

## Review Article

# Meta-analysis of the synergistic effect of magnetic resonance imaging and mammography in breast cancer detection in women with dense breasts

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**Abstract:** Objectives: This meta-analysis aimed to evaluate the combined effectiveness of Magnetic Resonance Imaging (MRI) and mammography in detecting breast cancer in women with dense breasts. Methods: A comprehensive search was conducted across PubMed, Web of Science, and EMBASE databases up to December 31, 2023, to identify relevant studies. Studies focusing on breast cancer detection in women with dense breast tissue and providing data on the sensitivity, specificity, or positive predictive value of combined MRI and mammography screening, or the use of MRI following a negative mammogram, were included. The meta-analysis was conducted using Stata 15.0, and study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Results: Ten studies, involving 51,602 participants, were included in the meta-analysis. The combined use of MRI and mammography for breast cancer detection in women with dense breasts yielded a pooled sensitivity of 0.87 (95% CI: 0.79-0.92), specificity of 0.95 (95% CI: 0.89-0.97), positive likelihood ratio of 2.55 (95% CI: 1.45-4.46), negative likelihood ratio of 0.11 (95% CI: 0.07-0.17), diagnostic score of 3.18 (95% CI: 2.35-4.02), and diagnostic ratio of 24.14 (95% CI: 10.44-55.81), and an area under the Summary Receiver Operating Characteristic curve of 0.97 (95% CI: 0.95-0.98). Conclusion: This meta-analysis demonstrated that the combination of MRI and mammography enhanced breast cancer detection in women with dense breasts. This synergistic approach significantly improves detection sensitivity in this high-risk group.

**Keywords:** Breast cancer, dense breast tissue, Magnetic Resonance Imaging (MRI), mammography, meta-analysis

## Introduction

Breast cancer is a widespread and complex disease that remains a significant health concern for women worldwide. It involves the uncontrolled growth of cells within the breast tissue, which, if left undetected and untreated, can metastasize to other parts of the body [1, 2]. Early detection through screening is essential for improving patient outcomes and survival rates, as it provides more treatment options and a higher chance of successful intervention [3].

Mammography, a form of low-dose X-ray imaging, has long been the primary method for breast cancer screening due to its ability to detect abnormalities such as tumors and calci-

fications [4]. However, the efficacy of mammography is greatly influenced by breast tissue density, which varies significantly among individuals. Breast tissue density refers to the ratio of glandular and connective tissue to fatty tissue [5]. Women with dense breast tissue, especially those with heterogeneous or extremely dense tissue, are at an elevated risk for breast cancer and may have reduced mammographic sensitivity [6, 7]. As a result, mammograms may fail to detect cancer in these women, leading to delayed diagnosis and treatment.

Magnetic Resonance Imaging (MRI) is an advanced imaging technique that uses a strong magnetic field and radio waves to generate detailed images of the body's internal structures [8, 9]. MRI is known for its superior soft

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tissue contrast, allowing for clear differentiation between various tissue types and the detection of abnormalities not visible on mammograms [10]. MRI is particularly useful in evaluating the extent of breast cancer, since it can identify smaller lesions and is more sensitive in detecting cancer in women with dense breast tissue [11]. Although MRI has the potential to complement mammography, studies on the combined use of both methods for breast cancer detection have yielded mixed results. Some research suggests that adding MRI to mammography significantly improves detection rates, especially in high-risk populations and those with dense breasts [12]. However, concerns about the cost-effectiveness of this approach, the possibility of increased false positives, and the invasiveness of MRI have been raised. This meta-analysis aims to thoroughly evaluate the sensitivity, specificity, and positive predictive value of MRI when used alongside mammography, while also addressing the benefits and challenges of this integrated imaging strategy.

### Materials and methods

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13], and the standards outlined in the Cochrane Handbook [14]. This study was registered on the INPLASY platform with registration number INPLASY2024100028.

#### *Literature search*

We conducted a search for studies examining the predictive value of MRI when used in conjunction with mammography for diagnosing breast cancer in women with dense breasts. The search was performed across the PubMed, Web of Science, and EMBASE databases, covering the period from the inception of each database through December 31, 2023. The search strategy included the following terms: “Magnetic Resonance Imaging” or “MRI Scans” or “Magnetic Resonance Images”, and “Mammography” or “X-ray Breast Tomosynthesis”, “Digital Breast Tomosynthesis”, and “Breast Cancer” or “Breast Neoplasms” or “Breast Tumor” or “Breast Carcinoma”, and “Dense Breasts”. Two experienced researchers independently conducted the search, and any discrepancies were resolved through consultation or by involving a third researcher.

#### *Literature screening*

Inclusion criteria were: (1) Studies focused on breast cancer detection in women with dense breast tissue; (2) English-language publications; (3) Studies reporting sensitivity, specificity, predictive diagnostic score, diagnostic ratio, positive likelihood ratio, negative likelihood ratio for combined mammography and MRI screening, or MRI follow-up after a negative mammogram.

Exclusion criteria included: (1) Reviews, conference abstracts, commentaries, or editorials; (2) Studies without full-text availability; (3) Studies lacking accuracy-related indicators or positive predictive values without underlying data.

Following deduplication, two researchers (YFL and DQL) independently screened the literature by reviewing titles, abstracts, and full texts when necessary, applying the predefined inclusion and exclusion criteria.

