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A Meta-Analysis Study Of Quantitative Intravoxel Incoherent Motion (DWI) And Dynamic Contrast-Enhanced MRI To Evaluate Neoadjuvant Chemotherapy In Breast Cancer

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ABSTRACT

Objective: The aim of the current study was to evaluate the diagnostic value of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and intravoxel coherent motion (DWI) in predicting breast cancer patient response to neoadjuvant chemotherapy (NAC).

Materials and Methods: We searched international databases including PubMed, Medline, Embase, and Science direct with appropriate keywords. The variance of each studies were calculated that assessed the use of Non-Gaussian DWI model (Intravoxel Incoherent Motion; perfusion fraction 'f' ; real diffusivity 'D' and pseudo-diffusivity 'D*') and dynamic contrast-enhanced of prediction of response of breast cancer. Pooling the sensitivity, specificity, and area under the curve were used to organize and summarize the studies. And the data were analyzed using STATA version 14. Finally, the results of the studies were entered into the random-effects meta-analysis.

Results: twenty one studies comprising 2161 patients were involved in the present study. The sensitivity and specificity of DCE-MRI were 0.693 (95% CI 0.560-0.826), and 0.754 (95% CI 0.605-0.903), respectively. The results showed a pooled PPV, and NPV based on the random effect model of 0.458 (95% CI 0.339-0.577), and 0.901 (95% CI 0.829-0.972) respectively. The pooled DCE-MRI accuracy to predict pCR to neoadjuvant chemotherapy was 0.768 (95% CI 0.720-0.817).

Conclusion: According to our results IVIM parameters and DCE-MRI is play a potential role in early prediction of response to NAC in BC. The superior sensitivity and specificity for diffusion-weighted advanced (IVIM) imaging and DCE parameter means that these approaches can be used as a suitable method in early prediction of response to breast tumors.

Keywords: *Early prediction, DCE-MRI, IVIM , Neoadjuvant chemotherapy, Breast cancer.*

INTRODUCTION

Breast cancer (BC) the most prevalent type of cancer in women is currently one of the causes of death from cancer in women (following lung cancer) and is thought to account for 15% of cancer fatalities (1, 2). Hence, there is a lot of interest in screening for breast cancer at an early stage(3).

Neoadjuvant chemotherapy (NAC) is currently a popular treatment for locally advanced breast cancer. Patients with advanced BC may benefit from a systemic, cytotoxic drug therapy before to surgery in order to reduce the tumor and increase the possibility of breast-conserving surgery(4). Early consideration of NAC therapy for breast cancer may lead to early tumor identification, clinical counseling for alterations in treatment selection, appropriate scheduling for surgery, and a decrease in unnecessary overtreatment(5-7). Achieving a minimum residual tumor is the best sign of a successful long-term outcome. For decision-making, surgical planning, and the prognosis of final outcomes, an accurate assessment of the therapeutic response to NAC is crucial(8).

A pathologically complete response can result from neoadjuvant chemotherapy in a limited fraction of patients with high clinical response rates (between 70 and 98 percent) (9, 10). According to studies, those who received NAC had a same chance of surviving as those who had adjuvant chemotherapy and a lower likelihood of having a mastectomy (i.e., are more likely to be qualified for breast conservation treatment)(11-13).

Magnetic resonance imaging (MRI), a non-invasive procedure, is a suitable radiological way to assess BC(14). The literature claims that tumor cellularity and tissue organization can be accurately reflected by diffusion-weighted imaging (DWI)(12, 15-17). Malignant tumors have increased cellularity, which restricts water molecule transport, which has its origins in less extracellular space. Due to this problem, there is a growing propensity to measure cellularity using the apparent diffusion coefficient (ADC)(18-20).

Intravoxel incoherent motion (IVIM) is a valued imaging technique capable of differentiation between diffusion via a biexponential model analysis based on multiple b-values (21, 22). In this line, Le Bihan and colleagues (22) developed a technique for IVIM that its effects on microcapillary perfusion are proved by some studies using DWI (23-25). The signal intensity at low b-values (0-200 sec/mm2) in DWI scenarios when several b-values are used (often range from 0 to 1,500 sec/mm2 for body imaging) denotes microcirculation inside capillaries. In the same manner, the signal intensity more accurately reflects tissue diffusivity the higher the b value (>200 sec/mm2)(25, 26). The IVIM method can offer several quantitative metrics that demonstrate the perfusion and diffusion of the tissues, including slow ADC, fast ADC, and a proportion of fast ADC values. DWI should be taken into account as it cannot reverse the impact of microcirculation. In contrast to results acquired using ADC, the slow ADC value can represent the real diffuse condition of water molecules since it eliminates the influence of blood circulation.

Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) of the breast is used for screening of BC in women with a total lifetime BC 20-25. Rapid diffusion of a low-molecular-mass contrast agent through the fenestration present in these abnormal micro capillaries is the basis of the DCE-MRI technique. Comparative studies have shown that the rate of enhancement is determined by the interstitial environment, which affects the diffusibility as well as temporal retention of the contrast agent, vascular fenestrations, functional permeability, and the vascular density of the lesion (27). When the signal intensity-time curves are analyzed, parameters related to tissue perfusion, microvascular vessel wall permeability, and extravascular-extracellular volume fraction can be used to identify the underlying pathophysiology(28, 29).

In this work, we used a meta-analysis to evaluate the usefulness of intravoxel coherent motion (DWI) and DCE-MRI in predicting response to NAC in BC patients.

MATERIALS & METHODS

Literature search strategy

In the study, a literature search was done up until February 2023 to find articles that provided information on the usefulness of IVIM and DCE-MRI for predicting NAC response in BC patients. The following keywords, along with their synonyms, abbreviations, Mesh terms, and all possible combinations, were used in a search of the Medline, Embase, and Google Scholar databases by the author: "Intravoxel Incoherent motion," "Dynamic Contrast-Enhanced Magnetic

Resonance Imaging," "Breast neoplasm," and "Neoadjuvant chemotherapy."

Study selection

The following criteria were considered to include studies in our review: 1) original articles written in English. 2)studies that compare the results of IVIM and DCE-MRI with a reference standard. 3) The results of the histopathological analysis were considered the reference standard. Also, our exclusion criteria were as the following: 1) review articles, editorial articles, book chapters, and case reports 2) articles that used imaging modalities except for IVIM and DCE-MRI. 3) evaluation of response in BC patients after receiving neoadjuvant chemotherapy.

Screening and data extraction

Two reviewers independently assessed identified articles considering inclusion and exclusion criteria. Initially, articles were screened by title and abstract. Then, these two authors evaluated selected articles by their full text. The articles selected by both of our reviewers were included in our article. If only one of our reviewers selected a study, a third reviewer evaluated that article to include in our study. Finally, included studies data were extracted by two independent authors.

The following information was considered to be extracted: first author, authors' country, year of publication, study design, sample size, gender, age, pathological complete response, specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), accuracy, and area under the curve (AUC). When there was a disagreement between the extracted data, all discrepant items were assessed by a third author.

Risk of bias in individual studies (Quality assessment)

The quality assessment of included studies was performed by an author, using QUADAS criteria which is a quality assessment tool in systematic reviews to evaluate the risk of bias and applicability of primary diagnostic accuracy studies. The Quality of the included studies was assessed in four domains, 1) patient selection,2) index test (s), 3) reference standard, and 4) flow and timing.

Risk of bias across studies

For estimation of publication bias the Begg's and Egger test was used.

Statistical analysis

the effect size and the 95% CI were calculated using Stata version 17. Also, the publication bias was assessed using Begg's test. We measured the heterogeneity of each group using the inconsistency index (I^2). An I2 greater than 50% or a P-value lower than 0.05 is recognized as significant heterogeneity. If the heterogeneity were high, a random-effect model was used to calculate the pooling effect and 95% CI. Otherwise, the fixed-effect was used. The performance of IVIM and DCE-MRI to pathological response prediction to NAC among patients with BC was determined by calculating pooled specificity, sensitivity, PPV, NPV, accuracy, and AUC with 95% confidence intervals (CI).

RESULTS

Study Selection

After the comprehensive search was done, 633 studies were identified. Then, 237 duplicated articles and 297 articles after the title and abstract screening were excluded. Finally, 117 articles were screened by their full text and 96 articles were excluded. Also, the reference lists of included articles were cross-checked. At last, 21 articles were included in our study (Fig. 1).

