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The role of Bi-exponential diffusion-weighted model (IVIM) in breast cancer differentiation and comparison of curve fitting methods: A systematic review and meta-analysis

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Abstract---Objective: The current meta-analysis aimed to analyze all published results about the diagnostic performance of intravoxel incoherent motion (IVIM) to assess the differential diagnosis between malignant and benign breast cancer and comparison of curve fitting methods. Methods: PubMed and Embase databases were systematically searched to find relevant articles published until November 2021 in English journals. Studies were evaluated in accordance with inclusion and exclusion standards. We evaluated study heterogeneity and publication bias. Using a bivariate model, aggregated summary values of sensitivity, specificity, and area under the curve were derived for each related parameters of the intravoxel incoherent motion (true diffusivity [D], pseudo-diffusivity [D*],

perfusion fraction [f]). Subgroup analysis was employed to investigate the impact of various field strengths and b values. Results: From 25 eligible studies, 2391 lesions (1652 malignant and 653 benign) were included. Publication bias was evident for studies that evaluated parameters of the intravoxel incoherent motion (D, D*, and f). Significant heterogeneity (P 0.05) was present for all parameters. The pooled sensitivity, specificity and area under the curve for f was 0.78, 0.69, and 0.83, respectively. D* was 0.69, 0.63, and 0.72, respectively. The highest performing parameter for IVIM was tissue diffusivity (D), and the pooled sensitivity, specificity and area under the curve were 0.86, 0.86, and 0.92, respectively. Conclusions: The current meta-analysis reports on intravoxel incoherent motion parameters, which have Superior diagnostic accuracy with high sensitivity and specificity. As a result, this technique can be used to distinguish between breast cancers.

Keywords---Intravoxel incoherent motion (IVIM), Breast Cancer, Diffusion-Weighted Imaging (DWI), differential diagnosis, meta-analysis.

Introduction

Breast cancer is one of the most prevalent malignant tumors in females, As the second greatest cause of cancer-related death in women⁽¹⁾. Magnetic resonance imaging (MRI) is increasingly being employed for the early identification and diagnosis of breast malignancies⁽²⁾. Diffusion and perfusion imaging are two of the most widely used functional MRI techniques for imaging breast cancer⁽³⁾. Diffusion imaging, also known as diffusion-weighted MRI (DWI), takes advantage of the water molecule's Brownian motion effects in the intra- and extracellular regions of the tissue and has the potential to offer biological details on the tumor blood micro-vasculature at the cellular level^(4,5). Diffusion-weighting coefficients, often known as b-values, are used in conventional DWI to generate the diffusion parameters. The apparent diffusion coefficients (ADC) can be estimated and images of diffusion parameters, such as ADC maps, can be reconstructed using the MRI water signal attenuation model⁽⁶⁾. The diffusion of water molecules in malignant tissues is typically constrained by tighter cellular membrane microstructure as a result of the active tumor cell development pattern, and the ADC values in tumors are consequently decreased. Malignant tissues, however, exhibit larger signal intensities in DWI pictures. DWI can consequently be used to identify, track, and forecast the progression of tumors^(2,3).

Perfusion phenomena may have an impact on the DWI measurement⁽⁷⁻⁹⁾. ADC values are frequently overestimated at the single-voxel level due to the capillary network's random distribution throughout the tissue and the impact of intravoxel incoherent motion on blood flow perfusion. Since the microscopic blood flow in a network of randomly oriented capillaries produces a pseudo-diffusion contribution to the total diffusion-weighted (DW) MR signal, DWI measurements also represent the contribution from tissue perfusion effects.

The intra-voxel incoherent motion (IVIM) concept was postulated to account for the molecular diffusion contribution motivated by thermal energy including the perfusion-based pseudodiffusion contribution after Le Bihan et al.^(7,8) has shown that blood circulation of blood in capillary network (perfusion) was capable of changing DW signal intensities at low b-values. The genuine diffusion component and the perfusion-based pseudo-diffusion component make up the diffusion measurement contribution in IVIM theory. It was believed that the IVIM study and its deduced diffusion parameters were strongly impacted by the choice of b-values in the DWI measurement⁽¹⁰⁾.

IVIM assessment in the imaging of several organs has drawn increased attention in recent years, for instance, in the imaging of normal livers and livers with cirrhosis^(11–14), kidney,^(15–17) and the prostate^(10,18). There was, however, no established technique or ideal set of b-values to distinguish between the diffusion or perfusion effects. Instead, multiple ranges of b-values were employed in the clinical assessment of IVIM characteristics from various institutions^(2,19,20). In clinical settings, the majority of research showed so when b values may be less than 200 s/mm², perfusion also have more dominating effects. Varied b-value thresholds would lead to different IVIM parameters^(21–23). The separation of perfusion with diffusion impacts may be achieved by choosing the best b-value thresholds, according to a computing approach Wurnig et al. suggested⁽²⁴⁾.

The advantage of employing IVIM MRI is that it can produce information on tissue perfusion without use of "conventional" intravenously administered MR contrast agents, so additional to the diffusion parameters, in diffusion-weighted imaging examinations of breast tissue with various b-values. IVIM analysis offers the capacity to measure tissue perfusion noninvasively and may concurrently extract precise information on tissue diffusion and perfusion. Previous research has shown that IVIM MRI has the ability to diagnose breast tumors clinically^(21–23,25,26). Limited data revealed that the IVIM-derived characteristics were extremely diverse and had significant errors, particularly for the parameters f and D*. However, currently published research employed different values and methodologies for IVIM analysis⁽²²⁾.

Therefore, using a meta-analysis technique, we sought to combine all the results that had been published concerning the diagnostic performance of IVIM to assess in the differentiation of malignant and benign breast cancer.

