Review Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.2024112126-137

Assessing Magnetic Resonance Imaging Sensitivity and Specificity for Detecting Occult Nipple-Areolar Complex Malignancy in Nipple-Sparing Mastectomy Candidates: A Systematic Review and Meta-Analysis

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ARTICLE INFO

Received:
5 March 2024
Revised:
5 April 2024
Accepted:
7 April 2024

Keywords:
Breast MRI, sensitivity and specificity, breast cancer (BC), meta-analysis, Nipple Areola Complex

ABSTRACT

Background: Approximately 8% of breast cancers originate within the central ducts near the nipple-areolar complex(NAC), which has revealed higher rates of occult involvement than previously thought. Precise preoperative imaging to assess NAC and subjacent tumor involvement has become critical to identify candidates for nipple-sparing mastectomy (NSM) while ensuring oncological safety. The aim of our study is to determine whether Magnetic Resonance Imaging (MRI) could be used for the detection of subtle neoplastic infiltration.

Method: Electronic databases including PubMed, Scopus, Web of Science, and EMBASE were systematically searched to identify all relevant studies published before 2024 on diagnostic performance of MRI in malignant extension to the nipple. The keywords included MRI, NAC, breast cancer, NSM, True Positive (TP), True Negative (TN), False Positive (FP), False Negative (FN) were extracted for analysis. Finally, 5 articles were selected for our meta-analysis. STATA version 15 was used to analysis data.

Result: Our meta-analysis showed a pooled sensitivity of 85%(95% CI: 77%-91%)with low heterogeneity(I^2 = 00.00%), and a pooled specificity of 82% (95% CI: 49%- 95%), with significant heterogeneity(I^2 = 98%). The pooled positive diagnostic likelihood ratio(pDLR) was 4.6(95% CI: 1.3-16.6, I^2 = 96.66%), and the negative diagnostic likelihood ratio(nDLR) was 0.18(95% CI: 0.10-0.33, I^2 = 50.06%).

Conclusion: Diagnostic MRI characteristics such as NAC enhancement, non-mass enhancement (NME) type, mass size (greater than 20 mm), and tumor-to-nipple distance (TND) were assocaited with the presence of NAC involement. Because of high diagnostic accuracy, MRI imaging can be used as a helpful tool for NAC diagnosis.

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INTRODUCTION

The nipple-areolar complex (NAC) is an integral anatomical region of the breast containing ducts. This anatomical area enables lactation through its unique cellular composition.[1-3] Approximately 8% of breast cancers originate within the central ducts near the NAC.[3,4]

Diagnosing lesions in this subareolar region are more difficult than in other quadrants, as they may mimic normal nipple anatomy.[1-3,5]

Infiltrating ductal carcinoma, ductal carcinoma in situ (DCIS), and Paget's disease can involve the NAC by extending from underlying mammary ducts.[6,7] Paget's disease involves migrating adenocarcinoma cells, known as Paget cells, from underlying DCIS into the epidermis of the NAC, resulting in a characteristic eczematous presentation during clinical examination. Invasive carcinomas arising in lactiferous ducts can also infiltrate the nipple stroma and dermis.[6,8-10]

Examination of mastectomy specimens has revealed higher rates of occult nipple cancer involvement than previously thought, from 8% to 58% in normal-appearing nipples.[4,6,7,11,12] Histopathological analysis demonstrated correlations between nipple cancer infiltration and central tumor location, large size, nodal metastases, lymphovascular invasion, and multicentricity/multifocality.[11,13-16]

With broadening selection criteria, meticulous preoperative imaging to assess nipple-areolar and subjacent tumor involvement has become critical for identifying nipple-sparing mastectomy (NSM) candidates to ensure oncologic safety.[6,7,11,14,17,18] However, mammograms and ultrasound often underestimate tumor size, while clinical exams and mammograms alone inadequately detect subtle nipple invasion by carcinoma in situ or Paget's disease, necessitating other modalities for staging.[6,9,19-24]

Breast magnetic resonance imaging (MRI) can predict NAC cancer involvement more precisely than mammogram or ultrasound by allowing assessment of NAC shape and contrast enhancement indicative of direct tumor spread. Additionally, MRI enables accurate tumor measurement and localization to inform surgical planning.[6,7,19,23,25,26]

Numerous studies have shown that tumor proximity to the NAC is a reliable imaging biomarker for cancer infiltration, while nipple enhancement asymmetry on MRI predicts occult involvement.[18,27-33] Non-mass enhancement (NME) patterns, ipsilateral nipple enhancement, and shorter tumor-nipple distance have also been associated with NAC invasion, serving as MRI indicators of occult involvement in nipple-sparing mastectomy candidates.[17,29,31,34,35]

This systematic review and meta-analysis investigates MRI which previously has been shown to detect occult NAC malignancy in NSM candidates. By comparing findings across published studies, we aim to determine the most accurate imaging predictors of nipple involvement and optimize MRI to discern subtle neoplastic infiltration better. The importance of MRI in assessing NAC malignancy can have a vital role in both prognostic and diagnostic processes of breast cancers. Due to the high rates of breast cancers, MRI can improve patient selection and surgical planning for safe oncologic outcomes.

