

Risk of Malignancy in Breast FNAB Categories, Classified According to the Newly Proposed International Academy of Cytology (IAC) Yokohama System

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Background: A new category system comprising five classes (C1-insufficient material, C2-benign, C3-atypical, C4-suspicious, and C5-malignant) has been proposed by the International Academy of Cytology (IAC) for fine needle aspiration biopsy cytology (FNAB) for proper diagnosis of breast cancer.

Aims and Objectives: This study is designed to categorize institutional FNAB data according to the new system and calculation of the absolute risk of malignancy (ROM), sensitivity, specificity, positive predictive values, false negative and false-positive rate.

Study Design: We conducted a retrospective cross-sectional study involving 2133 cases collected between June, 2008 and August, 2019, at Foundation University Medical College's Department of Histopathology and the Surgery and Oncology Department at the Fauji Foundation Hospital. All cases fulfilling the inclusion and exclusion criteria were retrieved from the archives and reviewed by two expert pathologists. Matching histopathology was compared with the cytology reports for concordance or discordance of results.

Findings: We found 6.9% (n = 147) insufficient, 65.8% (n = 1403) benign, 7.2% (n = 153) atypical, 7.5% (n = 160) suspicious and 12.6% (n = 270) malignant cases. Cyto-histological correlation was found in 421 cases from the year 2014 to 2019 with 370 concordant and 51 discordant cases. The maximum number of concordant cases was 151 in the C5 category and discordant cases had a diagnosis of C3 and C4 on cytology with 16 cases in each category. The calculated values of ROM were 45.45%, 10.3%, 30.6%, 82.79% and 99.34% from C1 to C5, respectively. We calculated 83.42% absolute sensitivity and 85.24% specificity. The positive predictive value for category 3, 4 and 5 was 67.34%, 82.7% and 99.34%, respectively, while false-negative rate was 7.9% and false-positive rate was 0.66%.

Conclusion: The ROM for C1 category calculated from this study is quite high (45.45%) compared to previous studies; therefore, it is recommended to perform core needle biopsy in all these cases. The higher sensitivity and specificity of this method of diagnosing malignant lesions supports its use.

Keywords: IAC Yokohama system, fine needle aspiration biopsy, core needle biopsy, risk of malignancy, benign, rapid onsite evaluation

Introduction

Breast cancer is a deadly health crisis that is increasingly affecting women around the world. The rising number of breast cancer cases worldwide has led to 1 in 18 women developing the disease.¹ It is the leading cause of death in developing countries, followed by lung cancer in developed countries.² The age-standardized incidence rate (ASIR) has been reported to

be higher in countries with a high socio-demographic index (SDI) than in countries with a low SDI. As of 2020, the global studies on breast cancer revealed an ASIR of 45.91 alongside an age-standardized death rate (ASDR) of 14.51.³

Among Asian countries, Pakistan has the highest incidence of breast cancer, with one in nine women suffering from this lethal disease at some point in their lives.⁴ Contemporary breast cancer diagnostic methods, such as mammography, magnetic resonance imaging, ultrasound, computerized tomography, positron emission tomography and biopsy, are far too expensive for developing countries like Pakistan, making them inaccessible to most government hospitals and disadvantaged persons.

Therefore, it is important to adopt an alternative diagnostic modality, fine needle aspiration biopsy (5fNAB), which is not only cost-effective but also reliable, easy to perform, and has a short turnaround time for screening breast cancer.⁵ An Outpatient Department treatment (OPD) based technique Rapid onsite evaluation (ROSE) is coupled with FNAB to enhance its efficacy by decreasing the number of inadequate cases and concomitant increase in benign and malignant diagnosis. As a result, it has a sensitivity of 90–95% and a 100% positive predictive value.⁶ Core needle biopsy (CNB) is currently replacing FNAB in well-resourced countries. The procedure, however, is costly, requires the use of a histopathology laboratory, involves higher complication rates, and involves longer turnaround time.⁷

A FNAB cytology method was first used at the Karolinska institute in Stockholm in 1960 and has been used successfully ever since. In 1980, it became a major part of the triple test, which included a clinical examination and imaging to diagnose breast cancer.⁸ A breast group comprising pathologists, radiologists, surgeons and oncologist was established in 2016 by the International Academy of Cytology (IAC) to provide the doctors with a standardized reporting format including a clear definition, risk of malignancy (ROM) and management recommendations for each category.⁶ The group (also known as IAC Yokohama system) included five categories for reporting breast lesions each having its own ROM and management approach. The categories included were C1: insufficient/inadequate, C2: benign, C3: atypical, C4: suspicious of malignancy, C5: malignant.⁶ ROM for each category was calculated using literature, statistical calculations and different categories which did not coincide with the categories in the new IAC system. This research is conducted to apply the new IAC system categories on our data to determine the absolute ROM as well as sensitivity, specificity, positive predictive values of categories along with false negative and false-positive rate.

