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RESEARCH ARTICLE
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A meta-analysis study to comparing MR spectroscopy and Intravoxel Incoherent motion (DWI) in the differentiation of benign and malignant breast lesions

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ABSTRACT

Background: Advanced diffusion models are none-contrast MR imaging techniques for the assessment of breast lesions. The value of accuracy in detecting BC in the diagnosis of breast cancer has not been systematically evaluated. The study aimed, using meta-analysis approach, to examine the diagnostic ability of MRI spectroscopy and intravoxel incoherent motion (DWI) used to assess the differentiation between benign and malignant breast lesions.

Materials and Methods: The study searched PubMed, MEDLINE, Cochrane, Embase, Scopus, Google Scholar, was used to find recent original studies that assessed the use of Non-Gaussian DWI model (Intravoxel Incoherent Motion; perfusion fraction ‘f’ ; real diffusivity ‘D’ and pseudo-diffusivity ‘D*’) and spectroscopy (1H) for the detection of breast cancer. The standardized mean difference (SMD) , pooling the sensitivity, specificity, and area under the curve were used to organize and summarize the studies. The QUADAS-2 and QUIPS programs were used to assess the quality of the included studies.

Results: fifty studies were included, with IVIM and spectroscopy being the most investigated . The presence of significant heterogeneity (P<0.05) was observed for all parameters. The results showed high differentiation ability found between malignant and benign cancer, where, malignant cancer has significantly lower D values (SMD=-1.54; P<0.0001) than benign cancer . While D*, f, and ^{1}H values were higher than benign caner (SMD=0.08, 0.71, and 1.42; P=0.0001). The best diagnostic performance was shown for D (sensitivity=86%; specificity= 0.86; AUC≤0.92) and for ^{1}H, f, and D* in breast tumors’ differential diagnosis (sensitivity=0.83, 0.78, 0.69; specificity= 0.76, 0.69, 0.63; AUC 0.73), respectively.

Conclusion: Our findings showed that their parameters play a potential role in differentiating breast tumours. Superior diagnostic accuracy, alongside, the high sensitivity and specificity for diffusion-weighted advanced imaging means that these approaches can be used as a suitable method in differentiating breast tumors.

Keywords: *Diffusion-weighted imaging, Intravoxel incoherent motion (IVIM), magnetic resonance spectroscopy , Classification tumors of the breast*

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INTRODUCTION

Breast cancer (BC) is one of the most prevalent Neoplasms and the second leading reason of death from cancer in women(1). Breast imaging is needed for different purposes, in screening for BC and classifying breast abnormalities. Accurate detection and diagnosis of BC has a major impact on disease-free survival and overall survival. Examination of BC using conventional mammography is challenging for the radiologist due to the low sensitivity of the dense breast parenchyma(2-4). Contrast/enhanced (DCE-MRI) is a standard MRI sequence in examination of BC, which can show the morphological and hemodynamics features of BC. However, False positive "specificity " remains variable results may lead to additional testing or unnecessary surgery due to background enhancement of parenchymal and overlapping kinetic enhancement patterns between BC(5-7).

As a non-invasive technique, magnetic resonance imaging (MRI) is an appropriate radiological method to evaluate BC(8, 9). According to the literature, Advanced diffusion models has potential to improve the sensitivity and specificity of MR imaging, without added contrast material is safer for patients and also cheaper and faster and attempt to capture more complex aspects of the tumor microenvironment can effectively reflect tumor cellularity and tissue organization(10-12). Due to enhanced cellularity that causes restricted water molecule movement, which roots in decreased extracellular space, diffusion in malignant tumors is restricted.

Intravoxel incoherent motion (IVIM) is a valued imaging technique capable of differentiation between diffusion via a biexponential model analysis based on multiple b-values (13, 14). In this line, Le Bihan and colleagues(14) developed a technique for IVIM that its effects on microcapillary perfusion are proved by some studies using DWI(15-18). In cases that several b-values (usually ranging from 0 to 1,500 sec/mm2 for body imaging) are applied in DWI, the signal intensity at low b-values (0-200 sec/mm2) indicates microcirculation within capillaries. In the same way, the higher the b value (>200 sec/mm2), the better the signal intensity reflects tissue diffusivity(17, 19). The IVIM technique can provide different quantitative parameters, such as perfusion fraction 'f' ; real diffusivity 'D' and pseudo-diffusivity 'D*', that show the perfusion and diffusion of the tissues(14).

In vivo proton (1H) magnetic resonance spectroscopy (MRS) of the breast, providing molecular information gained in a noninvasive manner, demonstrated that it is possible to detect compounds with choline in the majority of breast cancers(20, 21). A last meta-analysis that involved papers of vivo ^{1}H MRS have diagnostic performance the pooled sensitivity of 75%, specificity of 90%(22).

In summary, the none contrast MRI techniques are of great value in detection of BC, however, no comprehensive study to evaluate numerous parameters included in within these techniques. Therefore, the purpose of the current meta-analysis study is to assessment of the diagnostic accuracy of intravoxel incoherent motion, and MR spectroscopy could be a suitable method to improve differentiate and characterize BC in vivo.

MATERIALS AND METHODS

The study searched PubMed, MEDLINE, Cochrane, Embase, Scopus, Google Scholar, was used to find recent original studies by two researcher radiologists for identifying about Non-Gaussian (Intravoxel Incoherent Motion) and MRI spectroscopy (1H) for the detection of breast cancer. Which were published before the date of the searching (December 20022) . The research keywords used were ; "breast cancer"; "Intravoxel Incoherent Motion or biexponential" ; "MRI or magnetic resonance imaging" ; "breast and magnetic resonance spectroscopy"; "breast MRS"; "breast MR 1H spectroscopy"; "breast MR proton spectroscopy" and "breast MRI spectroscopy" .

Study Selection

After the initial assessment, The two researcher radiologists used a standard extraction form to summarize each publication separately, recording the information, including first author, publication year, study design (i.e., retrospective or prospective), size of population, blinding procedures, mean patient's age or median , strength of magnetic field, IVIM parameters and spectroscopy (i.e., a threshold value utilized for a parameter and a computational technique). Additionally, adequate information were including the values of the values of true–positive, false–negative, false–positive, and true–

negative. The results were categorized using the diagnostic criteria (if the reproduction of the reported values was not possible, the article was eliminated). Moreover, there was no limit for age or sample size.

Exclusion Criteria

The following studies were eliminated: Some studies were eliminated in cases such as; the conclusion revealed that there was no information data about diagnostic performance IVIM parameters and MRS, and/or chemotherapy follow-up breast imaging (diagnosis, classification, and carcinoma report) . Also, elimination included when the sensitivity and specificity were not evaluated , studies with animal subjects, reviews, case reports, letters, editorials, abstracts, comments, and *in vitro* studies. studies were eliminated with less than eight subjects.

Quality Assessment

Utilizing of the QUADAS-2 tool for quality assessment of the included studies for diagnostic studies and the QUIPS tool for prognostic. Two reviewers separately assessed the quality of each study, and any disagreements were settled by consensus. Four areas of the QUADAS-2 instrument were scored: patient selection, index test, reference standard, flow and time. Items were given a "yes," "no," or "unclear" score (23). Six QUIPS areas were evaluated: study participant selection; study attrition; assessment of prognostic factors; outcome measurement; study confounding; and statistical analysis and reporting. The "yes", "partial", "no," or "unsure" responses for three to seven areas within each domain were merged to assess the risk of bias. Each domain receives a "high," "moderate," or "low" total risk of bias grade(24). **Publication Bias and Heterogeneity Evaluation**

In this study, funnel plots were drawn to investigate publication bias in a visual manner. The presence of a publication bias is indicated through an asymmetric or skewed funnel plot. The asymmetry quantification was performed using the Egger test(25), and a p-value > 0.05 showed publication bias. The heterogeneity degree between the studies was calculated using the Cochran Q test and Higgins I^2 test(26) by Meta-Disc software (version 1.4). A p-value >0.05 for the Cochran Q test or an I^2 value of greater than 50% demonstrated statistically significant heterogeneity.