METHODS

This systematic review was conducted according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[36]

Search Strategy

The electronic databases PubMed, Scopus, Web of Science, and EMBASE were systematically searched to identify all studies on "diagnostic performance of MRI in malignant extension to the nipple" using targeted medical subject headings (MeSH). Two researchers independently searched using customized strategies for each database and assessed all relevant peer-reviewed articles published up to February 2024. This search was conducted using the following keywords: ((Nipple*) OR (Areola*) OR (Nipple-areola*)) AND (("Malignant invasion") OR ("tumor enhancement") OR ("tumor invasion") OR ("tumor extension")) AND (("Magnetic Resonance Imaging") OR ("MRI Scan*") OR ("Magnetic Resonance Imaging, Functional")). A review of the references of selected studies was also conducted to identify any additional articles, if the search process had not identified them.

Study Selection

In this systematic review and meta-analysis article, we reviewed all available studies to determine how MRI can be used to assess the invasion of breast malignancies into the NAC and the specificity and sensitivity of MRI, both quantitatively and qualitatively. Initial screening was conducted independently by two authors using titles and abstracts, and two authors chose eligible studies after reading the full texts of the selected articles. To resolve differences of opinion, a third author was consulted. All 5 studies were clinical trials.

Inclusion Criteria

Studies examining the utilization of MRI for assessing breast malignancies invading the nipple alveolar complex.

- Research reporting quantitative and/or qualitative measures of MRI specificity and sensitivity in detecting NAC malignancies.
- Clinical trials investigating MRI's efficacy specifically in evaluating NAC involvement in breast malignancies.
- Publications with accessible full-texts or abstracts from which data can be collected.

- Studies published in the English language.
- Research providing adequate data (TP, TN, FP, FN, sensitivity, or specificity) for meta-analysis on MRI's role in detecting NAC malignancies.
- Articles utilizing standardized MRI for assessing NAC involvement in breast malignancies.
- Publications involving human subjects or patients with confirmed breast malignancies.

Exclusion Criteria

- Studies without accessible full-texts or abstracts insufficient for data extraction.
- Research not published in the English language.
- Studies lacking sufficient data for inclusion in the meta-analysis or not specifically addressing NAC malignancies.
- Publications utilizing imaging modalities other than MRI for assessing breast malignancy invasion into the nipple alveolar complex.
- Articles focusing on non-MRI methods for evaluating NAC involvement in breast malignancies.
- Research involving animal models or in vitro studies without clinical relevance.

Data Extraction

After screening each article's title, abstract, and full text, the relevant studies were selected. For the final analysis, the following data were extracted: Author name, year, country, type of MRI, number of participants, NAC involvement, number of postmenopause patients, MR suspicious features, True Positive (TP), True Negative (TN), False Positive (FP), False Negative (FN), Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), False Negative Ratio (FNR), False Positive Ratio (FPR), and Gold standard.

Statistical Analysis

A bivariate model was used to obtain summary estimations of sensitivity, specificity, and area under the curve (AUC) data for diagnostic meta-analysis. DerSimonian and Laird random-effects modeling was used to quantify and pool independent diagnostic scores and their variations.[37] We took into account both between-study and within-study variations, both of which contributed to studyweighting. Forest plots were used to show study-specific estimates and 95% confidence intervals (CIs). The I^2 statistic was used to measure statistical heterogeneity, with less than 30% being low, 30% to 60% being moderate, and more than 60% being high. Stata version 15 (Stata Corp LP, College Station, TX, USA) was used for the analyses. P-values that were equal to or less than 0.05 were deemed to be statistically significant.

Publication Bias

The authors utilized Egger's funnel plot and Begg's test to analyze the publication bias of the selected papers, with $P<0.05$ being a significant publication bias. The authors conducted a linear regression analysis for publication bias, including intercept and slope parameters. It was computed using the following equation:

$y_i = a+\beta x_i+\epsilon_i$, $i = 1\dots r$ (r =the number of studies), y_i = standardized estimate, x_i = precision of studies, ϵ_i = error terms

RESULTS

Literature Search

The summary of the process of the study selection is depicted in Figure 1 Our search included all articles published before 2024. After applying the selected search term, we found 1870 articles from PubMed, 3490 from Scopus, Web of Science, and Embase. Initially, from the 5360 retrieved reports, 1776 articles were eliminated due to duplication. Based on inclusion and exclusion criteria, 3584 articles were excluded, and the remaining 142 articles were considered for complete text examination. Finally, five articles were selected for our meta-analysis (Figure 1).

