

Diagnostic accuracy of DWI in patients with ovarian cancer

A meta-analysis

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Abstract

Background: Diffusion weighted imaging (DWI) is recently developed for identifying different malignant tumors. In this article the diagnostic accuracy of DWI for ovarian cancer was evaluated by synthesis of published data.

Methods: A comprehensive literature search was conducted in PubMed/MEDLINE and Embase databases on the diagnostic performance of DWI for ovarian cancer published in English. Methodological quality was evaluated following Quality Assessment for Studies of Diagnostic Accuracy 2 (QUADAS 2) tool. We adopted the summary receiver operating characteristic (SROC) curve to assess the DWI accuracy.

Results: Twelve studies including 1142 lesions were analyzed in this meta-analysis to estimate the pooled Sen (sensitivity), Spe (specificity), PLR (positive likelihood ratio), NLR (negative likelihood ratio), and construct SROC (summary receiver operating characteristics) curve. The pooled Sen and Spe were 0.86 (95% confidence interval [CI], 0.83–0.89) and 0.81 (95%CI, 0.77–0.84), respectively. The pooled PLR and pooled NLR were 5.07 (95%CI, 3.15–8.16) and 0.17 (95%CI, 0.10–0.30), respectively. The pooled diagnostic odds ratio (DOR) was 35.23 (95%CI, 17.21–72.14). The area under the curve (AUC) was 0.9160.

Conclusion: DWI had moderately excellent diagnostic ability for ovarian cancer and promised to be a helpful diagnostic tool for patients of ovarian cancer.

Abbreviations: ADC = apparent diffusion coefficient, AUC = area under the curve, DOR = diagnostic odds ratio, DWI = diffusion weighted imaging, FN = false-negative, FP = false-positive, HIS = high signal intensity, MRI = magnetic resonance imaging, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SROC = summary receiver operating characteristic, TN = true-negative, TP = true-positive.

Keywords: diagnosis, DWI, meta-analysis, ovarian cancer

1. Introduction

Ovarian cancer is the fifth fatal cause related to cancer among women in both developing and developed countries, causing approximately 125,000 deaths annually.^[1,2] Ovarian cancer occurs frequently among women in perimenopause period, with few children and adolescents falling into this suffering. Since potentially curable ovarian cancers often do not produce any symptoms,^[3–5] early clinical diagnosis is very difficult and

ovarian cancer patients often present with an advanced stage at initial diagnosis. It is estimated that about 50% to 60% of the deaths in ovarian cancer patients are associated with local progress. Up to 10% of ovarian cancer patients suffer with distant metastases, including breast, gastrointestinal tract, and reproductive tract.^[6] Although aggressive surgery combined with chemotherapy has resulted in prolonged remission for ovarian cancer patients, most advanced women present with poor prognosis.^[7] The 5-year survival of early-stage patients with ovarian cancer exceeds 90%, while only 21% of advanced-stage patients survive 5 years upon first diagnosis.^[8] Thus, new diagnostic techniques are indispensable to detect ovarian cancer and ultimately formulate treatment decisions aimed at improving life quality and survival rate of ovarian cancer patients at early stage.^[9,10]

A variety of diagnostic methods have been adopted in ovarian cancer. Color doppler ultrasound and computer tomography (CT) are commonly used imaging techniques for ovarian cancer diagnosis.^[11] Cancer antigen 125 (CA125) as a serum biomarker of ovarian cancer has high specificity for early-stage disease (96–100%), but its sensitivity is poor.^[12–14] Magnetic resonance imaging (MRI) has high resolution for soft tissues and can clearly display the anatomic relationship. To date, MRI tends to be an accurate imaging technique for ovarian cancer because of its noninvasive nature and there is no risk of radiation exposure, and no need of patient preparation.^[15] MRI is substantially better than ultrasonography and CT.^[16] DWI is a newly developed magnetic resonance functional imaging technique based on water molecules movement rather than structure.^[17] Malignant tumors

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are composed of randomly organized tumor cells and the free movement of water molecules inside malignant dense mass is hindered. The inhibited diffusion of water is attributed to hypercellularity,^[18,19] thus DWI could provide unique information of tissue structure by tissue cellularity evaluation.^[20] Apparent diffusion coefficient (ADC) is calculated quantitatively to measure diffusion ability^[21] and in general malignant lesions present higher ADC compared with benign lesions. DWI has been used for early diagnosis of ischemic cerebral infarction over the past decade,^[22,23] but now researches concerning cancer are rapidly expanding and a growing amount of data is published. It was reported that DWI had a desired diagnostic accuracy for lung cancer, pancreatic cancer, and prostate cancer.^[24–26] ADC values are employed to differentiate between malignant and benign lesions and in general the former has a significantly lower ADC value.

