AAU CHS DEPARTMENT OF PATHOLOGY

Concordance of breast cytology based on the Yokohama classification with ultrasound ACR BIRADS category in women with breast swelling examined at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Retrospective cross sectional study

Research paper submitted to Addis Ababa University, College of Health Science, School of Medicine the Department of Pathology in partial fulfillment for the requirements of Specialty Diploma in Pathology

BY: Betelhem Gebreamlak Hailu (MD, Pathology Resident)

Advisors: Amanuel Damie (MD, Assistant Professor of Pathology)

Firdosa Ahmed (MD, Assistant Professor of Radiology)

January, 2025

Addis Ababa, Ethiopia

Declaration

I, the undersigned Betelhem Gebreamlak Hailu with registration number of GSR/4118/14, declare that this thesis entitled "Concordance of breast cytology based on the Yokohama classification with ultrasound ACR BIRADS category in women with breast swelling examined at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Retrospective cross sectional study" is my original work and has not been presented for a degree in any other university, and that all source of materials used for the thesis have been duly acknowledged.

Submitted by:

Full Name: Betelhem Gebreamlak Hailu, MD, final year Pathology resident;

Signature: _____Date:_____

Approved by:

This thesis has been submitted for examination with my approval.

Name of advisor: Dr. Amanuel Damie,MD,Assistant professor of Pathology;

Signature: _____Date:_____

Approval

We certify that we have read and evaluated the thesis by Betelhem Gebreamlak Hailu entitled "Concordance of breast cytology based on the Yokohama classification with ultrasound ACR BIRADS category in women with breast swelling examined at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Retrospective cross sectional study" and recommend that the thesis be accepted as fulfilling for the thesis requirement of Specialty Diploma in Pathology.

Submitted by:

Full Name: Betelhem Gebreamlak Hailu,MD, final year Pathology resident;

Signature: _____Date:_____

Approved by:

Name of advisor: Dr. Amanuel Damie,MD,Assistant professor of Pathology;

Signature: _____Date:_____

Name of Department Head: Rahell Hailu,MD,Assistant professor of Pathology;

Signature: _____Date:_____

Acknowledgement

I am grateful to Addis Ababa University, College of Health Science; Department of Pathology for providing me with this great opportunity of researching into my area of interest. I am also grateful to Churchil Health Center under ELSE KRONER CANCER CENTER.I present my gratitude to my advisor Dr Amanuel Damie for the edifying clues and unreserved support he gave me from the very beginning during the conception of the title to the development of the proposal, and to the completion of this research thesis. I am grateful to my second advisor Dr Firdosa Ahmed for the helpful advice she gave me throughout the research process. I present my sincere thanks to the data collectors and the supervisors for their devotion and heedful work they had throughout the challenging routine journey of the data collection process. To be honest, without the keenness and helpfulness of all the members of the two departments (Department of Pathology and Department of Radiology), the success of this research work would have not been true; thus, what I can say is I thank you all.

At last, but not least, prior to all, to whom I owe my life and through whom I had the strength, the Almighty God; I raise my hands in deep honest thanks, kneel down and say glory to you.

Table of Contents

List of tables

List of figures

Acronyms and Abbreviations

ACR	American College of Radiology
AOR	Adjusted Odds Ratio
BIRADS	Breast Imaging Reporting and Data System
CI	Confidence Interval
CNB	Core Needle Biopsy
COR	Crude Odds Ratio
FMOH	Federal Ministry of Health
FNAC	Fine Needle Aspiration Cytology
IAC	International Academy of Cytology
PR	Principal Researcher
ROM	Risk of Malignancy
TASH	Tikur Anbessa Specialized Hospital
WHO	World Health Organization

Abstract

Background: The fine needle aspiration cytology (FNAC) has been widely applied as part of the triple-test for breast cancer. The Yokohama system of classification of FNAC has been designed to boost the communications between clinicians and pathologists. Studying the concordance of FNAC based on the Yokohama classification with ultrasound breast imaging reporting and data system (BIRADS) categories is vital to promote the combined use of the two diagnostic systems.

Objective: To investigate concordance of FNAC based on the Yokohama classification with the ultrasound ACR BIRADS category in women with breast swelling examined at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia.

Method: Retrospective cross-sectional study was conducted from March 2024 to January 2025. A total of 116 women with breast swellings examined at Pathology and Radiology departments of TASH from January 1, 2022 to December 31, 2024, who had hospital records of both FNAC and ultrasound diagnostic results were included. Data were analyzed using STATA version 14. Descriptive statistics, Kappa weight and logistic regression analyses were used to describe the participants, assess concordance of the two systems and association of factors, respectively.

Result: Among the total of 116 patients included in this study, the FNAC test results of 49, 5, 8 and 54 patients were classified as benign, atypical, suspicious for malignancy and malignant, respectively based on the Yokohama system of classification. Also, the ultrasound test results of 41, 8, 14 and 53 patients were classified as benign, probably benign, suspicious for malignancy and highly suggestive of malignancy, respectively based on BIRADS. The concordance of the test results based on the two systems was 81.90% regarding all the four categories in each of the two systems, 91.80% with respect to the last two categories in each of the two systems, while it was 88.80% with respect to three merged categories based on their risk of malignancy (ROM).

Conclusion: The study revealed a high overall concordance of the breast lesion test results of FNAC based on the Yokohama system of classification with the ultrasound test results based on the ACR BIRADS categories. This shows that the integration of these two systems can foster the accuracy of the diagnostic approaches used for early detection of breast cancer cases.

Keywords: BIRADS, Breast swelling, FNAC, Yokohama classification, Concordance.

1. Introduction

1.1. Background

Breast cancer has become the most widespread cancer globally, recent estimates showed that it is ranking second in the cancer mortality list [1, 2]. The World Health Organization (WHO) estimates that more than half a million deaths worldwide are due to breast cancer [3]. Breast cancer affects both women and men while it mainly occurs in women, and thus women of all age are at higher risk [1-4]. The incidences as well as the survival rates vary among countries, while significant variations seen between the developed and the developing countries [1, 3-5]. Breast cancer is the most prevalent cancer in Ethiopia accounting for around twenty percent of the national cancer burden and a third of all cancer related deaths among women [6].

Early detections and treatment of breast cancer cases are known to be very important in order to reduce mortality [7]. However, in developing countries, such actions are challenged by several factors including poor quality of healthcare and economical issues related with high cost as well as complex diagnostic techniques [8].

In diagnosis of breast cancer, the application of multiple diagnostic techniques such as clinical examination, radiology and cytology, often referred to as “triple-test” is recommended in order to increase reliability [9]. The fine needle aspiration cytology (FNAC) is a safe, minimally invasive, accurate, and cost-effective modality to assess palpable and non-palpable breast lesions, which is best read in association with the other elements of the “triple test” [9-11]. Although, there are evidences showing the core needle biopsy (CNB) is replacing the role of the FNAC in most laboratories, the FNAC is recommended for its cost effectiveness and ease of application particularly in the low income and middle income countries [9-12].

In the recent times, the international academy of cytology (IAC) launched a scheme to categorize breast cytology with the aim to foster ease of communication among clinicians and pathologists, and to also help to promote the application of the FNAC [9]. The IAC Yokohama defined five categories, briefly; they are “insufficient”, “benign”, “atypical”, “suspicious” and “malignant” to classify breast cytology based on FNAC [9, 11, 13].

Bearing the usefulness of the information obtained to aware clinicians and pathologists about the reliability of the system in mind, several studies have been done in different countries and health institutions to scrutinize the risk of malignancy (ROM) in each of the five categories, sensitivity,

specificity, negative predictive value, positive predictive value and overall accuracy of the technique [14-16].

In the assessment of the ROM as well as other issues such as sensitivity, specificity, etc., almost all of the previous assessment studies applied the “histopathological” biopsy results as “gold standard" reference to compare prognostic value of the FNAC technique [17, 18]. Accordingly, a relatively agreeable number of findings are available in the existing literature. On the other hand, studies which investigated concordance of FNAC based on the Yokohama classification with the radiological assessment results of breast lesions are very rare [19].

Regarding the categorization of the radiological assessment results of breast lesions, the breast imaging reporting and data system (BIRADS) is the widely applied system of categorization which was designed according to the American College of Radiology (ACR) [18]. Application of the “triple test” to diagnose breast lesions follows clinical examination, followed by radiological assessment (often ultrasound imaging) and finally breast cytology [15]. To increase availability and accessibility of such “triple test” in developing countries including Ethiopia with affordable manner, integrating FNAC with the clinical and radiological tests is recommended. [13, 15, 18].

In view of that, this study was conducted to assess concordance of breast cytology based on the Yokohama classification with the ultrasound BIRADS category in women with breast swelling examined at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

1.2. Statement of the problem

Evidences indicated that breast cancer is a global health problem causing about half a million of deaths each year [3]. Although early detection and treatment of breast cancer is a priority to reduce associated deaths, the practicability of such essential intervention actions in developing countries is challenged by a number of factors [16]. Among the factors hindering practicability of early detection and treatment of breast cancer, the high cost and complexity of diagnostic techniques are at the forefront [13]. As well, the accuracy of test results is also challenged by depending on only a single diagnostic technique [20]. Hence, application of multiple tests often known as “triple test” is the most recommended approach [5].

