

Mapping The Diagnostic Spectrum: Systematic Review and Meta-Analysis on CESM VS MRI for Breast Lesions

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Abstract

Background: Breast cancer represents a major public health challenge and requires novel diagnostic approaches. Contrast-enhanced mammography (CEM) combined with magnetic resonance imaging (MRI) is one of the major imaging approaches in the assessment of breast lesions. **Aim and objective:** The study aimed to answer the question: "Why is it essential to comprehend the differences in sensitivity, specificity and accuracy for contrast-enhanced mammography and MRI in the diagnosis of breast lesions and how these parameters will assist in clinical scenarios and patient outcomes?". **Methods:** This was a systematic review and meta-analyses including 1272 subjects done to find out studies published between 2015 to 2024 on the comparison between contrast-enhanced spectral mammography (CESM) and MRI for the detection of breast lesions. Electronic database search was done in PubMed, Scopus, and Embase, and 12 articles were finally selected. **Results:** MRI was more sensitive (91% to 100%) and specific (23% to 100%) compared with CEM, which demonstrated sensitivity (65% to 100%) and specificity (28% to 100%). The estimated overall accuracy for MRI was 85.4%, and for CEM, it was 80.7%, with MRI being especially good at detecting invasive viruses of the breast. **Conclusion:** The key findings of our study were that although both CEM and MRI could diagnose breast cancer, there was a significant difference between the two tests in sensitivity and specificity, with MRI scoring better on both counts. MRI was the gold standard for breast imaging, particularly in higher-risk patient populations.

Keywords: Breast lesion, contrast-enhanced spectral mammography, MRI, diagnostic performance, sensitivity, specificity, accuracy.

1. Introduction

Breast cancer is an important public health concern around the world, and thus new ways of diagnosing it are sorely needed. CEM and MRI are some of the key tools for evaluating breast lesions among the host of imaging techniques (Cozzi A et al, 2019). Contrast-enhanced mammography offers a compromise between mammography and the general usage of contrast materials, which results in the good visualization of the breast tissues. MRI, on the other hand, is famed for having high sensitivity and specificity in the detection of breast cancer, particularly in women with dense breast tissue (Knopp et al, 1999).

The rising incidence of breast cancer has rekindled an interest in exploiting alternative imaging strategies for early diagnosis and better treatment. While MRI has been the gold standard for breast imaging, CEM has received increasing interest because of its accessibility, shorter time for examination, and lower costs (Lobbes et al, 2021). Some recent studies indicate comparable efficacy between the two in the diagnosis of malignant lesions, but the debate about relative advantages and disadvantages continues in the scientific literature.

This systematic review and meta-analysis aim to critically analyze the existing literature comparing the two imaging modalities and MRI for the diagnosis of breast lumps. Hence, we take a broad

approach of assessing various studies and gathering data to evaluate the diagnostic performance of both imaging tests in terms of the accuracy, sensitivity, and specificity involved, together with patient-related demographic data, lesion characteristics, and media.

Understanding the comparative effectiveness of CEM and MRI is important for clinical decision-making and the enhancement of patient care. The review, therefore, may inform best practices in breast imaging as healthcare systems seek a balance between cost-effectiveness and diagnostic accuracy. Through this systematic review, we endeavor to expand on the definite role of CEM in the diagnostic pathway and, where applicable, to complement or replace MRI in certain clinical scenarios. Breast cancer is the leading cause of morbidity and mortality among women worldwide; thus, its early detection and accurate diagnosis are paramount for ensuring appropriate treatment and better outcomes (Coleman, 2017). Traditional mammography has hitherto formed the cornerstone for breast cancer screening, but its limitations, especially in women with dense breast tissue, have attracted the attention of other imaging alternatives. Among these are CEM and MRI, which appear to have certain advantages in the enhancement of diagnosis.

CEM consists of a contrast-based procedure performed within the existing mammographic framework whereby an iodine-based contrast agent by intravenous infusion is introduced (Cozzi A, 2022). This method exploits the differences in the vascularity and

contrast enhancement between malignant and benign tissues, thus increasing the chances of detecting even those lesions that may not be readily detected with standard mammography. CEM sensitivity level comparable to that of MRI can work wonders for finding a diagnosis in cases of breast cancer, according to previous studies.

MRI remains the gold standard of breast imaging due to its high sensitivity, especially for the invasive breast cancer evaluation (Iima M and Le Bihan D, 2023). Its ability to produce detailed images of soft tissue structures is ostensibly relevant in the evaluation and subsequent planning for extent of disease or surgical procedures. However, MRI is expensive, requires longer examination, and subsequently requires specialized personnel and equipment, making it less accessible in some healthcare settings.

The primary aim of this systematic review and meta-analysis is to assess and compare diagnostic effectiveness between CEM and MRI concerning breast lumps.

With this combined research and clinical data, we hope to study the diagnostic accuracy, sensitivity, and specificity of both approaches. Besides this, we will evaluate other factors influencing the performance of CEM against MRI, including the patient demographic, lesion features, and breast density.

The importance and timeliness of this review stem from the fact that the healthcare landscape is ever changing while remaining steadfast in the final goal of cost-effective yet efficient diagnostic strategies. In weighing the pros and cons of CEM against MRI, we shall eventually provide an interpretation in support of breast cancer diagnosis that would be useful in clinical practice and decision-making. In the long run, these findings could help improve the quality-of-care patients receive, bearing in mind that women should receive the right imaging evaluation by the most efficacious means in the management of breast cancer.

2. Methodology

Table 1: Quality assessment of studies using QUADAS-II format

<i>Risk of Bias</i>					<i>Applicability Concerns</i>		
<i>Author</i>	<i>Patient selection</i>	<i>Index test</i>	<i>Reference Standard</i>	<i>Flow and Timing</i>	<i>Patient selection</i>	<i>Index test</i>	<i>Reference Standard</i>
<i>Luczynska et al, 2015</i>	Low	Low	Low	Low	Low	Low	Low
<i>Chou et al, 2015</i>	High	Low	Low	Low	Low	Low	High
<i>Fallenberg et al, 2016</i>	High	Low	Low	Low	Low	Low	High
<i>Wang et al, 2016</i>	Low	High	Low	Low	Low	Low	High
<i>Kim et al, 2018</i>	High	Low	Low	Low	Low	Low	High
<i>Yasin et al, 2019</i>	High	High	Low	Low	High	High	Low
<i>Xing et al, 2019</i>	Low	Low	Low	Low	Low	Low	Low
<i>Hegazy et al, 2020</i>	High	Low	Low	Low	Low	Low	High
<i>Rudnicki et al, 2021</i>	High	Low	Low	Low	Low	Low	High
<i>Feng et al, 2022</i>	Low	Low	Low	High	Low	Low	High
<i>Sumkin et al, 2023</i>	High	Low	Low	Low	Low	Low	High
<i>Sunen et al, 2024</i>	High	Low	Low	Low	Low	Low	High

Table 2: Study characteristics

S no	Author	Study design	Country of study	Key findings
1	Elżbieta Łuczyńska et al, 2015	7 months, Prospective clinical trial	Poland	Both imaging modalities were analyzed through the use of BI-RADS classification and CESM proved to have a higher sensitivity in detecting malignant lesions, especially in multifocal breast cancer. It depicted a great negative predictive value of 100%, indicating its utility in ruling out malignancy, while the NPV of CE-MRI was low at 65%. It can be used as an alternative method of diagnosis rather than CE-MRI, especially in locations where MRI is expensive.