#### *Data extraction*

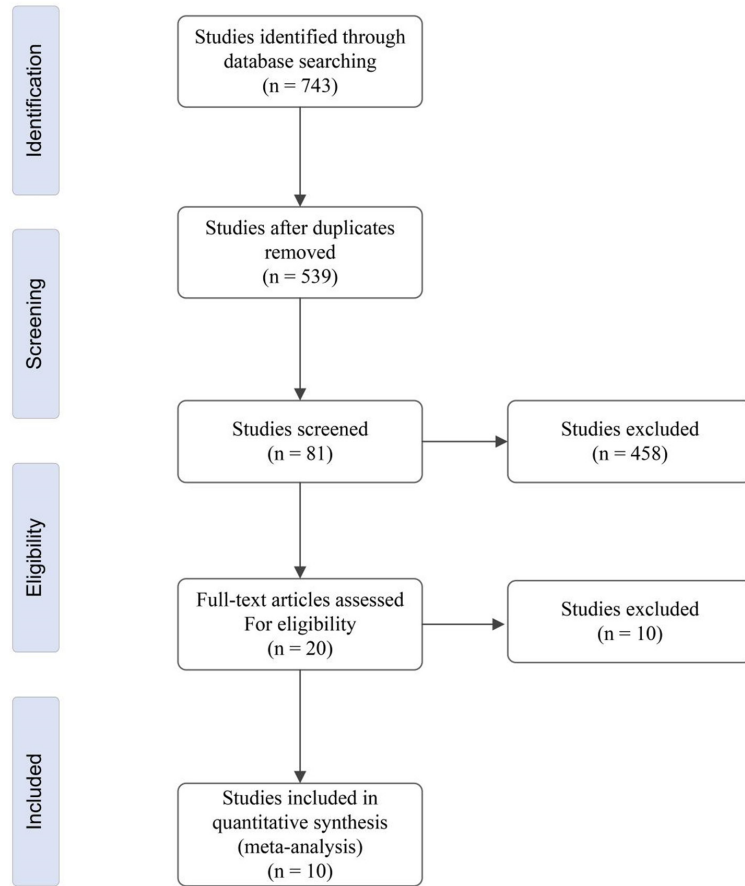
Two independent researchers (YFL and DQL) extracted the following data from the included studies: (1) General information: title, publication year, and authors; (2) Study characteristics: design type, setting; (3) Screening methodology: combined mammography and MRI or MRI following a negative mammogram; (4) Diagnostic reference standard; (5) Outcome data: true positives, false positives, true negatives, false negatives.

Discrepancies were resolved through discussion with the senior author (HW).

#### *Quality assessment*

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was used to evaluate the quality of the included studies, focusing on two dimensions: risk of bias and clinical applicability. The bias assessment included four domains: case selection (three questions), index test (two questions), reference standard (two questions), and flow and timing (four questions). Clinical applicability was evaluated separately for case selection, index test, and reference standard. A domain was considered to have poor clinical applicability if the actual situation poorly matched the research question, good applicability if it close-

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**Figure 1.** Selection flow chart for identifying studies eligible for inclusion in the meta-analysis.

ly matched, and unclear applicability if it was difficult to assess due to incomplete information. Two researchers (YFL and DQL) independently extracted data and assessed study quality, with discrepancies resolved through discussion and, if needed, by involving a third researcher.

### Statistical analysis

Statistical analyses were performed using Stata 15.0 (Stata Corp LLC). Forest plots were generated to summarize the pooled sensitivity, specificity, predictive diagnostic score, diagnostic ratio, positive likelihood ratio, and negative likelihood ratio of the studies. A summary receiver operating characteristic (SROC) curve was constructed to assess overall accuracy. Heterogeneity in sensitivity and specificity was evaluated using the  $I^2$  statistic alongside the Q-test. An  $I^2$  value  $\leq 25\%$  indicated low heterogeneity, an  $I^2$  value between 25% and 75% was considered moderate, and  $I^2 \geq 75\%$  indicated

high heterogeneity. Due to heterogeneity between studies and the negative correlation between sensitivity and specificity, a bivariate random-effects model was used to pool sensitivity and specificity. A sensitivity analysis was conducted to assess the robustness of the results. The Deeks test was applied to detect publication bias, with a  $P$ -value  $< 0.05$  indicating evidence of bias. Subgroup analyses were conducted to explore the influence of different study types, types of dense breast tissue, and detection methods on diagnostic accuracy. Studies were stratified into subgroups based on these characteristics. Pooled sensitivity, specificity, Diagnostic Odds Ratio, and Area Under the Curve (AUC) were calculated for each subgroup using random-effects models. Heterogeneity within each subgroup was also assessed using the  $I^2$  statistic and Q-test. Statistical significance was set at  $P < 0.05$ .

## Results

### Study selection

**Figure 1** illustrates the study selection process. A total of 743 studies were initially identified. After removing duplicates, 539 studies remained. Of these, 458 studies were excluded for not meeting the inclusion criteria. Of the remaining 81 studies, 61 were excluded due to repetitive or insufficient data. Subsequently, 20 studies underwent full-text review to assess eligibility. Ultimately, 10 original research articles were included in this meta-analysis.

### Characteristics of included studies

The main characteristics of the 10 studies included in the meta-analysis are summarized in **Table 1**. The studies were published between 2000 and 2021, with sample sizes ranging from 30 to 40,373 participants, totaling 51,602 individuals. Eight studies involved combined

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**Table 1.** Main features of the studies involved in the meta-analysis

