RESEARCH ARTICLE

Diagnostic Significance of Apparent Diffusion Coefficient Values with Diffusion Weighted MRI in Breast Cancer: a Meta-Analysis

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Abstract

Aims: Apparent diffusion coefficient (ADC) values of nodes in diffusion-weighted imaging (DWI) are widely used in differentiating metastatic from non-metastatic lymph nodes. The purpose of this meta-analysis was to demonstrate whether DWI could contribute to the precise diagnosis of breast cancer (BC) with and without lymph node metastasis (LNM). Materials and Methods: English and Chinese electronic databases were searched for relevant studies followed by a comprehensive literature search. Two reviewers independently assessed the methodological quality of the included trials based on the quality assessment of diagnostic accuracy studies (QUADAS). Summary odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated. Results: Final analysis of 624 BC subjects (patients with LNM = 254, patients without LNM = 370) were incorporated into the current meta-analysis from 9 eligible cohort studies. Combined ORs of ADCs suggested that ADC values in BC patients without LNM were higher than in patients with LNM (OR=0.56, 95%CI: 0.11-1.01, *p*=0.015). Subgroup analysis stratified by country indicated a low ADC value in BC patients with LNM rather than those without LNM among Chinese (OR=1.27, 95%CI: 0.89-1.66, *p*<0.001), Italians (OR=0.75, 95%CI: 0.13-1.38, *p*=0.018), and Egyptians (OR=1.27, 95%CI: 0.71-1.84, *p*<0.001). The findings of subgroup analysis by MRI machine type revealed that ADC values from diffusion MRI may be potential diagnostic indicators for BC using Non-Philips 1.5T (OR=1.10, 95%CI: 0.84-1.36, *p*<0.001). Conclusions: The main findings of our meta-analysis demonstrated that increased signal intensity on DWI and decreased signals on ADC are helpful in diagnosis of BC patients with or without LNM. DWI could therefore be an important imaging investigation in patients suspected of BC.

Keywords: Diffusion weighted MRI - apparent diffusion coefficient - breast cancer - meta-analysis

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Introduction

Breast cancer (BC), starting in the inner lining of milk ducts or the lobules, is the leading type of cancer in females around the world, estimated to be responsible for 29% (232,340) of all new cancer cases among women (Siegel et al., 2013). Clinically, BC is typically manifested by a lump or thickening different from the other breast tissue, one breast becoming larger or lower, a nipple changing position or shape or becoming inverted, skin puckering or dimpling, a rash on or around a nipple, discharge from nipples, constant pain in part of the breast or armpit, and swelling beneath the armpit or around the collarbone (Pediconi et al., 2012).

It has been reported that the prevalence of BC have been increased by up to 5% each year in developing countries and BC incidence in Japan, Singapore, and Korea have doubled or tripled in the past four decades (Coughlin and Ekwueme, 2009). In general, various risk factors may contribute to the pathogenesis of BC, such as high breast tissue density, obesity and radiation, family history, late age at first birth, alcohol intake, and so on (McCullough et al., 2009; Gibson et al., 2010). Although the impact of BC on human health has been decreased due to new medical therapy, the prognosis of BC remains unsatisfied as a result of lymph node metastasis (LNM) (Wu et al., 2013). In recent years, a variety of screening and diagnosing tools including magnetic resonance imaging (MRI) have been used in detection of BC, and diffusion-weighted imaging (DWI) has also been introduced to diagnose LN metastasis in BC (Fornasa et al., 2012; Siegel et al., 2013).