Quality Assessment

Newcastle-Ottawa scale (NOS) was employed to assess the quality of papers. Based on NOS, each paper was scored a maximum of 9 points based on these criteria: Sample size selection (4 points), comparability (2 points), assessment of the outcomes (3 points). A score of more than 6 was marked as a high-quality study. Studies with moderate quality had scores of 4-6., and the quality of studies scored below 4 was considered to be low (Table 1).

Study Characteristic

The characteristics of the five studies used for this meta-analysis are demonstrated in Table 1. The publication dates ranged from 2012 to 2020. Two studies were from South Korea, two from Japan, and one from Italy. Overall, the analysis included 653 participants who underwent MRI for the diagnosis of breast cancer. The total number of NAC involvements was 116, with two studies indicating that 24 patients were asymptomatic. Three studies documented 175 individuals in a post-menopausal state, and two out of five studies reported that 17 patients were diagnosed with NAC malignancy at the post-menopausal age.

Alonzo *et al.*[38] and Hwang et al.[39] disclosed the mean tumor size among patients with NAC involvement, which was 52.6mm and 47.9 ± 23.0mm, respectively. Additionally, they provided data on the mean tumor size in patients without NAC involvement, with values of 51.5 and 39.6, respectively. They also measured the mean distance between the tumor and NAC for positive and negative involvement. In a study by Alonzo *et al.*[38], these distances were 7.9 and 23.4, while in a study by Hwang *et al.*[39] they were 5.3 ± 6.4 and 13.5 ± 13.5, respectively. Yoo *et al.* also reported these distances to be 29.1 ± 16.7 in the negative NAC involvement group and 13.7 ± 8.7 in patients with NAC involvement.

Meta-analysis

In our meta-analysis, five articles were deemed eligible to participate in the diagnostic test accuracy (DTA) analysis. The pooled sensitivity of our analysis was found to be 85% (95% CI: 77%-91%), and the heterogeneity within the included studies was low (I^2 = 00.00%). The pooled specificity was also 82% (95% CI: 49%-95%), but our analysis revealed notable heterogeneity in specificity (I^2 = 98%).

Furthermore, we computed the pooled positive diagnostic likelihood ratio (pDLR) to be 4.6 (95% CI: 1.3-16.6, I^2 = 96.66%). This suggests that a positive outcome significantly enhances the probability of accurately determining occult NAC malignancy in nipple-sparing mastectomy candidates. In contrast, the pooled negative diagnostic likelihood ratio (nDLR) was calculated to be 0.18 (95% CI: 0.10-0.33, I^2 = 50.06%) as depicted in Figure 2.

A moderate level of diagnostic accuracy was concluded due to the pooled diagnostic odds ratio (DOR) of 24.72 (95% CI: 3.49-175.10). Notably, there was a substantial level of heterogeneity, evidenced by an I2 value of 89.4%, as illustrated in Figure 4. Therefore, the diagnostic performance of MRI for detecting occult NAC malignancy is good and efficient. Regrettably, the lack of data made conducting meta-regression and subgroup analysis impossible..

