RESEARCH PAPER

Cyto-Histopathological Correlation of Breast Lesions using the IAC Yokohama System

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ABSTRACT

Background

Breast carcinoma has become the leading malignancy among women in many Indian metropolitan areas. Fine Needle Aspiration Cytology (FNAC) is a rapid and cost-effective diagnostic tool, but its effectiveness depends on standardized reporting. The IAC Yokohama System (2016) was introduced to provide a uniform five-tier classification to improve communication between cytopathologists and clinicians.

Aim

The main aim of the study is to: 1. Apply the IAC Yokohama system for the diagnostic assessment and subsequent categorization of FNA samples and correlate them with histopathology examination (HPE); 2. Calculate ROM; 3. Calculate p-value.

Objectives

To categorize breast FNAC samples using the five-tier IAC Yokohama System. To perform cyto-histopathological correlation to assess the Risk of Malignancy (ROM) for each category. To determine the sensitivity, specificity, and overall diagnostic accuracy of the system.

Methods

A retrospective analysis was conducted over a two-year period (June 2019 to May 2021) involving 205 breast FNAC samples. Cases were classified according to the Yokohama categories: Insufficient (C1), Benign (C2), Atypical (C3), Suspicious (C4), and Malignant (C5). Histopathological correlation was available for 110 cases. Statistical analysis, including the calculation of sensitivity, specificity, and Risk of Malignancy (ROM), was performed using the chi-square test ($P < 0.001$).

Results

The majority of patients (46.8%) were in the 31–40 years age group. The distribution of categories was: C1 (6.89%), C2 (59.0%), C3 (3.28%), C4 (3.28%), and C5 (14.09%). The Risk of Malignancy (ROM) was 0% for C1, 3.07% for C2, and 100% for categories C3, C4, and C5. The system demonstrated a sensitivity of 95.3%, specificity of 100%, and an overall diagnostic accuracy of 94.5%.

Conclusions

The IAC Yokohama System provides a highly reliable and standardized framework for breast cytology reporting. It effectively stratifies the risk of malignancy, showing excellent specificity and sensitivity, which helps clinicians make informed decisions and reduces unnecessary surgical procedures.

Keywords: Cyto-Histopathological Correlation, IAC Yokohama System, Breast carcinoma, Fine Needle Aspiration Cytology, breast cytology.

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Introduction

Breast carcinoma is one of the most common malignancies among women in India, with a rising incidence attributed to urbanization and lifestyle changes, and has surpassed carcinoma cervix in several metropolitan areas. [1-5] Fine needle aspiration cytology (FNAC) is a key component of triple assessment and is widely used due to its simplicity, rapidity, and cost-effectiveness.[1]To standardize reporting, the International Academy of Cytology (IAC) introduced the Yokohama System in 2016, classifying breast cytology into five categories: insufficient, benign, atypical, suspicious, and malignant. This system improves diagnostic uniformity, enhances communication with clinicians, and enables estimation of the risk of malignancy (ROM). In the present study, breast

FNAC samples were categorized using the IAC Yokohama system and further analyzed. [1-5]

According to current trends, Indian women are more likely than women in the West to develop the disease at a younger age. The National Cancer Registry Program examined data from cancer registries for trends in cancer incidence between 1988 and 2013. The trend of BC has significantly increased across all population-based cancer registries [6]. In the registries of Bangalore (23.0% vs. 15.9%), Bhopal (23.2% vs. 21.4%), Chennai (28.9% vs. 17.7%), Delhi (21.6% vs. 20.3%), and Mumbai (24.1% vs. 16.0%), the cervix was the most common location of cancer in India in 1990. The situation had altered by 2000–2003, with the exception of Barshi's rural registry (16.9% vs. 36.8%), where breast cancer had surpassed all other cancer sites. The BC registrations in Bhopal, Chennai, and Delhi showed a notable upward trend. [7]

