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Turkish Federation of Breast Diseases Societies

European Journal of Breast Health is the official journal of the **Turkish Federation of Breast Diseases Societies**

The Senologic International Society (SIS) and the National Consortium of Breast Centers (NCBC) are the official supporters of the journal.

SIS ISS SENOLOGIC INTERNATIONAL SOCIETY INTERNATIONAL SCHOOL OF SENOLOGY

NCBC National Consortium of Breast Centers

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# European Journal of Breast Health



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European Journal of Breast Health

European Journal of Breast Health

# Aims and Scope

The European Journal of Breast Health (Eur J Breast Health) is an international, scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles journal. It is the official publication of the Turkish Federation of Breast Diseases Societies, and the Senologic International Society (SIS) is the official supporter of the journal.

The European Journal of Breast Health is published quarterly in January, April, July, and October. The publication language of the journal is English.

EJBH aims to be a comprehensive, multidisciplinary source and contribute to the literature by publishing manuscripts with the highest scientific level in the fields of research, diagnosis, and treatment of all breast diseases; scientific, biologic, social and psychological considerations, news and technologies concerning the breast, breast care and breast diseases.

The journal publishes original research articlesreviews, letters to the editor, brief correspondences, meeting reports, editorial summaries, observations, novel ideas, basic and translational research studies, clinical and epidemiological studies, treatment guidelines, expert opinions, commentaries, clinical trials and outcome studies on breast health, biology and all kinds of breast diseases, and very original case reports that are prepared and presented according to the ethical guidelines.

TOPICS within the SCOPE of EJBH concerning breast health, breast biology and all kinds of breast diseases:

Epidemiology, Risk Factors, Prevention, Early Detection, Diagnosis and Therapy, Psychological Evaluation, Quality of Life, Screening, Imaging Management, Image-guided Procedures, Immunotherapy, molecular Classification, Mechanism-based Therapies, Carcinogenesis, Hereditary Susceptibility, Survivorship, Treatment Toxicities, and Secondary Neoplasms, Biophysics, Mechanisms of Metastasis, Microenvironment, Basic and Translational Research, Integrated Treatment Strategies, Cellular Research and Biomarkers, Stem Cells, Drug Delivery Systems, Clinical Use of Anti-therapeutic Agents, Radiotherapy, Chemotherapy, Surgery, Surgical Procedures and Techniques, Palliative Care, Patient Adherence, Cosmesis, Satisfaction and Health Economic Evaluations.

The target audience of the journal includes specialists and medical professionals in surgery, oncology, breast health and breast diseases.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

The European Journal of Breast Health indexed in PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Embase, EBSCO, CINAHL, Scopus.

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European Journal of Breast Health

# Instructions to Authors

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European Journal of Breast Health

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• Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

**Abstract:** An English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

**Keywords:** Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

**Key Points:** All submissions except letters to the editor should be accompanied by 3 to 5 "key points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Key Points" targeting the experts and specialists of the field, each item should be written as plain and straightforward as possible.

**Manuscript Types**

**Original Articles:** This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with "Introduction", "Materials and Methods", "Results", "Discussion and Conclusion" subheadings. Please check Table 1 for the limitations for Original Articles.

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**Editorial Comments:** Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

**Review Articles:** Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

**Case Reports:** There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include "Introduction", "Case Presentation", "Discussion and Conclusion" subheadings. Please check Table 1 for the limitations for Case Reports.

**Letters to the Editor:** This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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**Current Opinion:** Current Opinion provides readers with a commentary of either recently published articles in the European Journal of Breast Health or some other hot topic selected articles. Authors are selected and invited by the journal for such commentaries. This type of article contains three main sections titled as Background, Present Study, and Implications. Authors are expected to describe the background of the subject/study briefly, critically discuss the present research, and provide insights for future studies.

# Instructions to Authors

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|---|---|---|---|---|---|
| Original Article | 3500 | 250 (Structured) | 30 | 6 | 7 or tatal of 15 images |
| Review Article | 5000 | 250 | 50 | 6 | 10 or total of 20 images |
| Case Report | 1000 | 200 | 15 | No tables | 10 or total of 20 images |
| Letter to the Editor | 500 | No abstract | 5 | No tables | No media |
| Current Opinion | 300 | No abstract | 5 | No tables | No media |

### Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software,and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

### Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

### References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. All authors should be listed if an article has six or less authors; it should not be represented by "et al." in articles. Arabic numbers in parentheses. References published in PubMed should have a PMID: xxxxxx at the end of it, which should be stated in parenthesis. The reference styles for different types of publications are presented in the following examples.

**Journal Article:** Little FB, Koufman JA, Kohut RI, Marshall RB. Effect of gastric acid on the pathogenesis of subglottic stenosis. Ann Otol Rhinol Laryngol 1985; 94:516-519. (PMID: 4051410)

**Book Section:** Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

**Books with a Single Author:** Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

**Editor(s) as Author:** Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

**Conference Proceedings:** Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

**Scientific or Technical Report:** Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

**Thesis:** Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki İlişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

**Manuscripts Accepted for Publication, Not Published Yet:** Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

**Epub Ahead of Print Articles:** Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

**Manuscripts Published in Electronic Format:** Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

### REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option

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**Editor in Chief: Prof. Vahit ÖZMEN**

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## SYSTEMATIC REVIEWS



## ORIGINAL ARTICLES

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European Journal of Breast Health

# From the Editor

Dear Readers,

The European Journal of Breast Health is celebrating its 20th anniversary. We want to thank our editors, editorial advisory board members, reviewers, authors, and you, our readers, and our publisher, who have contributed to our journal during this process.

The European Journal of Breast Health (Eur J Breast Health) is an international, scientific, open-access periodical published by an independent, unbiased, double-blinded, peer-reviewed journal. It is the official publication of the Turkish Federation of Breast Diseases Societies, and the Senologic International Society (SIS) and the National Consortium of Breast Centers (NCBC) are the official supporters of the journal. Our journal is indexed in PubMed, PubMed Central, Web of Science (ESCI), Scopus, DOAJ, EBSCO, Embase, CNKI, TURKMEDLINE, EBSCO - CINAHL Complete, Embase, and Gale, and the articles accepted in our journal are published free of charge. Our estimated Journal Impact Factor (JIF) Value for 2024 is 1.64.

Breast cancer treatment has always been a pioneer for other cancers throughout history. The hypothesis of radical surgical intervention in every patient, which started with WS Halsted in the 1870s, turned into a systemic treatment hypothesis in the 1970s, which proposed a multidisciplinary approach to each patient with surgery, chemotherapy, radiotherapy, and endocrine therapy. In the last millennium, thanks to a better understanding of the molecular biology of the tumor and tumor genetics, and treatment have started to be personalized medicine, the importance of immune checkpoints and immunotherapy in treatment has increased, and the life expectancy of patients has been prolonged.

One of the most significant changes in the treatment of breast cancer today is that nearly three-quarters of patients, including patients diagnosed at an early stage, start their first treatment with chemotherapy. The increase in the number of patients who respond entirely to neo-adjuvant chemotherapy and the survival time of the studies conducted with new modern therapies has made chemotherapy the first treatment, especially in breast cancer, which has a poor prognosis such as HER-2 positive and triple negative.

The disappearance or shrinkage of the tumor with neo-adjuvant chemotherapy and the conversion of the axilla from positive to negative have increased the rate of breast-conserving surgery and oncoplastic surgery for breast cancer. Studies also show that axillary dissection can be avoided in cases where the axilla is negative or axillary involvement significantly reduced after chemotherapy.

We want to thank everyone who has contributed to our journal's 20 years of existence. We wish to continue successfully serving breast health and science for extended periods.

Warm regards,

**Vahit Ozmen, MD, FACS**
**Professor of Surgery**
**Editor-in-Chief**
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# Advances in Breast Cancer Care: The Role of Artificial Intelligence and Digital Pathology in Precision Medicine

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**ABSTRACT**

Artificial intelligence (AI) and digital pathology are transforming breast cancer management by addressing the limitations inherent in traditional histopathological methods. The application of machine learning algorithms has enhanced the ability of AI systems to classify breast cancer subtypes, grade tumors, and quantify key biomarkers, thereby improving diagnostic accuracy and prognostic precision. Furthermore, AI-powered image analysis has demonstrated superiority in detecting lymph node metastases, contributing to more precise staging, treatment planning, and reduced evaluation time. The ability of AI to predict molecular markers, including human epidermal growth factor receptor 2 status, *BRCA* mutations and homologus recombination deficiency, offers substantial potential for the development of personalized treatment strategies. A collaborative approach between pathologists and AI systems is essential to fully harness the potential of this technology. Although AI provides automation and objective analysis, human expertise remains indispensable for the interpretation of results and clinical decision-making. This partnership is anticipated to transform breast cancer care by enhancing patient outcomes and optimizing treatment approaches.

**Keywords:** Artificial intelligence; breast cancer; pathology; AI

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**Key Points**

- Artificial intelligence (AI) can assist pathologists in enhancing the precision of molecular assessments in breast cancer, while also reducing the time required for evaluation.
- AI has the potential to predict key molecular markers, including HER2 status, BRCA mutations, and homologous recombination deficiency, directly from Hematoxylin & Eosin (H&E) slides.
- AI is best utilized as a complementary tool, working in tandem with pathologists to optimize the diagnostic workflow and ensure the most accurate and timely care for patients.

## Introduction

Breast cancer is one of the most prevalent and challenging diseases in the field of oncology. Given the diverse subtypes and variable responses to treatment, accurate diagnosis, prognosis, and prediction of treatment outcomes are vital for effective management. Microscopic examination, though reliable, is subject to known limitations, including intra- and inter-observer variability. In the era of artificial intelligence (AI), machine learning (ML) and deep learning (DL) algorithms enhance the ability of histopathologists to make more accurate and reproducible diagnoses. These technologies offer a plethora of advances, such as interpreting complex patterns in breast cancer histology, streamlining time-consuming tasks like lymph node metastasis detection, or scoring predictive immunohistocemical biomarkers faster and in a more accurate way, ultimately leading to better patient outcomes and more personalized treatment plans.

AI, encompassing ML and DL techniques, offers robust tools for analyzing complex datasets and uncovering patterns that may be imperceptible to humans. In breast cancer care, AI applications can aid in tasks ranging from automating histopathological analysis to predicting treatment outcomes. The emergence of biomarkers evaluable through immunohistochemistry (IHC) and the inclusion of parameters, such as tumor infiltrating lymphocyte (TIL) percentage and treatment effects in synoptic reports have rendered the reporting process for breast cancer increasingly detailed and labor-intensive (1, 2). The evaluation of these parameters, however, is relatively subjective,

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necessitating the development of more standardized methods and the use of objective tools to ensure consistency and reliability in reporting.

By addressing the need for reproducibility and leveraging the vast datasets generated from histological slides, AI can augment the capabilities of histopathologists and oncologists, leading to enhanced accuracy and efficiency in breast cancer management.

The aim of this review was to provide a comprehensive overview of the current state of AI in breast pathological analysis with its diagnostic, prognostic, and predictive aspects. The techniques employed, the clinical implications, and the challenges that need to be addressed for broader implementation will all be addressed in the following article.

**Breast Cancer Detection and Classification**

The accurate classification of breast cancer is critical, as each subtype responds differently to treatment protocols. Misclassification can lead to suboptimal treatment decisions and compromised patient outcomes. To address this challenge, a comprehensive evaluation of morphological, IHC, and molecular features is essential. These tools hold the potential to significantly reduce time required for diagnosis while increasing accuracy, allowing for quicker therapeutic decisions and high concordance (3-6). The emergence of AI in the field of breast cancer classification marks a significant departure from conventional diagnostics, making a more nuanced and comprehensive analysis of tumors possible for future discoveries.Among notable contributions to this field, Cruz-Roa et al. (5) and Fondón et al. (6) have demonstated the potential of AI in detecting invasive ductal carcinoma within the surrounding breast parenchyma. Studies such as those by Yamamoto et al. (3), Han et al. (4) and Sharma and Mehra (7) have shown how DL models can classify breast cancer with remarkable accuracy. Han et al. (4) further illustrated the ability of AI algorithms to distinguish between ductal, lobular, mucinous and papillary morphology of breast carcinoma as well as benign proliferative lesions of both stroma and epithelium. Sandbank et al. (8) have taken this a step further by developing an algorithm capable of distinguishing between low- and high-grade *in situ* ductal and lobular carcinoma, as well as differentiating *in situ* from invasive carcinoma. In addition, the algorithm was reported to be adept at differentiating atypical ductal hyperplasia from ductal carcinoma *in situ*. By distinguishing between low- and high-grade *in situ* lesions and between atypical ductal hyperplasia and ductal carcinoma *in situ*, this algorithm addresses one of the most critical challenges in histopathology - the accurate classification of early-stage lesions that carry different prognostic implications. Such precise differentiation is important for determining the appropriate treatment pathway, thereby reducing the likelihood of overtreatment or undertreatment.

**Breast Cancer Grading**

Cancer grading is widely recognized as the most important prognostic factor for the majority of tumor types, including breast cancer. However, intra- and inter-observer variability, coupled with the inherent subjectivity in histopathological assessment, makes histological grading far from perfect. While promising, molecular methods are often time-consuming and costly. This is where AI may again be of benefit with a transformative potential. AI algorithms, capable of stratifying tumors based on features beyond traditional morphology, offer a promising avenue for the future of cancer diagnostics.

The integration of AI in the histological grading of breast cancer marks a significant advance in pathological assessment, offering enhanced accuracy, reproducibility, and efficiency. The complexity of breast cancer diagnostics, characterized by diverse histopathological features, has historically posed challenges for consistent and reliable grading. Subsections like mitotic figure count, tubule formation, and nuclear grading are revolutionized by the AI models offering a predictive accuracy that enhances human analysis. This level of granularity in grading is not merely academic; it directly translates to more accurate patient prognoses and informs treatment efficacy. AI-driven approaches, particularly DL models, address these issues by providing objective analyses (Table 1).

**Evaluation of Tubule Formation**

One of the components of histological grading of breast cancer is assessment of tubule formation. Romo-Bucheli et al. (9) demonstrated the potential of DL classifiers in identifying tubule formation in estrogen receptor-positive (ER+) breast cancer whole slide images. Their findings showed a strong correlation between the tubule formation indicator and genetic risk categories, suggesting that automated quantification can offer a more consistent method for assessing tumor aggressiveness. Mantrala et al. (10) also demonstrated that AI models could accurately assess tubule formation, matching the performance of experienced pathologists and reducing inter-observer variability. This consistency is key to reliable prognostic evaluations and tailored treatment strategies.

This advance aids personalized treatment decisions by providing a reliable metric for tumor grading, opening up a new avenue for correlating histological features with genomic assays. This correlation is important as it could potentially reduce the need for costly genetic testing by substituting it with AI analysis of standard histological slides, making prognostic testing more accessible and cost-effective.

**Counting Mitoses**

Counting mitoses, a pivotal component of breast cancer grading, is also one of the most time-consuming processes for histopathologists from all levels of expertise. It is known to have significant inter- and intra-observer variability, yet it is directly associated with tumor aggressiveness and grading. AI has demonstrably enhanced the reliability of mitotic figure detection by removing time constraints and variability. Studies by Balkenhol et al. (11) and Li et al. (12) demonstrated the clear advantages of DL-based automated mitotic counting over traditional manual methods. Moreover, Pantanowitz et al. (13) and Nateghi et al. (14) addressed this issue by integrating an AI tool designed for mitotic figure detection. Their findings indicated significant improvements in accuracy, precision, and sensitivity in tumor proliferation rate assessment. These findings improve the consistency in grading by reducing interobserver variability, enhancing both workflow efficiency and diagnostic confidence.

**Nuclear Grade Assessment**

Nuclear grading, which involves assessing nuclear size, shape, and pleomorphism, can be subjective due to the variations in human interpretation. It requires expertise and, on many occasions, it is not an easy task to distinguish nuclear grade 1 from 2 or 2 from 3. Thus, grade 2 has been used as a safety net for many pathologists since this differentiation is more challenging simply due to inability to notice

**Table 1. Major AI-based digital pathology applications for classification and grading of breast cancer**

| Year | Author(s) | Study aim | # of Patients/ patches | AI approach used | Performance metrics |
|---|---|---|---|---|---|
| **2017** | **Yamamoto et al. (3)** | Detection and classification of ductal carcinoma in situ | 22 | SVM | 90.9% accuracy |
| **2017** | **Han et al. (4)** | Multi-classification of breast cancer histopathology images | 82 | Class structure-based deep CNN | 93.2% accuracy |
| **2017** | **Cruz-Roa et al. (5)** | Invasive tumor extent evaluation | 349 | Class structure-based deep CNN | 75.9% accuracy |
| **2018** | **Fondón et al. (6)** | Classify breast tissue samples into four malignancy levels | 150 | Feature vector + SVM | 75.8% accuracy |
| **2020** | **Sharma and Mehra (7)** | Automatic multi-classification of breast cancer histopathological images | 82 | SVM | 94% accuracy |
| **2022** | **Sandbank et al. (8)** | Subtypes of invasive carcinoma and TIL evaluation | 436 | CNN | AUC: 0.99 |
| **2016** | **Romo-Bucheli et al. (9)** | Automated tubule nuclei detection and correlation with Oncotype DX | 174 | Deep neural network | 89% accuracy |
| **2022** | **Mantrala et al. (10)** | Concordance in breast cancer grading by AI vs pathologists | 137 | Deep learning for semantic segmentation | 65.9% accuracy |
| **2019** | **Balkenhol et al. (11)** | Deep learning-assisted mitotic counting for breast cancer | 388 | CNN | R = 0.810 (95% CI: 0.76–0.86) |
| **2018** | **Li et al. (12)** | Detection, verification, and segmentation for mitosis | 50 | Deep detection network | F-score: 0.827 |
| **2020** | **Pantanowitz et al. (13)** | Accurate and efficient mitosis counting | 320 | R-CNN (region-based CNN) | Improved accuracy with AI |
| **2021** | **Nateghi et al. (14)** | Mitosis detection in tumor proliferation prediction | 73 | SVM | F-score: 0.738 |
| **2022** | **Wang et al. (15)** | Improved breast cancer histological grading | >1000 | CNN | AUC: 0.91 (95% CI: 0.88–0.93) |
| **2021** | **Elsharawy et al. (16)** | Improved grading for refined prognostic classification | >1000 | CNN | AUC: 0.68 (95% CI: 0.65–0.71) |
| **2021** | **Zewdie et al. (17)** | Classification of breast cancer types and grades using deep learning | 82 | Deep CNN | 96.75% accuracy |

SVM: Support vector machines; CNN: Convolutional neural network; TIL: Tumor infiltrating lymphocytes; AUC: Area under curve; CI: Confidence interval, AI: Artificial intelligence

subtle differences through the human eye. This subjectivity introduces variability into the diagnostic process, which can impact both grading accuracy and prognostic evaluations.

A significant advance in breast cancer grading lies in the use of DL models to enhance the stratification of intermediate Nottingham Histological Grade (NHG) 2 cases, which historically pose challenges due to their variability and intermediate prognostic value. By analyzing whole-slide histopathology images, these models identify subtle morphological patterns that differentiate NHG 2 tumors into lower- and higher-risk groups, mirroring the characteristics of NHG 1 and NHG 3 (15). This approach offers prognostic insights comparable to molecular assays but is faster, more cost-effective, and uses routine Hematoxylin and Eosin (H&E) slides.

AI models, such as those highlighted by Elsharawy et al. (16), can standardize the grading process, reducing variability and improving prognostic evaluations. Similarly, the study by Mantrala et al. (10) confirmed that AI could match human performance in grading nuclear pleomorphism, thus mitigating inconsistencies among pathologists and providing more reliable prognostic information. Their work showed that AI could successfully detect morphological attributes of the nucleus which are key to determining tumor grade, and provide survival stratification across various patient cohorts. These AI tools are not yet designed to replace the human eye but rather to enhance the histopathologist's ability to detect the subtle changes that can significantly impact the course of treatment (10, 15, 17). This integration supports more informed clinical decision-making and facilitates personalized treatment strategies, ultimately improving patient care and outcomes.

### Biomarker Quantification

#### ER, PR and HER2 Evaluation

Accurate and objective assessment of biomarkers plays a vital role in breast cancer diagnosis, prognosis prediction, and treatment

planning. The success of targeted therapies and endocrine therapy in breast cancer relies heavily on the precise quantification of estrogen and progesterone hormone receptors (ER and PR) and the human epidermal growth factor receptor 2 (HER2) protein. Traditional evaluation methods may be subjective and prone to errors. Fortunately, recent advances in AI and digital image analysis (DIA) offer promising solutions for achieving consistent and reliable biomarker quantification. AI algorithms were initially developed for basic IHC evaluation tasks, such as counting positive cells (i.e., DAB-stained brown cells) in manually selected tumor regions. However, with advances in tumor detection algorithms, these methods have evolved to integrate both tumor area and tumor cell detection and cell quantification. This enables not only the reliable counting of positive cells but also the assessment of their staining intensities, ultimately providing objective and consistent scores for biomarkers, including ER, PR, and Ki-67.

Recently, various groups have developed algorithms that have comparable performance to expert histopathologists, exhibiting high accuracy and consistency for the evaluation of ER, PR and Ki-67 in breast cancer (18, 19). These algorithms demonstrated strong correlation with expert decisions, indicating its feasibility in a clinical setting.

Similar results have been published for HER2 evaluation algorithms. Hartage et al. (20) validated their algorithm for HER2 IHC assessment, showing high correlation with fluorescent *in situ* hybridization results and improved consistency compared to manual scoring. Furthermore, Li et al. (21) investigated their model for HER2 IHC in predicting response to anti-HER2 neoadjuvant chemotherapy. DIA provided quantitative analysis of HER2 expression, revealing a significant correlation with pathological complete response (pCR) rates. This research suggests that DIA-based HER2 assessment can improve the prediction of treatment response, enabling more personalized treatment strategies. Notably, the assessment of HER2 status can be nuanced, with borderline cases posing a challenge for histopathologists. These findings highlight DIA's potential to streamline workflows and enhance the consistency of biomarker evaluations, especially in cases with equivocal results after manual scoring.

In conclusion, AI and DIA hold immense potential to revolutionize breast cancer diagnostics and personalized medicine approaches. By providing automated, standardized, and quantitative assessments, they can significantly improve the accuracy and consistency of biomarker analysis, leading to better diagnosis, more informed treatment decisions, and ultimately, improved patient outcomes. While further research is needed to optimize AI algorithms and ensure the generalizability of DIA methods, the integration of these technologies in objective biomarker quantification is a very promising step forward (Table 2).

### Ki-67 Proliferation Assessment

Ki-67 is a well-established prognostic marker for breast cancer. Traditionally, Ki-67 assessment involves manual counting, a time-consuming and error-prone process. AI-powered Ki-67 quantification, as described by Bodén et al. (22), represents a significant advance in the field. Unlike manual counting, AI provides the option of comprehensive analysis of the entire slide, offering a more objective and robust approach (18, 22, 23). Bodén et al. (22) demonstrated that AI-based Ki-67 assessment achieved a high correlation with manual counts by histopathologists. This comprehensive Ki-67 analysis by AI could lead to more accurate prognoses and individualized treatment plans, particularly when deciding on the use of neoadjuvant therapy.

### PD-L1 Scoring

AI-assisted programmed death-ligand 1 (PD-L1) scoring, particularly through the combined positive score, has garnered significant attention for its potential to standardize and enhance the accuracy of IHC-based evaluations in cancer treatment. While its application has been better established in non-small cell lung cancer (NSCLC), there is still room for improvement in other organ cancers. In NSCLC, AI tools have

**Table 2. Major AI-based digital pathology applications for molecular profiling of breast cancer**

| Year | First author | Study aim | #of Patients/ patches | AI approach used | Performance metrics |
|---|---|---|---|---|---|
| **2023** | **Abele et al. (18)** | AI-assisted analysis of Ki-67 and hormone receptors | 204 | CNN | Agreement rates: Ki-67 (87.6%), ER/PR (89.4%). |
| **2022** | **Shafi et al. (19)** | Validation of automated digital determination of estrogen receptor status | 97 | Computer vision-based DIA | Pearson's $r = 0.72$ |
| **2020** | **Hartage et al. (20)** | Validation of HER2 IHC digital imaging and FISH correlation | 612 | Computer vision-based DIA | Cohen's kappa (κ): 0.71 |
| **2020** | **Li et al. (21)** | Quantitative digital imaging of HER2 IHC to predict response to therapy | 153 | Computer vision-Based DIA | HER2 DIA connectivity & pCR (OR = 136.08, $p = 0.002$) |
| **2021** | **Bodén et al. (22)** | Human-in-the-loop Ki-67 assessment | 200 | DCNN based object detection | Cohen's kappa (κ): 0.84 |
| **2024** | **Dy et al. (23)** | Improved accuracy and agreement in Ki-67 assessments | 420 | CNN | Ki-67% error rate: 0.6% |

CNN: Convolutional neural network; DIA: Digital image analysis; IHC: Immunohistochemistry; FISH: Fluorescence *in situ* hybridization; pCR: Pathological complete response; DCNN: Deep convolutional neural network; OR: Odds ratio; HER2: Human epidermal growth factor receptor 2; AI: Artificial intelligence; ER: Estrogen receptor; PR: Progesterone receptor

already demonstrated considerable success in improving interobserver concordance. Algorithms, such as the dual-scale categorization-based DL methods have shown high concordance rates when compared to histopathologists, underscoring their potential in clinical applications (24).

However, in other cancers including breast cancer, AI applications in PD-L1 scoring are in the earlier stages of research and development. Initial studies in breast cancer, especially multi-institutional studies, show promise in improving scoring consistency between histopathologists. AI-assisted models have demonstrated significant potential, boosting concordance from moderate to excellent levels (25, 26). These models aid in overcoming the subjectivity of human evaluation, especially when scoring tumor-infiltrating immune cells, which is key in determining patient eligibility for immunotherapy.

AI models for PD-L1 scoring need to be further refined and validated across various cancers. The adoption of AI in scoring systems for cancers beyond the lung, such as urothelial carcinoma and head-and-neck squamous cell carcinoma, is expected to follow suit, offering an invaluable tool for clinicians to make more reliable, data-driven treatment decisions.

**AI-Powered TIL and Tumor Microenvironment Assessment**

AI has transformed how TILs and the broader tumor microenvironment (TME) are assessed, particularly in breast cancer. TILs, which are key immune response markers, play a critical role in the prognosis of cancers, such as HER2-positive and triple-negative breast cancer (TNBC). Traditionally, TIL evaluation, as with other histopathological evaluations, was subjective and prone to variability. However, AI offers a standardized and objective approach, reducing this variability and providing a consistent evaluation of the immune response within the TME (27, 28). AI-powered methods can quantify the spatial organization and interactions of TILs with other immune and tumor cells, which is vital when stratifying patients for immunotherapy. Studies have shown that AI-driven analysis of H&E and multiplex IHC images enhances the ability to predict treatment responses, such as pCR to chemotherapy, especially in HER2-positive and TNBC subtypes (27).AI models developed for this purpose have demonstrated higher accuracy in predicting pCR compared to manual assessments by histopathologists, underscoring the potential of AI to guide personalized treatment strategies (11, 29). AI also plays a critical role in advancing our understanding of the TME by identifying organizations and interactions that are difficult for human observers to discern. This includes quantifying the presence and behavior of immune cells like TILs, as well as mapping their interactions with tumor cells (30). This deeper analysis provides a more comprehensive understanding of the immune landscape, which is essential for optimizing treatment plans and enhancing the precision of immunotherapies.

**AI-Powered Lymph Node Metastasis Detection**

The accurate detection of lymph node metastasis is a key factor in staging and treatment planning in breast cancer. However, for small occult tumor foci in lymph nodes, traditional pathological assessment can be tricky and, in some cases, requires additional IHC studies. Fortunately, recent advances in AI offer promising solutions for more precise lymph node metastasis detection, potentially removing the need for the additional IHC step, saving both time and resources (31-35).

Several studies have investigated the application of DL algorithms for lymph node metastasis detection in breast cancer. Liu et al. (36) developed such an algorithm for identifying metastatic cancer cells in sentinel lymph node biopsies. The algorithm achieved impressive performance in detecting metastases, even for small foci. The study also demonstrated the robustness of the algorithm when faced with common tissue sample variations, indicating its potential for reliable performance in diverse clinical settings. Furthermore, the algorithm demonstrated a high sensitivity with low false positives, significantly reducing missed metastases compared to traditional methods.

Steiner et al. (35) evaluated the impact of DL assistance in histopathologists' evaluations of lymph nodes for metastatic breast cancer. The AI model significantly improved diagnostic accuracy, particularly for challenging micrometastases. Using AI resulted in reduced errors and review time, while also enhancing histopathological accuracy. Building on these findings, other groups have explored integrating AI into digital pathology workflows for efficient and accurate lymph node metastasis diagnosis (31). AI models, trained on a large dataset of H&E-stained slides, demonstrated high sensitivity and specificity in detecting lymph node metastases, significantly reducing false negatives. Importantly, the model accurately identified macro- and micrometastases, leading to more precise diagnoses (33, 37).Looking beyond breast cancer, a recent study Bándi et al. (38) explored continual learning strategies for cancer-independent detection of lymph node metastases. This approach aims to develop robust AI models that can detect metastases across various cancer types without requiring cancer-specific retraining. The continual learning models demonstrated high accuracy and reliability across diverse datasets encompassing breast, colon, and head-and-neck cancers. This approach allows for continuous learning and adaptation, enhancing the model's generalizability across different clinical scenarios. By employing a cancer-independent detection strategy, these models can be more broadly applicable in clinical practice, offering a scalable solution for lymph node metastasis detection across various cancers.

Radiomics presents a promising, AI-driven approach for also improving axillary lymph node staging in breast cancer, leveraging medical imaging to create predictive models with high sensitivity, specificity and efficiency. Despite its potential to replace invasive procedures, limited validation, retrospective study designs, and lack of cost-effectiveness analyses highlight the need for robust clinical trials and meta-analyses for clinical implementation (39). When combined with advances in AI-powered lymph node metastasis detection, including DL algorithms and cancer-independent models, radiomics can integrate seamlessly into digital pathology workflows. This integration offers a scalable solution for precise diagnosis and treatment planning across diverse cancer types.

**The Future: AI-Assisted Molecular Prediction**

Molecular subtyping of breast cancer is becoming increasingly important. Accurate subtype determination necessitates the evaluation of each tissue block of the tumor, yet reproducibility can be challenged by the heterogeneous nature of breast cancer tumors. The application of AI extends beyond traditional histopathological analysis. Its predictive capabilities are now at the molecular level. Farahmand et al. (40) used AI to predict HER2 status using H&E sections with high accuracy, which is vital for determining eligibility for targeted therapies, like trastuzumab. Similarly, the ability of AI to predict *BRCA* mutation status from histological images, as shown by Wang et al. (41) indicates its potential in genetic risk assessment and personalized medicine.

These holds promise for identifying patients carrying *BRCA1* and *BRCA2* mutations who are at high risk for developing hereditary breast cancer and guiding preventive measures. Several studies have shown promise in detecting molecular subtypes, particularly in distinguishing the basal-like subtype from luminal-A (42, 43). The objective must be to reduce the costs associated with molecular testing and mitigate the impact of limited experience by automating this classification process.

The integration of AI into molecular prediction also includes its potential to classify tumor recurrence risks based on histological features, circumventing the need for costly molecular assays. Whitney et al. (44) demonstrated that computer-extracted nuclear morphology features from routine H&E-stained images could accurately predict Oncotype DX risk categories for ER-positive breast cancer patients. By leveraging AI-driven analysis of nuclear architecture and shape, the study achieved significant classification accuracy, with an area under the curve of up to 0.83 in distinguishing between low and high recurrence risk groups. This method not only complements molecular testing but also offers a faster, cost-effective, and nondestructive alternative. As such, AI-driven histopathological tools are paving the way for precise recurrence risk stratification and personalized treatment planning, particularly in resource-limited settings where access to molecular assays may be constrained.

**AI-Enhanced Homologous Recombination Deficiency Detection**

Homologous recombination deficiency (HRD) status holds a substantial potential in determining the optimal treatment course for patients with breast cancer (45, 46). Traditional molecular methods to identify HRD status, while accurate, are often time-consuming, costly, and require specialized equipment, limiting their accessibility in resource-constrained settings. To address these challenges, AI has emerged as a promising solution. AI-powered tools use H&E slides to predict HRD status directly (47). These models analyze tissue samples with a high degree of accuracy, often surpassing traditional methods in identifying patients who may benefit from targeted therapies, like platinum-based chemotherapies and PARP inhibitors. By automating the detection process, AI enables faster, more scalable, and more accessible HRD testing. Furthermore, the ability to identify a broader range of HRD-positive patients can lead to more effective treatment strategies and potentially enhance survival rates.

**PIK3CA/AKT Pathway Alteration Detection**

ML, and particularly DL, have shown progress in detecting actionable genetic alterations of breast cancer directly from the H&E-stained slides. These AI models can detect subtle morphological changes linked to genetic mutations, providing an innovative approach to molecular analysis (48, 49).

In TNBC, DL models have proven highly effective in predicting *PIK3CA* mutations, demonstrating their reliability in molecular diagnostics (48). Similar methods have been successfully applied across multiple cancer types, including breast cancer, with strong predictive outcomes for detecting mutations like *PIK3CA* (49). These models use convolutional neural networks to analyze thousands of image files from histopathology slides, allowing them to recognize patterns linked to genetic alterations. This method enhances real-time prediction, positioning AI as a valuable tool in advancing pathology practices.

**Challenges, Risks and Practical Considerations in AI Integration for Breast Pathology**

Despite its transformative potential, AI in breast histopathology presents several challenges and risks that must be carefully addressed. Algorithmic bias remains a significant concern, as AI models trained on limited datasets may not generalize well to diverse populations. This may result in disparities in diagnostic accuracy, particularly for underrepresented demographic groups. Ensuring diverse, representative, and well-annotated datasets is vital to avoid bias and ensure equitable AI-driven diagnostics across various demographics. In addition, validation in diverse clinical settings is important to ensure that AI tools perform consistently across different laboratories, imaging systems, and staining techniques. Another challenge is the potential for misdiagnoses if AI tools are improperly calibrated or misinterpreted by users. Over-reliance on AI without adequate human oversight could lead to errors in classification, particularly in borderline or equivocal cases. Therefore, robust validation, external benchmarking, and continued histopathologist involvement are essential to mitigate these risks.

Integrating AI into pathology workflows necessitates a strategic approach that accounts for multiple factors, including specialized training for histopathologists and other laboratory personnel, the financial implications of adopting AI-driven solutions, compliance with regulatory standards, and seamless interoperability with existing digital pathology systems. Foremost, training and skill development are critical, as histopathologists must become proficient in using AI-assisted tools, interpreting AI-generated insights, and understanding the limitations of these systems. Institutions must invest in educational programs and workshops to ensure a smooth transition into AI-enhanced diagnostics. Cost considerations also play a significant role in the adoption of AI in pathology departments. While AI has the potential to improve efficiency and accuracy, the initial investment in infrastructure, software licensing, and continuous updates can be substantial. Pathology laboratories will need to conduct cost-benefit analyses to determine the financial viability of AI integration and explore funding or reimbursement models to support implementation. Finally, interoperability with existing pathology systems is essential for efficient workflow integration. AI tools must be compatible with various digital pathology platforms, whole slide imaging systems, and laboratory information management systems to facilitate seamless data exchange and avoid disruptions in clinical workflows. Ensuring standardized data formats and adherence to industry-wide interoperability frameworks can help maximize the potential benefit of AI while maintaining workflow efficiency.

Importantly, regulatory compliance will be crucial, as AI-driven diagnostic tools must meet strict guidelines set by regulatory bodies such as the Food and Drug Administration, Conformite Europeenne, and CAP to ensure patient safety, reliability, and ethical use. Institutions must navigate complex approval processes and ensure that AI systems are validated for clinical use before deployment. Addressing all these factors will be essential for the successful implementation of AI in pathological assessment, allowing for improved diagnostic accuracy, streamlined workflows, and enhanced patient outcomes.

## Discussion and Conclusion

The integration of AI into breast cancer pathological assessment represents a transformative advance toward achieving greater precision, standardization, and efficiency in diagnostic and prognostic assessments. AI systems enhance the capabilities of histopathologists by augmenting the accuracy of molecular-level evaluations, which is essential for personalized medicine. As AI technologies continue to evolve and are seamlessly integrated into clinical workflows, they are

poised to improve patient outcomes through rapid, reproducible, and detailed histopathological evaluation. AI algorithms, trained on annotated data provided by histopathologists, have the potential to reduce both cost and time associated with diagnostic evaluations while maintaining high-quality standards of care.The future of breast cancer pathology lies in the development of a synergistic relationship between AI and pathologists. The majority of the algorithms mentioned in this article operate as an adjunct to the pathologist, rather than a final decision maker. Human-in-the-loop systems offer an augmented diagnostic assistant or a second reader. AI technologies excel in increasing diagnostic accuracy, and detecting subtle patterns that may elude even the most trained human eye. Pathologists, with their clinical expertise and nuanced understanding of patient care, are essential for guiding the development of AI models, interpreting AI-generated insights, and ensuring that these tools are applied ethically and responsibly in clinical practice. This collaboration between AI and human expertise holds immense promise for realizing the full potential of personalized breast cancer management, leading to more effective, individualized treatment strategies and improved clinical outcomes.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: A.H.D.K., İ.K., N.K.; Concept: A.H.D.K., İ.K., N.K.; Design: A.H.D.K., İ.K., N.K.; Data Collection or Processing: A.H.D.K.; Analysis or Interpretation A.H.D.K., İ.K.; Literature Search: A.H.D.K., İ.K., N.K.; Writing: A.H.D.K., İ.K.

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**Systematic Review**

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# Prognostic Significance and Molecular Classification of Triple Negative Breast Cancer: A Systematic Review

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**ABSTRACT**

Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer defined by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression. Despite accounting for 15–20% of all breast cancer cases, TNBC is associated with poor prognosis and a high likelihood of recurrence and metastasis. Understanding the molecular subtypes of TNBC is important for developing targeted therapies and improving patient outcomes. This systematic review aimed to assess the prognostic significance of molecular subtypes of TNBC and the implications for therapeutic management. A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, to identify studies focusing on the molecular classification of TNBC and its prognostic relevance. Studies were included based on specific inclusion criteria, including original research evaluating clinical outcomes and survival data in molecularly classified TNBC cohorts. Data were extracted, synthesized, and analyzed to determine the prognostic implications of different TNBC subtypes. The review identified several distinct molecular subtypes of TNBC, including basal-like, mesenchymal, immune-modulatory, and luminal androgen receptor (LAR) subtypes. Basal-like TNBC was associated with poor prognosis and high rates of recurrence, while immune-modulatory TNBC exhibited better survival outcomes, particularly in patients with high levels of tumor-infiltrating lymphocytes. Mesenchymal and LAR subtypes exhibited diverse clinical behavior and varying therapeutic responses. Furthermore, key prognostic biomarkers, such as *BRCA1/2* mutations and programmed death-ligand 1 expression, were highlighted which have therapeutic implications. Molecular classification of TNBC provides valuable prognostic information and guides therapeutic strategies. Integrating molecular subtyping into clinical decision-making will be essential for the development of personalized treatments and improved outcomes for TNBC patients. However, further research is needed to refine classification systems and address existing therapeutic gaps in TNBC management.

**Keywords:** Triple negative breast cancer; tumor-infiltrating lymphocytes; luminal androgen receptor; disease-free survival; epithelial-mesenchymal transition; therapeutic strategies; biomarkers

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**Key Points**

- The prognostic significance of distinct molecular subtypes of triple-negative breast cancer (TNBC) based on clinical outcomes such as overall survival, disease-free survival, and response to therapy.
- The current molecular classification systems of TNBC and their relevance in clinical practice.
- The role of *BRCA1/2* mutations and other genetic alterations in the pathogenesis and treatment response of TNBC.
- The potential of immune-based therapies and novel targeted agents in the management of TNBC.

## Introduction

Breast cancer remains the most frequently diagnosed malignancy and the leading cause of cancer-related deaths among women worldwide, accounting for approximately 24.5% of all cancer cases and 15.5% of cancer-related mortalities in women (1). Breast cancer is a heterogeneous disease comprising several distinct subtypes with diverse clinical and molecular characteristics. Among these subtypes, triple-negative breast cancer (TNBC) is prminent as an entity that poses significant challenges in terms of prognosis and treatment.

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Characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, TNBC accounts for approximately 15–20% of all breast cancers and is associated with an aggressive clinical course and poor prognosis (2).

### Defining Triple-Negative Breast Cancer (TNBC)

TNBC is defined by the lack of expression of ER, PR, and HER2 receptors, distinguishing it from other breast cancer subtypes, such as luminal A, luminal B, and HER2-enriched breast cancers. The absence of these receptors precludes targeted treatments, such as endocrine therapy or HER2-targeted agents, rendering chemotherapy the primary systemic treatment option (3). Despite its histological definition, TNBC is a biologically heterogeneous group of tumors with diverse genetic, epigenetic, and transcriptomic profiles, contributing to variations in treatment response and clinical outcomes (4).

### Epidemiology and Clinical Features of TNBC

TNBC is more prevalent in younger women, particularly those under the age of 50 years, and is overrepresented among African-American and Hispanic women. In addition, it is more frequently observed in women with *BRCA1* germline mutations (5). Clinically, TNBC is characterized by a high histological grade, increased mitotic index, central necrosis, and a high frequency of lymphovascular invasion. These features contribute to the aggressive nature of the disease, with a propensity for early distant metastasis, particularly to visceral organs and the brain, and a relatively high recurrence rate within the first five years after diagnosis (6).

### Molecular Heterogeneity and Classification of TNBC

Given the clinical and biological heterogeneity of TNBC, numerous efforts have been made to subclassify this entity into distinct molecular subtypes that may inform prognosis and guide therapeutic strategies (Table 1). The pioneering work of Lehmann et al. (7) led to the identification of six distinct molecular subtypes of TNBC, namely basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) TNBC. These subtypes differ in their gene expression profiles, signaling pathways, and potential therapeutic targets.

**Table 1. Main classification systems of breast cancer**

| Classification system | Criteria used | Subtypes | Clinical and prognostic significance |
|---|---|---|---|
| Histopathological classification | Histological appearance and tumor morphology | Ductal carcinoma in situ, invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), others | Provides information on tumor grade, size, and lymph node involvement; helps in initial diagnosis and treatment planning. |
| Molecular classification (intrinsic) | Gene expression profiling and molecular markers | Luminal A, luminal B, HER2-enriched, basal-like, normal-like | Offers insights into tumor biology, prognosis, and treatment response; cornerstone of personalized treatment strategies. |
| Immunohistochemical classification | Expression of hormone receptors (ER, PR) and HER2 status, along with Ki-67 index | ER+/PR+/HER2-, ER+/PR+/HER2+, ER-/PR-/HER2+, triple-negative | Simplifies molecular classification using protein expression; widely used in clinical practice for treatment decision-making. |
| *PAM50* gene signature | Gene expression profiling using 50 marker genes | Luminal A, luminal B, HER2-enriched, basal-like, normal-like | Provides detailed prognostic information and categorizes tumors into intrinsic subtypes based on gene expression; used in research. |
| St. Gallen classification | Molecular and clinicopathological features | Luminal A-like, luminal B-like (HER2+ and HER2-), HER2-positive (non-luminal), triple-negative | Combines molecular and clinical features to stratify patients for treatment selection; commonly used in clinical practice guidelines. |
| The cancer genome atlas) | Comprehensive genomic characterization, including DNA mutations, copy number variations, and epigenetic changes | Four subtypes: Luminal A, luminal B, HER2-enriched, basal-like | Provides deep insights into the genomic landscape of breast cancer; helps identify potential therapeutic targets and resistance mechanisms. |
| WHO classification | Histopathology, molecular features, and clinical presentation | 21 different histological subtypes (e.g., IDC, ILC, medullary, mucinous) | Describes the histological diversity of breast cancer; helps in tumor categorization and understanding of prognosis. |
| Nottingham prognostic index (NPI) | Tumor size, lymph node status, and histological grade | NPI score used to stratify patients into low, intermediate, or high-risk categories | Predicts survival outcomes based on histological features; useful for risk assessment and guiding adjuvant therapy. |

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; WHO: World Health Organization

Among these, the basal-like (BL) subtype is further divided into BL1 and BL2 based on distinct gene expression patterns rather than BRCA mutation status. The BL1 subtype is characterized by the activation of cell cycle and DNA damage response pathways, which contribute to its heightened sensitivity to platinum-based chemotherapies (8). In contrast, the BL2 subtype exhibits enrichment in growth factor signaling pathways, which may influence its therapeutic response differently. Conversely, the LAR subtype is enriched in androgen receptor signaling and may respond to androgen receptor antagonists (9).

### Prognostic Significance of TNBC Subtypes

The prognostic significance of TNBC subtypes is a critical area of research (Table 2). Studies have shown that patients with the BL1 and IM subtypes exhibit a better response to neoadjuvant chemotherapy and have improved survival outcomes compared to those with the BL2 and MSL subtypes (10). The BL1 subtype, characterized by the activation of cell cycle and DNA damage response pathways, is particularly sensitive to platinum-based chemotherapies, contributing to better treatment outcomes. In contrast, the BL2 subtype, which is enriched in growth factor signaling pathways, demonstrates a less favorable response.

The IM subtype, characterized by high immune cell infiltration, has been associated with a favorable prognosis due to a robust antitumor immune response (11). On the other hand, the M and MSL subtypes, which are associated with epithelial-to-mesenchymal transition (EMT) and stem cell-like properties, have a poor prognosis and are less responsive to conventional chemotherapies (12).

### The Role of *BRCA1* and *BRCA2* Mutations in TNBC

Approximately 10-20% of TNBCs harbor germline mutations in the *BRCA1* or *BRCA2* genes, which are key regulators of homologous recombination-mediated DNA repair (13). *BRCA1*-mutated TNBCs are characterized by a high level of genomic instability and a distinct molecular profile that overlaps with the basal-like subtype (Figure 1) (14). The presence of *BRCA1/2* mutations has important therapeutic implications, as these tumors are more likely to respond to DNA-damaging agents, including platinum-based chemotherapies and poly ADP ribose polymerase (PARP) inhibitors (15). PARP inhibitors, such as olaparib and talazoparib, have demonstrated significant clinical benefit in patients with *BRCA*-mutated TNBC, providing a new, targeted therapeutic option for this subgroup (16).