Whenever there are new systems and diagnostic techniques in all areas of cancer, researching into the new systems is common [21]. Likewise, several studies have been conducted in the area of breast cancer to assess the implementation of the new IAC Yokohama system. Following that,

several studies have been done to assess risk of malignancy associated with each of the five categories, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the system, and revealed valuable findings [14, 16, 22]. However, previous studies which assessed the concordance of the FNAC based on the Yokohama system of classification with the ultrasound BIRADS done elsewhere are rare [19].

In Ethiopia, previous studies which focused on the diagnostic techniques of breast lesions are generally rare. Particularly, the studies which assessed the concordance of breast cytology based on the Yokohama classification with ultrasound BIRADS are almost nil [23]. Above all, to the knowledge of the principal researcher (PR), no similar other studies were done in the healthcare institution where this study was done. Thus, undertaking this study to assess the concordance of the breast cytology based on the Yokohama classification with the ultrasound BIRADS category in women with breast swelling examined at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia was assumed to be vital to fill some of the information gaps in the existing literature.

1.3. Significance of the study

Provision of quality services in diagnosing breast cancer depends on the use of the best possible diagnostic techniques [9]. Comparing the concordance of test results of two or more diagnostic techniques provides an informative clue about the reliability of the test methods applied. In view of that, the information generated by this study regarding the concordance of breast cytology based on the Yokohama classification with ultrasound BIRADS category in women with breast swelling examined at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia; can be used to fill some of the information gaps in the existing literature.

Furthermore, the information resulted from this study provides the clinicians with useful clues regarding the overall concordance of the test results of the two diagnostic techniques, and also point out the complementary categories which are more concordant and those categories which are not; eventually helping them to make informed judgments. As well, the information revealed by this study can also help future researchers to further investigate the factors which make the concordances and the disparities between the classification schemes of the two techniques.

1.4. Literature review

1.4.1. The Yokohama system for reporting breast fine needle aspiration cytology

The international academy of cytology (IAC) Yokohama system for reporting breast fine needle aspiration cytology (FNAC) was developed by a group of expert cytopathologists and clinicians in the breast field [9]. The system defined five categories to sort breast lesions by their risks of malignancy. The five classes are; insufficient, benign, atypical, suspicious and malignant [9-13].

The category insufficient refers to the smears that are too sparsely cellular or too poorly smeared or fixed to allow for a cytomorphological diagnosis. Benign breast FNAC diagnosis is made in cases that have unequivocally benign cytologic features, which may or may not be indicative of a specific benign lesion. Atypical refers to the presence of cytologic features seen predominantly in benign processes or lesions but with the addition of some features that are unusual in benign lesions and which may be seen in malignant lesions. Suspicious for malignancy is defined by the presence of some cytomorphological features that are usually found in malignant lesions, but with insufficient malignant features, either in number or quality, to make a definitive diagnosis of malignancy. A malignant cytological diagnosis is an unequivocal statement that the material is malignant, and the type of malignancy identified should be stated whenever possible [9-13, 16].

1.4.2. Implementations of the IAC Yokohama system

Regarding the implementations of the IAC system several studies done in different countries and institutions showed the uses of the system have been successful [9-11, 15]. Evidences showed each category has its own risk of malignancy and suggested management, clinical and radiologic information are critical for breast lesion management and implementation of the system has been generally useful [9]. After applying the Yokohama system for reporting breast cytopathology, authors suggested that using the system boosts the accuracy of diagnosing breast lesions, reduces missed diagnoses, and offers reliable estimates of risk of malignancy. Adopting the system is a vital step to improve the overall effectiveness of breast cytology reporting among clinicians and pathologists, leading to better communication and care [12].

At the same time, the need of conducting further studies especially regarding the concordance of the results of FNAC based on the classification of the new IAC Yokohama system with reference to other affordable diagnostic techniques applied in the “triple test” is vital for improvements and modifications to the current system [9-11, 15].

1.4.3. Classifying FNAC based on the Yokohama system

A retrospective study which was done to classify breast lesions based on the Yokohama system of reporting breast cytology in a tertiary care center in India analyzed a total of 762 FNAC slides re-examined and reclassified according to the IAC Yokohama system and reported as 3.8% cases as insufficient, 71.6% cases benign, 6.3% cases atypical, 3.1% cases suspicious and 15.2% cases as malignant. The study concluded as FNAC is a reliable diagnostic technique for the evaluation and management of breast lesions prior to surgery best suited with the Yokohama system [12].

A study done in another institution in India analyzed 144 FNAC cases with histopathological diagnosis based on the Yokohama system and showed the respective ROM for category 1 to 5 was 7.6%, 15.3%, 65.4%, 83.3% and 99.2%. Considering malignant cases as positive, sensitivity (86.8%), specificity (97.3%), positive predictive value(PPV) (99.2%), negative predictive value(NPV) (66.1%) and accuracy (89%) were shown. The study concluded that incorporation of the Yokohama system to categorize breast cytopathology adds diagnostic clarity, consistency and accuracy in reporting, which also helps the clinician to predict the ROM and patient outcome [16].

A retrospective cross-sectional study involving 2133 cases aimed to categorize FNAC data based on the new IAC system, calculate the ROM, sensitivity, specificity, positive predictive values, false negative, and false-positive rate was done at a hospital in Pakistan. It showed that 6.9% insufficient, 65.8% benign, 7.2% atypical, 7.5% suspicious and 12.6% malignant. The respective ROM for category 1 to 5 was 45.5%, 10.3%, 30.6%, 82.8% and 99.3%. The study also showed 83.4% sensitivity and 85.2% specificity. The PPV for category 3, 4 and 5 was 67.34%, 82.7% and 99.34%, respectively, with false-negative rate of 7.9% and false positive rate of 0.66%. It concluded that ROM for category 1 was higher compared to previous studies; thus suggested the use of core needle biopsy in such cases [14].

A retrospective study classified FNAC based on the Yokohama system and revealed 5%, 1.5%, 17.4%, 81.8% and 100% ROM for category 1 to 5, respectively. It concluded that the Yokohama system is a terrific system for accurately diagnosing FNAC with better reproducibility of reports and communication between the pathologist and clinician [10]. A systematic review and Meta analysis of data also revealed a pooled ROM of 17%, 1%, 20%, 86% and 100% respectively for

category 1 to 5. Finally, the study recommended that despite the early success of the Yokohama system more data would be needed to unravel the system's value in clinical practice [11].

A study was conducted to investigate the prognosis and application criteria of the two methods in real clinical practice the CNB and FNA. The study included 73,644 patients who underwent FNA and CNB. A multivariate Cox regression analysis showed that patients diagnosed using FNA had significantly worse overall survival and breast-cancer-specific survival than those diagnosed using CNB. The study sum up that, CNB should be performed preferably instead of FNAC in patients with BIRADS 5 lesions and non-palpable or centrally located tumors [24].

Another study which aimed to categorize the FNAC samples according to this Yokohama system of reporting and assess ROM for each category as well as the diagnostic yield of the FNAC, showed that FNAC samples were distributed as follows:- insufficient 5%, benign 71%, atypical probably benign 1%, suspicious for malignancy 2% and malignant 21%. The respective ROM for each category was 0% for insufficient, 4% for benign, 66% for atypical, 83% for suspicious for malignancy and 99% for malignant. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were respectively 94.6%, 98.9%, 98.6, 95.7% and 96.9%. The study concluded categorization of the FNAC according to Yokohama system of reporting helps pathologist in the diagnostic clarity and guides clinician in the proper patient management [25].

Similarly, a study done to categorize FNAC samples according to the Yokohama system the diagnostic accuracy, sensitivity and specificity and calculate the ROM for each category,a total of 63 women were included in the study. It showed insufficient 0, benign 34.9%, atypical 3.18%, suspicious 7.9%, and malignant 53.9%. The respective ROM for each category was 0% for insufficient, 4.5% for benign, 50% for atypical, 100% for suspicious, and 100% for malignant. In addition, the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 94.4%, 100%, 100%, 91.7% and 96.6%, respectively [26].

A study also showed that FNAC has high sensitivity, specificity, and accuracy in evaluation of breast lesions. A retrospective cohort study done in Bangalore showed the respective ROM for category 1 to 5 was 7.6% 15.3% 65.4%, 83.3% and 99.2%. It also showed 86.8% sensitivity, specificity of 97.32%, PPV of 99.2%, NPV of 66.06% and accuracy of 88.9% [27].

In many areas of cancer pathology, researchers worldwide are interested in making empirical studies and generating evidences regarding the sensitivity, specificity and other aspects of new diagnostic techniques or schemes [21, 28-30]. Likewise, in the pathological assessment of breast cancer, a number of many other studies were also done in different countries and institution showing a relatively similar results regarding the usefulness of the new IAC Yokohama system of classification in improving the communication between the clinician and pathologists about the FNAC results [4, 7, 8, 17, 22, 23, 31]. However, studies done in Ethiopia are very rare [23].

1.4.4. Concordance of FNAC with ultrasound results

Although there are relatively many numbers of studies in classification of FNAC in accordance of the Yokohama classification, the assessment of the concordance of FNAC with the ultrasound results was less researched issue. For instance, a retrospective study included 42 patients, was done to assess accuracy of ultrasound in the diagnosis of definite breast cancer based on the BIRADS, and correlated the radiological findings with the results of FNAC [19]. The study revealed high sensitivity of ultrasound (97%), positive predictive value of 92.5% and 90.5% overall accuracy [19].