This systematic review and meta-analyses followed the Preferred Reporting Item for Systematic Review and Meta-Analyses (PRISMA) guidelines (**Figure 1**) (Page MJ et al, 2021).

Literature search

A comprehensive literature search was done to find out studies published between 2015 to 2024 on the comparison between contrast enhanced spectral mammography (CESM) and MRI for detection of breast lesions. Electronic database search was done in PubMed, Scopus, and Embase using the keywords “Comparison”, “Contrast enhanced spectral mammography”, “MRI” and “Breast Lesions”.

Inclusion and exclusion criteria

The inclusion criteria were: 1.) Cases available with complete data 2.) Published in English. 3.) Females with suspicious breast lesions on prior imaging or clinical examination and breast cancer

The exclusion criteria were: - 1.) Case series, reports and systematic review and meta analyses 2.) Pregnant females 3.) Renal insufficiency 4.) History of allergic reaction to iodinated contrast agent 5.) Contraindications to MRI include pacemaker, claustrophobia, metal prosthesis, or aneurysmal clips

Data extraction

The eligibility of the article based on criteria search was completed by two authors (S.H. and S.S.) and the full text of the studies was analyzed by using Microsoft Excel 2016. The two authors assessed the methodology and the quality of the articles by using the Quadas 2 assessment tool (**Table 1**) (Whiting PF et al, 2011). Finally, a total of 12 studies met the quality of assessment. The data shows different studies from different parts of the world. The first author with year of publication, type of study, country of publication, sample size, specificity, sensitivity and accuracy for CESM and MRI were tabulated (**Table 2**).

2	Chen-Pin Chou et al, 2015	comparative study	Taiwan	CEDM, CET, and CE-MRI possessed greater accuracy as compared to standard digital mammography. Abnormal mammogram follow-ups can be performed by CEDM and CET, which are less advanced than MRIs. The techniques were more precise than standard digital mammography, as indicated by the Area Under the Curve (AUC) of the ROC morphology.
3	Wang et al, 2016	Preclinical study.	China	In the case of MRI, the value of the area under the ROC curve (AUC) was 0.96, and in the case of CESM, it was 0.88. This indicates better diagnostic performance in favor of MRI. The mean difference found by the Bland-Altman analysis for the tumor diameter measurement between CESM and MRI was 0.7 mm, with CESM showing a greater correlation to pathology (0.975) than MRI (0.952). The study proposed CESM as a viable alternative to MRI for breast cancer diagnosis, particularly in areas where MRI is less accessible.
4	Fallenberg et al, 2016	Prospective two center multi reader study	Germany	Compared to MG which had the lowest benefit in dense breasts at 0.76, CESM alone and CESM + MG had 0.84 and 0.83 respectively, which is a marked increase in comparison to their difference with MRI at 0.85. For size comparison the Pearson correlation coefficient for MG was 0.61, CESM was 0.69, CESM + MG was 0.70, and for MRI it was 0.79. The study concluded that CESM, both independently and with MG, surpassed MRI accuracy, but has a higher deficiency level under MG. CESM resulted in the lowest added radiation dosage compared to MG for patients with dense breasts making it the most beneficial to that patient demographic.
5	Eun Young Kim et al, 2018	single center prospective study, 12 months	South Korea	Sensitivity to detect index cancers was comparable to CEDM at 92.9% and CEMRI at 95.2% ($p = 0.563$), and for secondary cancers was also comparable at 83.9% for both. Changes in surgical management were not statistically significant (30.9% for CEDM vs 29.7% for CEMRI, $p = 0.610$), but CEDM did have significantly higher specificity for secondary cancers (81.1% vs 73.6%, $p = 0.219$) and higher positive predictive value (72.2% vs 65.0%, $p = 0.206$).
6	Rabab Yasin et al, 2019	period of study-17 months, prospective	Egypt	MRI gave a better detailed characteristics of the lesions based on the enhancement pattern. Due to the small size of lesions in two cases malignancy was missed in CESM. On the other hand, MRI detected even the smaller lesions.
7	Xing et al, 2019	Retrospective clinical study, 7 months	China	CESM was found to have a markedly reduced rate of 10.5% false positives in comparison with the 19.8% of MRI. This suggests that CESM may be a better modality for the diagnosis of breast cancer in high-risk populations.
8	Hegazy et al, 2020	retrospective study, 18 months	Egypt	For evaluating intraductal breast papilloma, Dynamic Contrast-Enhanced MRI (DCE-MRI) has been found to have superior sensitivity across all lesion sizes. DCE-MRI showed higher diagnostic capability than CESM since the area under the ROC curve was 0.69 compared to 0.57.
9	Wojciech Rudnicki et al, 2021	retrospective clinical, 27 days	Poland	Out of all observed lesions, 43% showed strong enhancement features on CESM while 31% demonstrated medium enhancement, and 26% weak enhancement. It is interesting to note that all 121 cases on MRI had contrast enhancement, however, CESM failed to demonstrate enhancement in 13 cases, all of which were benign. The study suggests both techniques are reliable in distinguishing compositional lesions from malignant ones ($AUC > 0.5$, $p < 0.05$).
10	Lei Feng et al, 2022	4-year 10 months retrospective	China	With a sensitivity of 98.3 percent (174 real positives), specificity of 63.6 percent (7 real negatives), and accuracy of 96.3 percent (181 of 188 lesions), CESM detected 178 suspect lesions and also reported 3 false negatives and 4 false positives. CE-MRI found 183 doubtful lesions, in contrast, therefore attaining a sensitivity of 99.4 percent (176 true positives) but lower specificity (4 true negatives), resulting in 7 false positives and 1 false negative. Compared to 22 lesions (40.7%) for CE-MRI, CESM was best in graphing malignant calcifications, with 35 out of 54 lesions (64.8 percent) rated as BI-RADS 5.
11	Sunen et al, 2024	1 yr 8 months, Prospective clinical study.	Spain	The synchronization between CESM and MRI scans was remarkably high (Pearson correlation coefficient $r: 0.97$), but MRI was better at predicting the residual tumor's size (Lin's coefficient 0.91 for MRI vs. 0.73 for CESM). The average CESM tumor size overestimation was 2.87 mm, while the MRI average overestimation was 0.51 mm.
12	Sumkin et al, 2023	prospective, 4 yr 6 months	United States	It was found that MRI was able to identify 102 out of 110 index malignancies, which gave it a sensitivity of 93% (95% CI: 86%, 97%), while CEM was able. Additionally, her MRI worsened the positive predictive value (PPV) of other lesions at 28% (13 of 46; 95% CI: 17%, 44%) but increased the number of nonindex lesions while CEM had a better PPV of 52% (14 of 27; 95% CI: 32%, 71%).