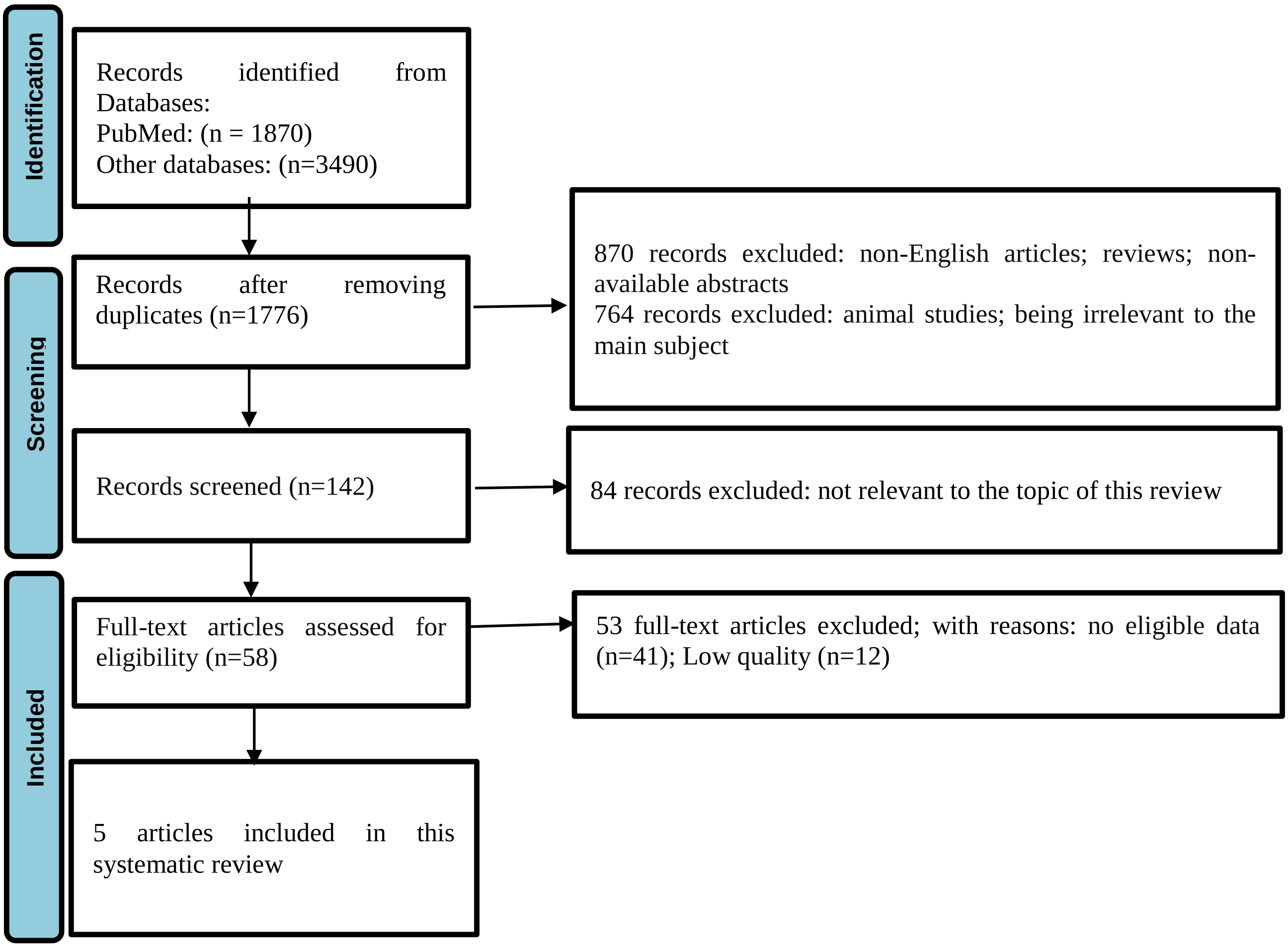

Figure 1. Flow diagram for the search and selection process of included studies according to PRISMA 2020

Table 1. Summary of the participants' characteristics

Author	Year	country	Type of MRI	Sample Size	NAC involvement	Postmenopause patients (numbers)	Postmenopause in NAC positive (numbers)	Postmenopause in NAC negative (numbers)	MR suspicious features	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV	FNR	FPR	Quality Assessment	Gold standard
Alonzo et al. (38)	2012	Italy	MRI	39	7		9	36		6	7	25	1	0.86(cut off<5mm) 1(cut off<10mm) 1(cut off<20mm)	0.78(cutoff<5 mm) 0.66(cut off<10mm) 0.50(cut off<20mm)	0.46	0.96	0.14	0.22	7	
Yoo et al. (48)	2017	South korea	3T	90	17				linear enhancement of the NAC directly from the primary tumor, unilateral NAC enhancement, and asymmetric thickness of the NAC.	14	33	40	3	0.82	0.55	0.30	0.93	0.28	0.45	9	Pathologic analysis
Hwang et al. (39)	2017	South korea	3T	98						17	55	23	3	0.85	0.29	0.24	0.88	0.15	0.71	8	
Seki et al. (49)	2019	Japan	-	168	25	56	8	48		20	6	137	5	0.8	0.958	0.769	0.965	0.2	0.042	7	Pathologic analysis
Seki et al. (50)	2021	Japan	3T	252	47	74			Nipple enhancement was considered abnormal if it was conspicuous compared with that of the contralateral nipple.	42	5	200	5	0.894	0.976	0.894	0.976	0.106	0.024	7	Pathologic analysis

Figure 3 displays the summary receiver operating curve (SROC), offering a visual representation of the overall diagnostic performance of each study. Based on the bivariate meta-analysis, the summary area under the curve (sAUC) was calculated to be 86% (95% CI: 83%-89%) which is available in Figure 3.