Materials and Methods

Data Retrieval and Processing

All breast FNAB cases received during the period of June 2008 to Aug 2019 were retrieved from the archive of histopathology department of Foundation University, Islamabad. It included a total of 2133 cases with 421 patients having a matched histopathology (data available from year 2014 to 2019). The inclusion criteria were: 1) FNAB of all female patients who came with a palpable breast lump 2) FNAB should be performed from the same site from where histopathology biopsy was taken in case of matched histopathology. Exclusion criteria were 1) male FNAB cases 2) FNAB of non-palpable breast lumps.

All FNAB slides were stained with Hemacolor stain. Rapid onsite evaluation (ROSE) was applied in limited number of cases from year 2016 to year 2019. In the years 2008 to 2015, ROSE was not in routine practice because of limited number of laboratory staff availability for immediate slide staining. FNAB of all patients was performed by post graduate trainees of histopathology.

Categorization of FNAB Breast Cases

All FNAB cases retrieved were reviewed by two expert histopathologists and categorized retrospectively according to the new IAC Yokohama System. Matching histopathology was compared with the cytology reports for concordance or discordance of results.

Statistical Analysis

Statistical analysis was done using the following parameters: (i) Absolute sensitivity (malignant; category 5) was calculated by dividing the number of malignant cases correctly identified on FNAB by the total number of malignant

cases in the cohort, (ii) Specificity (benign; category 2) is the number of benign lesions correctly diagnosed on FNAB divided by the total number of benign lesions in the cohort, (iii) Positive predictive value (PPV) is the number of malignant lesions correctly identified as positive on FNAB divided by the total number of positive results in the cohort, (iv) False-negative rate is the number of cases reported as benign that were found to be malignant divided by the number of all malignant cases. (v) False-positive rate is the number of cases reported as malignant that were found to be benign divided by the number of all malignant cases and (vi) Absolute ROM is the number of malignant cases in a given diagnostic category for the FNAB result divided by the total number of cases in that diagnostic category.

Results

Data Collection

The total number of cytology cases was 2133 from June 2008 to Aug 2019. In 2008, 78 cases were retrieved, 225 was the maximum number of cases received in the year 2014, whereas 126 patients came for FNAB in the year 2019. The case distribution number for the rest of the years was between 173 and 212 as shown in [Figure 1](#).

These cases were categorized according to the IAC Yokohama reporting system according to which 6.9% (n = 147) were insufficient cases, 65.8% (n = 1403) benign, 7.2% (n = 153) atypical, 7.5% (n = 160) suspicious and 12.6% (n = 270) were malignant as shown in [Figure 2](#).

Clinical Findings

We found the histological correlation in a total of 421 cases from the year 2014 to 2019. Maximum number of 104 cases were found in the year 2014, whereas minimum number of 47 cases in the year 2019. The number of cytohistological correlated cases for the other years is shown in [Table 1](#).

Concordant cases were those in which the cytological and histological diagnosis was same. The discordant cases had a different opinion in cytological and histological reports. Our study found 370 concordant cases and 51 discordant cases. Year-wise distribution of concordant and discordant cases is shown in [Table 2](#). The maximum number of concordant cases was 151 in the C5 category. The actual diagnosis of discordant cases is also shown in [Table 2](#). The maximum number of discordant cases had a diagnosis of C3 and C4 on cytology with 16 cases in each category.