Methods

Search strategy

Two radiologists independently conducted meta-analysis search using the terms "breast cancer" "Intravoxel Incoherent Motion" "biexponential" "MRI OR magnetic resonance imaging" "diffusion-weighted imaging OR DWI" "Breast or Breast Neoplasms, Ductal, Breast or Breast Neoplasms or Breast Diseases" to find articles published before November 2021 in the following databases: PubMed (<https://pubmed.ncbi.nlm.nih.gov>), Embase (<https://www.embase.com>), Web of Science (<https://apps.webofknowledge.com>), SEMANTIC SCHOLAR, Google Scholar, PROQUEST, and Cochrane Library databases (<https://www>

cochranelibrary.com). Only high-performing original articles written in English . Additionally, we used PubMed's "Related Articles" feature to search the databases indicated above. Additionally, a hand search was conducted on the reference list of accepted papers.

Study Selection and Data Extraction

After the initial assessment, two radiologists used a standard extraction form to summarize each publication separately, recording the following information: 1) Included the diagnostic accuracy of breast cancer underwent diagnostic IVIM; 2) constituted original research rather than a meta-analysis, a review article, case report or case series; 3) published in English 4) results are from humans and not animals 5) included IVIM protocol 6) included sufficient data, with >20 patients to calculate true positive (TP), false positive (FP), false negative (FN) and true negative (TN) for constructing a 2x2 contingency table; and 7) patients at high risk for breast cancer using pathological analysis (surgical resection, explant and/or biopsy) or imaging from follow-up corresponding to the guidelines for the standardization of breast imaging, diagnosis, classification. In addition, articles from the same institution, which involved an overlap period of patient recruitment, were considered to have an overlapping population .A total of 228 studies were excluded according to the following exclusion criteria: 1) they were not relevant to the present meta-analysis if they fit one of the followings conditions: Cancer type not involve breast cancer 2) the sensitivity and specificity were not evaluated;3) studies with animal subjects, reviews, case reports, letters, editorials, abstracts, comments, and *in vitro* studies; 4) studies were eliminated with less than eight subjects and those without sufficient data were included.

Quality and risk of bias assessment

The quality and risk of bias in the included studies were evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS). No studies were disqualified for being of low quality⁽²⁷⁾.

Statistical analysis

The Cochran's Q test for heterogeneity with a significance threshold of P 0.05 and I² statistic with values >75 percent to the existence of heterogeneity were used to evaluate the presence of heterogeneity. Using Stata version 12.0 (StataCorp, College Station, TX, USA), we created a bivariate regression model to combine the diagnostic performance with the sensitivity, specificity, diagnostic odds ratio (DOR), diagnostic sensitivity ratio (AUC), diagnostic positive likelihood ratio (PLR), and diagnostic negative likelihood ratio (NLR). The diagnostic values D, D*, and f in the differential diagnosis of breast cancers were also shown using Fagan's nomograms and summary receiver operating characteristic curves. The basic meta-regression model was employed to evaluate the impact of sample size and study year on the heterogeneity of pooled estimates.

Results

From several databases, a total of 228 relevant studies were found by looking for keywords in the titles and abstracts. After reviewing the titles and abstracts, 25 papers, including meta-analyses. After eliminating duplicate studies from the same authors or institutions, there were 106 articles left to investigate. 33 papers were further excluded due to the inclusion of animal research, non-breast studies and non-English studies, remaining 73 papers and eliminated an additional 48 papers: (a) conference abstracts and thoroughly reviewed the entire texts of the; (b) insufficient data to pool; (c) inadequate quality evaluation; (d) not evaluation with IVIM; and (e) malignancy not verified by pathology. Finally, 653 benign and 1652 malignant breast lesions from 25 suitable papers were included in the analysis. Figure 1 shows the flowchart outlining the procedure for choosing studies. Tables 1, 2 provide a full breakdown of the fundamental data with diagnostic performance with each included study.