The above study also showed that main ultrasound findings were masses either irregular in the majority (55%) of cases, poorly demarcated lesions in 26% and well defined in 14% of them. Axillary lymphadenopathy with malignant features noted in 50%. FNAC revealed mammary carcinoma in 93%, severe atypia in 7%, BIRADS V score in 76% of breast exam, BIRADS IV in 21% and the remaining 3% in BIRADS III category. Correlating these ultrasound findings of BIRADS with FNAC results, the ultrasound accuracy in the diagnosis of breast cancer was 90%. The study concluded as ultrasound is accurate diagnostic radiological modality for any breast lesion and noted as a recommended method to assess palpable breast mass or related cases [19].

Although the above study made great contributions in showing the joint efforts of the ultrasound and FNAC in identifying breast cancer, the detail about the matching pair between categories of FNAC based on the Yokohama system and the BIRADS's was overlooked. This showed there is a need to conduct more assessment with detail checking of concordance of the categories.

A study that retrospectively analyzed 1820 breast masses radiologically and classified according to the American College of Radiology BIRADS lexicon (67.6% being either BIRADS 4 or 5), sampled by FNA and immediately diagnosed by cytomorphology. Histopathological analysis and

ultrasound follow-up were the reference diagnostic tests of the study design. FNAC specimens were morphologically non-diagnostic in 3.1%, false negatives were observed in 1.5%, and there was only one false positive (0.06%) [18]. The study showed the importance of the application of combined diagnostic techniques.

A retrospective study which was done in India employed 272 female patients of ages ranging from 20 to 70 years, performed ultrasound for patients less than 35 years of age, it and performed mammography for the patients above 35 years of age. The imaging features were analyzed and classified according to the BIRADS. The study results showed that the results of FNAC were as accurate as tru-cut biopsy with 95.2% concurrence, and it was a high accuracy of radiologic findings with area under the curve of 0.914 [32]. Another retrospective study done in the same country in 249 patients showed that among 249 lesions, 10 were given an inadequate category on FNAB (6 lesions belonging to BIRADS 4a, 2 lesions belonging to 4b, and 2 lesions belonging to the 4c category). Among the rest of the cases, 151 were BIRADS 4a, 49 were BIRADS 4b, and 39 were BIRADS 4c lesions. FNAB shows high diagnostic accuracy in all BIRADS groups [33].

1.5. Conceptual Framework

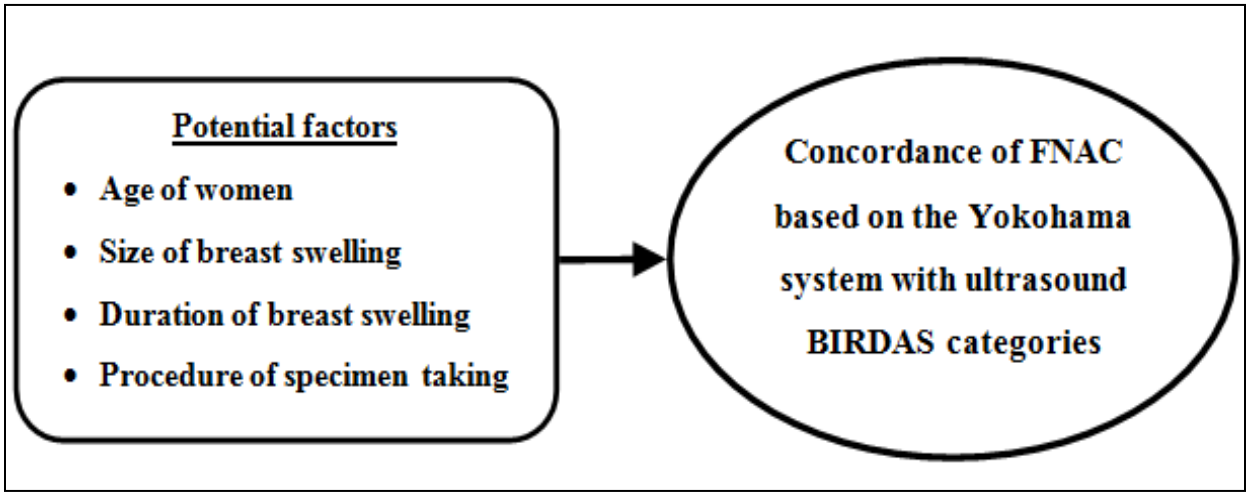

Figure 1: Conceptual framework for the association of potential factors with concordance FNAC based on the Yokohama classification with ultrasound BIRADS categories

2. Objectives of the study

2.1. General objective

- ❖ To investigate the concordance of breast cytology based on the Yokohama classification with ultrasound BIRADS among women with breast swelling examined at Tikur Anbessa specialized hospital in Addis Ababa, Ethiopia.

2.2. Specific objectives

- To classify FNAC results based on the Yokohama system
- To classify ultrasound results based on the ACR BIRADS categories
- To assess the concordance of the FNAC results based on the Yokohama system with ultrasound results based on the ACR BIRADS
- To examine association of potential factors with the overall concordance of FNAC based on the Yokohama system of classification with ultrasound ACR BIRADS categories

3. Methods and materials

3.1. Study area

This study was conducted at the Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia. The Pathology and the Radiology departments were the departments where the present study was focused to access the study participants.

3.2. Study design and period

Hospital based retrospective cross-sectional study design was used to assess the concordance of breast cytology based on the Yokohama classification and ultrasound BIRADS category in patients with breast swelling examined at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. The study was conducted from March 2024 to January, 2025.

3.3. Source population

All women who examined for breast cytology at Tikur Anbessa Specialized Hospital were the source population for this study.

3.4. Study population

All women who examined for breast cytology at Tikur Anbessa Specialized Hospital during the past three years (From January 1/2022 to December 31/2024; retrospectively) were the study population for this study from which the study participants were selected.

3.5. Inclusion and exclusion criteria

Inclusion criteria: All women who

- Examined for breast cytology at Tikur Anbessa Specialized Hospital from January 1/2022 to December 31/2024.
- Examined by the two techniques FNAC (either by freehanded or ultrasound guided) and ultrasound/radiologically
- Whose hospital record was complete for the required data, were included in this study.

Exclusion criteria: All women

- Whose hospital record was incomplete for required information to complete this study
- Whose hospital record was not clear to read, torn and contains ambiguous information
- Who diagnosed by only one of the two techniques
- Those with the ultrasound examination done outside Tikur Anbessa Specialized Hospital

- Whose test results were in ‘category 1’ of either the BIRADS or the Yokohama schemes; were not included in this study.

3.6. Sample size determination

Since the numbers of FNAC done for breast swelling at TASH were found to be very small, we applied a non-probability sampling technique; and all patients who had satisfied the predefined inclusion criteria (given above in Section 3.5) were included in our study.

3.7. Sampling procedure

In this study Tikur Anbessa Specialized Hospital was selected purposively. It was done with the intention of conducting the study to investigate concordance of breast cytology based on the Yokohama classification and ultrasound BIRADS category in patients with breast swelling at the hospital, satisfy the study requirements regarding the numbers of the study participants and the necessary data. To select the samples, firstly the medical records of all the patients with breast swelling were accessed; and then, all patients satisfying the inclusion criteria were selected and their medical records were prepared for the data extraction/culling.

3.8. Data collection method

Data was collected from TASH and Churchil Health Center under ELSE KRONER CANCER CENTER by use of a data culling checklist (see Annex 1), which was pilot tested for its practicality to cull data based on both diagnostic techniques and results of the breast cytology as well as the sociodemographic and related variables. The data regarding FNAC was checked and classified/re-classified based on the Yokohama system developed by the International Academy of Cytology (IAC) [9]. Likewise, ultrasound results data was checked and classified/re-classified based on BIRADS developed by the American College of Radiology (ACR) [34].

3.9. Description of the study variables

3.9.1. Dependent variable

The dependent variable for the present study is:

- **Concordance of FNAC based on Yokohama classification with ultrasound BIRADS category:** This variable was generated by assigning “1” for the successful of concordance between the two complementary categories of the two systems with respect to the same case (patient) and by assigning “0” for the non-concordance/disagreement.

In this study the main objective was assessing the concordance of the breast swelling diagnosis results of FNAC based on Yokohama classification with the ultrasound BIRADS category. For the purpose of describing the cases in each of the categories of the two systems, the Yokohama system of reporting FNAC and the BIRADS scheme of reporting ultrasound results were firstly analyzed as is, by their standard categories. The five standard categories in Yokohama system [9, 11], and the six standard categories in the BIRADS [34], with their respective risk of malignancy (ROM) are presented below (Table 1).

Subsequently, in further analyses the most related categories in each of the two systems were merged based on their respective ROM and new merged categories were generated for each of them. Merging related categories in each of the two schemes based on the respective ROM was proved by previous studies vital to generate complementary categories between the two systems which further facilitate rational appraisal of the concordance of the results obtained from the two schemes. Besides, for the purpose of making additional statistical analysis a "dummy" dependent variable was generated as described above, with "1" assigned for the overall concordance of the two systems and "0" for overall non-concordance of the two systems, done based on the newly generated and rationally comparable categories for each of the two systems [9, 11, 18, 19].

Table 1: Standard categories of the Yokohama and the BIRADS schemes with their ROM

Categories the Yokohama system	Category of the BIRADS system
1: Insufficient: ROM=10-28% [9, 11].	1: Negative: ROM=0% [34].
2: Benign: ROM=1-3% [9, 11].	2: Benign: ROM=0% [34].
3: Atypical: ROM=17-23% [9, 11].	3: Probably Benign: ROM > 0% but ≤ 2% [34].
4: Suspicious ROM=79-92% [9, 11].	4: Suspicious: > 2 but < 95% malignancy [34].
5: Malignant ROM=99-100% [9, 11].	5: Highly suggestive of malignancy: ROM ≥95% [34].
	6: Known biopsy proven malignancy: NA [34].