We performed a sensitivity analysis to assess how each study might impact the pooled DOR's result.In sensitivity analysis, it is important to assess the weight of each study and find the outlier studies to prevent high bias. As depicted in Figure 5, the overall pooled DOR was not significantly changed by excluding any included study. The results also indicated that each study did not influence the effect size notably.

To evaluate the potential impact of publication bias on our results, we conducted Deek's funnel plot asymmetry test. The findings from this analysis indicated no substantial publication bias across the diagnostic accuracy indices reported in each of the included studies.

DISCUSSION

Five of the research articles featured in the section on meta-analysis MRI was determined to have an 85% sensitivity and 82% specificity in detecting occult NAC cancer in our investigation.

As discussed earlier, the rate of unanticipated tumor involvement of the clinically normal nipple ranges from 8% to 58%, according to the analysis of mastectomy tissues. Therefore, estimating the NAC tumour involvement before surgery is critical in determining which individuals would benefit from an NSM.[17,40,41] MRI and mammography have been shown to predict nipple cancer involvement in several investigations.[42]

In a study by Byon, Hwang *et al.* 2023[43], four diagnostic MRI characteristics—NAC continuity, unilateral NAC enhancement, non-mass enhancement type (refers to lesions accompanied by NME or solely composed of NME, excluding pure mass lesions.), and mass size (greater than 20 mm)—were assessed concerning the presence or absence of NAC involvement. The estimated sensitivity and specificity for NAC involvement using a bivariate random-effects model were as follows: continuity to the NAC (Sensitivity: 71%, Specificity: 94%), unilateral NAC enhancement (Sensitivity: 58%, Specificity: 97%), NME type (Sensitivity: 55%, Specificity: 83%), and mass size > 20 mm (Sensitivity: 88%, Specificity: 58%). They concluded that unilateral NAC enhancement and continuity to the NAC could aid in predicting occult NAC involvement in breast cancer. The outcomes of our investigation are concordant with these observations, indicating a consistent alignment between the findings of our study and the results above. They also concluded that a reasonable cutoff value should be considered to obtain the required diagnostic performance with TND.

In the study of Berger, Luparia *et al.* 2017[44], a comparison was made between MRI and galactography for the detection of any lesion in patients with pathologic nipple discharge. However, the evaluation of MRI's diagnostic performance in cancer detection was limited to this modality. In this study, the bivariate showed that the pooled sensitivity for MRI and galactography was 92% and 69%, respectively.

For MRI, the pooled specificity was 76%, while for galactography, it was 39%. In alignment with our study results, they similarly concluded that MRI holds more excellent diagnostic value compared to galactography in any lesion, particularly in cases of isolated breast cancer within the same patient pool. In the detection and diagnosis of breast cancers, alternative modalities including ductoscopy and mammography may also pose competition to MRI.

Another meta-analysis study was conducted by Filipe, Patuleia *et al.* in 2021.[45] Regarding the diagnosis and treatment of patients with pathological nipple discharge, ductoscopy was compared to MRI. Ductoscopy demonstrated a sensitivity of 44% and a specificity of 98% for breast cancer detection. In comparison, MRI exhibited a sensitivity of 76% and a specificity of 84% for the same purpose. The outcome demonstrated that MRI has greater sensitivity, whereas ductoscopy had considerably greater specificity. In determining the presence of malignancy in individuals exhibiting pathological nipple discharge, their investigation demonstrated that ductoscopy offers a markedly superior diagnosis accuracy in this particular group of patients. Ductoscopy is a more cost-effective and efficient diagnostic method than MRI for identifying patients who need surgery to rule out cancer, which is inconsistent with the findings of our investigations.

In another study, Madsen, Mosebo *et al.* in 2021[46] compared the diagnostic accuracy of mammography and MRI in identifying the underlying malignancy in a more specific population (Paget's disease) by analyzing the available data. The researchers concluded that incorporating MRI alongside mammography resulted in a considerably higher degree of accuracy in identifying the underlying malignancy and appeared to improve surgical treatment for patients with Paget's disease and negative mammography.