### The Tumor Microenvironment in TNBC

The tumor microenvironment (TME) plays a crucial role in the progression and therapeutic resistance of TNBC. TNBCs are often characterized by high levels of tumor-infiltrating lymphocytes (TILs). TILs serve as a marker of an active antitumor immune response and are associated with improved survival outcomes (17). The presence of TILs is particularly relevant in the IM subtype of TNBC, which is characterized by an inflammatory TME and high expression of immune checkpoint molecules, such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) (18). Immune checkpoint inhibitors (ICIs), such as pembrolizumab and atezolizumab, have shown promising results in clinical trials for TNBC, particularly in patients with PD-L1-positive tumors (19). The integration of ICIs with chemotherapy has emerged as a potential therapeutic strategy to enhance antitumor immunity and improve outcomes in TNBC (20).

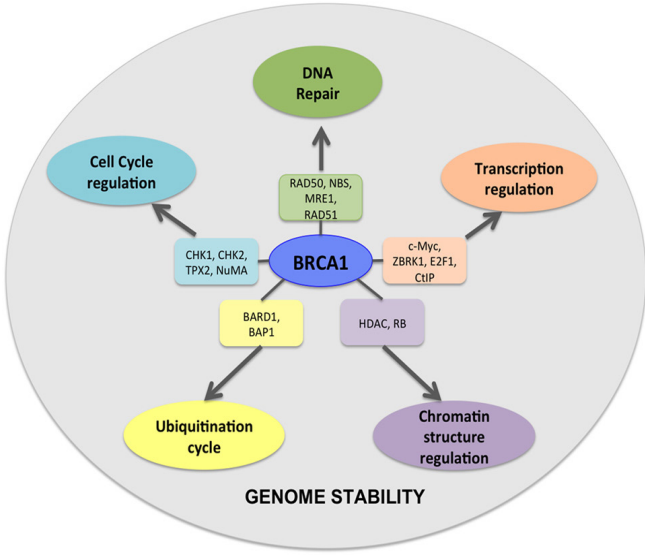


**Figure 1.** Showing the role of BRCA1 mutations in TNBC (13)

TNBC: Triple-negative breast cancer

### Challenges in the Management of TNBC

Despite recent advances in understanding TNBC biology and developing novel therapeutic agents, the management of TNBC remains challenging. The lack of targeted therapies, combined with the aggressive nature of the disease, results in a high rate of recurrence and metastasis, leading to poor long-term survival outcomes (21). The median overall survival (OS) for patients with metastatic TNBC is approximately 12–18 months, highlighting the urgent need for effective therapeutic strategies (22). Furthermore, the heterogeneity of TNBC poses significant challenges in identifying reliable prognostic and predictive biomarkers that can guide treatment decisions (23).

### Emerging Therapeutic Strategies in TNBC

The emergence of molecular profiling and next-generation sequencing (NGS) technologies has facilitated the identification of novel therapeutic targets in TNBC. Several targeted therapies, including PI3K/AKT/mTOR pathway inhibitors, CDK4/6 inhibitors, and anti-androgen agents, are currently being evaluated in clinical trials (24). In addition, antibody-drug conjugates (ADCs), such as sacituzumab govitecan, have shown promising efficacy in pretreated metastatic TNBC, providing a new treatment option for patients with advanced disease (25). The integration of targeted therapies with conventional chemotherapy and ICIs represents a promising approach to overcome therapeutic resistance and improve outcomes in TNBC (26).

### The Need for a Molecularly-Driven Classification of TNBC

Given the complex biology and heterogeneity of TNBC, there is a growing consensus on the need for a molecularly-driven classification system that can accurately stratify patients based on their molecular profiles and inform therapeutic decision-making. The identification of robust molecular subtypes with distinct prognostic and therapeutic implications is essential for the development of personalized treatment strategies and the optimization of clinical outcomes (27). Integrative analyses incorporating genomic, transcriptomic, proteomic, and immunological data are required to achieve a comprehensive understanding of the biology of TNBC and to identify novel therapeutic targets (28).

**Rationale and Objectives of the Systematic Review**

The current systematic review aims to comprehensively evaluate the prognostic significance and molecular classification of TNBC, with a focus on elucidating the clinical outcomes and therapeutic implications of distinct molecular subtypes. By synthesizing evidence from recent studies, this review seeks to provide a deeper understanding of the molecular landscape of TNBC and to identify potential biomarkers that can guide personalized treatment strategies. The specific objectives of this review are:

**Table 2. Prognostic tumor type groups in breast cancer**

| Tumor type group | Molecular features | Histological characteristics | Prognostic implications | Therapeutic considerations |
|---|---|---|---|---|
| Luminal A | ER+/PR+, HER2-, low Ki-67 | Low-grade, well-differentiated tumors; often associated with low mitotic activity. | Best prognosis among all subtypes; low risk of recurrence and high overall survival. | Highly responsive to endocrine therapy; chemotherapy usually not required. |
| Luminal B (HER2-) | ER+/PR+, HER2-, high Ki-67 | Higher grade than luminal A, increased mitotic index, and cellular atypia. | Intermediate prognosis; higher risk of recurrence and reduced survival compared to Luminal A. | Endocrine therapy combined with chemotherapy is often recommended. |
| Luminal B (HER2+) | ER+/PR+, HER2+, high Ki-67 | High grade, more aggressive behavior; may present with lymph node involvement. | Worse prognosis than luminal B (HER2-); increased risk of metastasis. | Requires combination of endocrine therapy, chemotherapy, and HER2-targeted therapies. |
| HER2-enriched | ER-/PR-, HER2+ | High-grade tumors with significant cellular atypia and high proliferation rate. | Poor prognosis due to high likelihood of recurrence and metastasis; HER2-targeted therapies have improved outcomes. | HER2-targeted therapies (e.g., trastuzumab, pertuzumab) combined with chemotherapy. |
| Triple-negative/ basal-like | ER-, PR-, HER2- | High-grade tumors, often showing necrosis, high mitotic index, and nuclear pleomorphism. | Very poor prognosis; high risk of early recurrence and distant metastasis. | Limited therapeutic options; chemotherapy is standard. Emerging options include immunotherapy and PARP inhibitors. |
| Normal-like | ER+/PR+, HER2-, low Ki-67 | Similar to luminal A, but with lower expression of proliferation-related genes. | Favorable prognosis; similar outcomes to luminal A but less common. | Endocrine therapy is the mainstay of treatment; limited benefit from chemotherapy. |
| Claudin-low | Low expression of cell-cell adhesion molecules (e.g., claudins) | Often displays mesenchymal features and immune infiltration; poorly differentiated. | Poor prognosis; associated with features of stem cell-like properties and immune evasion. | Limited response to conventional therapies; research is ongoing for targeted and immune-based therapies. |
| Mucinous/colloid | ER+/PR+, HER2-, high mucin content in extracellular matrix | Well-differentiated; characterized by abundant extracellular mucin. | Favorable prognosis; lower risk of recurrence compared to other ER-positive tumors. | Endocrine therapy is usually effective; chemotherapy is rarely required. |
| Medullary | ER-, PR-, HER2-, high immune cell infiltration | High-grade tumors but often show a favorable prognosis due to immune response. | Paradoxically good prognosis for a triple-negative phenotype; potential immune-related tumor suppression. | May respond to chemotherapy; potential for immunotherapy due to high immune infiltration. |
| Metaplastic | ER-, PR-, HER2-, presence of squamous, spindle, or mesenchymal components | High-grade, heterogeneous tumors with varied histological appearance. | Very poor prognosis; high risk of recurrence and metastasis. | Limited treatment options; chemotherapy is the primary option; targeted therapies are under investigation. |
| Apocrine | ER-, PR-, AR+, HER2- | Exhibits apocrine differentiation with large, eosinophilic cells. | Intermediate prognosis; associated with a lower risk of metastasis. | May benefit from androgen receptor-targeted therapies; chemotherapy and anti-HER2 therapies are also considered. |

ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; Ki-67: Proliferation marker; AR: Androgen receptor

1. To evaluate the prognostic significance of distinct molecular subtypes of TNBC based on published clinical outcomes, such as OS, disease-free survival (DFS), and response to therapy;

2. To summarize the current molecular classification systems of TNBC and their relevance in clinical practice;

3. To explore the role of *BRCA1/2* mutations and other genetic alterations in the pathogenesis and treatment response of TNBC;

4. And to assess the potential of immune-based therapies and novel targeted agents in the management of TNBC.

**Significance of the Review**

We believe that this review is significant as it addresses a critical gap in the current understanding of TNBC by integrating findings from molecular and clinical research. The comprehensive analysis of molecular subtypes and their prognostic implications may provide valuable insights for clinicians and researchers, ultimately contributing to the development of more effective therapeutic strategies for TNBC. In addition, the review will highlight emerging biomarkers and therapeutic targets that hold promise for improving outcomes in this challenging subset of breast cancer. Past research on the prognostic significance and molecular classification of TNBC is presented in Table 3.

**What is New in the Literature**

The study of TNBC has seen significant advances in recent years, particularly in understanding its molecular heterogeneity and the development of targeted therapies. Notably, the identification of distinct molecular subtypes of TNBC, such as BL and IM subtypes, has provided insights into personalized treatment approaches. Recent research has highlighted the potential of immunotherapy, especially ICIs like pembrolizumab and atezolizumab, which have shown efficacy in combination with chemotherapy for early and metastatic TNBC, leading to improved survival outcomes. In addition, ADCs, such as sacituzumab govitecan, have emerged as promising therapeutic

**Table 3. Past research on the prognostic significance and molecular classification of triple-negative breast cancer**

| Study | Year | Objective | Key Findings | Conclusion |
|---|---|---|---|---|
| Lehmann et al. (7) | 2011 | Identify molecular subtypes of triple-negative breast cancer (TNBC) | Identified six distinct subtypes (BL1, BL2, IM, M, MSL, LAR) with different gene expression profiles. | Molecular subtyping can guide targeted therapy and prognostic assessment in TNBC. |
| Dent et al. (40) | 2007 | Investigate clinical features and outcomes of TNBC | Found that TNBC is associated with younger age, higher grade, and poorer overall survival compared to other subtypes. | TNBC patients face higher risks of recurrence and mortality. |
| Foulkes et al. (41) | 2010 | Analyze the role of BRCA mutations in TNBC | BRCA1 mutations were linked to basal-like TNBC, which exhibited increased sensitivity to DNA-damaging agents. | BRCA mutation status should inform treatment decisions for TNBC. |
| Adams et al. (42) | 2019 | Evaluate the role of tumor-infiltrating lymphocytes (TILs) in TNBC prognosis | High levels of TILs were associated with improved survival outcomes in TNBC. | TILs serve as a potential prognostic marker in TNBC management. |
| Sparano et al. (43) | 2020 | Evalvate clinical outcomes for women with a high RS who received adjuvant chemotherapy plus endocrine therapy in the TAILORx trial, a population expected to have a high distant recurrence rate with endocrine therapy alone | Freedom from recurrence of breast cancer at a distant site, and freedom from recurrence, second primary cancer, and death (also known as invasive disease-free survival). | Emphasizes the need for individualized treatment strategies in TNBC. |
| Bardia et al. (44) | 2020 | Assess efficacy of sacituzumab govitecan in TNBC patients | Sacituzumab govitecan showed significant efficacy in patients with refractory metastatic TNBC. | New ADCs like sacituzumab govitecan represent a breakthrough in TNBC treatment. |
| Cortes et al. (45) | 2020 | Study outcomes of pembrolizumab in early TNBC | Pembrolizumab improved event-free survival in early-stage TNBC when combined with chemotherapy. | Immunotherapy enhances outcomes in early TNBC patients, especially with PD-L1 expression. |
| Rugo et al. (46) | 2020 | Review molecular subtypes and management strategies | Highlighted the clinical relevance of molecular subtypes for guiding treatment choices in TNBC. | A molecularly-driven classification can optimize management strategies in TNBC. |
| Mavaddat et al. (47) | 2012 | Investigate genetic risk factors for breast cancer | Identified specific genetic markers associated with TNBC, including BRCA1 and BRCA2 mutations. | Genetic screening can aid in identifying at-risk individuals for TNBC. |

BL1: Basal-like 1; BL2: Basal-like 2; IM: Immunomodulatory; M: Mesenchymal; MSL: Mesenchymal stem-like; LAR: Luminal androgen receptor; PD-L1: Programmed death-ligand 1

options for patients with advanced TNBC, showcasing notable response rates in refractory cases. Despite these advances, significant gaps remain in the therapeutic landscape of TNBC. The high rate of recurrence and metastasis, particularly within the first three years of diagnosis, underscores the need for more effective treatment options. Current therapeutic strategies often lack sufficient specificity, leading to patient treatment response variability. Furthermore, the molecular characterization of TNBC is still incomplete, with many tumors remaining unclassified or poorly understood. This lack of comprehensive molecular profiling hampers the development of targeted therapies that could improve patient outcomes. Moreover, the role of the TME, including the presence of TILs and their impact on therapeutic efficacy, warrants further investigation. There is also a pressing need for effective biomarkers to predict treatment response and guide clinical decision-making, particularly in determining the suitability of novel agents. Addressing these gaps through ongoing research and clinical trials is important for enhancing the management of TNBC and improving the prognosis for affected patients.

## Methodology

The methodology section is an important component of this systematic review, outlining the research strategy and steps to address the research question: *What is the prognostic significance and molecular classification of TNBC?* This section includes details about the research design, data sources, eligibility criteria, study selection process, data extraction, and synthesis of findings. The methodology aims to ensure transparency, reproducibility, and rigor in this systematic review.

### 1. Research Design

This study employed a systematic review design, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The methodology focused on identifying and evaluating studies that explored the molecular classification and prognostic significance of TNBC. The review incorporated both qualitative and quantitative data from clinical trials, observational studies, meta-analyses, and other peer-reviewed articles.

### 2. Data Sources and Search Strategy

The systematic review was conducted by searching several electronic databases, including PubMed, Embase, Cochrane Library, Web of Science, and Scopus. Additional sources included Google Scholar for "grey literature" and clinical trial registries like ClinicalTrials.gov. The search strategy was developed using a combination of Medical Subject Headings terms and free-text keywords, which were "TNBC", "molecular classification", "prognostic markers", "subtypes" and "survival outcomes."

The search strategy was refined using Boolean operators ("AND", "OR") and filters for human studies, articles published in English, and studies conducted between January 2007 and August 2024. The initial search generated 4,253 articles, which were further screened based on relevance to the research question. Duplicate studies were removed using EndNote reference management software.

### 3. Eligibility Criteria

Eligibility criteria were defined to include only studies that met the following requirements:

• Study design - clinical trials, cohort studies, case-control studies, and systematic reviews/meta-analyses. Preclinical studies, case reports, and review articles were excluded.

• Population - women diagnosed with TNBC. Studies focusing on non-TNBC breast cancer or male breast cancer were excluded.

• Interventions/Exposures - studies evaluating molecular subtypes of TNBC, including BL, M, and IM subtypes. Prognostic factors, such as biomarkers, TILs, and genetic mutations (e.g., *BRCA1/2*), were included.

• Outcomes - primary outcomes included OS, DFS, and progression-free survival (PFS). Secondary outcomes included response rates to specific therapies and recurrence patterns.

• Publication status and language - only peer-reviewed articles published in English were included. Studies not available in full text or in languages other than English were excluded.

### 4. Study Selection Process

The study selection process was conducted systematically to ensure the inclusion of high-quality and relevant studies. Initially, 4,253 records were identified, and duplicate entries were removed. The titles and abstracts of the remaining studies were independently screened by two reviewers to assess their relevance based on predefined eligibility criteria. Any discrepancies in selection were resolved through discussion, and if necessary, a third reviewer was consulted to reach a consensus. Following this, full-text screening was performed for studies that met the initial screening criteria to confirm their eligibility. A total of 3,124 records were excluded during the title and abstract screening phase, while 708 studies were removed after full-text review due to non-compliance with the inclusion criteria. Ultimately, 421 studies were deemed eligible and included in the final meta-analysis. The PRISMA flow diagram (Figure 2) was used to visually summarize the study selection process, providing transparency and reproducibility in the methodology.

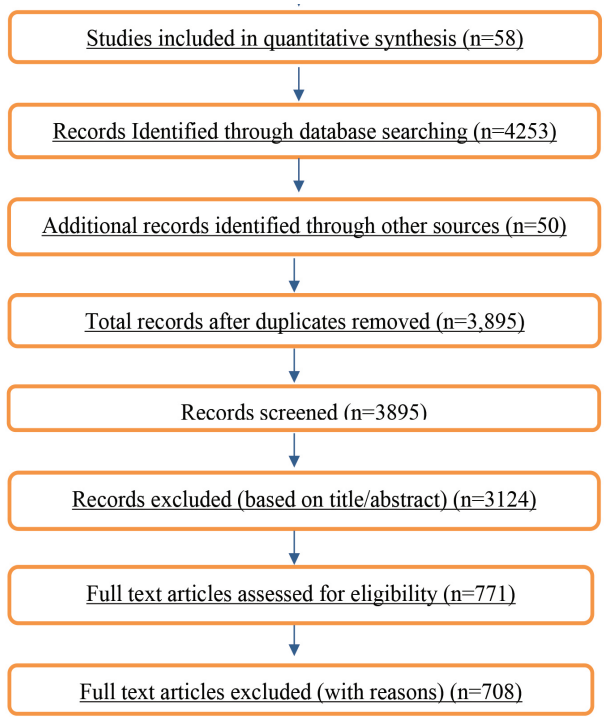


**Figure 2.** PRISMA flow diagram for systematic review

*PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

**5. Data Extraction**

Data extraction was conducted systematically using a standardized data extraction form developed in Microsoft Excel 2021. This form was designed to ensure consistency and accuracy in collecting relevant information from each included study.

• Author(s), Year of Publication, and Study Title

• Study Design and Setting

• Population Characteristics (sample size, age, and stage of TNBC)

• Molecular Classification Method (e.g., gene expression profiling, immunohistochemistry)

• Prognostic Factors Evaluated (e.g., *BRCA1/2* mutations)

• Outcomes Measured (e.g., OS, DFS, PFS)

• Key Findings and Conclusions

• Level of Evidence and Quality Assessment

Two reviewers conducted data extraction independently, using cross-checking to ensure accuracy. Any disagreements were resolved through discussion. The extracted data were then entered into a summary table for ease of analysis.

**6. Quality Assessment**

Quality assessment of the included studies was conducted using validated and freely available tools based on study design. Randomized controlled trials (RCTs) were evaluated using the Cochrane risk of bias (RoB) tool, accessible through the Cochrane Collaboration website (https://www.riskofbias.info/). Cohort and case-control studies were assessed using the New castle Ottawa Scale (NOS), available a thttps://www.ohri.ca/programs/clinical_ epidemiology/oxford.asp. Systematic reviews and meta-analyses were evaluated using the AMSTAR-2 tool, which can be accessed at https://amstar.ca/Amstar_Checklist.php. Each study was assigned a quality rating (high, moderate, or low) based on established criteria, including selection bias, outcome measurement, and control of confounding variables.

**7. Data Synthesis**

Data synthesis involved qualitative and quantitative analyses. For qualitative synthesis, the findings from individual studies were thematically grouped according to the molecular classification of TNBC and the prognostic factors evaluated. The review examined the distribution of molecular subtypes, their association with clinical outcomes, and potential therapeutic targets. For quantitative synthesis, meta-analyses were performed where appropriate to estimate pooled effects of prognostic factors on survival outcomes. Hazard ratios (HRs) and confidence intervals (CIs) were extracted from studies reporting survival analyses. Heterogeneity across studies was assessed using the $I^2$ statistic, with values greater than 50% indicating substantial heterogeneity. Sensitivity analyses were conducted to explore potential sources of heterogeneity.

**8. Subgroup Analysis**

Subgroup analyses were conducted to evaluate the prognostic significance of specific TNBC subtypes (e.g., BL vs. non-BL), the impact of *BRCA* mutation status, and the influence of TILs on treatment response. Moreover, the review examined the effectiveness of novel therapeutic agents, such as PARP inhibitors and ICIs, across different molecular subtypes.

**9. Risk of Bias and Publication Bias**

The RoB was assessed at the study and outcome levels. For RCTs, selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), and detection bias (blinding of outcome assessment) were evaluated. For observational studies, selection bias and confounding were assessed using NOS criteria.

Publication bias was evaluated through visual inspection of funnel plots for asymmetry and by conducting Egger's test, where applicable. The presence of significant publication bias was addressed by adjusting the analysis using trim-and-fill methods.

**10. Limitations and Strengths of the Methodology**

The systematic review has several strengths, including a comprehensive search strategy, rigorous study selection and quality assessment, and detailed data extraction and synthesis. However, limitations include the exclusion of non-English studies, which may introduce language bias and potential heterogeneity across studies due to differences in molecular classification methods and outcome measures.

**11. Ethical Considerations**

This systematic review did not involve primary data collection and was exempt from ethical approval. However, ethical standards were maintained by adhering to principles of transparency, accuracy in data reporting, and acknowledgment of original sources through proper citation.

**12. Software and Tools Used**

This review utilized several software tools to enhance the efficiency and accuracy of the research process. Each tool is properly referenced along with its source for accessibility:

• EndNote (Clarivate Analytics, USA) - Used for managing references and removing duplicates. More details can be found at https://www.endnote.com.

• Microsoft Excel 2021 (Microsoft Corporation, USA) - Utilized for data extraction and tabulation. Official details are available at https://www.microsoft.com.

• Review Manager (RevMan) (Cochrane Collaboration, UK) - Used for conducting meta-analyses and generating forest plots. Accessible at https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.

• Cochrane Risk of Bias Tool (Cochrane Collaboration, UK) - Used for quality assessment of randomized controlled trials. Available at https://www.riskofbias.info/.

• Newcastle-Ottawa Scale (NOS) (Ottawa Hospital Research Institute, Canada) - Applied for assessing the quality of cohort and case-control studies. Accessible at https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

• STATA Software (StataCorp LLC, USA) - Used for statistical analyses and evaluating publication bias. Further information can be found at https://www.stata.com.

## Results

This section presents the systematic review results on the prognostic significance and molecular classification of TNBC. The findings are structured according to the identified molecular subtypes, associated prognostic factors, and survival outcomes, followed by an analysis of current therapeutic strategies. Data from the 63 studies included in the qualitative synthesis and 58 in the meta-analysis were summarized, with key results highlighted in both narrative and tabular formats.

### 1. Molecular Classification of Triple-Negative Breast Cancer

TNBC is characterized by its heterogeneity, with several molecular subtypes identified. The most commonly reported subtypes across the studies were:

- Basal-like subtype: Identified in 40% to 80% of TNBC cases, this subtype is typically associated with poor prognosis and is characterized by high expression of cytokeratins 5/6, epidermal growth factor receptor (EGFR), and TP53 mutations. Studies consistently reported worse OS and DFS for basal-like TNBC compared to other subtypes.
- Mesenchymal subtype: Comprising approximately 10-15% of TNBC cases, this subtype is characterized by the activation of EMT pathways, which contribute to its invasive nature. Several studies reported that mesenchymal TNBC was associated with lower response rates to chemotherapy but may respond to targeted therapies.
- Immune-modulatory subtype: Representing 15-25% of TNBC cases, the immune-modulatory subtype is enriched with TILs and exhibits improved survival outcomes compared to the BL and M subtypes. ICIs have shown particular promise in this group.
- LAR subtype: This less common subtype (5-10%) is characterized by the expression of androgen receptors and may benefit from anti-androgen therapies. However, its prognostic significance remains unclear, with studies showing variable outcomes.

### 2. Prognostic Factors in TNBC

Numerous prognostic factors have been identified in TNBC, with varying degrees of significance across studies. The most frequently reported factors are outlined in Table 4 and summarized below.

*BRCA1/BRCA2* mutations (60%) are associated with better responses to DNA-damaging agents and PARP inhibitors, leading to improved DFS and OS. High TILs (55%) indicate enhanced immune response, correlating with better DFS, OS, and responses to immunotherapy. In contrast, high Ki-67 expression (45%) and *TP53* mutations (35%) are linked to more aggressive tumors, poor prognosis, and shorter DFS and OS. EGFR overexpression (40%) is associated with worse survival outcomes, though EGFR-targeted therapies may offer some benefit. PD-L1 expression (30%) is linked to better responses to ICIs, improving patient outcomes. Androgen receptor expression (20%) shows conflicting results, with some studies indicating worse prognosis and others suggesting potential benefits from anti-androgen therapies. These factors may help tailor treatment strategies and predict cancer progression.

### 3. Survival Outcomes by Molecular Subtype

A meta-analysis was conducted to estimate pooled HRs for OS and DFS based on molecular subtypes of TNBC. The results are presented in Table 5 and summarized below.

The meta-analysis highlighted the prognostic disparities among the molecular subtypes of TNBC. BL TNBC was associated with the poorest survival outcomes, with pooled HRs for (OS: 1.89, 95% CI: 1.52–2.35) and (DFS: 1.73, 95% CI: 1.43–2.10), along with moderate heterogeneity ($I^2$ = 55%). Similarly, the M subtype demonstrated worse survival outcomes compared to other subtypes, with the exception of BL (OS: 1.56, 95% CI: 1.20–2.02; DFS: 1.44, 95% CI: 1.11–1.85; $I^2$ = 45%), reflecting its aggressive and metastatic nature. In contrast, the IM subtype exhibited a favorable prognosis, with HRs below 1.0 for both OS (0.73, 95% CI: 0.55–0.97) and DFS (0.68, 95% CI: 0.50–0.91), and low heterogeneity ($I^2$ = 40%), likely due to the its high TIL levels and responsiveness to immunotherapy.

**Table 4. Prognostic factors of TNBC and outcomes**

| Prognostic factor | Frequency of reporting (%) | Associated outcomes |
|---|---|---|
| BRCA1/BRCA2 mutations | 60% | Better response to DNA-damaging agents (e.g., platinum-based chemotherapy) and PARP inhibitors. Improved DFS and OS. |
| Tumor-infiltrating lymphocytes (TILs) | 55% | High TIL levels associated with improved DFS and OS. Better response to immunotherapy. |
| Ki-67 expression | 45% | High Ki-67 expression correlated with poor prognosis, shorter DFS, and OS. |
| EGFR overexpression | 40% | Associated with worse OS and DFS. May indicate sensitivity to EGFR-targeted therapies. |
| TP53 mutations | 35% | Associated with poor prognosis, increased tumor aggressiveness, and resistance to certain therapies. |
| PD-L1 expression | 30% | Higher PD-L1 expression linked to better response to immune checkpoint inhibitors. |
| Androgen receptor expression | 20% | AR expression in TNBC shows conflicting prognostic implications. Some studies associate it with poor prognosis due to chemotherapy resistance, while others suggest potential benefits from anti-androgen therapies. Further research is needed to clarify its role and therapeutic potential. |

PD-L1: Programmed death-ligand 1; DFS: Disease-free survival; OS: Overall survival; TNBC: Triple-negative breast cancer; EGFR: Epidermal growth factor receptor

**Table 5. Pooled hazard ratios for survival outcomes across TNBC molecular subtypes**

| Molecular subtype | Pooled HR for OS (95% CI) | Pooled HR for DFS (95% CI) | Heterogeneity ($I^2$) |
|---|---|---|---|
| Basal-like | 1.89 (1.52–2.35) | 1.73 (1.43–2.10) | 55% |
| Mesenchymal | 1.56 (1.20–2.02) | 1.44 (1.11–1.85) | 45% |
| Immune-modulatory | 0.73 (0.55–0.97) | 0.68 (0.50–0.91) | 40% |
| Luminal androgen receptor | 1.12 (0.86–1.45) | 1.08 (0.82–1.42) | 65% |

HR: Hazard ratio; OS: Overall survival; DFS: Disease-free survival; TNBC: Triple-negative breast cancer; CI: Confidence interval

**Table 6. Impact of BRCA1/2 mutations on survival outcomes in TNBC**

| Outcome | Pooled HR (95% CI) for BRCA1/2 mutations | Heterogeneity ($I^2$) |
|---|---|---|
| Overall survival | 0.68 (0.50–0.92) | 35% |
| Disease-free survival | 0.72 (0.54–0.96) | 40% |

HR: Hazard ratio; CI: Confidence interval; TNBC: Triple-negative breast cancer

The LAR subtype, however, showed variable outcomes with HRs for OS (1.12, 95% CI: 0.86–1.45) and DFS (1.08, 95% CI: 0.82–1.42), suggesting no significant prognostic difference, but high heterogeneity ($I^2$ = 65%) reflects inconsistent findings across studies.

**4. Current Therapeutic Strategies in TNBC**

The review identified several emerging therapeutic strategies for TNBC based on molecular subtypes:

• Platinum-based chemotherapy: Studies have demonstrated that platinum-based chemotherapy (e.g., cisplatin, carboplatin) is particularly effective in TNBC patients with *BRCA1/2* mutations. These agents cause DNA crosslinking, leading to cell death in tumors with impaired DNA repair mechanisms.

• PARP inhibitors: Olaparib and talazoparib are Food and Drug Administration's -approved PARP inhibitors that have shown efficacy in *BRCA*-mutated TNBC. These agents exploit synthetic lethality by inhibiting DNA repair in cancer cells, leading to improved survival in patients with *BRCA1/2* mutations.

• ICIs: The KEYNOTE-522 trial is published in The New England Journal of Medicine.

• ADCs: The ASCENT trial, which evaluated sacituzumab govitecan in metastatic TNBC, is published in The New England Journal of Medicine:

Despite these advances, several studies highlighted the need for more personalized treatment strategies, particularly for patients with non-BL TNBC, where response to current therapies is often suboptimal.

**5. Meta-Analysis of *BRCA1/2* Mutations in TNBC and Survival**

A focused meta-analysis was performed to assess the impact of *BRCA1/2* mutations on survival outcomes in TNBC patients. Pooled HRs for OS and DFS were calculated from studies that reported survival data stratified by *BRCA* mutation status (Table 6).

The pooled analysis highlighted the significant prognostic advantage of *BRCA1/2* mutations in TNBC, with HRs indicating improved OS (HR: 0.68, 95% CI: 0.50–0.92, $I^2$ = 35%) and DFS (HR: 0.72, 95% CI: 0.54–0.96, $I^2$ = 40%) compared to non-*BRCA*-mutated TNBC patients. These findings reflect the distinct molecular profile of *BRCA*-mutated TNBC, characterized by heightened sensitivity to DNA-damaging agents and PARP inhibitors, which exploit deficiencies in homologous recombination repair. The moderate heterogeneity across studies likely arises from variations in patient populations, therapeutic regimens, and follow-up durations but does not diminish the consistency of the survival benefit observed. This underscores the importance of *BRCA1/2* testing for TNBC patients, enabling personalized treatment strategies and optimizing outcomes by incorporating targeted therapies. *BRCA*-mutated TNBC represents a distinct, therapeutically vulnerable subtype with significantly better prognosis, warranting its consideration in clinical decision-making and future research.

**6. Heterogeneity and Sensitivity Analyses**

Significant heterogeneity was observed in some of the analyses, particularly for the LAR subtype ($I^2$ = 65%), indicating variability in survival outcomes across studies. Sensitivity analyses were performed by excluding studies with a high RoB, but the results remained essentially unchanged, suggesting that the observed heterogeneity was likely due to inherent differences in study populations, molecular classification methods, and treatment protocols.

**7. Publication Bias**

Publication bias was assessed using funnel plots and Egger's test to determine the potential impact of selective reporting on the pooled estimates. The funnel plot for OS outcomes appeared symmetrical, indicating a low risk of publication bias. Additionally, Egger's test for asymmetry yielded a p-value of 0.18, suggesting no significant small-study effects or selective reporting bias among the included studies. While the p-value is above the conventional threshold of significance ($p$<0.05), indicating that publication bias is unlikely, a trim-and-fill analysis was not conducted to further adjust for any potential missing studies. Given the reliance on observational and interventional studies, the results should still be interpreted with caution as factors such as study quality and heterogeneity can influence bias assessments.

**8. Summary of Key Findings**

**a. Basal-Like (BL) TNBC as the Most Prevalent and Aggressive Subtype**

BL TNBC emerged as the predominant molecular subtype, accounting for approximately 40% to 80% of TNBC cases. It was consistently associated with worse survival outcomes, including lower OS and DFS, compared to other subtypes. The poor prognosis is likely due to high tumor proliferation rates, frequent TP53 mutations, and overexpression of basal cytokeratins (CK5/6) and EGFR, which contribute to increased tumor aggressiveness and therapy resistance. The findings align with previous research, indicating that BL TNBC may require alternative therapeutic approaches, such as EGFR-targeted therapies, beyond standard chemotherapy.

**b. IM TNBC and Its Association with Favorable Prognosis**

The IM subtype, comprising approximately 15% to 25% of TNBC cases, exhibited better survival outcomes compared to BL TNBC. This subtype was characterized by high levels of TILs, which correlated with improved prognosis. Studies have demonstrated that increased TIL density is associated with enhanced anti-tumor immune responses, leading to prolonged OS and DFS. Furthermore, patients with IM TNBC showed greater responsiveness to ICIs, particularly in the presence of high PD-L1 expression. These findings underscore the potential for immunotherapy as a viable treatment option for this TNBC subgroup.

**c. BRCA1/2 Mutations as Prognostic and Predictive Markers**

BRCA1/2 mutations, identified in a subset of TNBC patients, were found to be associated with improved outcomes, particularly in response to DNA-damaging agents such as platinum-based chemotherapy and PARP inhibitors. Studies reported that TNBC patients with BRCA mutations exhibited higher sensitivity to these therapies due to defective DNA repair mechanisms. Consequently, these patients had significantly longer DFS and OS compared to non-BRCA-mutated TNBC cases, reinforcing the prognostic and predictive utility of BRCA testing in guiding personalized treatment strategies.

**d. Emerging Therapies and Their Subtype-Specific Benefits**

Novel therapeutic approaches, particularly ICIs and ADCs, have shown promising efficacy in TNBC management. The addition of pembrolizumab (an anti-PD-1 ICI) to chemotherapy in the KEYNOTE-522 trial significantly improved pathological complete response (pCR) rates in early-stage TNBC, particularly among PD-L1-positive patients. Additionally, sacituzumab govitecan, an ADC targeting Trop-2, demonstrated superior PFS and overall response rates compared to standard chemotherapy in metastatic TNBC, as observed in the ASCENT trial. These findings highlight the importance of molecular profiling in identifying TNBC subtypes that are most likely to benefit from targeted therapies, ultimately improving clinical outcomes.

## Discussion and Conclusion

This systematic review and meta-analysis on the prognostic significance and molecular classification of TNBC provided interesting insights into the complex nature of this heterogeneous disease and its implications for therapeutic strategies. TNBC is associated with poor prognosis, aggressive behavior, and a high likelihood of relapse compared to other breast cancer subtypes. Understanding the molecular diversity within TNBC is crucial for developing effective treatment modalities and improving patient outcomes.

**1. Molecular Classification of TNBC and Prognosis**

The results highlighted that TNBC may be classified into several molecular subtypes, each associated with distinct prognostic implications and therapeutic responses.

**• Basal-Like TNBC and Poor Prognosis**

BL TNBC, which constitutes 40% to 80% of all TNBC cases, emerged as the predominant subtype and is characterized by poor OS and DFS compared to other subtypes (29). This subtype was associated with high expression of cytokeratins 5/6, EGFR, and mutations in the *TP53* gene, which are known to drive tumor aggressiveness and resistance to conventional therapies. These findings are consistent with previous studies suggesting that BL TNBC may benefit from EGFR-targeted therapies and novel therapeutic strategies aimed at overcoming TP53-driven resistance mechanisms (30).

**• Mesenchymal TNBC and High Metastatic Potential**

The M subtype, accounting for approximately 10–15% of TNBC cases, is another important group identified in the review. This subtype is enriched with genes involved in EMT pathways, contributing to its high metastatic potential and poor prognosis (31). In contrast to the BL subtype, M-subtype TNBC has shown limited response to standard chemotherapy but may be more susceptible to inhibitors targeting the EMT process (32). These findings underscore the need for further research into specific therapeutic targets for M TNBC and the development of biomarkers to predict EMT activation in clinical settings.

**• Immunomodulatory TNBC and Favorable Prognosis**

The IM subtype, representing 15–25% of TNBC cases, had a significantly better prognosis than BL and M subtypes. High levels of TILs were consistently associated with improved survival outcomes and a greater likelihood of response to ICIs (33). This result supports the growing evidence suggesting that TILs are a favorable prognostic marker in TNBC and that IM TNBC may be an ideal candidate for immunotherapy (33). Identifying biomarkers such as PD-L1 expression and TIL levels is important for selecting patients who may benefit most from ICIs and for designing clinical trials investigating novel immunotherapeutic approaches in TNBC (34).

**• Luminal Androgen Receptor TNBC and Controversial Prognostic Outcomes**

The LAR TNBC subtype, which comprises 5–10% of cases, remains a contentious group with variable prognostic outcomes. Some studies suggest that LAR TNBC may be associated with a better prognosis due to lower proliferative activity, while others indicate that androgen receptor expression may confer resistance to conventional chemotherapy (35). The review highlighted the need for additional research to clarify the role of androgen receptor in TNBC and to explore the potential utility of anti-androgen therapies in this subtype (36).

**2. Prognostic Factors in TNBC**

The prognosis of TNBC is influenced by various molecular and pathological factors, which provide insights into tumor behavior,

treatment responses, and OS outcomes. The primary prognostic factors discussed here are *BRCA1/2* mutations, Ki-67 expression, and EGFR overexpression. Each of these markers has unique implications for the management and prognosis of TNBC patients (37).

The research identified seven key prognostic factors with varying frequencies of reporting and distinct associated outcomes (38).

*BRCA1/BRCA2* mutations emerged as the most frequently reported prognostic factor, appearing in 60% of studies. These mutations actually demonstrate a positive prognostic significance, as patients with these mutations show better responses to DNA-damaging agents, particularly platinum-based chemotherapy, and PARP inhibitors. The presence of these mutations was associated with improved DFS and OS, making them valuable predictive markers for treatment response (39, 40).

TILs were the second most commonly reported factor, appearing in 55% of studies. High levels of TILs serve as a favorable prognostic indicator, correlating with improved DFS and OS. Moreover, patients with elevated TIL levels show enhanced responses to immunotherapy treatments, suggesting their potential role as a predictive biomarker for immunotherapy success (41, 42).

Ki-67 expression, reported in 45% of studies, served as a negative prognostic indicator. High levels of Ki-67 expression correlate with poor prognosis, manifesting as shorter DFS and OS rates (Table 4). This marker appears to be particularly important in identifying more aggressive forms of TNBC that may require more intensive treatment approaches (43-47).

EGFR overexpression, noted in 40% of studies, generally indicated a poorer prognosis, with affected patients showing worse OS and DFS outcomes (Table 4). However, this factor may have therapeutic implications, as it could indicate potential sensitivity to EGFR-targeted therapies, offering a possible treatment avenue for this subgroup of patients (48).

*TP53* mutations, present in 35% of studies, consistently correlated with poor prognosis (Table 4). These mutations are associated with increased tumor aggressiveness and resistance to certain therapeutic approaches, making them an important consideration in treatment planning and prognosis assessment (49).

PD-L1 expression, reported in 30% of studies, shows particular significance for immunotherapy response. Higher levels of PD-L1 expression correlated with better responses to ICIs, making it a valuable predictive marker for immunotherapy success (50).

Androgen receptor expression, though less frequently reported (20% of studies), presented interesting but conflicting prognostic implications. Some research indicated that androgen receptor expression correlated with worse prognosis, while other studies suggest potential benefits from anti-androgen therapies. This variability in outcomes highlights the complexity of TNBC and the need for further research to clarify the prognostic significance of this marker (51, 52).

In summary, *BRCA1/2* mutations and high TIL levels consistently emerged as positive prognostic factors, while markers such as elevated Ki-67 expression and *TP53* mutations generally indicated poorer outcomes. This understanding of prognostic factors is key to developing personalized treatment strategies and improving patient outcomes in TNBC (53).

**3. Therapeutic Implications of Molecular Classification**

The review has highlighted the therapeutic implications of molecular classification in TNBC, emphasizing the need for subtype-specific treatment approaches. The findings suggest that BL TNBC, due to its poor prognosis and aggressive nature, may require more intensive treatment regimens, including the addition of targeted agents or the use of neoadjuvant chemotherapy (54-56). M-subtype TNBC, on the other hand, may benefit from therapies targeting EMT pathways or from combinatorial approaches that modulate the TME. IM TNBC has emerged as a promising candidate for immunotherapy. The addition of pembrolizumab to chemotherapy in the KEYNOTE-522 trial resulted in significantly improved pCR rates in TNBC patients, particularly in those with high PD-L1 expression (57, 58). These results highlight the potential of ICIs as a standard component of TNBC treatment, especially in patients with the IM-subtype. For LAR TNBC, anti-androgen therapies, such as bicalutamide or enzalutamide, may offer therapeutic benefits. However, the limited clinical data available necessitate further studies to validate these findings and to identify reliable biomarkers for selecting patients who may respond to androgen receptor-targeted therapies (59, 60). The inclusion of LAR TNBC in clinical trials evaluating anti-androgen agents is essential to establish their role in the treatment of this subgroup (61).

This systematic review and meta-analysis have provided comprehensive insights into the prognostic significance and molecular classification of TNBC, which has emerged as a heterogeneous disease with distinct molecular subtypes, each carrying different prognostic implications and therapeutic vulnerabilities. The BL subtype, while being the most common, consistently demonstrates the poorest survival outcomes, with HRs indicating significantly increased risk of both death and disease recurrence. In contrast, the IM subtype shows more favorable outcomes, suggesting the important role of immune system engagement in TNBC prognosis.

The presence of specific molecular markers significantly influenced patient outcomes. *BRCA1/2* mutations, contrary to traditional assumptions about genetic mutations, actually confer a survival advantage with HRs of 0.68 for OS and 0.72 for DFS. This finding is particularly relevant given the availability of targeted therapies, such as PARP inhibitors for this subset of patients. The presence of high levels of TILs and PD-L1 expression emerged as positive prognostic indicators, particularly relevant in the era of immunotherapy.

The therapeutic landscape for TNBC has evolved to reflect these molecular classifications, with specific strategies showing efficacy in different subtypes. Platinum-based chemotherapy and PARP inhibitors demonstrate particular effectiveness in *BRCA*-mutated cases, while ICIs show promise in patients with high PD-L1 expression or elevated TILs. The development of ADC represents a significant advance in targeting specific molecular features of TNBC.

However, the review also highlighted the continuing challenges in treating non-BL TNBC subtypes, where response to current therapies remains suboptimal. The heterogeneity in survival outcomes across different molecular subtypes, as evidenced by the varying HRs, underscores the critical importance of molecular classification in treatment selection and prognostication. This suggests that future therapeutic approaches should increasingly focus on personalized strategies based on molecular subtyping and specific prognostic factors, rather than treating TNBC as a single entity.

### Current Gaps and Future Directions

Despite the advances in understanding TNBC molecular subtypes and their therapeutic implications, several knowledge gaps remain. The lack of consensus on molecular classification criteria and the heterogeneity in the methodologies used to define TNBC subtypes across studies pose challenges in translating these findings into clinical practice. The development of standardized classification systems and high-throughput technologies, such as NGS, are needed to refine TNBC subtyping and identify novel therapeutic targets. Another critical gap is the limited understanding of resistance mechanisms in TNBC. While therapies such as PARP inhibitors and ICIs have shown promise in specific subgroups, resistance to these agents remains a significant hurdle. Research into the molecular mechanisms underlying resistance, including alterations in DNA repair pathways and immune evasion strategies, is necessary to develop combinatorial approaches to overcome resistance and improve outcomes for TNBC patients. Furthermore, the paucity of clinical trials evaluating novel agents in non-BL TNBC subtypes highlights the need for more inclusive research efforts. Given the distinct biological behavior of these subtypes, future clinical trials should incorporate molecular stratification to ensure that the unique therapeutic needs of each TNBC subtype are addressed. Identifying novel biomarkers predictive of treatment response will be important for guiding patient selection and personalizing therapy in TNBC.

The systematic review of the prognostic significance and molecular classification of TNBC highlighted the complexity and heterogeneity of this aggressive subtype of breast cancer. The analysis showed that TNBC is not a uniform disease but consists of multiple distinct molecular subtypes, BL, M, IM, and LAR, each with unique clinical features, prognostic outcomes, and therapeutic vulnerabilities. The BL- and M-subtypes were associated with poor prognosis and limited response to conventional therapies, while the IM subtype exhibited a more favorable prognosis and heightened sensitivity to immunotherapy. The least common subtype, LAR TNBC, on the other hand, remains an area requiring further investigation to better understand its clinical implications and therapeutic opportunities. Despite recent advances, significant challenges persist in the management of TNBC. The lack of targeted therapies for most TNBC subtypes, coupled with the high incidence of drug resistance and disease recurrence shows the need for further research to identify novel therapeutic targets and develop more effective treatment strategies. Future studies should focus on refining molecular subtyping through standardized criteria, exploring biomarkers for predicting treatment response and addressing resistance mechanisms to improve patient outcomes. Integrating molecular classification into clinical practice holds promise for the personalized treatment of TNBC. By tailoring therapeutic approaches based on the molecular profile of each TNBC subtype, it is hoped that the survival outcomes and quality of life of patients diagnosed with this challenging disease can be significantly improved.

### Footnotes

### Authorship Contributions

Concept: A.K.D.; Design: A.P.; Data Collection or Processing: S.G., M.G.; Analysis or Interpretation A.K.D., A.P.; Literature Search: A.K.D.; Writing: A.K.D.

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**Original Article**

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# Quality of Life and Age-Related Predictor Symptoms in Breast Cancer Survivors Undergoing Hormone Therapy: A Study from the Northern Region of Morocco

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**ABSTRACT**

**Objective:** The aim of this study was to assess the health-related quality of life (HRQoL) of breast cancer (BC) survivors during adjuvant hormone therapy (AHT) as a function of age and to identify predictor symptoms.