DWI, as a modality utilized to assess the micro-structural characteristics of water diffusion in biological tissues, has been increasingly applied to evaluation the development of tumors in the body (Koh et al., 2007; Kim et al., 2009). The application of DWI is based on the principle that water molecules could explore tissue

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structures at a microscopic scale which is surpass the ordinary image resolution in the process of their random diffusion-driven displacements (Le Bihan et al., 2001; Cosottini et al., 2005). Water diffusion is known as a three-dimensional procedure which could be quantified via the measurement of the mean diffusivity (MD), the average apparent diffusion coefficient (ADC) along three orthogonal directions (Basser and Jones, 2002). DWI is capable of differentiating between tissue types on the basis of differences in the ADC and it has been indicated that BC showed restricted diffusion on DWI and had significantly lower ADC values compared with normal and benign breast tissues (Woodhams et al., 2005; Inoue et al., 2011; Lehman, 2012). It is widely accepted that the ADC is related with tissue cellularity and is generally lower in malignant cancers, in which water diffusion is more restricted for the fact that cell density is increased and extracellular space is reduced compared to the normal tissue (Choi et al., 2012; Bokacheva et al., 2013). As we all know, the speed of isotropic, random extracellular movement of water molecules, quantified by DWI as the ADC, is partially affected by the ratio between the volume occupied by cells and the extension of the extracellular space: the higher the ratio the slower the pace of extracellular water movement (Fornasa et al., 2012). After tumor invasion, the normal structure of lymph nodes is destroyed, and the normal tissue is replaced by tumor lymphatic tissue, leading to enlarged tumor cell nuclei, increased nuclear/cytoplasmic ratio, and significant nuclear specificity (Parsian et al., 2012). As a result, tumor cells increased and arranged closely, resulting in reduced extracellular space, vascular disorders in the lymph nodes, increased water molecules and restricted diffusion, thereby reducing the ADC value (Jeh et al., 2011; Choi et al., 2012). In this regard, we postulated that DWI may be valuable in the detection of LNM since it exhibits reduced ADC values in malignant BC. Several studies have illustrated that LNM in BC may be evaluated via the ADC quantified by DWI (Fornasa et al., 2012; Luo et al., 2012), while other documents also reported contradictory findings (Jeh et al., 2011; Choi et al., 2012). Therefore, the present meta-analysis was performed to assess the feasibility of DWI in the diagnosis of LNM in BC.

Materials and Methods

Data sources and keywords

To identify all pertinent papers that assessed the diagnostic value of diffusion MRI in LNM in BC, we comprehensively searched PubMed, Embase, Web of Science, Cochrane Library, CISCOM, CINAHL, Google Scholar, China BioMedicine (CBM) and China National Knowledge Infrastructure (CNKI) databases (last updated search in May 30st, 2014), utilizing selected common keywords regarding the diffusion MRI and BC. As for the keywords to be applied in our initial literature search, we selected ("Diffusion Magnetic Resonance Imaging" or "Diffusion MRI" or "Diffusion Weighted MRI" or "DWI" or "diffusion-weighted magnetic resonance imaging" or "MRI-DWI" or "diffusion-weighted imaging" or "diffusion-weighted-MRI") for the diagnostic factors, and ("breast neoplasms" or "breast cancer" or "breast tumor" or "breast carcinoma" or "mammary cancer" or "mammary carcinoma" or "mammary neoplasms" or "mastocarcinoma" or "breast neoplasms") for the outcome factors. No restriction was set to the language of the article. We also further scanned the bibliographies of relevant articles manually to identify additional potential relevant papers. When the enrolled papers supplied unclear additional data in their original publications, the first authors would be contacted and asked for clarifications.

Selection criteria

We searched throughout for all human-associated clinical cohort studies or diagnostic tests focus on the diagnosis of BC by diffusion MRI, which provided available data for b value and ADC value, included BC patients with or without LNM, and reported the adjusted odd ratios (ORs) and 95% confidence intervals (CI). We just extracted studies supplied the sample number and sufficient information about b value, ADC value and the four-fold (2×2) tables, excluded those articles with incomplete unavailable or inappropriate clinicopathologic data or those regarding BC not confirmed by histopathologic examinations. In addition, only the studies with the minimum number of samples greater than 40 were enrolled. Furthermore, merely the studies related to the accuracy of diffusion MRI in differential diagnosis between with LNM and without LNM BC were selected. However, when the extracted studies had subjects overlapping more than 50% with two or more papers, we merely enrolled the one whose population was the most comprehensive. At the same time, only the latest or complete study was included when the extracted studies were published by the same authors, after careful reexamination.

