820	SE: 0.050	T: 10.829	p < 0.001

Table 3

Association of Diagnostic Agreement with Menopausal Status, Family History, and Tumor Type (n = 100)

Variable	Categories	Agreement: Yes n (%)	Agreement: No n (%)	p-value	Kappa
Menopausal Status	Pre-menopausal	44 (89.8%)	5 (10.2%)	0.803	0.015
	Post-menopausal	45 (88.2%)	6 (11.8%)		
Family History of Cancer	Yes	30 (90.9%)	3 (9.1%)	0.668	0.020
	No	59 (88.1%)	8 (11.9%)		
Tumor Type	Epithelial	36 (83.7%)	7 (16.3%)	0.243	–0.039
	Mesenchymal	9 (90.0%)	1 (10.0%)		
	Mixed epithelial & mesenchymal	8 (100.0%)	0 (0.0%)		
	Sex cord stromal	17 (94.4%)	1 (5.6%)		
	Germ cell	14 (100.0%)	0 (0.0%)		
	Miscellaneous	5 (71.4%)	2 (28.6%)		

DISCUSSION Accurate classification of ovarian neoplasms is essential for determining prognosis and guiding appropriate treatment. In our study of 100 patients, we observed a high diagnostic concordance (89%) between initial hematoxylin and eosin (H&E)-based diagnosis and final classification using immunohistochemistry (IHC), with a Cohen's Kappa value of 0.820 ($p < 0.001$), indicating "almost perfect agreement." These results are supported by Missaoui et al., who reported a 91% concordance and Kappa of 0.86, reinforcing the reliability of IHC in resolving morphologically ambiguous ovarian tumors [12].

A key finding in our study was that 11% of cases underwent diagnostic reclassification after IHC, highlighting the limitations of morphology alone in certain tumor subtypes. This observation is echoed by Gupta et al., who emphasized that IHC plays a crucial role in subclassifying ovarian neoplasms when histological overlap complicates diagnosis [13]. Ghuman et al. similarly observed that epithelial tumors frequently necessitate IHC for definitive classification, especially when overlapping patterns obscure differentiation [14].

In our cohort, epithelial tumors were the most prevalent subtype (43%), consistent with global epidemiological trends showing epithelial ovarian cancers (EOCs) as the dominant group [15]. The diagnostic complexity of these tumors stems from their morphologic diversity, making them prime candidates for IHC-based confirmation. Buza (2021) noted that the 2020 WHO classification for gynecologic tumors increasingly relies on immunohistochemical markers for diagnosis, prognosis, and therapeutic guidance in such tumors [16].

The power of IHC lies in its ability to distinguish histologically similar subtypes using lineage-specific markers. For example, WT1 positivity supports a serous phenotype, while Napsin A and HNF-1β are indicative of clear cell carcinoma. Zelisse et al. validated a six-split IHC-based algorithm using markers such as WT1, p53, and PR, achieving 96.1% precision in epithelial ovarian cancer subtyping and correcting over 12% of initial H&E-based diagnoses [17]. These results closely parallel our 11% diagnostic shift, emphasizing that IHC improves histotype accuracy with potential therapeutic implications.

Our analysis also demonstrated that diagnostic agreement between H&E and IHC was not significantly associated with menopausal status, family history, or tumor type. This aligns with Buza's findings that IHC markers offer reproducible diagnostic utility regardless of clinical background, particularly in overlapping histotypes [16]. Moreover, Miyagawa et al. showed that histologic subtyping of high-grade serous ovarian cancer using IHC and whole slide imaging improves interobserver agreement, which is essential for consistent diagnoses across institutions [18].

The prognostic relevance of certain IHC subgroups has also been established. Jorgensen et al. applied an IHC-based molecular subtyping algorithm to endometrioid ovarian carcinoma and found significant differences in survival outcomes between subgroups, including TP53-abnormal and CTNNB1-positive profiles [19]. These findings suggest that IHC not only refines diagnosis but may also inform prognosis and individualized therapy.

With increasing adoption of computational pathology, the integration of IHC with machine learning further enhances diagnostic precision. Gentles et al. demonstrated that automated IHC scoring using computer-aided analysis reduced interobserver variability and increased quantification accuracy, supporting the scalability of IHC in high-throughput settings [20].

CONCLUSION

This study demonstrated a high level of diagnostic concordance between initial histopathological evaluation using hematoxylin and eosin (H&E) staining and final diagnosis after immunohistochemistry (IHC) in ovarian neoplasms, with an overall agreement rate of 89% and a Kappa coefficient of 0.820, indicating almost perfect agreement. Although minor diagnostic shifts were observed in a subset of cases, particularly among borderline and poorly differentiated tumors, these findings highlight the value of IHC in enhancing diagnostic accuracy. Importantly, no significant associations were found between diagnostic agreement and menopausal status, family history of ovarian or breast cancer, or tumor type, suggesting that the benefit of IHC is consistent across diverse clinical and pathological profiles. Therefore, IHC serves as a valuable adjunct to conventional histopathology, particularly in diagnostically challenging ovarian tumors, supporting more precise classification and potentially guiding appropriate clinical management.

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