A study found that the 5-year overall survival rate was 95% for patients in stage I, 92% for those in stage II, 70% for those in stage III, and only 21% for those in stage IV [8]. Due to early age at beginning, late disease stage at presentation, delayed initiation of definitive care, and insufficient or fragmented treatment, the survival rate of patients with breast cancer in India is lower than in Western nations [9]. Early detection and prompt treatment are the most effective interventions for BC management, according to the World Cancer Report 2020 [10]. greater cancer stages at diagnosis were associated with greater BC treatment costs, according to a 2018 systematic review of 20 studies. As a result, early BC diagnosis can reduce treatment expenses. [11]

The main aim of the study is to; 1. Apply the IAC Yokohama system for the diagnostic; 2. Assessment and subsequent categorization of FNA samples and correlate them with histopathology examination (HPE); 3. calculate ROM; 4. Calculate p-value. Objectives: To categorize breast FNAC samples using the five-tier IAC Yokohama System. To perform cyto-histopathological correlation to assess the Risk of Malignancy (ROM) for each category. To determine the sensitivity, specificity, and overall diagnostic accuracy of the system.

Materials and Methods

A retrospective analysis was conducted in the Department of Pathology over a two-year period, from June 2019 to May 2021. The study population comprised 205 female patients presenting with palpable breast lesions who underwent Fine Needle Aspiration Cytology (FNAC). To maintain diagnostic integrity, exclusion criteria were applied to omit male patients, cases with a prior history of biopsy or surgery at the same site, and patients with incomplete clinical records.[2]

FNAC was performed using a 22- or 23-gauge needle, and multiple smears were prepared for each case. Air-dried smears were processed with May-Grünwald Giemsa (MGG) stain for cytoplasmic evaluation, while wet-fixed smears were stained with Papanicolaou (Pap) and Hematoxylin and Eosin (H&E) to facilitate detailed nuclear study. All cytological samples were categorized according to the five-tier International Academy of Cytology (IAC) Yokohama System. [4, 12]

Histopathological follow-up was available for 110 cases, which served as the gold standard for cyto-histological correlation. Based on these data, diagnostic indices—including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy—were calculated. The risk of malignancy (ROM) was also determined for each of the five categories.

Statistical analysis

Statistical analysis was performed using the chi-square test, with a P-value of < 0.05 considered to indicate statistical significance. [13, 14]

Results

A total of 205 breast FNAC cases were analyzed and classified into five categories as per the IAC Yokohama system following detailed cytological evaluation. The patients were in the age range of 11–80 years, with the highest number of cases presenting in the 31–40 years age group. The youngest patient diagnosed with malignancy was 33 years, and the maximum number of malignant cases (n=10) was also observed in the 31–40 years group, **Table 1.**

All cases were categorized into the five diagnostic groups of the Yokohama system, and their percentage distribution is summarized in **Table 2.** Histopathological correlation was available in 95 cases, which were used for cyto-histopathological comparison and calculation of the risk of malignancy (ROM) for each category. Diagnostic parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were computed using appropriate statistical methods.

Statistical significance was assessed using the chi-square test for categorical variables. A p-value of less than 0.05 was considered statistically significant. In the present study, the calculated p-value was 0.0001, indicating a highly significant association.

Table 1: Age distribution of FNA sample

Age range	No. of cases	Percentage(%)
11–20	24	11.7%
21–30	72	35.1%
31–40	96	46.8%
41–50	81	39.5%
51–60	27	13.2%
61–70	4	2.0%
71–80	1	0.5%

In this study, the maximum number of breast lesions was observed in the 31–40 years age group (96 cases), followed by 41–50 years (81 cases) and 21–30 years (72 cases), while fewer cases were seen in younger (11–20 years: 24 cases) and older age groups (51–60 years: 27 cases, 61–70 years: 4 cases, 71–80 years: 1 case), indicating that breast lesions are most common in the third and fourth decades of life. The higher incidence in the 31–40 years age group can be attributed to active reproductive age with increased hormonal influence, particularly estrogen and progesterone, leading to a higher occurrence of benign proliferative breast conditions, along with increased health awareness and detection during this period.

Table-2: Distribution of breast lesions according to laterality.