A series of studies have assessed the performance of DWI for diagnosis of ovarian cancer. However, diagnostic accuracy of DWI in detecting ovarian cancer varied because of some factors such as field intensity, imaging parameters, disease staging, and so on. The study is aimed to evaluate the diagnostic performance of DWI in detecting ovarian cancer by synthesis of published data.

2. Materials and methods

2.1. Search strategy

Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. A systematic literature search was conducted independently by 2 investigators in PubMed/MEDLINE and Embase databases published before January 2016 without other restrictions. We used the following search terms: “ovarian cancer or ovarian tumor or ovarian neoplasm” and “DWI or diffusion weighted Imaging or DW imaging.” Also, manual search were performed for additional relevant studies. As this was a meta-analysis, no ethical approval was required.

2.2. Eligibility criteria and study selection

Two investigators, Xia Yuan and Yan Tie, screened all abstracts and checked relevant full-texts independently. Studies were enrolled in the meta-analysis if they satisfied the following criteria: the study adopted DWI in patient to determine the benignity or malignancy of ovarian masses; the study used histopathology of biopsy or surgery specimens as reference standard; the study provided sufficient data available to calculate true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) values.

Studies were excluded from the meta-analysis if meeting the following criteria: the study did not involve ovarian cancer; the study did not provide complete and available data; the study is other research type, such as review, letter, meeting abstract, and case report; the study whose sample size was fewer than 10 patients.

2.3. Data extraction and quality assessment

The same 2 investigators who conducted the literature searches have extracted the relevant data independently. A third reviewer was responsible for coordinating disagreements. To perform accuracy analyses, the following data items of each study were extracted: the name of the first author, year of publication, country of origin, number and age of subjects, *b* values, techniques, and MRI field strength. For each study, 2 × 2 contingency tables were

obtained with TP, FP, TN, FN results. If diagnostic accuracy was executed by different observers, only 1 contingency table by the most experienced observer was extracted or reconstructed.

Quality of relevant studies was examined according to QUADAS-2 which follows 14 items by scoring “yes” if done; “no” if not done; or “unclear” if it is not certain.^[27] The quality assessment was performed by Xia Yuan and Yan Tie independently.

2.4. Statistical analysis

With TP, TN, FP, FN from extracted 2 × 2 contingency tables, we quantified the pooled Sen, Spe, LR, and DOR with 95% confidence intervals (95% CI) to evaluate DWI diagnosis accuracy for ovarian cancer. Also, SROC curve was obtained to explain the interaction between Sen and Spe. Area under the curve (AUC) was calculated to assess the diagnostic ability of a test.^[28] The heterogeneity between enrolled articles was estimated statistically using the *Q* statistic of the Chi-squared value test and the inconsistency index (*I*²) and *I*² > 50% indicates the existence of significant heterogeneity.^[29] If so, a random effects model was adopted.^[30] On the opposite condition, the pooled analysis was performed using the fixed effects model.^[31] Statistical analyses were carried out by Meta Disc statistical software version 1.4 (XI. Cochrane Colloquium, Barcelona, Spain) and Stata software version 11.1 (STATA Corporation, College Station, TX).

2.5. Publication bias

Deeks funnel plot asymmetry test was used to assess publication bias by Stata 11.0 and *P* > .05 indicates the absence of potential publication bias.^[32]

3. Results

3.1. Literature search and selection of studies

The initial systematic literature search from the PubMed/MEDLINE and Embase databases yielded 169 relevant studies, of which 12 articles were finally identified. Thirty nine articles of full-text were reviewed and ultimately 27 studies were excluded. Thus, 12 studies^[33–44] were included in our final dataset for the meta-analysis. The flowchart of study selection was shown in Fig. 1.