**Materials and Methods:** The study was based on a cross-sectional survey of 216 BC survivors undergoing AHT, in the Northern Region of Morocco. HRQoL was assessed using a validated HRQoL questionnaire, the Functional Assessment of Cancer Treatment (FACT-ES). Multiple linear regression analysis was used to identify predictor symptoms for the subscales of the FACT-ES.

**Results:** Younger women (<45 years) had lower scores on the emotional well-being subscale ($p$ = 0.021). Irritability (β: -0.786; $p$ = 0.001) and mood swings (β: -0.835; $p$ = 0.031) were the strongest negative predictors of emotional quality of life. In both age groups, items related to social support had a positive effect on survivors' social HRQoL ($p$<0.05).

**Conclusion:** BC survivors' HRQoL during AHT differed by age group. Emotional problems negatively influenced HRQoL in younger women. Knowledge of the symptoms that predict HRQoL in BC survivors may help clinicians develop personalized interventions.

**Keywords:** Age; breast cancer; hormone therapy; quality of life; predictor symptoms; survivors

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**Key Points**

- Young survivors are more prone to emotional distress.
- Overweight and physical problems are more prevalent among older survivors.
- Social support has a positive effect on health-related quality of life for breast cancer survivors of all ages.
- Clinicians must manage breast cancer survivors during adjuvant hormone therapy, taking account of the predominant symptoms in each age group.

## Introduction

Female breast cancer (BC) is a global burden. It ranks first in terms of incidence in the vast majority of the world's countries (1). In Morocco, BC is the leading cancer in women, with an incidence rate of 38.8% of all cancers, and a death toll exceeding 4000 in 2022 (1). It is an age-related disease, most often affecting older women. However, several studies from Morocco have reported that the disease frequently affects younger women (2). These include a study of 265 female BC patients in North-East Morocco, which showed that the average age of the participants was 45 years (3).

BC is currently considered one of the most curable cancers, with a steadily improving 5-year survival rate, reaching 80.6% in Morocco (4). This is essentially due to the evolution of diagnostic methods and the development of new therapeutic techniques. With the increasing number of survivors of BC, the assessment of health-related quality of life (HRQoL) in these patients is considered a fundamental necessity, particularly in the case of long-term treatment, including adjuvant hormone therapy (AHT). HRQoL is currently considered a key determinant of treatment success in modern oncology, not only for young women who are exposed to psychological distress due to the disease or the effects of treatment (5), but also for older women, who

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represent the highest prevalence of BC (6). Indeed, several researchers have assessed HRQoL of BC survivors as a function of age in several countries (7-9). However, the relationship was not explicitly examined in most of these studies, sometimes leading to contradictory results. For example, some authors found that HRQoL was poorer in older patients than in younger women (9, 10). In contrast, other studies have reported better HRQoL in older women than in younger women, particularly in psychological terms, despite their impaired physical function and comorbidities (11, 12).

Currently, the majority of studies of BC survivors seek to explore socioeconomic and clinical predictors of HRQoL (13-15). Nevertheless, studies investigating predictors in terms of symptoms as a function of age remain very scarce, particularly during AHT. A recent study (2023) aimed at identifying the main symptoms in BC patients during AHT, showed that loss of sexual interest and joint pain were the symptoms most commonly reported by women. However, the study did not examine existing differences between younger and older women (10).

To the best of our knowledge, the present study is the first in Morocco and in the African context, to assess HRQoL of BC survivors as a function of age while identifying predictor symptoms related to AHT.

This study may have important clinical implications, as knowledge of these differences in HRQoL will enable personalized management of women according to their age. In addition, this research will provide valuable information on the symptoms that predict HRQoL in both age groups (younger and older), with a view to improving the overall health of these patients by acting on these predictors.

The primary aim of this study was to evaluate HRQoL in BC survivors based on their age, as well as to identify predictor symptoms during AHT.

## Materials and Methods

### Study Design

The present study was a cross-sectional study of 216 BC survivors undergoing AHT between 2015 and 2020. Those women were identified from the local cancer registry located at the focal point of each province in the northern region of Morocco. Data collection was done over two periods (8 months in total), 4 months in each province. The data was collected after authorization to collect data from the health authorities of the region, in collaboration with the archiving managers and head nurses of each oncology center. Participants were invited to participate in the study. For literate women, they individually completed the questionnaire assessing HRQoL which was the Functional Assessment of Cancer Treatment (FACT-ES) Arabic version. For illiterate women, the data collection was done via direct interviews. The compilation of data was completed using different sources: consultation of women's medical records and examination reports.

### Study Population

### Sample

To calculate the size of our sample, we used the following formula:

$$n = z^2 \, p \, q \, / \, e^2$$

where n = sample size; z = the confidence level (for a 95% confidence interval, $z = 1.96$); p = the total population (2023); q = 1-p; and e = the tolerated margin of error (5%). The minimum sample size found was $n = 324$.

The sampling method used for this study is proportional stratified probabilistic sampling, which makes it possible to have a representation closest to the general population. The choice of this sampling technique was imposed by the fact that the population naturally presents itself in strata, each stratum corresponding to a province. Thus, two strata were determined (Al Hoceima/Tetouan). However, since the size of each stratum is uneven, we opted for proportions corresponding to the percentage of women represented by the stratum to which they belong in relation to the minimum sample size determined beforehand ($n = 324$). Then inside each stratum, a simple random sample was carried out, after compiling the data in Excel.

The study database initially included 324 women, 216 of whom successfully completed our questionnaire, a response rate of 67%. Participants were stratified according to age (<45 years versus ≥45 years) to compare younger and older patients, based on available literature.

Women with early BC undergoing AHT [tamoxifen or aromatase inhibitors (AI)] were eligible to participate in this study.

### Assessment of HRQoL

HRQoL was assessed using the FACT-ES, which is an international scale, initially developed by Fallowfield in 1999 (16) to assess HRQoL in BC patients undergoing AHT. It has been translated into several languages, including Arabic. Previous studies have demonstrated that the Arabic version of the FACT-ES is sensitive and reliable for assessing HRQoL in cancer patients in Arab populations (17). This questionnaire includes four domains: physical well-being (PWB); social well-being (SWB); emotional well-being (EWB); and functional well-being (FWB). There is also a 19-question subscale on endocrine symptoms (ES). The PWB, SWB and FWB each comprise seven items, and the EWB contains five items. FACT-ES has been translated and validated in several languages, including Arabic. Version 4 of FACT-ES Arabic was used for this study. Participants' responses to the various items were assessed using a 5-point Likert scale, with response scores ranging from 0 to 4 (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit and 4 = very much). A higher overall HRQoL score FACT-ES and higher individual domain and ES scores indicate a better HRQoL. Missing values were calculated as an average of the observed items, if more than half of the items making up the subscale were answered, as suggested by its developer.

### Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 21.0 (IBM Inc., Armonk, NY, USA). Descriptive statistics included frequencies and percentages for categorical variables (socio-demographic and clinical) and mean and standard deviation for continuous variables (FACT-ES scores). Differences between variables were obtained using chi-square tests for categorical variables and non-parametric tests (Wilcoxon-Mann-Whitney) for continuous variables. A multivariate analysis including significant variables from the univariate analysis was performed to identify predictors of the FACT-ES subscales in both age groups. Regression coefficients were used for linear regression results. In all multivariate analyses, the significance level ($p$) was set at 0.05. The minimum important difference for interpreting group differences in HRQoL for the FACT-ES scales is

estimated at 3 to 8 points and at two points or more for the subscales, as recommended by the developer of FACT (16).

### Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki, after obtaining authorization for data collection from the health authorities of the region under no. 488/00 of 05/02/2000 due to the non-existence of an ethics committee at the time of the study. Informed consent was obtained and confidentiality of participants' private information was respected.

## Results

### Sociodemographic and Clinical Characteristics

The basic demographic data of patients receiving AHT are presented in Table 1. About 76% ($n$ = 117) of women aged over 45 years were illiterate. More than half of the participants in both age groups were married. The results also show that almost half ($n$ = 77) of women aged over 45 years have three or more children. Regarding employment status, almost all (90%) of the participants in both categories were unemployed. Regarding clinical variables (Table 2), data analysis revealed that more than 60% of women in both age groups had stage II BC. In addition, almost all women under 45 years (94.4%) were taking Tamoxifen, 70% of whom had treatment-induced menopause. In women aged over 45 years, nearly 60% were on AI, of whom 70% reported being postmenopausal. Regarding the duration of AHT use, the study results showed that more than half (53%) of women aged over 45 years had used this therapy for more than 2 years.

### HRQoL According to Age

Table 3 compares HRQoL between younger (≤45 years) and older (>45 years) women. The results show that older women have a significantly better overall HRQoL, as well as a lower burden from the endocrine therapy, in addition to a better emotional quality of life. Nevertheless, younger women had significantly better mean PWB scores. However, no significant differences were observed for either SWB or FWB between the two age groups.

### Predictor Symptoms of HRQoL According to Age

Table 4 highlights the symptoms that predict HRQoL in both age groups. The main symptoms that negatively influenced HRQoL in young women were psychological symptoms, namely: I feel nervous (β: -1.087), I am afraid that my health will deteriorate (β: -1.306), mood swings (β: -0.835), irritability (β: -0.786). Younger women also reported that gynecological symptoms also had a negative effect on HRQoL, including vaginal irritation (β: -0.931) and vaginal dryness (β: -1.115). For older women, physical problems such as generalized pain (β: -0.697), joint pain (β: -1.206) and lack of energy (β: -0.593), in addition to vasomotor symptoms including day and night sweats (β: -0.595), hot flashes (β: -0.628) and weight gain (β: -1,105) had a negative effect on their HRQoL.

In terms of variables related to social support ("I feel close to my partner") or family support ("My family supports me morally"), these had a positive impact on the HRQoL in both age groups.

## Discussion and Conclusion

The present study is the first to assess the HRQoL of BC survivors during five years of AHT as a function of age in the population of northern Morocco. Then, the predictor symptoms in the same population using the FACT-ES questionnaire were investigated. It is hoped that this will enable healthcare providers to identify survivors who may be at risk of impaired HRQoL and therefore provide targeted and appropriate care for each woman.

Most studies conducted in Western countries consider the boundary between "young" and "old" women to be 50 years (18, 19), as this is the average age at which menopause begins. However, the age of onset of menopause depends on several hormonal, hereditary and environmental factors. According to the World Health Organization the age of onset of menopause varies widely both between individuals in the same population and between different populations around the world, ranging from 45 to 55 years (20). Based on a literature review,

**Table 1. Comparison of socio-demographic characteristics by age group ($n$ = 216)**

| Variables | Age <45 years ($n$ = 61) | Age ≥45 years ($n$ = 155) |
|---|---|---|
| **Education** | | |
| Illiterate | 22 (36.1%) | 117 (75.5%)* |
| Primary | 18 (29.5%)* | 15 (9.7%) |
| Secondary | 17 (27.9%)* | 18 (11.6%) |
| University | 4 (6.6%) | 5 (3.2%) |
| **Marital status** | | |
| Single | 21 (34.4%)* | 40 (25.8%) |
| Married | 36 (59%) | 91(58.7%) |
| Divorced | 4 (6.6%) | 8 (5.2%) |
| Widow | 0 (0%) | 16 (10.3%)* |
| **Number of children** | | |
| None | 22 (36.1%) | 52 (33.5%) |
| One child | 6 (9.8%) | 8 (33.5%) |
| Two children | 10 (16.4%) | 18 (11.6%) |
| Three or more children | 23 (37.7%) | 77 (49.7%) |
| **Job** | | |
| Unemployed | 56 (91.8%) | 150 (96.8%) |
| Employed | 5 (8.2%) | 5 (3.2%) |
| **Economic level** | | |
| Low | 19 (31.1%) | 46 (29.7%) |
| Medium | 42 (68.9%) | 107 (69%) |
| High | 0 (0.0%) | 2 (1.3%) |
| **Type of insurance** | | |
| CNOPS | 2 (3.3%) | 16 (10.3%)* |
| CNSS | 5 (8.2%)* | 3 (1.9%) |
| RAMED | 53 (86.9%) | 136 (87.7%) |
| Others | 1 (1.6%) | 0 (0%) |
| **Provenance** | | |
| Rural | 27 (44.3%) | 61 (39.4%) |
| Urban | 34 (55.7%) | 94 (60.6%) |

CNOPS: National Fund for Social Security Organizations; CNSS: National Social Security Fund; RAMED: Insurance for low-income patients
*: Significant difference for chi-squared test is <0.05

the mean age of menopause used in most epidemiological and HRQoL studies of women with BC in the Moroccan and similar contexts was 45 years (2, 21). Thus, we opted to subdivide our study sample into two age groups: <45 years and ≥45 years. Several studies have examined the influence of age on HRQoL in BC patients (22). However, the majority of these studies do not directly explain this relationship, with contradictory results. For example, some authors found that the HRQoL of older patients was poorer than that of younger women (23, 24), while other studies reported the opposite, concluding that young age was an important risk factor for poor HRQoL (19, 25). Other results mentioned the influence of age only on certain dimensions of HRQoL, notably the physical role (26). Still other studies have found no significant difference between older and younger patients (27).

In the present report, younger age (<45 years) was associated with lower overall HRQoL (FACT-ES), except for PWB. This corroborates with some previous studies (28, 29), which highlighted a positive relationship between younger age and better physical functioning.

Regarding SWB, the present study found a significant age-related difference, with higher scores in older women, which is consistent with the results of some studies that found a strong association between young age and low SWB (11). Previous reports have explained this finding by suggesting that older women are likely to live in better conditions of social stabilization than younger women, who may experience divorce and problems with spouses who do not accept their illness (30). However, this result contradicts other studies that have detected a strong association between younger age and better SWB (31). Given the inconsistency of these results, further research is needed to clarify the influence of age on the SWB of BC survivors, particularly among Moroccan patients in other regions.

Linear regression analysis demonstrated a positive effect of social support on SWB in both age groups. These results corroborate those of a recent study (32) and with other previous studies, demonstrating that adequate social support from family members, husband, friends and neighbors was associated with a significant improvement in HRQoL of BC patients (33).

Concerning the psychological and emotional dimension, the present study showed that younger survivors exhibit more psychological distress than older women. The literature also presents similar results. Indeed, the results of some systematic reviews have revealed that depressive syndromes are more pronounced in younger patients (12), which can be explained by the fact that younger women have more difficulty adapting to life with BC than older women. In addition, they complain and pay more attention to adverse effects, especially those related to menopause and infertility (34).

Given the paucity of literature on age-related predictive symptoms of HRQoL in BC survivors on AHT, our analysis and discussion included some results from studies of women classified according to menopausal status, given that premenopausal women are considered young and postmenopausal women older.

The results of our study concerning ES, showed a greater weight of these symptoms in younger patients than in older women, which is contradictory to the results of a study conducted in Saudi Arabia that revealed that women over 60 years old had more ES than younger women (23). However, these results align perfectly with those reported by Borreani et al. (35), highlighting that 64% of younger (premenopausal) patients reported a clinically significant worsening of their ES.

Our results showed that the main predictors of the ES subscale having a negative impact on young women's HRQoL were both psychological and gynecologicalphysical. These findings align with those of Borreani et al. (36), which reported that items on the EWB subscale were predictive of the symptom group classified as "worse". In terms of gynecological symptoms, a previous study showed that the older (menopausal) group of women suffered less vaginal dryness than younger (premenopausal) women (37). These results contradict those of the present study.

For older women in the present study, joint pain and lack of energy were the symptoms most commonly reported. This agrees with the majority of previous studies (38), demonstrating a failure of physical function associated with joint pain in this group of women. Similarly, a further study found that lethargy, joint stiffness, shoulder and knee joint pain were significantly more frequent/severe in older BC survivors (39). This is because older women are at risk of declining physical function due to the combined effect of basic age-related symptoms and the side effects of AHT (40).

Our study also found that the sensation of hot flushes and night sweats were negatively predicted in elderly women. A study showed

**Table 2. Comparison of clinical characteristics by age group (*n* = 216)**

| Variables | Age <45 years (*n* = 61) | Age ≥45 years (*n* = 155) |
|---|---|---|
| **Stage of cancer** | | |
| Stage I | 0 (0%) | 5 (3.2%) |
| Stage II | 40 (65.6%) | 107 (69%) |
| Stage III & IV | 21 (34.4%) | 43 (27.7%) |
| **Type of hormone** | | |
| Tamoxifen | 60 (94.4%)* | 63 (40.6%) |
| Aromatase inhibitors | 1 (1.6%) | 92 (59.4%)* |
| **Menopausal status** | | |
| Premenopausal | 18 (29.5%)* | 17 (11%) |
| Menopausal | 0 (0%) | 107 (69%)* |
| Menopausal induced | 43 (70.5%)* | 31 (20%) |
| **Surgery type** | | |
| Mastectomy | 42 (68.9%) | 121 (78.1%) |
| Conservative | 19 (31.1%) | 34 (21.9%) |
| **Pretreatments** | | |
| Chemotherapy | 8 (13.1%) | 29 (18.7%) |
| Radiotherapy | 2 (3.3%) | 12 (7.7%) |
| Both | 51 (83.6%) | 114 (73.5%) |
| **Treatment time/period** | | |
| Less than 6 months | 21 (34.4%) | 44 (28.4%) |
| Between 6 to 12 months | 12 (19.7%) | 22 (14.2%) |
| Between 1 & 2 years | 5 (8.2%) | 7 (4.5%) |
| More than 2 years | 23 (37.7%) | 82 (52.9%)* |

*: Significant difference for chi-squared test is <0.05

**Table 3. Comparison of dimensions of HRQoL as a function of age**

| Quality of life dimensions | Age classes | Mean | SD | *p* (Mann-Whitney U) | Total |
|---|---|---|---|---|---|
| Physical well-being (PWB) | <45 years | 19.15 | 4.14 | 0.003* | 18.03±4.26 |
| | ≥45years | 16.98 | 2.32 | | |
| Social/family well-being (SWB) | <45 years | 18.57 | 3.85 | 0.488 | 18.93±3.65 |
| | ≥45years | 19.07 | 3.58 | | |
| Emotional well-being (EWB) | <45 years | 15.67 | 2.49 | 0.021* | 17.88±4.50 |
| | ≥45years | 18.97 | 4.51 | | |
| Functional well-being (FWB) | <45 years | 21.13 | 2.77 | 0.894 | 21.04±2.68 |
| | ≥45years | 21.01 | 2.66 | | |
| Endocrine symptom (ES) | <45 years | 39.64 | 2.36 | 0.001* | 46.48±8.80 |
| | ≥45years | 49.17 | 8.95 | | |
| FACT-ES | <45 years | 117.16 | 4.04 | 0.001* | 124.37±9.18 |
| | ≥45years | 127.21 | 9.10 | | |

SD: Standard deviation; *: The difference is significant at ≤0.05
FACT-ES score = PWB+SWB+EWB+FWB +ES; HRQoL: Health-related quality of life; FACT-ES: Functional Assessement of Cancer Treatment

**Table 4. Predictor symptoms of HRQoL as a function of age**

| Age | Dimensions (FACT-ES) | Sub-dimensions | Coefficients β | *p* |
|---|---|---|---|---|
| **<45 years** | Social well-being | My family supports me morally | 0.865 | **0.005*** |
| | | I feel close to my partner | 1.107 | **0.014*** |
| | Emotional well-being | I feel nervous | -1.087 | **0.004*** |
| | | I'm worried about my health getting worse | -1.306 | **0.002*** |
| | Functional well-being | I sleep well | 0.921 | **0.042*** |
| | | I enjoy my usual hobbies | 0.867 | **0.038*** |
| | Endocrine symptom | Vaginal irritation | -0.931 | **0.041*** |
| | | Vaginal dryness | -1.115 | **0.015*** |
| | | Mood swings | -0.835 | **0.031*** |
| | Physical well-being | Irritability | -0.786 | **0.001*** |
| | | I lack energy | -0.593 | **0.003*** |
| | | I have pain | -0.697 | **0.045*** |
| **≥45 years** | Social well-being | My family supports me morally | 1.002 | **0.002*** |
| | | I feel close to my partner | 0.352 | **0.033*** |
| | Endocrine symptom | Hot flashes | -0.628 | **0.043*** |
| | | Night and day sweats | -0.595 | **0.014*** |
| | | Weight gain | -1.105 | **0.048** |
| | | Joint pain | -1.206 | **0.006*** |

*: Significant influence at the 0.05 level; FACT-ES: Functional Assessement of Cancer Treatment; HRQoL: Health-related quality of life

similar results, highlighting that hot flushes and night sweats are less frequent in younger women and increase with age (41). Regarding weight gain, the results of a previous study demonstrated a strong relationship between weight gain and advanced age (post-menopausal) (42).

Finally, the inherent limitations of this study should not be overlooked. The most important limitations relate to the descriptive and cross-sectional nature of the study, as some factors were collected retrospectively, which may have influenced the results obtained. Another limitation is the study instrument. The FACT-ES does not include questions relating to spiritual well-being, whereas religious practice is an important daily activity for elderly patients and should be included in HRQoL surveys conducted in the Moroccan context, as suggested by a recent study (6). Despite its limitations, the conclusions drawn from this research may contribute to improving HRQoL in BC survivors on AHT. They may pave the way to identify optimal patient-centered interventions, while taking into account the HRQoL

predictors corresponding to each age group. This study may also provide valuable opportunities for further work. Thus, the results of this study may provide a basis for a subsequent study examining the influence of AHT associated symptoms on adherence and treatment compliance.

In conclusion, the present study showed that over the five years of AHT, older BC survivors had better HRQoL than younger women. The main predictors of HRQoL in the latter group were symptoms related to psychological distress and gynaecological problems. Joint pain and impaired physical function had a negative impact on HRQoL in older women. The results of our study add to previous data in the literature and suggest self-management of BC survivors on AHT, through the implementation of interventions targeting predictors relative to each age group.

### Ethics

**Ethics Committee Approval:** The study was conducted in accordance with the Declaration of Helsinki, after obtaining authorization for data collection from the health authorities of the region under no. 488/00 of 05/02/2000 due to the non-existence of an ethics committee at the time of the study.

**Informed Consent:** Informed consent was obtained and confidentiality of participants' private information was respected.

### Footnotes

### Authorship Contributions

Concept: F.E.B., A.L., Z.B.A.; Design: F.E.B., A.L., N.B., R.A., S.B.; Data Collection or Processing: F.E.B., N.B., Z.B.A.; Analysis or Interpretation: F.E.B., A.L., N.B., R.A.; Literature Search: F.E.B., A.L., Z.B.A., R.A.; Writing: F.E.B., S.B.

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Original Article

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# Enhancing Quality of Life: The Effect of Complete Decongestive Therapy on Jordanian Women With Breast Cancer After Axillary Lymph Node Dissection

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## ABSTRACT

**Objective:** This study aimed to compare the incidence of breast cancer-related lymphedema (BCRL) between a control group and women with breast cancer who underwent complete decongestive therapy (CDT). Moreover, the quality of life (QOL) was assessed and compared between the intervention group receiving CDT and the control group.

**Materials and Methods:** A quasi-experimental design with a purposeful sampling approach was employed for enrollment. All participants had undergone surgical interventions, specifically axillary lymph node dissection (ALND), for breast cancer at a public healthcare facility between February and July 2023. Over an 18-week period, the intervention group followed a structured CDT protocol, which included receiving skin care instructions, undergoing 30-minute manual lymphatic drainage sessions on the affected arm, wearing compression sleeves for 12 hours daily, and participating in exercise sessions three times per week.

**Results:** In total 180 women, 90 in the CDT group and 90 controls were recruited. The CTD intervention group experienced a notable reduction in the incidence of BCRL development and a significant improvement in QOL across the three assessment times (baseline vs week 9 and week 9 vs week 18) during the study ($p$<0.001). In contrast, the control group showed an increased rate of BCRL development and a significant decline in QOL when comparing the same three time points ($p$<0.001).

**Conclusion:** Implementing CDT within the first year following ALND led to a significant reduction in the incidence of BCRL and a marked improvement in the QOL for women with who underwent surgery and ALND for breast cancer.

**Keywords:** Breast cancer related to lymphedema; complete decongestive therapy; incidence rate; quality of life; breast cancer surgery

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### Key Points

- Complete decongestive therapy (CDT) is a preventative, ameliorating therapy for breast cancer-related lymphedema (BCRL).
- CDT should be used to manage BCRL in the early stage and in high-risk groups to prevent BCRL development under the supervision of a lymphedema expert.
- CDT is considering the best treatment strategy that nurses can use to control BCRL and enhance quality of life for women with breast cancer. It requires less invasive procedures, and can be done at home.
- The benefits of CDT vary based on the level of commitment of patients to perform CDT.
- Lymphedema nurse specialists were essential for close monitoring, supervision and encouragement of women at home to continue CDT as scheduled.
- The findings of this study provide a basic impression and evaluation of actual prevention methods and managing activities in Jordanian public hospitals.

## Introduction

Globally, breast cancer represents the highest annual cancer incidence among women, with 2.26 million documented cases each year, accounting for 24.5% of all cancer types in women (1). In Jordan, 2,403 new cases of breast cancer were reported in 2020, making up 38.5% of all cancer cases among women (2). The rising incidence of breast cancer in Jordan has consequently led to an increase in the number of individuals undergoing treatment.

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Breast cancer therapy, particularly surgical intervention, significantly impacts patients' quality of life (QOL), leading to noticeable physical, psychosocial, and emotional challenges following mastectomy (3). Physically, women treated for breast cancer face a lifelong risk of developing breast cancer-related lymphedema (BCRL), a chronic and potentially debilitating consequence of breast cancer treatment (4). Early-onset BCRL, occurring within 12 months of breast cancer surgery, has been closely associated with axillary lymph node dissection (ALND), with peak onset observed between 6 and 12 months in a cohort of 2,171 prospectively screened women (5). Approximately 21.4% of cases of BCRL were reported following breast cancer surgery (6). In particular, patients who undergo ALND followed by radiation therapy had a greater incidence of BCRL at 19.5% than those who received either treatment alone (7). A variety of risk factors are believed to contribute to the development of BCRL. These include breast cancer surgery particularly modified radical mastectomy (8), supraclavicular fossa radiation, and the use of taxane-based chemotherapy have all been identified as significant contributors (9). In addition, the removal of more than 18 ALN and a higher number of lymph nodes with metastatic involvement have been strongly associated with an elevated risk of BCRL (10, 11).Furthermore, ALND is considered a more substantial risk factor for BCRL compared to sentinel lymph node biopsy (SLNB) (12). ALND is associated with a significantly higher incidence of BCRL, with studies reporting rates ranging from 20% to 40%. This elevated risk is due to the extensive disruption of lymphatic vessels after removal of multiple lymph nodes, which impairs the normal drainage of lymph fluid and increases the likelihood of fluid accumulation in the arm. In contrast, SLNB is associated with a much lower incidence of BCRL, with reported rates ranging from 5% to 10%. This reduced risk is attributed to the removal of fewer lymph nodes (typically 1-3 nodes), which preserves the integrity of the lymphatic system and minimizes disruption to lymphatic drainage (13, 14)

Radiotherapy in general has been linked to an increased risk of BCRL (8). The specific design of the radiation field has also been identified as a contributing factor to the likelihood of BCRL development (10). Notably, the use of 2D radiotherapy techniques demonstrated a significant correlation with a higher incidence of lymphedema when compared to 3D radiotherapy techniques ($p$<0.001) (15). Furthermore, patients who received conventional radiotherapy exhibited significantly higher rates of lymphedema (42.2%) than those treated with hypofractionated radiotherapy (8.5%) ($p$<0.001) (16).

Lymphedema is a severe and distressing side effect of cancer treatment that significantly diminishes the QOL for survivors (17), impacting their physical, social, spiritual, psychological, sexual, and occupational lives (18, 19). Therefore, preventing, managing, and reducing the progression of lymphedema is essential (20). Implementing complete decongestive therapy (CDT) is an effective and safe strategy that has been shown to significantly reduce edema (21) and positively influence all domains of QOL (22).

CDT is one of the most widely recommended therapeutic approaches for managing BCRL. It is a comprehensive program that combines multiple therapeutic modalities, including manual lymphatic drainage, bandaging, compression garments, exercise, and self-care. This method should be administered by a skilled lymphedema therapist who ensures patients are trained in the correct techniques (23).

However, there is a lack of studies in Jordan to provide a comprehensive understanding of the incidence of BCRL. To the best of our knowledge and based on an extensive literature review, the present study is the first nursing research in Jordan to implement CDT for BCRL management. Consequently, the aim of this study was to assess the effectiveness of CDT in reducing the development of BCRL and improving QOL among Jordanian women undergoing breast cancer treatment within the first-year post-surgery. Specifically, the study was designed to test the following research hypotheses:

1. The incidence of BCRL is lower in the intervention group who would undergo CDT, compared to the control group who did not have CDT but underwent other normal post-surgical care.

2. Women in the intervention group will experience better QOL outcomes than those in the control group.

## Materials and Methods

### Design

This study adopted a quasi-longitudinal experimental design, which allowed for the examination of changes and outcomes over time within two distinct groups, an intervention group and a control group, without the use of random assignment. This approach was particularly suitable for assessing the long-term effects of CDT on BCRL incidence and QOL among Jordanian women who underwent ALND.

### Participants

The inclusion criteria consisted of Jordanian women with breast cancer who had undergone ALND and who received radiotherapy or adjuvent chemotherapy within the first year after breast cancer surgery. Women were excluded if they had a history of bilateral ALND, previous infections at the surgical site, or a history of heart disease. Using purposive sampling, 180 women who had undergone ALND were recruited, with 90 in the control group and 90 in the intervention group, from a government hospital between February and July 2023. Participants were assigned to groups based on non-random allocation. Each patient had been chosen to be in the control group or an intervention group.

### Intervention

The CDT intervention group received both written materials and verbal instructions on skin care. Participants were provided with compression sleeves to wear for 12 hours daily, starting at the beginning of their exercise routine. Prior to engaging in physical activities, the women were trained to perform manual lymphatic drainage three times a week for 30 minutes. The exercise regimen included an eight-stretching routine, consisting of: ball exercise, wand exercise, elbow winging, shoulder blade stretches, shoulder blade squeeze, side bends, chest wall stretch, and shoulder stretch. Each exercise was repeated 5–7 times per session, with stretches held for 15–30 seconds, and the entire routine lasted 15 minutes, performed three days a week over 18 weeks, as previously described (24). In addition, the program incorporated five moderate-intensity resistance exercises for the upper limb (shoulder press, chest press, lateral pulldown, biceps curls, and triceps extension). Each exercise involved 6–10 repetitions, with a 60–90 second recovery period between sets (25). These sessions also lasted 15 minutes and were conducted three times a week for 18 weeks. Throughout the 18-week period, the principal investigator closely monitored each participant in the intervention group every other day via a WhatsApp group.

**Outcomes**

Demographic and clinical data were collected through interviews and electronic medical records. At the eighteenth week, the researchers repeated circumferential measurements to evaluate the volume of the affected arm. Participants completed the short form-12 (SF-12) scale tool to assess their QOL (26), and an adherence tool to measure their commitment to the CDT protocol. These assessments were administered every nine weeks throughout the study period.

**Tools**

**Short Form-12 Scale**

The Arabic version of the SF-12 is a self-reported patient outcome measure designed to evaluate health-related QOL (26). It consists of two main components: the physical component (PC-12), which includes items 1 to 5 and item 8, and the mental component (MC-12), which includes items 6 to 12, excluding item 8. Scores range from 0 to 100, with higher scores indicating better physical and mental functioning. A score of 42 or lower on the MC-12 may suggest "clinical depression", while a score of 50 or lower on the PC-12 has been proposed as a cutoff to indicate a physical health condition (26).

The SF-12 Arabic version has demonstrated strong validity and reliability. The Cronbach's alpha for the SF-12 Arabic was 0.84, indicating high internal consistency. Furthermore, the scales and individual items showed substantial correlations, further supporting its construct validity (26).

**Structured Patients' Adherence Tool**

The researchers evaluated patients' adherence to the CDT domains over the 18-week period using a structured questionnaire developed specifically for this study. The questionnaire encompassed four key domains: arm care (18 items), massage steps (11 items), exercise (12 items), and wearing a compression sleeve (1 item). Participants recorded their level of commitment to each domain on a weekly basis from week 1 through week 18.

The pilot study was conducted to determine the feasibility of this research. I gathered information from twenty patients with breast cancer. I distributed all the questionnaires so they could assess their knowledge of all the terms in the tools as well as their understanding the language usage. Following a week, ten patients underwent CDT every other day for one week while ten patients considered as control group. Patients in both groups said they were aware of the terminology, no any vulgar language. Patients in the intervention group carried out CDT without difficulty, and reported this intervention need time. Thus, based on the pilot study results, which showed that CDT could be performed with this study and that it was applicable and feasible, I made the decision to carry out the full investigation like adherence tool.The tool underwent testing for both validity and reliability. A Cronbach's alpha value greater than 0.5 was established as the threshold for acceptable reliability. The tool was distributed to ten women with breast cancer who had undergone ALND, and a Cronbach's alpha score of 0.72 was achieved, indicating good reliability for the Adherence Tool. Additionally, the face validity of the tool was verified and approved by an institutional committee comprising six senior professionals, including medical, surgical, and radiological physicians.

To make sure there was adherence to the program, the researcher followed up with them in the what's up group with close observation every other day (Sunday, Thursday, & Wednesday) the researcher asked the patient to fill out a chart that the researcher had prepared to record the steps of CDT performance, and the researcher encouraged patients to fill out diary or write notes, and take photos by themselves during performing CDT to ensure patients' commitment to the program. The patient had recorded the commitment weekly from week 1 to week 18.

The researcher instructed the patients had put a check mark (✓) when they adhered to the skin care instructions each week (or) a cross (X) when they did not adhere to the instructions for each item. The second domain was patients adhering to manual massage steps. Patients must adhere to all massage steps to facilitate lymphatic drainage and reduce arm swelling at a rate of three days per week. The researcher instructed the patients to do massage steps three days a week, then the patients wrote the number (3). Also, when patients did the massage steps two days a week, they wrote the number (2). When the patients did massage steps only one day a week, they wrote the number (1) and in cases of non-compliance with taking the steps during the week, patients wrote the number (0). The third domain was exercise. Patients must commit to doing all exercises to maintain the arm and range of motion and prevent lymphedema at a rate of three days per week. When the patients did the exercise three days a week, they wrote the number (3). When the patients did the exercise two days a week, they wrote the number (2). When the patients did the exercise only one day a week, they wrote the number (1), and in the case that patients did not fully commit to doing the exercise during the week, they wrote the number (0). The fourth domain was commitment to wear compression sleeves before exercise and stay 12 hours during the day, three days per week. When patients worn a compression sleeve three days a week, they wrote the number (3). When patients worn the compression sleeve two days a week, they wrote the number (2). When patients worn the compression sleeve one days a week, they wrote the number (1), and in the event of non-compliance with wearing the compression sleeve completely during the week, patients wrote the number (0), as shown in Appendix G.

The researcher calculated the total score of patients adherence tool for all items, which represented the commitment level for patients. The total score for arm care was 18. The total score for massage was 33. The total score for exercise was 36 and the total score for compression sleeve was 3.

The lower total score of the patients adherence to all items indicated minimum commitment specifically. A higher total score of the patients adherence for all items indicated greater commitment of the intervention group to CDT.

**Sample Size**

G*Power software version 3.1 (27) was used to calculate the sample size, with a power of 90%, a significance level (*p*-value) of 0.05, and a one-tailed independent t-test assuming an effect size of 0.5. Based on these parameters, the minimum required sample size for each group was 70, resulting in a total minimum sample size of 140 breast cancer patients. However, to account for potential attrition and missing data, the actual sample size was increased to 180 participants.

**Statistical Analysis**

The researchers used IBM SPSS, version 25, for data analysis (IBM Inc., Armonk, NY, USA). Descriptive statistics were employed to summarize the demographic and clinical characteristics of the patients and their disease profiles. To identify cases of BCRL, the researchers considered a difference of 2 cm or more in at least one measurement

location between the affected and unaffected arms in both groups. Differences in QOL between the intervention and control groups were assessed using an independent t-test. In addition, repeated measures ANOVA was conducted to analyze changes in patients' QOL at nine-week intervals, enabling intragroup comparisons over time.

### Ethical Consideration

The study was conducted in the oncology department of a leading government hospital in Jordan. Approval for data collection was granted by the Institutional Review Board, as well as the scientific research ethics committee of the hospital. Written informed consent was obtained from all participating patients prior to their involvement. The research adhered to the ethical standards outlined by followed Good Clinical Practice guidelines throughout the study. The researcher had obtained approval from the scientific research Ethics Committee in this Government Hospital to collect the data at February 1, 2023, approval number was MOH/REC/2023/33.

## Results

There were 183 women in the study sample. Based on non-random criteria, it was split into two groups: 91 women in the CTD intervention group and 92 women in the control group. Due to their incapacity to pay for their hospital treatment, two women in the control group were dropped from the follow-up at week nine. At week nine, one woman in the CTD intervention group was hospitalized due to pulmonary edema. The final sample consisted of 180 women, 90 in each group, as shown in the flow chart of participants (Figure 1).

### Baseline and Week Nine Demographic and Clinical Comparison

The demographic and clinical characteristics of the participants and their disease profiles are outlined in Table 1. The mean age of the women was 48.97 years (standard deviation ± 6.92), and the mean number of ALN dissected was 11.49 (±6.33). The majority of women (118 out of 180, 65.6%) had positive cancer cells detected in their ALN. The majority had metastatic internal mammary lymph node involvement ($n$ = 150, 83.2%). Approximately 50% (83 women) underwent radiation therapy as part of their treatment regimen. Those patients received a total radiation dose ranging from 40 to 50 Gy. The radiation was administered over 15, 19, or 20 sessions, reflecting the use of both hypofractionated and moderate-course treatment schedules (Table 1).

The incidence rate of developing BCRL was markedly lower in the intervention group ($n$ = 15; 16.6%) compared to the control group ($n$ = 58; 64.5%) in the first nine weeks of the study.

### Comparison Between the Intervention and Control Groups at Week Nine and Eighteen

The QOL, encompassing both physical and mental components, demonstrated significant differences between the intervention and control groups ($p \leq 0.001$). The incidence rate of developing BCRL was notably lower in the intervention group ($n$ = 5; 5.6%) compared to the control group ($n$ = 69; 76.7%) (Table 1). Similarly, the QOL, including both its physical and mental dimensions, varied significantly between the CTD intervention and control groups ($p \leq 0.001$) (Table 2).

### Patient's Adherence to CDT Domains from Week One to Week Eighteen

From week one to week eighteen, 90% of the women demonstrated commitment to CDT. Specifically, 96% adhered to their skin care regimen, 87.5% performed the recommended massages, 90% participated in the 12 prescribed types of exercise, and 87% consistently used compression bandages. This implies a high level of compliance with the intervention protocol (Table 3).

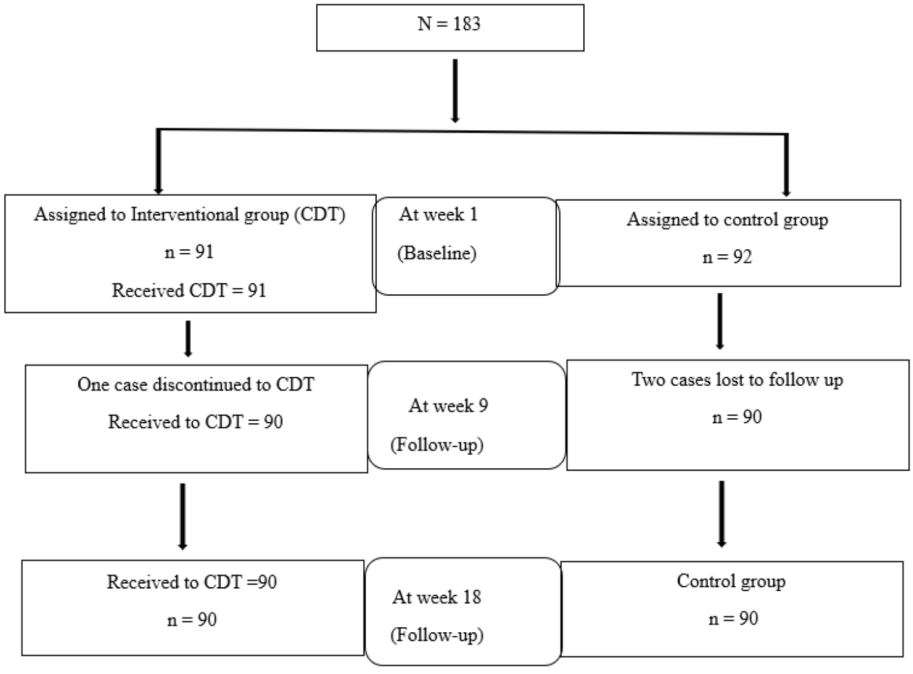


**Figure 1.** The flow diagram illustrating the progression of participants through the study groups

*CTD: Complete decongestive therapy*

**Table 1. Descriptive statistics of demographic and clinical characteristics for women with breast cancer (*n* = 180)**

| Variable | CTD intervention group *n* = 90 | | Control group *n* = 90 | | Total sample *n* = 180 | |
|---|---|---|---|---|---|---|
| | Frequency | % | Frequency | % | Frequency | % |
| **Age in years** (M ± SD)<br>Intervention = 48.3±7.3<br>Control = 49.6±6.5 | | | | | | |
| **Marital status** | | | | | | |
| Married | 69 | 76.7 | 68 | 75.6 | 137 | 76.1 |
| Divorced | 4 | 4.4 | 12 | 13.3 | 16 | 8.9 |
| Widowed | 7 | 11.1 | 6 | 4.4 | 14 | 7.8 |
| Single | 10 | 7.8 | 4 | 6.7 | 13 | 7.2 |
| **Education level** | | | | | | |
| Secondary | 41 | 45.6 | 38 | 42.2 | 79 | 43.9 |
| Illiterate and primary | 19 | 21.1 | 29 | 32.3 | 48 | 32.3 |
| Diploma | 17 | 18.9 | 15 | 16.7 | 32 | 17.8 |
| University degree | 13 | 14.4 | 8 | 8.9 | 21 | 11.7 |
| **Side of breast cancer** | | | | | | |
| Right side | 46 | 51.1 | 49 | 54.4 | 95 | 52.8 |
| Left side | 44 | 48.9 | 41 | 45.6 | 85 | 47.2 |
| **TNM staging** | | | | | | |
| Stage 1 | 6 | 6.7 | 4 | 4.5 | 10 | 5.6 |
| Stage 2 | 31 | 34.4 | 31 | 34.4 | 62 | 34.4 |
| Stage 3 | 42 | 46.7 | 46 | 51.1 | 88 | 48.9 |
| Stage 4 | 11 | 12.2 | 9 | 10 | 20 | 11.1 |
| **Grading** | | | | | | |
| Grade 1 | 5 | 5.6 | 7 | 7.8 | 12 | 6.7 |
| Grade 2 | 55 | 61.1 | 48 | 53.3 | 103 | 57.2 |
| Grade 3 | 30 | 33.3 | 35 | 38.9 | 65 | 36.1 |
| **Estrogen receptor** | | | | | | |
| Positive | 68 | 75.6 | 75 | 83.3 | 143 | 79.4 |
| Negative | 22 | 24.4 | 15 | 16.7 | 37 | 20.6 |
| **Progesterone receptor** | | | | | | |
| Positive | 60 | 66.7 | 70 | 77.8 | 130 | 72.2 |
| Negative | 30 | 33.3 | 20 | 22.2 | 50 | 27.8 |
| **Human epidermal receptor 2** | | | | | | |
| Positive | 45 | 50 | 40 | 44.4 | 85 | 47.2 |
| Negative | 45 | 50 | 50 | 55.6 | 95 | 52.8 |
| **Type of breast surgery** | | | | | | |
| Breast conserving surgery | 52 | 57.8 | 53 | 58.9 | 105 | 58.3 |
| Modified radical mastectomy | 33 | 36.6 | 31 | 34.4 | 64 | 35.6 |
| Simple mastectomy | 5 | 5.6 | 6 | 6.7 | 11 | 6.1 |
| Positive cancer cell in ALN | 56 | 62.2 | 62 | 68.9 | 118 | 65.6 |
| Negative cancer cell in ALN | 34 | 37.8 | 28 | 31.1 | 62 | 34.4 |
| **Number of ALN dissected Mean ± SD** | **11.54** | **11** | **11.44** | **12** | **11.49** | **6.33** |

**Table 1. Continued**

| Variable | CTD intervention group *n* = 90 | | Control group *n* = 90 | | Total sample *n* = 180 | |
|---|---|---|---|---|---|---|
| | Frequency | % | Frequency | % | Frequency | % |
| **Location of metastatic LN** | | | | | | |
| Supraclavicular LN | 1 | 1.1 | 1 | 1.1 | 2 | 1.1 |
| Mediastinal (chest) regions | 5 | 5.6 | 4 | 4.4 | 9 | 5 |
| Retroperitoneal LN | 3 | 3.3 | 2 | 2.2 | 5 | 2.8 |
| Pelvic LN | 2 | 2.2 | 2 | 2.2 | 4 | 2.3 |
| Internal mammary LN | 73 | 81.1 | 77 | 85.7 | 150 | 83.2 |
| No LN metastatic | 6 | 6.7 | 4 | 4.4 | 10 | 5.6 |
| **Total radiation dose** | | | | | | |
| Did not receive RT | 51 | 56.7 | 46 | 51.1 | 97 | 53.9 |
| Received 40 Gray RT | 27 | 30 | 29 | 32.2 | 56 | 31.1 |
| Received 50 Gray RT | 12 | 13.3 | 15 | 16.7 | 27 | 15 |
| **Total radiation session** | | | | | | |
| Did not receive radiation | 51 | 56.8 | 46 | 51.1 | 97 | 53.9 |
| Received 15 radiation session | 22 | 24.4 | 29 | 32.2 | 51 | 28.8 |
| Received 19 radiation session | 12 | 13.3 | 9 | 10 | 21 | 11.7 |
| Received 20 and more | 5 | 5.5 | 6 | 6.7 | 11 | 5.6 |
| **Incidence of BCRL week 1** | | | | | | |
| No BCRL | 56 | 62.2 | 56 | 62.2 | 112 | 62.2 |
| BCRL present | 34 | 37.8 | 34 | 37.8 | 68 | 37.8 |
| **Incidence of BCRL at week 9** | | | | | | |
| No BCRL | 75 | 83.3 | 32 | 35.6 | 107 | 59.4 |
| BCRL present | 15 | 16.7 | 58 | 64.4 | 73 | 40.6 |
| **Incidence of BCRL at week 18** | | | | | | |
| No BCRL | 85 | 94.4 | 21 | 23.3 | 106 | 58.9 |
| BCRL present | 5 | 5.6 | 69 | 76.7 | 74 | 41.1 |

TNM staging: T: Tumor; N: Lymph node; M: Metastatic; ALN: Axillary lymph node; RT: Radiotherapy; BCRL: Breast cancer-related lymphedema; SD: Standard deviation; CTD: Complete decongestive therapy; LN: Lymph node

**Table 2. Comparison of outcome variables between groups at weeks 9 and 18**

| Variable | CTD intervention group *n* = 90 | | Control group *n* = 90 | | t | df | p |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | | |
| **Total score of outcome variables at week 9** | | | | | | | |
| SF-12 (QOL) | 61.70 | 17.82 | 38.84 | 17.15 | -8.77 | 178 | <0.001 |
| Physical components SF-12 | 61.02 | 21.58 | 38.72 | 19.79 | -7.23 | 178 | <0.001 |
| Mental components SF-12 | 62.38 | 19.32 | 38.96 | 19.49 | -8.10 | 178 | <0.001 |
| **Total score of outcome variables at week 18** | | | | | | | |
| SF-12 (QOL) | 74.99 | 14.90 | 33.03 | 17.33 | -17.42 | 178 | <0.001 |
| Physical components SF-12 | 75.42 | 17.80 | 32.55 | 20.77 | -14.87 | 178 | <0.001 |
| Mental components SF-12 | 74.56 | 18.46 | 33.52 | 18.03 | -15.09 | 178 | <0.001 |

QOL: Quality of life; SD: Standard deviation; CTD: Complete decongestive therapy; SF-12: Short Form-12

### Results of Intragroup Comparisons Over the Three Time Points of the Study

A repeated measures ANOVA was used to evaluate changes in general, physical, and mental QOL across the three time points of the study (baseline vs 9 weeks vs 18 weeks). The results revealed that in the CTD intervention group, general, physical, and mental QOL significantly increased over the three time points ($p$<0.001 for all three). However, in the control group, QOL significantly decreased over the same periods ($p$<0.001). There were significant differences in general QOL ($p$<0.001), physical QOL ($p$<0.001), and mental QOL ($p$ = 0.016) between week 1 and week 9. Significant differences were also observed in general QOL ($p$<0.001), physical QOL ($p$ = 0.002), and mental QOL ($p$ = 0.003) between week 9 and week 18. Thus, the changes in general, physical, and mental QOL were statistically significant ($p$<0.001) between week 1 and week 18 (Table 4).