Data extraction

In order to reduce the bias and enhance the credibility, two investigators extracted information from the retrieved papers according to the selection criteria separately, and arrived at a consensus on all the items through discussion and reexamination. The following relevant data were extracted from eligible studies prospectively in the final analyses: surname of first author, year of publication, source of publication, study type, study design, sample size, age, ethnicity and country of origin, type of MRI machine, number of lesions, "gold standard", contrast agent, diagnostic accuracy, b value and ADC value in BC patients with different LNM situation. All authors approved the final determinant of the studies to be enrolled.

Quality assessment

The quality of involved studies was assessed independently by two authors based on a tool for the quality assessment of studies of diagnostic accuracy studies (QUADAS) (Whiting et al., 2006). The QUADAS criteria included 14 assessment items. Each of these items was scored as "yes" (2), "no" (0), or "unclear" (1). QUADAS score ranged from 0 to 28; and score≥22 indicates a good quality.

Statistical analysis

To calculate the effect size for each study, the summary ORs with 95%CI were used for without LNM versus with LNM category of ADC value with the utilization of Z test. In order to supply quantitative evidence of all selected studies and minimize the variance of the summary ORs with 95%CI, we conducted the current statistical meta-analyses by utilizing a random-effects model (DerSimonian and Laird method) or a fixed-effects model (Mantel-Haenszel method) of individual study results under the situation where data from independent studies could be combined. Random-effect model was applied when heterogeneity exist among studies, while fixed-effects model was applied when there was no statistical heterogeneity. The subgroup meta-analyses were also conducted by country and MRI machine type to explore potential effect modification, and heterogeneity across the enrolled studies was evaluated by the Cochran's *Q*-statistic (A P value less than 0.05 were treated as statistically significant) (Jackson et al., 2012). As a result of low statistical power of the Cochran's *Q*-statistic, I^2 test was also measured to reflect the possibility of heterogeneity between studies (Peters et al., 2006). The I^2 test values ranged from 0% (no heterogeneity) to 100% (maximal heterogeneity). The one-way sensitivity analysis was conducted to assess whether the results could have been affected significantly through deleting a single study in our meta-analysis one by one to reflect the influence of the individual data set to the pooled ORs. The funnel plot was constructed to evaluate publication bias which might affect the validity of the estimates. The symmetry of the funnel plot was further evaluated by Egger's linear regression test (Zintzaras and Ioannidis, 2005). All tests were two-sided and a *p* value of <0.05 was regarded as statistically significant. To make sure that the results are credible and accurate, two investigators inputted all information in the STATA software, version 12.0 (Stata Corp, College Station, TX, USA) separately and arrived at an agreement.

Results

Included studies

Our present meta-analysis hit a total of 9 cohort studies that provided information on the correlation between diffusion MRI and diagnosis of BC. Seven studies were conducted in populations of Asian descent and 1 in populations of Caucasian and African descent, respectively, including 624 subjects at all (254 BC patients with LNM and 370 BC patients without LNM), which were published between 2010 and 2013. The characteristics and methodological quality of the extracted studies were present in Table 1. The countries where the studies were performed were China (n=2), Japan (n=3), Italy (n=1), Korea (n=2), and Egypt (n=1). MRI machine type in this current meta-analysis included Siemens 1.5T, Philips 1.5T, GE 1.5T, and Siemens 3.0T. Additionally, as for the step of screening, a flow chart of the study selection process was displayed in Figure 1. Initially, a total of 603 papers were selected from the 9 databases through screening the title and key words (Nakajo et al., 2010; Razek et al., 2010; Jeh et al., 2011; Nakai et al., 2011; Choi et al., 2012; Fornasa et al., 2012; Luo et al., 2012; Kamitani et al., 2013; Luo et al., 2013). Followed by excluding the duplicates (n=2), letters, reviews or meta-analysis (n=128), non-human studies (n=137), and the studies not related to research topics (n=145), the left studies (n=191) were reviewed and additional 179 studies were excluded in that they were not case-control or cohort study (n=48), not relevant to diffusion MRI (n=62), or not relevant to BC (n=69). After the remaining 12 trails being further reviewed, 9 papers were enrolled in the final analysis. During the final selection process, the major reason for abandon was not supplying enough information (n=3). All quality scores of the included studies were higher than 22 (high quality). From 2001 to 2014, the number of articles selected from those electronic databases is shown in Figure 2.