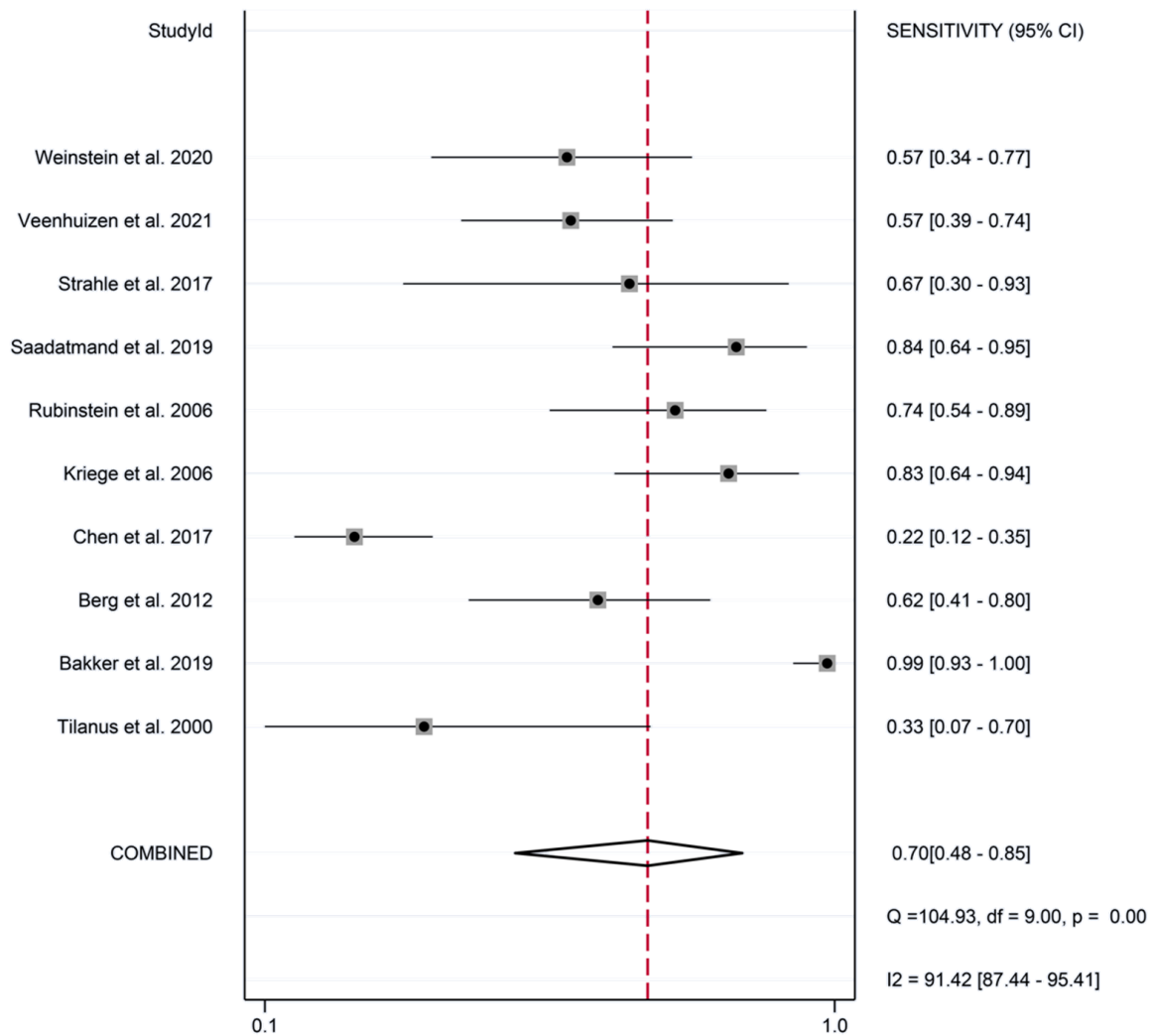
Author	Year	Sample size	Study type	Age (years)	Detection method	Reference standard	Breast density type
Tilanus et al. [25]	2000	109	Observational study	41.5	M (-): MRI M (+): biopsy	Pathology + 12-month follow-up	Dense
Bakker et al. [26]	2019	40,373	RCT	50-70	M (-): MRI M (+): biopsy	Pathology + 24-month follow-up	Extremely dense
Berg et al. [27]	2012	2809	RCT	56.8	MRI+M	Pathology + 12-month follow-up	Dense
Chen et al. [28]	2017	356	Prospective study	48.2	M (-): MRI M (+): biopsy	Pathology + 12-month follow-up	Dense
Kriege et al. [29]	2006	1952	Screening study	25-70	MRI+M	Pathology + 36-month follow-up	Dense
Rubinstein et al. [30]	2006	30	Prospective study	41.4	MRI+M	Pathology + 6-month follow-up	Dense
Saadatmand et al. [31]	2019	1355	RCT	44.7	MRI+M	Pathology + 12-month follow-up	Dense
Strahle et al. [32]	2017	671	Prospective study	55.7	MRI+M	Pathology	Dense
Veenhuizen et al. [33]	2021	3436	Prospective multicenter trial	54	MRI+M	Pathology + 24-month follow-up	Extremely dense
Weinstein et al. [34]	2020	511	Retrospective study	58	MRI+M	Pathology + 6-month follow-up	Dense

RCT: randomized controlled trial; M: mammography; MRI: magnetic resonance imaging; M (-): MRI: MRI imaging was conducted for individuals with negative mammography results.