## Discussion and Conclusion

This study is probably the first quasi-experimental investigation into the effects of CDT following breast cancer surgery with SLND conducted in a government hospital setting in Jordan. The primary objective was to explore the impact of CDT on both the incidence rate of BCRL and the QOL among patients. By addressing these important outcomes, the study provides valuable insights into the potential benefits of CDT as an intervention for improving patient well-being and managing post-surgical complications. The findings and broader implications of these results are elaborated upon in the following sections, shedding light on the significance of incorporating CDT into standard post-operative care practices for breast cancer patients in similar settings.

**Table 3. Adherence of CDT for the intervention group ($n$ = 90) from week one to week eighteen**

| Domains of CDT | % week 1 to 9 | % week 10 to 18 | % week 1 to week 18 |
|---|---|---|---|
| **Arm care** | 96% | 96% | 96% |
| **Massage** | 91% | 84% | 87.5% |
| **Exercise** | 93% | 87% | 90% |
| **Wearing sleeve compression** | 91% | 84% | 87.5 |
| **The total score of 4 domains** | 93% | 87.5% | 90.25 |

CTD: Complete decongestive therapy

**Table 4. Comparison of the intervention and control groups in terms of QOL at the three times of the study (week 1, 9 & 18)**

| | | CTD intervention group | | Control group | |
|---|---|---|---|---|---|
| **Outcome variable** | **Phases of study** | **Mean ± SD** | **Changes at different three phases of the study *p*-value** | **Mean ± SD** | **Changes at different phases of the study *p*-value** |
| SF-12 (General QOL) | Week 1 | 44.75±20.31 | <0.001 | 45.88±19.03 | <0.001 |
| | Week 9 | 61.70±17.82 | W18 > W9 > W1 | 38.84±17.15 | W1 > W9 > W18 |
| | Week 18 | 74.99±14.90 | W1 < W9 (<0.001)<br>W9 < W18 (<0.001)<br>W1 < W18 (<0.001) | 33.03±17.33 | W1 > W9 (<0.001)<br>W9 > W18 (<0.001)<br>W1 > W18 (<0.001) |
| Physical components of S-12 (QOL) | Week 1 | 45.51±24.74 | <0.001 | 47.31±22.76 | <0.001 |
| | Week 9 | 61.02±21.58 | W18 > W9 > W1 | 38.72±19.79 | W1 > W9 > W18 |
| | Week 18 | 75.42±17.80 | W1 < W9 (<0.001)<br>W9 < W18 (<0.001)<br>W1 < W18 (<0.001) | 32.55±20.77 | W1 > W9 (<0.001)<br>W9 > W18 (0.002)<br>W1 > W18 (<0.001) |
| Mental components of S-12 (QOL) | Week 1 | 44.00±21.04 | <0.001<br>W18 > W9 > W1<br><br>W1 < W9 (<0.001)<br>W9 < W18 ($p$≤0.001)<br>W1 < W18 ($p$≤0.001) | 44.44±20.43 | ≤0.001<br>W1 > W9 > W18<br><br>W1 > W9 (0.016)<br>W9 > W18 ($p$ = 0.003)<br>W1 > W18 ($p$≤0.001) |

QOL: Quality of life; SD: Standard deviation; CTD: Complete decongestive therapy; SF-12: Short Form-12

**The Incidence of BCRL**

Within the first year following breast surgery, the incidence of BCRL was 37.8% in both the CTD intervention and control groups at week one. By comparison, a review of 84 cohort studies involving 58,358 breast cancer patients reported an overall lymphedema incidence of 21.9% (28). Furthermore, a meta-analysis and systematic review of 16 studies with 3,515 breast cancer patients found the occurrence of lymphedema after ALND within one year to be 16.5% (29). The incidence of BCRL observed in our cohort was notably higher than reported in previous studies. Several factors may explain this increased incidence. Patients in both groups had predisposing factors associated with cancer treatment that contributed to the development of BCRL. Over one-third underwent modified radical mastectomy, 65.6% had positive lymph nodes, and approximately half had right-sided breast cancer; all factors linked to a higher rate of BCRL.

In the CTD intervention group, adherence to CDT domains was associated with a reduced rate of BCRL, dropping from 37.8% at week one to 5.6% by the end of week 18. This outcome was attributed to continuous monitoring by a lymphedema nurse specialist, regular follow-ups to ensure proper implementation of CDT, and participants recording their adherence in diaries. In contrast, the control group experienced a significant increase in BCRL development, with a rate of 76.7% by week 18. This rise may have been due to the absence of written health education about CDT, lack of supervision by a lymphedema nurse specialist, and/or no referrals to the physiotherapy department for BCRL prevention or management.

**Complete Decongestive Therapy Adherence in the Intervention Group**

We believe the 90% commitment level to CDT was achieved through close supervision by the lymphedema nurse specialist. This specialist conducted follow-ups every other day via a dedicated WhatsApp group. These follow-up sessions addressed questions, provided guidance and encouragement, and monitored progress. All CDT-related equipment, such as compression sleeves and bandages, was provided to all patients free of charge, eliminating financial barriers and further contributing to the high commitment rate. These combined factors ensured consistent participation and adherence to the therapy protocol throughout the study period.

**General QOL (Physical and Mental)**

The results revealed that the general QOL, encompassing both physical and mental components, showed significant variations both within and between groups at weeks 9 and 18. Within the CTD intervention group, there was a notable improvement in mean QOL scores across all three time-points of the study. In contrast, the control group experienced a decline in QOL over the same period. The decline in QOL observed in the control group is in keeping with the findings of a systematic review and meta-analysis encompassing 39 studies. These studies demonstrated that patients with BCRL experienced significant reductions in QOL, with the most pronounced negative impacts on physical well-being, functional abilities, and social domains (30). Specifically, when the SF-12 tool was used, patients with BCRL reported deterioration in both the physical and mental aspects of QOL (30). The reasons for this decline in QOL among BCRL patients include factors such as advanced age, lower education levels, unemployment, reduced family income, and psychological distress (10). Notably, all these predictive factors were present in the study sample of the present study, which helps explain the poorer QOL observed in the control group. The improvement in QOL observed in the intervention group is consistent with the findings of a meta-analysis that highlighted the positive impact of CDT on QOL (31). Further studies have corroborated that CDT significantly enhances QOL for patients with BCRL, particularly when initiated in the early stages (32). Notably, these benefits were especially evident when CDT was performed at home under supervision via a mobile application, emphasizing the effectiveness of remote monitoring and guidance (33). Some prior studies have reported mixed findings regarding the impact of CDT on QOL. For instance, one study found only a 5% improvement in QOL among patients who received CDT and this improvement was not significant (34). The lack of significance was attributed to factors including a smaller sample size and lower levels of patient commitment to the CDT protocol. While other studies have consistently validated that CDT positively influences QOL, the duration and design of those studies may have limited their ability to detect significant changes.

In contrast, the present study spanned 18 weeks and was structured into three distinct phases, allowing for a more comprehensive evaluation of the effects of CDT. The extended duration and phased approach provided sufficient time to observe meaningful improvements in QOL, leading, in our opinion, to more accurate and robust conclusions than those drawn from prior research. This methodological rigor highlights the reliability of the findings and the importance of adequate study length and patient adherence in assessing the effectiveness of CDT.

**Axillary Lymph Node Surgery (ALND vs SLND)**

In the present study the surgeon was questioned about their decision to perform ALND. The surgeon explained that the decision was based on literature review and evidence-based practice. Specifically, ALND is typically performed when SLNB had revealed the presence of cancer in the sentinel lymph node(s), as this indicates a higher likelihood of additional nodal involvement (35). Moreover, ALND was more likely when there was clinical or imaging evidence of lymph node involvement prior to surgery, such as palpable lymph nodes or suspicious findings on ultrasound, MRI, or positron emission tomography-computed tomography scans (35). In addition, most of the women in this study were at advance stages (3&4), where ALND is often included as part of the surgical plan to ensure the comprehensive removal of cancerous tissue and to achieve optimal disease control (36). This approach aligns with current guidelines and clinical practices, which emphasize the importance of tailoring surgical interventions to the individual patient's disease characteristics and stage (35, 36).

**Radiation Therapy**

Radiotherapy, in general, has been associated with a heightened risk of BCRL (8). Among 1,052 women who underwent breast-conserving therapy (BCT) with adjuvant radiotherapy, 9.6% experienced BCRL. This study highlighted several significant risk factors associated with the onset of BCRL, including the administration of adjuvant chemotherapy (37). These findings align with the present study population, in which women undergoing adjuvant chemotherapy were included, and approximately half of them also received radiation therapy and underwent BCT.

Most of women received 15 sessions of radiotherapy in this study. The primary difference between patients who received 15, 19, or 20 radiation sessions after breast cancer surgery lies in the total dose of radiation delivered, the treatment duration, and potentially the treatment intent (curative *vs.* palliative) (38). The 15 sessions are

ideal for low-risk patients, offering a shorter, more convenient treatment schedule, patients reported cancer control, late side effects, better QOL and fewer disruptions to daily activities compared to those receiving more sessions (15, 38). The 19 or 20 sessions are used for intermediate-risk patients and the choice of regimen is patient-specific, emphasizing personalized care to optimize outcomes and QOL (15).

### Strengths

The study benefited from an adequate sample size and duration, ensuring robust results. A high level of adherence to CDT was achieved, supported by the use of self-recorded diaries to monitor commitment. In addition, the presence of a lymphedema nurse specialist provided continuous supervision, encouragement and guidance to patients in performing CDT.

### Study Limitations

The study employed a quasi-experimental design and was conducted at a single governmental hospital, limiting the generalizability of the findings. Patients also reported that CDT required considerable time and effort to perform correctly, which may have influenced adherence and outcomes.

### Implications

This study has significant implications for clinical practice and patient care, particularly in the context of breast cancer treatment and post-operative management. The findings demonstrate that implementing CDT within the first year following breast cancer surgery in women who underwent ALND and received adjuvant chemotherapy or radiotherapy can substantially reduce the incidence of BCRL and enhance patients' QOL. The CDT intervention group, under the supervision of a lymphedema nurse specialist, showed a marked reduction in BCRL incidence and significant improvements in QOL, while the control group experienced an increasing BCRL rate over the study period and a concurrent decline in QOL. These results underscore the importance of early intervention, structured follow-ups, and patient adherence to CDT protocols. The study also highlights the potential benefit of having lymphedema nurse specialists to providing continuous monitoring, education, encouragement and support, which we believe were key to achieving high adherence rates and positive outcomes in our study. Furthermore, the rigorous design, spanning 18 weeks with three distinct phases, provided robust evidence for the effectiveness of CDT, offering a model for integrating such interventions into standard post-operative care. However, the quasi-experimental design and single-site setting limit generalizability, suggesting the need for broader, multi-centre studies to validate these findings. Overall, this study advocates for the adoption of CDT in clinical practice, emphasizing the need for dedicated resources, patient education, and specialist involvement to improve long-term health outcomes for breast cancer survivors.

Implementing CDT within the first year following breast cancer surgery was shown to significantly reduce the incidence rate of BCRL and enhance patients' QOL in a single center in Jordan. Early intervention with CDT helps mitigate the risk of lymphedema development and addresses symptoms before they become severe, leading to better physical, emotional, and social outcomes for patients. A key factor in the success of CDT may be the involvement of lymphedema nurse specialists, who are dedicated to delivering consistent follow-up, providing tailored therapies and encouragement, and ensuring patients adhere to the treatment protocol. This expertise and ongoing support not only improve treatment efficacy but also empowers patients to manage their condition effectively, ultimately contributing to improved long-term health and well-being.

## Ethics

**Ethics Committee Approval:** The researcher had obtained approval from the scientific research Ethics Committee in this Government Hospital to collect the data at February 1, 2023, approval number was MOH/REC/2023/33.

**Informed Consent:** Written informed consent was obtained from all participating patients prior to their involvement.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: S.S.; Concept: S.S.; Design: S.S., M.A.; Data Collection or Processing: S.S.; Analysis or Interpretation: S.S., M.A.; Literature Search: S.S.; Writing: S.S., M.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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**Original Article**

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# Differences in Age, Stage and Biology of Breast Cancer Presentations at A Private Breast Unit in Johannesburg Before and During The COVID-19 Pandemic

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## ABSTRACT

**Objective:** Prior to the 2020 Coronavirus disease 2019 (COVID-19) pandemic, breast cancer (BC) was already a major healthcare concern globally, including in South Africa (SA). The pandemic forced adjustments in BC management and may have also impacted BC presentation characteristics due to social behavior changes. The aim of this study was to describe BC presentations before and during the COVID-19 pandemic at a single facility in SA.

**Materials and Methods:** A retrospective record review was conducted to compare BC presentations before and during the COVID-19 pandemic. The "before" period spanned 11 January 2019 to 31 March 2020 and the "during" period spanned 1 April 2020 to 20 December 2021. The variables analysed included patient age, BC stage at presentation, and tumor biology.

**Results:** A total of 731 patients were seen in the "before" period, and 636 in the "during" period. While there was a significant ($p$<0.0001) decrease in the mean number of patients who presented to the unit per month during the pandemic, no significant differences were observed in age, BC stage at presentation, or tumor biology between the two study periods.

**Conclusion:** Despite a significant reduction in new BC cases during the COVID-19 pandemic in SA, patient age, BC stage, and tumor biology remained unchanged. The rapid implementation of digital tools for healthcare management is likely to have played an important role in maintaining patient access to care.

**Keywords:** Breast cancer; pandemic; age; stage; biology; presentation

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## Key Points

- A 36.7% decrease was noted in the number of patients presenting with breast symptoms during compared to before the pandemic.
- No significant differences were observed in patient age at presentation, breast cancer (BC) stage, or tumor biology between BC patients presenting before and during the Coronavirus disease 2019 pandemic.
- It was hypothesized that the lack of difference in presenting characteristics may be attributed to inadequate BC screening in South Africa, even before pandemic restrictions, whereas in the West, severe restrictions on access to BC screening resulted in later stages at presentation.
- The absence of this pattern in this study may also be due to Milpark Breast Cancer Centre of Excellence adaptations for managing care during pandemic restrictions.
- These adaptations included online communication between members of the multidisciplinary team, allowing for quick diagnosis of breast cancer stage and biology.

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## Introduction

Breast cancer (BC) was already a significant healthcare concern in South Africa, as well as globally, prior to the 2020 Coronavirus disease 2019 (COVID-19) pandemic (1). However, little research exists on how the pandemic may have affected BC presentation in low- and middle-income countries (LMICs).

The existing literature highlights the ongoing prevalence of BC globally, with South Africa facing additional diagnostic and management challenges due to widespread poverty and limited resources. Despite efforts to address BC, projections show the burden of BC in sub-Saharan Africa will double by 2030 (2).

Research suggests that the pandemic led to disruptions in healthcare access and delays in cancer diagnosis and treatment (3), attributed to resource diversion and fears of COVID-19 infection (4). While some studies suggest no significant changes in BC stage at diagnosis during the pandemic (5), there is a lack of data on how the COVID-19 pandemic has affected BC diagnosis and management in LMICs.

Given the evident disruptions caused by the COVID-19 pandemic and the lack of specific data on its effects on BC presentation and management in LMICs, investigating changes in BC presentation trends during the pandemic is warranted. Understanding these trends may be helpful when adapting BC management strategies and delivering quality care in South Africa and similar settings. The aim of this study was to fill existing gaps in the literature regarding BC diagnostic trends during the pandemic. Specifically, changes in patient age, BC stage, and tumor biology at presentation were investigated in a South African population before and during the COVID-19 pandemic.

## Materials and Methods

### Study Design

This study was a retrospective cohort review. It was conducted at the Netcare Milpark Breast Cancer Centre of Excellence (BCCE), which is a private breast unit in Johannesburg, South Africa. A secondary electronic database, the Medical Information Technology Database Accreditation System was used to collect data from the Milpark BCCE. Data from all patients who were exclusively diagnosed and treated for the first time at the BCCE during our study period were collected. Patients included in this study were above the age of 18 years and provided informed consent for their data to be used for research purposes.

### Study Period

The study was divided into two time periods: patients presenting between 1st January 2019 and 31st March 2020 (a total of 15 months prior to the South African national COVID-19 lockdown) and those presenting during the national lockdown from 1st April 2020 to 20 December 2021 (a total of 20 months).

### Variables

Variables included patient age at first presentation with BC, the stage of disease at which they presented, and the biological characteristics of their BC. Patients ages were divided into three categories: those who presented at less than 36 years of age, those aged between 36 and 54 years, and those who were older than 54 years of age.

The stage of BC at first presentation was divided into eight groups according to the American Joint Committee on Cancer 7th edition classification system. Patients diagnosed with more than one tumour were classified according to the tumour of higher stage. The patients who were classified under "unknown stage" consisted of those for whom a stage was not determined at the time of data collection. This group consisted of patients whose data were not available, or not correctly recorded into the database.

Biological type of BC at first presentation was stratified according to the four primary BC molecular subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), and triple-negative BCs. Patients who presented with more than one tumor of different molecular subtypes were categorised according to the more aggressive subtype with regard to treatability and clinical behaviour.

### Statistical Analysis

Data analysis was performed using Stata 17.0 BE - Basic Edition (Manufacturer: StataCorp LLC; phone: +19796964600; email: support@stata.com). Deidentified data containing age, stage, and molecular subtype were obtained from the BCCE database curator and then further stratified by the two study sub-periods.

The continuous variable of age was grouped into three ordinal categories. A t-test was performed to determine if there was a statistically significant difference in the mean age. To determine if there were statistically significant changes in the ratios of age, clinical stage and molecular subtype, a chi-square test was performed. Lastly, an Exact Poisson test was performed to compare the number of patients seen before and during the COVID-19 Pandemic. Confidence intervals (CIs) of 95% were used. A $p$-value of <0.05 was considered significant.

### Study Ethics

Ethical approval was obtained from the Wits Human Research Ethics Committee (approval number M220952, date: 12.10.2022). Study site permission was obtained from the hospital CEO and database curator (approval number UNIV-2023-0009, date: 31.03.2022). All enrolled patients provided consent prior to the inclusion of their data in the database for anonymized research.

## Results

### Study Cohort

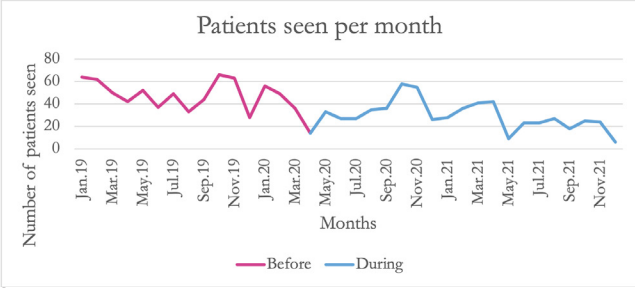
A total of 1,364 patients were included in the study. Patients were known with primary BC and were diagnosed and treated at the BCCE between 1 January 2019 and 20 December 2021. A total of 731 patients were included in the pre-COVID study period, and 636 patients presented during the COVID period.

### Patient Presentation Rate

During the COVID-19 pandemic, there was a significant decrease in the number of patients presenting with BC per month compared to the pre-pandemic period ($p$<0.0001) (Figure 1). In the first period the mean number of patients per month was 48.7 versus 31.8 patients per month during the pandemic.

### Age

The mean age of patients was 32.26 years (95% CI: 31.37–33.15) before the COVID-19 pandemic and 32.20 years (95% CI: 31.06–33.15) during the pandemic ($p$ = 0.83). A chi-square test was also performed to compare the differences in each age group before and during the pandemic. Across all three age groupings, there was no significant difference in age at presentation ($p$ = 0.19). Table 1 below shows patient age at BC presentation in both study sub-periods.




**Stage**

**Figure 1.** Number of patients seen per month before and during the COVID-19 pandemic. Figure 1 shows an initial decline in patient numbers at the onset of the COVID-19 pandemic, followed by fluctuating trends during the COVID-19 pandemic period

*COVID-19: Coronavirus disease 2019*

Most patients during the study period presented to the BCCE with a single tumour and, therefore, a single stage of BC. BC stages are shown in Table 2. A chi-square test was performed, and the differences in BC stage at presentation between the two study periods were not significant ($p$ = 0.12).

### Breast Cancer Molecular Subtype

Molecular subtypes were classified as luminal A, luminal B, HER2+, triple-negative, or unknown based on their initial biopsy for all patients in the study. Comparison of the proportions of each of these subtypes in the two study periods is shown in Table 3. Overall, there was no significant difference in the distribution of patient tumour biology before and during the COVID-19 pandemic ($p$ = 0.24).

**Table 1. Age of patients at diagnosis before and during the COVID-19 pandemic**

| Age at diagnosis | Frequency before COVID-19 | Percentage before COVID-19 | Frequency during COVID-19 | Percentage during COVID-19 | *p*-value |
|---|---|---|---|---|---|
| <36 years old | 26 | 3.56 | 37 | 5.82 | |
| 36-54 years old | 301 | 41.17 | 251 | 39.46 | 0.19 |
| >54 years old | 404 | 55.27 | 348 | 54.72 | |
| Total | 731 | 100.00 | 636 | 100.00 | |

COVID-19: Coronavirus disease 2019

**Table 2. Clinical stage of patients seen before and during the COVID-19 pandemic**

| Clinical staging | Frequency before COVID-19 | Percentage before COVID-19 | Frequency during COVID-19 | Percentage during COVID-19 | *p*-value |
|---|---|---|---|---|---|
| Stage 0 | 65 | 8.89 | 51 | 8.02 | |
| Stage IA | 203 | 27.77 | 168 | 26.42 | |
| Stage IB | 0 | 0.00 | 1 | 0.16 | |
| Stage IIA | 273 | 37.35 | 272 | 42.77 | |
| Stage IIB | 91 | 12.45 | 82 | 12.89 | 0.12 |
| Stage IIIA | 47 | 6.43 | 32 | 5.03 | |
| Stage IIIB | 28 | 3.83 | 15 | 2.36 | |
| Stage IIIC | 0 | 0.00 | 2 | 0.31 | |
| Unknown | 24 | 3.28 | 13 | 2.04 | |
| Total | 731 | 100.00 | 636 | 100.00 | |

COVID-19: Coronavirus disease 2019

**Table 3. Breast cancer type seen before and during the COVID-19 pandemic**

| Breast cancer type | Frequency before COVID-19 | Percentage before COVID-19 | Frequency during COVID-19 | Percentage during COVID-19 | *p*-value |
|---|---|---|---|---|---|
| Luminal A | 235 | 32.15 | 182 | 28.62 | |
| Luminal B | 219 | 29.96 | 219 | 34.43 | |
| HER2 | 102 | 13.95 | 91 | 14.31 | 0.24 |
| Triple negative | 86 | 11.76 | 63 | 9.90 | |
| Unknown | 89 | 12.18 | 81 | 12.74 | |
| Total | 731 | 100.00 | 636 | 100.00 | |

COVID-19: Coronavirus disease 2019; HER2: Human epidermal growth factor receptor 2

## Discussion and Conclusion

The COVID-19 pandemic resulted in significant adjustments to BC management both globally (3) and in South Africa. Changes included reductions in non-essential hospital visits, outpatient clinic consultations, and BC screening (6). Many elective surgeries were cancelled, and medical management strategies were altered (6).

A 2020 retrospective study conducted at Groote Schuur Hospital in South Africa found that 18% fewer BC surgeries were performed in 2020 compared to 2019 (7). Notably, a 21-day "Level 5" nation-wide lockdown was established in South Africa between 26th March and 16th April 2020 during the COVID-19 pandemic. During this period, all citizens and residents were confined to their homes except to obtain essential goods, seek emergency medical care, or if they were essential workers. Non-essential businesses were forced to close (8). Following the cessation of the Level 5 lockdown, strict regulations remained in place until the National State of Disaster was lifted two years later, on 5 April 2022. Throughout this period, various levels of restrictions applied, and citizens and residents were encouraged to stay at home and minimize non-essential contact with others. Many people also chose to avoid healthcare and social settings as far as possible due to fear of exposure to the severe acute respiratory syndrome coronavirus (4).

At the BCCE, new patients were still provided with in-person appointments for initial assessments. Patients and healthcare workers wore personal protective equipment, including face masks. Follow-up consultations were conducted virtually, and multidisciplinary team meetings were held online.

The results of the present study demonstrated a significant decrease in the number of patients who presented to BCCE each month during the pandemic compared to the number of patients seen per month prior to it. This finding aligns with a study conducted by Van Wyngaard et al. (7) which reported a 35.9% decrease in patients presenting with new breast symptoms per month between 2019 and 2020. However, a noticeable discrepancy exists between our study and that of Van Wyngaard et al. (7). Groote Schuur Hospital experienced a greater decline in patients presenting with BC compared to the private BCCE unit (9). Considering that Groote Schuur Hospital is a public institution, its patient cohort is likely to experience greater economic and social disadvantage (10). The population may have been more affected by access to transport due to the pandemic lockdown restrictions at the time (8).

There were no significant differences in patient age at presentation, BC stage, or tumor biology between BC patients presenting before and during the pandemic. This aligns with findings of multiple similar international studies, including one in Rochester, New York, by Tonneson et al. (5), which found that tumor biology did not change during the pandemic. A similar finding was reported at a university referral centre hospital in northern Italy (11). The lack of significant changes in age or tumour biology, both in the present study and other international studies, is likely attributable to the fact that these variables are not directly affected by the pandemic itself nor any of its associated restrictions. This is because such restrictions do not impact major non-modifiable risk factors for BC, including age, sex, and genetic predisposition (12).

In addition, there were no significant changes in BC stage at presentation. In contrast, a 2021 European case-control study found that delayed management of BC patients resulted in more advanced disease at presentation (13). Similarly, when comparing "pre-COVID" to "COVID-era" data, The American Society of Breast Surgeons reported that BC patients presented with more advanced-stage disease, particularly stage III BC, in the latter period (14). Cairns et al. (14) attributed this shift to severe restrictions in BC screening in the USA during the pandemic.

A 2022 systematic review by Li et al. (15) analysed 74 studies assessing the impact of the COVID-19 pandemic on BC screening and diagnosis. The review found a reduction in BC screening volume and a higher proportion of advanced-stage BC during the pandemic. However, of the 74 studies included, 41% were from North America, 35% from Europe and only one study was from Africa. This highlights either a lack of cancer screening programs in Africa or insufficient reporting of the data from existing programs, both of which warrant further attention. The lack of African data also limits direct comparisons between the findings of the present study and those of international studies, as differences in healthcare infrastructure, population demographics, and screening practices may play a significant role (15). In the South African public healthcare sector, there is no existing national BC screening program (16). The use of BC screening among private medical aid users is also suspected to be minimal in South Africa and across Africa as a whole. Given that BC screening in South Africa was already inadequate before the COVID-19 pandemic, it is logical that a further decrease in screening may not have significantly impacted BC stage at diagnosis. The lack of changes in BC stage and biology in the two periods of this study may also be attributed to the BCCE's coordination of care, particularly its emphasis on online communication between members of the multidisciplinary team, which enabled the timely diagnosis of BC stage and biology. These adaptations likely contributed to maintaining quality of care throughout the COVID-19 pandemic.

### Study Limitations

Two major limitations of this study are the omission of race categories and the study's location at a single private institution. It is well recognized that racial composition in South African patient populations often mirrors socioeconomic disparities (17). Consequently, as a private healthcare unit, the BCCE is likely to predominantly serve a wealthier socioeconomic minority (18). It is essential to consider this disparity to ensure that BC research and treatment accurately reflect the diversity of South Africa's population. Future studies should aim to include data from both public and private breast units to provide a more representative analysis. Moreover, further research from South Africa and other LMICs is needed to assess the long-term impact of the COVID-19 pandemic on BC presentation, diagnosis, and care in public healthcare settings.

During the COVID-19 pandemic, the BCCE's use of digital solutions facilitated clear communication, ensuring swift BC diagnosis and management despite national restrictions. We recommend the continued use of digital tools, such as online communication platforms implemented in the peak of the COVID-19 pandemic, to facilitate multidisciplinary meetings at BCCE. These platforms improved meeting attendance and reduced the time to diagnosis at the BCCE (19). The integration of digital technologies not only enhances patient care through communication but also improves patient access to healthcare.

BC remains a significant burden on both South African and global healthcare systems. This study highlights the importance of adapting

BC management strategies to local contexts. The findings of this study can serve as a framework for further BC research in the context of global healthcare emergencies, particularly within the South African public health sector.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from the Wits Human Research Ethics Committee (approval number M220952, date: 12.10.2022). Study site permission was obtained from the hospital CEO and database curator (approval number UNIV-2023-0009, date: 31.03.2022).

**Informed Consent:** All enrolled patients provided consent prior to the inclusion of their data in the database for anonymized research.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: C-A.B.; Concept: C.M., C-A.B.; Design: C.M., C-A.B.; Data Collection or Processing: N.K., D.d.C., D.v.L.; Analysis or Interpretation: N.K., D.d.C., D.v.L.; Literature Search: N.K., E.D.; Writing: N.K., D.d.C., E.D., A.M., C.M., C-A.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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**Original Article**

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# Vitamin D Deficiency and Mastalgia: A Prospective Controlled Study on Prevalence and the Therapeutic Impact of Supplementation

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**ABSTRACT**

**Objective:** To investigate the relationship between vitamin D deficiency and mastalgia and assess the effectiveness of vitamin D supplementation in alleviating mastalgia symptoms.

**Materials and Methods:** A prospective investigational study conducted in an Indian tertiary teaching centre. Participants were included if the presented with mastalgia and controls without mastalgia were also were recruited. Exclusion criteria were malignant pathology; fibroadenoma; other benign breast diseases; or recent therapeutic vitamin D supplementation. Vitamin D deficiency was classified as <20 ng/mL. Women in the mastalgia group with deficiency received 60,000 IU weekly oral vitamin D for eight weeks. Symptom severity was evaluated using a visual analog scale (VAS) at baseline and follow-up intervals of 4, 8, and 12 weeks. Difference in serum vitamin D levels between groups and changes in VAS scores post-supplementation was assessed.

**Results:** A total of 200 women, including 100 with mastalgia and 100 without (control group), were recruited over two years.The mean serum vitamin D level was significantly lower in the mastalgia group (25.29±7.7 ng/mL) compared to controls (31.46±8.5 ng/mL, $p$<0.0001). Vitamin D deficiency was more prevalent in the mastalgia group (26% *vs.* 9%, $p$ = 0.001). Post-supplementation, 46% of deficient patients in the mastalgia group reported symptom improvement, with 21% achieving complete resolution. However, 54% reported persistent symptoms despite achieving sufficient vitamin D levels.

**Conclusion:** Vitamin D deficiency is more prevalent in Indian women with mastalgia, and supplementation provides symptomatic relief for some patients. However, a significant proportion of patients continue to experience symptoms, suggesting other underlying factors contributing to mastalgia. Further research is needed to explore these factors and optimize management strategies.

**Keywords:** Mastalgia; vitamin D deficiency; serum vitamin D levels; vitamin D supplementation; prospective study; randomized controlled study; symptom relief; visual analog scale

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**Key Points**

- This work investigates the association between vitamin D deficiency and mastalgia and explores the therapeutic potential of supplementation in alleviating symptoms, aiming to bridge critical gaps in our understanding of this prevalent condition.

## Introduction

Mastalgia, or breast pain, is one of the most frequently reported breast complaints among women, affecting up to 70% at some point in their lives (1-3). Despite its prevalence, the etiology of mastalgia remains enigmatic, with treatments often yielding inconsistent results. Various hormonal, anatomical, and lifestyle factors have been implicated, but none provide a comprehensive explanation or solution (2). Recently, attention has focused on the potential role of vitamin D deficiency in mastalgia, driven by its established link to musculoskeletal and nonspecific chronic pain (4). This connection is particularly intriguing given the widespread prevalence of vitamin D deficiency globally and its known role in modulating inflammation, immune response, and hormonal balance (5, 6). While studies have investigated the impact of vitamin D supplementation on breast pain, these largely focus on patient populations without robust comparisons to the general population, leaving a significant gap in understanding whether vitamin D levels truly differ in mastalgia patients (4, 7, 8).

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In this first study we aimed to assess whether vitamin D deficiency is disproportionately associated with mastalgia as compared to those in the general population and if supplementation would offer symptomatic relief.

## Materials and Methods

This prospective, investigational, controlled study was conducted at a tertiary teaching centre in central India from November 2023 to August 2024. Ethics approval was obtained from the Institutional Ethics Committee Netaji Subhash Chandra Bose Medical College (IEC/2022/8629-129, date: 26.08.2022) and study was registered with the clinical trials registry of India (CTRI/2023/11/059708).

Patient eligibility and selection: all female patients presenting with the complaint of breast pain reporting to our department were identified. All patients were evaluated as per protocol and underwent a triple assessment that included complete clinical examination, ultrasonography and/or X-ray mammography of bilateral breasts and fine needle aspiration cytology or core needle biopsy, if indicated. All unwilling females, or those with malignant pathology, fibroadenomas, patients taking oral contraceptive pills, pregnant females, recent surgery, trauma, abscess, other benign breast disease or recent therapeutic vitamin D supplementation were excluded from the study. Healthy controls were recruited using convenience sampling from the same outpatient clinic, ensuring comparable demographic characteristics including age, body mass index (BMI), menopausal status, and parity. All participants provided informed consent after receiving detailed information about the study.

Blood samples were collected from all participants to measure serum vitamin D levels using an electrochemiluminescence method. Vitamin D levels were classified as sufficient (30–100 ng/mL), insufficient (20–29 ng/mL), and deficient (<20 ng/mL). Patients in the mastalgia group with vitamin D deficiency received 60,000 IU oral weekly vitamin D supplementation for eight weeks in accordance with established guidelines (9). A visual analog scale (VAS) scores for mastalgia severity was recorded for all patients in the mastalgia group at baseline, and at 4,8, and 12 weeks. Patients were considered to have complete response in terms of pain if their VAS score fell below 3/10 and a partial response if VAS fell to 4 or 5/10 (10). Patients were followed up at 4, 8 and 12 weeks.

### Sample Size

Based on literature review (4, 11) approximately 40 to 50% in the general population and 60 to 80% among those with mastalgia have Vitamin D deficiency. Assuming that 50% of the subjects in the reference population have the factor of interest, the study would require a sample size of 91 for each group to achieve a power of 80% for detecting a difference in proportions of 0.20 between the two groups (test - reference group) at a two sided p-value of 0.05. Assuming a 10% drop out rate, a total sample size of 200 (equal group sizes) was taken (12).

### Statistical Analysis

Data were entered and analyzed using MedCalc online statistical software (https://www.medcalc.org/calc/). Descriptive statistics were used to summarize demographic characteristics, vitamin D levels, and symptom scores for the mastalgia group. Continuous variables, such as serum vitamin D levels and VAS scores, were expressed as means with standard deviations, while categorical variables were presented as frequencies and percentages.

Comparative analysis was performed using independent t-tests to evaluate the difference in mean serum vitamin D levels between the mastalgia and control groups. The association between vitamin D levels and the presence of mastalgia was further analyzed using chi-square tests for categorical comparisons. McNemar's test was employed to compare pre- and post-supplementation symptom improvement in the mastalgia group (https://www.sciencedirect.com/topics/medicine-and-dentistry/mcnemar-test). A $p$-value of <0.05 was considered statistically significant for all analyses.

## Results

A total of 200 women participated in the study, with 100 women in the mastalgia group and 100 women in the control group. The mean age of participants, BMI, menopausal status and parity were comparable between the two groups (Table 1). The mean serum vitamin D level in the mastalgia group was 25.29±7.7 ng/mL, while in the control group, it was 31.46±8.5 ng/mL ($p$<0.0001). The mastalgia group exhibited a higher proportion of participants with vitamin D deficiency (26% *vs.* 9%, $p$ = 0.001). The proportion of women with vitamin D insufficiency was comparable between the two groups. The number of Vitamin D sufficient women was higher in control group compared to the mastalgia group (35% *vs.* 57%, $p$ = 0.001) (Table 2).

Within the mastalgia group, 54% had cyclical and 46% had non-cyclical type of pain. Participants with vitamin D deficiency ($n$ = 26) received Vitamin D supplementation, but two patients were lost to follow-up. After supplementation, 46% of patients reported symptomatic improvement based on VAS scores. Of these, 21% experienced complete resolution of symptoms, while 25% reported partial improvement. However, 54% of patients reported no response despite

**Table 1. Baseline clinical and demographic profile**

| Factor | Patients $n$ = 100 | Controls $n$ = 100 | $p$ |
|---|---|---|---|
| Age (mean ± standard deviation) | 29.99±8.14 | 28.67±6.0 | 0.19 |
| Body mass index (mean ± standard deviation) | 21.2±3.5 | 22.0±4.0 | 0.13 |
| **Menopausal Status, n (%)** | | | |
| Pre-menopausal | 91 (91) | 88 (88) | 0.5 |
| Post-menopausal | 9 (9) | 12 (12) | |
| Parity | | | |
| Nulliparous | 35 (35) | 48 (48) | 0.06 |
| Multiparous | 65 (65) | 52 (52) | |

**Table 2. Status of vitamin D nutrition in women with mastalgia and controls**

| Vitamin D status | Patients | Control | $p$ |
|---|---|---|---|
| Deficient | 26 | 9 | 0.001 |
| Insufficient | 39 | 34 | 0.46 |
| Sufficient | 35 | 57 | 0.001 |

achieving sufficient serum vitamin D levels post-supplementation (Table 3). The resolution of mastalgia between patients with sufficient vitamin D levels (12/35, 34.3%) and those with Vitamin D deficiency (11/24, 45.8%) was not statistically significant ($p$ = 0.53). Subgroup analysis showed no significant difference in Vitamin D levels between cyclical (54%) and non-cyclical (46%) mastalgia patients ($p$ = 0.39). Symptom improvement post-supplementation was similar in both groups.

## Discussion and Conclusion

In this first study, the relationship between vitamin D levels and mastalgia was explored in an Indian population, comparing the serum vitamin D levels of women with mastalgia to those in the general population. Moreover, the therapeutic effects of vitamin D supplementation in women with mastalgia and vitamin D deficiency on mastalgia symptoms were investigated. Serum vitamin D levels were generally lower in the mastalgia group compared to the control group and vitamin D supplementation resulted in symptomatic improvement in many women with mastalgia. However, there was no response to supplementation in most deficient women.

Mastalgia is a common clinical complaint among women, significantly impacting their quality of life. Despite the high prevalence of this condition, its etiopathogenesis remains poorly understood, often resulting in empirical treatments with variable outcomes. Our findings suggest that vitamin D deficiency may play a contributory role in the pathogenesis of some mastalgia, potentially through its effects on inflammatory pathways, muscle metabolism, and nociceptive signaling. The lower serum vitamin D levels observed in the mastalgia group and pain relief in many patients after supplementation align with prior studies, reinforcing the biological plausibility of this association (4, 13). The controlled design of the present study enables a clearer delineation between vitamin D deficiency and mastalgia compared to earlier uncontrolled studies. In addition, the longitudinal follow-up design allows for assessment of short and mid-term effects of supplementation, providing insights into treatment duration and sustained impact.

Vitamin D plays a crucial role in musculoskeletal function, immune modulation, and pain regulation (14). Its deficiency has been linked to increased inflammatory cytokines levels, altered nociceptive signaling, and estrogen imbalance, all of which may contribute to mastalgia (15). Furthermore, vitamin D receptors are expressed in breast tissue, suggesting a potential role in breast pain modulation (16). These mechanisms provide a plausible link between vitamin D deficiency and mastalgia, reinforcing the rationale for supplementation in affected individuals.

However, our study is not without limitations. The lack of a blinded, placebo-controlled design limits the ability to attribute symptom improvement solely to vitamin D supplementation, as a placebo effect cannot be ruled out. The reliance on convenience sampling for controls may introduce selection bias. Furthermore, the lack of a placebo-controlled design limits conclusions regarding the causal role of vitamin D. Mastalgia often improves without intervention, and a 54% non-response rate suggests multifactorial causes beyond vitamin D deficiency. Another potential limitation of our study is that we did not stratify vitamin D levels based on seasonal variations. Given the known impact of seasonal sun exposure on vitamin D synthesis, future studies should assess whether seasonal fluctuations influence the prevalence of vitamin D deficiency in mastalgia patients. Furthermore, while our study was powered adequately to detect a significant difference between groups, larger multicenter studies with a greater sample size are needed to confirm the generalizability of the results. However, the strengths of our study include its prospective design and inclusion of a control group with similar demographics to the study group, which enhances the validity of our findings. The use of standardized tools such as electrochemiluminescence for serum vitamin D measurements and VAS for symptom assessment enhances the data collection, analysis and reliability of the results. By focusing on a population with diverse demographic and socioeconomic backgrounds, our study offers valuable insights into the relationship between vitamin D levels and mastalgia, and the broader applicability of vitamin D supplementation as a potential intervention for mastalgia. However, further research is needed to confirm these findings. Future studies should consider larger sample sizes, randomized controlled designs, and longer longitudinal follow-ups to assess the long-term benefits of vitamin D supplementation. Despite its limitations, our study adds to the growing body of evidence suggesting that vitamin D deficiency may be an important, modifiable factor in the management of mastalgia. Given the observed partial response to supplementation, a combination approach addressing other potential contributors to mastalgia, including stress management and hormonal modulation, may enhance therapeutic outcomes.

Vitamin D deficiency was more prevalent in Indian women with mastalgia, and supplementation provided symptomatic relief for many patients. Given that a significant proportion of women are vitamin D deficient, addressing this deficiency through supplementation could also alleviate other symptoms and conditions increasingly attributed to vitamin D deficiency. Such supplementation, which is both cost-effective and safe, has the potential to offer broad health benefits without causing any harm. However, a significant proportion of patients continue to experience symptoms, suggesting other underlying factors contributing to mastalgia. A randomized, placebo-controlled trial would better establish the therapeutic efficacy of vitamin D supplementation for the treatment of mastalgia.

**Table 3. Impact of Vitamin D nutrition supplementation on mastalgia**

| Group | Vitamin D status post-intervention | | No response (VAS >6/10) | *p* |
|---|---|---|---|---|
| Deficient (n-24) | Sufficient (n-24) (100%) | Complete response (VAS <3/10) *n* = 5 (21%) Partial response (VAS = 4 or 5/10) *n* = 6 (25%) | *n* = 13 (54%) | <0.0001 |

VAS: Visual analog scale

**Presentation:** This study was presented in best oral award category during Asian Society of Mastology annual conference, Dehradun, India, November 2023.

### Ethics

**Ethics Committee Approval:** Ethics approval was obtained from the Institutional Ethics Committee Netaji Subhash Chandra Bose Medical College (IEC/2022/8629-129, date: 26.08.2022) and study was registered with the clinical trials registry of India (CTRI/2023/11/059708).

**Informed Consent:** Informed consent was obtained from all participants prior to inclusion in the study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: G.N.S., S.K.Y., D.B.S., D.S., S.S.; Concept: G.N.S., S.K.Y., D.B.S., D.S., S.S.; Design: G.N.S., S.K.Y., D.B.S., D.S., S.S.; Data Collection or Processing: G.N.S., S.K.Y., D.B.S., D.S., S.S.; Analysis or Interpretation: G.N.S., S.K.Y., D.B.S., D.S., S.S.; Literature Search: G.N.S., S.K.Y., D.B.S., D.S., S.S.; Writing: G.N.S., S.K.Y., D.B.S., D.S., S.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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**Original Article**

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# Breast Imaging: Correlation Between Axillary Lymph Nodes Apparent Diffusion Coefficient and Pathological Lymphovascular Invasion in Patients With Invasive Breast Cancer

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**ABSTRACT**

**Objective:** Together with local invasion, one of the important characteristics of cancer is its capacity to spread, resulting in metastases. Before cancer cells metastasize to a secondary site, they must first enter and spread through the blood and lymph vasculature, this is known as lymphovascular invasion (LVI). This LVI and, to a much lesser extent, perineural and neural invasion are one of the biologic prerequisites for systemic spread and metastases. To evaluate the correlation between pre-operative apparent diffusion coefficient (ADC) of the ipsilateral enlarged axillary lymph nodes (LNs) and presence of LVI on post-operative pathology, in patients with invasive breast cancer.