RESULTS

Study selection

By the keywords, We found 282 papers in databases searching and forward and backward citations for the articles published between database inceptions. After duplicates removal, there were 49 articles left for investigation. By screened, from which 233 full-text documents were reviewed in the present study (22 clearly did not match the inclusion criteria ; 37 were not in the field of interest, 29 were review articles, 34 study involved with other than BC) . Moreover, 61 studies were excluded on account of lack of information (the sensitivity and specificity were not evaluated) . 50 of those met the eligibility criteria were included in the meta-analysis. The process of selecting articles is described in Figure 1.

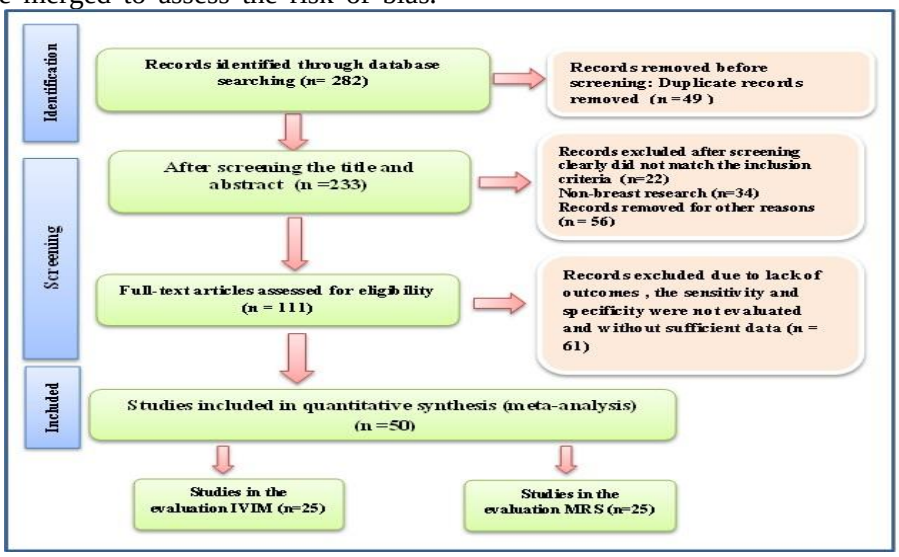

FIGURE 1: Detailed Summary of included studies assessment.

J Popul Ther Clin Pharmacol Vol 30(13):e390–e402; 13 May 2023.

Characteristics of articles and patients

A total of 50 papers were included in this meta-analysis evaluating diagnostic intravoxel incoherent motion and spectroscopy for differentiation of benign and malignant breast lesions . the authors included a table presenting each included study citation, years , study design , sample size, mean age, MRI parameters. 25 IVIM studies of those met the eligibility criteria included 2391 lesions (1592 malignant and 829 benign) and 25 studies of MRS included 1680 lesions (1052 malignant and 627 benign). Details of included studies are provided Table 1.

TABLE 1: Overview of studies included

Author	Year	SD (P/R)	Pat. No.	Age: Median (range)	MRI Model	Field strength	Diffusion Model	b-values (seconds/mm2)
He [27]	2021	P	215	52.1 ± 11.0	Siemens	3.0T	ADC, IVIM	0, 30, 50, 80, 120, 160, 200, 500, and 1000
Meng (28)	2020	P	123	58 ± 10	GE	3T	IVIM	0, 50, 75, 100, 150, 200,400, 800, 1,000
Chan (29)	2019	P	25	NA	Siemens	1.5 T	IVIM	0, 15, 30, 45, 60, 100, 250, 400, 550,700, 850, 1000
Song (30)	2019	R	85	54 (35–81)	Siemens	3T	IVIM	0, 10, 20, 30, 50, 70, 100, 150, 200, 400, 600, 1,000
Zhao (31)	2018	R	141	50.2 ± 10.5	GE	3T	ADC, IVIM	0, 50, 100, 150, 200, 400, 500, 1,000, 1,500
Mao (32)	2018	R	124	45.3±8.7	Siemens	3.0 T	IVIM	0, 50, 100, 150, 200, 250, 300, 400, 600, 800, 1000, and 1200
Jiang (33)	2018	P	66	45 ± 10	GE	3T	IVIM	0, 10, 30, 50, 70, 100, 150, 200, 400, 600, 1,000, 1,500
Iima (34)	2018	P	199	58.5 (20–88)	Siemens	3T	IVIM, non-Gaussian DWI	5, 10, 20, 30, 50, 70, 100, 200, 400, 600, 800, 1,000, 1,500, 2,000, 2,500
Suo (35)	2017	P	101	54.6 ± 15.7	Philips	3 T	ADC,IVIM	0, 10, 30, 50, 100, 150, 200, 500, 800, 1000, 1500, 2000, 2500
Lin (36)	2017	P	98	48 (17–77)	Philips	3T	IVIM	0, 50, 100, 150, 200, 500, 800
Kawashima (37)	2017	R	137	58 (32–85)	GE	3T	IVIM	0, 20, 40, 80, 120, 200, 400, 600, 800
Ma (38)	2017	P*	128	48.2 ± 5.1	Siemens	3T	IVIM	0, 50, 100, 150, 200, 250, 300, 400, 600, 800, 1,000, 1,200
Chen (39)	2017	NA	29	47 (15–62)	Siemens	3T	IVIM	0, 50, 100, 150, 200, 300, 400, 800, 1,000
Lee (40)	2017	R	82	53 (34–77)	Siemens	3T	IVIM	0, 25, 50, 75, 100, 150, 200, 300, 500, 800
Wang (41)	2016	R	54	46.85 ± 8.63	GE	3 T	ADC, IVIM	0, 10, 20, 50, 100, 200, 300, 400, 600, 800
Liu (42)	2016	P	59	NA	Philips	1.5 T	ADC, IVIM	0, 10, 20, 30, 50, 70, 100, 150, 200, 400, 600, 100
Kim (18)	2016	P	275	51 (28–83)	Philips	3T	IVIM	0, 30, 70, 100, 150, 200, 300, 400, 500, 800
Cho (43)	2016	R	62	48.4±11.1	Siemens	3 T	ADC, IVIM	0, 30, 70, 100, 150, 200, 300, 400, 500, 800
Dijkstra (44)	2016	P*	139	47 (22–75)	Siemens	1.5 T	ADC, IVIM	0, 50, 200, 500, 800, 1000
Suo (17)	2015	R	30	50 (27–79)	Philips	3T	IVIM	b50, 50, 100, 150, 200, 500, and 800
Iima (45)	2015	R	23	52.4(31–74)	Siemens	3 T	ADC,IVIM	3, 5, 10, 20, 30, 50, 70, 100, 200, 400, 600, 800,1000, 1500, 2000, 2500
Fusco (46)	2015	NA	31	37.2 ±10.4	Siemens	1.5T	IVIM	0, 50, 100, 150, 400, 800, 1000
Bokacheva (47)	2014	R	40	49 (28–70)	GE	3 T	ADC,IVIM	0, 30, 60, 90, 120, 400, (450 in 7 cases), 600, 800, 1000
Liu (48)	2013	P	81	48 (20–76)	Philips	1.5 T	ADC,IVIM	0, 10, 20, 30, 50, 70, 100, 150, 200, 400, 600, 100
Sigmund (49)	2011	P	44	53.1 (39–85)	Siemens	3-T	IVIM	0, 30, 70, 100, 150, 200, 300, 400, 500, and 800
Jacobs (50)	2005	P	9	56 ± 11	GE	1.5 T	MRS	
Baek (51)	2008	P	36	52 (35–73)	Philips	1.5T	MRS	
Kim (52)	2003	P	35	4–75	GE	1.5T	MRS	
Lipnick (53)	2010	P	24	18–65	Siemens	1.5T	MRS	
Gruber (54)	2011	P	44	50 (25–82)	Siemens	3-T	MRS	
Montemezzi (55)	2017	P	140	50 (18–86)	Philips	3T	MRS	
Sardanelli (20)	2009	P	45	60 ± 15	Siemens	1.5 T	MRS	
Suppiah (56)	2013	P	61	49.7 (20 -83)	GE	3 T	MRS	
Ramazan (57)	2016	P	51	44.76±12.98	Siemens	3 T	MRS	
Aribal (58)	2016	P	138	<18	Siemens	3 T	MRS	
Roebuck (59)	1998	P	17	47 (25-68)	GE	1.5 T	MRS	
Thakur (60)	2011	P	88	<18	GE	1.5 T	MRS	
Dorrius (61)	2012	R	26	48.7 (32–69)	Siemens	1.5 T	MRS	
Sah (62)	2012	P	189	45.6±10.4	Siemens	1.5 T	MRS	
Mizukoshi (63)	2013	NA	208	54.5 (20 -79)	Siemens	1.5 T	MRS	
Meisamy (64)	2005	R	55	47 (24 – 66)	Siemens	4 T	MRS	
Yeung (65)	2001	NA	30	50 (20–80)	Philips	1.5 T	MRS	
Tse (66)	2003	P	40	55.9 (37–80)	Philips	1.5 T	MRS	
Huang (67)	2004	P	50	50.2 (34–71)	Picker	1.5 T	MRS	
Kousi (68)	2012	NA	27	53 ± 12	GE	3 T	MRS	
Tozaki (21)	2009	R	171	49 (16–89)	Siemens	1.5 T	MRS	
Bartella (69)	2006	P	57	≤18	GE	1.5 T	MRS	