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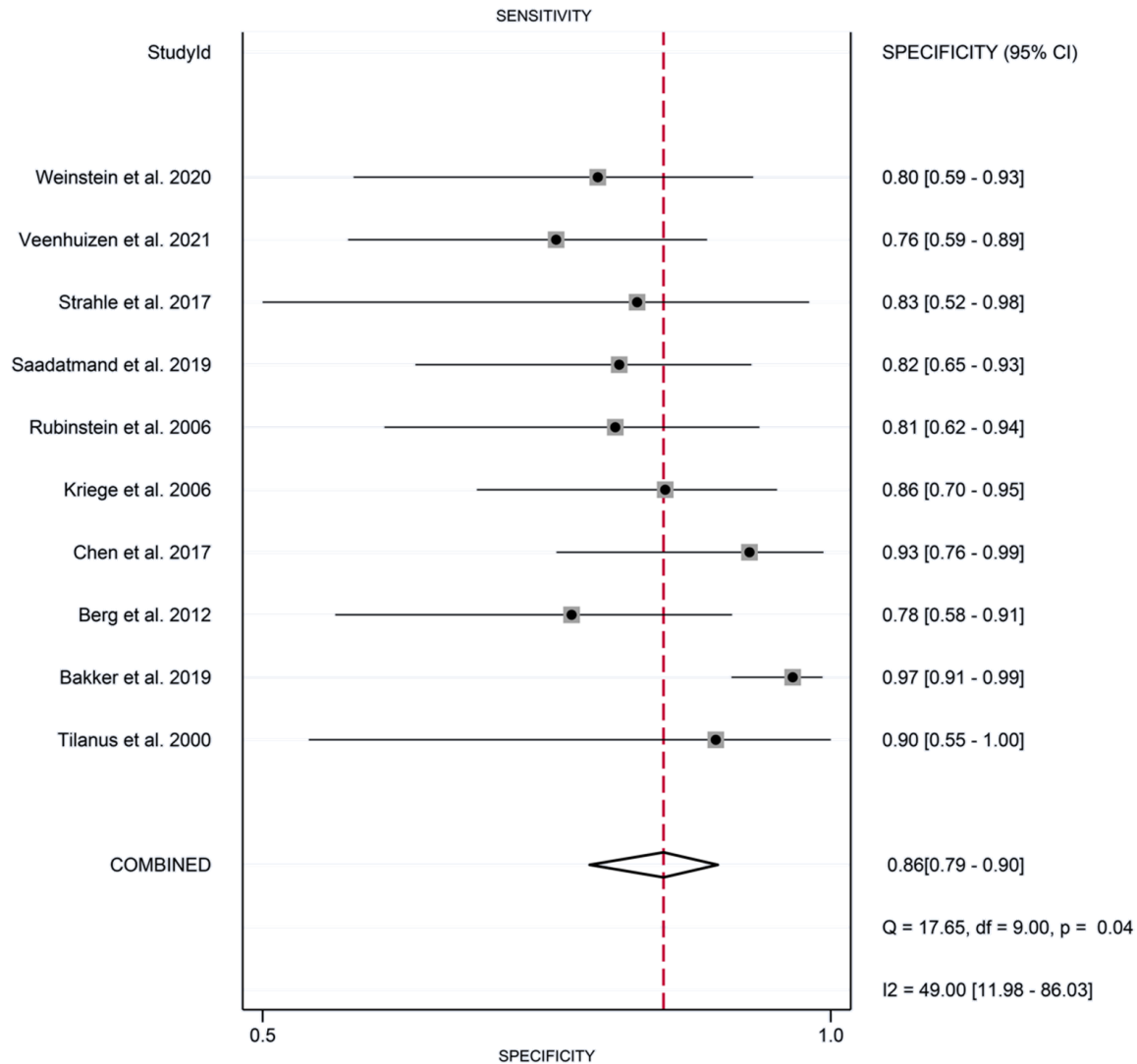
**Table 2.** Quality assessment of the ten included studies

Included study	Risk of bias				Clinical applicability		
	Patient selection	Index text	Reference standard	Flow and timing	Patient selection	Index text	Reference standard
Tilanus et al. [25]	Low risk	Low risk	Low risk	High-risk	Low risk	Low risk	Low risk
Bakker et al. [26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Berg et al. [27]	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk
Chen et al. [28]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Kriege et al. [29]	High risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Rubinstein et al. [30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Saadatmand et al. [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Strahle et al. [32]	High risk	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk
Veenhuizen et al. [33]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Weinstein et al. [34]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk



**Figure 2.** Forest plots of pooled sensitivity of synergistic effect of magnetic resonance imaging and mammography in the detection of breast cancer in women with dense breasts.

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**Figure 3.** Forest plots of pooled specificity of synergistic effect of magnetic resonance imaging and mammography in the detection of breast cancer in women with dense breasts.

MRI and mammography (MRI+M) screenings for all participants. Two studies first performed mammography screening, followed by MRI for participants with negative mammography results, and biopsy for those with positive mammograms.

### Quality evaluation

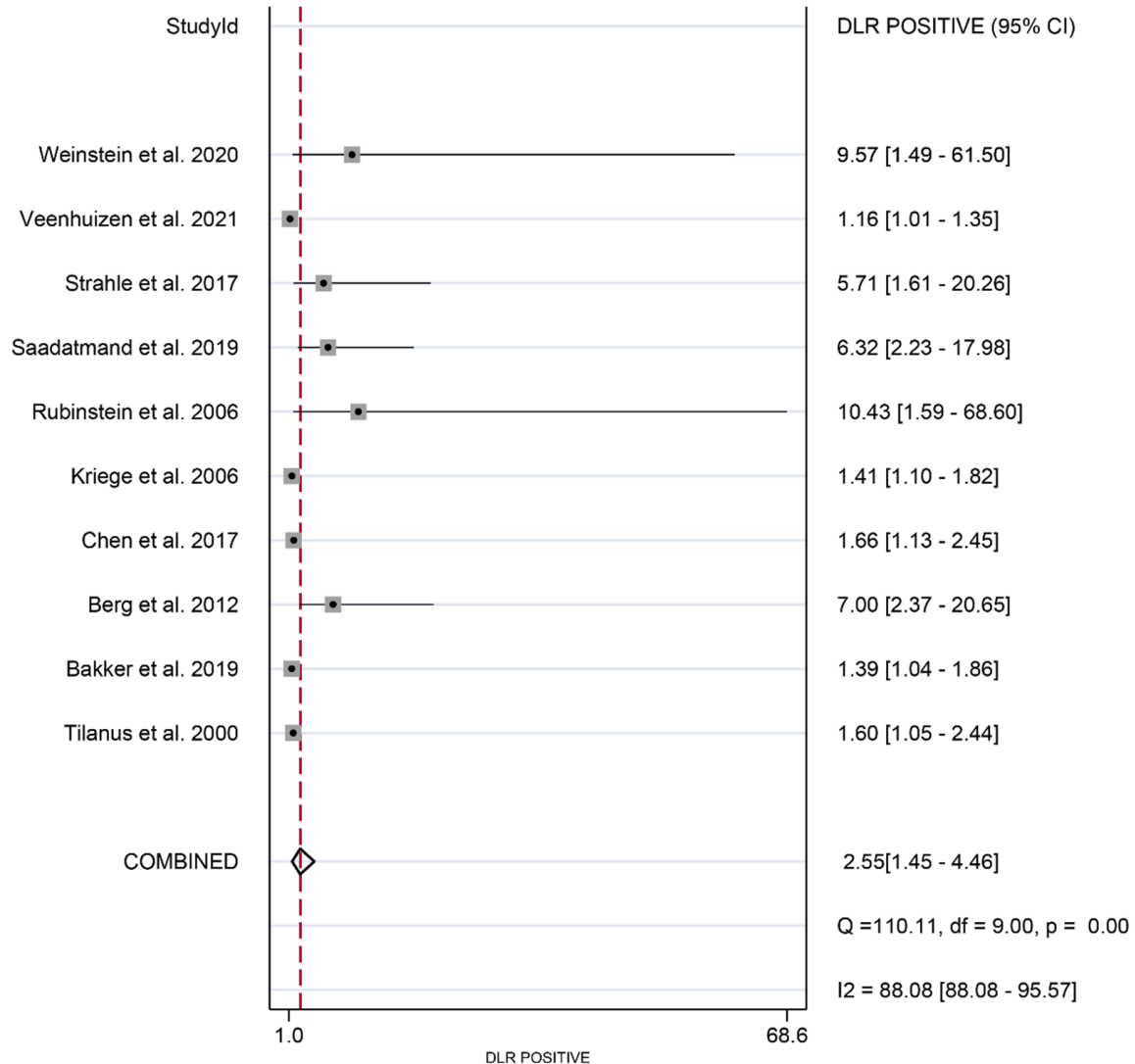
As depicted in **Table 2**, one study exhibited a high-risk bias concerning the flow and timing of data collection, while two studies showed high-risk bias in patient selection. Overall, the QUADAS-2 assessment indicates that most