**Materials and Methods:** This retrospective study was approved by the institutional review board. It included 100 female patients (mean age, 49 years; range, 30–68 years) with invasive breast cancer, who underwent preoperative magnetic resonance imaging (MRI) and breast surgery. On pre-operative MRI, the ADC was calculated for the ipsilateral enlarged axillary LN. Presence or absence of LVI was assessed on post-operative histopathology. Statistical analysis was performed to investigate any correlation between the ADC value of the axillary LNs and LVI in these patients.

**Results:** The mean ADC value of the ipsilateral enlarged axillary LNs was significantly lower in LVI positive cases compared to LVI negative cases ($0.735 \times 10^{-3}$ mm$^2$/s) *vs*. ($1.024 \times 10^{-3}$ mm$^2$/s), ($p$<0.001). Moreover, the mean Ki-67 in LVI positive cases was 46.12%, compared to 21.58% for LVI negative cases. This higher Ki-67 level in LVI positive cases indicates a greater degree of proliferation and thus the more aggressive nature of these tumors, and this was positively correlated with ADC values of the ipsilateral enlarged axillary LNs.

**Conclusion:** In cases of invasive breast cancer, the ADC value of the ipsilateral enlarged axillary LNs assessed on pre-operative MRI, and Ki-67 status of the tumor were significantly correlated to the LVI status on histopathological assessment. This ADC value may be useful as a predictor of axillary LN involvement, metastasis, and prognosis in invasive breast cancer.

**Keywords:** Invasive breast cancer; lymphovascular invasion; axillary lymph nodes; apparent diffusion coefficient; MRI

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**Key Points**

- Breast cancer is the most common cancer in women, with lymphovascular invasion detected in about 24.3% of cases, leading to higher metastasis and recurrence rates.
- Lymphovascular invasion is confirmed through histopathology, making it hard to detect preoperatively with standard imaging techniques.
- Diffusion-weighted imaging and the apparent diffusion coefficient can provide data on tumor cell density and aggressiveness, potentially predicting lymphovascular invasion presence.

## Introduction

Breast cancer is the most common cancer in women, accounting for 30% of all new cancer cases and about 15% of total deaths in females, according to the latest cancer statistics in (1, 2) and is thus a serious threat to the health of women (3). Lymphovascular invasion (LVI) is defined as the presence of tumor emboli in lymphatic and vascular spaces within the area that surrounds an invasive carcinomas. LVI is detected in about 24.3% of patients with breast cancer (4). LVI is a key prognostic factor in cases of invasive breast cancer as patients with LVI positivity showed a higher rates of distant metastasis and also higher

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local recurrence rates after treatment (5). LVI is also associated with high Ki-67 levels. Ki-67 is an important immunohistochemical (IHC) marker used for evaluation of invasiveness, the proliferation activity, and prognosis in human tumors (6).

As LVI presence is confirmed histopathologically, based on a surgically excised specimen that contains the primary tumor and the peritumoral breast tissue, it is difficult to detect the presence of LVI by preoperative biopsy that contains the primary lesion only. So, preoperative multiplanar imaging with magnetic resonance imaging (MRI) of these cases may be expected to provide data that can predict the presence of LVI (7). Imaging modalities, such as ultrasound, computed tomography, and MRI, which is the most commonly used modality, cannot identify LVI accurately, because of various anatomical and morphological limitations of these modalities (8).

Diffusion-weighted imaging (DWI) is a specific functional MRI technique that evaluates the thermal motion of the water molecules within the tissue ultrastructure. The apparent diffusion coefficient (ADC) is a quantitative assessment parameter of DWI, which provides essential data about the density and aggressiveness of tumor cells (9, 10). Many earlier studies have discussed the role of the ADC in predicting LVI in invasive breast cancer patients with positive sentinel lymph nodes (LNs) (11).

The aim of the present study was to evaluate the correlation between pre-operative ADC of axillary LNs and the presence of LVI in post-operative histopathology in patients with invasive breast cancer. A further aim was to evaluate any correlation between Ki-67 and LVI.

## Materials and Methods

This retrospective study included 100 female patients with single, unilateral, invasive breast cancer with positive ipsilateral axillary LNs, who underwent preoperative MRI and then breast surgery. Surgery was either conservative breast surgery or mastectomy, based on the size, and extension of the breast lesion, and axillary LN dissection was done in all the study patients. This study was done in the period from March 2023 to March 2024.

Ethics approval was approved and obtained by Mansoura Faculty of Medicine Institutional Research Board (approval number: R.24.04.2598, date: 18.05.2024). Informed consent was waived because this was a retrospective, anonymized study. Retrospective data were collected and analyzed from existing image archives.

### Inclusion Criteria

Patients with unilateral, single, invasive breast cancer and with positive ipsilateral axillary LNs were included. Positive ipsilateral axillary LNs were confirmed clinically and radiologically. Invasive breast cancer patients, that is those with either invasive ductal or invasive lobular carcinoma, are characterized by the invasion of breast cancer cells into the basement membrane and spread from breast ducts or lobules to nearby breast tissue. By definition the breast cancer in these patients is no longer ductal carcinoma *in situ*, but has become an invasive type of breast cancer. The invasion and type of breast cancer also the Ki-67 level were determined on tru-cut needle biopsy from breast lesions which were performed in all patients before breast surgery or at the start of other types of therapy. Values for Ki-67 were evaluated by the histopathologist following recognized protocols for manual counting.

Criteria of molecular subtyping of breast cancer were:

1. Luminal subtype (subdivided into luminal A and luminal B)

Luminal A: human epidermal growth factor receptor 2 (HER2) negative [estrogen receptor (ER) positive, progesterone receptor (PR) negative/low, HER2 negative, Ki-67 proliferative index high]

Luminal B: HER2 positive (ER positive, PR positive or negative, HER2 positive, Ki-67 proliferative index varies)

2. Triple negative subtype (ER negative, PR negative, HER2 negative):

3. HER2 enriched (HER2 positive; ERBB2 positive): ER negative, PR negative, HER2/neu amplified or overexpressed.

The presence or absence of LVI was assessed on post-operative histopathological examination for all patients. These histopathological data were the "gold standard" to correlate the radiological data by.

### Exclusion Criteria

Patients were excluded if they had bilateral breast cancer, as the aim was to assess LVI in breast cancer cases with ipsilateral enlarged axillary LNS, not with contralateral axillary LNs, and to correlate the pre-operative axillary LN ADC value with the post-operative LVI status of the breast lesion on the ipsilateral side. Patients were also excluded if they had unilateral breast cancer but there were multiple breast lesions, to ensure that the lesion evaluated on MRI was the same lesion assessed on post-operative pathology. Finally, patients were also excluded if they did not have pre-operative breast MRI or the diffusion study with an ADC map was not available.

### MRI Technique

In all patients, MRI of the breast was performed using a 1.5 Tesla machine (Philips Ingenia, Best, The Netherlands). Examination of patients was performed in the prone position with the use of a dedicated 16-channel breast coil. DWI was obtained by a single shot spin echo sequence with the following parameters; (TR/TE/NEX): 5800/139 ms/1, b values used were 0, 500, and 1000 $mm^2$/sec. Diffusion gradients were sequentially applied in X, Y, and Z axes. Slice thickness was 4 mm, with 1 mm interslice gap, a 300-360 mm field of view, and matrix of (128x256). Total acquisition time was about 120 sec. Orthogonal diffusion images and ADC maps for all cases were performed.

### Diffusion-Weighted Imaging Post-Processing

Four sets of DWI were obtained for each section. The first three sets of images (known as trace images), corresponding to sensitization gradients, were sequential applications in the three orthogonal planes. The ADC map (the last set), corresponding to the average diffusion images, where measurement of ADC for any region of interest (ROI) can be measured. The ADC maps were calculated by the MRI scanner in-built software.

### Image Analyses

Conjoint interpretation of the MRI studies of the patients was done by three radiologists of 10, 10 and 12 years experience. The radiologists were blinded to patient pathological data. The ADC value was calculated for the most suspicious ipsilateral enlarged axillary LN. The ROIs were manually and carefully drawn along the solid area of the ipsilateral most suspicious LN and copied to the corresponding ADC maps, avoiding the areas with necrosis if present within the LN. No

less than three ROIs were used within the same ipsilateral enlarged LN, and then the mean ADC value for the lesion was calculated. ROI size was 20 $mm^2$.

### Histopathological and Immunohistochemical Evaluation

Presence or absence of LVI was assessed on post-operative histopathological examination. These histopathological data were the gold standard to correlate the radiological data with.

### Statistical Analysis

Data analysis was done by SPSS software, version 25 (IBM Inc., Armonk, NY, USA). Description of qualitative data was done using number and percentage. Quantitative data were described using mean ± standard deviation for data distributed normally after testing for normality using the Kolmogorov-Smirnov test. The obtained results significance was judged at the $p<0.05$ level.

If quantitative data was non-normal, the Mann-Whitney U test was used to compare between two studied groups while the Student t-test was used to compare two independent groups for normally distributed data. Receiver operating characteristics curve was used to calculate sensitivity and specificity of continuous variables with calculation of the optimal cut off point. Predictive values and accuracy were assessed using cross tabulation.

## Results

This retrospective study included 100 female patients with a mean age of 49 years with a range of 30–68 years, with single unilateral invasive breast cancer and positive ipsilateral axillary LNs. Tumor data of the cases are shown in Table 1. Of the 100 patients, 61 had LVI on histopathological analysis and 39 did not.

**Table 1. Laterality, number, and pathological types of the breast tumors in the studied cases**

| Patient data | *n* | % |
|---|---|---|
| Tumor laterality | | |
| Unilateral | 100 | 100 |
| Bilateral | 0 | 0 |
| No. of the tumor in each study case | 1 | 100 |
| Pathological types of breast cancer in the studied patients | | |
| Invasive duct carcinoma | 93/100 cases | 93% |
| Invasive lobular carcinoma | 5/100 cases | 5% |
| Mixed mucinous carcinoma | 2/100 cases | 2% |

The mean ADC value of the ipsilateral enlarged axillary LNs was significantly lower in patients with LVI than in LVI negative cases with ADC values of $0.735 \times 10^{-3}$ $mm^2/s$ *vs.* $1.024 \times 10^{-3}$ $mm^2/s$, respectively ($p<0.001$) (Table 2 and Figure 1).

In Figure 1, the mean Ki-67 in LVI positive cases was 46.12%, while this was 21.58% for LVI negative cases. This higher KI-67 level in LVI positive cases indicates a greater degree of proliferation and thus the more aggressive nature of these tumors, and this was positively correlated with ADC values of the ipsilateral enlarged axillary LNs.

In Table 3, the optimal cut-off point for ADC value in differentiating between LVI positive and negative cases was 0.889. Similarly, the cut off point for Ki-67 for differentiating between LVI positive and negative cases was 27.5% ($p<0.001$). The analysis showed relatively high sensitivity but only moderate specificity for ADC and Ki-67 when differentiating between LVI positive and negative cases, as shown in Table 3 and Figures 2 and 3.

Correlation between LVI and IHC parameters and MRI features of the tumors are shown in Table 4. There was a significant correlation between LVI and the number of infiltrated LNs. In LVI negative cases, all cases except for six (%) showed unaffected dissected LNs. In the six exceptions, each patient exhibited one infiltrated LN histopathologically. However, in LVI positive cases most patients had infiltrated dissected LNS, with a median of 4 infiltrated LNs per patient. However, once again there were six exceptions who had no infiltrated dissected LNs.

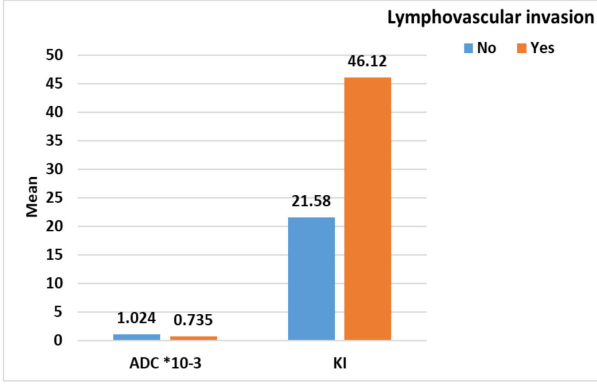


**Figure 1.** Mean ADC and Ki-67 % in differentiating between cases with and without LVI

*LVI: Lymphovascular invasion; ADC: Apparent diffusion coefficient*

**Table 2. Comparison of mean ADC and Ki-67 in differentiating between cases with and without LVI**

| | Lymphovascular invasion | | Test of significance |
|---|---|---|---|
| | Negative for LVI (*n* = 39) | Positive for LVI (*n* = 61) | |
| ADC x$10^{-3}$ | 1.024±0.22 | 0.735±0.17 | *t* = 7.24<br>*p*<0.001* |
| Ki-67 | 21.58±13.15 | 46.12±22.59 | *z* = 6.24<br>*p*<0.001* |

t: Student t-test; z: Mann-Whitney U test; *: Statistically significant; LVI: Lymphovascular invasion; ADC: Apparent diffusion coefficient

In terms of IHC characteristics of the tumors, the luminal A molecular subtype was significantly correlated with negative LVI (28.2 %) *vs.* 8.2% for cases with positive LVI. However, luminal B molecular subtype was significantly correlated with positive LVI (65.6%) *vs.* 30.8% for negative LVI.

The number of infiltrated LNs was also significantly correlated with the ADC value of the axillary LNs, as shown in Table 5 and Figure 4. There was a significant negative correlation between this ADC value and the number of infiltrated LNs. The other IHC and MRI criteria of the tumors in the studied cases did not show significant correlation with the ADC value of the axillary LNS, with the exception of the having a non-circumscribed speculated margin which was significantly correlated with a lower ADC value (mean, 0.831±0.27), while circumscribed margin was significantly correlated with a higher ADC value (mean, 1.26±0.0), as shown in Table 6.

## Discussion and Conclusion

Breast cancer is the most common cancer worldwide and the major cause of cancer related mortalities in women (12). Most breast cancer related mortalities are due primary tumor proliferation or due to distant metastasis (13). LVI is defined histopathologically as presence of tumor cells within the lymphatic or vascular spaces that encircles the primary carcinoma. Its positivity indicates a higher risk of cancer local recurrence or distant metastasis; so, its detection is important as a diagnostic or prognostic assessment of patients with breast cancer (14). Many studies have indicated the importance of the LVI in surgical intervention determination, providing guidance tool for neoadjuvant therapy evaluation, and suggesting optimal resection margins of the tumors (15, 16). However, identifying this LVI status accurately pre-operatively is a challenge, because it is identified accurately on histopatological examination following surgery.

Evaluation of LVI status in breast cancer patients, pre-operatively, may be done with the aid of some MRI morphological features, as the peritumoral edema, "adjacent vessel" sign, the DWI, and status of axillary LN on MRI (17-20). Dynamic MRI may play an important role in assessing LVI status, as it provides high quality multiplanar images and highly significant morphologic and functional data. It provides information on the volume, permeability, and the tumor vascular system angiogenesis (20, 21).

In our study we aimed to highlight the correlation between the ADC of the ipsilateral suspicious axillary LNs, and the LVI status in patients with invasive breast cancer.

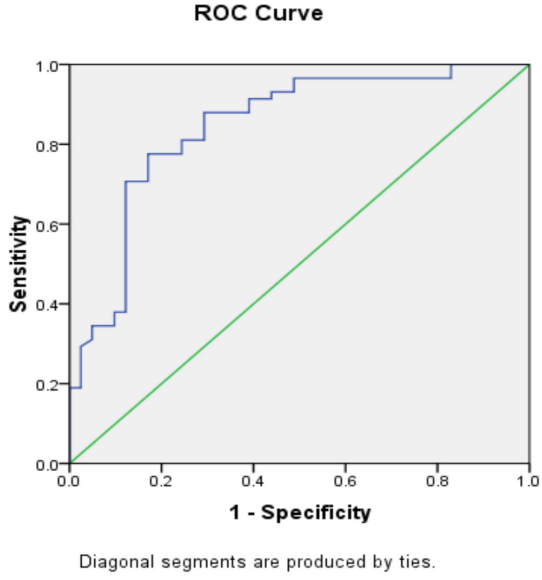


**Figure 2.** ROC curve of ADC in differentiating between cases with and without LVI

*LVI: Lymphovascular invasion; ADC: Apparent diffusion coefficient; ROC: Receiver operating characteristics curve*

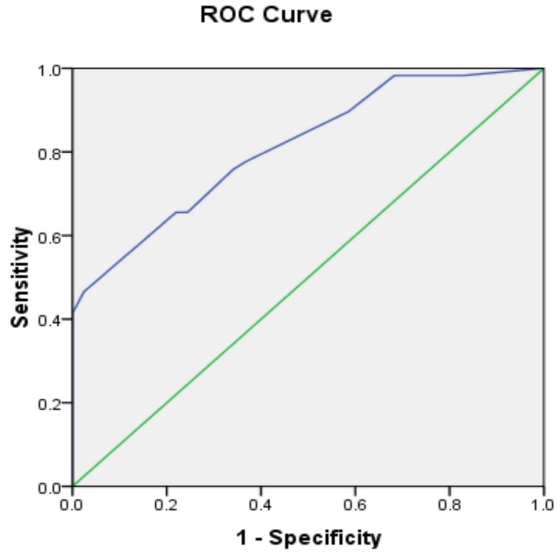


**Figure 3.** ROC curve of Ki-67 in differentiating between cases with and without LVI

*LVI: Lymphovascular invasion; ADC: Apparent diffusion coefficient; ROC: Receiver operating characteristics curve*

**Table 3. Validity of ADC and Ki-67 in differentiating between cases with and without LVI**

| | AUC (95% CI) | *p* | Optimal cut-off | Sensitivity % | Specificity % | PPV% | NPV% | Accuracy % |
|---|---|---|---|---|---|---|---|---|
| ADCx10$^{-3}$ | 0.845 (0.764–0.926) | <0.001 | 0.889 | 87.9% | 70.7% | 81.0% | 80.6% | 80.1% |
| Ki-67 | 0.812 (0.731–0.893) | <0.001 | 27.5% | 75.9% | 65.9% | 75.9% | 65.9% | 71.7% |

PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under curve; LVI: Lymphovascular invasion; ADC: Apparent diffusion coefficient; CI: Confidence interval

**Table 4. Correlation between lymphovascular invasion and clinicopathological features of the studied cases**

| | LVI | | Test of significance | *p* |
|---|---|---|---|---|
| | No | Yes | | |
| Number of infiltrated LNs Median (minimum-maximum) | 0 (0–1) | 4 (0–17) | $z = 7.61$ | <0.001* |
| Tumor grade, *n* (%) | | | | |
| I | 3 (7.7) | 2 (3.3) | | |
| II | 26 (66.7) | 34 (55.7) | $\chi^2 = 3.0$ | 0.223 |
| III | 10 (25.6) | 25 (41) | | |
| ER score | | | | |
| Median (minimum-maximum) | 8 (0–8) | 7 (0–8) | $z = 1.22$ | 0.223 |
| PR score | | | | |
| Median (minimum-maximum) | 7 (0–8) | 5 (0–8) | $z = 1.26$ | 0.209 |
| HER2 status | | | | |
| -VE | 31 (79.5) | 53 (86.9) | $\chi^2$=0.969 | 0.325 |
| +VE | 8 (20.5) | 8 (13.1) | | |
| Molecular subtype | | | | |
| Luminal A | 11 (28.2) | 5 (8.2) | | |
| Luminal B | 12 (30.8) | 40 (65.6) | $\chi^2 = 13.12$ | 0.004* |
| HER-enriched | 8 (20.5) | 8 (13.1) | | |
| Triple negative | 8 (20.5) | 8 (13.1) | | |
| Amount of fibroglandular tissue (FGT) | | | | |
| Entirely fatty | 0 | 7 (11.5) | | |
| Scattered FGT | 15 (38.5) | 30 (49.2) | | |
| Heterogenous dense breast | 18 (46.2) | 19 (31.1) | $\chi^2 = 7.65$ | 0.054 |
| Extremely dense breast | 6 (15.4) | 5 (8.2) | | |
| BPE | | | | |
| Minimal | 0 | 7 (11.5) | | |
| Mild | 17 (43.6) | 22 (36.1) | $\chi^2 = 4.91$ | 0.179 |
| Moderate | 19 (48.7) | 28 (45.9) | | |
| Marked | 3 (7.7) | 4 (6.6) | | |
| Mass shape | | | | |
| Irregular | 33 (84.6) | 52 (85.2) | $\chi^2 = 0.007$ | 0.931 |
| Lobulated | 6 (15.4) | 9 (14.8) | | |
| Mass margin | | | | |
| Non-circumscribed speculated | 18 (46.2) | 32 (52.5) | | |
| Non-circumscribed irregular | 19 (48.7) | 29 (47.5) | $\chi^2 = 3.32$ | 0.190 |
| Circumscribed | 2 (5.1) | 0 | | |
| Mass internal enhancement pattern | | | | |
| Heterogenous | 35 (89.7) | 50 (82) | $\chi^2 = 1.128$ | 0.288 |
| RIM | 4 (10.3) | 11 (18) | | |
| Kinetic curve type | | | | |
| Pateau curve | 8 (20.5) | 9 (14.8) | $\chi^2 = 0.559$ | 0.455 |
| Washout curve | 31 (79.5) | 52 (85.2) | | |

z: Mann-Whitney U test; $\chi^2$: Chi-square test; *: Statistically significant; LVI: Lymphovascular invasion; HER2: Human epidermal growth factor receptor 2; ER: Estrogen receptor; PR: Progesterone receptor; BPE: Background parenchymal enhancement; LNs: Lymph nodes

**Table 5. Correlation between ADC value and number of infiltrated LNs, ER & PR score**

| | ADC value | |
|---|---|---|
| | r | *p*-value |
| No of infiltrated LNs | -0.492 | 0.001* |
| ER score | -0.159 | 0.119 |
| PR score | -0.104 | 0.301 |

r: Spearman correlation coefficient; LNs: Lymph nodes; ADC: Apparent diffusion coefficient; ER: Estrogen receptor; PR: Progesterone receptor

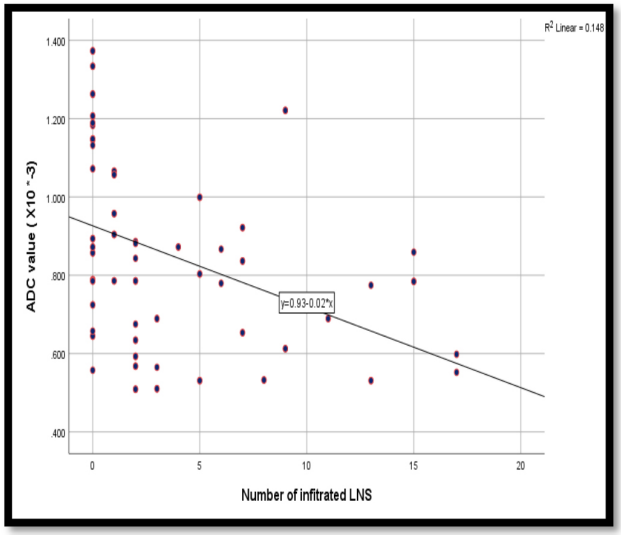


**Figure 4.** Scatter plot showing correlation between ADC & number of infiltrated LNs

*ADC: Apparent diffusion coefficient; LNs: Lymph nodes*

Markedly enlarged in size and abnormal LNs in morphology, especially when markedly different from other visible axillary LNs, are highly suggestive of nodal metastasis. Features of cortical thickening, loss of the fatty hilum, round shape or a (long-to-short axis ratio) of less than 2 are considered as typical morphologic criteria that can be seen with LNs metastasis (22). Also, according to Baltzer et al. (23), irregular margin, heterogenous cortex, perifocal edema which is seen as high T2 signal intensity in surrounding soft tissue, and asymmetry of the LNs in number or size compared with the contralateral side are findings suggestive of LN metastasis.

In our study, the mean ADC value of the ipsilateral enlarged axillary LNs was significantly lower in LVI positive than in LVI negative cases of invasive breast cancer ($0.735 \times 10^{-3}$ mm$^2$/s) *vs.* ($1.024 \times 10^{-3}$ mm$^2$/s), ($p$<0.001), with cut off point for ADC value in differentiating between LVI positive and negative cases was 0.889 as shown in Figures 5 and 6.

In our study, the mean Ki-67 in LVI positive cases was 46.12%, while was 21.58% for LVI negative cases. The cut-off point for Ki-67 in differentiating between LVI positive and negative cases was 27.5 ($p$-value less than 0.001). This higher Ki-67 level in LVI positive cases reflected the more aggressive nature of these tumors and their higher proliferation activity, and this correlated positively with ADC values of the ipsilateral enlarged axillary LNs as shown in Figures 7 and 8.

This is consistent with the results of Liu et al. (24), study in which the LVI positive group had higher Ki-67 expression level (>30%) than the LVI negative group and the difference was statistically significant ($p$ = 0.012).

Also agreed with results of literatures which confirmed that higher KI-67 is associated with higher tumor grade, LVI, metastasis, and recurrence rate (25-27).

Our results agreed with the results of Klingen et al. (28) who reported that LVI was associated with some features of aggressive breast cancer as LN positive tumors and higher Ki-67 expression.

Also our results were in line with a review that has shown that the presence of LVI correlates with locoregional LN involvement (29).

Also, our study results agreed with results of Zhang et al. (30), retrospective study, who found a strong association between the LN status and the LVI status.

In Yang et al. (31), study they found correlation between LN criteria including larger size, and presence of necrosis, with the LVI status. But, they didn't include the ADC value of the axillary LN on the LN status data. Also, they found a border line correlation of the Ki-67 level with the LVI status.

Some studies recently, have shown that ADC value may be a good prognostic factor correlated to aggressiveness of tumors in breast cancer patients (32-34). Other current retrospective cohort studies concluded that ADC values of breast tumors were lesser in the LVI positive groups than the negative ones (11, 35). Lower ADC value is related to decrease in osmosis speed within tumor tissues and to higher proliferation rates of tumor cells. LVI was significantly concomitant to a higher cell proliferation level of the tumor (high Ki-67 level) (11).

Our results agreed with results of Byon et al. (36) , retrospective study that included 435 cases of breast cancer which compared "standard lower axillae" and "combined entire axilla" MRI protocols, they determined that axillae positivity (odds ratio: 5.9) and positive peritumoral edema (odds ratio: 12.3) at the standard protocol of MRI were predictive factors of high level axillary LNs metastasis, and with exclusion of axillary findings, peritumoral edema or mutifocality and multicentricity were predictive factor of high level axillary LNs metastasis, also, the LVI and the peritumoral edema were prognostic factors of advanced axillary LNs metastasis.

Our results agreed with Chen et al. (37), who found that the LVI in axillary LN metastasis group was significantly higher than that in non -axillary LN metastasis group (37.50% *vs.* 6.10%, $p<0.001$). And their logistic regression analysis suggested that LVI was one of the risk factors for axillary LN metastasis in patients with invasive breast cancer.

Our results showed relatively high sensitivity and moderate specificity for ADC and Ki-67 in differentiating between LVI positive and negative cases (87.9% sensitivity, 70.7% specificity) for ADC and (75.9% sensitivity, 65.9%) for Ki-67, with (81.0% PPV, 80.6% NPV, 80.1% accuracy) for ADC, and (85.9% PPV, 75.9% NPV, 71.7% accuracy) for Ki-67.

**Table 6. Relationship between ADC value and clinicopathological features**

| | ADC value | Test of significance | *p* |
|---|---|---|---|
| | Mean ± standard deviation | | |
| Tumor grade | | | |
| I | 0.825±0.25 | | |
| II | 0.838±0.26 | F = 0.604 | 0.549 |
| III | 0.893±0.21 | | |
| HER2 status | | | |
| -VE | 0.855±0.25 | *t* = 0.124 | 0.902 |
| +VE | 0.864±0.16 | | |
| Molecular subtype | | | |
| Luminal A | 0.849±0.23 | | |
| Luminal B | 0.853±0.26 | F = 0.028 | 0.994 |
| HER-enriched | 0.864±0.16 | | |
| Triple negative | 0.869±0.24 | | |
| Amount of fibroglandular tissue | | | |
| Entirely fatty | 0.847±0.15 | | |
| Scattered fibroglandular tissue | 0.784±0.23 | F = 3.17 | 0.028 |
| Heterogenous dense breast | 0.928±0.25 | | |
| Extremely dense breast | 0.940±0.17 | | |
| BPE | | | |
| Minimal | 0.787±0.19 | | |
| Mild | 0.827±0.22 | F = 0.931 | 0.429 |
| Moderate | 0.876±0.26 | | |
| Marked | 0.959±0.17 | | |
| Mass shape | | | |
| Irregular | 0.843±0.24 | *t* = 1.35 | 0.180 |
| Lobulated | 0.934±0.23 | | |
| Mass margin | | | |
| Non-circumscribed speculated | 0.831±0.27 | | |
| Non-circumscribed irregular | 0.867±0.19 | F = 3.34 | 0.039* |
| Circumscribed | 1.26±0.0 | | |
| Mass internal enhancement pattern | | | |
| Heterogenous | 0.867±0.24 | *t* = 1.05 | 0.298 |
| RIM | 0.797±0.16 | | |
| Kinetic curve type | | | |
| Pateau curve | 0.909±0.16 | *t* = 0.997 | 0.321 |
| Washout curve | 0.845±0.252 | | |

F: One-Way ANOVA test; t: Student t-test; HER2: Human epidermal growth factor receptor 2; ER: Estrogen receptor; PR: Progesterone receptor; BPE: Background parenchymal enhancement

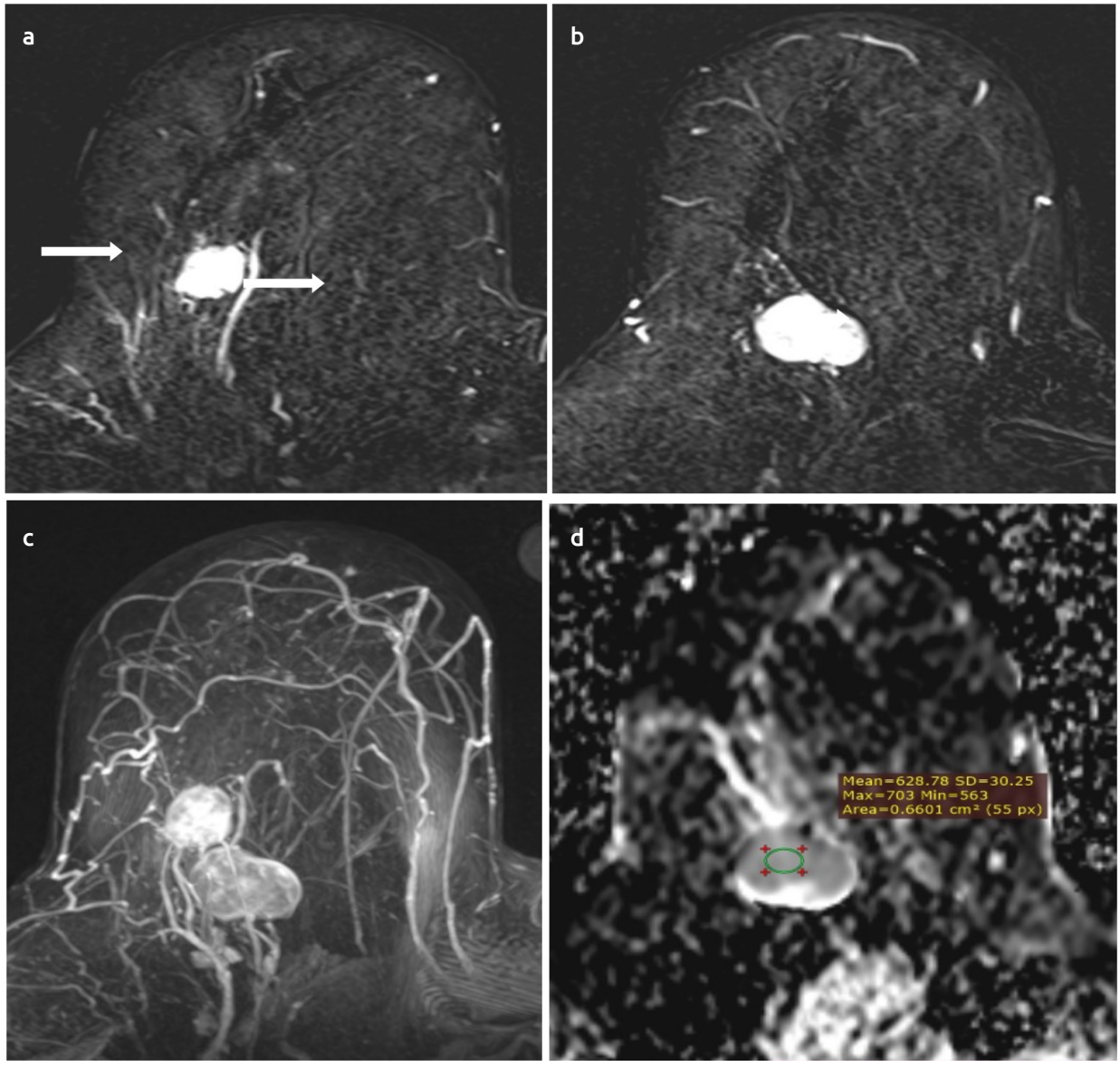


**Figure 5.** Fifty-five years old female with luminal B right breast cancer. Post-operative pathology revealed: High grade infiltrating duct carcinoma with low grade DCIS component (5%), with detected lymphovascular emboli, no perineural invasion. Examination of Ki-67 stained slide revealed nuclear staining in 30% of tumor cells. a. Post contrast subtraction MRI image showing malignant looking irregular mass in right breast (white arrow). b. Post contrast MRI subtraction image showing ipsilateral enlarged axillary tail suspicious LN (white arrow). c. Subtraction MIP image showing the mass and the LN. d. Mean ADC value of this LN was $0.628x10^{-3}$ $mm^2/s$

*LNs: Lymph nodes; ADC: Apparent diffusion coefficient; MRI: Magnetic resonance imaging; DCIS: Ductal carcinoma in situ; MIP: Maximum intensity projection*

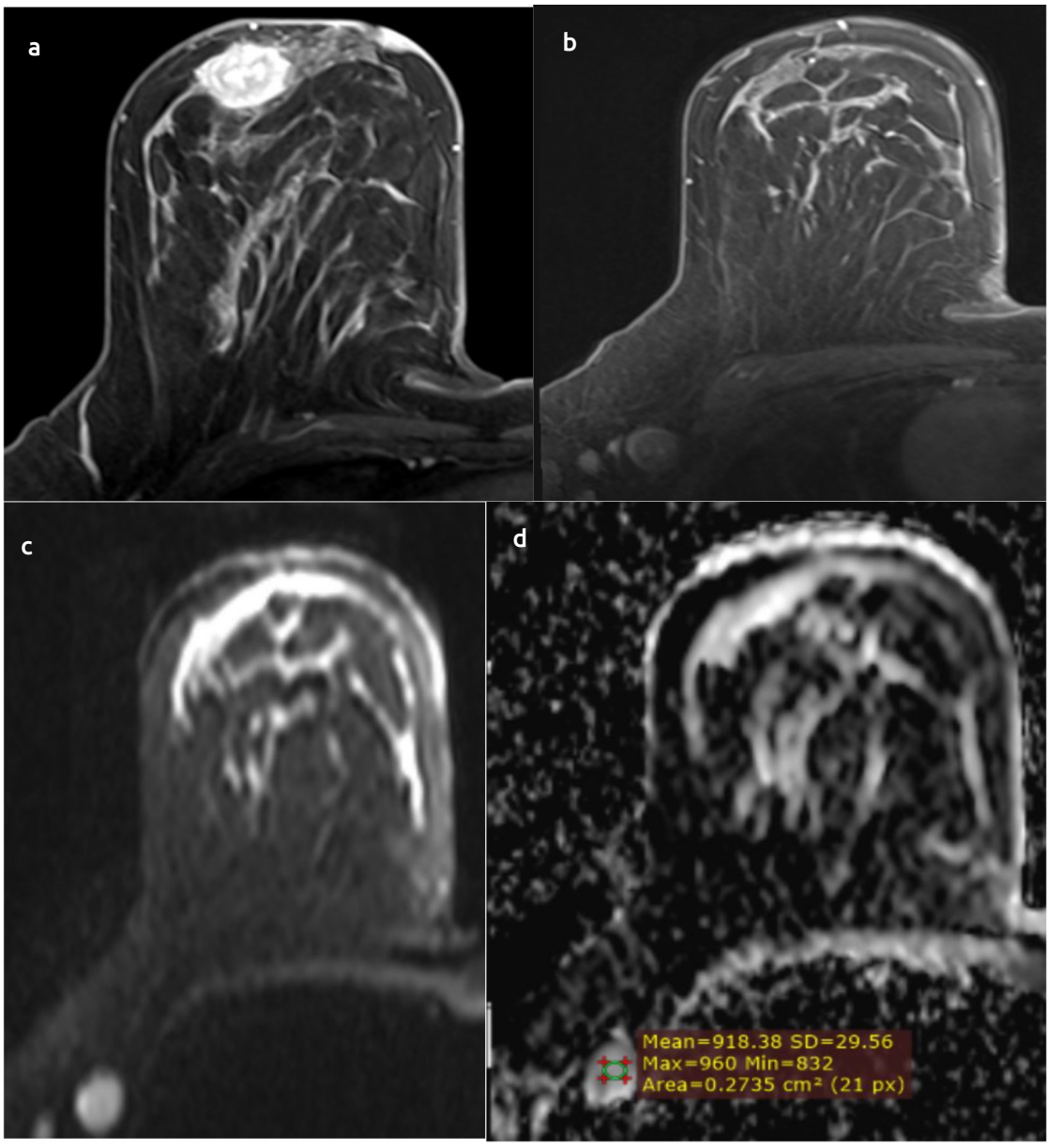


**Figure 6.** Thirty-two years old female with luminal B right breast cancer. Post-operative pathology revealed: Grade II invasive duct carcinoma associated with high grade ductal carcinoma *in situ* about 5%. No lymphovascular invasion or perineural spread. Ki-67: Positive nuclear reaction in about (20) % of tumor cells. a. Post contrast subtraction MRI image showing malignant looking irregular mass in right breast b. Post contrast MRI subtraction image showing ipsilateral enlarged suspicious axillary LN (white arrow). c. Diffusion image showing high SI of the LN. d. ADC map showing low SI and restricted diffusion of the LN. Mean ADC value of this LN was 0.905 x$10^{-3}$ $mm^2$/s

*LNs: Lymph nodes; ADC: Apparent diffusion coefficient; MRI: Magnetic resonance imaging; SI: Sacroiliac*

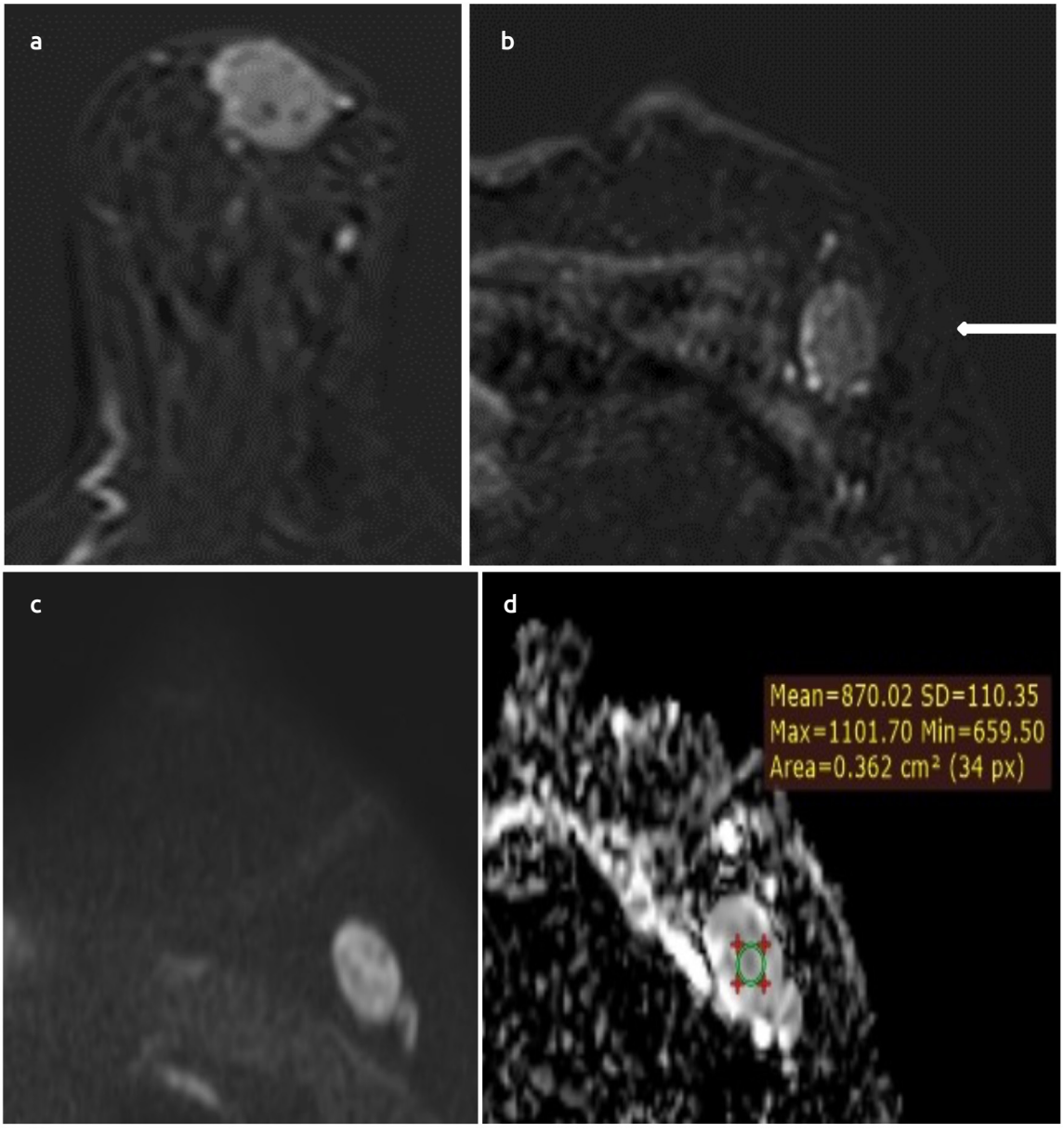


**Figure 7.** Forty-one years old female patient with triple negative left breast cancer. Post-operative pathology revealed grade III invasive duct carcinoma, with negative lymphvascular invasion. Ki-67 was about 70%, high proliferation index. a. Subtraction post contrast image showing left retroareolar suspicious mass. b. Subtraction post contrast image showing enhanced suspicious left axillary LN (white arrow). c. Diffusion image showing high SI of the LN in diffusion image. d. ADC map showing mean ADC value of the axillary LN of 0.870 x$10^{-3}$ $mm^2$/s

*LNs: Lymph nodes; ADC: Apparent diffusion coefficient*

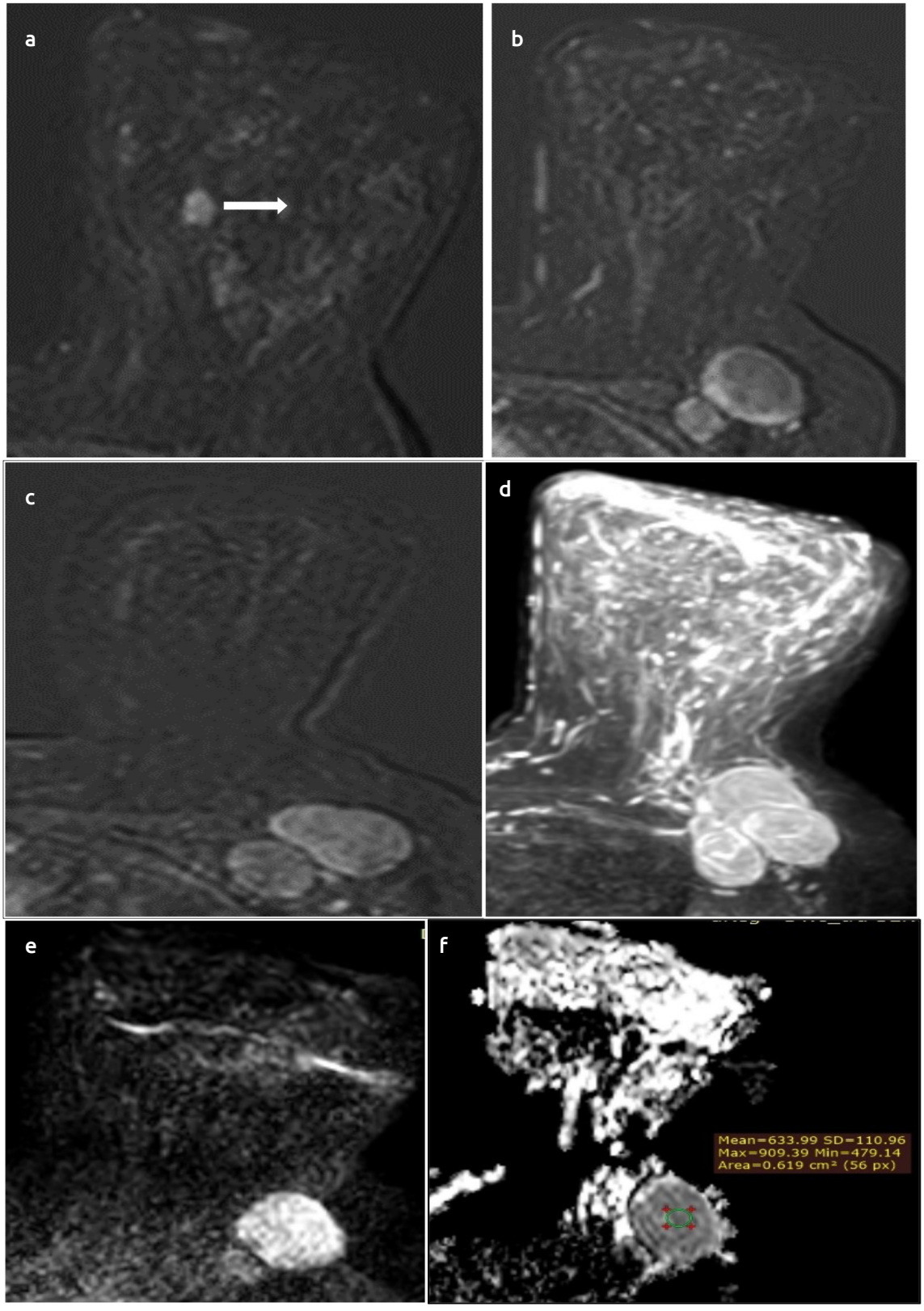


**Figure 8.** Forty-nine years old female patient with triple negative left breast cancer. Post-operative pathology revealed grade II invasive duct carcinoma with scattered foci of high-grade ductal carcinoma *in situ*, with positive lymphvascular invasion and perineural spread. Ki-67 was about 80%, high proliferation index. a. Subtraction post contrast image showing small suspicious mass in left breast (arrow). b, c. Subtraction post contrast images showing enhanced suspicious left axillary LNs. d. subtraction MIP images showing the left axillary LNs. e. Diffusion image showing high SI of the left axillary LN. f. ADC map showing ADC value of the largest suspicious left axillary LN of 0.633 $x10^{-3}$ $mm^2/s$

*LNs: Lymph nodes; ADC: Apparent diffusion coefficient; SI: Sacroiliac; MIP: Maximum intensity projection*

Our results are consistent with the overall sensitivity, specificity in predicting LVI of Kayadibi et al. (38), study who used machine learning and radiomics based on 3D segmentation of ADC maps can be used to predict LVI status in breast cancer in their study, the area under the curve and accuracy were 0.726 and 63.5% in the training data respectively, and (0.732 and 76.7%) in the test data, respectively. Overall sensitivity and positive predictive values were 68% and 69.6% in the training data, and 84.6% and 78.6% respectively in the test data in their study.