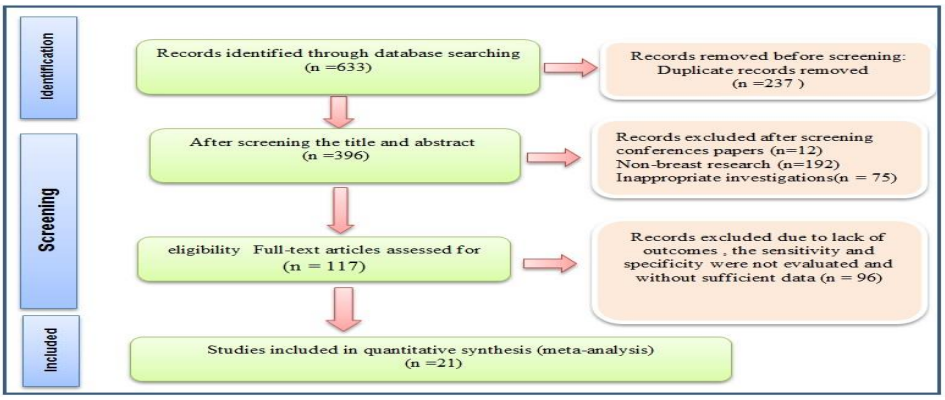

FIGURE 1. Detailed Summary of included studies assessment.

Characteristics of included studies

The characteristics of 21 studies including 2161 patients are shown in Table 1,2. of all studies, 15 studies enrolled patients retrospectively, and the remaining six articles enrolled patients prospectively.

TABLE 1. Features of the studies that were analyzed in the meta-analysis of DCE-MRI performance

Study	Year	No. P	Age (year)	Study design	Preoperative therapy (drugs used in regimens)	Receptor status
Bufi et al. (30)	2015	225	47	Retrospective	doxorubicin, taxane, cyclophosphamide	143 Luminal; 37 Triple negative, 17 HER2+, 28 Hybrid
Li et al. (31)	2020	384	49	Retrospective	paclitaxel, anthracycline, cyclophosphamide, trastuzumab	162 HR+/HER2−, 60 HR+/HER2+, 30 HR−/HER2+, 132 HR−/HER2− (triple negative)
Zhou et al. (32)	2020	55	50	Retrospective	taxol, 5-fluorouracil, epirubicin, cyclophosphamide, doxorubicin	22 Luminal A, 9 Luminal B, 13 HER2+, 11 Triple negative
Gampenrieder et al. (33)	2019	246	50	Retrospective	anthracycline, taxane, trastuzumab, pertuzumab	57 Luminal A, 29 Luminal B, 33 HER2+/HR-, 37 HER2+/HR+, 90 Triple Negative
Pesapane et al. (34)	2021	83	47.26	Retrospective	Chemotherapy, hormone therapy	44 ER+, 41 PR+, 31 HER2+
Chen et al. (35)	2020	28	48.48	Retrospective	doxorubicin, cyclophosphamide, docetaxel, trastuzumab	19 ER+, 11 PR+, 15 HER2+
Dongfeng et al.(36)	2012	60	55.4	Retrospective	paclitaxel, pirarubicin	31 ER+
Fan et al. (37)	2021	114	48	Retrospective	N/A	12 Luminal A, 58 Luminal B, 20 Basal-like, 24 HER2+
Tudorica et al. (38)	2016	59	-	Retrospective	N/A	N/A
Zhou et al. (39)	2021	87	-	Retrospective	taxane, anthracyclines, cyclophosphamide, carboplatin, trastuzumab	37 HR+/HER2-, 36 HER2+, 14 Triple Negative
Tateishi et al. (40)	2012	142	57	Prospective	5-fluorouracil, epirubicin, cyclophosphamide, doxorubicin, paclitaxel,	100 ER+, 82 PR+, 111 HER2+

					herceptin, docetaxel	
Tokuda et al. (41)	2021	29	55	Prospective	paclitaxel, trastuzumab, 5-fluorouracil, epirubicin, cyclophosphamide	7 Luminal A, 13 Luminal B, 3 HER2+, 6 Triple Negative
De Los Santos et al. (42)	2011	81	50	Retrospective	doxorubicin, paclitaxel, cyclophosphamide	45 HR+, 23 HER2+
Moon et al. (43)	2008	212	45.5	Prospective	taxane, anthracyclines, trastuzumab	101 ER+, 68 PR+, 63 HER2+
Craciunescu et al. (44)	2009	20	46.5	Retrospective	paclitaxel, liposomal doxorubicin, hormone therapy	N/A
Schott et al. (45)	2005	43	48	Prospective	doxorubicin, docetaxel	25 ER+

Studies quality assessment

The Quality of included studies was assessed using the QUADAS-2 quality assessment tool. Included studies were assessed in four main domains. The unclear risk of bias in index text and the reference standard was caused by not stating whether or not investigators were blinded when evaluating the index test or reference standard. The patient selection was unclear and at risk of bias in two studies and the risk of bias in one study was unclear in the domain of flow and timing. Figure 2 shows the quality assessment.