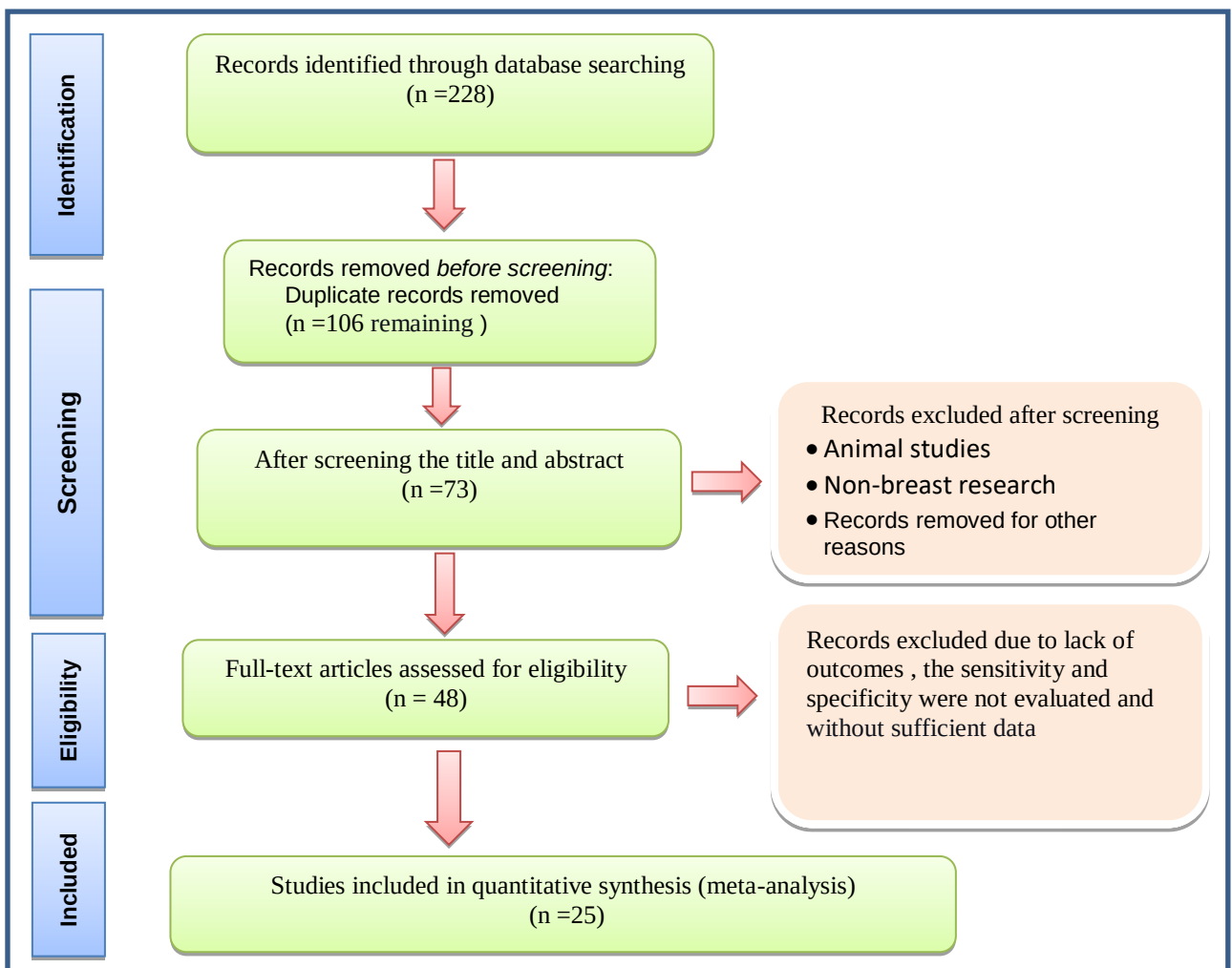


Figure 1: Detailed Summary of included studies

Diagnostic Performance for the Differential Diagnosis Of Breast Cancer Sensitivity

Table 3 shows the results of the pooled analysis of IVIM parameters. High heterogeneity between studies was measured for parameters. Forest plots of sensitivity, specificity, Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) with 95% confidence intervals per study by true diffusivity [D], pseudo-diffusivity [D*], perfusion fraction [f]. Vertical lines denote pooled summary estimates of sensitivity and specificity. According to the results of the random-effects model, the pooled sensitivity was estimated as D parameter showed a good diagnostic interpretation 86% (0.83 to 0.89), 95% CI in differential diagnosis of breast lesions, there was significant heterogeneity between studies (I^2 :71.9%, of chi² test for heterogeneity: p = 0.0002 and T^2 : 32.07) then the pooled sensitivity was estimated as f parameter showed 78% (0.73 to 0.82), 95% CI in differential diagnosis of breast lesions, there was significant heterogeneity between studies (I^2 :39.9%, of chi² test for heterogeneity: p =< 0.0918 and T^2 : 14.97) and the pooled sensitivity was estimated as D* parameter showed 69% (0.65 to 0.73), 95% CI in differential diagnosis of breast lesions, there was significant heterogeneity between studies (I^2 :92.6%, of chi² test for heterogeneity: p =< 0.000 and T^2 : 107.89) more information was shown in figure 2.

Using Effects Model, was estimated as D parameter showed Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) Reported as 5.51 (95% CI 4.24, 7.17) and 0.16 (95% CI 0.11, 0.24), Respectively; estimated as D parameter showed Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) Reported as 1.78 (95% CI 1.45, 2.18) and 0.39 (95% CI 0.26, 0.59), Respectively and was estimated as f parameter showed Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) Reported as 2.58 (95% CI 1.93, 3.44) and 0.31 (95% CI 0.31, 0.40), Respectively.

Specificity

According to the results of the random-effects model, the pooled specificity was estimated as D parameter showed a good diagnostic interpretation 86% (0.83 to 0.89), 95 % CI in differential diagnosis of breast lesions, there was significant heterogeneity between studies (I^2 :4%, of chi² test for heterogeneity: p = 0.04338 and T^2 : 9.04) then the pooled specificity was estimated as f parameter showed 69% (0.63 to 0.74), 95 % CI in differential diagnosis of breast lesions, there was significant heterogeneity between studies (I^2 :54.2%, of chi² test for heterogeneity: p =< 0.0202 and T^2 : 19.65) and the pooled specificity was estimated as D* parameter showed 63% (0.57 to 0.69), 95 % CI in differential diagnosis of breast lesions, there was significant heterogeneity between studies (I^2 :70%, of chi² test for heterogeneity: p =< 0.0008 and T^2 : 26.70) more information was shown in figure 2.

Figure 3 showed Summary receiver operating characteristic (SROC) curves; Plotting curves of the D, D*, and f values. Showed the D curve (AUC 0.92, Q* Index 0.86), f curve, (AUC 0.83, Q* Index 0.76), and D* curve, (AUC 0.72, Q* Index 0.67).

Meta-regression

To identify the cause of heterogeneity between studies the effect of variables like years of study and sample size of different studies on pooled sensitivity and specificity were assessed. The effect of the year of Study (P: 0.80) and sample size on heterogeneity between studies in the estimation of pooled sensitivity was not statistically significant (P: 0.49). Also, the effect of the year of Study (P: 0.17) and sample size on heterogeneity between studies in the estimation of pooled specificity was not statistically significant (P: 0.72). The distribution of sensitivity and specificity according to different sample sizes is shown in figure4.

Publication bias

According to the results of Begg's and Egger's test, there was a significant publication bias about the reported sensitivity (Begg's test P: 0.001, and Egger's test P: 0.001). Also According to the results of Begg's and Egger's test, there was a significant publication bias about the reported specificity (Begg's test P< 0.001, and Egger's test P< 0.001).