Laterality	Number	Percentage
Right	65	31.7%
Left	125	61.0%
Bilateral	15	7.3%
Total	205	100%

In this study, the majority of breast lesions were observed on the left side (61.0%), followed by the right side (31.7%), while bilateral involvement was relatively uncommon (7.3%). This indicates a clear predominance of left-sided breast lesions compared to the right, with only a small proportion of cases affecting both breasts simultaneously.
Left-sided predominance occurs because the left breast is usually slightly larger with more glandular tissue, making it more prone to lesions; minor anatomical and hormonal differences and possible sampling variation may also contribute.

Table 3: Distribution of Cases According to IAC Yokohama System

S. No.	IAC Yokohama Category	Total No. of Cases	Percentage (%)
1	Insufficient(C1)	21	6.89%
2	Benign(C2)	121	59.0%
3	Atypical(C3)	10	3.28%
4	Suspicious of malignancy(C4)	10	3.28%
5	Malignant(C5)	43	14.09%
	Total	**205**	**100%**

Table 3, In this study, the majority of cases were categorized as benign (59.0%), followed by malignant cases (14.09%), while insufficient, atypical, and suspicious categories constituted a smaller proportion (6.89%, 3.28%, and 3.28% respectively), indicating that most breast lesions evaluated under the IAC Yokohama system were non-malignant.

Benign lesions are more common due to hormonal influences during reproductive age, higher incidence of non-neoplastic conditions (fibroadenoma, fibrocystic change), and because screening detects many harmless lesions early,

Figure 1-4.

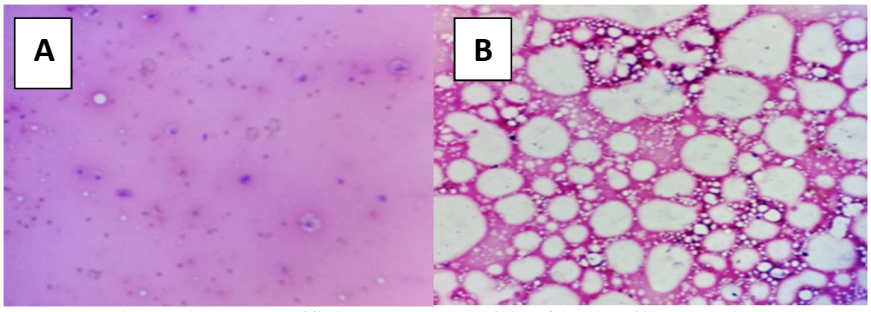

Figure 1: A): Insufficient category (C1); Giemsa 40x, showing only cyst macrophages, B): H&E 10x, corresponding histology showing fatty changes showing fibrocystic disease

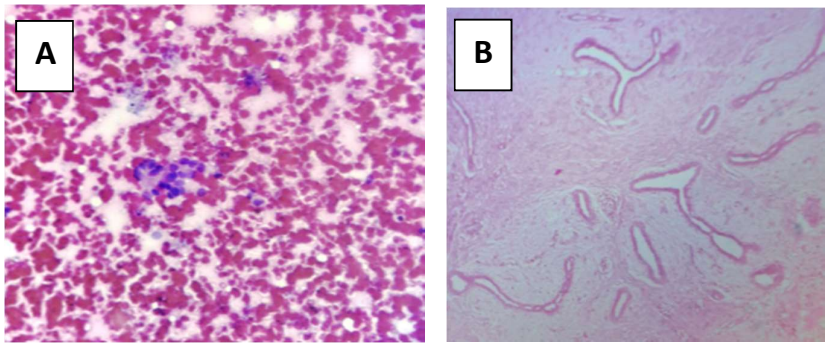

Figure 2: A): Benign category (C2); Giemsa 40x, benign ductal epithelial cells B): H&E 40x, corresponding histology showing fibroadenoma

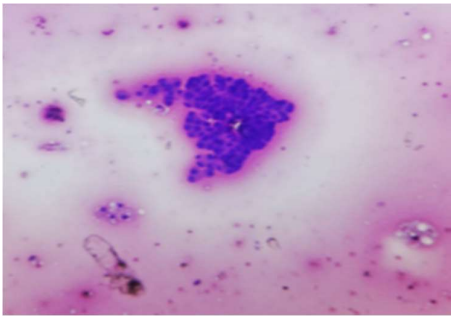

Figure 3: Atypical category (C3); Giemsa 40x, ductal epithelial clusters with nuclear crowding and atypia