FIGURE 2. Evaluation of quality of included studies using the QUADAS-2 tool

Quantitative analysis evaluation of IVIM response:

In three articles on IVIM as an MRI parameter, there were pre-treatment differences among responders and non-responders. Reem Bedair et al (46) reported that prior to NAC, non-responders had a higher mean Dt than responders ($0.85 \pm 0.05 \times 10{-}3mm2/s$ and $1.02 \pm 0.05 \times 10{-}3mm2/s$, respectively) (p=0.02). In addition, responders had a better function concerning the *f* fraction, which was not statistically significant (p = 0.09). Also, the f was significantly lower in non-responders of the TNBC subtype (12.4 ± 4.1 % vs. 10.9 ±1.2 %, p = 0.01). Following NAC, enhanced mean values in Dt were not associated with a significant difference between response groups (36% vs. 23%, p = 0.14). Moreover, decreased *f* fraction in responders (29 %) was considerably different from the increase found in *f* in pNCR (5 %, p = 0.05). Che et al. found similar results (47). At the mid-treatment period, the D presented excellent diagnostic prediction performance by the area of the curve 0.851 (95% CI=0.666–0.956), which is a bit higher than the D* value (AUC=0.579, 95% CI=0.379– 0.762, P=0.025). Nevertheless, the f value presented an acceptable diagnostic performance (AUC=0.772, 95% CI=0.575– 0.908). The optimal cutoff of D during the NAC to differentiate pCR from non-pCR was 0.971×10–3mm2/s, which showed a sensitivity of 100% (95% CI=66.4%–100%) and a specificity of 63.2% (95% CI=38.4%–83.7%). At the beginning of the follow-up, Yunju Kim et al (48) recommended the administration of IVIM-DW imaging factors of good and minor responders pre and post NAC. Prior to NAC, while Dmean was lower in poor responders versus good responders (P ≤0.043). After NAC, Dmean, was lower in poor responders (P≤ 0.037). We found no difference between the study groups concerning D* and f values both prior to and following NAC (P ≥0.07). While Gene Y. Cho et al (49) The values of average Dt of responders was lower than before NAC was 0.99 (0.55, 2.16) μm2/ms, the average values fp, and Dp for responders were 8.7 (4.8, 19.3)%, and 25.54 (15.99, 37.14) μm2/ms. while 1.05 (0.96, 1.21) μm2/ms, 11.7 (5.2, 14.2)%, and 17.16 (16.9, 25.79) μm2/ms for non-responders. The results for all parameters are summarized in Table 2.

TABLE 2: Findings on the prediction of response to therapy based on the value of the IVIM variables and the size of the tumor

Author	Year	IVIM mean ($\times 10^{-3}$ mm²/s) or % change												Tumor size			P-value
		Pre-NAC						Post- NAC						Before NAC (cm)	After NAC (cm)	%Change	
		Response or Baseline			Nonresponse			Response			Nonresponse						
		D	D*	F	D	D*	F	D	D*	F	D	D*	f				
Suo et al (50)	2021	1.00 ± 0.83	15.62 ± 4.18	9.27 ± 3.66	0.98 ±0.80	15.44 ± 3.70	9.27 ± 2.98	0.78 ± 0.68	− 3.06 ± 6.36	1.78± 4.33	0.25 ± 0.35	− 1.97 ± 6.35	0.82 ±3.86	39.8± 21.2	NA	− 34.0± 18.9	0.009
Kim et al (48)	2018	1.22	5.87	45.17	1.10	7.33	43.33	1.37↑	6.04↑	49.56↑	1.15↑	6.58↓	45.23↑	4.15 (2.2–9.3)	3.05 (1.1–7.8)	−20.22 (−54.9–4.4)	0.023
Cho et al (49)	2017	1.02	25.05	8.8	NA	NA	NA	0.99↓	25.54↑	8.7↓	1.05↑	17.16↓	11.7↑	13.84 (3.43, 44.45)	13.80 (3.43, 37.00)	−40.2%.	0.452
Che et al (47)	2016	0.92	10.10	32.40	0.83	9.40	24.40	1.36± 0.30↑	8.98↓	14.51± 7.25↓	0.98± 0.23↑	20.00↑	20.69± 5.10↓	4.89_1.52	2.57 (2.03, 4.16)	-39.2%	<0.001
ReemBedair et al (46)	2017	0.85 ± 0.05	NA	12.10 ± 2.02	1.02 ± 0.05	NA	10.32 ± 1.15	1.30 ± 0.14 (↑36 %)	NA	8.48 ± 1.54 (↓29 %)	1.28 ± 0.15 (↑23 %)	NA	10.53 ± 2.51 (↑5 %)	1.2 – 12	4.1 ± 0.4	1.5 ± 0.2	0.14