Table1: Overview of studies included

Author	Year	SD (P/R)	Pat. No.	Age: Median (range)	Machine type	Field Strength	Parameters	b-values (s/mm ²)	Malignant	Benign
He M ⁽²⁸⁾	2021	P	215	52.1 ± 11.0	Siemens	3.0T	ADC, IVIM	0, 30, 50, 80, 120, 160, 200, 500, and 1000	152	63
Meng N ⁽²⁹⁾	2020	P	123	58 ± 10	GE	3T	IVIM	0, 50, 75, 100, 150, 200, 400, 800, 1,000	65	58
Chan SW ⁽³⁰⁾	2019	P	25	NA	Siemens	1.5 T	IVIM	0, 15, 30, 45, 60, 100, 250, 400, 550, 700, 850, 1000	20	5
Song SE ⁽³¹⁾	2019	R	85	54 (35–81)	Siemens	3T	IVIM	0, 10, 20, 30, 50, 70, 100, 150, 200, 400, 600, 1,000	85	0
Zhao M ⁽³²⁾	2018	R	141	50.2 ± 10.5	GE	3T	ADC, IVIM	0, 50, 100, 150, 200, 400, 500, 1,000, 1,500	119	22
Mao X ⁽³³⁾	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	77	47
Jiang L ⁽³⁴⁾	2018	P	66	45 ± 10	GE	3T	IVIM	0, 10, 30, 50, 70, 100, 150, 200, 400, 600, 1,000, 1,500	31	35
Lima M ⁽³⁵⁾	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	152	47
Suo S ⁽³⁶⁾	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	57	44
Lin N ⁽³⁷⁾	2017	P	98	48 (17–77)	Philips	3T	ADC, IVIM	0, 50, 100, 150, 200, 500, 800	51	47
Kawashima ⁽³⁸⁾	2017	R	137	58 (32–85)	GE	3T	IVIM	0, 20, 40, 80, 120, 200, 400, 600, 800	137	-
Ma D ⁽³⁹⁾	2017	P ^a	128	48.2 ± 5.1	Siemens	3T	IVIM	0, 50, 100, 150, 200, 250, 300, 400, 600, 800, 1,000, 1,200	81	47
Chen W ⁽⁴⁰⁾	2017	NA	29	47 (15–62)	Siemens	3T	IVIM	0, 50, 100, 150, 200, 300, 400, 800, 1,000	18	11
Lee YJ ⁽⁴¹⁾	2017	R	82	53 (34–77)	Siemens	3T	IVIM	0, 25, 50, 75, 100, 150, 200, 300, 500, 800	-	-
Wang ⁽⁴²⁾	2016	R	54	46.85 ± 8.63	GE	3 T	ADC, IVIM	0, 10, 20, 50, 100, 200, 300, 400, 600, 800	31	23
Liu ⁽⁴³⁾	2016	P	59	NA	Philips	1.5 T	ADC, IVIM	0, 10, 20, 30, 50, 70, 100, 150, 200, 400, 600, 100	36	23
Kim Y ⁽⁴⁴⁾	2016	P	275	51 (28–83)	Philips	3T	IVIM	0, 30, 70, 100, 150, 200, 300, 400, 500, 800	228	47
Cho ⁽⁴⁵⁾	2016	R	62	48.4 ± 11.1	Siemens	3 T	ADC, IVIM	0, 30, 70, 100, 150, 200, 300, 400, 500, 800	50	12
Dijkstra ⁽⁴⁶⁾	2016	P ^a	139	47 (22–75)	Siemens	1.5 T	ADC, IVIM	0, 50, 200, 500, 800, 1000	116	23
Suo S ⁽²²⁾	2015	R	30	50 (27–79)	Philips	3T	IVIM	b50, 50, 100, 150, 200, 500, and 800	-	-
Lima ⁽²¹⁾	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	9	8
Fusco ⁽⁴⁷⁾	2015	NA	31	37.2 ± 10.4	Siemens	1.5T	IVIM	0, 50, 100, 150, 400, 800, 1000	15	16
Bokacheva ⁽²⁵⁾	2014	R	40	49 (28–70)	GE	3 T	ADC, IVIM	0, 30, 60, 90, 120, 400, (450 in 7 cases), 600, 800, 1000	26	14
Liu ⁽²³⁾	2013	P	81	48 (20–76)	Philips	1.5 T	ADC, IVIM	0, 10, 20, 30, 50, 70, 100, 150, 200, 400, 600, 100	40	41
Sigmund ⁽⁴⁸⁾	2011	P	44	53.1 (39–85)	Siemens	3-T	IVIM	0, 30, 70, 100, 150, 200, 300, 400, 500, and 800	24	20