3. Results

Screening flow

According to the search strategy set in advance, a total of 515 articles were retrieved in the target database (Figure 1). Then 315 duplicate articles were removed. During the title and abstract screening phase, a total of 148 articles were removed from 206 records due to guidelines and standard inconsistency. A total of 45 articles were removed from 58 records during full text screening process. Finally, 12 studies with a total of 1272 subjects were studied (Figure 1).

The forest graphs were plotted for sensitivity, specificity and accuracy for CESM and MRI The heterogeneity for CESM sensitivity, specificity and accuracy were I2 = 88.9%, 95.3% and 78.8% respectively while for MRI I2 = 85.2%, 85.2% and 79.3 % respectively (Figure 2 a,b and c).

Funnel’s test and egger’s test

The funnel plots showed asymmetry for sensitivity, specificity and accuracy for CESM and MRI attributed to chronological and geographical variances (Figure 3 a,b and c).

The Egger’s test for CESM for sensitivity, specificity and accuracy showed $p < 0.001$, $p = 0.013$, $p = 0.003$ respectively while the Egger’s p-values for sensitivity, specificity and accuracy for MRI were $p = 0.028$, $p = 0.051$, $p = 0.098$ respectively (Egger M et al, 1997).

Higher sensitivity was demonstrated by MRI in breast cancer diagnosis showing a cent percentage for big lesions. CESM depicted a sensitivity ranging from 65% to 100%. As far as the specificity was concerned, MRI showed a high rate ranging from 23% to 100% whereas CESM showed 28% to 100%. The PPV for CESM was higher at 62.22% to 96.4% while MRI showed 68% to 96.3%. MRI exhibited an area under curve of 0.96 whereas CESM showed 0.88 indicating higher diagnostic performance. The overall estimated accuracy for MRI was 85.4% while that for CEM 80.7%.

Meta regression analysis was also performed for the two diagnostic techniques regarding sensitivity, specificity and accuracy (Figure 4 a,b and c).

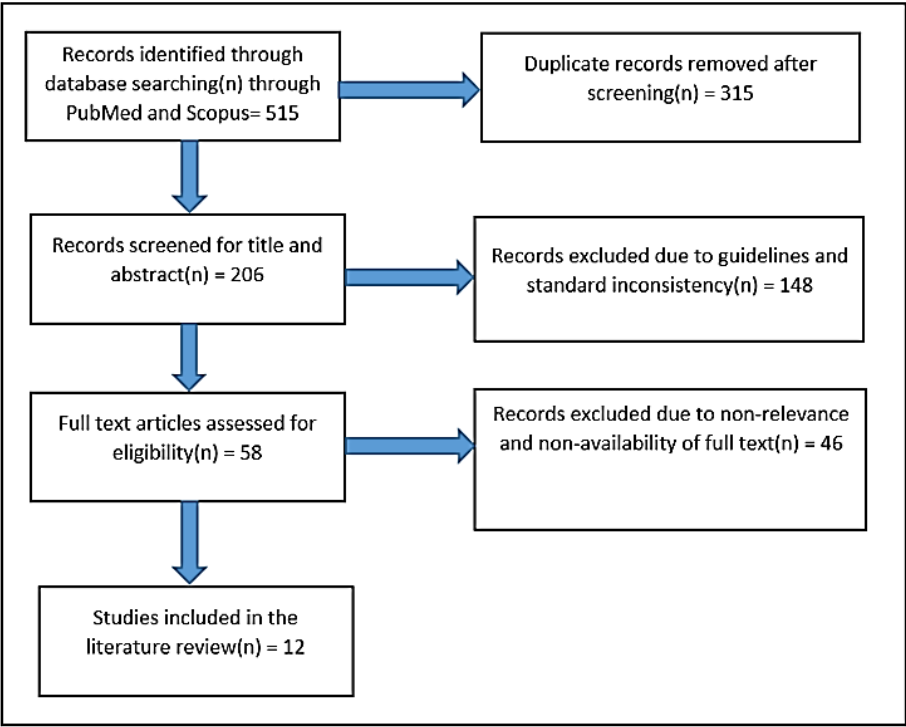
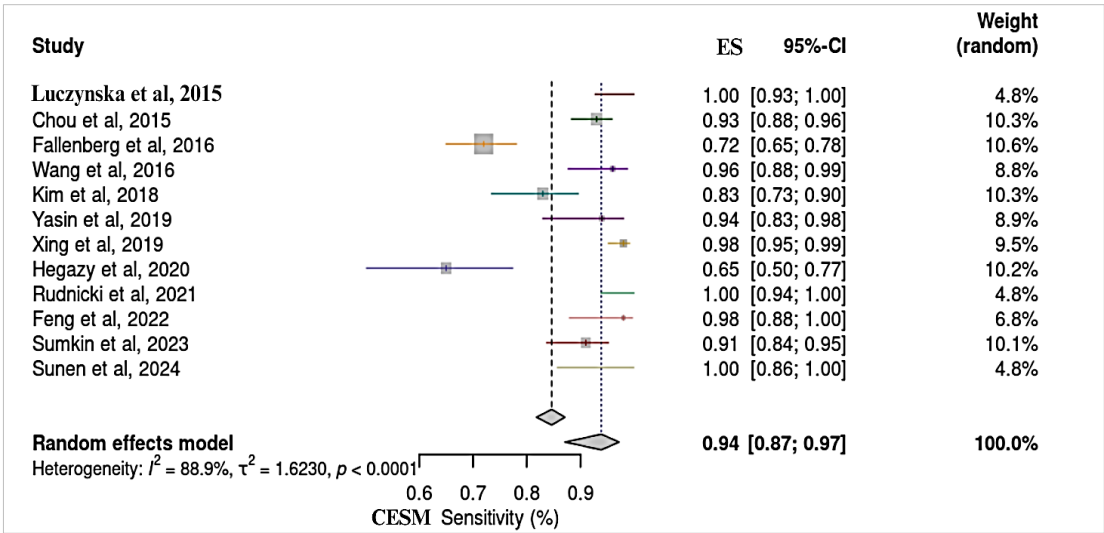