Note: ROM=Risk of malignancy, NA=Not available

3.9.2. Independent variables

The independent variables for the present study are

- Sociodemographic factor:
    - Age
- Clinical and pathological factors:
    - Size of breast swelling (in centimeter, categorized in accordance of literature)
    - Duration of breast swelling (In weeks/categorized for purpose of analyses)
    - Procedure of specimen taking (Freehanded or ultrasound guided)

3.10. Operational definitions

- **Concordance**: If the FNAC result category based on the Yokohama system is matching exactly with the complementary ultrasound BIRADS category for the same case (patient), the two systems are said to be concordance for that patient.
- **Duration of swelling:** The estimated time of breast swelling from its onset to the time of diagnosis (as identified by the women) shown in the medical record of the patient. For the purpose of statistical analyses, it is presented in weeks.
- **Freehanded:** Refers to the procedure which the fine needle aspiration cytology specimen is collected without the ultrasound guidance.
- **Non-concordance**: If the FNAC result category based on the Yokohama system is not exactly fitting with the complementary ultrasound BIRADS category for the same case (patient), the two systems are said to be non-concordance for that patient.
- **Procedure of specimen taking:** Refers to the procedure which the fine needle aspiration cytology specimen was taken, i.e. whether freehanded or via ultrasound guidance.
- **Size of swelling**: The size of breast swelling as measured by a standard unit (centimeter) and dimensions of measurement and reported in the medical record of patients, which further can be classified for the sake of ease of statistical analysis.
- **Ultrasound guided**: Refers to the procedure by which the fine needle aspiration cytology specimen is collected with ultrasound guidance.

3.11. Data quality control

To ensure data quality, training was given to the data collectors and supervisors for one day. The checklist was pre-tested for viability and reliably culling of the Pathologic as well as Radiologic data from the hospital records of patients. On spot checks, re-reviewing of records, and checking of completed checklists and quality of recordings was done via vigilant supervisions. Above all, in the classification/reclassification FNAC results based on the Yokohama system, pathologists worked in pair, and the FNAC results classified by one of the pathologists were blindly checked by the other pathologist [9]. Likewise, in the classification/reclassification of radiological data into BIRADS' category, radiologists worked in pair, and the ultrasound results classified by one of the radiologists were blindly checked by the other [34]. Besides, whenever disagreements

were occurring between classifications of the FNAC results for the same patient made by the two pathologists separately, a third pathologist was invited and allowed to re-check that case blindly; and finally, the disagreements were let to be solved through teamwork. In the same way, a similar approach was used to solve disagreements occurring in the classification of the ultrasound results for the same patient based on the BIRADS made by the two radiologists separately.

3.12. Data processing and analysis

Data was entered in Epi.Info Version 7 software; while further statistical analyses were done using STATA version 14.0. Descriptive statistics such as means were used to describe the study participants (patients) in terms of numeric variables i.e. age, size of lump and duration of lump. Frequencies and percentages were used to describe the clinical feature of the cases diagnosed in the study participants, the site of lump, the results in each of the categories of FNAC based on Yokohama system and ultrasound based on BIRADS; the patients in different categories of each of the aforesaid numeric variables after relevant recoding of variables.

Kappa-weighted analysis was used to analyze the concordance of the two systems. The Kappa values, percentage of agreement and the P-values were used to explain concordance of the two systems. Logistic regression model with bi-variable and multivariable analysis was used to study the association of potential factors with the overall concordance of FNAC results based on the Yokohama classification with the ultrasound BIRADS. In the modeling process, first bi-variable logistic regression analysis was done to see the unadjusted effect of each independent variable (potential factor) on the dependent variable (overall concordance of the two systems) via crude odds ratio (COR), 95% confidence interval (CI) and P-value. Finally, a multivariable logistic regression model was fitted for all independent variables (factors) with P-values of less than 0.25 in the bi-variable analyses. This was done intentionally to include more numbers of independent variables which may potentially affect the dependent variable when analyzed together with other independent variables, and to see adjusted effects [35]. Given, as this study was done based on secondary data, the independent variables included in this study are limited due to utilization of secondary data. Strength of associations was verified using adjusted odds ratio (AOR) and the corresponding 95% CI. For all the analyses done in this study the associations with P-values <

0.05 were regarded as statistically significant. Finally, the results of the statistical analyses were presented in graphs, tables and texts.

3.13. Ethical consideration

Ethical clearance and approval was obtained from the department of Pathology, College of Health Science, Addis Ababa University; and it was further communicated to the medical directors, responsible administrators and heads of the respective departments of Tikur Anbessa specialized hospital. The names of the study participants (patients) were not taken and anonymity of personal information was kept confidential throughout the study.

3.14. Dissemination of results

The findings of this study are primarily disseminated to the Department of Pathology, College of Health Science Addis Ababa University. Besides, the study results can be presented on seminars and conferences. As well, the study findings will be submitted for medical journals for possible publication.

4. Results

4.1. Description of the study participants

A total of 116 patients were included in this study. The age of the study participants ranged from 6 years to 80 years, with an average of 38.25 years. The size of the breast swelling of the patients ranged from 0.8 cm to 12 cm, with an average size of 3.35 cm. As well, the duration of the breast swelling of the patients included in this study ranged from 1 week to 364 weeks, with an average duration of 55.4 weeks (Table 2).

Table 2: Summary statistics for the numeric variables of the study participants (N=116)

Variable	Observation	Minimum	Maximum	Mean	Standard Deviation
Age in years	116	6	80	38.25	15.16
Size of swelling in centimeter	116	0.8	12	3.35	1.87
Duration of swelling in week	116	1	364	55.41	70.09

Besides, this study also gathered data regarding the clinical feature of the patients with respect to breast swelling, site of swelling and the procedure the FNAC specimens were taken. Accordingly, the majority of the patients (N=97,83.62%) included in this study had clinically identified breast swelling, (N=10,8.62%) patients had breast swelling and pain, (N=4,3.45%) patients had breast swelling and ulceration, and (N=3,2.59%) had breast pain. In about 58% of the patients, the swelling were found at the upper outer quadrant and in (N=15,12.93%) of the patients at the central area of the breast (Table 3).

Table 3: Summary statistics for the categorical variables of the study participants (N=116)

Variable	Category	Frequency (%)
Clinical features	Breast swelling	97 (83.62)
	Breast swelling and pain	10 (8.62)
	Breast swelling and ulceration	4 (3.45)
	Breast pain	3 (2.59)
	Breast swelling and pussy discharge	1 (0.86)
	Nipple discharge	1 (0.86)
Site of swelling	Upper outer quadrant	67 (57.76)
	Central area	15 (12.93)
	Upper inner quadrant	13 (11.21)
	Lower outer quadrant	7 (6.03)
	Lower inner quadrant	5 (4.31)
	Retroareolar area	5 (4.31)
	Subareolar area	2 (1.72)

	Periareolar area	1 (0.86)
	Supraareolar area	1 (0.86)
Procedure of specimen taking	Free handed	111 (95.69)
	Ultrasound guided	5 (4.31)

4.2. Classification of FNAC results based on the Yokohama system

As per the predetermined exclusion criteria set based on the main objective of this study, patients either with FNAC results grouped at category one (i.e. Inadequate/Insufficient) of the Yokohama system or those with ultrasound test results grouped at category one (i.e. Negative) of the American College of Radiology (ACR) proposed breast imaging reporting and data system (BIRADS) classifications were excluded, giving a total of 116 patients. And finally, the FNAC and the ultrasound test results of each of the 116 patients included in this study were classified based on the Yokohama system of classification and the ACR BIRADS, respectively.

According to the classification of the FNAC test results of the total of 116 patients, 49 (42.24%) of the patients were benign (category 2), 5 (4.31%) of the patients were atypical (category 3), 8 (6.90%) of the patients were suspicious for malignancy (category 4) and 54 (46.55%) of the patients were malignant (category 5) in reference to standard categories of the Yokohama system (Figure 2).