Table2: Diagnostic outcome of each studies

	Author	Year	Thresh old	AUC	Sensitivi ty	Specificit y	TP	FP	FN	TN
ADC	He M (28)	2021	<0.983	0.915	91.45%	82.54%	NA	NA	NA	NA
	Zhao M (32)	2018	1.15	0.9	0.857	0.893	63	2	17	20
	Lin N (37)	2017	1.203	0.931	0.894	0.843	46	5	7	40
	Cho (45)	2016	NA	0.69	0.58	0.833	29	2	21	10
	Wang(42)	2016	NA	NA	0.808	0.677	46	14	11	30
	Bokacheva (25)	2014	1.54	0.72	0.65	0.71	17	4	9	10
D	He M (28)	2021	<0.952	0.909	90.13%	80.95%	NA	NA	NA	NA
	Meng N (29)	2020	1.01	0.809	0.7385	0.9138	48	5	17	53
	Zhao M (32)	2018	1.09	0.92	0.929	0.88	11	3	8	19
	Mao X (33)	2018	1.21	0.883	83.0	57.4	NA	NA	NA	NA
	Lin N (37)	2017	1.096	0.945	0.872	0.843	44	7	7	40
	Cho (45)	2016	NA	0.77	0.66	0.917	33	1	17	11
D*	Wang(42)	2016	NA	NA	0.937	0.874	53	6	4	38
	Liu (43)	2016	1.02	0.917	0.89	0.83	32	4	4	19
	Bokacheva (25)	2014	1.52	0.75	0.85	0.64	22	5	4	9
	He M (28)	2021	>0.873	0.574	42.76%	77.78%	NA	NA	NA	NA
	Meng N (29)	2020	26.58	0.67	0.7385	0.547	85	10	34	12
	Zhao M (32)	2018	43.18	0.674	0.714	0.86	19	2	7	12
F	Lin N (37)	2017	99.056	0.682	0.702	0.588	36	19	15	28
	Cho (45)	2016	NA	0.5	1	0.25	50	9	0	3
	Liu (43)	2016	140.88	NA	0.86	0.74	31	6	5	17
	Bokacheva (25)	2014	0.58	0.84	0.85	0.86	22	2	4	12
	Meng N (29)	2020	4.99	0.766	0.7385	0.7586	48	14	17	44
	Zhao M (32)	2018	20.3	0.885	0.857	0.893	50	2	17	20
	Mao X (33)	2018	7.86	0.601	64.9	57.4	NA	NA	NA	NA
	Lin N (37)	2017	7.87	0.802	0.863	0.66	44	16	7	31
	Cho (45)	2015	NA	0.72	0.833	0.726	42	3	8	9
	Liu (43)	2016	7.2	NA	0.86	0.74	31	6	5	17
	Bokacheva (25)	2014	4.9	0.79	0.73	0.86	19	2	7	12

Table3: 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*	9	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%

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve; I², inconsistency index

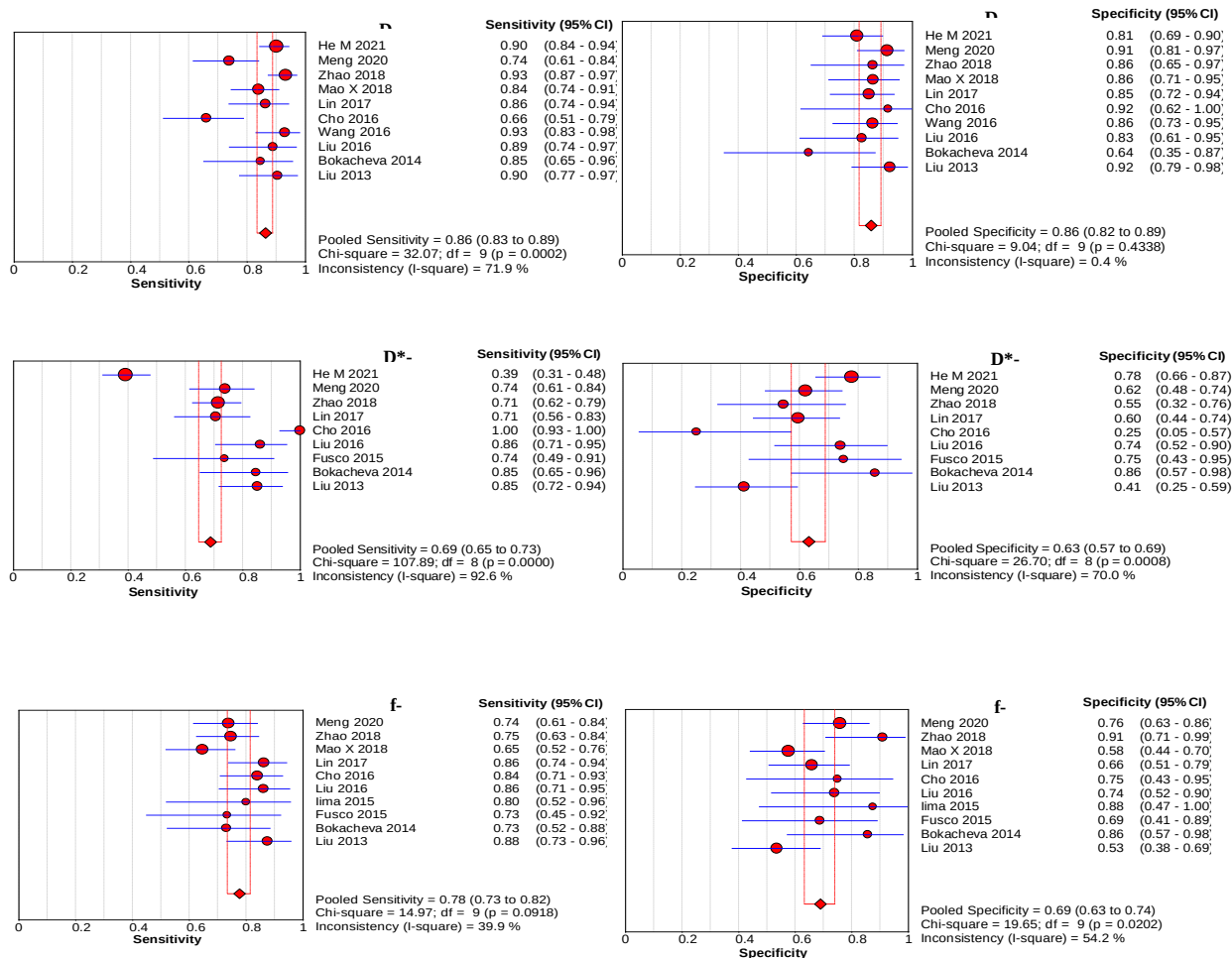


Figure 2: Forest Plot Illustrating Sensitivity and Specificity with Corresponding 95% Confidence Intervals of study by using true diffusivity [D], pseudo-diffusivity [D*], perfusion fraction [f]. Vertical lines denote pooled summary estimates of sensitivity and specificity.