Figure 1. Flowchart for selection of studies



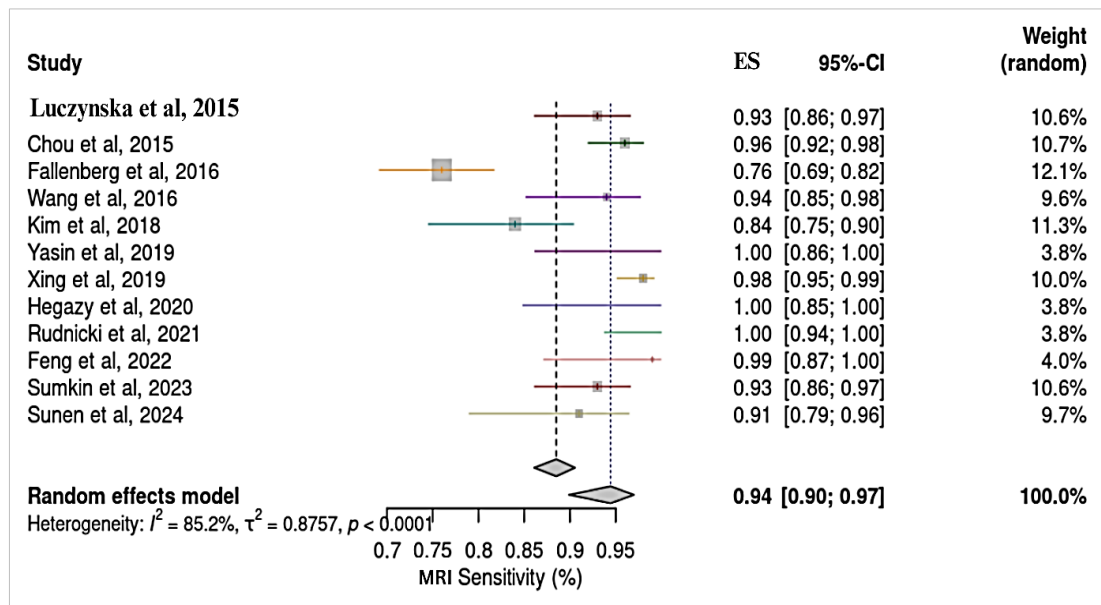


Figure 2 a) CESM vs MRI sensitivity forest plot

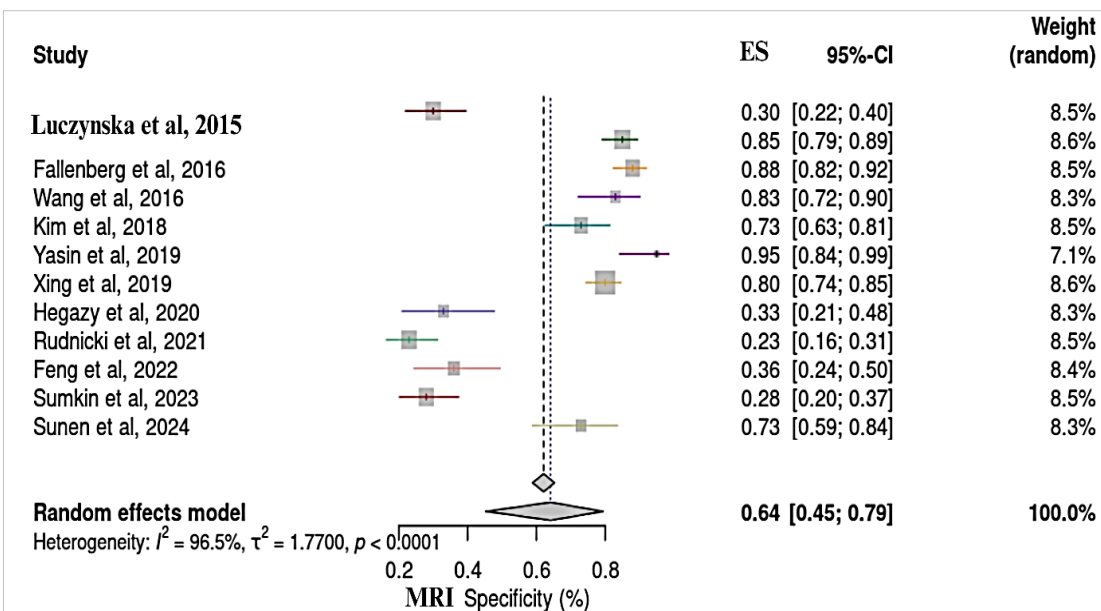
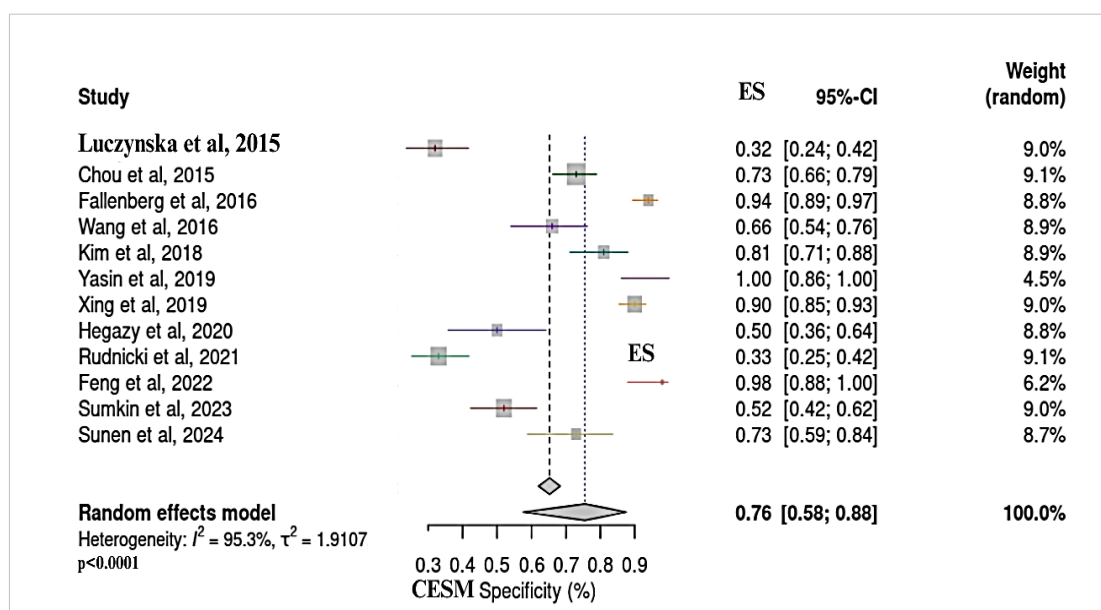