Vassiou (70)	2013	P	26	53±12	GE	3 T	MRS	
Basara (71)	2013	NA	77	30–76	GE	1.5 T	MRS	
Su (72)	2006	NA	36	48 (35-66)	Philips	1.5 T	MRS	

IVIM = intra-voxel incoherent motion, P = prospective , R = retrospective , MRS= magnetic resonance spectroscopy

Assessment of Data Quality

For our purposes, the overall quality of the studies that were included was assessed to be good, taking into account QUADAS-2 and QUIPS findings. Figures 2 and Supplementary Materials Tables S2 and S3 describe the results of the quality evaluation. In terms of the QUADAS-2 evaluation, the risk of bias was rated as low or moderate for each of the four QUADAS-2 domains across all diagnostic investigations. All of the diagnostic investigations gave minimal priority to the applicability issues. Similar to the QUIPS evaluation, all prognostic studies for all six QUIPS categories rated the risk of bias as low or moderate.

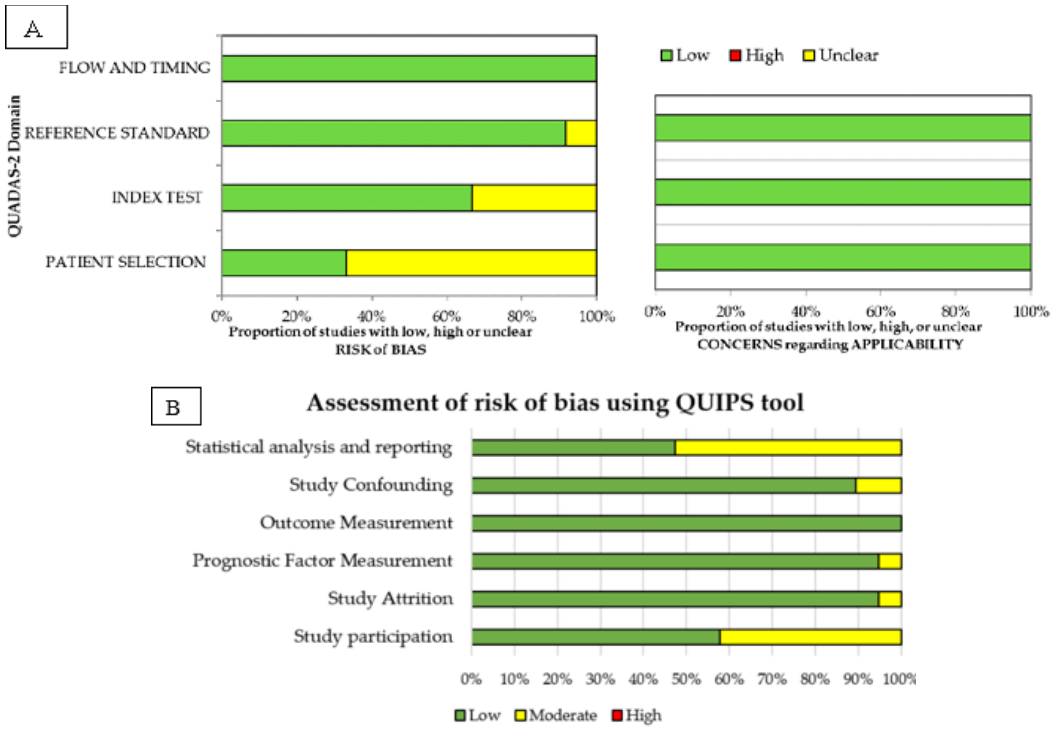

FIGURE 2: (A) QUADAS-2 tool quality evaluation for diagnostic studies (B) Prognostic studies quality evaluation utilizing the QUIPS tool.

Quantitative Analysis

Measurement of IVIM Model Used for of Breast Lesions

Nineteen papers on the topic of IVIM used in distinguishing breast lesions were involved for investigation. The Chi^2 for D , and f (χ^2 = 90.68 , and 76.76 respectively, P<0.001) and D* (χ^2 =281.32, P=71) the heterogeneity test (I^2 = 83%, 77% and 94%) proposed in height heterogeneity between the comprised papers. The plot in Figure 3 demonstrations the apportionment of the IVIM model between breast lesions. A random-effects pattern leading to an SMD of the D, f -1.54 [-1.85, -1.22] , 0.71 [0.48, 0.93] (P<0.001) and D* 0.08 [-0.35, 0.51] (P = 0.71) between breast lesions. indicated that benign lesions had a significantly high (D) than malignant lesions. And (f value) indicated that malignant lesions had a significantly high than benign lesions.

Measurement of Spectroscopy (^{1}H) Value Used for of Breast Lesions

Twenty-five papers on the topic of Spectroscopy (1H) used in distinguishing breast lesions were involved for investigation. The χ^2 = 103.88, p-value less than 0.001 of the heterogeneity test (I^2 = 86%) proposed in height heterogeneity between the comprised papers. In Figure 4, the plot illustrates the **^{1}H** apportionment between

breast lesions. A random-effects pattern leading to an SMD of 1.42 [1.02, 1.81] (P<0.001) between breast lesions indicated that malignant lesions had a significantly high than benign lesions.