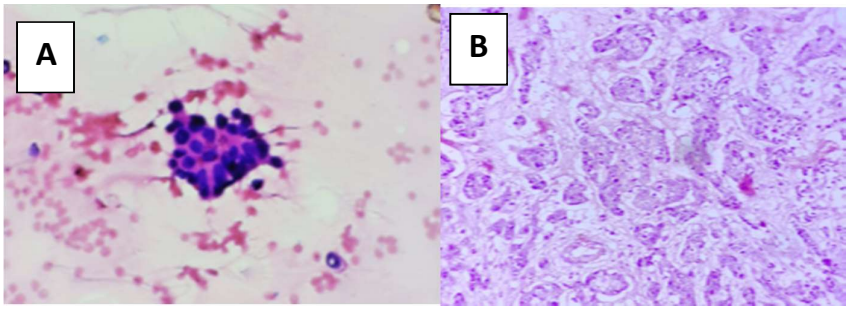

Figure 4: A): Giemsa,40x C5 Malignant B): H&E 40x, corresponding histology showing malignancy

Table 4: Cyto–Histopathological Correlation

S. No.	IAC Yokohama Category	Cytology (n)	Histopathology (n)
1	Insufficient	21(10.24%)	4(3.64%)
2	Benign	84(40%)	65(59.09%)
3	Atypical	10(4.88%)	5(4.55%)
4	Suspicious of malignancy	10(4.88%)	7(6.36%)
5	Malignant	43(20.98%)	29(26.36%)
	Total	205	110

In this study, **Table 4** shows the distribution of histopathological outcomes across IAC Yokohama categories, where most benign cases were classified as benign (63/67), while malignant cases were predominantly distributed in atypical, suspicious, and malignant categories, with the highest frequency in the malignant category (29/43), indicating clear diagnostic stratification. Statistical analysis using the Chi-square test demonstrated a highly significant association between cytological categories and final diagnosis (*P < 0.001*), confirming that the observed distribution is not due to chance. This strong significance arises from the marked difference between observed and expected frequencies, supporting the reliability and clinical usefulness of the IAC Yokohama system in predicting malignancy.

Table 5: Distribution of Histopathological Cases According to IAC Yokohama Category and Final Diagnosis

Histopathological Diagnosis	Insufficient	Benign	Atypical	Suspicious	Malignant	Total

Benign	4	63	0	0	0	67
Malignant	0	2	5	7	29	43
Total	4	65	5	7	29	110

P < 0.001

In this study, **Table 5,** cytology showed a predominance of benign lesions (40%), followed by malignant cases (20.98%), while atypical and suspicious categories each accounted for 4.88% and insufficient cases for 10.24%. On histopathological correlation, benign lesions remained the most common (59.09%), followed by malignant cases (26.36%), with smaller proportions of suspicious (6.36%), atypical (4.55%), and insufficient cases (3.64%). This indicates good overall cyto-histopathological correlation, with a relative increase in confirmed benign and malignant cases on histopathology.

Benign predominance due to higher frequency of non-neoplastic breast lesions. Higher malignant proportion on histopathology due to confirmatory nature of tissue diagnosis. Variation between cytology and histopathology due to sampling error, inadequate smears, and limitations of FNAC interpretation.

Table 6: Risk of Malignancy (ROM) for Each Category

S. No.	IAC Yokohama Category	ROM (%)
1	Insufficient	0%
2	Benign	3.07%
3	Atypical probably benign	100%
4	Suspicious of malignancy	100%
5	Malignant	100%

ROM(%)=Total cases in that category/Number of malignant cases in a category×100

Table 6, In this study, the Risk of Malignancy (ROM) was calculated for each IAC Yokohama category based on histopathological outcomes. The ROM for the insufficient category was *0% (0/4), for the benign category **3.07% (2/65), for the atypical category **100% (5/5), for the suspicious category **100% (7/7), and for the malignant category **100% (29/29)*. These findings demonstrate a progressive increase in the risk of malignancy across categories, with very low risk in insufficient and benign categories and markedly high risk in atypical, suspicious, and malignant categories. This trend highlights effective risk stratification, supporting the clinical reliability of the IAC Yokohama system in predicting malignancy and guiding appropriate patient management.