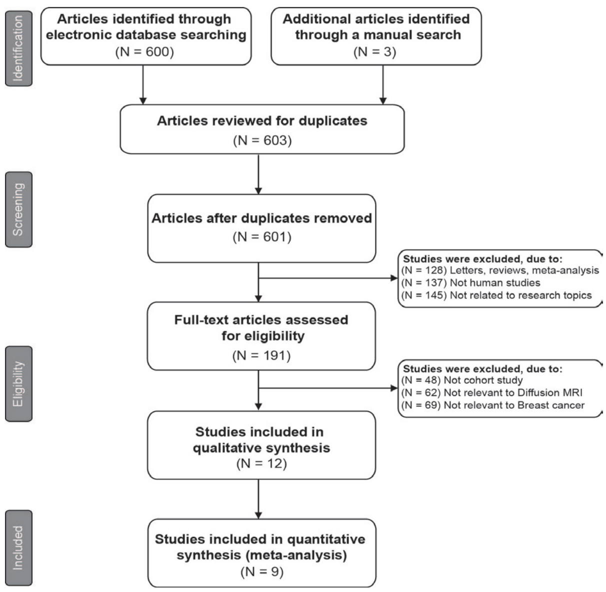

Figure 1. Flow Chart Shows Study Selection Procedure. Nine Cohort Studies were Included in this Meta-analysis

Table 1. Main Characteristics and Methodological Quality of All Eligible Studies

First author	Year	Country	Ethnicity	Sample size LNM+	LNM-	Age (years)	MRI machine type	b_value (s/mm²)	QUADAS
Luo N	2013	China	Asians	45	34	53 (30~63)	Non-Philips 1.5T	0/800	27
Kamitani T	2013	Japan	Asians	28	53	54 (34~82)	Philips 1.5T	0/500/1000	25
Luo NB	2012	China	Asians	23	23	54 (30~63)	Non-Philips 1.5T	0/800	25
Fornasa F	2012	Italy	Caucasians	24	19	-	Non-Philips 1.5T	0/800	22
Choi BB	2012	Korea	Asians	41	76	51 (24~85)	Philips 1.5T	0/1000 0/750	25
Nakai G	2011	Japan	Asians	15	34	-	Non-Philips 1.5T	0/800	22
Jeh SK	2011	Korea	Asians	34	72	52 (31~81)	Philips 1.5T	0/750	24
Razek AA	2010	Egypt	Africans	32	27	46 (24~67)	Non-Philips 1.5T	0/200/400	24
Nakajo M	2010	Japan	Asians	12	32	58.0 ±12.0	Philips 1.5T	0/500/1000/1500/2000	26

*MRI: magnetic resonance imaging, QUADAS: quality assessment of studies of diagnostic accuracy studies

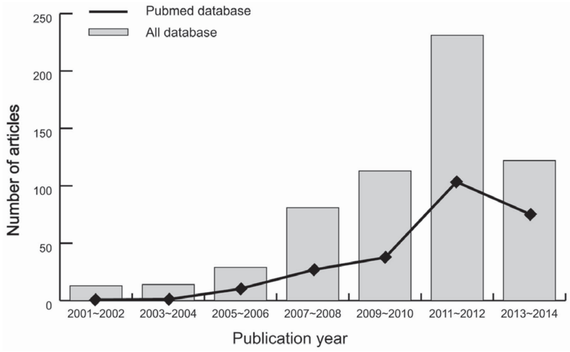

Figure 2. The Distribution of the Number of Topic-Related Literature in Electronic Database over the Last Decade