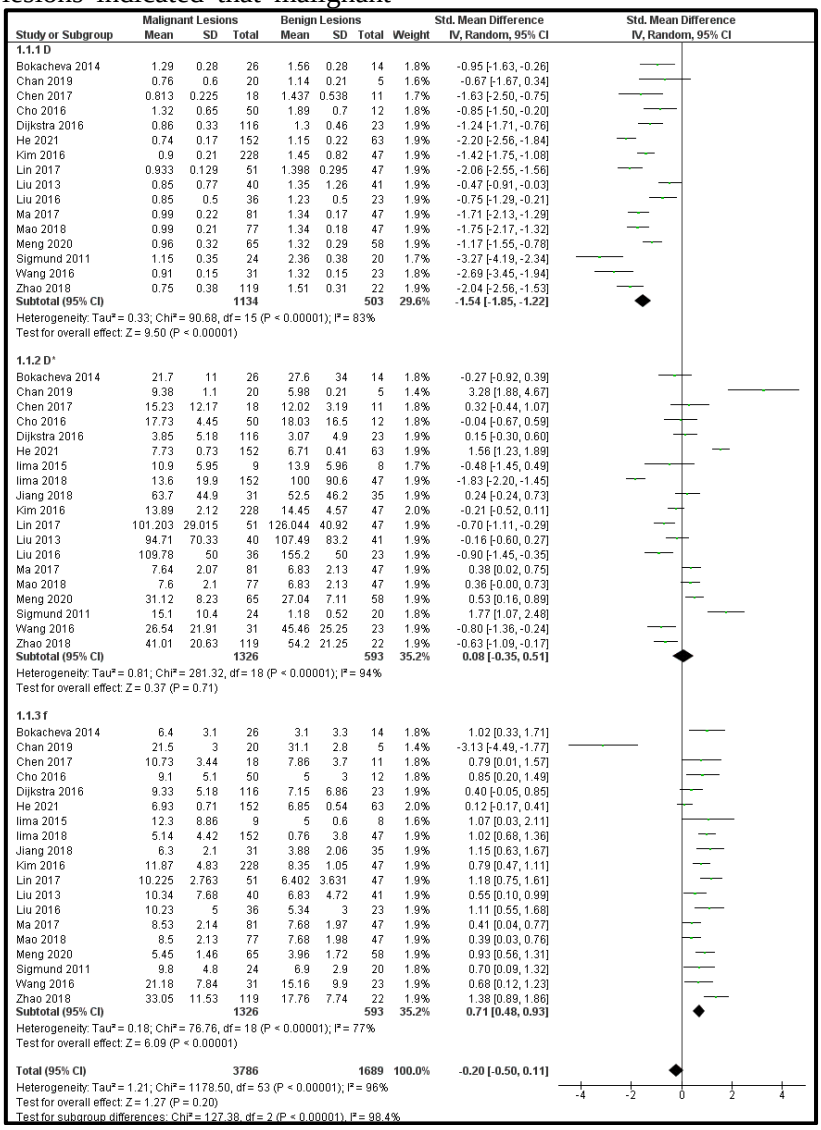

FIGURE 3: Forest Plot Illustrating Mean Value and Standardized Mean Differences (SMD) in the IVIM parameters among lesions benign and malignant**.**

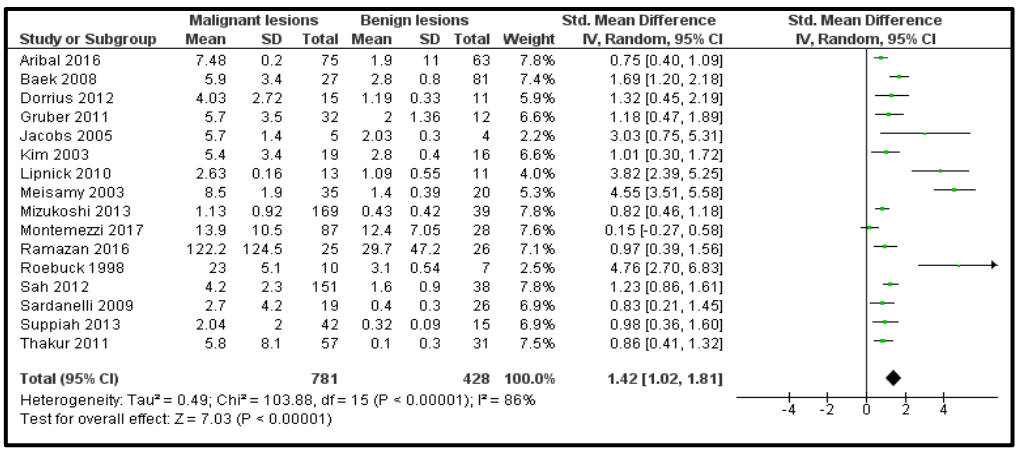

FIGURE 4: Forest Plot Illustrating Mean Value and Standardized Mean Differences (SMD) in the ^{1}H MRS among lesions benign and malignant**.**

Measurement Performance

Table 2 shows a list of diagnostic performance as evaluated of breast tumors by pooling sensitivity, specificity, negative likelihood ratio (NLR), positive likelihood ratio (PLR), area under curve (AUC), and diagnostic odds ratio (DOR). The test likelihood of the D, D*, f, and ^{1}H values.

Forest plots of sensitivity and specificity for all parameters with Corresponding 95% Confidence Intervals, Provided that values are extracted from true– positive, false–negative, false–positive, and true–negative. True diffusivity (D) for 10 articles showed a good diagnostic interpretation with (86% sensitivity and 86% specificity (Figure 5) , 95 % CI AUC 0.92) in differential diagnosis of breast lesions, and f of 10 articles showed (sensitivity 0.78, specificity 0.69 (Figure 5), 95 % CI AUC 0.83), D* of 9 articles showed (sensitivity 0.69, specificity 0.63 (Figure 5), 95 % CI AUC 0.72). ^{1}H of 25 articles showed (sensitivity 0.83%, specificity 0.76% (Figure 6), 95 % CI AUC 0.91).

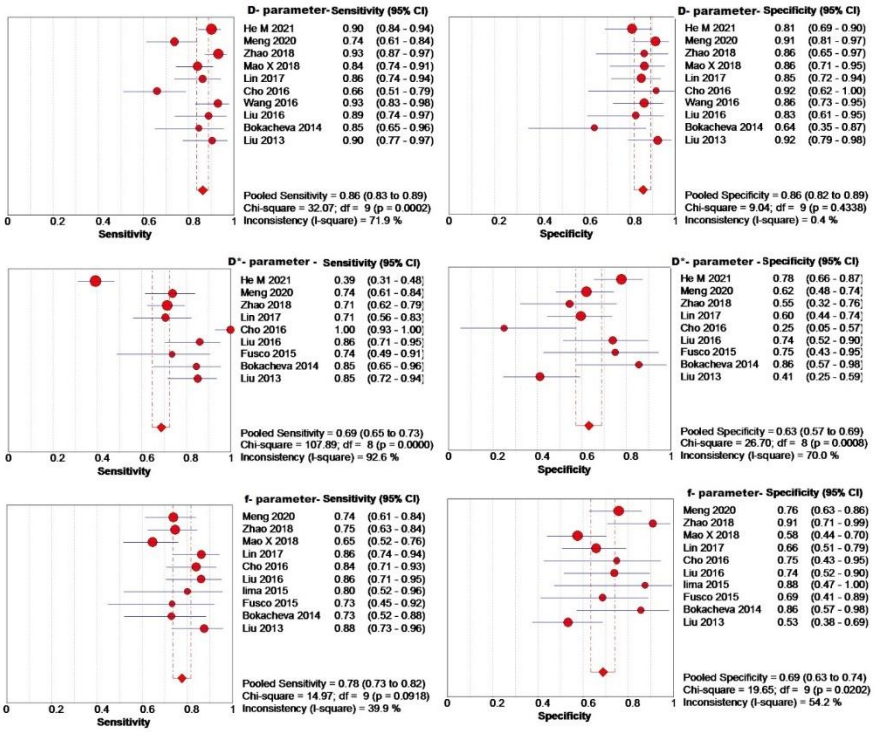

FIGURE 5: Forest Plot Illustrating Sensitivity and Specificity of intravoxel incoherent motion (IVIM) parameters with Corresponding 95% Confidence Intervals of 10 articles; Using Effects Model; Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR).