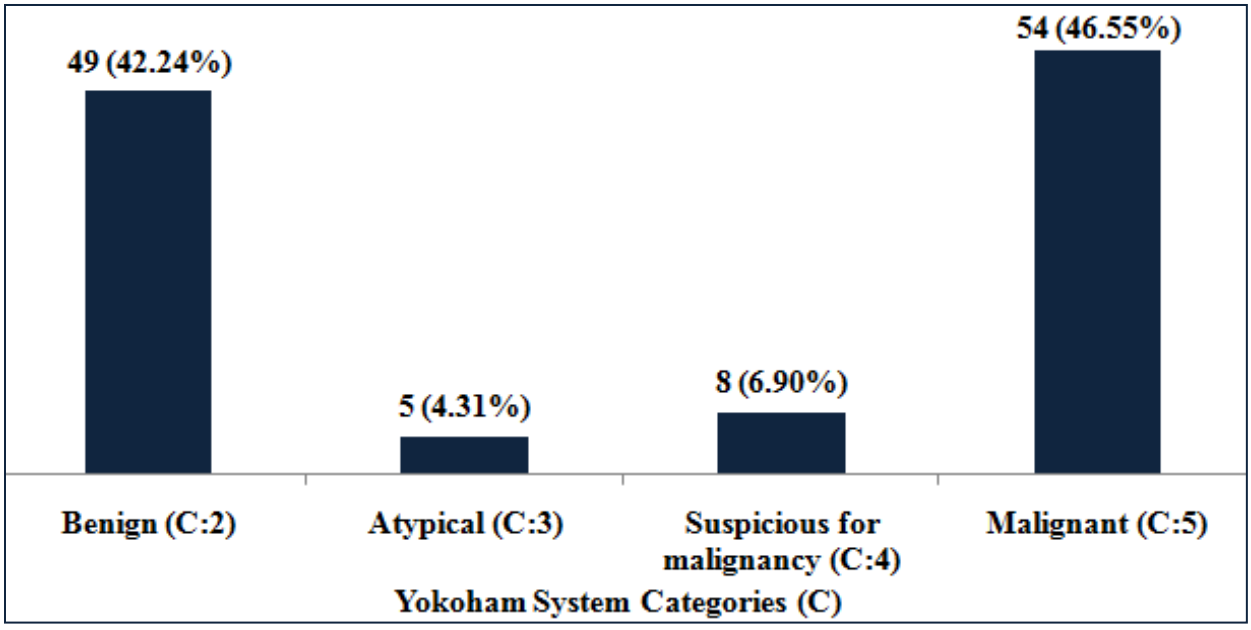

Figure 2: Classification of FNAC results based on Yokohama system in patients (N=116)

4.3. Classification of ultrasound results based on the ACR BIRADS

Akin to the classification of the FNAC results of each of the 116 patients included in this study based on the Yokohama system of classification, the ultrasound test results of each of the 116 patients were classified based on the ACR BIRADS. Accordingly, among the total 116 patients whose ultrasound test results of their breast lumps classified the based on the ACR BIRADS, the ultrasound test results of 41 (35.34%) patients were benign (category 2), 8 (6.90%) patients were probably benign (category 3), 14 (12.07%) patients were suspicious for malignancy (category 4) and 53 (45.69%) patients were highly suggestive of malignancy (category 5) in accordance with the standard categories of the ACR BIRADS (Figure 3).

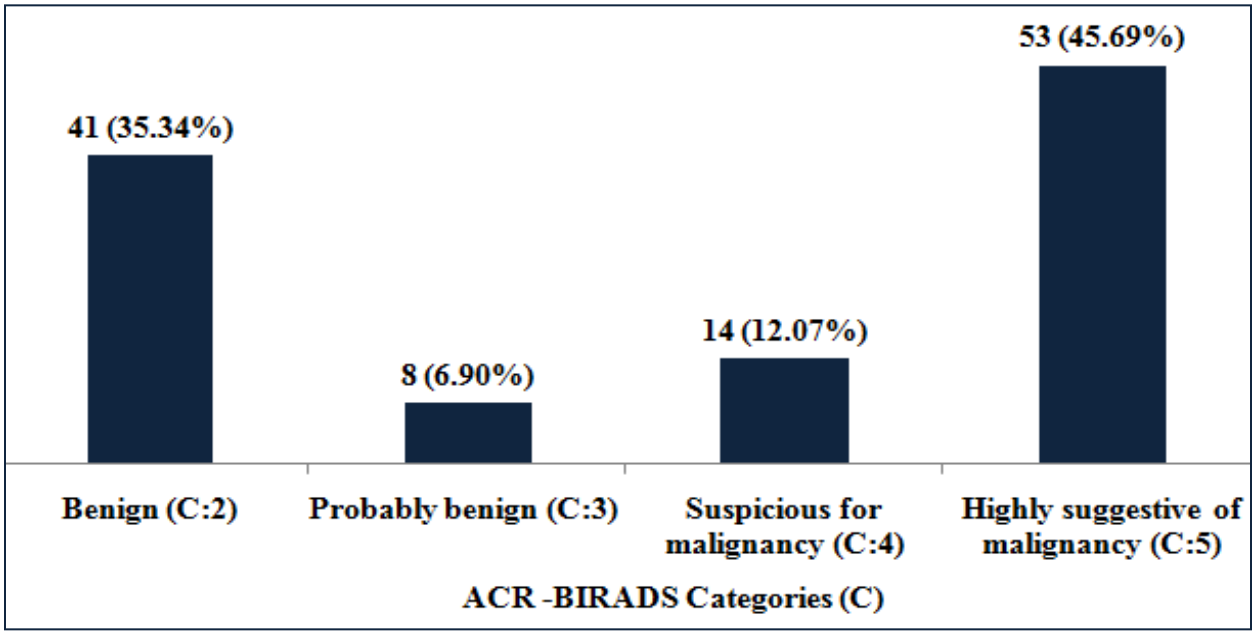

Figure 3: Classification of ultrasound results based on ACR BIRADS in patients (N=116)

4.4. Concordance of FNAC based on Yokohama with ultrasound ACR BIRADS

4.4.1. Concordance based on the four standard categories of the two system

The concordance of the two systems was done based on the four standard categories of each of the two systems (Table 4).

The Kappa weight analysis showed that of the 49 cases classified as benign by the Yokohama system, 38 cases were exactly matched with the benign category of the ACR BIRADS, while 7 cases were in probably benign category and 4 cases in the suspicious for malignancy. Besides, of the 5 cases classified as atypical by the Yokohama system 2 cases were in the benign, 1 case was in the probably benign and 2 cases in the suspicious for malignancy categories. Among the total

of 8 cases classified as suspicious for malignancy by the Yokohama system 1 case was in the benign, 5 cases were in the suspicious for malignancy and 2 cases were in the highly suggestive of malignancy categories. Among the total of 54 cases classified as malignant by the Yokohama system 3 cases were in the suspicious for malignancy and 51 cases were in the highly suggestive of malignancy categories (Table 4).

Besides, Kappa weight analysis results showed that the concordance of the two systems based on the four standard categories of the two systems was 81.90%, and this agreement between the two systems was statistically significant as shown by a *P-value* of less than 0.001 (Table 4).

Table 4: Kappa analysis for concordance of the two systems by standard categories (N=116)

Panel A: Table of assessment based on the standard categories of the two system					
Yokohama System Categories	ACR-BIRADS Categories				
	Benign (2)	Probably Benign (3)	Suspicious for malignancy (4)	Highly suggestive of malignancy (5)	Total
Benign (2)	38	7	4	0	49
Atypical (3)	2	1	2	0	5
Suspicious for malignancy (4)	1	0	5	2	8
Malignant (5)	0	0	3	51	54
Total	41	8	14	53	116

Panel B: Additional summary results of Kappa analysis on the concordance of the two system					
Agreement	Expected agreement	Kappa	Std. Err.	Z	*P-value*
81.90%	37.33%	0.7111	0.0660	10.77	0.0000

4.4.2. Concordance based on the last two standard categories

The four categories of each of the two systems seem complementary to each other, i.e. category two of Yokohama with category two of ACR BIRADS, category three of Yokohama with category three of ACR BIRADS, etc. However, the complementary categories in each of the two systems often are not comparable each other due to the differences in their estimated risk of malignancy (ROM). In view of that, in addition to the four standard categories, the study analyzed concordance of the two systems based on the last two categories i.e. category 4 and 5 of Yokohama and BIRADS, with the assumption that the two categories of the two systems are more comparable each other regarding their ROM.

During the analysis of the concordance of the two systems regarding only the last two categories, firstly, the study included the observations (patients) with only category 4 and category 5 in both two systems. As shown in earlier sections, a total of 62 cases were classified in category 4 and

category 5 of the Yokohama system (Figure 2); and a total of 67 cases were classified in category 4 and category 5 of the BIRADS (Figure 3). Also, as shown in an earlier section one of the 62 cases in category 4 and category 5 of the Yokohama system was fitting outside the two categories (category 4 and 5) of the BIRADS, and six of the 67 cases in category 4 and category 5 of the BIRADS were fitting outside the two categories (category 4 and 5) of the Yokohama system (see Table 4). This showed the total observations with only category 4 and category 5 in the two systems, selected for analysis of the concordance of the two systems with respect to the last two standard categories (category 4 and 5) ,were 61 (N=61) (Table 5).

The Kappa weight analysis done for the concordance of the Yokohama system with the BIRADS with respect to the two standard categories (i.e. category 4 and 5) showed, of the total of 7 cases classified in category 4 (suspicious for malignancy) of the Yokohama system, 5 cases exactly matched to category 4 (suspicious for malignancy) of the BIRADS, while 2 of the cases were in category 5 (highly suggestive of malignancy) of BIRADS. Of the total of 54 cases classified in category 5 (malignant) of the Yokohama system, 51 cases exactly matched to category 5 (highly suggestive of malignancy) of BIRADS, while 3 of the cases were in category 4 (suspicious for malignancy) of the BIRADS (Table 5).

The Kappa weight analysis results also showed that concordance of the two systems with respect to the last two standard categories (category 4 and 5) was 91.80%, and this agreement of the two systems was statistically significant at a *P-value* < 0.001 (Table 5).