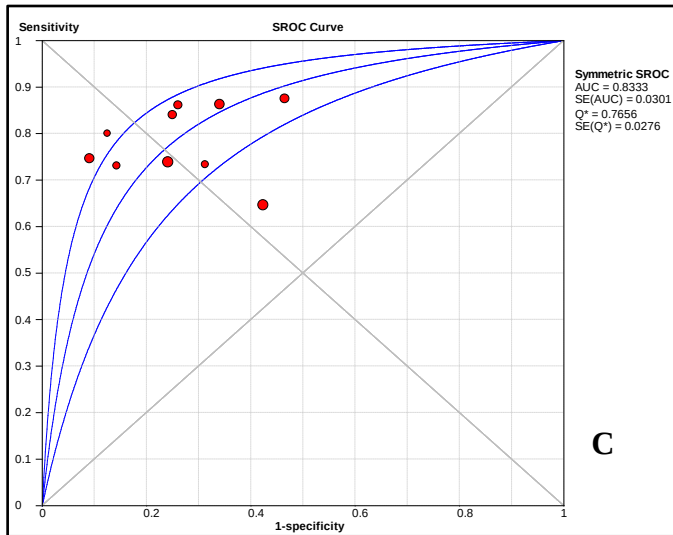
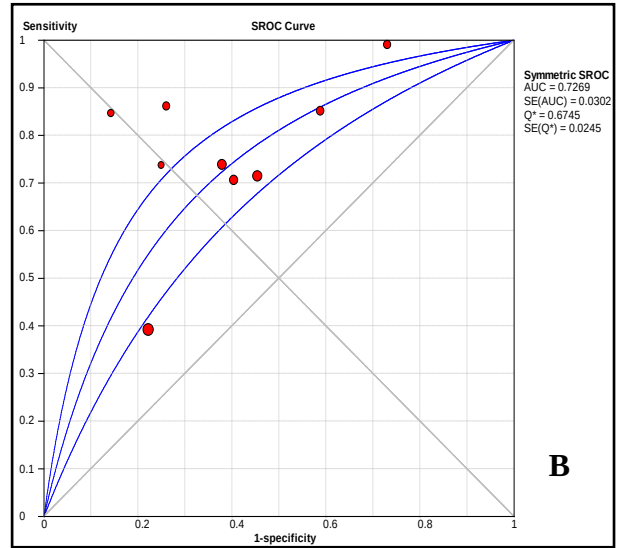
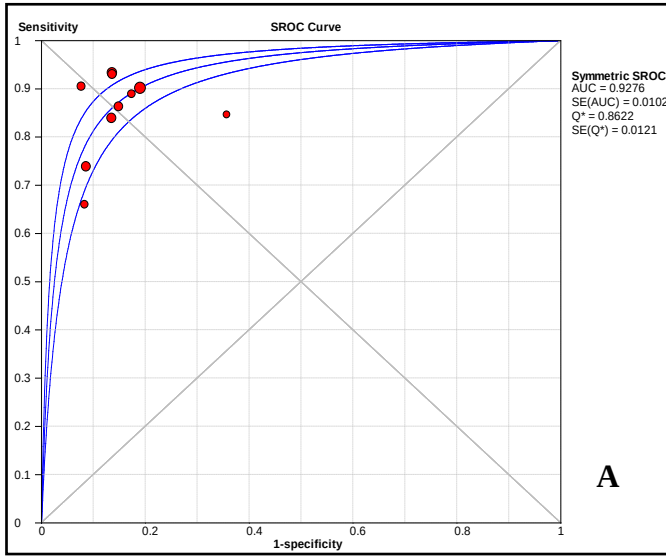


Figure 3: SROC curves; Plotting Sensitivity and Specificity in Receiver Operating Characteristic Space for Individual Articles; **A)** true diffusivity **B)** [D], pseudo-diffusivity [D*], **C)** f perfusion fraction [f].

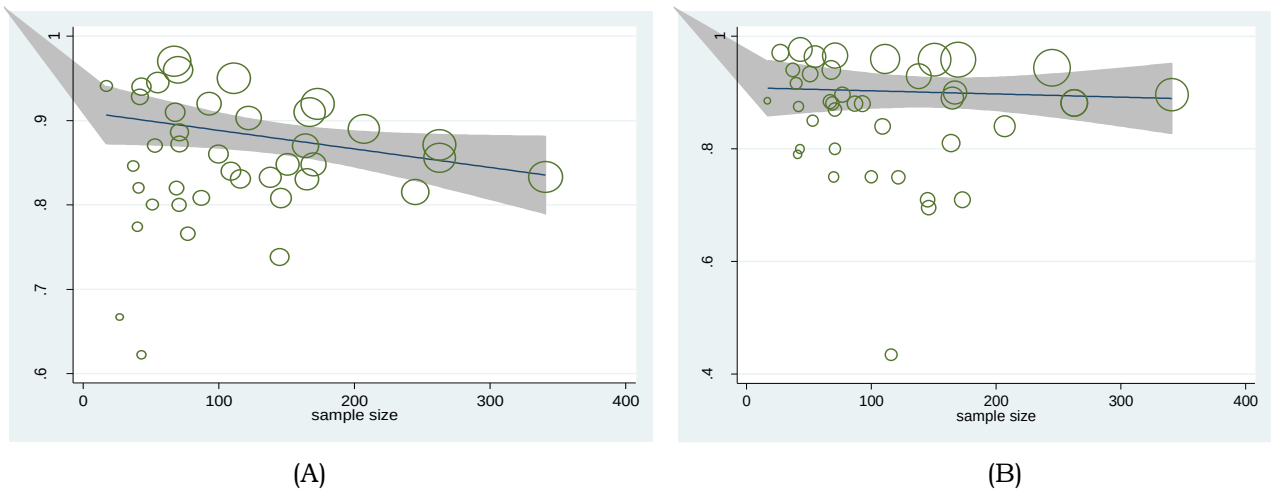


Figure 4: The distribution of estimated sensitivity (a) and specificity (b) according to different sample sizes