Mammography exhibited a sensitivity of 39%, while MRI demonstrated a higher sensitivity of 68%, with a significant difference between the two (P=0.0025). Both mammography and MRI had a

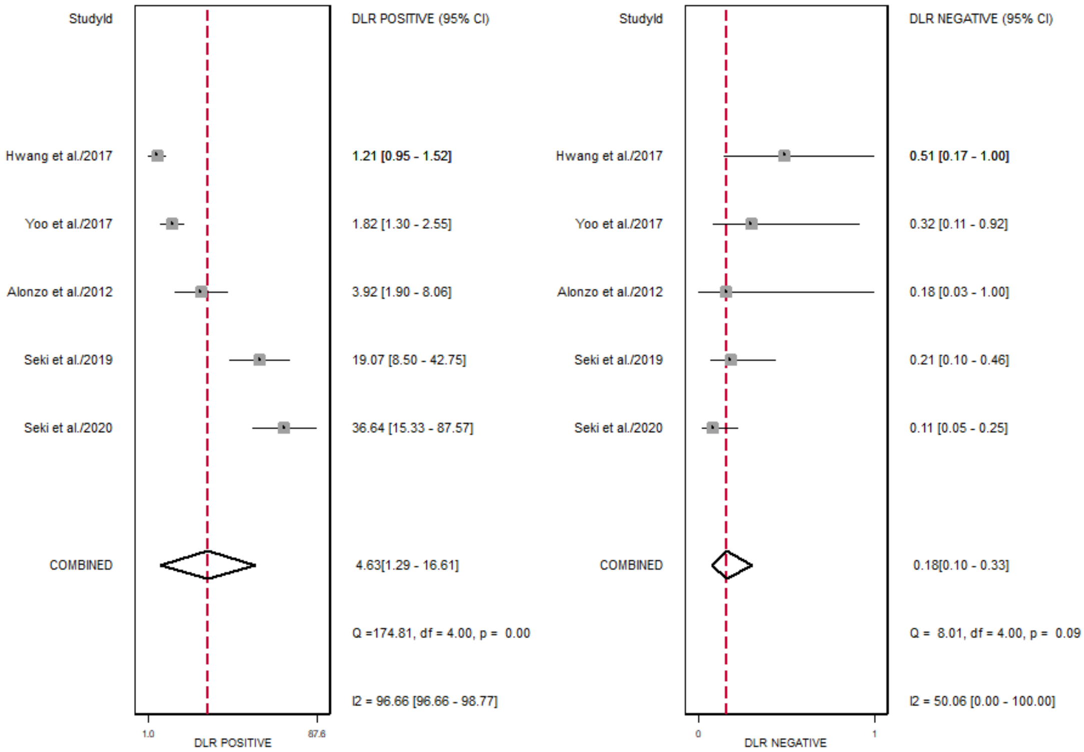

Figure 2. Diagnostic performance of MRI in NAC. forest plots of positive and negative diagnostic likelihood ratio.

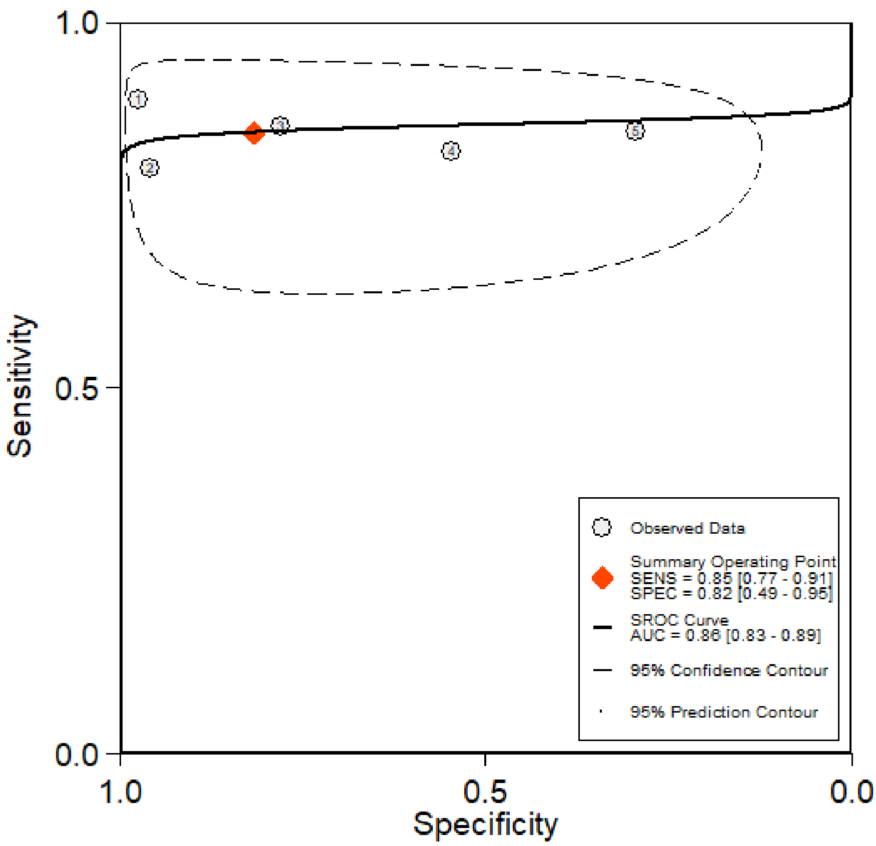

Figure 3. Diagnostic accuracy curves illustrating both confidence and prediction, which show the relative specificity and sensitivity of using MRI as a diagnostic tool for NAC