studies had a low risk of bias and minimal concerns regarding applicability.

### Meta-analysis of combined effects

The meta-analysis revealed the following pooled results: sensitivity of 0.87 (95% CI: 0.79-0.92) (**Figure 2**), specificity of 0.86 (95% CI: 0.79-0.90) (**Figure 3**), positive likelihood ratio of 2.55 (95% CI: 1.45-4.46) (**Figure 4**), and negative likelihood ratio of 0.11 (95% CI: 0.07-0.17) (**Figure 5**). Additionally, the diagnostic score was 3.18 (95% CI: 2.35-4.02) (**Figure 6**), diagnostic ratio was 24.14 (95% CI:

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**Figure 4.** Forest plots of pooled positive likelihood ratio of synergistic effect of magnetic resonance imaging and mammography in the detection of breast cancer in women with dense breasts.

10.44-55.81) (**Figure 7**), and the area under the SROC curve was 0.97 (95% CI: 0.95-0.98) (**Figure 8**).

### Sensitivity analysis

The sensitivity analysis indicated that excluding any single study, studies with  $\geq 2$  outcomes or overlapping participants, or studies with high or unknown risk in certain quality assessment aspects did not significantly affect the pooled sensitivity and specificity. This suggested that the results were robust (**Table 3**).

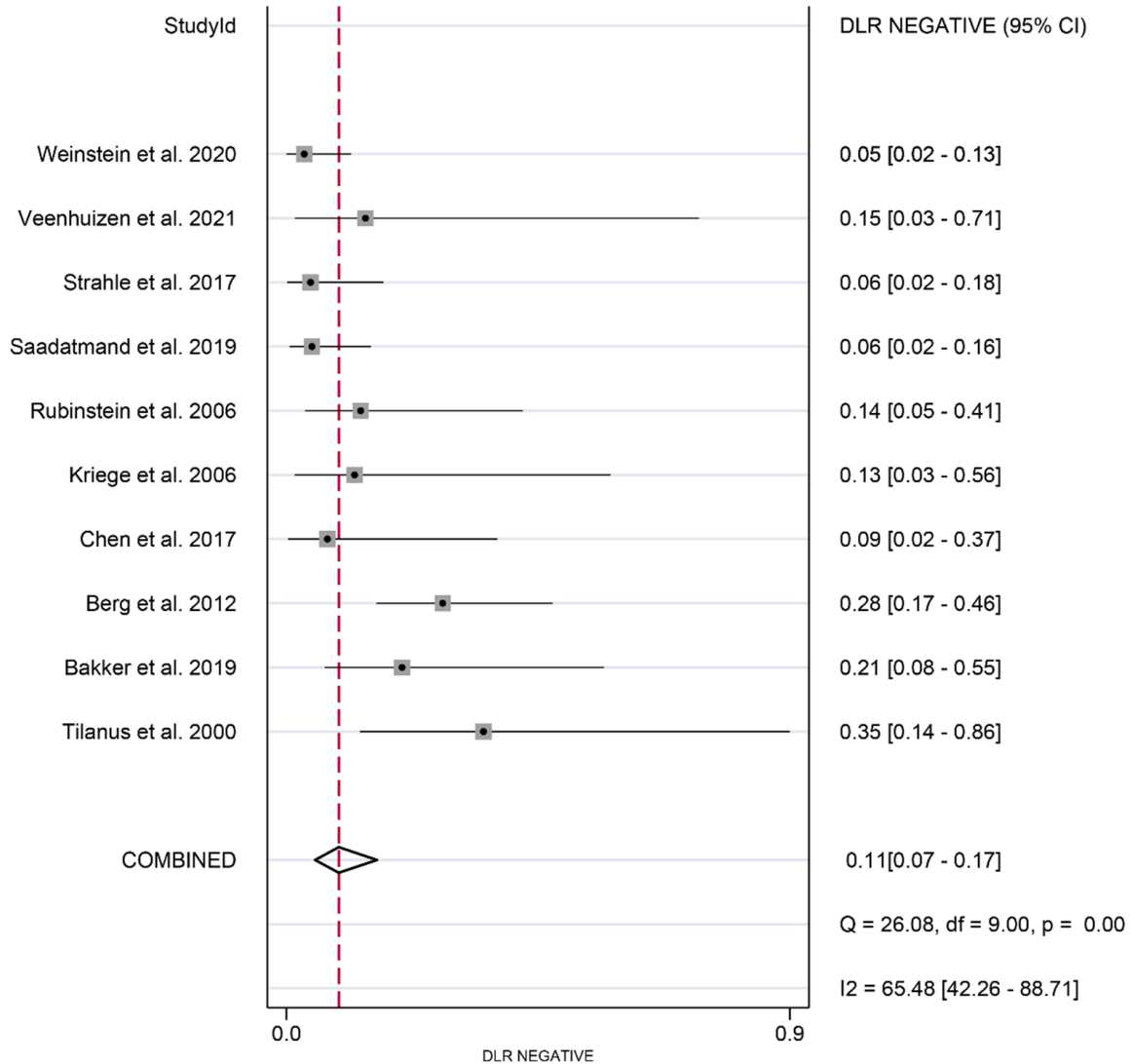
### Publication bias

The funnel plot generated by Deeks' test did not show significant asymmetry (**Figure 5**), indicating a low risk of publication bias, with a *P*-value of 0.61.