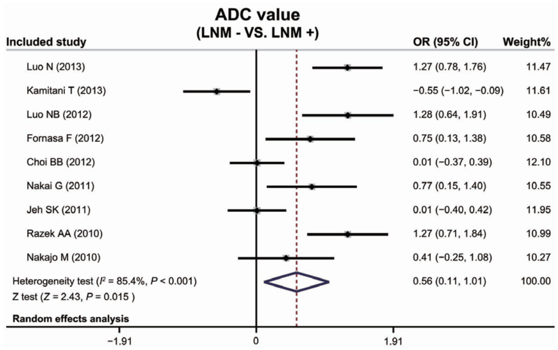

Figure 3. Forest Plots on the Difference in the Frequency of ADC Value between Non-metastatic Lymph Nodes and Metastatic Lymph Nodes in Breast Cancer Patients

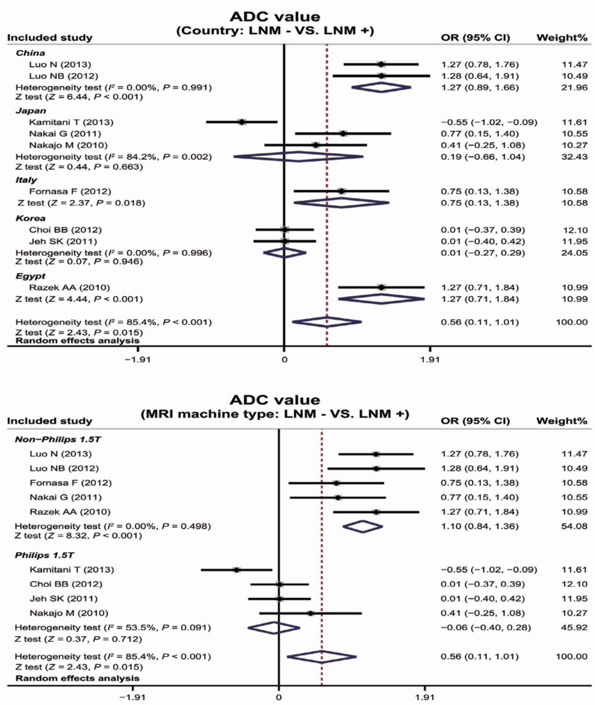

Figure 4. Subgroup Analyses by MRI Machine Type and Country on the Difference of ADC Value between Non-metastatic Lymph Nodes and Metastatic Lymph Nodes in Breast Cancer Patients

Diagnostic value of diffusion MRI in BC

As shown in Figure 3, the major finding of the present meta-analysis revealed that ADC value in BC patients without LNM was higher than that in the patients with LNM (OR=0.56, 95%CI: 0.11-1.01, p=0.015). Subgroup analysis based on country suggested a high ADC value in BC patients without LNM rather than in BC patients with LNM among Chinese (OR=1.27, 95%CI: 0.89-1.66, p<0.001), Italian (OR=0.75, 95%CI: 0.13-1.38, p=0.018), Egyptian populations (OR=1.27, 95%CI: 0.71-1.84, p<0.001), but the similar relationship was not detected in Japan and Korea populations (both p>0.05) (Figure 4). Further subgroup analysis based on MRI machine type implied that ADC value from diffusion MRI may be a potential diagnostic indicator for BC by using Non-Philips 1.5T (OR=1.10, 95%CI: 0.84-1.36, p<0.001), while not using Philips 1.5T (p>0.05), which was shown in Figure 4.