We concluded that the ADC value of the ipsilateral enlarged axillary LNs, and Ki-67 status of the tumor were highly correlated to the status of LVI in cases of invasive breast cancer. So, may be used as a tool for prediction of the axillary LN involvement, metastasis, and prognosis of the patients with invasive breast cancer.

### Ethics

**Ethics Committee Approval:** Ethics approval was approved and obtained by Mansoura Faculty of Medicine Institutional Research Board (approval number: R.24.04.2598, date: 18.05.2024).

**Informed Consent:** Informed consent was waived because this was a retrospective, anonymized study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: F.A.S., G.H.A.E.; Concept: A.M.M.; Design: A.M.M., F.A.S.; Data Collection or Processing: A.M.M., G.H.A.E.; Analysis or Interpretation: A.M.M., F.A.S., G.H.A.E.; Literature Search: A.M.M., G.H.A.E.; Writing: A.M.M., G.H.A.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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**Original Article**

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# Male Breast Cancer in Portugal: A Descriptive Analysis of a 20-Year Cohort

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## ABSTRACT

**Objective:** Male breast cancer (MBC) is a rare malignancy, representing less than 1% of all breast cancer cases. Despite the rising incidence, MBC research remains limited, with most data extrapolated from female breast cancer (FBC). This study evaluated the clinicopathological features, treatment strategies, and survival outcomes of MBC patients in Portugal over two decades.

**Materials and Methods:** A retrospective analysis of MBC cases from the Portuguese National Oncology registry (2001-2021) was conducted. Clinicopathological features, therapeutic strategies, and overall survival (OS) were assessed across three disease categories: localized, locally advanced, and metastatic. Hormone receptor status, human epidermal growth factor receptor 2 (HER2) expression, and Ki-67 index were recorded, and survival was estimated using Kaplan-Meier methods.

**Results:** A total of 620 MBC cases were included with median age at diagnosis 68 years (interquartile range: 60–77). Localized disease accounted for 60.3% of the cases, locally advanced for 24.5%, and metastatic 15.2%. Most tumours were invasive carcinoma of no special type (86%), and hormone receptor-positive (estrogen receptor: 96.6%; progesterone receptor: 85.6%). HER2 -disease was noted in 11.6% of cases and triple-negative in 1.6%. Mastectomy was the primary surgical intervention while tamoxifen was the most widely used adjuvant endocrine therapy-exemestane therapy (A-ET). ET was the most prescribed first-line therapy. Median OS was 86 months for localized, 70 months for locally advanced, and 41 months for metastatic disease.

**Conclusion:** This study highlights the unique challenges of MBC, including late-stage diagnoses and reliance on FBC-derived protocols. Findings suggest an urgent need for male-specific clinical trials and molecular research to optimise treatment and outcome. In Portugal increased awareness and early detection initiatives will be important to advance MBC care.

**Keywords:** Breast neoplasm; HER2 protein; hormone receptors; male breast cancer; mastectomy; survival analysis

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### Key Points

- Male breast cancer is rare, accounting for less than 1% of all breast cancer cases, with limited research specific to male patients.
- The majority of tumours were hormone receptor-positive, while human epidermal growth factor receptor 2-positive and triple-negative disease was less common, consistent with female breast cancer subtypes.
- Mastectomy was the primary surgical approach, and tamoxifen was the most commonly prescribed adjuvant therapy.
- This study highlights the need for male-specific clinical trials, increased awareness, and early detection to improve outcomes.

## Introduction

Male breast cancer (MBC) is a rare condition, accounting for less than 1% of all breast cancer (BC) cases worldwide, including in Portugal (1-4). Despite a rising incidence in recent decades (5), research on MBC remains limited, with most data extrapolated from female breast cancer (FBC) studies (6, 7).

MBC is often diagnosed at a later stage, with larger tumours, lymph node involvement, and distant metastases (7-11). Approximately half

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of cases are localized, with the remainder being regional or distant (12, 13). Histologically, invasive carcinoma of no special type accounts for 90% of MBC cases (7, 8, 13, 14), and most tumours express hormone receptors, predominantly of the luminal subtype (13, 15).

Risk factors for MBC include genetic predispositions, such as BRCA2 mutations, hormonal imbalances, and lifestyle factors. Elevated estrogen levels due to obesity, cirrhosis, or Klinefelter's syndrome significantly increase risk (14-20). Due to a lack of male-specific trials, MBC treatment usually follows FBC protocols (13). Surgery, particularly modified radical mastectomy, is the mainstay for early-stage disease, followed by adjuvant therapies. Tamoxifen is the standard treatment for hormone receptor-positive MBC, whereas aromatase inhibitors require additional gonadotropin-releasing hormone agonists for efficacy (21-25). Systemic therapies for metastatic disease are in line with FBC guidelines (Abreu).

MBC prognosis is influenced by delayed diagnosis, older age, and comorbidities (21). Survival outcomes vary by stage and molecular subtype, with early-stage MBC showing better prognoses than metastatic cases (3, 15).

The aim of this study was to analyse the clinical and pathological characteristics, treatment approaches, and survival outcomes of MBC patients in Portugal over two decades, addressing knowledge gaps and highlighting the need for tailored management strategies.

## Materials and Methods

### Patient Selection

We retrospectively collected MBC patients from Portugal's national oncological registry, National Oncology Registry (RON), from January 2001 to December 2021. The study included biologically male patients who had been histologically diagnosed with primary BC. Exclusion criteria included patients with incomplete or absent information about receptor expression on immunohistochemistry (IHC) and those with malignancies of skin origin or sarcoma histology on the breast. Initially, patients with incomplete or absent disease staging information, including clinical (c) and/or pathological (p) tumour node metastasis (TNM) staging, were excluded. However, an amendment to the protocol was made to enhance the cohort's representativeness. Patients with unknown tumour size (T) or nodal status (N) were included in the analysis if the TNM stage was known and other relevant clinical or histological data were available. These cases were explicitly categorised as "T unknown" or "N unknown".

This study was approved by the Data Protection and Ethics Committee of IPO-Porto (Opinion EPD 83/2024, date: 19.04.2024), as well as the RON Committee. The need for individual informed consent was waived due to the retrospective nature of the study and the absence of personally sensitive information.

### Data Collection

The variables collected included the patient's demographics, clinicopathological characteristics of the disease, treatment modalities, such as surgery, systemic therapy, and survival outcomes. The Eastern Cooperative Oncology group (ECOG) performance status and the Charlson comorbidity index were collected according to medical records. Localised disease was defined as tumour staging c/pT1, c/pT2 without lymph node involvement (c/pN0). Locally advanced disease referred to tumours c/pT3 or c/pT4 and/or involving regional lymph nodes (c/pN1 or higher). Metastatic disease was determined/defined when distant metastases were present at diagnosis. Hormone receptors, human epidermal growth factor receptor 2 (HER2) overexpression, and Ki-67 were defined according to the medical record or the histopathological report. Hormone receptors were considered positive if the percentage of positive cancer cells was >1%. Cases with HER2 IHC "0", "1+", and "2+" with fluorescence *in situ* hybridization (FISH) negative were considered as negative. Cases with HER2 IHC "2+" with FISH positive and "3+" were considered positive. Ki-67 was considered positive if the expression was equal to or greater than 20% and negative if it was less than 20%.

Triple-negative disease was defined as cases where hormone receptors [estrogen receptor (ER) and progesterone receptor (PR)] were negative (<1% staining by IHC) and HER2 was considered negative (IHC 0 or 1+, or IHC 2+ with negative FISH testing).

The primary endpoint was overall survival (OS), defined as the time from first pathologic diagnosis to death from any cause or last follow-up. Survival status was defined according to outpatient records on 31 December 2023. Secondary endpoints included disease relapse, defined as any recurrence post-treatment (local, regional, or distant), and progression-free survival (PFS), measured from diagnosis to disease progression or death.

### Statistical Analysis

For continuous variables, the median and respective interquartile range are presented. The underlying normality of data was assessed using the Kolmogorov-Smirnov test with Lilliefors correction. For categorical variables, results are presented as absolute and relative frequencies. Regarding the estimation of OS, the non-parametric Kaplan-Maier estimator was used. Comparisons between survival times for independent groups were performed using the log-rank test. All results with a *p*-value less than 0.05 were considered statistically significant. Data analysis was performed using the software R version 4.2.2.

## Results

### Patient Characteristics

We investigated 1,439 patients diagnosed with MBC from January 2001 to December 2021. Of these, 819 patients were excluded due to insufficient information regarding the disease's staging and/or IHC classification (Figure 1).

The study included 620 men diagnosed with BC. The patients' characteristics are presented in Tables 1A-1C. The median age at diagnosis was 68 (60–77) years. Median ECOG performance status was 1 (0–1), and the median Charlson comorbidity index was 2 (2–2) across the entire cohort. Geographically, as presented in Figure 2, most cases were located in Lisbon (38.1%), followed by Setubal (12.4%) and Oporto (8.4%). Of all 620 MBC cases, 60.3% of patients were classified as having localized disease, 24.5% locally advanced disease, and 15.2% metastatic disease. Most patients presented with cT1 or cT2 (24.7% and 29.5%, respectively) and had ER/PR-positive disease without HER2 expression (85.3%), while 12.7% had ER/PR/HER2-positive disease. Two patients presented with HER2-overexpressing MBC, and 10 had triple-negative disease. The median OS in the overall population was 70 months [95% confidence interval (CI): 58–87]. Patients with luminal-like disease had a median OS of 68 months (95% CI: 56–87). Those with ER/PR/HER2-positive disease had a

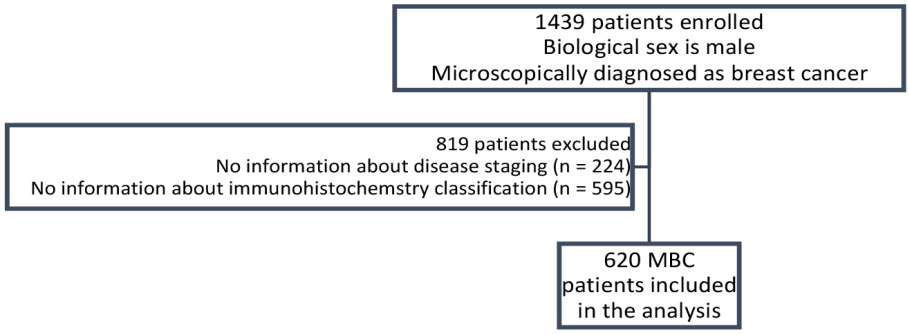


**Figure 1.** Flowchart outlining the patient selection criteria for MBC incidence across Portugal

*MBC: Male breast cancer*

**Table 1A. Clinical and pathological characteristics of the study population**

| Variable | Overall population (*n* = 620) |
|---|---|
| Median age (IQR) | 68.0 (60.0–77.0) |
| **ECOG performance status** | |
| 0 | 200 (32.3%) |
| 1 | 62 (10.0%) |
| 2 | 18 (2.9%) |
| 3 | 10 (1.6%) |
| 4 | 7 (1.1%) |
| Unknown | 323 (52.1%) |
| Charlson comorbidity index (median, IQR) | 2.0 (2.0–2.0) |
| **Tumor topography** | |
| Central portion (subareolar) | 236 (38.1%) |
| Unspecified breast | 189 (30.5%) |
| Overlapping regions | 102 (16.5%) |
| Upper outer quadrant | 43 (6.9%) |
| Other regions | 48 (7.7%) |
| Unknown | 2 (0.3%) |
| **Histology** | |
| Non-special type carcinoma | 533 (86.0%) |
| Lobular carcinoma | 26 (4.2%) |
| Other histologies | 41 (6.6%) |
| Unknown | 20 (3.2%) |
| **Receptor Status** | |
| ER positive/negative | 599 (96.6%)/21 (3.4%) |
| PR positive/negative/unknown | 531 (85.6%)/53 (8.6%)/36 (5.8%) |
| HER2 positive/negative/unknown | 72 (11.6%)/463 (74.7%)/85 (13.7%) |
| **Ki67** | |
| ≥ 20% | 437 (70.5%) |
| Unknown | 183 (29.5%) |
| **Grade** | |
| 1 | 73 (11.8%) |
| 2 | 367 (59.2%) |
| 3 | 132 (21.3%) |
| Unknown | 48 (7.7%) |
| **T Stage** | |
| T0/is | 11 (1.8%) |
| T1 | 153 (24.7%) |
| T2 | 83 (13.4%) |
| T3 | 36 (5.8%) |
| T4 | 30 (4.8%) |
| Unknown | 207 (33.4%) |
| **N stage** | |
| N0 | 175 (28.2%) |
| N1 | 167 (26.9%) |
| N2 | 45 (7.3%) |
| N3 | 8 (1.3%) |
| Unknown | 225 (36.3%) |
| **Stage at diagnosis** | |
| Stage I | 222 (35.8%) |
| Stage II | 152 (24.5%) |
| Stage III | 152 (24.5%) |
| Stage IV | 94 (15.2%) |
| Overall survival (median, 95% CI, months) | 70 (58-87) |

CI: Confidence interval; ER: Oestrogen receptor; HER-2: Human epidermal growth factor receptor 2 disease; IQR: Interquartile range; N: Nodal; PR: Progesterone receptor; T: Tumour; ECOG: Eastern cooperative oncology group; IQR: Interquartile range

**Table 1B. Disease stage and treatment modalities**

| Variable | Localized (*n* = 374) | Locally advanced (*n* = 152) |
|---|---|---|
| **Surgery performed** | | |
| Mastectomy[a] | 360 (96.3%) | 136 (89.5%) |
| Breast-conserving surgery | 14 (3.7%) | - |
| Unknown | - | 16 (10.5%) |
| **Surgical radicality** | | |
| R0 | 22 (5.9%) | 4 (2.6%) |
| Unknown | 352 (94.1%) | 148 (97.4%) |
| **Adjuvant endocrine therapy** | | |
| Tamoxifen | 213 (57.0%) | 83 (54.6%) |
| Anastrozole | 11 (2.9%) | 2 (1.3%) |
| ET+GnRHa | 14 (3.7%) | 4 (2.6%) |
| Letrozole | 6 (1.6%) | - |
| Switch ai to tamoxifen (or vice versa) | 5 (1.3%) | 4 (2.6%) |
| Unknown | 125 (33.4%) | 59 (38.8%) |
| Disease recurrence | 12 (3.2%) | 12 (7.9%) |
| Overall survival (median, 95% CI, months) | 86 (62-106) | 70 (53-94) |

a: The specific type of mastectomy (modified radical, nipple-sparing, skin sparing or radical mastectomy) was not consistently reported in the dataset
ET: Endocrine therapy; CI: Confidence interval; ET+GnRHa: Endocrine therapy combined with gonadotropin-releasing hormone agonist; R0: Complete resection

**Table 1C. Survival outcomes and metastatic treatment**

| Variable | Metastatic (*n* = 94) |
|---|---|
| Metastatic sites | |
| Bone | 36 (38.3%) |
| Lung/pleura | 25 (26.6%) |
| Liver | 11 (11.7%) |
| Skin | 7 (7.4%) |
| Unknown | 15 (16.0%) |
| Systemic treatment (first-line) | 32 (34.0%) |
| Fulvestrant | 8 (25%) |
| Letrozole | 2 (6.3%) |
| Exemestane | 1 (3.1%) |
| Ribociclib + letrozole | 5 (15.6%) |
| Palbociclib + letrozole | 2 (6.3%) |
| Taxane + double blockade | 6 (18.8%) |
| Taxane monotherapy | 4 (12.5%) |
| Taxane - anthracycline sequence | 2 (6.3%) |
| Taxane - platinum combination | 2 (6.3%) |
| Systemic treatment (second-line) | 12 (12.9%) |
| Fulvestrant | 5 (41.7%) |
| Letrozole | 1 (8.3%) |
| Capecitabine | 3 (25.0%) |
| Everolimus + fulvestrant | 1 (8.3%) |
| Sacituzumab-govitecan | 1 (8.3%) |
| Vinorelbine | 1 (8.3%) |
| Overall survival (median, 95% CI, months) | 41 (25–65) |

CI: Confidence interval

median OS of 80 months (95% CI: 45-NA). For patients with triple-negative disease, three death events occurred, and the median OS was 119 months (95% CI: NA; NA). Regarding the two patients with HER2-overexpressing disease, one died one month after diagnosis, and the other was alive at the end of follow-up. Kaplan-Meier survival curves for each stage and each subtype are presented in Figure 3 and Figure 4.

### Localized Disease

The median age for patients with localised disease was 67 (60–76) years. Regarding IHC subtypes, 85.6% were classified as luminal-like disease, 12.6% as luminal-like with HER2-positive, 0.3% as HER2-overexpression and 0.8% as triple negative disease. Most patients with localized disease underwent mastectomy (96.3%) while a smaller proportion underwent breast-conserving surgery (3.7%). Tamoxifen was the most commonly prescribed adjuvant endocrine therapy (A-ET), used in 57.0%, as summarized in Table 1B. Anastrozole was the second most prescribed ET, used in 2.9% of the patients. The combination of ET with gonadotrophin-releasing hormone analogue (GnRHa) was used in 3.7% of the cases, while letrozole alone was used in 1.6%. Adjuvant therapy data was missing in 33.4% of the patients. Disease relapse was experienced in 12 patients. The median OS was 86 months (95% CI: 62–106).

### Locally Advanced Disease

The median age for patients with locally advanced disease was 71 (61–78) years. As in localized disease, locally advanced tumours were predominantly luminal-like (84.9%) subtypes. Luminal-like HER2-positive disease was present in 11.2% of cases, while HER2 overexpression and triple-negative subtypes accounted for 0.7% and 2.0%, respectively. Most patients with locally advanced disease underwent mastectomy (89.5%), as presented in Table 1B. However, the type of surgery was not documented in 10.5% (n=16). Regarding A-ET, tamoxifen was the most commonly used adjuvant treatment, similarly to localised disease, prescribed to 54.6% of patients. A combination of ET with a GnRH analogue was used in 2.6% of patients, as well as a switch in therapy between aromatase inhibitors and tamoxifen (or vice versa). Adjuvant treatment data was missing in 38.8% of the cases. Data regarding neoadjuvant/adjuvant chemotherapy was missing in all cases. Disease relapse was experienced in 12 patients. Concerning survival, patients with locally advanced disease had a median OS of 70 months (95% CI: 53–94).

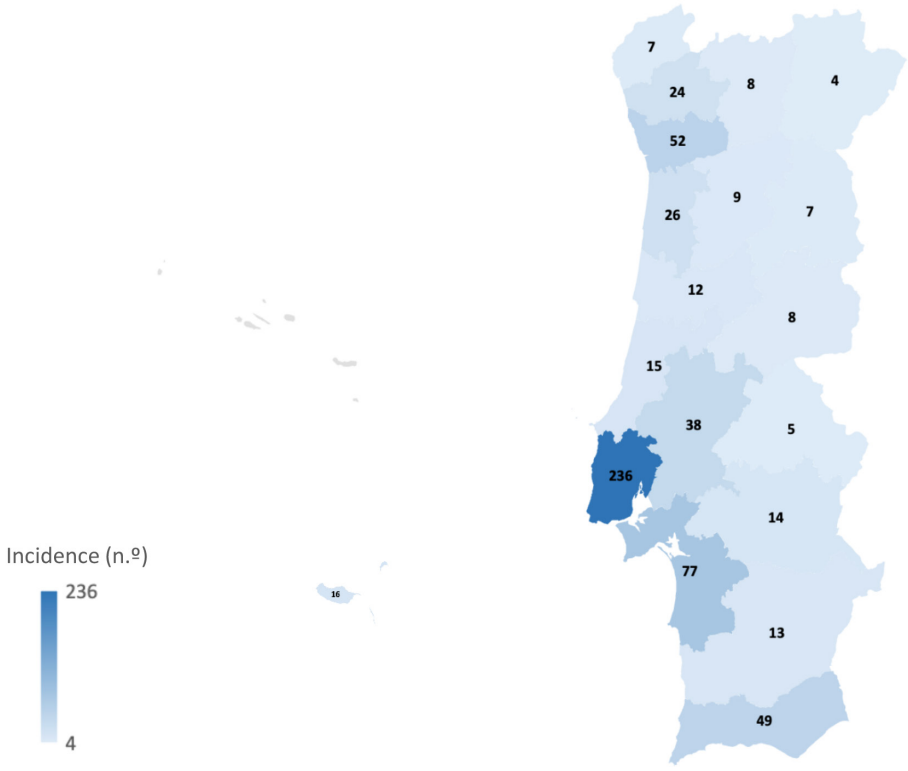


**Figure 2.** Map illustrating the incidence (n.º) of MBC across districts in Portugal between January 2001 to December 2021

*MBC: Male breast cancer*

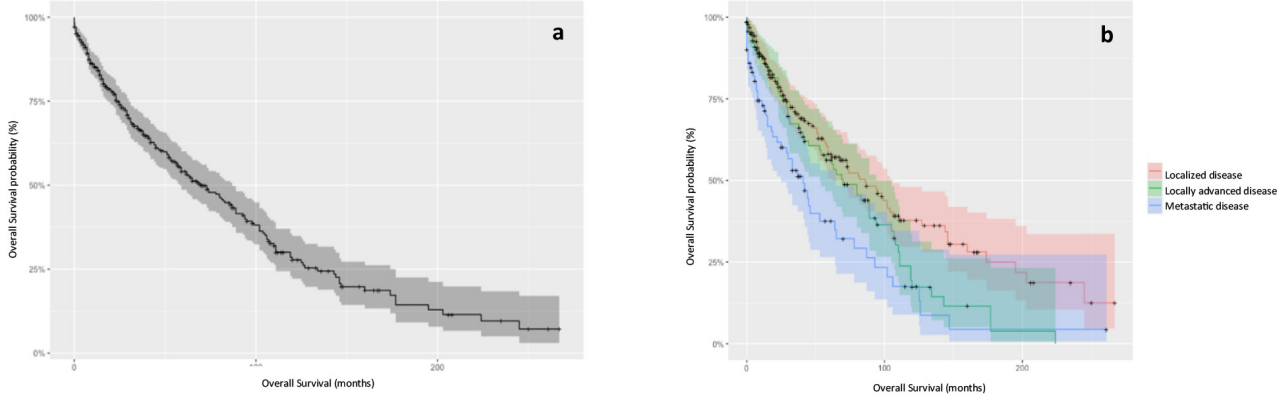


**Figure 3.** Kaplan-Meier curves for overall survival for MBC patients. (a) Depicts the total population. (b) Depicts patients with localized, locally advanced and metastatic disease

*MBC: Male breast cancer*

### Metastatic Disease

The median age at diagnosis for metastatic disease was 68 (58-78) years. The most frequent sites of metastases were bone (38.3%), lung/pleura (26.6%), and liver (11.7%), as detailed in Table 1C. Regarding IHC subtypes, 88.3% of the patients had luminal-like disease, 6.4% had luminal-like with HER2 co-expression and 4.3% triple negative-like. The information about systemic treatment was available in 32 (34%) of metastatic disease patients. Of those, 11 received ET as a first-line treatment, eight fulvestrant, two letrozole and one exemestane. Seven patients were treated with cyclin-dependent kinase 4/6 inhibitors (iCDK4/6) in combination with endocrine therapy: five patients with the combination of ribociclib and letrozole and two with palbociclib and letrozole. The remaining patients received chemotherapy as first-line treatment. Disease progression on first-line therapy was reported in twelve patients; of those, six received second-line ET. The median duration of first-line treatment for metastatic disease was 5 (3.3–6.7) months. Due to small numbers and incomplete/absent data, median PFS calculation was not performed. In addition, one patient with ER/PR-positive disease was treated with PARP inhibitors, with a presumed BRCA pathogenic variant, though no direct confirmation was available in the database. The median OS for metastatic disease was 41 months (95% CI: 25–65).

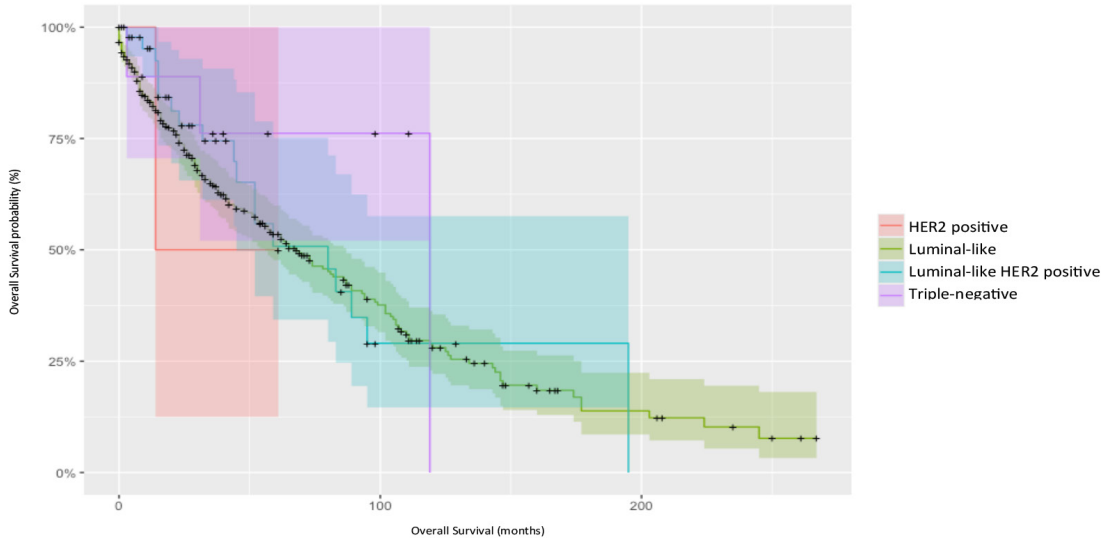


**Figure 4.** Kaplan-Meier curves for overall survival for MBC patients, stratified by IHC subtypes

*HER2: Human epidermal growth factor receptor 2 disease; IHC: Immunohistochemistry; MBC: Male breast cancer*

## Discussion and Conclusion

This study comprehensively analysed MBC patients in Portugal over two decades, highlighting this rare malignancy's clinical and pathological characteristics, treatment modalities, and survival outcomes. Our findings corroborate established MBC trends while providing valuable insights into specific characteristics observed within this study population. MBC was predominantly diagnosed in older men, with a median age of 68 years. Our findings are consistent with previous literature and earlier Portuguese studies, which reported median ages ranging from 63 to 68 years (2, 3, 15, 26, 27). These results underscore the consistent pattern of older age at diagnosis in MBC compared to FBC. Furthermore, within our cohort a significant proportion of patients presented with localised or locally advanced disease, while 15.2% were diagnosed with metastatic disease. The proportion of patients with metastatic disease in this study markedly exceeds international reports (3.8%) and national averages (7.2%) (13, 15). The higher prevalence of advanced-stage disease may reflect delays in recognition and diagnosis, underscoring the pressing need for heightened awareness among both patients and healthcare providers.

In terms of histopathological characteristics, invasive carcinoma of no special type accounted for the majority of cases, in line with prior Portuguese and global studies (3, 7, 8, 14, 15). Hormone receptor positivity was highly prevalent, with ER positive and PR positive-disease exceeding 90% across all stages. This aligns with findings by Abreu et al. (15) and André et al. (3), who reported ER-positivity rates of 91–95% and PR-positivity rates of 75–89%. HER2-positivity was observed in approximately 11.6% of cases, corresponding to rates of 6.8–8.1% reported in earlier studies (28). Triple-negative-like disease was rare, at 1.6%, matching the previously reported range of 0.3–3.2%, further emphasising the differences between MBC and FBC (3, 13).

Concerning treatment patterns, surgical intervention remained central to MBC management, with mastectomy being the most commonly employed approach. This strategy is consistent with established treatment guidelines and findings from previous global and Portuguese studies, which highlight the anatomical constraints of the male breast that limit the feasibility of breast-conserving surgery (15, 21, 22). A-ET, particularly tamoxifen, was widely used and reflects the predominance of hormone receptor-positive tumours (13, 15). These findings underscore the continued reliance on extrapolated FBC protocols due to the scarcity of male-specific evidence.

The median OS in our cohort was 70 months, markedly lower than the global median OS of 10.4 years reported by Cardoso et al. (13). According to the methodology of our study, localized disease was defined as c/pT1 or c/pT2 and c/pN0; locally advanced disease as c/pT3 or c/pT4 and/or c/pN1 or higher, and metastatic disease as the presence of distant metastases at diagnosis. These methodological differences in disease classification at presentation may partly explain the observed disparity in survival outcomes. Specifically, the median OS for localized disease was 86 months (95% CI: 62–106), while patients with locally advanced disease had a median OS of 70 months (95% CI: 53–94). The median OS for metastatic disease was notably lower, at 41 months (95% CI: 25–65). While direct comparison with global literature is limited, Cardoso et al. (13) reported a median OS of 10.4 years (95% CI: 8.8–11.8) for early-stage disease (N0M0), 8.4 years (95% CI: 7.1–9.4) for N-positive, M0 disease, and 2.6 years (95% CI: 2.0–3.7) for M1 disease (13).

Notable variations in survival outcomes were observed across subtypes. For instance, luminal-like disease demonstrated a median OS of 68 months, which is significantly lower than the 10.5 years reported by Abreu et al. (15). Paradoxically, triple-negative-like disease exhibited an unexpectedly high median OS of 119 months, contrasting with the poor prognosis typically associated with this subtype, as evidenced in earlier studies (1.3 years) (15). These findings may be attributed to the small sample size of triple-negative cases and the limited number of deaths (three) recorded. Of the two patients with HER2-overexpressing disease, one succumbed 14 months after diagnosis. However, the small sample sizes of these subtypes constrain the robustness of our analysis and limit comparisons with existing literature.

Notably, factors such as tumour size greater than 2 cm and nodal involvement, which have been highlighted as significant prognostic factors in previous Portuguese studies by Abreu et al. (15, 28-30) were

not observed to have a similar impact on survival outcomes in our cohort.

Over the past two decades, advances in systemic therapy have redefined BC treatment and may hold significant potential for MBC. CDK4/6 inhibitors have become the standard of care for hormone receptor-positive disease, improving survival and disease control. Novel HER2-targeted therapies, such as antibody-drug conjugates and tyrosine kinase inhibitors, have expanded options for HER2-positive patients, while immune checkpoint inhibitors have enhanced outcomes in triple-negative BC. Despite these advances in FBC, their impact on MBC remains unclear, highlighting once again the need for further research.

**Study Limitations**

This study has several limitations that warrant consideration. The retrospective design restricts the ability to establish causal relationships and depends on the completeness of medical records, which may introduce reporting biases. A substantial proportion of patients (819 out of 1439) were excluded due to insufficient information on disease staging ($n$ = 224) or IHC classification ($n$ = 595), potentially leading to selection bias and limiting the generalizability of the findings. Despite this, an analysis of the excluded cohort revealed that their basic demographic and clinical characteristics, such as mean age at diagnosis (67.5 years, standard deviation 12.2), tumour topography (predominantly central region of the breast, 38.1%), and morphology (86% carcinoma SOE), were comparable to those of the included cohort. This suggests that the potential impact of selection bias may be mitigated. A substantial number of included cases (33.4% for tumour size and 36.3% for nodal status) had staging information classified as "unknown". To improve representativeness, these patients were included in the analysis if their TNM stage was known and relevant clinical or histological data were available. This approach reduced the loss of valuable information but highlights the challenge of data collection during the study period. Moreover, these findings underscore the importance of improving national cancer registries to enhance data collection on staging and disease characteristics. Strengthening cancer registries will support more accurate epidemiological studies and inform clinical decision-making in MBC. Another limitation of our study was that while mastectomy was the predominant surgical approach, the specific type of procedure (simple, modified radical, or radical) was not consistently reported in the dataset. This lack of detail prevents a more granular analysis of surgical outcomes. Moreover, the study did not include molecular subtyping, such as genetic profiling or analysis of genomic alterations, which constrains its capacity to explore the molecular landscape and heterogeneity of MBC. Key factors such as BRCA mutation status, androgen receptor expression, and other emerging biomarkers were not assessed, limiting insights into the genetic and epigenetic underpinnings of MBC. While trends associated with age, ECOG score, and Charlson index were identified, none achieved statistical significance, possibly due to the sample size or cohort heterogeneity, highlighting the need for further research with larger datasets. In addition, systemic therapy data for metastatic patients were incomplete, with detailed information available for only 26.6% of cases, potentially skewing the analysis of treatment efficacy. Moreover, the absence of comprehensive data on relapse management for localized and locally advanced cases hinders a complete understanding of long-term treatment outcomes. These limitations emphasize the critical need for better policies. National Registries must have the capacity to use data very effectively in order to support public health policy proposals and inform political decisions. Prospective, male-specific studies like EORTC 10085/TBCRC/BIG/NABCG International MBC Program that is ongoing, are eagerly awaited to better understand and manage MBC. This study emphasised the unique characteristics and challenges associated with managing MBC. Despite its rarity, MBC presents a complex interplay of late-stage diagnosis, hormonal receptor expression, and comorbidities that influence outcomes. While current treatment strategies rely heavily on FBC cancer protocols, this study highlights the need for dedicated male-specific research to optimise treatment and improve survival outcomes. Efforts should focus on early detection programs and male-specific clinical trials to address these unique challenges. While routine screening for MBC is not widely recommended due to its low incidence, high-risk individuals "particularly BRCA mutation carriers" require targeted surveillance strategies. According to National Comprehensive Cancer Network and European Society for Medical Oncology guidelines, men with BRCA1 or BRCA2 mutations should undergo annual clinical breast exams from age 35 years and perform regular breast self-examinations (31-33). Mammography is not routinely advised but may be considered in cases of gynecomastia or palpable abnormalities (31-33). Given the challenges in early detection and the limited MBC-specific evidence, further research is needed to refine screening protocols and improve outcomes in high-risk male populations. In parallel, a deeper understanding of the molecular landscape of MBC is essential to identify targeted treatment opportunities. Future studies should explore the role of personalized treatment approaches, paving the way for tailored therapeutic strategies and improved patient care.

To conclude, we advocate for action to support potential initiatives like using advanced technologies such as artificial intelligence to improve national clinical data management. Aligned with European Union publications (EU health data centre and a common data strategy for public health, 2021), we urge the need to endorse policy options on how to set up health data centres with a common strategy for health data, as a way to achieve a public health datafication multi-level process. This would also create a central coordination and support structure together with advanced digital public health functions, having the potential to alter public health significantly, including for MBC.

## Ethics

**Ethics Committee Approval:** This study was approved by the Data Protection and Ethics Committee of IPO-Porto (Opinion EPD 83/2024, date: 19.04.2024), as well as the RON Committee.

**Informed Consent:** The need for individual informed consent was waived due to the retrospective nature of the study and the absence of personally sensitive information.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: M.A.M., S.D.O.; Concept: M.A.M., S.D.O.; Design: M.A.M., T.D.G., S.D.O.; Data Collection or Processing: M.A.M., T.D.D., T.D.G.; Analysis or Interpretation: M.A.M., T.D.D., T.D.G., R.Q.F.; Literature Search: M.A.M., R.Q.F., I.T.F., D.C.S., L.F., S.D.O., R.E., F.R.V.; Writing: M.A.M., T.D.D., T.D.G., R.Q.F., I.T.F., D.C.S., L.F., S.D.O., R.E., F.R.V.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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**Original Article**

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# Health-Related Quality of Life in Breast Cancer Patients during Chemotherapy: A Cross-Sectional Study Using the EORTC QLQ-C30 and BR45

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## ABSTRACT

**Objective:** To assess health-related quality of life (HRQoL) using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Breast Cancer (EORTC QLQ-BR45) in conjunction with the Core questionnaire (EORTC QLQ-C30) in breast cancer patients receiving chemotherapy.

**Materials and Methods:** This prospective, cross-sectional study was conducted in the oncology department of a tertiary care hospital for six months. Patients aged ≥18 years, diagnosed with breast cancer, and who had received at least three chemotherapy cycles were included in the study. The EORTC (QLQ-BR45 and QLQ-C30) questionnaires were used to assess HRQoL at chemotherapy cycle 3 (C3) and at C6 and C9. Data were analyzed using the Mann-Whitney U and Friedman tests for significance ($p$<0.05).

**Results:** The study showed improved global health status (C3:37.29%, C6:42.37%, C9:50%), high cognitive functioning (C3:89.83%, C6:91.53%, C9:96.55%), but decreasing emotional functioning (C3:66.10%, C6:49.15%, C9:36.21%). Symptom burden peaked in the sixth cycle but diminished over time with a trend towards fatigue (C3:64.41%, C6:67.80%, C9:37.93%), dyspnea (C3:54.24%, C6:55.93%, C9:32.76%), and pain (C3:42.37%, C6:52.54%, C9:34.48%). The study indicated satisfaction with body image (C3:61.02%, C6:67.80%, C9:67.24%) but decreased sexual functioning (C3:40.68%, C6:44.07%, C9:46.55%). Distress related to hair loss ($p$ = 0.0001) increased over time.

**Conclusion:** There was increased symptom burden at C6, underscoring the need for early interventions. We observed severe symptoms in elderly. However, lack of comorbidities and metastasis improved the emotional wellbeing in patients. These findings accentuate the importance of personalized and holistic care approaches in oncology.

**Keywords:** Breast cancer; EORTC QLQ-BR45; EORTC QLQ-C30; health-related quality of life; PROM

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### Key Points

- Younger patients and those who had surgery reported better functional outcomes, whereas older patients reported more severe symptoms, highlighting the need for age-specific treatment measures.
- The absence of comorbidities and metastasis was associated with improved emotional functioning, but there were challenges, such as increased insomnia.
- Symptom burden peaked during the sixth cycle of chemotherapy before progressively reducing, underscoring the need for early interventions to manage symptoms effectively.

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## Introduction

Breast cancer is the most prevalent cancer worldwide, surpassing lung cancer by 11.7% in 2020 (1). It has among the highest per-patient expenditures in the health-care system and is diagnosed in one out of every eight women during their lifetime (2). In practically all constituent nations, it is one of the top three causes of early mortality (30–69 years) (3). According to a population-based study from the United States Cancer Statistics database, from 2010 through 2014, over 2.64 million cases and 1.7 million deaths from breast cancer will occur worldwide by 2030 (4, 5).

India has witnessed an estimated incidence of 13.5% of breast cancer cases and a 10.6% death rate, resulting in a cumulative risk of 2.81%, according to Globocan data 2020 (1). The Indian Ministry of Health and Family Welfare recorded 14,726/1,42,283 new cases in 2016, 15,522/1,50,842 in 2017, and 16,358/1,59,924 in Maharashtra in 2018. This demonstrates a clear increase in breast cancer cases in recent times (6). However, more advanced screening methods have made it possible to diagnose breast cancer sooner, and as new treatment choices have emerged, breast cancer survival has increased (7). Patients with breast cancer now have much-improved prognoses and outcomes, with a 10-year survival rate of approximately 78% (8). Depending on the site of metastasis, new therapeutic modalities have led to increased survival of patients with metastatic breast cancer. Approximately 90% of women who have breast cancer live for at least five years following their diagnosis (7). As a result of this advance, more breast cancer patients experience the short- and long-term effects of their disease and treatment, which has shifted the focus of care from immediate treatment outcomes to long-term health-related quality of life (HRQoL) (8).

HRQoL has emerged as a primary clinical outcome in cancer research over the past few decades. It encompasses physical, psychological, and social functioning and disease- and treatment-related symptoms (9, 10). QoL has also been acknowledged as a major outcome in clinical trials, potentially enhancing patient satisfaction and treatment effects (11, 12). Measuring QoL in cancer patients is important for predicting treatment responses, estimating survival times, and identifying common issues. Although QoL generally improves over time after breast cancer diagnosis, survivors often report worse QoL than healthy women and experience symptoms, such as sleep disturbance, cognitive impairment, fatigue, and various physiological reactions, including pain, nausea, vomiting, hair loss, and skin changes (13).

With improved survival rates, understanding the evolving needs of breast cancer patients has become more important. Although many studies have evaluated patients QoL, few have comprehensively examined patients from diagnosis to >10 years post-treatment, considering factors such as age, cancer stage, and treatment history (7). Moreover, there is little literature on QoL during active therapy, except for studies on the positive impact of breast conservation surgery on body image.

The aim of this study was to evaluate the HRQoL of breast cancer patients undergoing chemotherapy using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Breast Cancer (EORTC QLQ-C30), a general cancer-specific questionnaire that offers a comprehensive assessment of key QoL domains, and the EORTC QLQ-BR45, a breast cancer-specific module designed to examine disease and treatment-related factors. It was hoped that this investigation would facilitate an in-depth exploration of QoL determinants and identifying critical areas for targeted intervention in breast cancer patients undergoing chemotherapy.

## Materials and Methods

This prospective, cross-sectional study was conducted at the oncology department of a tertiary care hospital and was approved by the Institutional Ethics Committee of Bharati Hospital & Medical College, Pune (approval number: BVDUMC/IEC/23, date: 07.11.2023). The study was conducted over a period of six months from November 2023 to May 2024. Informed consent was obtained from all individual participants included in the study.

### Inclusion Criteria

Patients aged 18 years and above, diagnosed with breast cancer and receiving chemotherapy, regardless of the stage of diagnosis, and who completed at least three cycles of chemotherapy were eligible for inclusion.

### Exclusion Criteria

Patients who had undergone surgical intervention without subsequent administration of chemotherapy and those who refused to provide consent to participate in the study were excluded.

### Study tool

HRQoL was assessed using the EORTC QLQ-C30 version 3 and QLQ-BR45 Breast Phase IV module (14).

The EORTC QLQ-C30 consists of 30 questions that evaluate QoL based on physical, psychological, and social status. The three main components are: functional scales, physical, role, emotional, cognitive, and social functioning; symptom scales, fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial issues; and Global Health Status, which is an overall assessment of the patient's health and quality of life, offering a holistic view of well-being.

The EORTC QLQ-BR45 consists of 45 questions specifically designed for patients with breast cancer and evaluates both symptomatology and functional aspects. The functional scales included body image, breast satisfaction, sexual function, sexual enjoyment, and future perspectives. Symptom scales include systemic therapy side effects, hair loss concerns, arm symptoms, breast symptoms, endocrine therapy-related symptoms, skin mucosis symptoms, and endocrine sexual symptoms.

The EORTC QLQ-C30 and EORTC QLQ-BR45 scoring manuals were used to calculate the scores, and the range of responses was from 1 (not at all) to 4 (very much). The patient's health state and overall quality of life were the two questions used to assess the patient's global health status, with ratings ranging from one (very poor) to seven (excellent).

Both questionnaires were completed by all participants after the third chemotherapy cycle (C3) and after the subsequent sixth and ninth cycles (C6 and C9, respectively).

### Statistical Analysis

All data were collected using Microsoft Office Excel 2019 for preliminary analysis. Continuous variables are represented as mean and standard deviation, and categorical variables are expressed as frequencies and percentages. Statistical analyses were performed using

SPSS, version 20 (IBM Inc., Armonk, NY, USA). The Mann-Whitney U test was used to compare the distribution of questionnaire scores between the patient groups, with significance set at $p<0.05$. The Friedman test was used to detect repeated measurement differences between the different cycles (C3 *vs.* C6 *vs.* C9).

## Results

This was a prospective, cross-sectional study that assessed HRQoL among female patients with breast cancer undergoing chemotherapy. Of the 206 patients with cancer admitted to the oncology ward during the study period, 64 patients with breast cancer received chemotherapy. From this group, 58 patients met the study criteria, participated in the study, and completed both questionnaires at three consecutive follow-up points, C3, C6 and C9.

The mean age of participants was 54.6±11.2 years, with more than a third (34.4%) being over 60 years old. Most of the participants had completed primary school (55.5%), were professionally inactive (91.3%), lived in urban areas (62%), and were married (86.2%). A small fraction of the patients were tobacco chewers (13.7%), while only one patient (1.7%) reported alcohol consumption. A significant percentage of patients experienced loss of appetite (75.8%) and changes in food taste (70.6%). Body mass index analysis revealed that 53.4% of patients were within the normal weight range, 3.4% were underweight, and 13.7% were obese.