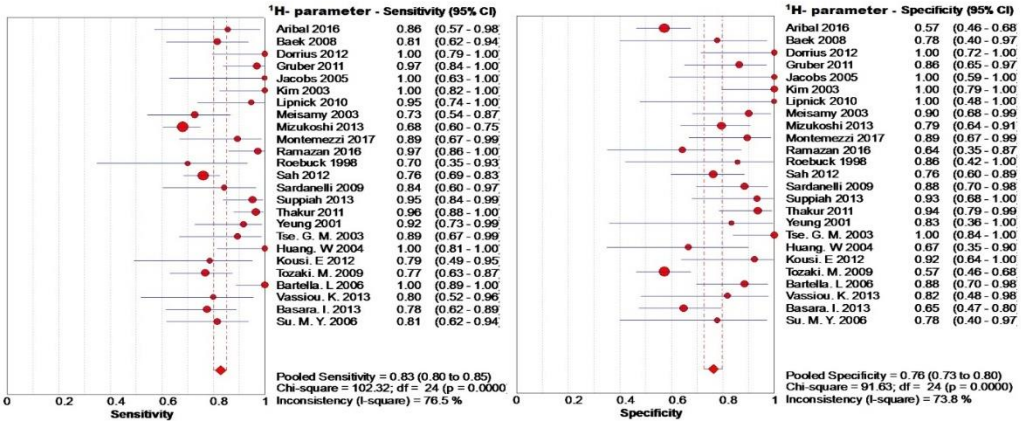

FIGURE 6: Forest Plot Illustrating Sensitivity and Specificity of the **(MRS)** with Corresponding 95% Confidence Intervals of 25 articles; Using Effects Model; Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) Reported as 4.60 (95% CI 3.24, 6.52) and 0.18 (95% CI 0.13, 0.25),Respectively.

TABLE 2: The included studies diagnostic in the current meta-analysis

Indicators	No. of Studies	No. Lesions	Sensitivity	Specificity	PLR	NLR	DOR	AUC	I^2	
									Sensitivity %	Specificity %
D	10	1637	0.86 (0.83, 0.89)	0.86 (0.82, 0.89)	5.51 (4.24, 7.17)	0.16 (0.11, 0.24)	39.69 (26.82, 58.72)	0.92	71.9%	40.2%
D*	10	1919	0.69 (0.65, 0.73)	0.63 (0.57, 0.69)	1.78 (1.45, 2.18)	0.39 (0.26, 0.59)	5.10 (3.03, 8.58)	0.72	92.6%	70.0%
F	10	1919	0.78 (0.73, 0.82)	0.69 (0.63, 0.74)	2.58 (1.93, 3.44)	0.31 (0.31, 0.40)	9.71 (5.64, 16.70)	0.83	39.9%	54.2%
^1H	25	1680	0.83 (0.80, 0.85)	0.76 (0.73, 0.80)	4.60 (3.24, 6.52)	0.18 (0.13, 0.25)	34.41 (18.74, 63.19)	0.91	76.5%	73.8%

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve; I^2, inconsistency index; proton (^1H) magnetic resonance spectroscopy.

The results in figure 7 showed Summary receiver operating characteristic (SROC) curves; Plotting Sensitivity and Specificity curves of the D, D*, f and ^1H values. Showed the D curve a good diagnostic performance (AUC 0.92 , Q* Index 0.86) in the differential diagnosis of breast tumors, which was comparable to other parameters : followed by the MRS curve, (AUC 0.91, Q* Index 0.85) , f curve, (AUC 0.83, Q* Index 0.76) , and D* curve, (AUC 0.72, Q* Index 0.67) .

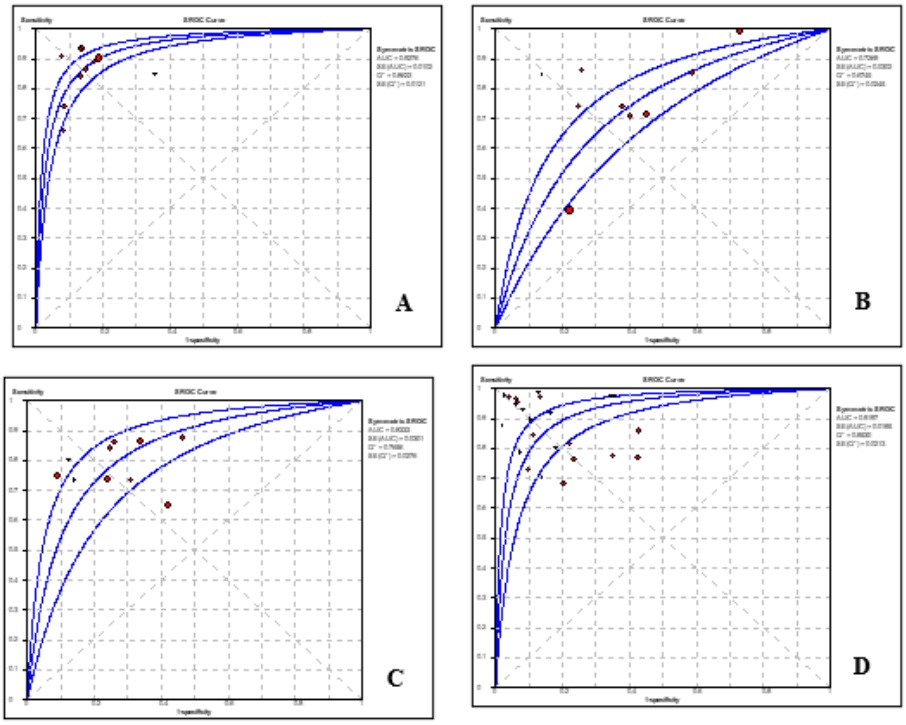

FIGURE 7: SROC curves; Plotting Sensitivity and Specificity in Receiver Operating Characteristic Space for Individual Articles; A) tissue diffusivity (D), B) pseudo-diffusivity (D*), C) the perfusion fraction (f), D) MRS

DISCUSSION

Some research addressed meta-analyzes of the diagnostic performance of the DWI model in BC assessment[73, 74] but did not compare it with other techniques such as spectroscopy of which can provide details on directional features and tissue complexity[17,18]. The results showed promising noninvasive diffusion-weighted imaging techniques that can be incorporated into the MRI protocol for breast lesion evaluation. All

the values including AUC, sensitivity, and specificity for the study parameters (see results section; Quantitative Analysis) showed superiority in reversing tumor cellularity and perfusion with no need for a contrast agent with good diagnostic performance and promising potential for incorporating breast protocols. Our meta-analysis provides a comprehensive study of a timely summary of the above topic by synthesizing all public data with strict inclusion requirements and quality evaluations. The combination of these methods could further improve the specificity of breast lesion detection.