Figure 2 b) CESM vs MRI specificity forest plot

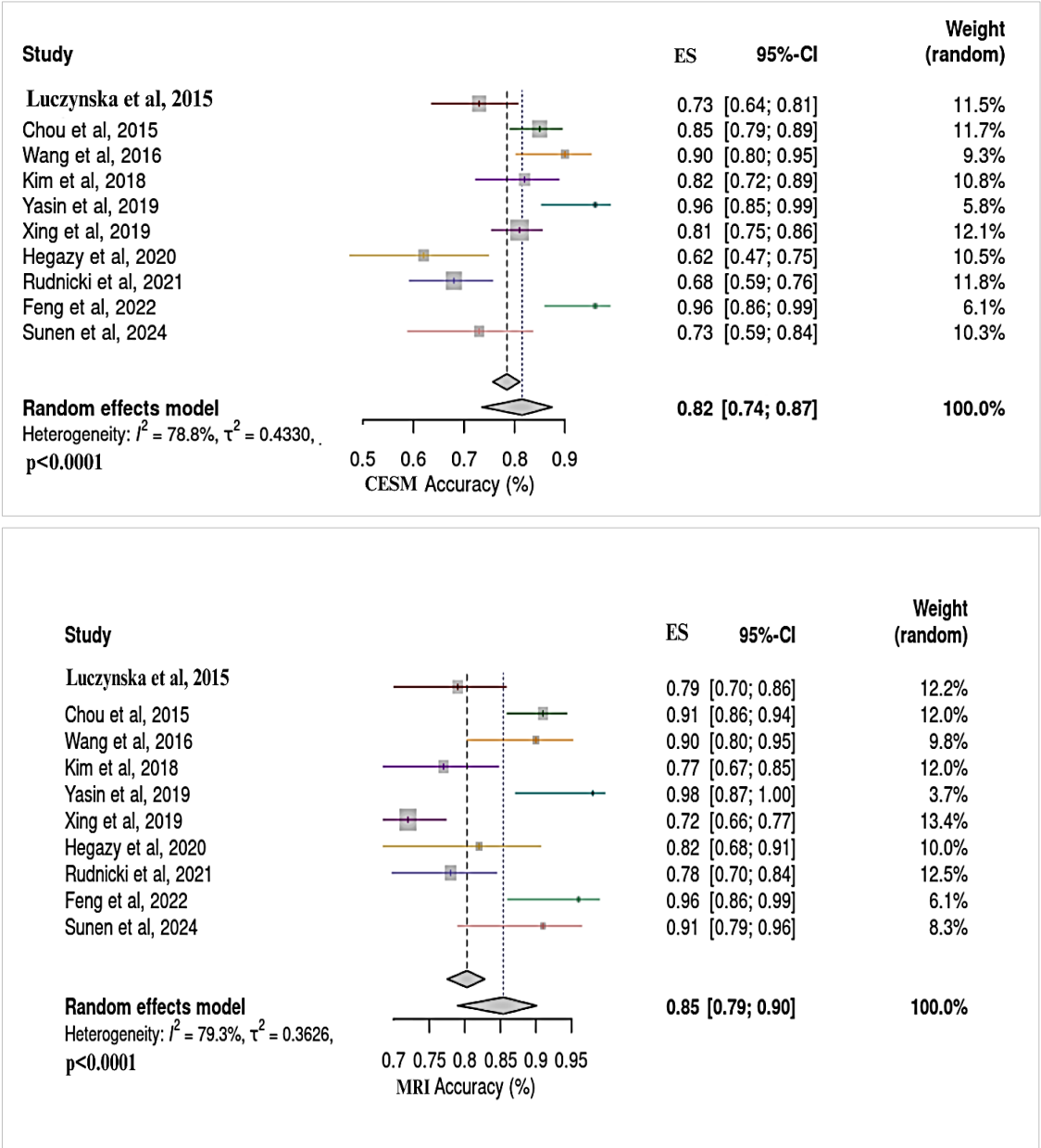


Figure 2 c) CESM vs MRI accuracy forest plot

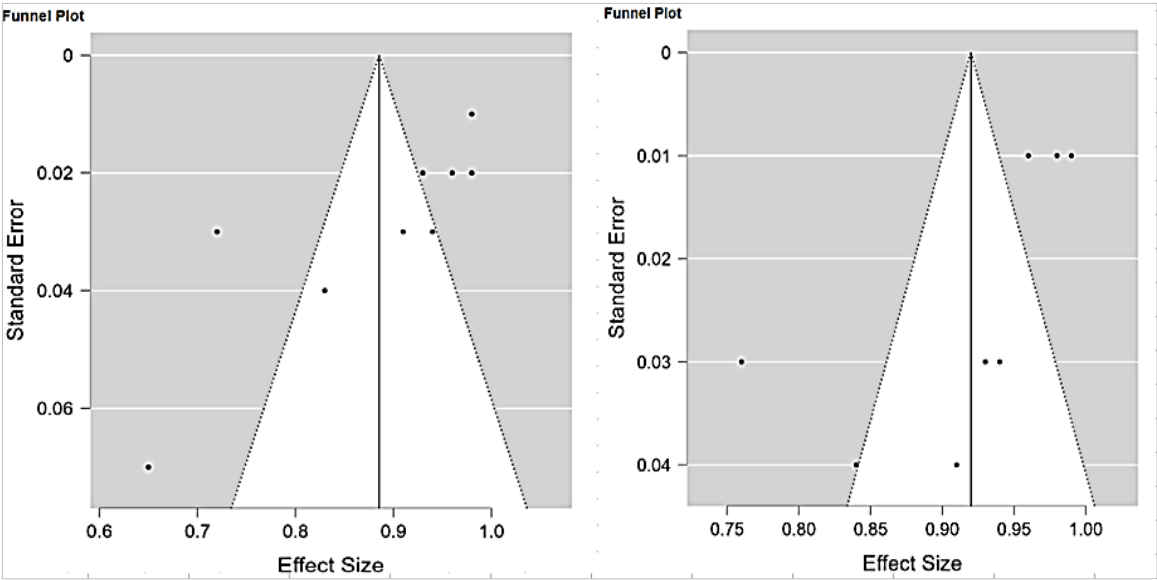