Table 5: Kappa analysis for concordance of the two systems by two standard categories (N=61)

Panel A: Table of assessment based on the standard categories of the two system			
Yokohama System Categories	ACR-BIRADS Categories		
	Suspicious for malignancy (4)	Highly suggestive of malignancy (5)	Total
Suspicious for malignancy (4)	5	2	7
Malignant (5)	3	51	54
Total	8	53	61

Panel B: Additional summary results of Kappa analysis on the concordance of the two system					
Agreement	Expected agreement	Kappa	Std. Err.	Z	P-value
91.80%	78.42%	0.6202	0.1277	4.86	0.0000

4.4.3. Merging categories in each system based on risk of malignancy (ROM)

Assessment of the concordance of FNAC results based on the Yokohama system with ultrasound test results based on the ACR BIRADS, with respect to the four standard categories, i.e. category

2 to category 5, may bias the results due to differences between each pair of the complementary categories of the two systems. This is mainly linked with the difference in the risk of malignancy (ROM) empirically revealed for each of the categories [14]. As such, 'benign' in the Yokohama system indicates a 0 to 3% ROM, while 'benign' in the ACR BIRADS indicates 0% ROM. Also, 'probably benign' (category 3 of BIRADS), roughly shows 0 to 2% ROM. Bearing these figures in mind, 0% ROM (category 2 of BIRADS) and 0 to 2% ROM (category 3 of BIRADS) are in the range of 0 to 3% ROM (category 2 of Yokohama). So, comparing complementary categories belonging to each of the systems (e.g. category 2 of Yokohama with category 2 of BIRADS), as they are identical, without considering the ROM estimated for each category in the two systems, may lead to erroneous results which also lead to erroneous conclusions [9, 11, 34].

In this study, with the aim to create complementary categories with comparable ROM in the two systems, we merged some consecutive categories in each system, in line with previous empirical evidences [9, 11, 34]. Accordingly, the Yokohama system's category 2 was kept as is, coded as 1 and it has a total of 49 cases. Category 3 and category 4 of Yokohama were merged together, coded as 2 and it has a total of 13 cases. Category 5 was kept as is, coded as 3 and it has a total of 54 cases. Likewise, category 2 and category 3 of the BIRADS were merged together, coded as 1 and has a total of 49 cases. Category 4 of the BIRADS was kept as is, coded as 2 and it has a total of 14 cases. Category 5 of the BIRADS was kept as is, coded as 3 and it has a total of 53 cases. Finally, three new merged categories in each of the two systems were made for the total of 116 patients included in this study, ready for further analysis in the next section (Table 6).

Table 6: Merged categories of the Yokohama system and BIRADS based on ROM (N=116)

System	Category	Code [a]	Frequency (%)
Yokohama	Benign (C:2)	1	49 (42.24)
	Atypical (C:3) and Suspicious for malignancy (C:4)	2*	13 (11.21)
	Malignant (C:5)	3	54 (46.55)
ACR-BIRADS	Benign (C:2) and Probably benign(C:3)	1*	49 (42.24)
	Suspicious for malignancy (C:4)	2	14 (12.07)
	Highly suggestive of malignancy (C:5)	3	53 (45.69)

Note: *=*New categories formed by merging 'standard' categories based on the ROM,* [a]*=Code is used to assign new and comparative categories suitable to make further analysis in this study.*

4.4.4. Concordance based on three categories merged by ROM

Concordance of the two systems was assessed based on the three merged categories ready based on ROM as shown earlier (Section 4.4.3). The Kappa weight analysis results for concordance of

the two systems based on the three merged categories revealed, of the total 49 cases classified in code 1 of the Yokohama system (standard category 2 of Yokohama), 45 cases matched to code 1 of BIRADS (category 2 and 3 of BIRADS), while 4 of the cases were in code 2 of the BIRADS (category 4 of BIRADS). Among the total 13 cases classified in code 2 of the Yokohama system (category 3 and 4 of Yokohama), 7 cases matched to code 2 of the BIRADS (category 4 of the BIRADS), 4 cases were in code 1 of the BIRADS (category 2 and 3 of BIRADS), while 2 of the cases were in code 3 of BIRADS (category 5 of BIRADS). Among the total 54 cases classified in code 3 of the Yokohama system (category 5 of the Yokohama), 51 cases matched to code 3 of BIRADS (category 5 of BIRADS), while 3 of the cases were in code 2 of the BIRADS (category 4 of BIRADS) (Table 7).

Besides, the Kappa weight analysis results also showed that concordance of the two systems with respect to the three merged categories was 88.80%, and this agreement of the two systems was statistically significant at a *P-value* < 0.001 (Table 5).

Table 7: Kappa analysis for concordance of the two systems by merged categories (N=116)

Panel A: Table of assessment based on the merged complementary categories of the two system					
Yokohama System Categories		ACR-BIRADS Categories			
		Benign (2) and Probably benign (3)	Suspicious for malignancy (4)	Highly suggestive of malignancy (5)	Total
	Code [a]	1	2	3	
Benign (2)	1	45	4	0	49
Atypical (3) and Suspicious for malignancy (4)	2	4	7	2	13
Malignant (5)	3	0	3	51	54
Total		49	14	53	116

Panel B: Additional summary results of Kappa analysis on the concordance of the two system					
Agreement	Expected agreement	Kappa	Std. Err.	Z	P-value
88.80%	40.47%	0.8118	0.0729	11.14	0.0000

Note: [a]*=Code is assigned for the new merged categories in each system suitable for making this analysis.*

4.4.5. Overall concordance of the two systems after merging based on ROM

For further analysis of the association of potential factors which might be linked with the overall concordance of FNAC results based on the Yokohama system of classification, and ultrasound results based on the ACR BIRADS, the study generated a dummy variable of 0 and 1. The variable was generated based on the three merged categories based on ROM. Accordingly, among the total of 116 patients included in this study, the FNAC test results based on the

Yokohama system of classification and the ultrasound results based on the ACR BIRADS were exactly matched for 103 (88.80%) of the patients. However, for 13 (11.20%) of the study participants, the test results of breast swelling obtained from the two diagnostic techniques were not concordance with each other (Figure 4). In view of that, in generating of the dummy variable, for further statistical analysis, concordance of the two systems was considered 'success' and coded by 1 (i.e. Concordance=1) while none-concordance of the two systems was considered 'failure' and coded by 0 (i.e. Not concordance=0).

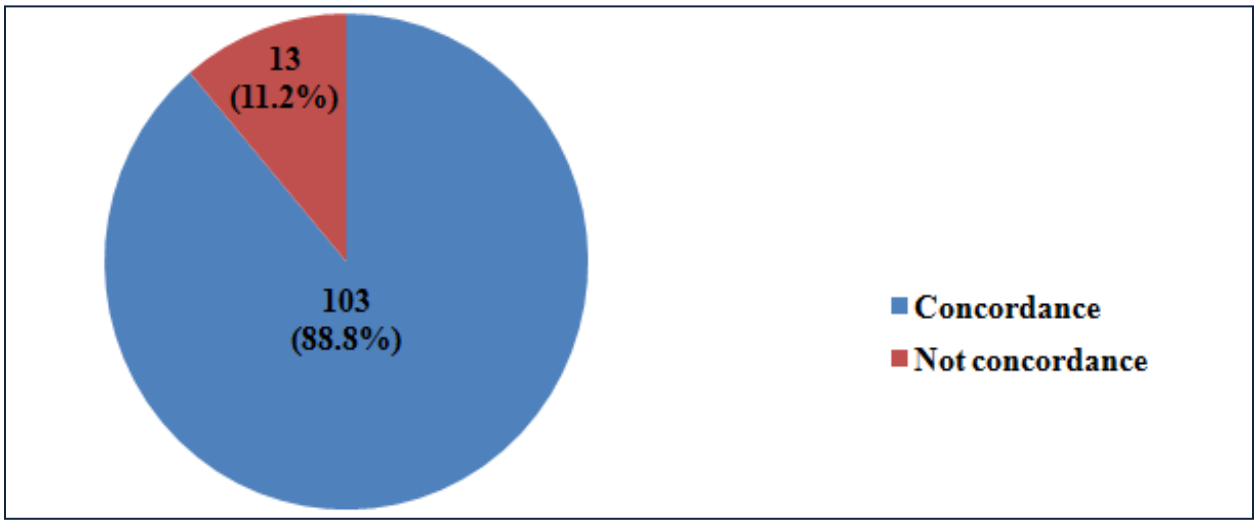

Figure 4: Overall concordance of the Yokohama system with BIRADS in patients (N=116)

4.5. Logistic regression analysis of factors associated with overall concordance

One of the specific objectives of this study was to examine the potential factors associated with the concordance of the breast swelling test results from two diagnostic techniques as given by the two respective classification schemes. Accordingly, a conceptual framework with four potential factors was anticipated for their link with the overall concordance of the FNAC results based on the Yokohama system with the ultrasound test results based on BIRADS. The factors were age of woman, size of swelling, duration of swelling and procedure of specimen taking.

Logistic regression model with bi-variable and multivariable analysis was used to examine the association of potential factors with overall concordance of FNAC based on Yokohama system with ultrasound BIRADS. In the modeling process, first, a bi-variable logistic regression analysis was done to see unadjusted effect of each independent variable on the dependent variable, and then a multivariable logistic regression model was fitted for all independent variables with *P-values* of less than 0.25 in the bi-variable analysis [35]. For rational interpretation of results the

numerical variables, age of woman, size of swelling and duration of swelling were coded to categorical forms. Thus, the study participants were grouped into three age groups, i.e. less than 26 years (22 patients), age of 26 to 49 years (66 patients) and age of above 49 years (28 patients). Likewise, the numeric variables size of swelling and duration of swelling were re-coded into categorical forms with two and three categories, respectively (Table 8).