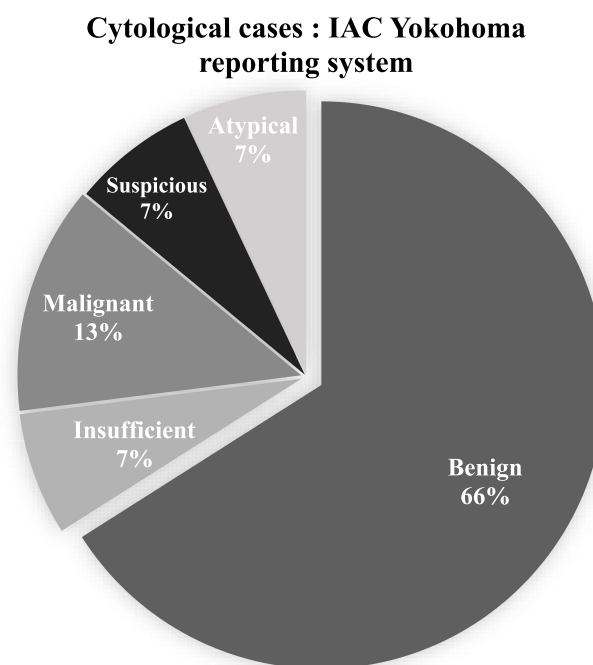


Figure 1 FNAB statistical data number of FNAB breast cases from year 2008–2019 retrieved from institutional database.

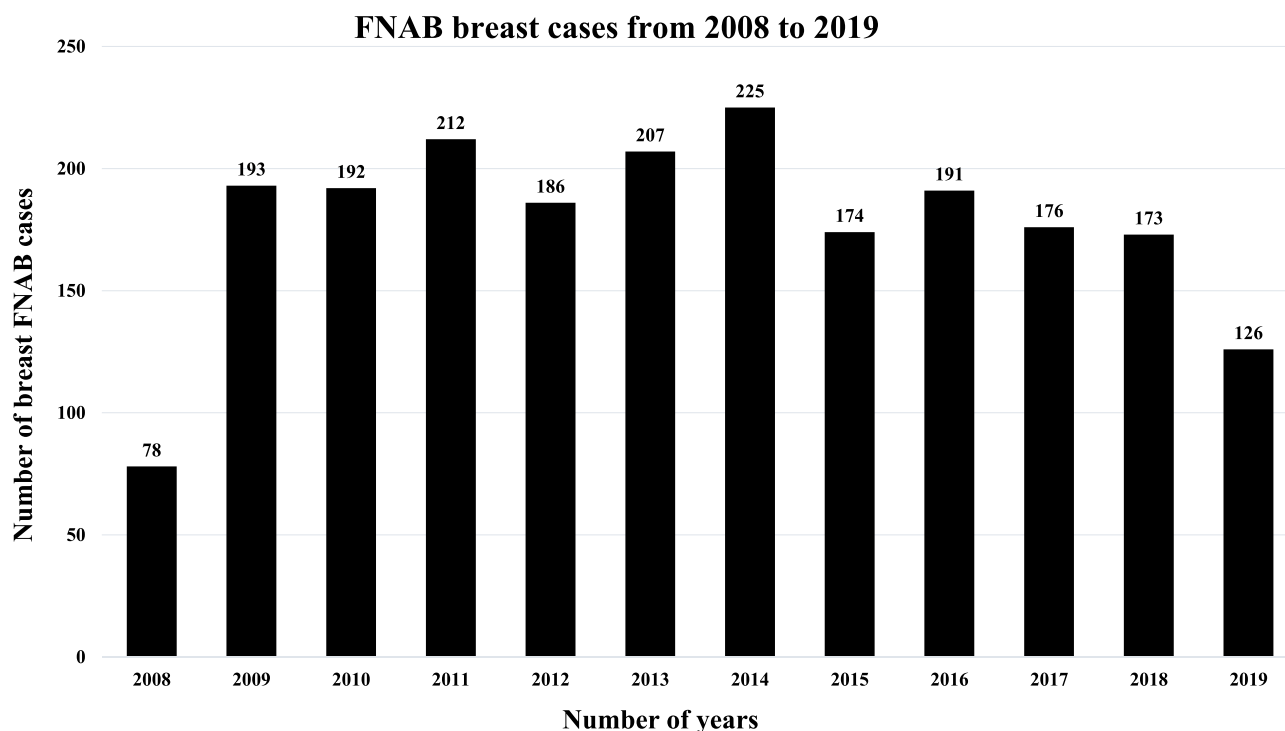


Figure 2 Percentage distribution of cytological cases according to the new IAC Yokohama reporting system.

The ROM for each cytological category was calculated and is shown in [Table 3](#). The highest ROM for insufficient C1 category was 45.45%.