All patients received chemotherapy (100%), with 56.8% undergoing surgery, and one patient (1.7%) received radiotherapy. Postmenopausal status was prevalent in 89.6% of patients, while 10.3% were premenopausal. Comorbidities were reported by 36.2% of patients, and the majority (81%) did not show any signs of metastasis. The sociodemographic characteristics of patients are presented in Table 1.

### EORTC QLQ-C30 and BR45 Scores at the Third, Sixth, and Ninth Cycles of Chemotherapy

In the analysis of the QLQ-C30 questionnaire, reported global health status improved throughout treatment, with scores increasing from 54.17 in C3 to 56.75 in C6, and 60.09 in C9. Significant improvements were noted across multiple functional domains following the third cycle of chemotherapy**.** Specifically, physical ($p = 0.026$), emotional ($p = 0.002$), social ($p = 0.002$), and cognitive functioning ($p = 0.006$) scores showed significant improvement in C6 and C9. Although reported role functioning showed a slight decline, this was not significant.

Symptom scales revealed statistically and clinically significant changes. There was an increasing trend in rported fatigue ($p = 0.028$) and dyspnea ($p = 0.012$) as treatment progressed. Conversely, several other symptoms were reported to improveme after C3. Significant improvements were noted in scores for nausea and vomiting ($p<0.001$), pain ($p = 0.008$), appetite loss ($p<0.001$), constipation ($p<0.001$), and diarrhea ($p = 0.001$), which collectively contributed to a lower overall symptom burden for patients as they progressed through their chemotherapy regimen.

Several statistically significant changes were also observed in the QLQ-BR45 scores over the three time points. Patients reported a modest reduction in future worries ($p = 0.043$), indicating a slightly more positive outlook as the treatment advanced. However, distress related to hair loss emerged as a prominent concern with a highly significant increase ($p<0.001$). In addition, significant improvements in reported arm symptoms ($p = 0.008$), breast symptoms ($p = 0.001$), endocrine therapy symptoms ($p = 0.001$), and skin mucosis symptoms ($p<0.001$) were observed, all of which demonstrated marked reductions in the subsequent cycles when compared to C3 responses (Figure 1 and Table 2).

### Analysis of Demographic Factors and Associations With EORTC

**Table 1. Socio-demographics characteristics of breast cancer patients ($n = 58$) undergoing therapy at the third chemotherapy cycle which was equivalent to this study baseline**

| Characteristics | Variables | Number (%) |
|---|---|---|
| Age (in years) | 18–40 | 5 (8.6) |
| | 41–50 | 19 (32.7) |
| | 51–60 | 14 (24.1) |
| | >60 | 20 (34.4) |
| | Mean ± standard deviation | 54.6±11.2 |
| Education | Illiterate | 4 (6.8) |
| | Primary school | 32 (55.1) |
| | Secondary school | 17 (29.3) |
| | Above secondary school | 5 (8.6) |
| Occupational status | Professionally inactive | 53 (91.3) |
| | Professionally active | 5 (8.6) |
| Residence | Urban | 36 (62) |
| | Rural | 22 (37.9) |
| Marital status | Married | 50 (86.2) |
| | Widowed | 8 (13.7) |
| Social behaviors | Tobacco chewer | 8 (13.7) |
| | Alcohol consumer | 1 (1.7) |
| Food habits | Loss of appetite | 44 (75.8) |
| | Normal appetite | 14 (24.1) |
| | Change in taste | 41 (70.6) |
| Body mass index (in kg/m²) | Underweight (<18.5) | 2 (3.4) |
| | Normal weight (18.5–24.9) | 31 (53.4) |
| | Overweight (25–29.9) | 17 (29.3) |
| | Obese (30–39.9) | 8 (13.7) |
| Treatment | Chemotherapy | 58 (100) |
| | Surgery | 33 (56.8) |
| | Radiotherapy | 1 (1.7) |
| Comorbidity | Yes | 21 (36.2) |
| | No | 37 (63.7) |
| Menopausal status | Postmenopausal | 52 (89.6) |
| | Premenopausal | 6 (10.3) |
| Metastasis | No | 47 (81.0) |
| | Yes | 11 (18.9) |

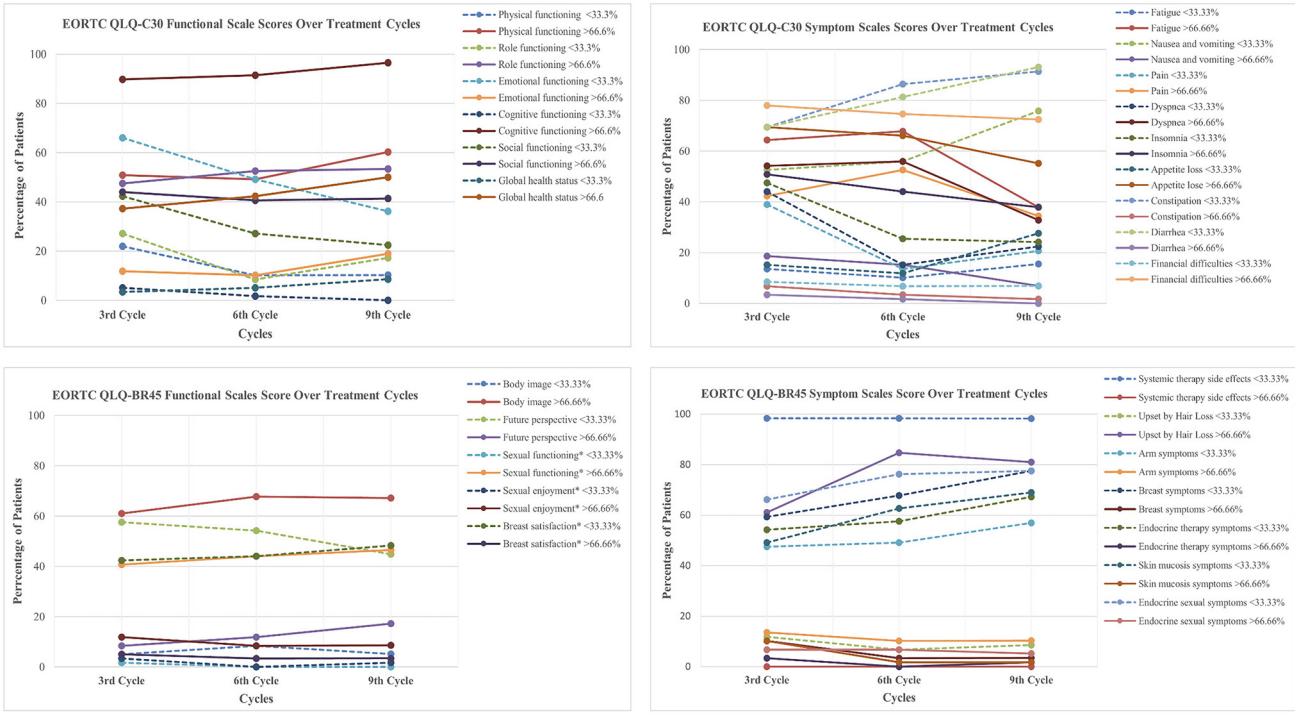


**Figure 1.** The EORTC QLQ-C30 and EORTC QLQ-BR45 scores (cycles three, six, and nine)

*A higher score on functional scales indicates better functioning, while a higher score on symptom scales indicates worse functioning. Scoring <33.33% suggests a significant deterioration in QoL, while a score >66.66% indicates an improved QoL. Scoring <33.33% suggested a lower symptom burden, and scoring >66.66% indicated a significant symptom burden. Sexual enjoyment: applicable only to sexually active patients in the last four weeks before responding to the questionnaire. Upset by hair loss: applicable only to patients who have observed hair loss in the last week of responding to the questionnaire. Breast satisfaction: applicable only to patients who underwent surgery. *Reverse scoring items.*

### QLQ-C30 Scores

Patients aged <50 years and those who had undergone surgery reported better physical functioning scores ($p$ = 0.004 and $p$ = 0.044, respectively). Cognitive functioning scores were also higher in patients aged <50 years ($p$ = 0.015). However, this group of patients reported an increasing concern with fatigue ($p$ = 0.007), pain ($p$ = 0.010), and dyspnea ($p$ = 0.007). Patients with no comorbidities and those with non-metastatic disease reported improvements in emotional functioning ($p$ = 0.050 and $p$ = 0.007, respectively). Nonetheless, patients with comorbidities reported a significant increase in insomnia ($p$ = 0.007) and financial difficulties ($p$ = 0.040). The absence of metastasis was also associated with an overall improvement in the global health status ($p$ = 0.019). Pain was a significant symptom burden for postmenopausal women ($p$ = 0.049). The analysis of the variables of the EORTC QLQ-C30 questionnaire is presented in Tables 3 and Table 4.

### Analysis of Demographic Factors and Associations With EORTC QLQ-BR45 Scores

Patients with non-metastatic disease reported statistically significant changes in body image ($p$ = 0.004) and future perspective ($p$ = 0.006), whereas those aged ≥50 years suffered from more arm symptoms ($p$ = 0.004) and endocrine therapy symptoms ($p$ = 0.0001). Endocrine sexual symptoms were reported to be mildly persistent in patients who did not undergo surgery ($p$ = 0.027) and those who did not have any comorbidities ($p$ = 0.034). The analysis of the variables of the EORTC QLQ-BR45 is presented in Tables 5 and Table 6.

## Discussion and Conclusion

The global health status of patients during chemotherapy improved significantly over the three cycles, indicating an improved quality of life as the therapy progressed. During each cycle, the functional scale scores showed positive outcomes, where the majority of patients recorded scores higher than 66.66%, with reported cognitive functioning acheiving the highest scores, indicating that most patients demonstrated a sound mental capacity. while emotional functioning stayed below 33.33%. This could be due to physical side effects, psychological distress, and impact on daily life (15). A study by Kshirsagar and Wani (16) and Jassim and Whitford (17) also reported similar outcomes and found a significant reduction in emotional function. However, their studies did not clarify the cycle in which the data were collected, and it remains unclear whether there was a significant increase or decrease in emotional functioning throughout the progression of therapy.

Symptom scales indicated a negative impact on QoL, with an increased frequency of fatigue, followed by dyspnea and pain until the sixth cycle. Perceived financial issues recorded the highest scores (C3:77.97%, C6:74.58%, and C9:72.41%), while perception of problems with constipation and diarrhea received the lowest scores. Ionescu et al. (18) published similar results for both functional and symptom scales, with higher scores for cognitive functioning. However, insomnia (28.99%) was the most distressing symptom reported in their study, followed by fatigue (3.83%) and pain (12.85%).

**Table 2. Mean scores of the EORTC QLQ-C30 and BR45 at the third, sixth, and ninth chemotherapy cycles**

| Items | Mean (SD) 3rd Cycle | Mean (SD) 6th Cycle | Mean (SD) 9th Cycle | *p* |
|---|---|---|---|---|
| **Global health status/QoL** | | | | |
| Global health status/QoL | 54.17 (15.39) | 56.75 (15.17) | 60.09 (19.40) | 0.070 |
| **Functional scales/items** | | | | |
| Physical functioning | 59.08 (26.88) | 62.87 (24.31) | 65.38 (24.25) | **0.026*** |
| Role functioning | 58.33 (27.26) | 58.33 (28.83) | 57.02 (31.33) | 0.983 |
| Emotional functioning | 31.18 (20.68) | 32.04 (22.01) | 39.62 (24.31) | **0.002*** |
| Cognitive functioning | 85.92 (19.70) | 89.37 (17.30) | 92.40 (12.33) | **0.002*** |
| Social functioning | 47.99 (35.88) | 50.29 (34.41) | 53.80 (33.04) | **0.006*** |
| **Symptom scales/items** | | | | |
| Fatigue | 64.56 (21.37) | 62.26 (22.22) | 54.58 (29.49) | **0.028*** |
| Nausea and vomiting | 31.61 (28.56) | 26.72 (25.35) | 15.50 (20.62) | **0.0001*** |
| Pain | 54.02 (26.91) | 54.02 (25.04) | 46.20 (28.35) | **0.008*** |
| Dyspnea | 54.02 (31.11) | 48.85 (27.37) | 39.18 (28.95) | **0.012*** |
| Insomnia | 48.28 (35.96) | 42.53 (31.71) | 39.18 (28.26) | 0.076 |
| Appetite loss | 66.67 (36.94) | 61.49 (32.92) | 44.44 (31.71) | **0.0001*** |
| Constipation | 12.64 (22.36) | 5.17 (15.04) | 2.92 (11.41) | **0.0001*** |
| Diarrhea | 10.92 (18.08) | 6.32 (14.59) | 1.75 (7.51) | **0.001*** |
| Financial difficulties | 64.94 (28.22) | 66.09 (28.95) | 65.50 (29.52) | 0.905 |
| **EORTC QLQ-BR45** | | | | |
| **Functional scales/items** | | | | |
| Body image | 72.99 (23.89) | 71.70 (25.26) | 73.68 (24.64) | 0.482 |
| Future perspective | 16.67 (21.85) | 18.97 (23.46) | 25.15 (27.66) | **0.043*** |
| Sexual functioning | 82.26 (29.17) | 85.48 (24.62) | 86.46 (23.36) | - |
| Sexual enjoyment | 50.00 (28.33) | 56.67 (27.44) | 53.33 (32.20) | - |
| Breast satisfaction | 14.22 (27.26) | 11.76 (22.67) | 10.29 (22.10) | - |
| **Symptom scales/items** | | | | |
| Systemic therapy side effects | 0.00 (0.00) | 0.00 (0.00) | 0.00 (0.00) | - |
| Upset by hair loss | 63.79 (36.02) | 78.16 (29.65) | 74.85 (31.67) | **0.0001*** |
| Arm symptoms | 32.76 (25.10) | 30.46 (24.85) | 25.34 (21.49) | **0.008*** |
| Breast symptoms | 26.58 (21.71) | 21.55 (19.37) | 18.42 (20.09) | **0.001*** |
| Endocrine therapy symptoms | 31.21 (14.89) | 28.45 (13.94) | 25.26 (17.09) | **0.001*** |
| Skin mucosis symptoms | 30.84 (22.10) | 25.96 (17.27) | 21.64 (17.31) | **0.0001*** |
| Endocrine sexual symptoms | 16.38 (24.63) | 11.78 (22.35) | 9.94 (19.38) | - |

*Statistically significant; higher scores on functional scales/items indicate better functioning; higher scores on symptom scales/items indicate more symptoms; SD: Standard deviation

The patients were notably content with their body image. However, sexual dysfunction posed a serious challenge. According to the score values, most patients either declined to answer this section or had no interest in engaging in any sexual activity during the four weeks before completing the questionnaire, whereas patients who were sexually active experienced sexually related issues. This concurs with the observations of Kidayi et al. (3), who highlighted the cultural context of Tanzania, where people are hesitant or forbidden from freely discussing sexual matters. Therefore, there were relatively fewer responses to the sexuality questions, which influenced the statistical evaluation. In India, such topics are often considered taboo and rarely discussed in the community and as a result, sexual dysfunction remains an unidentified and neglected condition in breast cancer patients who, in most cases, experience a decline in sexual desire induced by cancer and treatment (19, 20).

There was a significant improvement in the future perspective of patients, indicating hope for disease therapy success. The symptom burden was comparatively low for breast, endocrine therapy, and skin mucosis symptoms and showed significant improvement throughout

therapy. However, chemotherapy-induced hair loss progressed throughout each cycle, leaving many patients in distress, which aligns with findings of a study from Brazil (21).

Regarding the functional scales in the QLQ-C30, this study showed that patients aged <50 years had a positive impact on physical and cognitive functioning compared with those aged ≥50 years. In the context of symptom scales, fatigue and shortness of breath were elevated in patients aged ≥50 years. This group of patients, as well as those who were postmenopausal, had body pain. These findings are consistent with the study by Imran et al. (22) highlighting the impact of age and menopausal status on functional and symptom scales.

Based on the results of the QLQ-BR45, the older population (≥50 years) experienced endocrine therapy symptoms, including hot flashes, excess sweating, joint pain, fatigue, and mood changes. Arm symptoms (discomfort, swelling, stiffness, numbness, tingling sensation, or sensitivity) were also evident in this age group. This may be because older patients who are postmenopausal at the time of diagnosis potentially experience menopausal symptoms, such as hot flashes and vaginal dryness, but the addition of chemotherapy-induced menopause may exacerbate these already existing symptoms and pose additional issues, including deterioration of bone health, resulting in the prevalence of pain symptoms (23). Nisha et al. (24) prospectively suggested and confirmed a significant worsening of bone health associated with cytotoxic chemotherapy, as evidenced by 2% reduction in bone mineral density, which continued to worsen during follow-up, even after the completion of chemotherapy.

There was a notable transition from premenopausal to postmenopausal status in one patient, which presents evidence that patients below the age of 50 years, with a premenopausal status at cancer diagnosis are at risk of premature ovarian failure and compromised future fertility due to chemotherapy-induced ovarian suppression. Premenopausal women may experience higher rates of chemotherapy-induced amenorrhea and ovarian toxicity, which could increase the risk of infertility, early menopause, and hormonal imbalance post-treatment (25). Ursini et al. (11) expressed QoL in terms of implications associated with age, where

**Table 3. Analysis of variables in the functional scales and global health status in the EORTC QLQ-C30**

| Variables | PF mean (SD) | RF mean (SD) | CF mean (SD) | EF mean (SD) | SF mean (SD) | Global Health Status mean (SD) |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| ≥50 years (*n* = 36) | 56.60 (23.49) | 54.78 (28.37) | 86.88 (17.80) | 34.11 (22.89) | 48.15 (33.28) | 56.56 (16.23) |
| <50 years (*n* = 21) | 73.86 (23.35) | 64.55 (28.63) | 94.18 (13.10) | 35.45 (21.84) | 56.35 (35.47) | 58.73 (17.09) |
| *p*-value | **0.004*** | 0.185 | **0.015*** | 0.741 | 0.273 | 0.533 |
| **Menopausal status ▲** | | | | | | |
| Pre-menopause (*n* = 6) | 75.93 (49.46) | 70.37 (58.18) | 98.15 (34.24) | 31.02 (44.90) | 74.07 (65.51) | 63.89 (32.43) |
| Post-menopause (*n* = 51) | 61.44 (24.21) | 56.97 (21.05) | 88.56 (5.39) | 35.02 (23.71) | 48.48 (36.26) | 56.59 (19.17) |
| *p*-value | 0.243 | 0.415 | 0.208 | 0.284 | 0.205 | 0.267 |
| **Comorbidities** | | | | | | |
| Yes (*n* = 20) | 62.89 (23.69) | 51.67 (30.95) | 90.00 (17.95) | 28.89 (23.19) | 51.67 (30.49) | 58.19 (19.01) |
| No (*n* = 37) | 63.00 (25.52) | 62.01 (26.98) | 89.34 (15.86) | 37.48 (21.52) | 50.90 (36.23) | 56.91 (15.11) |
| *p*-value | 0.861 | 0.225 | 0.726 | **0.050*** | 0.873 | 0.580 |
| **Surgery** | | | | | | |
| Yes (*n* = 33) | 67.88 (24.02) | 56.57 (30.01) | 90.74 (14.53) | 36.87 (23.72) | 48.32 (32.95) | 58.08 (15.86) |
| No (*n* = 24) | 56.20 (24.46) | 60.88 (27.00) | 87.96 (19.02) | 31.48 (20.33) | 55.09 (35.78) | 56.37 (17.50) |
| *p*-value | **0.044*** | 0.686 | 0.685 | 0.365 | 0.471 | 0.626 |
| **Presence of metastasis▼** | | | | | | |
| Yes (*n* = 10) | 63.33 (19.08) | 47.78 (21.32) | 89.44 (15.46) | 21.67 (18.52) | 44.44 (26.74) | 50.00 (15.32) |
| No (*n* = 47) | 62.88 (25.93) | 60.64 (29.70) | 89.60 (16.85) | 37.35 (22.31) | 52.60 (35.54) | 58.92 (16.42) |
| *p*-value | 0.919 | 0.066 | 0.472 | **0.007*** | 0.816 | **0.019*** |
| **Change in taste** | | | | | | |
| Change (*n* = 40) | 61.03 (22.29) | 55.56 (29.20) | 90.31 (13.88) | 31.48 (21.16) | 50.14 (31.83) | 56.13 (15.33) |
| No change (*n* = 17) | 67.16 (29.36) | 64.51 (27.10) | 87.96 (21.33) | 41.36 (23.84) | 53.40 (39.17) | 60.03 (18.77) |
| *p*-value | 0.276 | 0.147 | 0.722 | 0.637 | 0.484 | 0.211 |

*Statistically significant; higher scores on functional scales/items indicate better functioning (PF, physical functioning; RF: Role functioning; EF: Emotional functioning; CF: Cognitive functioning; SF: Social functioning; SD: Standard deviation). ▲: Observed transition from the premenopausal state to postmenopausal state in one patient in cycle six. ▼: Observed non-metastatic state from the presence of metastasis in one patient in cycle nine

**Table 4. Analysis of variables in symptom scales in the EORTC QLQ-C30**

| Variables | FA mean (SD) | NV mean (SD) | PA mean (SD) | DY mean (SD) | SL mean (SD) | AP mean (SD) | CO mean (SD) | DI mean (SD) | FI mean (SD) |
|---|---|---|---|---|---|---|---|---|---|
| **Age** | | | | | | | | | |
| ≥50 years (*n* = 36) | 65.74 (23.34) | 22.84 (23.08) | 57.10 (23.26) | 54.32 (25.21) | 46.30 (31.52) | 57.41 (36.12) | 7.72 (19.12) | 4.94 (11.90) | 64.81 (28.76) |
| <50 years (*n* = 21) | 50.26 (23.77) | 25.93 (28.52) | 40.21 (28.50) | 33.86 (31.39) | 38.62 (33.44) | 56.61 (33.14) | 5.82 (14.09) | 7.41 (16.33) | 65.61 (28.69) |
| *p*-value | **0.007*** | 0.739 | **0.010*** | **0.007*** | 0.240 | 0.632 | 0.936 | 0.416 | 0.890 |
| **Menopausal status▲** | | | | | | | | | |
| Pre-menopause (*n* = 6) | 50.00 (48.81) | 21.30 (49.49) | 28.70 (51.69) | 37.04 (57.97) | 40.74 (66.70) | 51.85 (70.60) | 7.41 (36.05) | 14.81 (23.54) | 61.11 (54.68) |
| Post-menopause (*n* = 51) | 61.22 (26.47) | 24.29 (31.21) | 53.49 (24.79) | 47.93 (32.11) | 43.79 (26.95) | 57.73 (30.73) | 6.97 (14.26) | 4.79 (23.49) | 65.58 (34.77) |
| *p*-value | 0.808 | 0.203 | **0.049*** | 0.678 | 0.732 | 0.482 | 0.906 | 0.135 | 0.712 |
| **Comorbidities** | | | | | | | | | |
| Yes (*n* = 20) | 62.78 (24.96) | 25.83 (25.20) | 48.61 (24.98) | 48.33 (27.05) | 31.11 (31.81) | 46.67 (34.83) | 6.67 (14.78) | 7.22 (15.15) | 75.00 (25.77) |
| No (*n* = 37) | 58.56 (24.39) | 22.97 (25.23) | 52.10 (27.35) | 45.95 (30.50) | 50.15 (30.77) | 62.76 (33.86) | 7.21 (18.75) | 5.11 (12.87) | 59.76 (28.82) |
| *p*-value | 0.514 | 0.602 | 0.757 | 0.756 | **0.007*** | 0.054 | 0.392 | 0.597 | **0.040*** |
| **Surgery** | | | | | | | | | |
| Yes (*n* = 33) | 56.12 (25.86) | 23.06 (23.77) | 47.47 (27.60) | 43.77 (32.52) | 39.39 (33.46) | 52.86 (36.89) | 7.41 (18.78) | 5.72 (13.50) | 65.66 (29.53) |
| No (*n* = 24) | 65.43 (21.79) | 25.23 (27.12) | 55.56 (24.39) | 50.93 (23.72) | 49.07 (30.11) | 62.96 (31.43) | 6.48 (15.46) | 6.02 (14.07) | 64.35 (27.59) |
| *p*-value | 0.117 | 0.852 | 0.293 | 0.733 | 0.185 | 0.265 | 0.828 | 0.551 | 0.710 |
| **Presence of metastasis▼** | | | | | | | | | |
| Yes (*n* = 10) | 62.96 (23.77) | 22.78 (22.52) | 55.56 (27.80) | 52.22 (27.24) | 38.89 (32.85) | 57.78 (33.83) | 3.33 (10.17) | 5.56 (15.37) | 74.44 (29.92) |
| No (*n* = 47) | 59.42 (24.81) | 24.23 (25.78) | 49.88 (26.24) | 45.63 (29.66) | 44.44 (32.29) | 56.97 (35.31) | 7.80 (18.53) | 5.91 (13.38) | 63.12 (28.09) |
| *p*-value | 0.352 | 0.699 | 0.517 | 0.227 | 0.927 | 0.878 | 0.834 | 0.972 | 0.169 |
| **Change in taste** | | | | | | | | | |
| Change (*n* = 40) | 61.44 (23.42) | 19.52 (21.47) | 53.28 (24.20) | 47.86 (26.76) | 43.31 (29.77) | 60.11 (32.82) | 4.56 (11.50) | 5.70 (14.04) | 63.82 (28.89) |
| No change (*n* = 17) | 57.00 (26.96) | 33.64 (29.76) | 45.68 (30.58) | 44.44 (34.26) | 43.83 (37.66) | 50.62 (38.71) | 12.35 (25.32) | 6.17 (13.07) | 67.90 (28.20) |
| *p*-value | 0.917 | 0.133 | 0.848 | 0.868 | 0.419 | 0.595 | 0.180 | 0.668 | 0.505 |

*Statistically significant: Higher scores on symptom scales/items indicate more symptoms. (FA: Fatigue; NV: Nausea and vomiting; PA: Pain; DY: Dyspnea; SL: Insomnia; AP: Appetite loss; CO: Constipation; DI: Diarrhea; FI: Financial difficulties; SD: Standard deviation). ▲: Observed transition from premenopausal state to postmenopausal state in one patient in cycle six. ▼: Observed non-metastatic state from the presence of metastasis in one patient in cycle nine

**Table 5. Analysis of variables in functional scales in the EORTC QLQ-BR45.**

| Variables | BI mean (SD) | FU mean (SD) | SX‡ mean (SD)# | SE‡ mean (SD)^ | BS‡ mean (SD)¶ |
|---|---|---|---|---|---|
| **Age** | | | | | |
| ≥50 years (*n* = 36) | 75.31 (23.71) | 19.14 (24.20) | 97.84 (7.96) | 77.78 (17.21) | 11.38 (18.65) |
| <50 years (*n* = 21) | 69.97 (24.48) | 22.75 (25.28) | 67.08 (30.31) | 47.22 (27.66) | 13.96 (31.55) |
| *p*-value | 0.475 | 0.452 | - | - | - |
| **Menopausal status▲** | | | | | |
| Pre-menopause (*n* = 6) | 73.69 (25.44) | 20.92 (20.61) | 89.45 (24.23) | 53.70 (33.21) | 12.41 (17.21) |
| Post-menopause (*n* = 51) | 70.37 (23.96) | 16.67 (25.04) | 60.00 (23.14) | 52.78 (25.92) | 11.11 (24.56) |
| *p*-value | 0.817 | 0.371 | - | - | - |
| **Comorbidities** | | | | | |
| Yes (*n* = 20) | 73.47 (22.58) | 16.67 (25.67) | 88.15 (25.78) | 44.44 (23.57) | 5.13 (12.18) |
| No (*n* = 37) | 73.27 (24.93) | 22.52 (23.85) | 81.63 (25.29) | 57.14 (30.08) | 16.94 (28.46) |
| *p*-value | 0.993 | 0.133 | - | - | - |
| **Surgery** | | | | | |
| Yes (*n* = 33) | 69.87 (23.20) | 20.88 (24.55) | 89.09 (25.50) | 51.85 (33.79) | 8.24 (16.23) |
| No (*n* = 24) | 78.13 (24.56) | 19.91 (24.81) | 78.63 (24.76) | 53.97 (26.82) | 66.67 (43.03) |
| *p*-value | 0.154 | 0.710 | - | - | - |
| **Presence of metastasis▼** | | | | | |
| Yes (*n* = 10) | 53.61 (19.14) | 8.89 (17.72) | 93.52 (15.48) | 66.67 (0.00) | 16.03 (36.23) |
| No (*n* = 47) | 77.54 (22.71) | 22.93 (25.24) | 82.68 (27.14) | 51.85 (29.72) | 11.04 (20.51) |
| *p*-value | **0.004*** | **0.006*** | - | - | - |
| **Change in taste** | | | | | |
| Change (*n* = 40) | 70.66 (23.07) | 17.38 (22.57) | 87.57 (23.94) | 50.00 (30.78) | 13.13 (23.48) |
| No change (*n* = 17) | 79.17 (25.33) | 27.16 (27.53) | 79.03 (28.21) | 58.33 (25.13) | 10.78 (25.58) |
| *p*-value | 0.201 | 0.551 | - | - | - |

*Statistically significant; higher scores on functional scales/items indicate better functioning (BI: Body Image; FU: Future Perspective; SX: Sexual Functioning; SE: Sexual Enjoyment; BS: Breast Satisfaction; SD: Standard deviation). ǂ: Missing data due to refusal to answer the questions regarding SX, SE, and BS (#: *n* = 32; ^: *n* = 10; ¶: *n* = 34). ▲: Observed transition from premenopausal state to postmenopausal state in one patient in cycle 6. ▼: Observed non-metastatic state from the presence of metastasis in one patient in cycle 9

induction of early menopause and possible infertility increased the risk of adverse effects in younger women. This patient group is more likely to have a lower QoL and is more vulnerable to the emotional burden and psychological impact of breast cancer.

The present study showed that emotional functioning was significantly better in patients who did not have any comorbidities. Endocrine sexual symptoms and insomnia were also prevalent in this subgroup. However, the perception of worsened financial burden was significantly higher in comorbid patients, resulting in further deterioration of the symptom scales.

Patients who underwent surgery experienced good physical functioning, whereas those who did not undergo surgery showed an increase in endocrine sexual symptoms. Jassim et al. (17) suggested reasons for disrupted sexual function, such as low self-esteem, abrupt menopause, vaginal dryness, a partner's difficulties comprehending one's feelings, and body image issues.

Based on the findings of the EORTC QLQ-BR45, improved emotional function and an overall positive outcome in the global health status were recorded in non-metastatic patients compared to metastatic patients. Guo et al. (26) found that the prevalence of psychological burdens, such as depression, anxiety, and stress, were high in patients with metastatic breast cancer. Furthermore, the present study emphasized that future concerns about illness were relieved, and body image was less altered in patients who did not present with metastasis, when compared to the metastatic breast cancer group. There was a positive transition from metastatic to non-metastatic status in one patient.

In the present study, the QoL did not correlate with the chemotherapy agent given or the stage of cancer; hence, the results are based on the perceptions of patients who received a variety of chemotherapeutic regimens regardless of disease stage. Furthermore, the assessment of QoL before commencing or after completing therapy was not performed, as the two QoL instruments were applied at only three

**Table 6. Analysis of variables in symptom scales in the EORTC QLQ-BR45**

| Variables | SYS mean (SD) | HU mean (SD) | ARM mean (SD) | BR mean (SD) | ET mean (SD) | SM mean (SD) | ES mean (SD) |
|---|---|---|---|---|---|---|---|
| **Age** | | | | | | | |
| ≥50 years (*n* = 36) | 0.00 (0.00) | 71.91 (29.24) | 36.01 (24.06) | 24.00 (21.64) | 32.84 (14.08) | 28.70 (18.13) | 12.58 (23.39) |
| <50 years (*n* = 21) | 0.00 (0.00) | 71.96 (38.89) | 19.05 (19.80) | 19.58 (18.58) | 21.11 (14.93) | 20.99 (20.07) | 13.36 (20.66) |
| *p*-value | 1.000 | 0.404 | **0.004*** | 0.501 | **0.0001*** | 0.056 | 0.677 |
| **Menopausal status▲** | | | | | | | |
| Pre-menopause (*n* = 6) | 0.00 (0.00) | 71.02 (30.55) | 31.59 (20.10) | 22.88 (19.44) | 29.67 (10.55) | 26.29 (23.18) | 13.24 (16.97) |
| Post-menopause (*n* = 51) | 0.00 (0.00) | 79.63 (33.27) | 14.20 (23.78) | 18.06 (20.76) | 18.70 (15.54) | 22.22 (18.69) | 9.72 (22.93) |
| *p*-value | 1.000 | 0.442 | 0.094 | 0.807 | 0.070 | 0.543 | 0.441 |
| **Comorbidities** | | | | | | | |
| Yes (*n* = 20) | 0.00 (0.00) | 75.00 (32.26) | 30.56 (25.19) | 19.31 (21.89) | 29.94 (15.78) | 21.57 (16.34) | 6.94 (16.03) |
| No (*n* = 37) | 0.00 (0.00) | 70.27 (33.44) | 29.33 (23.39) | 24.02 (19.81) | 27.75 (15.26) | 28.18 (20.24) | 16.07 (24.61) |
| *p*-value | 1.000 | 0.366 | 0.987 | 0.254 | 0.519 | 0.157 | **0.034*** |
| **Surgery** | | | | | | | |
| Yes (*n* = 33) | 0.00 (0.00) | 69.70 (34.04) | 29.41 (24.35) | 22.39 (22.51) | 27.31 (14.90) | 24.47 (19.16) | 9.93 (22.61) |
| No (*n* = 24) | 0.00 (0.00) | 75.00 (31.52) | 30.25 (23.61) | 22.34 (17.85) | 30.19 (16.10) | 27.78 (19.15) | 16.90 (21.53) |
| *p*-value | 1.000 | 0.458 | 0.974 | 0.638 | 0.789 | 0.414 | **0.027*** |
| **Presence of metastasis▼** | | | | | | | |
| Yes (*n* = 10) | 0.00 (0.00) | 81.11 (29.45) | 32.96 (19.91) | 16.11 (20.31) | 31.56 (17.21) | 27.41 (21.71) | 11.67 (21.60) |
| No (*n* = 47) | 0.00 (0.00) | 69.98 (33.17) | 29.08 (24.76) | 23.70 (20.68) | 27.87 (15.20) | 25.53 (18.79) | 13.12 (22.87) |
| *p*-value | 1.000 | 0.054 | 0.863 | 0.429 | 0.485 | 0.863 | 0.619 |
| **Change in taste** | | | | | | | |
| Change (*n* = 40) | 0.00 (0.00) | 79.77 (25.13) | 30.48 (21.79) | 20.80 (18.65) | 30.46 (14.95) | 26.50 (19.44) | 9.83 (19.56) |
| No change (*n* = 17) | 0.00 (0.00) | 54.94 (41.03) | 28.19 (28.28) | 25.77 (24.19) | 24.32 (15.79) | 24.49 (18.68) | 19.44 (26.50) |
| *p*-value | 1.000 | 0.062 | 0.462 | 0.211 | 0.295 | 0.965 | 0.153 |

*Statistically significant; higher score in symptom scale/items indicates more symptoms (SYS: Systemic therapy side effects; HU: Upset by hair loss; ARM: Arm symptoms; BR: Breast symptoms; ET: Endocrine therapy symptoms; SM: Skin mucosis symptoms; ES: Endocrine sexual symptoms; SD: Standard deviation). ▲: Observed transition from premenopausal state to postmenopausal state in one patient in cycle 6. ▼: Observed non-metastatic state from the presence of metastasis in one patient in cycle 9

specific points in time during chemotherapy. Thus, it is challenging to identify patterns of QoL over the long term or changes in their relationship with cancer-related symptoms. Further longitudinal studies and clinical trials should be conducted, leveraging large populations to track QoL outcomes over extended periods, including during and after chemotherapy, to better understand the trajectory of patient well-being.

### Study Limitations

The limitations of this study include the small sample size, single-center design, and lack of baseline assessment before treatment, which may limit generalizability. Cultural factors may influence self-reported data, particularly for sensitive topics. Despite these limitations, this study provides valuable insights into the QoL of breast cancer patients during chemotherapy.

In conclusion, this study demonstrated that the quality of life of Indian patients with breast cancer during chemotherapy was influenced by a complex interplay of treatment-related factors, many of which are likely to affect patients from other populations, and patient demographics. A relatively stable global health status and good cognitive functioning were observed, with mild improvements in emotional functioning over time. Symptom burden peaked in the sixth cycle before gradually decreasing. Younger patients and those who underwent surgery showed better functional outcomes, although the latter experienced increased endocrine sexual symptoms. Older patients reported more severe symptoms than younger patients. The absence of comorbidities and metastasis was associated with improved emotional functioning, albeit with some trade-offs such as increased insomnia. These findings highlight the importance of personalized and holistic care in oncology. Potential areas for targeted interventions have been identified which may enhance patient well-being throughout the treatment journey. Furthermore, the pivotal role of clinical pharmacists in optimizing medication management, minimizing adverse effects, and providing patient education was evident.

Future research should focus on finding and assessing therapies targeted for specific patient subgroups to improve HRQoL outcomes in patients with breast cancer during chemotherapy. By integrating these insights into clinical practice, it may be possible to work towards more patient-centred and effective cancer care.

### Ethics

**Ethics Committee Approval:** This prospective, cross-sectional study was conducted at the oncology department of a tertiary care hospital and was approved by the Institutional Ethics Committee of Bharati Hospital & Medical College, Pune (approval number: BVDUMC/IEC/23, date: 07.11.2023).

**Informed Consent:** Informed consent was obtained from all individual participants included in the study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: A.C.; Concept: A.R.; Design: A.H.A., A.R.; Data Collection or Processing: A.H.A., P.K., J.S., J.P.K., S.R.K.; Analysis or Interpretation: A.H.A., J.S., A.C., A.R.; Literature Search: A.H.A., P.K., J.S., J.P.K., S.R.K., A.R.; Writing: A.H.A., P.K., J.S., J.P.K., S.R.K., A.C., A.R.

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Original Article

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# Organized Breast Cancer Screening in Diabetic Women: A Prospective Study Among 100,000 Women from the Grand-Est Region (France), from 2020 to 2022

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**ABSTRACT**

**Objective:** The risk of breast cancer in type 2 diabetic women is increased by 10–20%. Diabetic women have a higher risk of being diagnosed with advanced breast cancer and having complications with its treatments. In France, women aged between 50 and 74 years old are invited to undergo organized breast cancer screening (OBCS). The objective of this study was to evaluate OBCS participation in a large cohort of diabetic women.

**Materials and Methods:** Based on data from Social Security reimbursement databases, we studied OBCS participation rate of 50–74 years old diabetic women from the Grand-Est region (France) between 2020 and 2022, according to four age brackets and their geographical areas.

**Results:** In 2020, among the 99,302 diabetic women, 16,340 (16.45%) underwent OBCS versus 24% in the general population. In 2021, among the 100,390 diabetic women, 20,914 (20.83%) underwent OBCS, versus 29% in the general population. In 2022, among the 101,694 diabetic women, 18,576 (18.27%) underwent OBCS, versus 24% in the general population. OBCS participation in 50–54 years old and 70–74 years olds were significantly lower ($p$<0.0001 in 2020; $p$<0.0001 in 2021; $p$<0.0037 in 2022). There was a significant link between OBSC participation and geographical area ($p$<0.0001).

**Conclusion:** The OBCS participation rate in women with type 2 diabetes was significantly lower than the general population, and associated with age and area. These findings suggest a need to inform patients and health care professionals about the higher risk of breast cancer in diabetic women to improve OBCS rates with the proven associated health benefits.

**Keywords:** Breast cancer screenings; diabetic women; organized breast cancer screnning; type 2 diabetes

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**Key Points**

- Breast cancer risk in women with type 2 diabetes is increased by 10–20%.
- Breast cancer mortality is higher in women with type 2 diabetes.
- Organized breast cancer screening participation rate in diabetic women is low.
- Lower participation is observed in women with type 2 diabetes aged 50–54 and 70–74.
- The analysis of barriers to screening participation must be encouraged.

## Introduction

Breast cancer and type 2 diabetes are two major public health problems globally (1, 2). In 2021, 529 million people worldwide suffered from diabetes. Type 2 diabetes is the most common form, accounting for 96% of all cases (2). In 2020, 2.26 million women were diagnosed with breast cancer, and almost 685,000 died from it (1). As the prevalence of obesity continuously increases, so does the incidence of breast cancer and type 2 diabetes (1, 3, 4).

Type 2 diabetes and breast cancer share extrinsic risk factors, including post-menopausal overweight and obesity (5, 6), sedentary lifestyle, and

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lack of physical activity (7, 8). Type 2 diabetes is considered a risk factor for hormone-dependent breast cancer (9), because of diabetes-associated insulin resistance. The latter leads to hyperinsulinemia and activation of insulin signaling and growth factors implicated in the pathogenesis of breast cancer. Hyperinsulinemia, also decreases the production of sex hormone binding globulin, a key feature of hormonal breast cancer (10-13).

A diabetic woman has a 15% higher risk of breast cancer (14), which rises to 22% after adjusting for body mass index (14). At diagnosis, tumors in diabetic women are larger with more lymph node involvement, or even metastatic from the outset (15). It should also be highlighted that diabetic comorbidities, including heart disease or kidney disease, possibly contraindicate optimal breast cancer treatment (16). Anthracyclines, one of the main cytolytic drug groups used for breast cancer and Trastuzumab and Pertuzumab used for human epidermal growth factor receptor 2 overexpressed breast cancer, induce a high risk of cardiotoxicity in diabetic patients (17-19). Diabetic patients with heart failure do not receive adjuvant or neoadjuvant treatments as recommended (16). Lymphedema, which can occur after an axillary node clearance and is frequently associated with obesity, is more often observed in diabetic women, with a direct impact on women's lives (20). In the case of breast reconstruction after mastectomy, diabetic women are at greater risk of delayed wound-healing, infection and prosthesis removal (21, 22). They are also at greater risk of breast cancer mortality and all-cause mortality (16), even in the absence of delayed diagnosis (23).

Women with diabetes are invited to participate in organized breast cancer screening (OBCS) in the same way as the general population (24). In France, since 2004, OBCS has been offered to asymptomatic 50–74-year-old women, once every two years. This screening consists of a free of charge mammogram, breasts and axilla clinical examination and breast ultrasound in selected cases. Eligible women receive an invitation from the French Regional Cancer Screening Coordination Centers, with a double-reading mammogram by two certified radiologists (25).

In France, individual breast cancer screening (IBCS) is also available. IBCS consists of an individualized prescription of breast imaging. IBCS is being offered to women with a personal history of breast cancer, a "high" or "very high" risk of breast cancer, or with symptoms of breast cancer. Women at "high" risk of breast cancer are those with: a personal history of breast cancer; abnormal image on last mammogram; existence of lobular neoplasia; existence of atypical epithelial hyperplasia; or high-dose thoracic irradiation. Women at "very high" risk of breast cancer have a hereditary form of breast cancer and presence of genetic mutations, notably *BRCA1* and *BRCA2* (25).

The French National Authority for Health specifies that "special attention" should be paid to breast cancer screening in diabetic patients due to their high risk of breast cancer (24). Despite this, diabetic women tend to participate less in OBCS than the general population. In 2022, in France, only 44.9% of women from the general population took part to OBCS (26). To the best of our knowledge, only two French studies have been conducted so far to assess OBCS participation of diabetic women. In 2008, Constantinou et al. (27) studied 2056 women, including 157 diabetic women. Diabetic women participated significantly less in OBCS [odds ratio: 0.55 (0.36–0.83)]. In 2018, Bernard (28) studied 5161 women, including 456 diabetic women. Only 16% of diabetic women had taken part in OBCS, compared to 52% of non-diabetic women. However, these two studies were biased, due to their small numbers of diabetic women and lack of IBCS evaluation.The aim of the present study was to evaluate participation in OBCS and IBCS among diabetic women within the Grand-Est region in France, from 2020 to 2022 in a prospective cohort. Our secondary objective was to assess differences in participation depending on geographical area and women's age.

## Materials and Methods

This prospective, descriptive, epidemiological study investigated OBCS participation of type 2 diabetic women from the Grand-Est region in France for the years 2020, 2021, and 2022.

The medical department of the Grand-Est region provided us with aggregated statistical data extracted from the French Health Insurance reimbursement databases. These data were anonymous and protected by the following regulatory bodies: European Regulation RGPD n° 2016–679 of April 27, 2016; *Loi informatique et libertés* n° 2018–486 of June 20, 2018, and its Decree of application n° 2019- 536 of May 29, 2019, consolidating Ordinance n° 2018–1125 of December 2018 modifying the law of January 6, 1978. The agreement is attached in Appendix A (supplemental files). The approval of the Committee for the Protection of Individuals was not required.

### Inclusion Criteria

The study period runs from January 1, 2020, to December 31, 2022. Women included in the study were those alive on January 1 of the year n+1 studied, as well as those eligible for OBCS according to French recommendations (asymptomatic 50–74-year-old women, without high risks of breast cancer as personal history of cancer of the breast, uterus and/or endometrium, atypical hyperplasia or benign proliferative disease, chest radiation before the age of 30, and a family history of breast and/or ovarian cancer among relatives) (25). They were between 50 and 74 years old and categorized into four age groups: 50–54, 55–64, 65–69 and 70–74 years old. They were beneficiaries of the French primary health insurance fund in one of the 10 areas of the Grand-Est region: Ardennes (08), Aube (10), Marne (51), Haute-Marne (52), Meurthe-et-Moselle (54), Meuse (55), Moselle (57), Bas-Rhin (67), Haut-Rhin (68), and Vosges (88).

The population of diabetic women was elected according to one of the following inclusive criteria: having a long-term illness of type 2 diabetes (LTI 8 E11), having undergone at least three antidiabetic treatments (Anatomical Therapeutic Chemical A10A or A10 B) that year, or having been hospitalized during the current year for a cause related to type 2 diabetes or one of its complications according to the French Information Systems Medicalization Program (Table 1).

### Exclusion Criteria

The exclusion criteria were recognition of long-term illness for breast cancer (LTI D05), breast carcinoma *in situ* (LTI D05), or hospitalization during the year with a breast cancer-related French Information Systems Medicalization Program code (Table 1).