The combined estimates of the curve representing receiver operating characteristic (ROC), AUC, sensitivity and specificity (Figure 5, 6 and 7) were comparable with intravoxel incoherent-motion and spectroscopy. Where IVIM can determine true molecular diffusion and the movement of water molecules in the capillary lattice using a diffusion-weighted acquisition technique[23] and ^{1}H-MRS can obtain further information on the biological status of tissues and make more complex statistical analyses possible to be performed(19)

Within this research, the SMDs analysis for breast cancers D parameters in this investigation supported lower values while higher f and ^{1}H-MRS values were reported compared to benign lesions. This is related to the fact that the extracellular space may be reduced and water molecule diffusion can be restricted in BC, which lowers the diffusion coefficients (D). While BC typically has a dense cell structure and great spreading capacity which are the reason for obtaining higher f values than benign tissue (with high specificity of 0.76 and an AUC of 0.85). The high (non-significant) D* values is mostly caused by the increased angiogenesis in BC's (11). The above-mentioned reason is behind the specificity of 0.59 and an AUC of 0.71 for the D* value.

Even though different studies showed IVIM diffusion Imaging of the breast has superior diagnostic precision [24-46], there are currently no standard procedures. This is due to the fact that the number and the range of utilized b values can vary widely in addition to the threshold values of the IVIM parameters: D, f and D*.

The D diffusion in MRI imaging has standardized thresholds values because of the dependence of the quantification of D on the selection values of b (74) which is helpful in diagnostic procedures. Where, Dorrius (75) has shown that values b of both 0 and 1000 mm^2/s combination are the most favorable conditions. He has also highlighted the aforementioned b-value combination to give the greatest percentage difference between benign and cancerous lesions in the D. It is recommended that the use of further b-values leads to better distinguish between perfusion and diffusion(76), particularly lowest b values, where perfusion contributes mostly to signal decay.

Based on the clinical breast use DWI recommendations from the European Society of Breast Radiology (EUSOBI)(77), the choice of b values is critical. The value of the ADC depends largely on the choice of b-values since water diffusion in tissue is a non-Gaussian process (bending the DWI signal attenuation curve across b-values), with ADC values decreasing using larger b-values. Higher b values could improve the specificity of DWI while lowering SNR rates. As a suitable compromise for standardization, the working group decided on a high b value of 800 mm^2/s (77).

Quantitative spectroscopy could be a fundamental enhancement in the qualitative detection techniques utilized in breast ^{1}H-MRS. Quantification might be specifically essential in the breast due to the further variability of the sensitivity of the ^{1}H-MRS measurement more than in brain tissue [78]. The reason for the aforementioned issue is mainly the extremely variable nature of adipose tissue content in the breast and the greater difference in coil reception efficiency(78). Moreover, quantitative techniques cause to obtain further information on the biological status of tissues and make more complex statistical analyses possible to be performed(79).

LIMITATIONS

The current study has a number of limitations. The analysis of a small number of published DTI parameters publications comes first. Second, some studies that did not report TP, FN, FP, and TN findings, based on the sensitivity, specificity, and number of cancerous and benign lesions, we estimated these results. Third, We didn't compare with diffusion kurtosis imaging (DKI), which provides data reflecting tissue complexity and directional features. Combining these sequences could further increase specificity in breast lesion detection. Finally, there have not been enough articles on breast cancer's histologic and

molecular subtypes to make a definitive judgment.

CONCLUSION

The conclusions from this study can be summarized as follows: The high sensitivity and specificity obtained for intravoxel incoherent motion and spectroscopy lead to the recommendation of these methods as a helpful tool in the characterization of breast lesions. The estimated IVIM, MRS values demonstrated superior diagnostic interpretation for distinguishing amount of benign and cancerous breast lesions, with high sensitivity and specificity accepted in the present meta-analysis. The True diffusivity (D) showed higher diagnostic ability than other parameters. Therefore, intravoxel incoherent motion method can be employed as a suitable method to distinguish breast tumors.

REFERENCE

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
2. Aberle DR, Chiles C, Gatsonis C, Hillman BJ, Johnson CD, McClennan BL, et al. Imaging and cancer: research strategy of the American College of Radiology Imaging Network. Radiology. 2005;235(3):741-51.
3. Boisserie-Lacroix M, Hurtevent-Labrot G, Ferron S, Lippa N, Bonnefoi H, Mac Grogan G. Correlation between imaging and molecular classification of breast cancers. Diagnostic and interventional imaging. 2013;94(11):1069-80.
4. Morris EA. Diagnostic breast MR imaging: current status and future directions. Radiologic Clinics of North America. 2007;45(5):863-80.
5. Plana MN, Carreira C, Muriel A, Chiva M, Abraira V, Emparanza JI, et al. Magnetic resonance imaging in the preoperative assessment of patients with primary breast cancer: systematic review of diagnostic accuracy and meta-analysis. European radiology. 2012;22(1):26-38.
6. Arian A, Dinas K, Pratilas GC, Alipour S. The breast imaging-reporting and data system (BI-RADS) Made Easy. Iranian Journal of Radiology. 2022;19(1).
7. Arian A, Delazar S, Aghasi M, Jahanbin B, Ahmadinejad N. Does MRI have added value in ultrasound-detected BIRADS-3 breast masses in candidates for assisted reproductive therapy? European Journal of Radiology Open. 2023;10:100474.
8. Brandão AC, Lehman CD, Partridge SC. Breast magnetic resonance imaging: diffusion-weighted imaging. Magnetic Resonance Imaging Clinics. 2013;21(2):321-36.
9. Arian A, Ahmadi E, Gity M, Setayeshpour B, Delazar S. Diagnostic value of T2 and diffusion-weighted imaging (DWI) in local staging of endometrial cancer. Journal of Medical Imaging and Radiation Sciences. 2023.
10. Basser PJ. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR in Biomedicine. 1995;8(7):333-44.
11. Padhani AR, Liu G, Mu-Koh D, Chenevert TL, Thoeny HC, Takahara T, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia. 2009;11(2):102-25.
12. Woodhams R, Ramadan S, Stanwell P, Sakamoto S, Hata H, Ozaki M, et al. Diffusion-weighted imaging of the breast: principles and clinical applications. Radiographics. 2011;31(4):1059-84.
13. Malayeri AA, El Khouli RH, Zaheer A, Jacobs MA, Corona-Villalobos CP, Kamel IR, et al. Principles and applications of diffusion-weighted imaging in cancer detection, staging, and treatment follow-up. Radiographics. 2011;31(6):1773-91.
14. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology. 1986;161(2):401-7.
15. Koh D-M, Collins DJ, Orton MR. Intravoxel incoherent motion in body diffusion-weighted MRI: reality and challenges. American Journal of Roentgenology. 2011;196(6):1351-61.
16. Le Bihan D, Breton E, Lallemand D, Aubin M, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology. 1988;168(2):497-505.
17. Suo S, Lin N, Wang H, Zhang L, Wang R, Zhang S, et al. Intravoxel incoherent motion diffusion-weighted MR imaging of breast cancer at 3.0 tesla: comparison of different curve-fitting methods. Journal of Magnetic Resonance Imaging. 2015;42(2):362-70.
18. Kim Y, Ko K, Kim D, Min C, Kim SG, Joo J, et al. Intravoxel incoherent motion diffusion-weighted MR imaging of breast cancer: association with histopathological features and subtypes. The British journal of radiology. 2016;89(1063):20160140.
19. Sigmund E, Cho G, Kim S, Finn M, Moccaldi M, Jensen J, et al. Intravoxel incoherent motion