Table 8: Bi-variable and multivariable logistic regression analyses of factors (N=116)

Variable	Category	Total	Concordance		COR (95% CI)	*P-value*	AOR (95% CI)	*P-value*
			Yes	Not				
Age in years	< 26	22	20	2	Reference			
	26 to 49	66	58	8	0.7 (0.1, 3.7)	0.699	-	-
	> 49	28	25	3	0.8 (0.4, 5.5)	0.850	-	-
Size of swelling	≤ 2 cm	33	26	7	Reference			
	> 2 cm	83	77	6	3.5 (1.1, 11.2)	0.039*	2.9 (0.8, 10.3)	0.093
Duration of swelling in week	1 to 26	59	49	10	Reference			
	27 to 52	32	30	2	3.1 (0.6, 14.9)	0.166	2.7 (0.5, 13.6)	0.236
	> 52	25	24	1	4.9 (0.6, 40.5)	0.141	4.4 (0.5, 38.1)	0.182
Procedure of specimen taking	FH	111	99	12	Reference			
	UA	5	4	1	0.5 (0.1, 4.7)	0.532	-	-

Note: *COR=Crude odds ratio, AOR=Adjusted odds ratio, CI=Confidence interval, cm=centimeter, FH= Freehanded, UA=Ultrasound aided.*

Among the four independent variables (factors) assessed for their unadjusted effect with overall concordance of FNAC based on the Yokohama system with ultrasound BIRADS via bi-variable logistic regression analysis, only the size of swelling showed a statistically significant association as given by the crude odds ratio (COR) with 95% confidence interval (CI) of [COR=3.5, 95% CI (1.1, 11.2)], and the resulting P-value=0.039 (Table 8). This showed that the overall concordance of FNAC results based on the Yokohama system with ultrasound BIRADS was 3.5 times higher among women with breast swelling size of greater than 2 centimeters compared to the women with breast swelling size of less than or equal to 2 centimeters. However, none of the other independent variables showed a significant association in the bi-variable analysis. As well, although the two independent variables, size of swelling and duration of swelling were selected for multivariable analysis both of them did not show statistically significant association with the overall concordance of the two systems after adjusted for each other, considering a *P-value* of less than 0.05 (Table 8).

5. Discussion

Integration of diagnoses techniques such as clinical examination, radiological assessments and breast cytology, is the most widely applied procedure by healthcare providers known to be useful to ensure the early detections of breast cancer cases [13, 15, 18]. To foster the integration of such diagnoses techniques and make them available in affordable way, empirical evidence regarding the concordance of the test results obtained from each of the components, particularly the breast cytology and the radiological assessments is decisive. Accordingly, this study tried to assess the concordance of breast cytology based on the Yokohama classification with ultrasound BIRADS category in women with breast swelling examined at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

In this study, the concordance of FNAC results based on the Yokohama system of classification with the ultrasound BIRADS was checked via three different approaches. The first approach was assessment of the concordance of FNAC results based on the Yokohama system of classification with ultrasound BIRADS, with reference to the four standard categories (i.e. category 2, category 3, category 4 and category 5) in each system. Based on this approach, the concordance of breast lesion test results of FNAC based on the Yokohama system of classification with the ultrasound test results based on the ACR BIRADS' classification was 81.90%. This finding was lower than the concordance of breast lesion test results of the two techniques reported by previous studies which were conducted in Iraq [19], and India [32, 33]. As well, this finding was also lower than the level of concordance of breast lesions test results of the two techniques obtained based on the second and the third approaches we used in this study.

The lower level of concordance of the breast lesions test results of the two systems revealed by this study based on the first approach, in comparison with the findings of previous studies as well as the level of concordance we obtained in this study via the other two approaches, might be explained by differences in the numbers of categories included. Given, the previous studies were mainly focused on the assessment of the concordance of the two systems with respect to category 4 and category 5 [19, 32, 33].

In the second approach, the study focused on only selected categories and assessed the concordance of the FNAC test results based on the Yokohama system of classification with the ultrasound BIRADS with respect to category 4 and category 5 in each system. Based on this

approach, the concordance of the breast lesion test results of FNAC based on the Yokohama system of classification with ultrasound BIRADS' classification was 91.80%. This finding was comparable with the finding of a previous study (90.50%) which was conducted in Iraq [19].

In this study, we used a third approach to assess the concordance of breast lesion test results of the two systems. In this approach, we included the four standard categories of the two systems, while we merged related categories within each system based on their risk of malignancy (ROM) so as to get merged complementary categories, which become more comparable. Accordingly, the concordance of breast lesion test results of the FNAC based on the Yokohama system of classification and the ultrasound test results based on the BIRADS was 88.80%. This finding was comparable with our own finding in approach two (91.80%), and the finding of a previous study which was conducted in Iraq [19].

Nevertheless, all of the findings of this study i.e. 81.90% obtained based on the first approach, 91.80% obtained based on the second approach and 88.80% obtained based on the third approach regarding the concordance of the breast lesion test results of the FNAC based on the Yokohama system of classification and the ultrasound test results based on the BIRADS, were all lower than the 95.0% and 95.5% level of concordance which were reported by previous studies conducted in India [32, 33]. Although there are notable differences between the present study and the previous studies, regarding the setting where conducted such disparities might be also associated with the availability of efficient cytopathologists in aspiration and clarification of the findings and well-qualified technicians to ensure the preparation of quality smear, as well as the availability of efficient radiologists, and the presence and use of up-to-date equipments [19].

Furthermore, the present study was also tried to assess the association of age of women, size of swelling, duration of swelling and the procedure of specimen taking (either freehanded or ultrasound guided) with the overall concordance of the breast lesion test results of FNAC based on the Yokohama system of classification with the ultrasound test results based on BIRDAS. However, the findings revealed that none of the factors showed statistically significant association. In fact, factors related with occurrence of breast cancer were well studied [36]. This was the first attempt done to explore the patient and case related factors that may affect concordance of the two diagnostic techniques.

5.1. Strength and limitations of the study

The present study has several strengths. These include, the study was a first of its type to assess the concordance of the two systems in Ethiopian context in general and, in Tikur Anbessa Specialized Hospital in particular. Besides, the study applied different approaches to assess the concordance of the two systems regarding the inclusion or the consideration of the number of the categories used while comparing the two techniques. Furthermore, this study was also the first of its type that tried to assess the factors which might be associated with the concordance of the two systems. On the other hand, the present study has also a number of limitations. First, the study was conducted in only a single health institution, including patients from other hospitals would have been better to get a bigger picture of the concordance of the two systems in comprehensive way. As well, regarding the factors assessed only limited potential factors were included due to the potential limitations associated with the utilization of secondary data.

6. Conclusion and recommendation

6.1. Conclusion

The present study assessed the concordance of FNAC test results based on the Yokohama system of classification with the ultrasound test results based on the BIRADS by using three different approaches. In the first approach, the concordance of the two systems was assessed with respect to their four standard categories, and 81.90% concordance was revealed. In the second approach, the concordance of the two systems was assessed with respect to the two standard categories, and 91.80% concordance was revealed. In the third approach, the concordance of the two systems was assessed with respect to the merged categories based on the respective risk of malignancy (ROM), and 88.80% concordance was revealed. In all of the three approaches, the concordance of the two systems revealed by the present study was high. This shows that application of the two techniques (FNAC and ultrasound) together can increase early detection of breast cancer cases.

Moreover, as the two diagnostic techniques are highly concordance, the application of either of the two diagnostic techniques separately in resource limited situations is also valuable to increase accessibility, availability and affordability of breast lesion diagnosis services in as many as possible health care facilities in context of developing countries. Besides, using the Yokohama system of classification to categorize the fine needle aspiration cytology test results is helpful so as to foster communication and comparison of results.

6.2. Recommendation

Based on the findings of the present study the following recommendations have been given to the respective bodies.

Clinicians

To be very cautious in interpretation of each diagnostic modality if the results are really different.

Further researchers

Further researchers should conduct similar assessment studies in other hospitals in the country. As well, to fill the gaps due to utilization of secondary data future studies should also focused on the utilization of primary data by applying prospective study approaches.

7. References

1. Sung H FJ, Siegel RL, et al,: **Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries**. *CA Cancer J Clin* 2021, **71**:209-249.

2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F: **Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed [26 July, 2016].** 2024.

3. **Breast cancer: prevention and control. WHO, [Accessed: July 26, 2024] Available from: http://www.who.int/cancer/detection/breastcancer/en/**

4. Tari DU, Morelli L, Guida A, Pinto F: **Male Breast Cancer Review. A Rare Case of Pure DCIS: Imaging Protocol, Radiomics and Management**. *Diagnostics* 2021, **11**(2199):1-16. https://doi.org/10.3390/diagnostics11122199.

5. Gupta S: **Breast cancer: Indian experience, data, and evidence**. *South Asian J Cancer* 2016, **5**(3):85.

6. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F: **Global Cancer Observatory: Cancer Today (Ethiopia). Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed [26 July, 2016].** 2024.

7. The American Society of Breast Surgeons: **Consensus Guideline on Concordance Assessment of Image-Guided Breast Biopsies and Management of Borderline or High-Risk Lesions**. In.; 2018.

8. R J, BH PS, A V, G B: **Categorization of Fine Needle Aspirates of Breast Lesions Using 'Yokohama Grading System for Reporting Breast Cytopathology' – A Retrospective Study In Tertiary Care Hospital**. *Journal of Dental and Medical Sciences* 2022, **21**(11):31-36. http:/doi:10.9790/0853-2111043136.

9. Yu W, Gan Q, Gong Y: **The Yokohama System for Reporting Breast Cytopathology**. *Journal of Clinical and Translational Pathology* 2023 **3**(2):99–105. http:/doi:110.14218/JCTP.12023.00006.