Figure 3 a) CESM vs MRI sensitivity funnel plots

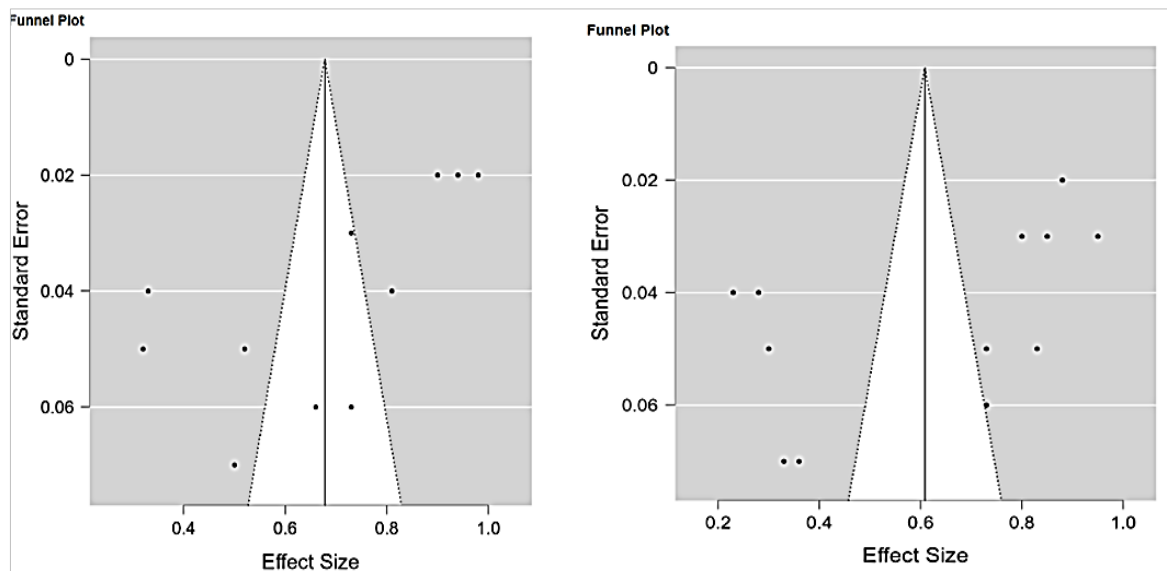


Figure 3 b) CESM vs MRI specificity funnel plots

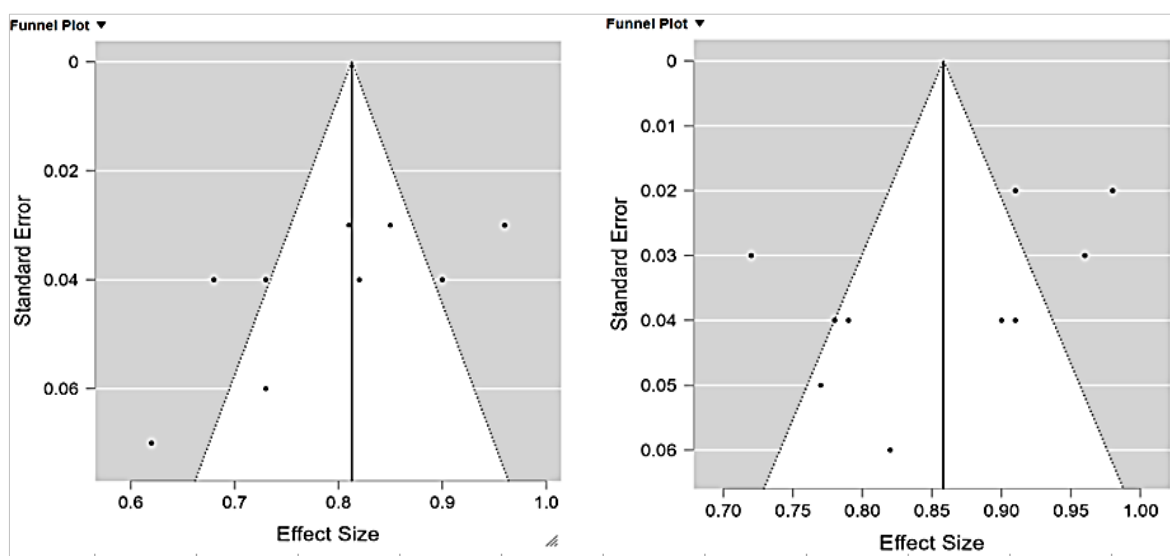
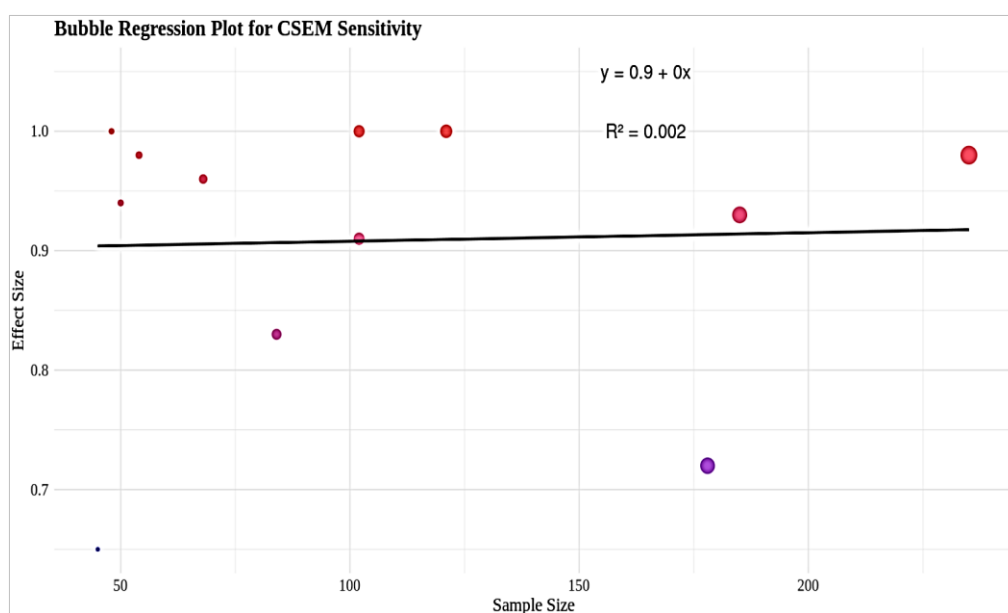