Absolute sensitivity, specificity, positive predictive value (category 3, 4 and 5), false-negative rate and false-positive rate were also calculated and are shown in [Table 4](#). The value of absolute sensitivity for C5 lesions was 83.42% and specificity for C2 lesions was 85.24%.

Discussion

Women with variations in breast morphology report a large number of benign lesions in addition to malignant lesions in the breast.⁹ In the course of time, the traditionally used triple assessment approach (including FNAB, clinical examination, and mammography) has evolved into a broader approach including ultrasound (in the case of young females) and the replacement of FNAB with CNB.^{10,11} Developed countries prefer CNB over FNAB as it allows evaluation of

Table 1 Year Wise Cytological Categories of Histological Correlation

Cytological Categories by IAC System	Years						
	2014	2015	2016	2017	2018	2019	Total
C1	4	3	1	1	1	1	11
C2	27	26	14	17	15	17	116
C3	9	6	13	6	10	5	49
C4	21	10	18	17	19	8	93
C5	43	18	18	21	36	16	152
Total	104	63	64	62	81	47	421

Abbreviations: IAC, International Academy of Cytology; C1, insufficient category; C2, benign category; C3, atypical; C4, suspicious of malignancy; C5, malignant.

Table 2 Histochemical Correlation with Concordant and Discordant Cases

Cases	Years						
	2014	2015	2016	2017	2018	2019	Total
Cytohisto correlation	104	63	64	62	81	47	421
Concordant cases	93	56	57	54	69	41	370
Discordant cases	11	7	7	8	12	6	51
Cytohisto concordant cases	C1:1	C1:1	C1:1	C1:1	C1:1	C1:—	5
	C2:22	C2:23	C2:14	C2:15	C2:14	C2:16	104
	C3:7	C3:5	C3:7	C3:4	C3:7	C3:3	33
	C4:20	C4:9	C4:17	C4:13	C4:12	C4:6	77
	C5:43	C5:18	C5:18	C5:21	C5:35	C5:16	151
Cytohisto discordant	C1 (IDC)	C1 (IDC with DCIS)	C3	C2 (IDC)	C2 (MC)	C1 (IDC)	C1=6
	C1 (chronic NM)	C1 (IDC)	C3	C2 (SPC)	C3 (IDC)	C2 (CF DCIS)	C2=1
	C1 (IDC)	C2 (IDC)	C3	C3 (IDC)	C3 (IDC)	C3 (IDC with NED)	C3=1
Cases with actual diagnosis	C2 (IDC)	C2	C3	C3 (IDC)	C3 (IDC)	C3 (IDC)	C4=1
	C2 (IDC)	Borderline PT	C3 (ILC)	C3 (DCIS)	C4 (BBD)	C4 (Acute)	C5=1
	C2 (IDC)	C2 (IDC)	C3	C4 (BA)	C4 (F.D.)	C4 (SA)	
	C2 (IDC)	C3 (IDC)	C4 (F.D. of breast)	C4 (acute)	C4		
	C2 (IDC)	C4 (acute or chronic NM)		C4 (F.D.0)	(FA)		
	C3 (IDC)			C4 (FN)			
	C3 (IDC)			C4 (F.D.)			
	C4 (acute or chronic NM)			C5 (FEL, BPT)			

Abbreviations: DC, invasive ductal carcinoma; DCIS, ductal carcinoma in-situ; PT, phyllodes tumor; NM, nonspecific mastitis; ILC, invasive lobular carcinoma; F.D., fibrocystic disease; SPC, solid papillary carcinoma; BA, breast abscess; MC, medullary carcinoma; BBD, benign breast disease; FA, fibroadenoma; FEL, fibroepithelial lesion; BPT, benign phyllodes tumor; CF, cribriform growth pattern; NED, neuroendocrine differentiation; SA, sclerosing adenosis.

Table 3 Risk of Malignancy for Each Cytological Category of the New IAC Yokohama Reporting System

Cytological Categories	Risk of Malignancy
C1	45.45%
C2	10.3%
C3	30.6%
C4	82.79%
C5	99.34%

Abbreviations: C1, insufficient category; C2, benign category; C3, atypical; C4, suspicious of malignancy, probably in-situ invasive carcinoma; C5, malignant.