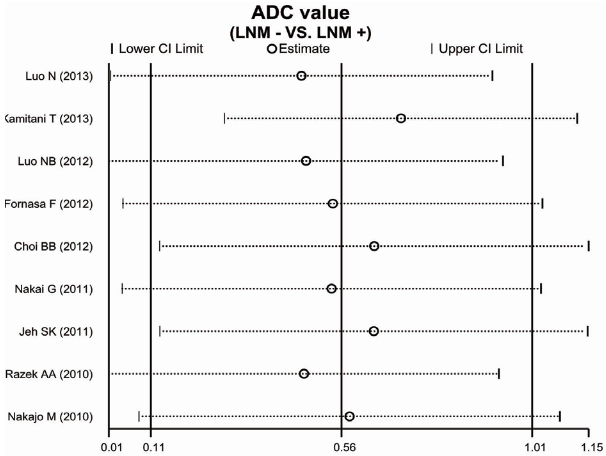

Figure 5. Sensitivity Analysis of the Summary Odds Ratio Coefficients on the Difference in the Frequency of ADC Value between Non-metastatic Lymph Nodes and Metastatic Lymph Nodes in Breast Cancer Patients

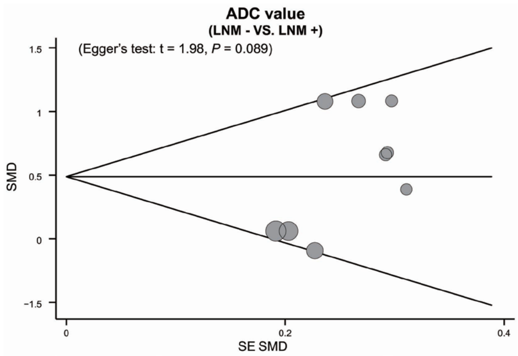

Figure 6. Funnel Plot of Publication Biases on the Difference in the Frequency of ADC value between Non-metastatic Lymph Nodes and Metastatic Lymph Nodes in Breast Cancer Patients

Sensitivity analysis and publication bias

A leave-one-out sensitivity analysis was carried out to evaluate whether the present meta-analysis is stable. Each study enrolled in our meta-analysis was evaluated one by one to reflect the effect the significance of pooled ORs. The overall statistical significance does not change when any single study was omitted. Therefore, the current meta-analysis data is relatively stable and credible (Figure 5). The graphical funnel plots of those 9 studies present to be symmetrical, and Egger's test showed no publication bias (p>0.05) (Figure 6).