Figure 3 c) CESM vs MRI accuracy funnel plots



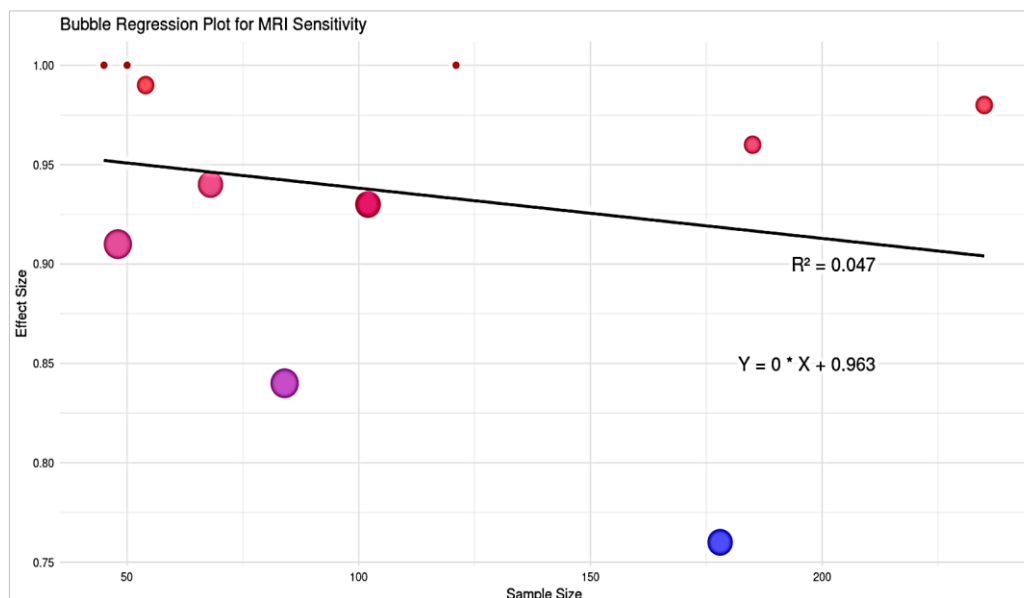


Figure 4 a) Bubble regression analysis for CESM vs MRI sensitivity

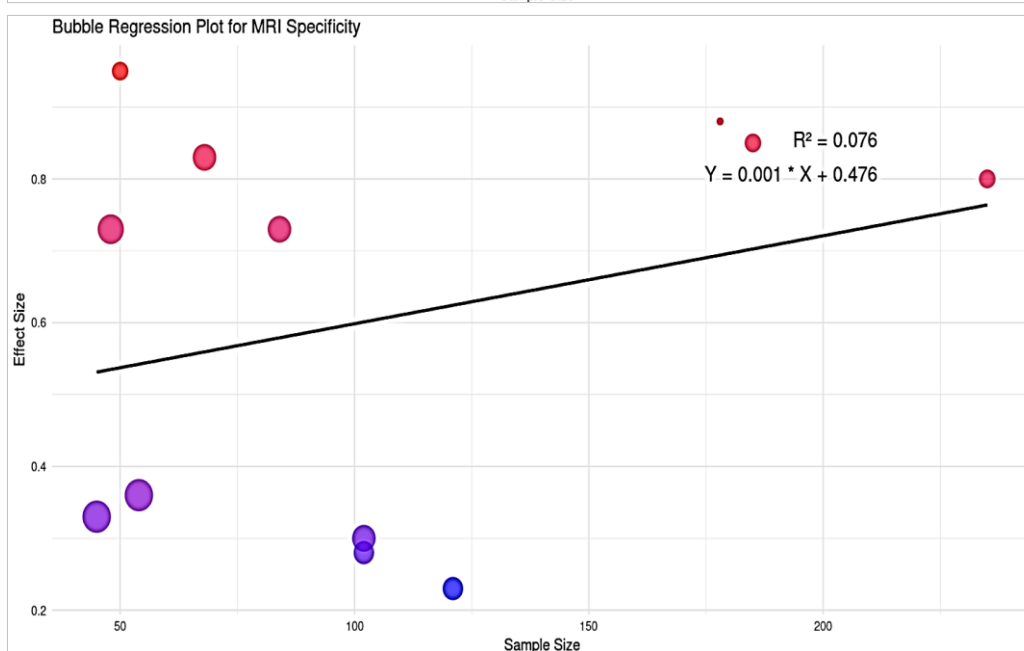
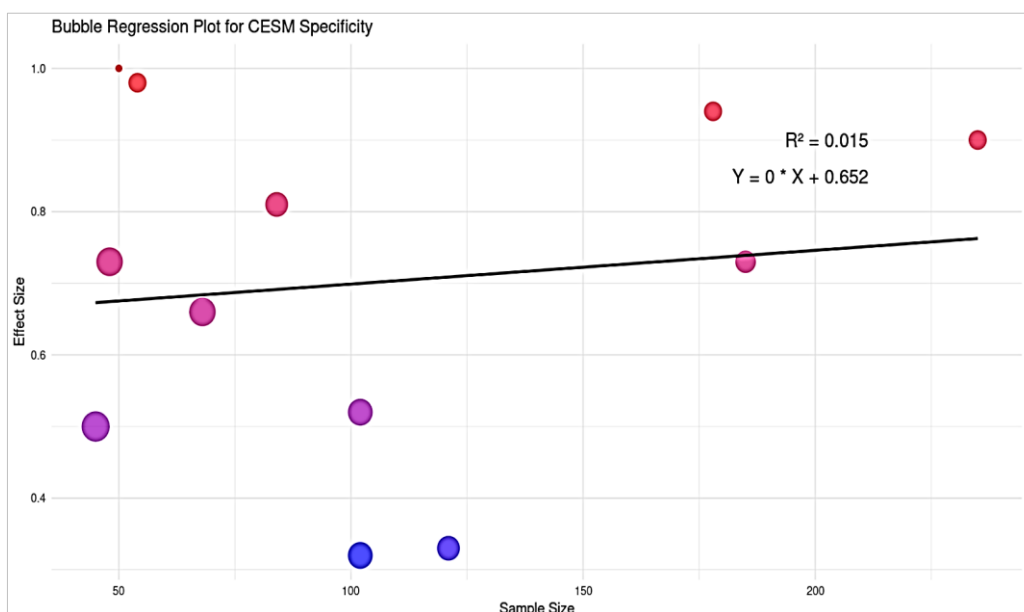


Figure 4 b) Bubble regression analysis for CESM vs MRI specificity

Statistical Analysis

SPSS version 28 was used for data analysis. R Studio was used for plotting graphs.

4. Discussion

A study reported that contrast enhanced spectral mammography showed a sensitivity of 94.1% in detection of malignancy especially in the case of multifocal breast cancer when compared to MRI that showed a sensitivity of 91% indicating the benefits of CESM over MRI in particular clinical cases (Table 3) (Luczynska E et al, 2015). This was further supported by another author (Khoddam S et al, 2024). Another study demonstrated contradiction by specifying that CESM was inferior to MRI in diagnosis of smaller lesions (Chou CP et al, 2015). The author also threw light on the superiority of dynamic contrast enhanced MRI(DCE-MRI) with a sensitivity of 100% in larger lesion(>5mm) while a sensitivity of 63.6% was reported for CESM specially for lesions between 5-10 mm supported by another author (Phillips J et al, 2023). This was further corroborated on by another author stating a 99.4% sensitivity of MRI in comparison to a 98.3% for CESM. A high specificity of 63.6% was depicted by CESM in comparison to a specificity of 36.4% for MRI showing the crucial role of CESM in the diagnosis of benign lesion without false positives (Fallenberg E M, 2017). This was further supported by another author (Sogani J et al, 2021). Similar trends in sensitivity and specificity were echoed in a study by another author (Wang Q et al, 2016). The study demonstrated lesser false positives for contrast enhanced digital mammography (CEDM: 66.7% vs contrast enhanced MRI:93.3%). However, similar sensitivities were noted(CEDM: 92.9% vs 95.2% for CEMRI). Another author further elucidated upon the effectiveness of CESM with a sensitivity of 94.1% (Kim E et al, 2018). This was further elucidated upon by another author (Miller F H et, 2010). However,