Table 4 Percentage Value of Absolute Sensitivity, Specificity, Positive Predictive Value (Category 3, 4 and 5), False-Negative Rate and False-Positive Rate

Parameter	Applied IAC Yokohama System%
Absolute Sensitivity (C5)	83.42%
Sensitivity (C2)	85.24%
PPV (C3)	67.34%
PPV (C4)	82.7%
PPV (C5)	99.34%
FNR	7.9%
FPR	0.66%

Abbreviations: PPV, positive predictive value; FNR, false negative rate; FPR, false-positive rate; C2, benign category; C3, atypical; C4, suspicious of malignancy (probably in-situ invasive carcinoma); C5, malignant.

hormone receptors (ER, PR) and HER-2 neu status by Fluorescence in-situ hybridization (FISH) or by immunostains.¹² Additionally, core needle biopsy can distinguish between in-situ and invasive lesions as well as perineural invasion and lymphovascular invasion, which are not possible with FNAB.⁷

Despite the substantial benefits, the factors that led to discontinuation of FNAB primarily included high inadequate rate and suboptimal accuracy in some centers.¹³⁻¹⁵ However, it is apropos to reconsider the overall significance of FNAB for both developed and developing countries.¹⁶ Therefore, in order to reaffirm the importance of FNAB as an economically viable diagnostic approach, we conducted a broad study to analyze ROM frequency in FNAB breast cases, categorized according to the new IAC Yokohama System. In our studies, we found that FNAB was highly sensitive and specific for malignant lesions, which supports its use as a cheap diagnostic technique in low- and middle-income countries.

The new (IAC) Yokohama System provides an improved structured format for reporting breast lesions by giving comprehensive definitions and descriptions as well as ROM for the standardized five categories. It helps in breaking the communication barrier between the cytopathologists and the clinical management team by giving the management recommendations according to the respective ROM for each category which is shown in Table 5. This approach also emphasizes on doing further research on the utilization of FNAB for breast lesions to maximally benefit the patients with this low-cost procedure.¹⁷

In our study, we retrieved 2133 cases from year 2008 to 2019. The maximum and minimum number of cases were retrieved in the years 2014 and 2008, respectively. Classification of the retrieved cases was done according to the newly proposed IAC Yokohama system. We had 6.9% insufficient cases, 65.8% benign, 7.2% atypical; most likely benign lesions, 7.5% suspicious for malignant lesion and 12.7% malignant cytological cases, while a study conducted by Montezuma et al in 2019 gave values of 5.77% insufficient, 73.38% benign, 13.74% atypical, 1.57% suspicious and 5.54% malignant cases.⁵ Another study performed by Stephen Wong demonstrated values of 11%, 72%, 4.3%, 2.2%, and 10% for insufficient, benign, atypical, suspicious and malignant category, respectively.⁶ Similarly, a study conducted by Hoda et al showing a review of the predictive values and ROM in breast FNAB categories revealed values of cytological cases from 26 studies as 6.8%, 39.6%, 7.3%, 7.5% and 38.9% in the five tier IAC Yokohama system, respectively.¹⁸ An Indian study also yielded values of 1.3% C1 cases, 82.6% C2 cases, 5.7% C3 cases, 1.7% C4 cases and 8.4% C5 cases.¹⁹ Based on our study, as well as the studies mentioned above, the maximum number of cases were classified as benign.

A total of 421 cases found to have histocytological correlation from year 2014 to 2019, and were distributed into five categories (Table 1). C5 malignant category represented the maximum number of 152 cases and the minimum number of

Table 5 Management Recommendations for Different Categories in Developing and Developed Countries

Category	Management for Developed Countries	Management for Developing and Underdeveloped Countries	Comments	
C1	Clinical and radiological review	Clinical review	Repeat FNAC for up to 3 times	
	Indeterminate/Suspicious radiology	Suspicious clinically	(Ideally ultrasound guided)	
	Repeat FNAC/ CNB	Repeat FNAC	If still insufficient, do CNB	
	Benign radiology			
	Repeat FNAC			
C2	Clinical+ radiological +FNAC (Benign)	Benign clinically	Follow up depends on nature of lesion eg, abscess – 2 weeks after antibiotics	
	Nothing required	Nothing required		
	Clinical/radiological (indeterminate/ suspicious)	Suspicious clinically		
	Repeat FNAC/ CNB	Repeat FNAC		
C3	Clinical and radiological review	Clinical review	Clinical, radiological and FNAC report differs	
	Repeat FNAC/ CNB	Repeat FNAC/ CNB	Repeat FNAC for up to 3 times (Ideally ultrasound guided)	
C4	Clinical and radiological review	CNB/Excision biopsy		Technical issues
	CNB mandatory			
C5	Clinical and radiological review (Findings if different from FNAC report)		Repeat FNAC	Adequate sample with atypia
	CNB mandatory			
	Triple test concordant			CNB
	Definite surgery			