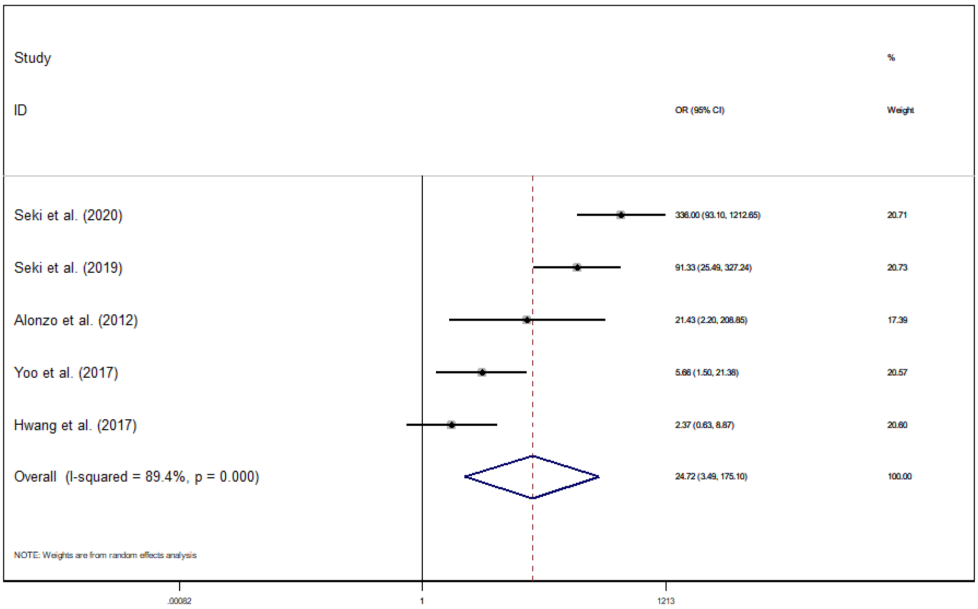

Figure 4. Forest plot demonstrating diagnostic odds ratio (DOR) of MRI in NAC detection

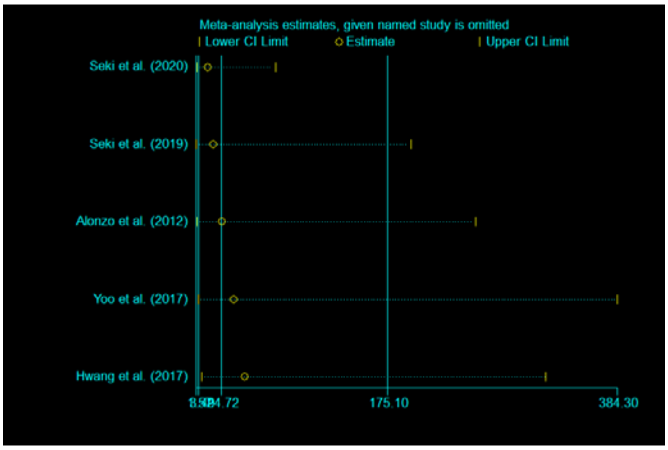

Figure 5. Sensitivity analysis

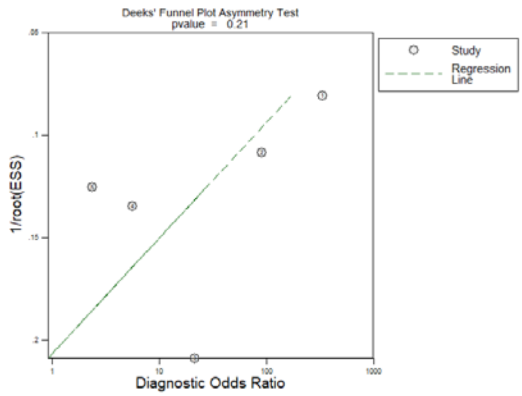

Figure 6. Publication bias of included studies

specificity of 100%, with the specificity range for MRI varying from 29% to 100%. While these results are consistent with our study, it is essential to note that the sample size was small and the population under investigation was specific.