an author showed that MRI was superior in distinguishing benign and malignant lesions (Yasin R et al, 2019). This was further discussed in another study (Patel B K et al, 2018). A study suggested CESM as a better alternative for breast cancer detection in high risk population with a positive predictive value(PPV) of 94.7% for CESM in comparison to a 90.5% for MRI (Xing D et al, 2019). This was further elaborated upon in another study (Chen JH et al, 2014). In another study, the effectiveness of both the tools was depicted with different performance metrics as a sensitivity of 93% and a specificity of 87% for MRI and a sensitivity and specificity of 91% and 80% respectively for CESM were depicted (Hegazy RM et al, 2020). Another author reported higher accuracy for cancer detection in breast in case of MRI when compared to CEDM (Rudnicki W et al, 2021). Yet another author further supported this by stating that residual tumor size diagnosis with MRI showed more accuracy than CEM (Feng L et al, 2022). Similar findings were stated by another author (Baltzer PA et al, 2015). A study found a higher area of 0.96 under the ROC (receiver operating characteristic curve) for MRI when compared to 0.88 for CESM indicating superiority of MRI in diagnosis (Sumkin JH et al, 2019). This was reported in another study.

Finally, a study showed that MRI detected 102 out of 110 index malignancies (sensitivity: 93%) whereas CEM detected 100 cases(sensitivity: 91%) (Sunen I et al, 2024). However, overestimation of tumor size by 1.5 cm in 24% of cases by MRI was noted while 11% by CEM was noted. MRI showed a lower PPV of 28% for additional biopsies while CEM showed 52%.

These studies emphasize the careful balance between sensitivity and specificity in breast imaging. They show that while MRI is excellent for detecting cancers, CEM might outperform it in terms of specificity minimizing unnecessary procedures. So, both techniques offer advantages in clinical practice, depending on the clinical context. The strengths and limitations of various studies were tabulated (Table 4).

Table 3: Sensitivity, specificity and accuracy for CESM and MRI in various studies

Author	Sample Size	Sensitivity (%)		Specificity (%)		Accuracy (%)	
		CESM	MRI	CESM	MRI	CESM	MRI
Luczynska et al, 2015	102	100	93	32	30	73	79
Chou et al, 2015	185	93	96	73	85	85	91
Fallenberg et al, 2016	178	72	76	94	88	-	-
Wang et al, 2016	68	96	94	66	83	89.6	89.6
Kim et al, 2018	84	83	84	81	73	82.1	77.4
Yasin et al, 2019	50	94	100	100	95	96.4	98.2
Xing et al, 2019	235	98	98	90	80	81	71.7
Hegazy et al, 2020	45	65	100	50	33	62.22	82.22
Rudnicki et al, 2021	121	100	100	33	23	68	78
Feng et al, 2022	54	98	99	98	36	96.3	95.7
Sumkin et al, 2023	102	91	93	52	28	-	-
Sunen et al, 2024	48	100	90.9	72.7	72.7	73	91

Table 4: Strengths and limitations of various studies

S No	Author (Year)	Strengths	Limitations
1	Luczynska et al, 2015	High sensitivity of 94.1% for CESM – effective for malignant lesion diagnosis, Specially in multifocal breast cancer	Limited follow-up data and small sample size
2	Chou et al, 2015	High accuracy for MRI depicted and the author insisted on future studies	Potential bias in patient selection
3	Fallenberg et al, 2016	Comprehensive analysis done for the two techniques	Small sample size
4	Wang et al, 2016	The use of AUC was valuable in comparing modalities	Potential differences in imaging protocols
5	Kim et al, 2018	Decreased false positive rate emphasized	Long-term follow-up data lacking
6	Yasin et al, 2019	Emphasis on specific population led to better results	Lack of control group data

7	Xing et al, 2019	The PPV comparisons played crucial for clinical decision making	Variability in imaging techniques may yield different results
8	Hegazy et al, 2020	High sensitivity of 100% for large lesions > 5 mm with DCE-MRI	Potential bias if the study population is not generalized
9	Rudnicki et al, 2021	Effective results yielded due to direct enhancement pattern comparison	Lack of follow-up data
10	Feng et al, 2022	Large sample size and robust data	The results might be affected by variations in imaging protocols
11	Sumkin et al, 2023	Vivid comparison of MRI and CESM for diagnosis of malignancies, overestimation of tumor size by MRI reported	Small sample size, potential bias
12	Sunen et al, 2024	The need for high accuracy to detect residual tumor size with MRI emphasized upon	Lack of generalizability

5. Conclusion

Our analysis confirms that this systematic review and meta-analysis highlight the need for the assessment of diagnostic performance of CEM and MRI for detecting breast lumps. They have provided evidence that both modalities form strong bases for diagnosis; however, MRI always presents better sensitivity and specificity in many studies. This enhanced capability is especially seen when detecting invasive breast cancers and in patients with denser tissue, where traditional mammographic modalities fall short.

These results have widespread implications for clinical practice. Given the rising numbers of confirmed cases of malignant breast cancer and the quest for early detection, MRI, with its increased sensitivity, can result in the better detection of malignancy and hence better clinical decision-making for earlier treatments and, hence, possibly better outcomes and survival. Due to the high specificity of MRI, false positives are significantly reduced, therefore then concept for minimizing unnecessary biopsy and all sorts of anxieties around it.

From this perspective, our study supports the need to climb the ladder towards using MRI as the primary imaging modality with respect to diagnosis, at least in that high-risk population or those with complicated breast imaging scenarios. CEM, because of its advantages like accessibility and short time of examination, was favored by physicians; however, the evidence presented in this review sustains an assertion that MRI remains the gold standard of breast imaging.

In light of these findings, we suggest that breast imaging protocols present new opportunities for systematic review on the incorporation of MRI, especially when the risk of breast cancer assessment is heightened or when initial imaging test results are inconclusive. Future studies should further dissect through comparative effectiveness of these modalities based on a technological innovation in the imaging world and the changing holistic picture in breast cancer diagnosis.

Our study aligned with the aim of comparing the two diagnostic criteria for breast lump so as to draw conclusion regarding the more effective tool out of the two to promote future research for better outcomes.

Strengths and Limitations

The major strengths of our study were that the systematic review and meta analyses included both prospective as well as retrospective study and the period of studies taken for the review was 10 years. However, the limitation was that high heterogeneity was reported in the meta-analyses attributed to the chronological and geographical variations.

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Conflicts of Interests

The authors report no conflict of interest.

Author Contributions

Conceptualization and methodology, S.H. and S.S.; Formal analysis, S.H., S.S., J.H.; Visualization and writing – original draft S.H., S.S., J.H.; Writing – review and editing, S.H., S.S. and J.H. All authors have read and agreed to the final version of the manuscript.

Ethical Approval

Not Required because the study was a systematic review and meta analyses including studies already published during the period 2015-2024.

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