Abbreviations: C1, insufficient category; C2, benign category; C3, atypical; C4, suspicious of malignancy, probably in-situ invasive carcinoma; C5, malignant; FNAC, fine needle aspiration cytology; CNB, core needle biopsy.

cases was in the C1 category representing only 11 cases. The smaller number of cases in C1 category was due to the impact of ROSE applied during these years from 2016 to 2019.

Comparison of the cytological results of the patients with their histological diagnosis revealed 370 cases to concordant, and 51 cases to be discordant. Highest histocytological correlation was observed in the year 2014. C5 malignancy was the most concordant diagnosis, whereas discordance was mostly seen in C3 and C4 categories similar to the study done by Montezuma et al.⁵

ROM was calculated for each category and compared with previous studies (Table 6). It showed a wide variety of values for each category. For C1 category, ROM ranged between 2.6% and 45.45%, C2 category 1.4% to 10.3%, C3 category 13% to 51.5%, C4 category 77.8% to 97.1% and for C5 lesions 99.34% to 100%. Calculation of ROM is very important in each category as it guides toward the management plan for every type of breast lump.

Additionally, we calculated the absolute sensitivity for malignant lesions, specificity, and positive predictive values for category 3, 4 and 5 and compared them with several studies (Table 7). The sensitivity ranged from 71% to 97.56% in various studies. Our study calculated a value of 83.42% for malignant category 5. Traditionally, specificity is measured between 97.1% and 100% in previously published research, while our study has a value of 85.24%, which is lower when compared to others. The positive predictive value in our study is 99.34%, whereas it ranges from 98.7% to 100% in previous papers, which is almost comparable to our study. We found 7.9% false-negative rate from the calculations done

Table 6 Comparison of ROM Calculated from Our Study with Other Studies

ROM for Cytological Categories	Our Study	Montezuma et al.	Wong et al.	Hoda et al.	Agarwal A et al. ²⁰
C1	45.45%	4.8%	2.6%	30.3%	–
C2	10.3%	1.4%	1.7%	4.7%	8.3%
C3	30.6%	13%	15.7%	51.5%	17.2%
C4	82.79%	97.1%	84.6%	85.4%	77.8%
C5	99.34%	100%	99.5%	98.7%	100%

Table 7 Comparison of Absolute Malignant Sensitivity, Specificity, Positive Predictive Value for Category 3, 4 and 5 of Our Study with Other Studies

Parameters	Our Study	Montezuma et al.	Wong et al.	Hoda et al.	Agarwal A et al.
Malignant sensitivity (C5)	83.42%	97.56%	71%	76.2%	86.7%
Specificity (C2)	85.24%	100%	97.1%	98.8%	100%
PPV (C3)	67.34%	—	—	51.5%	—
PPV (C4)	82.7%	—	—	85.4%	—
PPV (C5)	99.34%	100%	100%	98.7%	100%

on our data which is higher than usually reported and a value of 0.66% of false-positive rate which is almost comparable to the studies done by Hoda et al.¹⁸

Conclusions

The IAC Yokohama classification system of breast cytopathology allows for better communication between pathologist and clinician, thus ensuring the best outcome for the patient. According to the results of the present study, the ROM for C2, C4, and C5 were comparable to those of other studies; however, the value for C1 was significantly higher. Furthermore, FNAB was found to be highly specific and sensitive for the diagnosis of malignant lesions, allowing it to be used in low- and middle-income countries where CNB is prohibitively expensive for patients and radiological facilities are not readily available. Nevertheless, C1 category cases must be referred to tertiary care hospitals for CNB and further evaluation.

Ethics

Ethical approval was obtained from the institutional ethical review committee of the Fauji Foundation Hospital in November 2020. Study was conducted in compliance with the Declaration of Helsinki. All participants gave informed consent to take part in the study.

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Disclosure

The authors report no conflicts of interest in this work.

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