imaging of tumor microenvironment in locally advanced breast cancer. Magnetic resonance in medicine. 2011;65(5):1437-47.
20. Sardanelli F, Fausto A, Di Leo G, De Nijs R, Vorbuchner M, Podo F. In vivo proton MR spectroscopy of the breast using the total choline peak integral as a marker of malignancy. American journal of roentgenology. 2009;192(6):1608-17.
21. Tozaki M, Fukuma E. 1H MR spectroscopy and diffusion-weighted imaging of the breast: are they useful tools for characterizing breast lesions before biopsy? American Journal of Roentgenology. 2009;193(3):840-9.
22. Sharma U, Jagannathan NR. In vivo MR spectroscopy for breast cancer diagnosis. BJR| Open. 2019;1(1):20180040.
23. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36.
24. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Annals of internal medicine. 2013;158(4):280-6.
25. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629-34.
26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.
27. He M, Ruan H, Ma M, Zhang Z. Application of diffusion weighted imaging techniques for differentiating benign and malignant breast lesions. Frontiers in Oncology. 2021;11:694634.
28. Meng N, Wang XJ, Sun J, Huang L, Wang Z, Wang KY, et al. Comparative Study of Amide Proton Transfer-Weighted Imaging and Intravoxel Incoherent Motion Imaging in Breast Cancer Diagnosis and Evaluation. Journal of Magnetic Resonance Imaging. 2020;52(4):1175-86.
29. Chan S-W, Chang Y-C, Huang P-W, Ouyang Y-C, Chang Y-T, Chang R-F, et al. Breast tumor detection and classification using intravoxel incoherent motion hyperspectral imaging techniques. BioMed research international. 2019;2019.
30. Song SE, Cho KR, Seo BK, Woo OH, Park KH, Son YH, et al. Intravoxel incoherent motion diffusion-weighted MRI of invasive breast cancer: Correlation with prognostic factors and kinetic features acquired with computer-aided diagnosis. Journal of Magnetic Resonance Imaging. 2019;49(1):118-30.
31. Zhao M, Fu K, Zhang L, Guo W, Wu Q, Bai X, et al. Intravoxel incoherent motion magnetic resonance imaging for breast cancer: a comparison with benign lesions and evaluation of heterogeneity in different tumor regions with prognostic factors and molecular classification. Oncology Letters. 2018;16(4):5100-12.
32. Mao X, Zou X, Yu N, Jiang X, Du J. Quantitative evaluation of intravoxel incoherent motion diffusion-weighted imaging (IVIM) for differential diagnosis and grading prediction of benign and malignant breast lesions. Medicine. 2018;97(26).
33. Jiang L, Lu X, Hua B, Gao J, Zheng D, Zhou Y. Intravoxel incoherent motion diffusion-weighted imaging versus dynamic contrast-enhanced magnetic resonance imaging: comparison of the diagnostic performance of perfusion-related parameters in breast. Journal of Computer Assisted Tomography. 2018;42(1):6-11.
34. Iima M, Kataoka M, Kanao S, Onishi N, Kawai M, Ohashi A, et al. Intravoxel incoherent motion and quantitative non-Gaussian diffusion MR imaging: evaluation of the diagnostic and prognostic value of several markers of malignant and benign breast lesions. Radiology. 2018;287(2):432-41.
35. Suo S, Cheng F, Cao M, Kang J, Wang M, Hua J, et al. Multiparametric diffusion-weighted imaging in breast lesions: Association with pathologic diagnosis and prognostic factors. Journal of Magnetic Resonance Imaging. 2017;46(3):740-50.
36. Lin N, Chen J, Hua J, Zhao J, Zhao J, Lu J. Intravoxel incoherent motion MR imaging in breast cancer: quantitative analysis for characterizing lesions. Int J Clin Exp Med. 2017;10(1):1705-14.
37. Kawashima H, Miyati T, Ohno N, Ohno M, Inokuchi M, Ikeda H, et al. Differentiation between luminal-A and luminal-B breast cancer using intravoxel incoherent motion and dynamic contrast-enhanced magnetic resonance imaging. Academic Radiology. 2017;24(12):1575-81.
38. Ma D, Lu F, Zou X, Zhang H, Li Y, Zhang L, et al. Intravoxel incoherent motion diffusion-weighted imaging as an adjunct to dynamic contrast-enhanced MRI to improve accuracy of the differential diagnosis of benign and malignant breast lesions. Magnetic Resonance Imaging. 2017;36:175-9.
39. Chen W, Zhang J, Long D, Wang Z, Zhu JM. Optimization of intra-voxel incoherent motion measurement in diffusion-weighted imaging of breast cancer. Journal of Applied Clinical Medical Physics. 2017;18(3):191-9.
40. Lee YJ, Kim SH, Kang BJ, Kang YJ, Yoo H, Yoo J, et al. Intravoxel incoherent motion (IVIM)-derived parameters in diffusion-weighted MRI: Associations with prognostic factors in invasive ductal carcinoma. Journal of Magnetic Resonance Imaging. 2017;45(5):1394-406.