Alaref, Hassan *et al.* in 2021 analyzed the utility of breast MRI as a screening tool for high-risk women and compared its significance with traditional methods, such as mammography and ultrasound in the early detection of invasive breast cancer. They confirmed that due to its high sensitivity and specificity, breast MRI is superior to mammogram and ultrasound in detecting early breast cancer. On the other hand, its utilization should be avoided when not necessary. Likewise, the findings of this systematic review study are in conformity with the findings of our own standard study about the superiority of MRI in detecting breast cancers. Furthermore, they advocated that developments in breast MRI sequences and techniques, such as the application of diffusion weight sequences, the use of high magnetic fields (up to 7 T), spatial resolution improvements, and spectroscopy, are encouraging instruments that will contribute to MRI's excellence.

Another meta-analysis and systematic review study was conducted by Eisen, Fletcher *et al.* in 2023.[47] The objective was to provide a comprehensive overview of how the supplementary data regarding the extent of the disease acquired through preoperative breast MRI impacts surgical management, survival, recurrence rates, re-excision, and early detection of bilateral cancer in newly diagnosed breast cancer patients. They reached the conclusion that pre-operative breast MRI significantly reduces the need for reoperations (including re-excisions and conversion to mastectomy) and recurrence. Their findings were consistent with our own; nevertheless, the RCT trial data they utilized were inadequate and posed a significant risk of bias. However, missing the involvement of the nipple alveolar complex and the MRI parameters in predicting the outcome demonstrated a notable difference when compared to our investigation.

This study offers some advantages. First, the samples were screened specifically for malignant invasion into the NAC. Moreover the MRI characteristics were thoroughly examined and compared.

Limitations

Our analysis had some limitations. Firstly, conducting comparisons was challenging due to the small sample sizes and limited number of studies included. The second limitation was that the majority of articles in this field did not evaluate nipple alveolar complex invasion specifically, so there was a paucity of data regarding NAC malignancy. Thirdly, certain articles did not highlight the specific modality (MRI) that we were evaluating in our research, and others concentrated on the application of the imaging modality for therapeutic purposes rather than diagnosis. Finally, it was not possible to assess the impact of variability in breast MRI sequences and protocols. In Alonzo study[38], we used data of <5mm cut-off for patients undergoing MRI (postmenopausal and premenopausal women) and for Hwang[39] study, we used data from strands to nipple in delay phase.

CONCLUSION

Overall, the included studies showed that MRI had a high diagnostic accuracy strength for identifying the NAC involvement in breast cancer. With a 85% sensitivity of MRI in NAC diagnosis, MRI could be suggested as a beneficial and efficient radiologic tool for diagnosing NAC malignancy. These findings can be used in detection settings and help to better diagnosis and prevention of breast cncer.

Search Srategy

((Nipple*) OR (Areola*) OR (Nipple-areola*)) AND (("Malignant invasion") OR ("Malignant involvement") OR ("Malignant extension") OR ("Malignant enhancement") OR ("tumor invasion") OR ("tumor involvement") OR ("tumor extension") OR ("tumor enhancement") OR (enhancement) OR (Extension) OR (Invasion) OR (involvement)) AND (("Magnetic Resonance Imaging") OR ("Imaging, Magnetic Resonance") OR ("NMR Imaging") OR ("Imaging, NMR") OR ("Tomography, NMR") OR ("Tomography, MR") OR ("MR Tomography") OR ("NMR Tomography") OR ("Steady-State Free Precession MRI") OR ("Steady State Free Precession MRI") OR (Zeugmatography) OR ("Chemical Shift Imaging*") OR ("Imaging*, Chemical Shift") OR ("Shift Imaging*, Chemical") OR ("Magnetic Resonance Image*") OR ("Image, Magnetic Resonance") OR ("Resonance Image, Magnetic") OR ("Magnetization Transfer Contrast Imaging") OR ("MRI Scan*") OR ("Scan*, MRI") OR ("Tomography, Proton Spin") OR ("Proton Spin Tomography") OR (fMRI) OR ("MRI, Functional") OR ("Functional MRI") OR ("Functional MRIs") OR ("MRIs, Functional") OR ("Functional Magnetic Resonance Imaging") OR ("Magnetic Resonance Imaging, Functional") OR ("Spin Echo Imaging*") OR ("Echo Imaging*, Spin") OR ("Imaging*, Spin Echo")).

ETHICAL CONSIDERATIONS

The Iranian National Committee for Medical Ethics has approved this study.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

None.

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How to Cite This Article

Ahmadinejad N, Taherkhani A, Hajibeygi R, Gorjizad M, Yaghoobpoor S, Mortazavi Ardestani R, et al. Assessing Magnetic Resonance Imaging Sensitivity and Specificity for Detecting Occult Nipple-Areolar Complex Malignancy in Nipple-Sparing Mastectomy Candidates: A Systematic Review and Meta-Analysis. Arch Breast Cancer. 2024; 11(2):126-37.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/906