**Patients with type 1 diabetes were excluded.**

Mammography execution was evaluated. A mammogram was considered performed if a mammography procedure was reimbursed under the Common Classification of Medical Procedures (CCMP) during the studied year. In France, there are three CCMP codes: QEQK001 for bilateral mammography, QEQK005 for unilateral

**Table 1. Inclusion and exclusion criteria for type 2 diabetic population**

| | | |
|---|---|---|
| **Inclusion criteria for type 2 diabetic population** | | |
| **One of three criteria** | | |
| **LTI** | **Drug tracers** | **Hospitalization ICD code** |
| LTI Type 2 diabetes active in year n:<br>- E11 | At least three deliveries in year n of oral antidiabetics or insulin.<br><br>ATC codes used:<br>- A10A: Insulins and analogues<br>- A10B: Blood glucose-lowering drugs other than insulins. | FISMP: Beneficiaries hospitalized in MSOD or FRD for diabetes in year n (PD, RD or SAD in MSOD; PME or EC in FRD)<br>FISMP (diabetes) :<br>- E11 Non-insulin-dependent diabetes mellitus<br>FISMP (diabetes complications):<br>- G59.0 Diabetic mononeuritis<br>- G63.2 Diabetic polyneuritis<br>- G73.0 Myasthenic syndrome during endocrine disease<br>- G99.0 Autonomic nervous system neuropathy during endocrine and metabolic diseases<br>- H28.0 Diabetic cataract<br>- H36.0 Diabetic retinopathy<br>- I79.2 Peripheral angiopathy in diseases classified elsewhere<br>- L97 Lower limb ulcer, not elsewhere classified<br>- M14.2 Diabetic arthropathy<br>- M14.6 Nervous arthropathy<br>- N08.3 Glomerulopathy in diabetes mellitus. |
| **Exclusion criteria for type 2 diabetic population** | | |
| **One of three criteria** | | |
| **LTI** | **Drug tracers** | **Hospitalization ICD code** |
| LTI Breast cancer active in n:<br>- C50 or<br>- D05 | None | FISMP: women hospitalized for breast cancer in MSOD or FRD during year n (PD, RD or SAD in MSO; PME or EC in SSR)<br>- C50<br>- D05 |

LTI: Long-term illness; ATC: Anatomical therapeutic chemical classification; ICD: International Classification of Diseases; FISMP: French Information Systems Medicalization Program; MSOD: Medicine, surgery or obstetrics department; FRD: Follow-up and rehabilitation department; PD: Principal diagnosis; RD: Related diagnosis; SAD: Significant associated diagnosis; PME: Principal morbid event; EC: Etiological condition

mammography, and QEQK004 for mammography performed in OBCS programs. Mammograms with CCMP codes QEQK001 and QEQK005 are prescribed for IBCS or follow-up of breast-pathology. All the Social Security data tables are given in Appendix B (supplemental files).

## Results

### Study Population

For the 2020–2021 and 2021–2022 periods, 102,138 and 104,266 diabetic women were eligible for OBCS respectively. For the 2020–2021 and 2021–2022 periods, there were 815,251 and 882,445 women in the general population.

In 2020, 2021 and 2022, 99,302, 100,390 and 101,694 diabetic women were eligible for OBCS respectively. In 2020, 2021 and 2022, there were 796,223, 815,251 and 882,445 women in the general population.

### Participation in OBCS

#### - By Period

During the two-year 2020–2021 period, among the 102,138 diabetic women, 37,625 (36.84%) underwent OBCS versus 419,626 women (51%) from the general population. During the two-year 2021–2022 period, among the 104,266 diabetic women, 40,160 (38.52%) underwent OBCS versus 438,522 (50%) from the general population.

#### - By Year

In 2020, among the 99,302 diabetic women, 16,340 (16.45%) underwent OBCS versus 189,264 women (24%) from the general population. In 2021, among the 100,390 diabetic women, 20,914

(20.83%) underwent OBCS versus 237,481 women (29%) from the general population. In 2022,

among the 101,694 diabetic women, 18,576 (18.27%) underwent OBCS versus 209,654 women (24%) from the general population (Table 2).

**- By Age Group of the Diabetic Population**

In 2020, the diabetic age group with the lowest attendance was the 50–54-year-old group (Table 3), with 1,476 of 9,636 women (15.32%) having undergone OBCS. In 2021 and 2022, the diabetic group with the lowest attendance was the 70–74-year-old group, with 5,742 women of 28,658 (20.04%) having undergone OBCS in 2021, and 5,233 women of 29,630 (17.66%) in 2022.

In 2020, 2021, and 2022, the diabetic age group with the highest OBCS attendance was the 65–69-year-old group, with rates of 17.20%, 21.55% and 18.78%, respectively. The association between OBCS attendance and age was significant in 2020, 2021, and 2022 ($p$<0.0001, $p$<0.0001, and $p$<0.0037, respectively).

**- By Area**

In 2020, 2021, and 2022, the area with the highest OBCS attendance rates among diabetic women was Bas-Rhin (67), with 18.51%, 24.26% and 22.28%, respectively, and the area with the lowest OBCS attendance rates among diabetic women was Moselle (57), with 14.74%, 16.67% and 14.54%, respectively. The relationship between OBCS participation and area was significant in 2020, 2021, and 2022 ($p$<0.0001, $p$<0.0001 and $p$<0.0001, respectively) (Table 3).

**- By Age Group and Area**

The area the least represented in OBCS by diabetic women, all ages combined, was Meuse (55), and the most represented was Bas-Rhin (67) (Tables 4, 5, and 6), the relationship between age, area, and OBCS participation was significant in 2020, 2021, and 2022 ($p$ = 0.0003, $p$ = 0.0002, and $p$ = 0.001, respectively).

**- Individual Breast Cancer Screening**

In 2020, 2021, and 2022, only 4% of diabetic women underwent an IBCS versus 8% of the general population (Table 2).

## Discussion and Conclusion

This was the first large-scale French epidemiological study to evaluate OBCS participation rates of women with type 2 diabetes. As demonstrated, there was low-rate OBCS participation compared to non-diabetic peers, which was significantly related to area and age of diabetic women. These observations clearly corroborate the findings of Constantinou et al. (27) and Bernard (28). Several foreign studies draw the same conclusions (29-32), highlighting the fact that this low participation rate persisted despite the Pink October/Breast Cancer Awareness Month screening campaigns and ever-growing breast cancer awareness among women (33, 34).

Furthermore, only 4% of diabetic women resorted to IBCS, despite an estimated 10% of French breast cancer screenings being individual screenings (35). Not only did diabetic women make less use of OBCS than the general population, but they also made less use of IBCS. Since diabetic women are at greater risk of developing breast cancer, it may be thought that this patient group were undergoing IBCS-based follow-up within the two-year OBCS interval, but this was not the case.

This study displays several strengths, which deserve to be emphasized. First, our data originate from the French Health Insurance reimbursement databases, thus ensuring data reliability. Secondly, as the Grand-Est region is heavily affected by type 2 diabetes, we can extrapolate our results to other regions.

However, our study has limitations as well. First, the general population also included diabetic women, which does not enable reliable comparisons of the two populations. Moreover, unlike the diabetic population, the general population did not exclude women that did not rely on organized screening, owing to their high and very high breast-cancer-related risk factors. However, our data were superimposed onto the French participation rates according to French public health data. In 2020, the OBCS participation turned out to be very low, owing to the COVID-19 pandemic-related closure of the French Regional Cancer Screening Coordination Centers and radiology practices. It is also important to point out that type 2 diabetic patients were particularly affected by the COVID-19 pandemic, which is a factor limiting their participation in OBCS, in addition to the closure of screening centers from March to May 2020. Away from the pandemic, participation rates are on the rise, but remain below the European target of 70%: in 2022, the OBCS participation rate was 44.8%, and in 2023, 48.2% (26).

In the present study, disparities between age and area were observed, and it is thus possible for us to draw a parallel between our data and the barriers to OBCS participation already described, including socio-economic and socio-demographic factors, along with factors relating to women's health status and their medical follow-up (36-38). Indeed, women within the extreme age range groups, including 50–54 and 70–74-year-olds, displayed lower participation, as previously reported by several other authors (15, 20). Prior to age 50, over 30% of women had already undergone IBCS (39). Once these women reached the

**Table 2. OBCS and IBCS by year (2020, 2021 and 2022) in the general and diabetic populations**

| | 2020 | | 2021 | | 2022 | |
|---|---|---|---|---|---|---|
| | General population | Diabetic population | General population | Diabetic population | General population | Diabetic population |
| | $n$ = 796,223 | $n$ = 99,302 | $n$ = 815,251 | $n$ = 100,390 | $n$ = 882,445 | $n$ = 101,694 |
| OBCS only | 189,264 (24%) | 16,340 (16.45%) | 237,481 (29%) | 20,914 (20.83%) | 209,654 (24%) | 18,576 (18.27%) |
| IBCS only | 60,913 (8%) | 3,697 (4%) | 63,593 (8%) | 3,889 (4%) | 66,172 (7%) | 4,027 (4%) |

OBCS: Organized breast cancer screening; IBCS: Individual breast cancer screening

eligible age for OBCS, they possibly kept on undergoing IBCS at the expense of OBCS. After the age of 74, women tend to lose interest in gynecological follow-ups. Moreover, the end of OBCS at 74 years old may be misperceived by women and their doctors as the absence of breast cancer risk (40). All this could similarly be perceived prior to the age of 74 years, resulting in a OBCS participation drop among 70–74-year-old women.

**Table 3. Baseline characteristics of diabetic women**

| | 2020 | | 2021 | | 2022 | |
|---|---|---|---|---|---|---|
| | Diabetic population *n* = 99,302 | | Diabetic population *n* = 100,390 | | Diabetic population *n* = 101,694 | |
| **OBCS participation** | No | Yes | No | Yes | No | Yes |
| | *n* = 82,962 (83.55%) | *n* = 16,340 (16.45%) | *n* = 79,476 (79.16%) | *n* = 20,914 (20.83%) | *n* = 83,118 (81.73%) | *n* = 18,576 (18.27%) |
| **Age** | | | | | | |
| 50–54 | 8,160 (84.68%) | 1,476 (15.32%) | 7,879 (79.83%) | 1,991 (20.17%) | 8,208 (81.25%) | 1,894 (18.75%) |
| 55–64 | 29,698 (83.71%) | 5,780 (16.29%) | 27,986 (78.87%) | 7,497 (21.13%) | 29,182 (81.74%) | 6,517 (18.26%) |
| 65–69 | 21,721 (82.80%) | 4,513 (17.20%) | 20,695 (78.45%) | 5,684 (21.55%) | 21,331 (81.22%) | 4,932 (18.78%) |
| 70–74 | 23,383 (83.65%) | 4,571 (16.35%) | 22,916 (79.96%) | 5,742 (20.04%) | 24,397 (82.34%) | 5,233 (17.66%) |
| | *p*<0.0001 | *p*<0.001 | *p*<0.0001 | *p*<0.0001 | *p*<0.0037 | *p*<0.0037 |
| **Areas** | | | | | | |
| Ardennes 08 | 5,016 (84.77%) | 901 (15.23%) | 4,744 (79.93%) | 1,191 (20.07%) | 5,012 (84.08%) | 949 (15.92%) |
| Aube 10 | 4,377 (82.03%) | 959 (17.97%) | 4,277 (78.19%) | 1,193 (21.81%) | 4,501 (81.93%) | 993 (18.07%) |
| Marne 51 | 8,435 (82.52%) | 1,787 (17.48%) | 7,857 (76.50%) | 2,414 (23.50%) | 8,470 (81.25%) | 1,955 (18.75%) |
| Haute-Marne 52 | 2,819 (83.80%) | 545 (16.20%) | 2,586 (77.52%) | 750 (22.48%) | 2,752 (82.27%) | 593 (17.73%) |
| Meurthe-et-Moselle 54 | 10,137 (84.33%) | 1,884 (15.67%) | 9,825 (81.16%) | 2,280 (18.84%) | 10,186 (83.55%) | 2,006 (16.45%) |
| Meuse 55 | 2,751 (84.28%) | 513 (15.72%) | 2,684 (80.65%) | 644 (19.35%) | 2,689 (81.21%) | 622 (18.79%) |
| Moselle 57 | 16,619 (85.26%) | 2,874 (14.74%) | 16,316 (83.33%) | 3,263 (16.67%) | 16,949 (85.46%) | 2,884 (14.54%) |
| Bas-Rhin 67 | 16,035 (85.26%) | 3,643 (18.51%) | 15,183 (75.74%) | 4,862 (24.26%) | 15,943 (77.72%) | 4,571 (22.28%) |
| Haut-Rhin 68 | 11,432 (83.63%) | 2,238 (16.37%) | 10,922 (78.14%) | 3,056 (21.86%) | 11,362 (80.13%) | 2,818 (19.87%) |
| Vosges 88 | 5,341 (84.28%) | 996 (15.72%) | 5,082 (80.12%) | 1,261 (19.88%) | 5,254 (81.60%) | 1,185 (18.40%) |
| | *p*<0.0001 | *p*<0.0001 | *p*<0.0001 | *p*<0.0001 | *p*<0.0001 | *p*<0.0001 |

OBCS: Organized breast cancer screening

**Table 4. Organized breast cancer screening in diabetic women in 2020 by age and area**

| Areas | Age | | | | |
|---|---|---|---|---|---|
| | 50–54 | 55–64 | 65–69 | 70–74 | Total |
| Ardennes 08 | 67 (4.54%) | 301 (5.21%) | 261 (5.78%) | 272 (5.95%) | 901 |
| Aube 10 | 99 (6.71%) | 293 (5.07%) | 287 (6.36%) | 280 (6.13%) | 959 |
| Marne 51 | 195 (13.21%) | 637 (11.02%) | 469 (10.39%) | 486 (10.63%) | 1,797 |
| Haute-Marne 52 | 40 (2.71%) | 189 (3.27%) | 147 (3.26%) | 169 (3.70%) | 545 |
| Meurthe-et-Moselle 54 | 161 (10.91%) | 656 (11.35%) | 511 (11.32%) | 556 (12.16%) | 1,884 |
| Meuse 55 | 50 (3.39%) | 175 (3.03%) | 128 (2.84%) | 160 (3.50%) | 513 |
| Moselle 57 | 247 (16.73%) | 1,066 (18.44%) | 760 (16.84%) | 801 (17.52%) | 2874 |
| Bas-Rhin 67 | 334 (22.63%) | 1,277 (22.09%) | 1,030 (22.82%) | 1,002 (21.92%) | 3643 |
| Haut-Rhin 68 | 205 (13.89%) | 854 (14.78%) | 599 (13.27%) | 580 (12.69%) | 2238 |
| Vosges 88 | 78 (5.28%) | 332 (5.74%) | 321 (7.11%) | 265 (5.80%) | 996 |
| Total | 1,476 | 5,780 | 4,513 | 4,571 | 1,6340 |

**Table 5. Organized breast cancer screening in diabetic women in 2021 by age and area**

| Areas | Age | | | | |
|---|---|---|---|---|---|
| | 50–54 | 55–64 | 65–69 | 70–74 | Total |
| Ardennes 08 | 107 (5.37%) | 401 (5.35%) | 342 (6.02%) | 341 (5.94%) | 1,191 |
| Aube 10 | 113 (5.68%) | 402 (5.36%) | 307 (5.40%) | 371 (6.46%) | 1,193 |
| Marne 51 | 232 (11.65%) | 869 (11.59%) | 631 (11.10%) | 682 (11.88%) | 2,414 |
| Haute-Marne 52 | 72 (3.62%) | 267 (3.56%) | 197 (3.47%) | 214 (3.73%) | 750 |
| Meurthe-et-Moselle 54 | 218 (10.95%) | 795 (10.60%) | 621 (10.93%) | 646 (11.25%) | 2,280 |
| Meuse 55 | 56 (2.81%) | 209 (2.79%) | 177 (3.11%) | 202 (3.52%) | 644 |
| Moselle 57 | 268 (13.46%) | 1,194 (15.93%) | 897 (15.78%) | 904 (15.74%) | 3,263 |
| Bas-Rhin 67 | 499 (25.06%) | 1,824 (24.33%) | 1,294 (22.77%) | 1,245 (21.68%) | 4,862 |
| Haut-Rhin 68 | 303 (15.22%) | 1,135 (15.14%) | 859 (15.11%) | 759 (13.22%) | 3,056 |
| Vosges 88 | 123 (6.18%) | 401 (5.35%) | 359 (6.32%) | 378 (6.58%) | 1,261 |
| Total | 1,991 | 7,497 | 5,684 | 5,742 | 20,914 |

**Table 6. Organized breast cancer screening in diabetic women in 2022 by age and area**

| Areas | Age | | | | |
|---|---|---|---|---|---|
| | 50–54 | 55–64 | 65–69 | 70–74 | Total |
| Ardennes 08 | 86 (4.54%) | 340 (5.22%) | 273 (5.54%) | 250 (4.78%) | 949 |
| Aube 10 | 104 (5.49%) | 294 (4.51%) | 278 (5.64%) | 317 (6.06%) | 993 |
| Marne 51 | 237 (12.51%) | 703 (10.79%) | 465 (9.43%) | 550 (10.51%) | 1,955 |
| Haute-Marne 52 | 66 (3.48%) | 190 (2.92%) | 161 (3.26%) | 176 (3.36%) | 593 |
| Meurthe-et-Moselle 54 | 165 (8.71%) | 722 (11.08%) | 530 (10.75%) | 589 (11.26%) | 2,006 |
| Meuse 55 | 54 (2.85%) | 235 (3.61%) | 159 (3.22%) | 174 (3.33%) | 622 |
| Moselle 57 | 283 (14.94%) | 1,026 (15.74%) | 747 (15.15%) | 828 (15.82%) | 2,884 |
| Bas-Rhin 67 | 497 (26.24%) | 1,593 (24.44%) | 1,223 (24.80%) | 1,258 (24.04%) | 4,571 |
| Haut-Rhin 68 | 292 (15.42%) | 1,030 (15.80%) | 748 (15.17%) | 748 (26.54%) | 2,818 |
| Vosges 88 | 110 (5.81%) | 384 (5.89%) | 348 (7.06%) | 343 (6.55%) | 1,185 |
| Total | 1,894 | 6,517 | 4,932 | 5,233 | 18,576 |

In Aube, Marne, Bas-Rhin, and Haut-Rhin, participation rates were low but exceeding regional averages. In Ardennes, Meurthe-et-Moselle, and Moselle, participation rates were below regional averages. Several factors could account for these either better or poorer rates of OBCS attendance. As previously mentioned, women's socio-economic status is considered a major barrier to OBCS participation. Compared with the general population, women with type 2 diabetes displayed lower socio-economic and socio-educational levels (41-46). According to the French National Institute of Statistics and Economic Studies monetary poverty rates, most areas with low OBCS participation rates likewise displayed high monetary poverty rates (47). A link between OBCS participation and professional activity was thus observed, given that half of the Grand-Est region's inhabitants performed more than 20% of their jobs in agriculture and industry. These sectors are deemed more affected by low socio-economic status. The Grand-Est region comprises both rural and urban areas. There is a well-known link between residence place and OBCS. In 2018, almost 40% of the French population lived in rural areas (48), where access to services was more difficult, which could account for women living there participating less in OBCS than women living in urban areas (49). This could be explained by either distance from radiology services (50), density of general practitioners, or both. Areas with low OBCS participation rates tend to be mostly rural, with few accredited radiology services and low medical density. We can also see a link between the high turnout in Marne and Bas-Rhin regions along with the presence of medical schools and university hospitals. Meurthe-et-Moselle area, despite its socio-economic advantages, numerous radiology services and general practitioners, and presence of a medical faculty, displayed low rates of OBCS participation. In their study evaluating IBCS, Quintin et al. (39) showed that Meurthe-et-Moselle had a high rate of IBCS. This could explain why OBCS participation rate in this area was lower, despite the advantages mentioned above.

There were other factors linked to type 2 diabetes that could explain why diabetic women participated less in OBCS. In 2005, Lipscombe et al. (29) showed that low OBCS participation persisted after adjusting for age, comorbidities, income, and residence place, suggesting that type 2 diabetes *per se* could represent a barrier to OBCS participation, which was recently verified by Chan et al. (51). Type 2 diabetes is a complex disease, requiring time-consuming management and therapeutic education (52, 53), leading health professionals to prioritize diabetes management over cancer prevention (54). We could anticipate that the number of annual consultations would correlate with better screening follow-up, which actually was not the case (29). For health professionals, it is crucial to find enough time to properly explain the benefits of breast cancer screening to their patients, whilst listening to their fears and preconceptions (55). Diabetic women often display a poor self-image (56), over 80% of them being overweight or obese (57), both known to be barriers to OBCS participation (27, 58-60). These two patient populations could actually fear being stigmatized on account of their weight (61). Performing a logistic regression analysis on the diabetic population of the Grand-Est region may identify factors associated with non-participation in OBCS.

Our prospects for improving screening attendance are as follows. Informing patients and physicians of the increased breast cancer risk in diabetic women could help raise awareness of OBCS (62). Cardiovascular mortality was previously the leading mortality cause in type 2 diabetes patients, which is no longer the case because of prevention measures. Today, the leading mortality cause in diabetic patients is cancer (63, 64). Collier et al. (65) demonstrated that 28% of deaths among diabetic patients were caused by cancer, versus 24% by cardiovascular causes. In 2023, an English study carried out by Ashley et al. (66) investigated the knowledge and understanding of increased complication risk among diabetics. In both the general and diabetic populations, no one cited breast cancer as a type 2 diabetes complication, whereas microvascular and macrovascular complications were widely cited. Next, these authors analyzed 25 websites for healthcare professionals and for the public, with only three of them mentioning breast cancer risk as a potential complication (diabetes.co.uk, diabetes.org.uk, niddk.nih.gov), whereas the American Diabetes Association did not consider diabetes as a risk for breast cancer on its website.

One key to improving screening participation would be to increase awareness of the increased breast cancer risk among diabetic women and healthcare professionals, in our opinion. Education, information, and prevention all resulted in a reduction of macrovascular and microvascular complications. To maximize awareness, we wish to set up a campaign with posters being distributed to general practitioners. Along with raising awareness among diabetic patients, this would also raise awareness among the people surrounding them. It has been proven that if women were surrounded by family and friends, the latter would likely encourage them to more actively participate in OBCS (67-69).

In conclusion, participation in breast cancer screening by diabetic women was poorer than among their non-diabetic peers, a finding of concern given their increased risk of developing breast cancer. It is important to understand the barriers to OBCS participation, particularly those associated with type 2 diabetes. Informed patients and healthcare professionals will be one step towards further improving breast screening attendance among women with type 2 diabetes.

### Ethics

**Ethics Committee Approval:** Date were anonymous and protected by the following regulatory bodies: European Regulation RGPD n° 2016-679 of April 27, 2016; Loi informatique et libertés n° 2018-486 of June 20, 2018, and its Decree of application n° 2019-536 of May 29, 2019, consolidating Ordinance n° 2018-1125 of December 2018 modifying the law of January 6, 1978. The approval of the Committee for the Protection of Individuals was not required.

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### Footnotes

### Authorship Contributions

Surgical and Medical Practices: M.P., E.F., O.P.; Concept: M.P., E.F., O.P., C.M.; Design: M.P., E.F., O.B.; Analysis or Interpretation: M.P., E.F., T.O., O.P., C.M.; Literature Search: M.P., C.M.; Writing: M.P., E.F., O.P., C.M.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Case Report

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# Isolated Hydatid Cyst of the Breast: A Rare Pseudotumor of the Breast

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**ABSTRACT**

Although rare, a hydatid cyst of the breast represents a mammary pseudotumor. We present the case of a 49-year-old woman with no significant medical history, who was diagnosed with an isolated hydatid cyst of the breast confirmed by histopathological examination. This patient consulted for breast asymmetry and a feeling of heaviness in the left breast, with no clinical signs of systemic hydatidosis. The diagnosis was suggested by echo-mammography and confirmed postoperatively by histopathological examination. Although rarely reported, primary hydatid cyst of the breast can cause symptoms that mimic neoplasia. Surgical excision alone proved effective in treating this type of breast cyst.

**Keywords:** Hydatid cyst; breast, echo-mammography; surgery; wide excision; histopathology

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**Key Points**

- Hydatid cyst of the breast presents a distinct challenge in breast pathology.
- Isolated hydatid cyst of the breast is very rare.
- Its clinical presentation, imaging characteristics, and management is essential for accurate diagnosis and effective treatment.

## Introduction

Although rare, a hydatid cyst of the breast presents a distinct challenge in breast pathology due to its ability to mimic other benign or malignant conditions (1-3). This disease, resulting from the larval stage of the tapeworm Echinococcus, generally targets organs such as the liver and lungs but can also affect the breast (4). Therefore, a thorough understanding of its clinical presentation, imaging characteristics, and management is essential for accurate diagnosis and effective treatment. In this study, we report the case of a hydatid cyst of the breast.

## Case Report

A 49-year-old woman from a hydatid cyst endemic area presented with breast asymmetry and a feeling of heaviness in the left breast. The patient reported a progressive increase in the size of her left breast over the past few months. She had no family history of breast cancer, and no significant medical or surgical history. There were no clinical signs of systemic hydatidosis. She was a homemaker with no specific contact with animals. Examination revealed a soft, partially resilient nodule in the upper inner quadrant of the left breast measuring approximately 10 cm, mobile, with well-defined limits, without any inflammatory signs or adenopathy. The right breast was normal. The rest of the clinical examination was unremarkable.

An echo-mammography was performed, revealing a heterogeneous liquid lesion in the upper inner quadrant of the left breast measuring 82 x 24 mm with irregular contours, containing serpiginous membranes and peri-lesional fluid, suggesting a ruptured hydatid cyst of the breast (Figure 1).

The diagnosis of a hydatid cyst of the breast was suggested by this radiological appearance. However, hydatid serology was negative, and no additional hydatid lesions were detected on abdominal-pelvic ultrasound and chest X-ray. The patient underwent surgery for the excision of the left breast mass. The cyst was removed with a wide excision of the adjacent breast tissue through a curvilinear peri-areolar incision, followed by extensive lavage of the residual cavity with

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hypertonic serum and two-layer closure. The histopathological report showed the histological appearance of a hydatid cyst of the left breast with healthy margins (Figures 2, 3, 4, and 5). The patient underwent a thoraco-abdominal-pelvic computed tomography (CT) scan, which confirmed the absence of lesions suggesting a hydatid cyst of the lung or liver. The patient did not experience any recurrence within eight years following the surgery.

Consent was obtained from the patient for publication of the case.

## Discussion and Conclusion

A hydatid cyst, also known as echinococcosis, results from a parasitic infection caused by the larvae of the tapeworm *Echinococcus granulosus* (2). It is typically found in organs such as the liver and lungs, though it can also occur in other organs, including the breast (1). Isolated breast involvement is very rare, with a reported incidence rate of 0.27% (2).

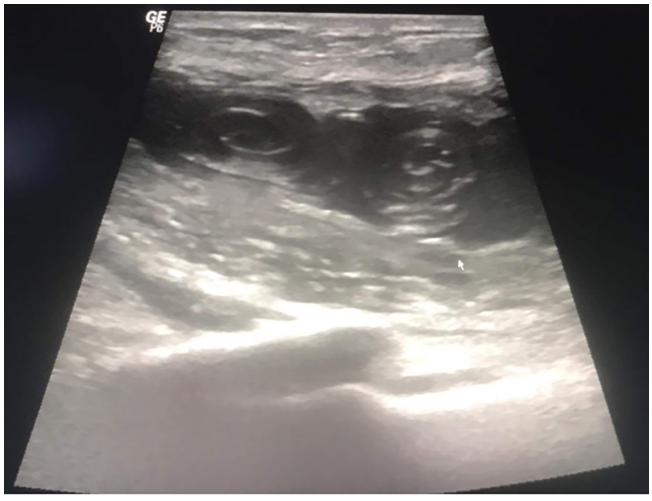

**Figure 1.** Breast ultrasound revealing a heterogeneous liquid lesion in the upper inner quadrant of the left breast measuring 82 x 24 mm with irregular contours, containing serpiginous membranes and peri-lesional fluid, suggesting a ruptured hydatid cyst of the breast

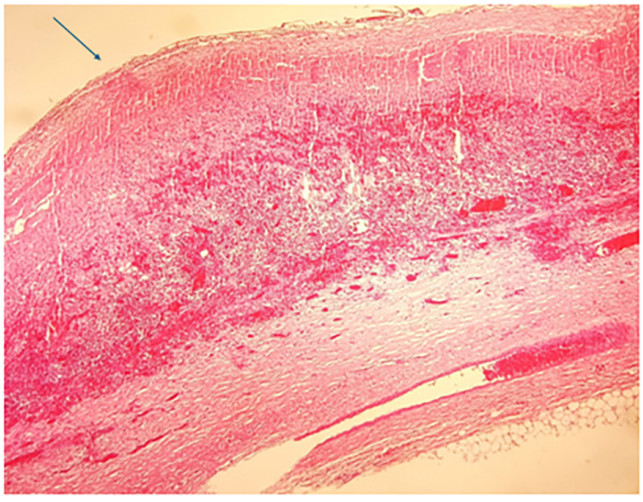

**Figure 2.** H&E x40

Echinococcosis is primarily contracted by humans through ingestion of *Echinococcus granulosus* eggs, commonly found in the feces of infected dogs. These eggs contaminate soil, water, or food sources, and once ingested, hatch into larvae in the human digestive tract. These larvae migrate to various organs, forming cysts, and eventually develop into adult tapeworms. Alternatively, direct contact with infected animals, such as handling contaminated fur or organs, can also transmit the infection to humans (4). These cysts gradually develop over years, often remaining asymptomatic until they reach a considerable size (2). If untreated, they can lead to severe complications, such as rupture, infection, or even anaphylactic shock (4). Treatment generally involves the surgical removal of the cyst (4).

Imaging findings suggestive of a hydatid cyst of the breast typically reveal a well-defined, round or oval mass with clear borders on mammography, sometimes with a fluid-air level (2). On ultrasound, the cyst appears as a fluid-filled structure with an anechoic content enclosed by a thin wall (2). The Gharbi classification system is used to categorize hydatid cysts based on their ultrasound appearance. It was developed by radiologist Gharbi and colleagues in 1981 (5). The classification includes five types:

Type I: a purely anechoic cyst with a well-defined wall, representing a simple cyst.

Type II: a cyst with a detached endocyst membrane floating in the cystic fluid, creating a "water lily sign" or "daughter cyst".

Type III: a cyst containing multiple daughter cysts, giving a heterogeneous or "honeycomb" appearance inside the cyst.

Type IV: a cyst with a heterogeneous internal structure, with solid or semi-solid components, debris, or membranes.

Type V: a complex cyst with a completely solid appearance, showing no cystic components.

Subsequently, more elaborate classifications have been used for hydatid cysts, including the standardized classification by the World Health Organization (6). Ultrasound aids in the characterization and management of hydatid cysts, helping clinicians assess the severity and complexity of cystic lesions (6).

CT plays a limited role in the evaluation of hydatid cysts of the breast. It may be used in specific cases, particularly when there is diagnostic

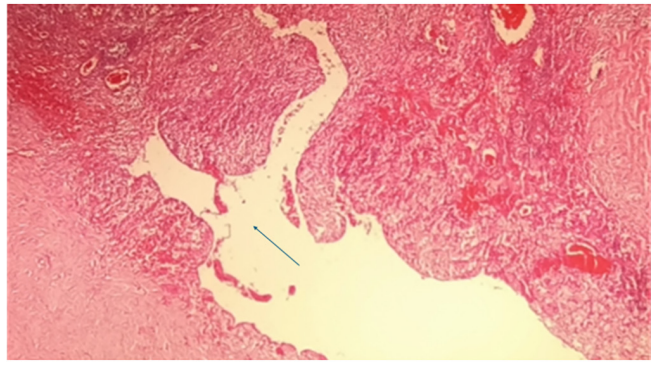

**Figure 3.** H&E x100

**Figures 2 and 3.** These microphotographs show the hydatid cyst wall (arrow) surrounded by fibro-hyalinized and inflamed pericyst with a polymorphous inflammatory infiltrate containing lymphocytes, plasma cells and numerous histiocytes associated with congestive vessels

*H&E : Haematoxylin and eosin stain*

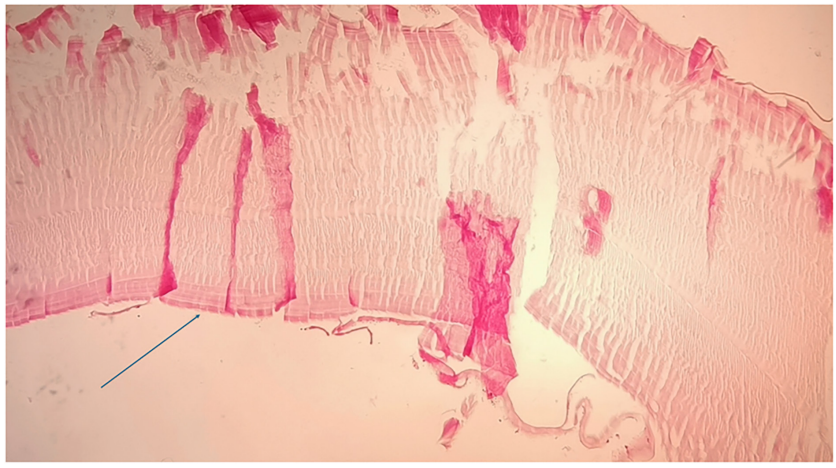

**Figure 4.** H&E x100

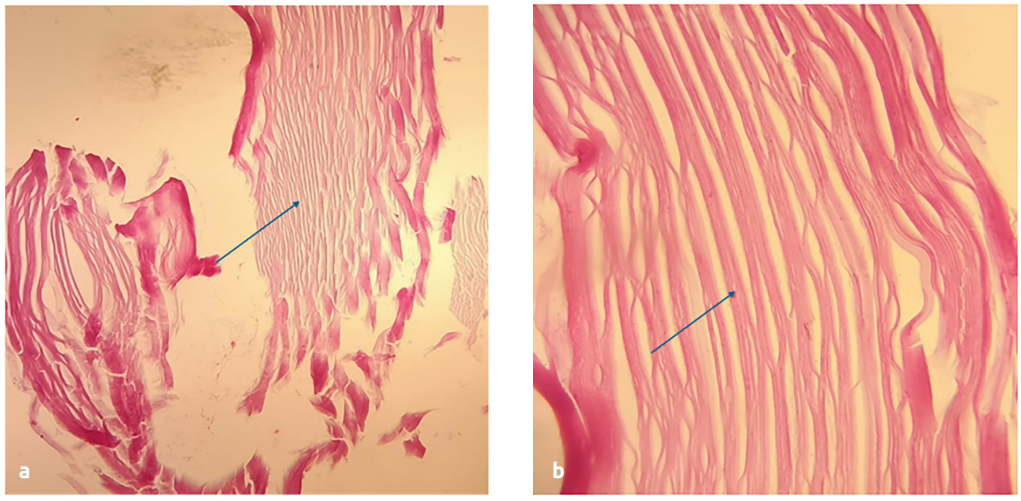


**Figure 5.** a: H&E x100, b: H&E x400

**Figures 4 and 5.** These microphotographs show the acellular laminated layers with parallel striations (blue arrow) typical of a hydatid cyst

*H&E : Haematoxylin and eosin stain*

uncertainty or to assess potential complications, such as cyst rupture or involvement of adjacent structures (7). Magnetic resonance imaging may provide additional details to further characterize the lesion and evaluate its relationship with adjacent breast tissue, typically depicting the cyst as a well-defined lesion with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (7, 8).

Histopathological examination of a hydatid cyst typically reveals distinctive features. These include a laminated hyaline cyst wall, forming the outer layer and acting as a protective barrier against the host's immune response. Beneath this layer is the germinal layer, where the parasite proliferates, characterized by numerous protoscoleces capable of developing into adult tapeworms. The cyst's interior contains clear fluid as well as daughter vesicles or hydatid sand. In addition, the surrounding host tissue often shows signs of chronic inflammation and fibrosis in response to the presence of the cyst. These histopathological findings are key for confirming the diagnosis of a hydatid cyst (9).

The presence of hydatid cysts in the body can cause various symptoms, depending on the size, location, and number of cysts. Symptoms can range from asymptomatic to severe, such as pain, fever, and potentially life-threatening complications if the cyst ruptures or become infected (10). Typically, a hydatid cyst of the breast presents as a generally non-painful mass, may be resilient or not, and of variable size but slowly increasing over time (11). Although the majority of breast hydatid cysts are identified during surgery and afterward, there are a few rare instances reported in the literature where the diagnosis was verified prior to surgery after a cyst puncture (12). By offering important details on the type of lesion and directing the proper course of treatment, cyst puncture might be crucial in the diagnosis and treatment of hydatid cysts of the breast. To reduce the chance of problems and prevent the infection from spreading, it must be performed carefully (11, 12).

The treatment of choice remains surgical excision, especially if the cyst is large or causes symptoms, such as pain or discomfort. Surgical intervention aims to completely remove the cyst while preserving as much breast function as possible (13). Early diagnosis and intervention are essential to manage this potentially life-threatening condition (10).

It is important to note that hydatid cysts can sometimes recur after initial treatment, although this is relatively rare with appropriate management. The recurrence rate varies from 1% to 11% postoperatively (14). Once the cyst is removed, antiparasitic treatment can be administered to reduce the risk of recurrence (13).

Although rare, a hydatid cyst of the breast is important to recognize, as it can sometimes be a differential diagnosis for breast cancer. The diagnosis can be suggested based on clinical context, history, and lifestyle habits, but it is generally challenging and requires radiological examinations. Mammography combined with breast ultrasound can diagnose certain hydatid cysts by the presence of pathognomonic signs, but diagnosis can sometimes be difficult. The treatment is surgical, and the diagnosis confirmation is histological.

### Ethics

**Informed Consent:** Consent was obtained from the patient for publication of the case.

### Footnotes

**Authorship Contributions:** Concept: B.B.; Design: B.B.; Data Collection or Processing: M.R., D.C.; Analysis or Interpretation: M.R., D.C., A.B.A., M.M., S.B.; Literature Search: I.B.; Writing: I.B.

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Letter to the Editor

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# Comment to "Adverse Effects of Intraparenchymal and Peritumoral Application of Isosulfan Blue Dye in Sentinel Lymph Node Mapping in Breast Cancer: A Systematic Review and Meta-Analysis"

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**Dear Editor,**

We commend Agilinko et al. (1) for their systematic review and meta-analysis investigating the adverse effects of isosulfan blue dye in sentinel lymph node (SLN) mapping for breast cancer. Their findings provide valuable insights into the safety profile of this widely used agent, particularly in highlighting the lower adverse event rates associated with peritumoral administration compared to intraparenchymal techniques. However, we wish to highlight several methodological limitations that could have impacted the strength and interpretability of the study's conclusions.

A key limitation is the absence of a formal risk of bias assessment for the included studies. Established tools such as the Cochrane risk of bias tool or the Newcastle-Ottawa scale are integral to determining the reliability of pooled evidence (2). Without evaluating potential biases in study design, data collection, or reporting, the certainty and generalizability of the findings are less clear. The omission of such an assessment leaves room for the possibility that methodological weaknesses in the included studies may have influenced the results.

In addition, while the authors conducted subgroup analyses based on the route of administration, they did not perform a broader sensitivity analysis to assess the stability of their findings. For instance, excluding studies with small sample sizes, lower-quality reporting, or methodological inconsistencies could have provided a clearer picture of the robustness of the pooled estimates (3). This step is particularly critical given the observed heterogeneity in the meta-analysis, as indicated by the I-squared statistic. Sensitivity analysis would help determine whether the findings remain consistent under different scenarios, strengthening their applicability in clinical practice.

The study also missed an opportunity to employ the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to evaluate the certainty of evidence. GRADE provides a structured approach to appraising factors such as risk of bias, inconsistency, imprecision, and publication bias, offering transparent guidance on the strength of recommendations (4, 5). Incorporating GRADE would have enhanced the clinical relevance of the study by providing a clearer understanding of the confidence clinicians can place in the results.

While the meta-regression exploring dose-response effects between the volume of dye administered and adverse events did not find significant associations, the analysis may have benefited from incorporating additional variables. Factors such as patient comorbidities, concurrent medications, and the use of preoperative prophylaxis could have offered a more nuanced understanding of predictors for adverse reactions. Including these variables in future studies could enhance the evidence base regarding the factors influencing patient safety.

This study raised important questions about clinical practice, particularly the finding that peritumoral administration was associated with lower adverse event rates than intraparenchymal injection. While this result is promising, additional research is needed to confirm the conclusion across diverse populations and healthcare settings. Furthermore, as novel agents, such as indocyanine green, gain traction

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in SLN mapping, future studies should compare their efficacy and safety with isosulfan blue to guide the evolution of clinical practice.

The study by Agilinko et al. (1) provides a foundation for understanding the safety profile of isosulfan blue, but further methodological enhancements could have strengthened its conclusions. Risk of bias assessment, sensitivity analyses, and the application of GRADE would have added greater clarity and confidence to the findings. We hope these points stimulate further discussion and refinement in future systematic reviews on this important topic.

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**Footnotes**

**Authorship Contributions**

Design: R.S.; Writing: R.M., S.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Letter to the Editor

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# Ultrasound Imaging and Guidance for Tamoxifen-Associated Achilles Tendinopathy

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**Dear Editor,**

A 62-year-old woman with a body mass index of 22 kg/m$^2$ was seen for intermittent right ankle pain persisting for the last two years. She identified the pain mainly over the Achilles tendon and this was worse during walking. Her medical history was notable for breast cancer, treated with modified radical mastectomy five years earlier. She had been receiving tamoxifen since then, but it was stopped six months prior to presentation due to severe ankle pain. Cessation of tamoxifen led to moderate symptom relief. Her medical history was otherwise unremarkable. On physical examination, the right Achilles tendon was painful to palpation. Ultrasound examination revealed significant tendinosis (particularly at the myotendinous junction) and partial rupture in the right Achilles tendon (Figure 1). Ultrasound-guided platelet-rich plasma injection was performed in the ruptured area as well as the myotendinous junction (Video 1). Three weeks after the intervention, her complaints were reported to have improved by 50% and the tendon thickness at the level of the lateral malleolus (1) decreased from 6.0 mm to 4.6 mm. Her bone mineral density measurement revealed osteopenic values (T-scores ranged from -1.3 to -2.2) in both lumbar vertebrae and femur. Following a follow-up visit, cold therapy, and exercises (range of motion, stretching, and strengthening of ankle muscles) were started. During this conservative treatment, her symptoms gradually decreased further. The patient is still under uneventful follow-up two months later.

## Discussion

Drug-induced tendinopathy can be caused by a variety of medications, including statins, fluoroquinolones, steroids, and aromatase inhibitors. Increased metalloproteinase and collagenase activity and decreased collagen synthesis may be contributory in the pathogenesis. Tendinopathy can ensue and resolve in a widely variable period (two weeks - four years) after the drug initiation/discontinuation (2).

Tamoxifen is a selective estrogen receptor modulator (SERM) which is commonly used for the treatment of breast cancer - particularly in premenopausal women with estrogen receptor positive breast cancer (3). It has both estrogenic and anti-estrogenic effects on various tissues through regulation of the expression level and/or activity of the estrogen receptors. Although its effects on tendons are less well-documented, estrogen is known to enhance collagen synthesis in tendons and reduce tendon stiffness (4). Regarding SERMs, tamoxifen may adversely affect tendons/ligaments, potentially leading to rupture, through mechanisms such as increased metalloproteinase 13 activity, decreased tensile strength, and reduced maximum load at failure (5-7).

Since the presented patient did not have potential risk factors for Achilles tendinopathy/rupture, as she was non-obese, sedentary, had no trauma and got better after drug discontinuation, tamoxifen appears to be the most likely reason for Achilles tendon injury. Needless to say, further studies are needed to explore the possible causal relationship

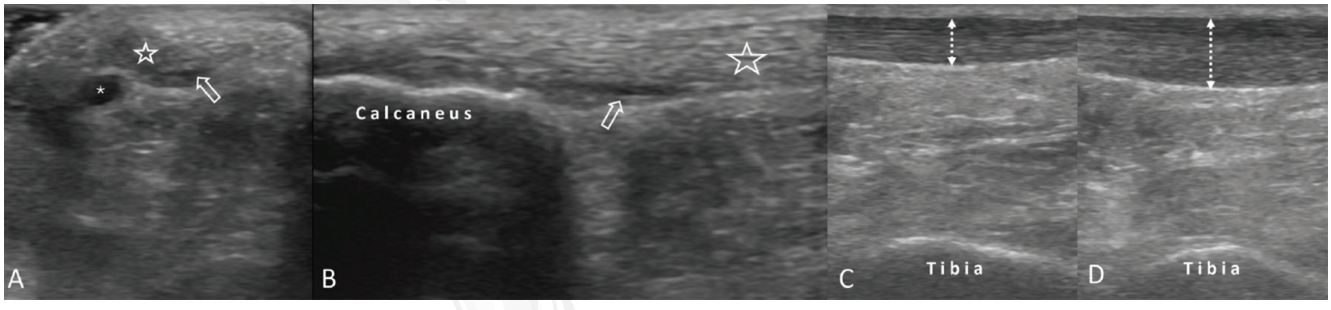


**Figure 1.** Axial **(A)** and longitudinal **(B)** ultrasound images demonstrate Achilles tendon *(stars)*, ruptured area *(arrows)* and a small ganglion cyst *(asterisk)*. Comparative longitudinal ultrasound images **(C, D)** show the swollen Achilles tendon on the symptomatic side **(D)**

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between tamoxifen use and tendinopathy whereby ultrasound imaging and guidance would be contributory.

**Video 1. Real time ultrasound guidance during platelet-rich plasma injection for ruptured area *(arrow)* of the Achilles tendon *(star)*. The needle *(arrowhead)* is inserted using the direct in-plane technique. Asterisk, injection material; curved arrow, small anechoic ganglion cyst.**

### Footnotes

### Authorship Contributions

Concept: M.K., L.Ö.; Design: M.K., L.Ö.; Literature Search: B.Y., A.F.Ç.; Writing: B.Y., A.F.Ç., M.K., L.Ö.

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