### Subgroup analysis

Statistically significant differences in diagnostic accuracy were observed across subgroups categorized by study type, breast tissue density, and detection method. The subgroup analysis in **Table 4** indicates that combining MRI

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**Figure 5.** Forest plots of pooled negative likelihood ratio of synergistic effect of magnetic resonance imaging and mammography in the detection of breast cancer in women with dense breasts.

with mammography yielded high diagnostic performance across all subgroups, particularly in women with dense breasts. The analysis demonstrated consistent sensitivity and specificity across the categories, highlighting the complementary role of MRI in enhancing breast cancer detection. The high AUC values further confirm the reliability of this combined imaging approach.

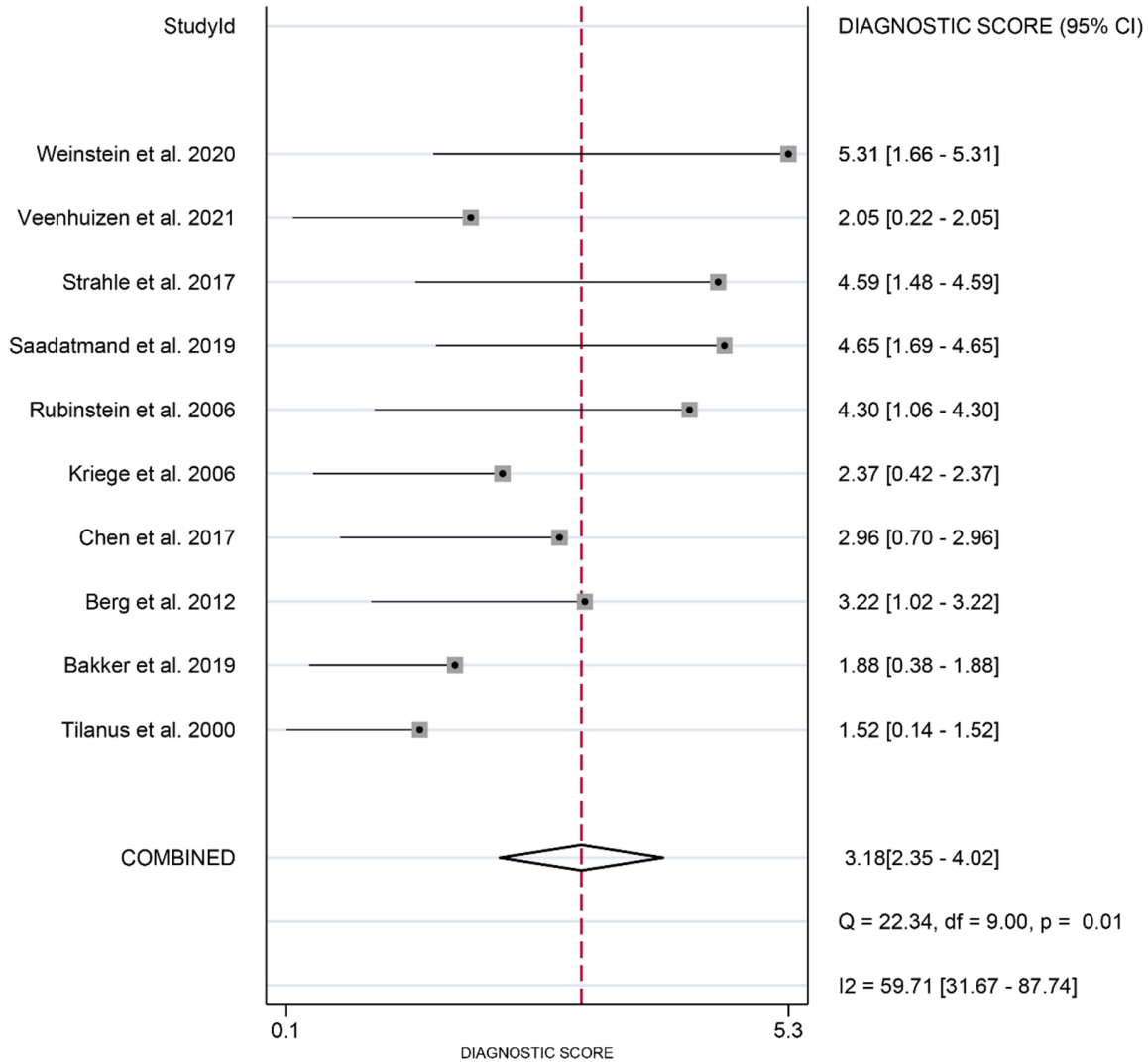
### Discussion

Breast cancer remains a significant global health issue, and early detection is critical for improving treatment outcomes and survival rates. While mammography has long been re-

garded as the gold standard for breast cancer screening, its effectiveness varies because of the differences in breast tissue density among individuals [15, 16]. Women with denser breast tissue, particularly those with heterogeneous or extremely dense tissue types, face a higher risk of breast cancer and may experience reduced mammographic sensitivity [17]. Notably, a substantial proportion of Asian women - more than half - have dense breast tissue. As dense breast tissue is an established independent risk factor for breast cancer, there is growing interest in the benefit of combining MRI with mammography for enhanced detection [18]. MRI is valued for its superior soft tissue contrast resolution, allowing it to identify