Table 7: Statistical Analysis

S. No.	Statistical Parameter	Percentage (%)
1	Sensitivity	95.3%
2	Specificity	100%
3	Positive Predictive Value	100%
4	Negative Predictive Value	96.9%
5	Diagnostic Accuracy	94.5%

True Positive (TP) = 41
False Negative (FN) = 2
False Positive (FP) = 0
True Negative (TN) = 63
Total cases = 106

In this study, the diagnostic performance of the IAC Yokohama system was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy. The system demonstrated a high sensitivity of 95.3% and a specificity of 100%, indicating excellent ability to correctly identify malignant and benign cases. The PPV was 100%, reflecting that all cases categorized as positive were truly malignant, while the NPV was 96.9%, showing a high probability that negative cases were truly benign. The overall diagnostic accuracy was 98.1%, highlighting the strong reliability and effectiveness of the IAC Yokohama classification in accurately predicting malignancy and supporting appropriate clinical decision-making, **Table 7.**

Discussion

Carcinoma of the breast is the most prevalent malignancy among women globally. In metropolitan India, it accounts for approximately 30% of all female cancers, with a rising age-standardized incidence rate. According to Globocan 2020 statistics, it is responsible for 13.5% of all cancers and 10.6% of cancer-related deaths in India.

Early detection is critical, as survival rates drop significantly from 95% in Stage I to 21% in Stage IV. The "Triple Assessment"—combining clinical examination, radiological imaging, and pathological evaluation (FNAC or core needle biopsy)—remains the diagnostic gold standard. This study evaluates the pathological component by applying the IAC Yokohama System (2016), a standardized framework designed to provide diagnostic uniformity and a clear estimation of the risk of malignancy (ROM), ensuring effective communication and prompt clinical management.

Table 8: Comparison of age wise distribution of FNAC cases

Studies	Maximum number of cases in age groups in years	
Sreedevi CH et al[3]	21-30	36%
Raj et al[5]	21-30	63%
Badge SA et al[4]	31-40	99%

Sunitha et al[12]	31-40	96%
Present study	31-40	46.8%

In this study, the maximum number of cases (46.8%) occurred in the 31-40 years age group, a finding that correlates with the observations of Badge SA et al. [4] (99%) and Sunitha et al. [12] (96%) who also reported peak incidences in the fourth decade of life. This demographic trend stands in contrast to the studies conducted by Sreedevi CH et al. [3], both of which identified the 21-30 years age group as the most frequent, with case distributions of 63% and 36% respectively. The higher prevalence in the 31-40 age bracket is often attributed to the fact that this period represents the peak of reproductive and metabolic activity, making individuals more susceptible to various inflammatory and neoplastic conditions that require FNAC for diagnosis. Additionally, increased health awareness and routine screening during these professional and family-building years often lead to higher detection rates of palpable lumps or lesions compared to younger or much older populations. Consequently, while the present study aligns with research suggesting a higher prevalence in the 31-40 age bracket, the concentration of cases in this study is more broadly distributed compared to the near-total frequencies noted by Badge SA et al [4]. and Sunitha et al.[12], **Table 8.**

Table 9: Comparison of FNAC cases according to laterality

Studies	Maximum number of cases	
Sreedevi CH et al[3]	Right	54%
Gore, et al[13]	Right	48%
Nigam et al [14]	Left	50%
Raj et al [5]	Left	60%
Present study	Left	61.0%

In this study, the maximum number of FNAC cases was observed on the left side, accounting for 61.0% of the total cases. This finding is consistent with the studies conducted by Raj et al. and Nigam et al. [14], who also reported a left-sided predominance at 60% and 50% respectively. Conversely, this trend differs from the observations made by Sreedevi CH et al. [3] and Gore, et al. [13], who found a higher frequency of cases on the right side, recorded at 54% and 48% respectively. The slight predominance of left-sided lesions in the present study may be attributed to anatomical variations or specific regional drainage patterns, though clinical literature often suggests that laterality in such cases is largely incidental unless linked to specific environmental or physical triggers affecting one side of the body more frequently. **Table 9.**