Evaluation of DCE-MRI diagnostic performance

In 16 papers, the effectiveness of DCE-MRI in predicting the pathological response to NAC was assessed. Therefore, using meta-analysis, the information on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the curve (AUC) was pooled. DCE-MRI sensitivity was 0.693 (95% CI 0.560-0.826) and specificity was 0.754 (95% CI 0.605-0.903) according to a pooled analysis of data from 14 papers. A pooled PPV based on the random-effect model was 0.458 (95% CI 0.339-0.577) in the meta-analyses of the data from 6 papers, and a pooled NPV was 0.901 (95% CI 0.829-0.972). The combined DCE-MRI accuracy of six papers was 0.768 (95% CI 0.720-0.817) for predicting pCR to

NAC. Finally, reported the area under the receiver operating characteristic curve (AUC),revealing a pooled AUC of 0.779 (95% CI 0.702-0.856).

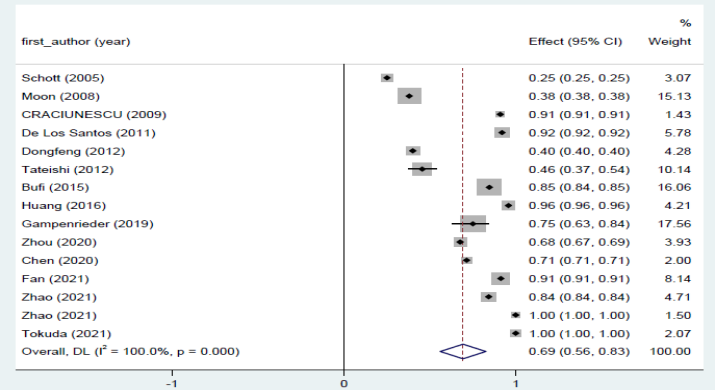

FIGURE 3. Plot demonstrating the DCE-MRI's sensitivity to predict the pathological response to neoadjuvant chemotherapy in BC patients

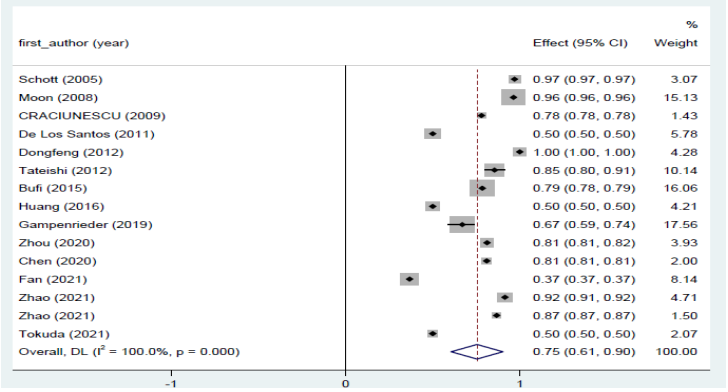

FIGURE 4. Plot demonstrating the DCE-MRI's specificity for predicting patients with BC's pathological response to neoadjuvant chemotherapy

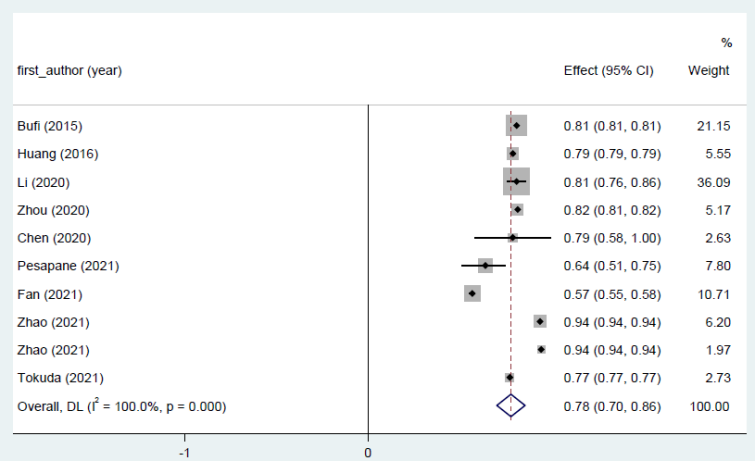

FIGURE 5. Forest plot demonstrating the diagnostic AUC of DCE-MRI to forecast the pathological response to neoadjuvant chemotherapy in BC patients