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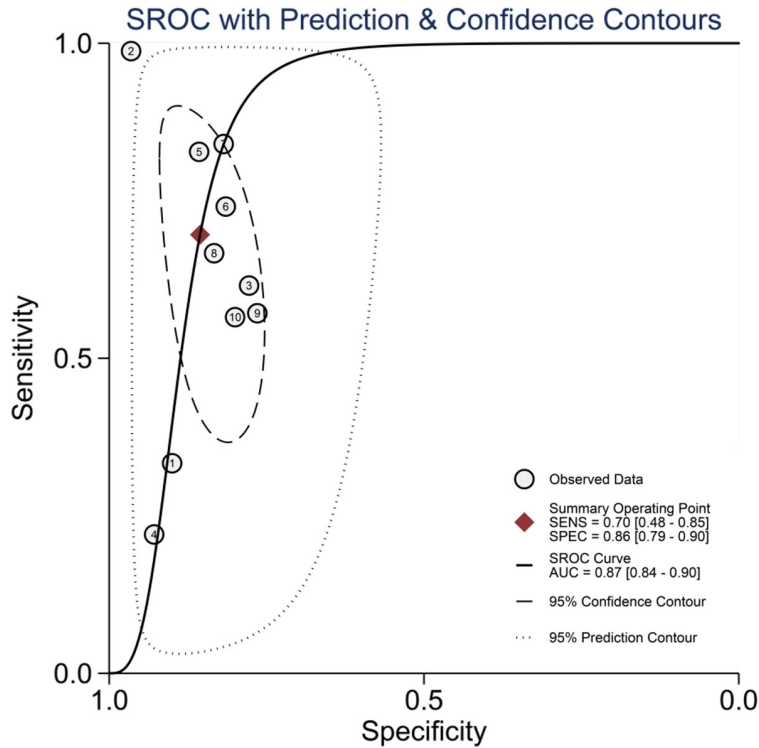


**Figure 6.** Forest plots of diagnostic score of synergistic effect of magnetic resonance imaging and mammography in the detection of breast cancer in women with dense breasts.

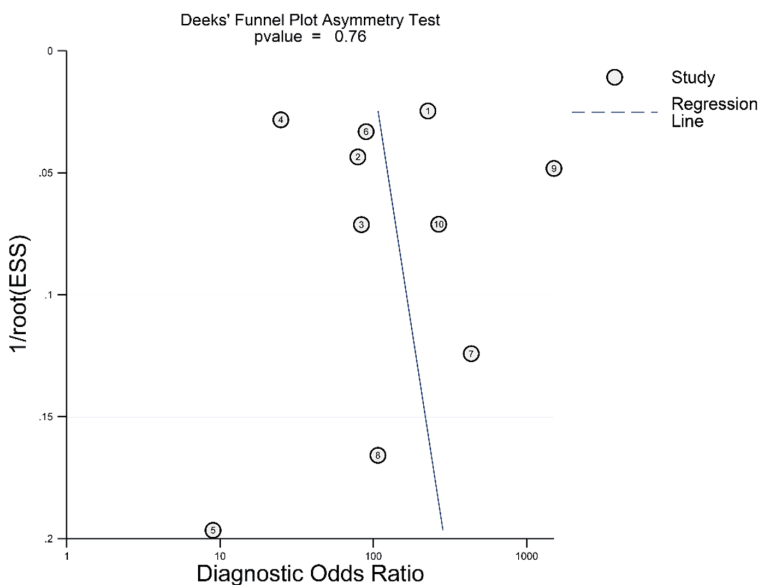
lesions that may be missed on mammography. However, primary studies on the efficacy of this combined approach have yielded inconsistent results [19].

The meta-analysis demonstrated that the combined use of MRI and mammography resulted in a pooled sensitivity of 0.87 (95% CI: 0.79-0.92) and a pooled specificity of 0.95 (95% CI: 0.89-0.97) for detecting breast cancer in women with dense breast tissue. These findings imply that adding MRI to mammography significantly enhances sensitivity for breast cancer detection in this population. The high specificity further indicates that this dual-modality approach is reliable for excluding can-

cer, thus reducing the likelihood of false positives and unnecessary biopsies. The increased sensitivity of MRI in breast cancer detection, as evidenced in this meta-analysis, can be attributed to its ability to visualize smaller lesions and its superior contrast resolution, which allows better differentiation between tissue types. This is especially important for women with dense breast tissue, where mammography alone may be less effective since dense parenchyma can mask abnormalities. These results align with the findings of Comstock et al. [20], who reported improved sensitivity in breast cancer detection when MRI was added, although with a slight decrease in specificity.



**Figure 7.** Summary receiver operating characteristic curve of the accuracy of synergistic effect of magnetic resonance imaging and mammography in the detection of breast cancer in women with dense breasts.



**Figure 8.** Deek's funnel plot of the accuracy of synergistic effect of magnetic resonance imaging and mammography in the detection of breast cancer in women with dense breasts.

ty. Techniques such as dynamic contrast-enhanced MRI (DCE-MRI) provide insights into tumor perfusion and permeability, both crucial factors for tumor growth and progression [21]. This ability helps explain why MRI can detect cancers that are not visible on mammography. Additionally, Alaref et al. [22] demonstrated the potential of diffusion-weighted imaging (DWI)-based MRI in detecting breast cancer in women with dense breasts, suggesting that MRI's multifaceted approach - evaluating lesions from multiple perspectives - was superior to mammography, which primarily relies on calcifications and morphologic features.