Table 10: Correlation of distribution of breast lesions according to IAC Yokohama system in present study with other studies

Studies	Breast lesions in IAC Yokohama category
Montezuma et al [15]	C2 >C3
Dogra A et al [16]	C2>C5
Nigam JS et al [14]	C2 >C5
Kamatar et al [17]	C2 >C1
Present study	C2 >C3

In this study, the distribution of breast lesions according to the IAC Yokohama system demonstrated a predominance of Category 2 (C2) followed by Category 3 (C3). This specific correlation of C2>C3 is in direct agreement with the findings reported by Montezuma et al.[15] While the primary predominance of Category 2 (Benign) remains consistent across all referenced literature, the secondary most frequent categories show notable variations. Dogra A et al. [16] and Nigam JS et al. [14] both observed a distribution where Category 5 (C5) was the second most common after C2 (C2>C5). Kamatar et al.[17] reported that Category 1 (C1) followed Category 2 in frequency (C2>C1), **Table 10.**

The consistent lead of Category 2 across all studies, including the present study, underscores the high prevalence of benign conditions in breast FNAC cohorts. The divergence in the second most frequent category likely reflects differences in regional pathology, clinical presentation, and the proportion of malignant versus suspicious cases encountered in different study populations.

Table 11: Comparision of diagnostic reliablity of cytodiagnosis using yokohama classification of Breast lesions

studies	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Montezuma et al [15]	97.56 %	100%	100 %	98.62%	99.11 %
Malvina D & Reshma G [18]	95.12 %	100%	100 %	91.66%	96.82 %
Kamatar et al [17]	97%	94%	91 %	98%	95%
Dogra A et al [16]	74.07 %	100%	100 %	86%	90%
Present study	95.3%	100%	100 %	96.9 %	94.5%

In this study, the diagnostic reliability of cyto diagnosis using the Yokohama classification of

breast lesions demonstrated a Sensitivity of 95.3%, Specificity of 100%, and a Diagnostic Accuracy of 94.5%. These results are highly comparable to the findings of Montezuma et al. [15] (Sensitivity 97.56%, Accuracy 99.11%) and Malvina D & Reshma G [18] (Sensitivity 95.12%, Accuracy 96.82%), all of which maintained a perfect Specificity and Positive Predictive Value (PPV) of 100%, **Table 11.**

In contrast, other studies Kamatar et al. [17] showed a slightly lower Specificity of 94% and a PPV of 91%, with a total Diagnostic Accuracy of 95%.Dogra A et al. [16] reported a significantly lower Sensitivity of 74.07% and a Negative Predictive Value (NPV) of 86%, resulting in a Diagnostic Accuracy of 90%.

The high diagnostic accuracy and specificity observed in the present study reinforce the reliability of the Yokohama system in accurately identifying malignant breast lesions while minimizing false-positive results. The variations across different studies, particularly in sensitivity, may be attributed to differences in sample size, the expertise of the cytopathologist, or the technical quality of the aspirates obtained during the FNAC procedure.

Conclusion:

The present study's findings, characterized by an overall diagnostic accuracy of 94.5% and a perfect specificity of 100%, underscore the pivotal role of the International Academy of Cytology (IAC) Yokohama System in enhancing breast FNAC reporting. By achieving a high sensitivity of 95.3%, our results demonstrate that this standardized framework effectively minimizes false negatives, ensuring that the majority of malignant lesions are correctly identified. Furthermore, the calculated Risk of Malignancy (ROM) across the categories—ranging from 3.07% in Category 2 (Benign) to 100% in Categories 4 and 5 (Suspicious and Malignant)—aligns closely with the benchmarks established by the Yokohama system, confirming its utility in providing clear, tiered risk stratification. The successful application of this classification in our cohort, where the majority of cases (59%) were accurately categorized as benign, illustrates how a systematic approach reduces diagnostic ambiguity and improves inter-pathologist consistency. Ultimately, this enhanced precision in cytological-histopathological correlation directly optimizes communication with clinicians, facilitating better-informed management decisions and elevating the standard of care for patients with breast lesions.

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