Publication Bias

After publication bias evaluation, according to Begg's test, no publication bias was observed. The results of Begg's test and Begg's funnel plot are presented in Figure 6.

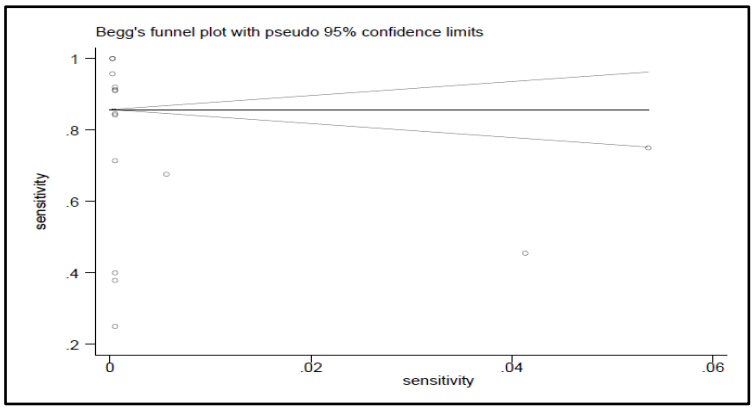

FIGURE 6.

DISCUSSION

NAC has been standardized to decrease the tumor or downstaging the tumor of breast cancer patients, and it can decrease the progression of breast cancer and enhance the survival and quality of life of breast cancer patients (51, 52). The previous studies showed that there are differences in the clinicopathological consequences and developments after NAC for different types of invasive breast carcinoma (52, 53).

The present study aimed to assess the value of DCE-MRI perfusion in the prediction of response to neoadjuvant chemotherapy in BC. Results showed that DCE-MRI is a sensitive and specific method with an acceptable NPV for the prediction of response to neoadjuvant chemotherapy in BC.

In a systematic study performed by Prevos et al. (54) on the assessment of early response to NAC in patients with BC, they showed that the value of MRI in this regard is still unclear. A study by Marinovich et al. (55) in 2012 also determined that the heterogeneity of the study method precluded definitive conclusions. Many differences were observed between different studies in clinical-pathological details such as tumor type, NAC regimen, pathological reaction, and imaging such as time point testing and analysis methods including pharmacokinetic models.

According to a meta-analysis study conducted by Jun et al. (2019), DCE-MRI is capable of monitoring NAC therapy for BC with high sensitivity and specificity despite a high degree of heterogeneity in published studies (4). Also, a study conducted by Cheng et al. (2020), reported that DCE-MRI can be performed as a valuable adjunctive method to evaluate the pathologic response of BC to NAC and as a useful method for monitoring effectiveness during NAC (56). These studies evaluated the assessment of DCE-MR in the response of BC to NAC but our study aimed to survey the value of IVIM and DCE-MRI perfusion in the prediction of response to NAC in BC patients.

LIMITATIONS

First, the different pathological kinds of BC were not identified in the research we analyzed, and NAC therapy could result in various outcomes depending on the pathological subtypes of breast cancer. Second, it was hard to compare the entire pathological response rates between research, which may also contribute to heterogeneity. The successful response of NAC in some studies included total pathological recovery while in others it included partial pathological recovery. One such drawback was the inconsistent timing of DCEM in the included trials. For research purposes, DCE-MRI has been performed after the first cycle of NAC in several studies, while for practical purposes, it has been performed after two cycles of NAC. The therapeutic impacts of NAC in BC are determined according to DCEMRI parameters after two courses of NAC.

CONCLUSION

The study's findings demonstrated that a sensitive and specific approach with a respectable NPV may be used to assess the response prediction to NAC in BC IVIM and DCE-MRI. The use of IVIM and DCE-MRI can improve diagnostic performance in the monitoring of BC therapy in terms of outcomes of sensitivity and specificity.

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