10. Ahuja S, Malviya A: **Categorization of Breast Fine Needle Aspirates Using the International Academy of Cytology Yokohama System Along with Assessment of Risk of Malignancy and Diagnostic Accuracy in a Tertiary Care Centre**. *J Cytol* 2021, **38**:158-163. http:/doi:110.4103/JOC.JOC_4131_4121.

11. Nikas IP, Vey JA, Proctor T, AlRawashdeh MM, Ishak A, Ko HM, Ryu HS: **The Use of the International Academy of Cytology Yokohama System for Reporting Breast Fine-Needle Aspiration Biopsy. A Systematic Review and Meta-Analysis**. *Am J Clin Pathol* 2023, **159**:138-145. http:/doi:ORG/110.1093/AJCP/AQAC1132.

12. Yadav R, Singh N, Bakna M, Bhadkariya A, Singh A: **Cytomorphological spectrum of breast fine needle aspiration cytology using the International Academy of Cytology Yokohama System and evaluation of associated risk of malignancy–A retrospective study in a tertiary care center**. *Surgical and Experimental Pathology* 2024, **7**(6):1-7. https://doi.org/10.1186/s42047-42024-00148-42042.

13. Field AS, Raymond WA, Schmitt F: **The International Academy of Cytology Yokohama System for Reporting Breast Fine-Needle Aspiration Biopsy Cytopathology: Recent Research Findings and the Future**. *Cancer Cytopathology* 2021:847-851. http:/doi:810.1002/cncy.22450,wileyonlinelibrary.com.

14. Niaz M, Khan AA, Ahmed S, Rafi R, Salim H, Khalid K, Kazi F, Anjum A, Waheed Y: **Risk of Malignancy in Breast FNAB Categories, Classified According to the Newly Proposed International Academy of Cytology (IAC) Yokohama System**. *Cancer Management and Research* 2022, **14**:1693–1701.

15. Dharmalingam P, MukundaPai M, Nargund A, G C, L KB, Okaly GVP, D MS, R AKA: **Doing More with Less: Fine Needle Aspiration Cytology in Pediatric Neoplasms**. *J Cytol* 2021, **38**:121-132. http:/doi:110.4103/JOC.JOC_4197_4120.

16. Sreevidyalatha GM, Balaji TG, Manjunath L, Krishnamurthy SP: **Breast fine-needle aspiration cytology reporting using international academy of cytology Yokohama system: A single institution experience**. *Asian Journal of Medical Sciences* 2023, **14**(10):204-209. http:/doi:210.3126/ajms.v3114i3110.56146.

17. Brahmaiah J, Bhavadeep S, Kumar VH, Malapaka S, Govardhan T, Rentala S: **A study to classify the fine needle aspirates of breast lumps as per the IAC Yokohama system for reporting breast cytopathology along with histopathological correlation**. *Oncology and Radiotherapy* 2024, **18**(4):1-6.

18. Suciu V, Chamieh CE, Soufan R, Mathieu M-C, Balleyguier C, Delaloge S, Balogh Z, Scoazec J-Y, Chevret S, Vielh P: **Real-World Diagnostic Accuracy of the On-Site Cytopathology Advance Report (OSCAR) Procedure Performed in a Multidisciplinary One-Stop Breast Clinic**. *Cancers* 2023, **15**(4967):1-23. https://doi.org/10.3390/cancers15204967.

19. Khaleel M: **Correlating Fine Needle Aspiration Cytology Results of Mammary Malignancy with Corresponding Ultrasound BIRADS Score**. *Asian Pac J Cancer Care* 2022, **7**(1):37-40. http:/doi:10.31557/APJCC.32022.31557.31551.31537.

20. Ethiopia Ministry of Health: **National guideline for breast health, early diagnosis and timely breast cancer management in Ethiopia (2024-2028)**. In. Addis Ababa, Ethiopia: Ministry of Health; 2024: 1-90.

21. Anand N, Agrawal T, Gupta A, Shukla S, Pradhan R, Husain N: **Diagnostic Efficacy of BRAFV600E Immunocytochemistry in Thyroid Aspirates in Bethesda Category IV and Papillary Thyroid Carcinoma**. *J Cytol* 2021, **38**:113-119. http:/doi:110.4103/JOC.JOC_4248_4120.

22. Sigamani K, Chandran N: **Application of International Academy of Cytology Yokohama System for Reporting Breast Fine Needle Aspiration Cytology- A Retrospective Study**. *National Journal of Laboratory Medicine* 2022, **11**(2):63-66. http:/doi:10.7860/NJLM/2022/55194.52618.

23. Tefera A, Terefe L, Biresa K: **Cytomorphologic Study of Breast Lesions: Spectrum of Lesions and Histopathological Correlation**. *Pathol Lab Med Open J* 2024, **5**(1):1-11. http:/doi:10.17140/PLMOJ-17145-17114.

24. Gwak H, Woo SS, Oh SJ, Kim JY, Shin H-C, Youn HJ, Chun JW, Lee D, Kim SH: **A Comparison of the Prognostic Effects of Fine Needle Aspiration and Core Needle Biopsy in Patients**

with Breast Cancer: A Nationwide Multicenter Prospective Registry. *Cancers* 2023, **15**(4638):1-12. https://doi.org/10.3390/cancers15184638.

25. Kamatar PV, Athanikar VS, Dinesh U: **Breast Fine needle Aspiration Biopsy Cytology Reporting using International Academy of Cytology Yokohama System-Two Year Retrospective Study in Tertiary Care Centre in Southern India**. *National Journal of Laboratory Medicine* 2019, **8**(3):1-3. http:/doi:10.7860/NJLM/2019/42442:42362.

26. Cunha MD, Kini RG: **Breast fine needle aspiration biopsy cytology reporting using international academy of cytology Yokohama system: A single institution experience**. *International Journal of Clinical and Diagnostic Pathology* 2020, **3**(3):303-306. https://doi.org/310.33545/pathol.32020.v33543.i33543e.33300.

27. Nargund A, Mohan RH, Pai MM, Sadasivan B, Dharmalingam P, Chennagiri P, Handra CR: **Demystifying Breast FNAC's Based on the International Academy of Cytology, Yokohama Breast Cytopathology System- A Retrospective Study**. *Journal of Clinical and Diagnostic Research* 2021, **15**(3):1-5. http:/doi:10.7860/JCDR/2021/45366.14606.

28. Onder S, Kurtulan O, Kavuncuoglu A, Akdogan B: **Comparison of Diagnostic Performances of Urine Cytology Before and After the Use of The Paris System Criteria: An Institutional Experience from Turkey**. *J Cytol* 2021, **38**:133-139. http:/doi:110.4103/JOC.JOC_4138_4121.

29. Verma V, Khan A, Rao RN, Nath A, Hashim Z: **Role of Endobronchial Ultrasound Guided Transbronchial Needle Aspiration with Cellblocks in Diagnosis and Subtyping of Intrathoracic Lesions: Two Year Experience from a Tertiary Care Center**. *J Cytol* 2021, **38**:120-126. http:/doi:110.4103/JOC.JOC_4155_4121.

30. Bharati V, Kumari N, Rao S, Sindhwani G, Chowdhury N: **The Value and Limitations of Cell Blocks in Endobronchial Ultrasound‐Guided Fine‐Needle Aspiration Cytology: Experience of a Tertiary Care Center in North India**. *J Cytol* 2021, **38**:140-144. http:/doi:110.4103/JOC.JOC_4210_4120.

31. Aithmia R, Pangotra M, Sharma S: **IAC Yokohama Reporting of Breast Cytology to Assess Risk of Malignancy and Predictive Values**. *Saudi J Pathol Microbiol* 2022, **7**(7):267-271. http:/doi:210.36348/sjpm.32022.v36307i36307.36003.

32. Gupta P, Puri N, Syed A, Chowdhury N, Rao S, Sharda P, Ravi B, Mehrotra S, Kapoor A, Pandey D: **Concordance between birads and pathologic findings in breast lesions: A retrospective study**. *Breast J* 2019, **2019**(00):1–3.

33. Agrawal S, Anthony ML, Paul P, Singh D, Agarwal A, Mehan A, Singh A, Joshi PP, Kumar A, Syed a *et al*: **Accuracy of Breast Fine-Needle Aspiration Biopsy Using the International Academy of Cytology Yokohama System in Clinico-Radiologically Indeterminate Lesions: Initial Findings Demonstrating Value in Lesions of Low Suspicion of Malignancy**. *Acta Cytologica* 2021, **2021**(65):220–226.

34. The American Cancer Society: **Breast Cancer Early Detection and Diagnosis**. *cancerorg | 18002272345* 2022:1-79.

35. Bursac Z, Gauss H, Williams DK, Hosmer DW: **Purposeful selection of variables in logistic regression**. *BioMed Central* 2008, **3**(17):1-8. http:doi:10.1186/1751-0473-1183-1117.

36. Hassen F, Enquselassie F, Ali A, Addissie A, Taye G, Tsegaye A, Assefa M: **Association of risk factors and breast cancer among women treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: a case–control study**. *BMJ Open* 2022, **12:e060636.**:1-8. http:doi:10.1136/bmjopen-2021-060636.

8. Annex

8.1. Annex 1: Data culling form (checklist)

SN	MRN	FNAC No.	Age	Parity	duration	Size	BIRADS	Yokohama	Diagnosis
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									
20									
21									