This meta-analysis provided further insight into the diagnostic utility of combining MRI and mammography for breast cancer detection. The positive likelihood ratio of 2.55 (95% CI: 1.45 to 4.46) indicated a significant increase in the odds of breast cancer when both MRI and mammography are positive, compared to when only mammography is positive. This suggests that a positive result is more likely to reflect true breast cancer, thus supporting more confident diagnosis and timely intervention. Conversely, the negative likelihood ratio of 0.11 (95% CI: 0.07 to 0.17) shows that a negative result from the combined screening substantially reduces the probability of breast cancer. This is crucial for reducing patient anxiety and avoiding unnecessary tests or invasive procedures, such as biopsies. The diagnostic score of 3.18 (95% CI:

Another key advantage of MRI is its ability to assess tumor vascularity and metabolic activi-

2.35 to 4.02) and diagnostic ratio of 24.14 (95% CI: 10.44 to 55.81) further substantiate

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**Table 3.** Sensitivity analysis of synergistic impact of magnetic resonance imaging and mammography in the detection of breast cancer in women with dense breasts

Included study	Sensitivity	Specificity
Tilanus et al. [25]	0.93 (0.86-0.95)	0.85 (0.83-0.90)
Bakker et al. [26]	0.94 (0.87-0.96)	0.86 (0.83-0.92)
Berg et al. [27]	0.94 (0.83-0.95)	0.84 (0.81-0.89)
Chen et al. [28]	0.92 (0.83-0.93)	0.87 (0.83-0.92)
Kriege et al. [29]	0.93 (0.82-0.94)	0.84 (0.81-0.91)
Rubinstein et al. [30]	0.94 (0.82-0.95)	0.85 (0.83-0.92)
Saadatmand et al. [31]	0.92 (0.84-0.96)	0.87 (0.83-0.92)
Strahle et al. [32]	0.93 (0.83-0.94)	0.86 (0.81-0.90)
Veenhuizen et al. [33]	0.94 (0.83-0.96)	0.85 (0.80-0.92)
Weinstein et al. [34]	0.95 (0.88-0.96)	0.86 (0.83-0.92)

**Table 4.** Subgroup analysis of magnetic resonance imaging and mammography in diagnosis of breast cancer in women with dense breasts

Classification	Studies	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUC (95% CI)
Study type					
RCT	3	0.88 (0.80-0.93)	0.94 (0.90-0.96)	130.9 (72.5-237.0)	0.97 (0.95-0.98)
Observational study	1	0.85 (0.77-0.91)	0.92 (0.89-0.94)	69.3 (44.8-107.5)	0.96 (0.94-0.97)
Prospective study	4	0.89 (0.82-0.95)	0.96 (0.91-0.98)	135.2 (79.3-249.0)	0.98 (0.95-0.99)
Screening study	1	0.86 (0.81-0.94)	0.95 (0.92-0.98)	139.6 (83.6-258.3)	0.95 (0.92-0.97)
Retrospective study	1	0.87 (0.81-0.95)	0.93 (0.87-0.96)	137.5 (81.9-251.6)	0.97 (0.94-0.98)
Dense type of breast tissue					
Extremely dense	3	0.90 (0.82-0.94)	0.93 (0.89-0.95)	144.8 (84.9-246.0)	0.97 (0.95-0.98)
Heterogeneous dense	4	0.87 (0.79-0.92)	0.95 (0.92-0.97)	221.1 (137.8-353.7)	0.96 (0.94-0.97)
Homogeneous dense	3	0.86 (0.78-0.91)	0.91 (0.88-0.93)	81.2 (56.5-116.1)	0.95 (0.93-0.97)
Detection method					
MRI + Mammography	7	0.88 (0.80-0.93)	0.93 (0.90-0.95)	100.7 (70.4-144.3)	0.97 (0.95-0.98)
Mammography negative followed by MRI	3	0.87 (0.79-0.92)	0.91 (0.88-0.93)	78.2 (54.1-113.0)	0.96 (0.94-0.97)

RCT: randomized controlled trial; CI: Confidence Interval; DOR: Diagnostic Odds Ratio; AUC: Area Under the Curve.

the robustness of the combined screening approach. These metrics suggest that the combined method is more likely to correctly identify breast cancer, and the high diagnostic ratio suggests that the screening effectively identifies true cases while minimizing false positives. These findings reinforce the idea that MRI supplementation to mammography significantly enhances breast cancer screening performance.

The issue of false positives is particularly significant, as it can lead to increased anxiety, additional testing, and unnecessary biopsies for patients. It is essential to balance the benefits of early cancer detection with the psychological and financial burdens caused by false positives. The results of this meta-analysis call for further investigation into optimizing the use

of MRI alongside mammography, including the development of better criteria to identify patients who would benefit the most from MRI screening.

While this meta-analysis suggests a promising role for the combination of MRI and mammography in breast cancer detection, the clinical applicability of this approach must be evaluated in light of practical challenges. MRI is more expensive than mammography, and there is potential for increased false positives and the invasiveness of the procedure. Early diagnosis and treatment are crucial for improving breast cancer prognosis and reducing disease burden. Mammography, ultrasound, and MRI are widely used in breast cancer screening, with each offering significant diagnostic value. Mammography, in particular, is recommended

globally as a routine breast cancer screening method, contributing to a substantial reduction in breast cancer mortality.

Previous meta-analyses have revealed that mammography alone has a sensitivity of 0.74 and specificity of 0.93 in detecting breast cancer in women with dense breasts [23]. This study found that MRI-assisted mammography for this population results in a slight decrease in specificity but a notable increase in sensitivity. Another study compared the effectiveness of mammography alone to mammography combined with other imaging techniques [24]. The findings revealed that combining mammography with MRI significantly improves breast cancer detection rates compared to mammography alone. Specifically, the weighted average sensitivity and specificity were 0.92 and 0.91 for women with non-dense breasts, and 0.82 and 0.80 for women with dense breasts, respectively.

Despite the strengths of this meta-analysis, several limitations exist. First, the included studies varied in sample size, design, and reference standards for breast cancer diagnosis, which may have affected the reliability of the combined results. Additionally, the meta-analysis did not account for factors such as patient age, menopausal status, and hormonal factors, which may have influenced the diagnostic accuracy of combined MRI and mammography. These factors should be considered in future research.

In conclusion, this meta-analysis underscored the synergistic effect of MRI and mammography in detecting breast cancer in women with dense breasts. The findings suggest that combined imaging modalities significantly improve sensitivity in this high-risk group. However, the clinical applicability of this approach must be carefully weighed against challenges such as cost and the risk of false positives.

### Disclosure of conflict of interest

None.

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