Intravoxel Incoherent Motion Diffusion-Weighted Imaging Fitting Methods

At the current, the majority of DW-imaging investigations characterize the apparent diffusion coefficient using the well-known mono-exponential model (ADC).

$$S_b = S_0 e^{-b \cdot \text{ADC}} \quad \text{Equation 1}$$

Microperfusion and molecular diffusion are described by a more advanced model in IVIM imaging. The bi-exponential IVIM model can distinguish between the signal attenuation caused by spin dephasing effects caused by microcirculation and that caused by regular confined passive diffusion.

$$S = S_0 [(1-f)e^{-b \cdot D} + f e^{-b \cdot D^*}] \quad \text{Equation 2}$$

Due to the limited signal-to-noise ratio, fitting data to these models while imaging living tissue can be challenging (SNR). Standard ROI analysis can be used to collect signal data from the entire tumor or only a segment of it, for example, at the tumor's most dangerous area. From there, it is possible to calculate the average of the pixel values or to create parametric maps that enable voxel by voxel analysis and the production of histograms. Following the collection of signal values from IVIM images, a variety of fitting techniques may be used to extract the IVIM parameters.

Fitting Method 1: Monoexponential fit

The monoexponential fit (Equation 1) is used to determine the ADC. This approach does not take perfusion effects into consideration, but it can be used to IVIM scans since they are simply diffusion scans with multiple b-values, allowing you to select two acceptable b values for analysis.

Fitting Method 2: Stretched-exponential fit

The stretched-exponential model improves upon Method 1;

$$S_b = S_0 e^{-b \cdot DDC^\alpha} \quad \text{Equation 3}$$

where DDC is the distributed diffusion coefficient and α is the heterogeneity index ranging from 0 to 1. If $\alpha = 1$, the model simplifies to Method 1. Lower values of α result from nonexponential behaviour caused by the addition of 'proton pools' with a range of diffusion rates within the imaged voxel or from a process where the motion is intermittent [58].

Fitting Method 3: Free biexponential fit

The signal decay data is fitted to Equation 2 using an unconstrained bi-exponential fit. This can be computed using a nonlinear fitting algorithm, such as nonlinear least squares or damped least squares (Levenberg-Marquardt). This method is sensitive to outliers and can lead to misleading results if underlying assumptions are not true.

Fitting Method 4: Constrained bi-exponential fit

The signal decay data is fitted to Equation 3.4 using a bi-exponential fit, using a nonlinear fitting algorithm with bound constraints, for example: $0 < f < 10\%$, $0 < D < 0.001 \text{ mm}^2/\text{s}$, $0 < D^* < 0.01 \text{ mm}^2/\text{s}$, $D < D^*$. These limits filter spurious and physiologically meaningless results.

Fitting Method 5: Segmented fit

Assuming that D^* is significantly greater than D (at least by an order of 10), and its influence on diffusion-weighted signal is weak when the b-value is large enough (typically $> 200 \text{ s/mm}^2$), then in this higher b-value regime the pseudo-diffusion component D^* can be neglected and D can be obtained by a simplified mono-exponential fit as in Method 1. Then, D^* and f can be calculated using a bi-exponential fit as in Methods 3 or 4.

Fitting Method 6: Over-segmented fit

High b-value data is fitted using the mono-exponential fit to obtain D as in Method 5, and then a mono-exponential fit is extrapolated back to zero to calculate f using;

$$f = (S_0 - \text{intercept})/S_0 \quad \text{Equation 4}$$

D and f are then used to constrain a bi-exponential fit to obtain D^* as in Methods 3 or 4.

Fitting Method 7: Triexponential

A tri-exponential model can be applied, where f_n represents the perfusion fraction of each compartment and D_n represents the joint diffusion and pseudo-diffusion coefficients of each compartment;

$$S = S_0 [f_1 e^{-bD1} + f_3 e^{-bD2} + f_3 e^{-bD3}]$$

$$\text{Equation 5}$$

Table 4: Summary of b-values, fitting methods used and IVIM parameters calculated in the reviewed breast literature

Author, year	Number of malignant lesions	Field Strength	DWI sequence	B-values (s/mm ²)	Curve fitting method(s)	D (10 ⁻³ mm ² /s)	D* (10 ⁻³ mm ² /s)	f(%)
Tamura 2010 (49)	58	3.0 T	Single shot spin-echo EPI	0, 700, 1400, 2100, 2800, 3500 s/mm ²	Method 3	0.18 ±0.09	2.10 ±0.68	0.67±0.13
Sigmund 2011 (48)	24	3.0 T	Single shot spin-echo EPI	0, 30, 70, 100, 150, 200, 300, 400, 500, 800 s/mm ²	Method 6	1.15 ±0.35	15.1 ±10.4	9.8 ±4.8
Lima 2015 (21)	16	3.0 T	Single shot spin-echo EPI	0, 3, 5, 10, 20, 30, 50, 70, 100, 200, 400, 600, 800, 1000, 1500, 2000, 2500 s/mm ²	Method 5 (Using kurtosis for D)	0.98 ±0.22	6.8 ±1.2	13.6 ±2.2
Bokacheva 2014 (25)	26	3.0 T	Single shot spin-echo TSE	0, 30, 60, 90, 120, 400, 600, 800, 1000 s/mm ²	Method 6	1.29 ±0.28	21.7 ±11.0	6.4 ±3.1
Liu 2013 (23)	40	1.5 T	Single shot spin-echo EPI	0, 20, 30, 40, 50, 70, 100, 150, 200, 400, 600, 1000 s/mm ²	Method 5	0.85 (0.77, 0.98)	94.71 (70.33, 113.23)	10.34 (7.68, 11.88)
Cho, 2012 (50)	14	3.0 T	Single shot spin-echo TSE	0, 30, 70, 100, 150, 200, 300, 400, 500, 800 s/mm ²	Method 3 Method 6	1.01±0.397 1.323 ±0.472	8.97 ±4.258 15.31±9.634	28.40 ±15.99 13.31 ±5.05
Cho, 2016 (45)	14	3.0 T	Single shot spin-echo TSE	0, 70, 300, 800 s/mm ²	Method 3 Method 6	1.088 ±0.390 1.195 ±0.471	11.028 7.981 13.183±6.529	24.89 ±11.39 16.83 ±9.06
Suo 2015 (22)	30	3.0 T	Single shot spin-echo EPI	0, 50, 100, 150, 200, 500, 800 s/mm ²	Method 1 Method 5 Method 6	0.70 ±0.11 0.83 ±0.19 0.77 ±0.15	98.24 ±59.25 159.50±9.032 69.28±46.19	16.33 ±5.21 7.61 ±2.33 6.10 ±3.19
Cho 2015 (51)	50	3.0 T	Single shot spin-echo TSE	0, 30, 70, 100, 150, 200, 300, 400, 500, 800 s/mm ²	Method 6	1.32 (0.65)	17.73 (4.45)	9.1 (5.1)
Luciani 2008 (12)	24 including 18 IDC	1.5 T	Single shot spin-echo EPI	0, 50, 100, 250, 800	Method 4	0.90±0.30	N/A	N/A