Discussion

In the present meta-analysis, we concluded a series of studies from relevant studies intending to found the changes of ADC ratios calculated from DWI, and to evaluate the ability of DWI to diagnose LNM in patients with BC. Several investigation regarding the ADC measurement with DWI have been widely performed, and taking the Asian Pacific Journal of Cancer Prevention for example, published articles mainly concentrated on the diagnosis and differential diagnosis of human tumors. For instance, evidence indicated that DWI might be useful for detection of recurrence and metastasis of lung cancer, or ADC measurements may be utilized to improve the differential diagnosis accuracy of benign and malignant focal liver lesions, DWI has higher potential than other imaging methods like positron emission tomography in assessing pulmonary nodules and masses, yet no more other publishes focused on the differential diagnosis of BC which may restrict a wide references and applications of DWI in the differential diagnosis of human tumors (Han et al., 2014; Usuda et al., 2014a; 2014b). The most important conclusion of the current study is that the ADC values of lymph nodes with metastasis was apparently lower compared to those of benign or normal lymph nodes, indicating that DWI might be an useful method in the characterization and diagnosis of malignant LNM in BC patients by means of measuring the ADC values. DWI has been widely supported to provide quantitative and qualitative functional information from water molecules diffusion, which primarily reflects the degree of tissues cellularity, and meanwhile, several evidence has showed that DWI has been evaluated in various cancers including cervical cancer and BC (Hamstra et al., 2007; Park et al., 2010; Downey et al., 2013). The technology of DWI adopts DW gradient pulses to produce signals which are susceptible to the localized diffusivity of water molecules and thus can indirectly measure cell density, microstructure, cell organization or LNM (Padhani et al., 2009). In addition, the diffusion of water molecules in biological tissues was closely associated with the tissue microenvironment (Fornasa et al., 2012). Under the pathological conditions, the alterations of tissue microenvironment, such as loss of membrane integrity and distribution changes of macromolecule, may change the rates of water molecules diffusion, and finally it may present in the image of DWI (Woodhams et al., 2011). Moreover, ADC value was considered as one of the most important quantitative parameters of DWI to reflect the mobility of water molecules in biological tissues, which has shown to be decreased in various malignancies of different organs (Kim et al., 2009; Padhani et al., 2009). Consequently, DWI with ADC values can be regarded as a useful method in the diagnosis and quantitative measurement of neoplasms. In this study, we found that DWI appears higher signal intensity and decreased signal on ADC maps of LNM was exhibited in BC patients. The possible mechanism may be that the high cellularity or even necrosis in LNM producing by the cancerous mammary epithelial cells, may decreased the extracellular and intracellular spaces, and then restrict the mobility of water molecules and finally leading to the decreasing ADC values (Fornasa et al., 2012). These findings are in line with a previous study which also indicated that the ADC values of lymph nodes with metastasis were obviously lower compared to those of benign lymph nodes, which may provide a diagnostic value for the evaluation of LNM in BC (Luo et al., 2013).

In addition, we carefully performed stratified analyses according to the country and MRI machine types in order to found out the source of inter-study heterogeneity and explore the association between ADC values and LNM in BC. The primary findings of the country-stratified analyses have revealed that the ADC values on DWI were apparently decreased in LNM among China, Italy and Egypt populations, while no such association was found in Japan and Korea populations. These results have revealed that the correlation of ADC values with LNM in BC was closely connected with country. In the subgroup study based on MRI machine types, we found that the decreased ADC values were negative related to the LNM when the ADC values calculated from the Non-Philips 1.5T MRI scanners, but there was no significantly statistically significance in the subgroup of Philips 1.5T MRI scanners. This result implied that the MRI machine types may affect the association between ADC values and LNM. In summary, our results are in agreement with most previous documents that ADC values can be served as a dependable parameter to detect the LNM in BC patients and may strengthen the diagnostic performance of BC, and furthermore the method of DWI can be used as is an attractive and noninvasive technique for differentiating BC with LNM.

Although our meta-analysis was a practical way to generate a more powerful estimate of true effect-size with less random error than individual studies, it did come with some potential limitations. First, our dataset was small, and the included number of BC tissues with LNM was too small relative to the number of BC tissues without LNM. Second, due to the study was a retrospective design, the acquisition parameters and the b-value as well as the ADC value were not optimized, which may be a possibly source of bias that have an influence on the whole results. More importantly, detection methods utilized for some patients determined to be negative for LNM was not clearly, and the specificity and sensitivity of such method were all uncertain, which may restricted the diagnostic accuracy to predict patients with or without LNM, and hence yielded false negatives (some patients with LNM could have been regarded as negative for LNM) affected our statistical analysis results via revealing no statistically significance in the research. Finally, usual reliable statistical packages (STATA) are only able to calculate unweighted kappa coefficients for multiple raters, where they are inappropriate for ordinal scales for their treatment of all disagreements equally. Despite the above limitations, our study is the first example to explore the usefulness of DWI in differentiating metastatic lymph nodes in patients with BC.

In brief, the mean ADC value of LNM is significantly lower than that of patients without LNM. Consequently, the combination of the detect-ability of that high or low signal intensity on DWI and the threshold ADC value may hold a stronger diagnostic accuracy for differentiating LNM from BC without LNM. Due to several limitations addressed previously, further clinical researches with more integral data and larger sample-size would be better to obtain a more generally applicable statistical analysis.

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