41. Wang Q, Guo Y, Zhang J, Wang Z, Huang M, Zhang Y. Contribution of IVIM to conventional dynamic contrast-enhanced and diffusion-weighted MRI in differentiating benign from malignant breast masses. Breast Care. 2016;11(4):254-8.
42. Liu C, Wang K, Chan Q, Liu Z, Zhang J, He H, et al. Intravoxel incoherent motion MR imaging for breast lesions: comparison and correlation with pharmacokinetic evaluation from dynamic contrast-enhanced MR imaging. European radiology. 2016;26:3888-98.
43. Cho GY, Moy L, Kim SG, Baete SH, Moccaldi M, Babb JS, et al. Evaluation of breast cancer using intravoxel incoherent motion (IVIM) histogram analysis: comparison with malignant status, histological subtype, and molecular prognostic factors. European radiology. 2016;26:2547-58.
44. Dijkstra H, Dorrius MD, Wielema M, Pijnappel RM, Oudkerk M, Sijens PE. Quantitative DWI implemented after DCE-MRI yields increased specificity for BI-RADS 3 and 4 breast lesions. Journal of Magnetic Resonance Imaging. 2016;44(6):1642-9.
45. Iima M, Yano K, Kataoka M, Umehana M, Murata K, Kanao S, et al. Quantitative non-Gaussian diffusion and intravoxel incoherent motion magnetic resonance imaging: differentiation of malignant and benign breast lesions. Investigative radiology. 2015;50(4):205-11.
46. Fusco R, Sansone M, Filice S, Granata V, Catalano O, Amato DM, et al. Integration of DCE-MRI and DW-MRI quantitative parameters for breast lesion classification. BioMed research international. 2015;2015.
47. Bokacheva L, Kaplan JB, Giri DD, Patil S, Gnanasigamani M, Nyman CG, et al. Intravoxel incoherent motion diffusion-weighted MRI at 3.0 T differentiates malignant breast lesions from benign lesions and breast parenchyma. Journal of Magnetic Resonance Imaging. 2014;40(4):813-23.
48. Liu C, Liang C, Liu Z, Zhang S, Huang B. Intravoxel incoherent motion (IVIM) in evaluation of breast lesions: comparison with conventional DWI. European journal of radiology. 2013;82(12):e782-e9.
49. Sigmund EE, Cho GY, Kim S, Finn M, Moccaldi M, Jensen JH, et al. Intravoxel incoherent motion imaging of tumor microenvironment in locally advanced breast cancer. Magnetic resonance in medicine. 2011;65(5):1437-47.
50. Jacobs MA, Barker PB, Argani P, Ouwerkerk R, Bhujwalla ZM, Bluemke DA. Combined dynamic contrast enhanced breast MR and proton spectroscopic imaging: a feasibility study. Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2005;21(1):23-8.
51. Baek HM, Chen JH, Yu HJ, Mehta R, Nalcioglu O, Su MY. Detection of choline signal in human breast lesions with chemical-shift imaging. Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2008;27(5):1114-21.
52. Kim J-K, Park S-H, Lee HM, Lee Y-H, Sung N-K, Chung D-S, et al. In vivo 1H-MRS evaluation of malignant and benign breast diseases. The Breast. 2003;12(3):179-82.
53. Lipnick S, Liu X, Sayre J, Bassett LW, DeBruhl N, Thomas MA. Combined DCE-MRI and single-voxel 2D MRS for differentiation between benign and malignant breast lesions. NMR in Biomedicine. 2010;23(8):922-30.
54. Gruber S, Debski B-K, Pinker K, Chmelik M, Grabner G, Helbich T, et al. Three-dimensional proton MR spectroscopic imaging at 3 T for the differentiation of benign and malignant breast lesions. Radiology. 2011;261(3):752-61.
55. Montemezzi S, Cavedon C, Camera L, Meliadò G, Caumo F, Baglio I, et al. 1 H-MR spectroscopy of suspicious breast mass lesions at 3T: a clinical experience. La radiologia medica. 2017;122:161-70.
56. Suppiah S, Rahmat K, Mohd-Shah M, Azlan C, Tan L, Aziz Y, et al. Improved diagnostic accuracy in differentiating malignant and benign lesions using single-voxel proton MRS of the breast at 3 T MRI. Clinical radiology. 2013;68(9):e502-e10.
57. Ramazan A, Demircioglu O, Ugurlu U, Kaya H, Aribal E. Efficacy of single voxel 1H MR spectroscopic imaging at 3 T for the differentiation of benign and malign breast lesions. Clinical Imaging. 2016;40(5):831-6.
58. Aribal E, Asadov R, Ramazan A, Ugurlu MÜ, Kaya H. Multiparametric breast MRI with 3T: Effectivity of combination of contrast enhanced MRI, DWI and 1H single voxel spectroscopy in differentiation of Breast tumors. European Journal of Radiology. 2016;85(5):979-86.
59. Roebuck JR, Cecil KM, Schnall MD, Lenkinski RE. Human breast lesions: characterization with proton MR spectroscopy. Radiology. 1998;209(1):269-75.
60. Thakur SB, Brennan SB, Ishill NM, Morris EA, Liberman L, Dershaw DD, et al. Diagnostic usefulness of water-to-fat ratio and choline concentration in malignant and benign breast lesions and normal breast parenchyma: an in vivo 1H MRS study. Journal of Magnetic Resonance Imaging. 2011;33(4):855-63.
61. Dorrius MD, Pijnappel RM, Van Der Weide Jansen M, Jansen L, Kappert P, Oudkerk M, et al. The added value of quantitative multi-voxel

MR spectroscopy in breast magnetic resonance imaging. European radiology. 2012;22:915-22.
62. Sah RG, Sharma U, Parshad R, Seenu V, Mathur SR, Jagannathan NR. Association of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status with total choline concentration and tumor volume in breast cancer patients: An MRI and in vivo proton MRS study. Magnetic resonance in medicine. 2012;68(4):1039-47.
63. Mizukoshi W, Kozawa E, Inoue K, Saito N, Nishi N, Saeki T, et al. 1 H MR spectroscopy with external reference solution at 1.5 T for differentiating malignant and benign breast lesions: comparison using qualitative and quantitative approaches. European radiology. 2013;23:75-83.
64. Meisamy S, Bolan PJ, Baker EH, Pollema MG, Le CT, Kelcz F, et al. Adding in vivo quantitative 1H MR spectroscopy to improve diagnostic accuracy of breast MR imaging: preliminary results of observer performance study at 4.0 T. Radiology. 2005;236(2):465-75.
65. Yeung DK, Cheung HS, Tse GM. Human breast lesions: characterization with contrast-enhanced in vivo proton MR spectroscopy—initial results. Radiology. 2001;220(1):40-6.
66. Tse GM, Cheung HS, Pang L-M, Chu WC, Law BK, Kung FY, et al. Characterization of lesions of the breast with proton MR spectroscopy: comparison of carcinomas, benign lesions, and phyllodes tumors. American Journal of Roentgenology. 2003;181(5):1267-72.
67. Huang W, Fisher PR, Dulaimy K, Tudorica LA, O'Hea B, Button TM. Detection of breast malignancy: diagnostic MR protocol for improved specificity. Radiology. 2004;232(2):585-91.
68. Kousi E, Tsougos I, Vasiou K, Theodorou K, Poultsidi A, Fezoulidis I, et al. Magnetic resonance spectroscopy of the breast at 3T: pre- and post-contrast evaluation for breast lesion characterization. The scientific world Journal. 2012;2012.
69. Bartella L, Morris EA, Dershaw DD, Liberman L, Thakur SB, Moskowitz C, et al. Proton MR spectroscopy with choline peak as malignancy marker improves positive predictive value for breast cancer diagnosis: preliminary study. Radiology. 2006;239(3):686-92.
70. Vassiou K, Tsougos I, Kousi E, Vlychou M, Athanasiou E, Theodorou K, et al. Application value of 3T 1H-magnetic resonance spectroscopy in diagnosing breast tumors. Acta Radiologica. 2013;54(4):380-8.
71. Başara I, Örgüç Ş, Coşkun T. Single voxel in vivo proton magnetic resonance spectroscopy of breast lesions: experience in 77 cases. Diagn Interv Radiol. 2013;19(3):221-6.
72. Su M, Baik H, Yu HJ, Chen J-h, Mehta RS, Nalcioglu O. Comparison of choline and pharmacokinetic parameters in breast cancer measured by MR spectroscopic imaging and dynamic contrast enhanced MRI. TECHNOLOGY IN CANCER RESEARCH AND TREATMENT. 2006;5(4):401.
73. Chen X, Li W-l, Zhang Y-l, Wu Q, Guo Y-m, Bai Z-l. Meta-analysis of quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesions. BMC cancer. 2010;10(1):1-11.
74. Shi R-y, Yao Q-y, Wu L-m, Xu J-r. Breast lesions: diagnosis using diffusion weighted imaging at 1.5 T and 3.0 T—systematic review and meta-analysis. Clinical breast cancer. 2018;18(3):e305-e20.
75. Dorrius MD, Dijkstra H, Oudkerk M, Sijens PE. Effect of b value and pre-admission of contrast on diagnostic accuracy of 1.5-T breast DWI: a systematic review and meta-analysis. European radiology. 2014;24:2835-47.
76. Federau C. Intravoxel incoherent motion MRI as a means to measure in vivo perfusion: A review of the evidence. NMR in Biomedicine. 2017;30(11):e3780.
77. Baltzer P, Mann RM, Iima M, Sigmund EE, Clauser P, Gilbert FJ, et al. Diffusion-weighted imaging of the breast—a consensus and mission statement from the EUSOBI International Breast Diffusion-Weighted Imaging working group. European radiology. 2020;30:1436-50.
78. Bolan PJ, Meisamy S, Baker EH, Lin J, Emory T, Nelson M, et al. In vivo quantification of choline compounds in the breast with 1H MR spectroscopy. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2003;50(6):1134-43.
79. Haddadin IS, McIntosh A, Meisamy S, Corum C, Snyder ALS, Powell NJ, et al. Metabolite quantification and high-field MRS in breast cancer. NMR in Biomedicine: An International Journal Devoted to the Development and Application of Magnetic Resonance In vivo. 2009;22(1):65-76.