Discussion

Utilizing the IVIM imaging model and numerous b values, IVIM imaging is used to reflect tissue diffusivity and microcapillary perfusion, as opposed to standard DWI using a pair of b values. Biexponential IVIM imaging modeling can yield three parameters, like D, the diffusion-related parameter (that shows the true molecular diffusion of the nonvascular compartment related to Brown movement); D*, the pseudo-diffusion coefficient (that macroscopically shows the incoherent movement of blood in the microvascular compartment); and f, the perfusion fraction (that shows the percentage of incoherent signal due to the vascular compartment in each voxel as a proportion of the total incoherent signal)⁽⁸⁾.

To achieve correct representation of the diffusion of water molecules and blood microcirculation perfusion, the IVIM model should have b-values greater than 200 s/mm² ⁽²⁾. Breast tumors that were benign and those that were malignant could be consistently distinguished by D. After accounting for the effects of

microcirculation perfusion, D represents the genuine diffusion of water molecules, and research by us and others has demonstrated that the D value of malignant lesions is much lower than that of benign lesions^(23,25,53). The ratio of total diffusion to microcirculation perfusion is represented by the letter f . The f value of malignant lesions was discovered to be much higher than that of benign lesions in a study by Liu et al. ⁽²³⁾. This difference was assumed to be due to the increased microcirculation blood volume of malignant tumors.

Interestingly, compared to benign lesions, malignant breast tumors showed a considerably higher f value but a non-significantly higher D^* value. This was mostly caused by breast cancer's enhanced angiogenesis ⁽⁴³⁾. In comparison to the D^* value's specificity of 0.59 and AUC of 0.71, the f value showed a better specificity of 0.76 and AUC of 0.85. Additionally, the included studies' mean D^* values for breast cancer ranged from 3.85 to 109.78 103 mm²/s, indicating that the D^* value was not robust and could not be used to further improve diagnostic sensitivity and specificity. In contrast, the f value was able to more accurately reflect tissue perfusion. According to Liu et al. ⁽⁴³⁾, the IVIM model's D^* value may not be accurate due to the IVIM's poor measurement repeatability and low signal-to-noise ratio.

The correlation findings indicated that there were no threshold effects that were significant in the ADC ($r = 0.100$, $P = 0.873$), D ($r = 0.342$, $P = 0.452$), D^* ($r = 0.029$, $P = 0.957$), and f values ($r = 0.829$, $P = 0.524$); as a consequence, these factors were not the primary causes of the heterogeneity. It is important to look into the apparent heterogeneity shown by the ADC, D , D^* , and f values. The accuracy of the computations of the diffusion and perfusion coefficients may be impacted by the usage of 1.5T and 3.0T MR scanners with a variety of b-value combinations in these experiments, different research used different post-processing techniques; some ^(41,45) examined the entire lesion using histogram analyses, while the others focused on the lesion's biggest part as the region of interest. Finally, there were discrepancies between the tumor subtypes in the malignant and benign groups; this might have led to various biological traits and resultant changes in IVIM levels.

Our findings demonstrated that the curve-fitting methods used to determine the IVIM's parameters differed significantly from Methods 1 and 7. The preliminary findings might provide some of the justification for the significant differences in IVIM-derived parameters that were found between studies that were published in the past but used different calculating techniques (b-value combination is another major concern). The complexity of mathematical procedures using varied numbers of free parameters could be the reason of the discrepancies between various calculating techniques. To obtain more accurate estimations of IVIM generated parameters, various curve fitting techniques with or without previous assumptions have been devised.

Our meta-analysis was constrained. First, the small number of studies that contributed to the pooled estimates led to wide confidence intervals, which constrained the interpretation of the similar areas under the curve. Second, because we included several studies from the same author that could have employed the same patient group, overrepresentation of a sample might be a

drawback of our pooled estimates. Thirdly, we estimated true-positive, false-negative, true-positive, and true-negative results for studies that did not publish them using the sensitivity, specificity, and number of malignant and benign lesions. A noninteger number of lesions was the reason for the exclusion of numerous studies ($n = 24$). The minimal number of articles also prevented us from including other non-monoexponential models.

Conclusion

The current meta-analysis summarizes all the results that had been published concerning the diagnostic performance of IVIM which have Superior diagnostic accuracy with high sensitivity and specificity. As a consequence, the IVIM technique is a helpful method that may be used to distinguish breast cancer from benign breast lesions, evaluate the amount of the tumor's invasiveness, and do so. Using IVIM characteristics to characterize breast cancer offers a novel method for properly assessing breast cancer. Future research should incorporate more studies.

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