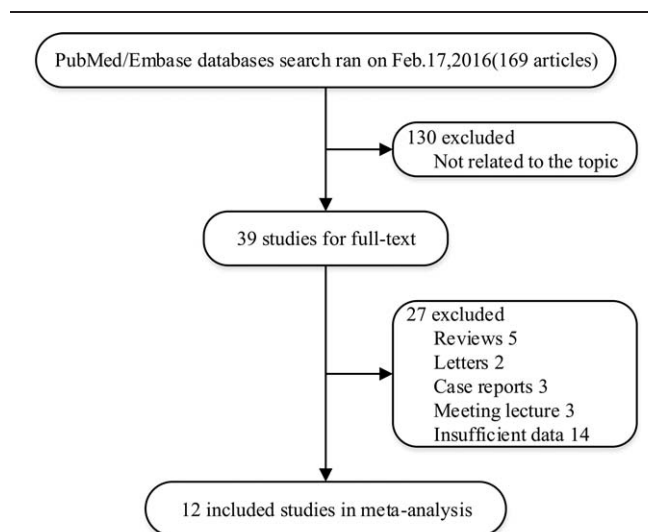


Figure 1. Flow chart of selection process for eligible studies.

Table 1**Main characteristics of all studies included in the meta-analysis.**

Author, year	Country	Design	Reference standard	No. of patients	No. of lesions	Age (y)	QUADAS score	TP	FP	FN	TN
Zhang, P. (2012)	China	Retrospective	Histopathology	191	202	56.5	13	85	7	43	67
Malek, M. (2014)	Iran	Retrospective	Histopathology	47	56	36.5	12	24	10	3	19
Takeuchi, M. (2010)	Japan	Retrospective	Histopathology	47	49	59	11	29	2	10	8
Cappabianca, S. (2013)	Italy	Retrospective	Histopathology	91	91	NA	12	35	11	0	45
Kovač, J. D. (2015)	Serbia	Retrospective	Histopathology	162	162	60.6	10	124	6	0	32
Low, R. N. (2009)	USA	Retrospective	Histopathology	NA	19	NA	10	6	1	3	9
Li, W. (2012)	China	Retrospective	Histopathology	127	131	NA	11	77	5	8	41
Fujii, S. (2008)	Japan	Retrospective	Histopathology	119	123	52	13	36	37	6	44
Fan, X. (2015)	China	Retrospective	Histopathology	64	88	46.7	9	54	5	4	25
Kierans, A. S. (2013)	USA	Retrospective	Histopathology	NA	37	NA	12	6	3	3	25
Takeuchi, M. (2013)	Japan	Retrospective	Histopathology	38	40	55	10	22	1	5	12
Zhang, H. (2014)	China	Prospective	Histopathology	NA	144	NA	12	38	11	3	92

FN = false-negative; FP = false-positive; NA = not available; TN = true-positive; TP = true-positive.

3.2. Study characteristics

Table 1 summarized the main characteristics of the included studies and Table 2 summarized imaging features of each study. In the 12 studies included in meta-analysis, a total of 1142 examinations were evaluated by DWI. We used histopathologic findings as the reference standard for the final result of DWI for ovarian cancer in all 12 studies. Of 12 studies, 5 studies used 3T MRI scanner with the others using 1.5T MRI scanner. Typical *b*-values for imaging were 0, 500, 800, and 1000 s/mm². Two methods were adopted to identify malignant lesions, one of which was to visually identify high signal intensity (HSI) areas and the other was to quantitatively calculate ADC value from region of interest on images. In 2 of the 13 studies, malignant lesions were identified by both HSI and ADC value, and 2 used the method of HSI alone. The remaining articles were only identified by ADC value, one of which calculated the ADC entropy instead of the mean ADC. ADC value of malignant lesion ranged from 0.878 to 2 s/mm², and benign lesion ranged from 1.13 to 1.9 s/mm². In general, malignant lesions had a lower ADC value.

3.3. Assessment of study quality

Detailed information about the QUADAS questionnaire of all enrolled studies is shown in Table 3. The overall quality of the studies was favorable, with all articles fulfilled 9 or more of the 14 items.

3.4. Diagnostic accuracy

A random effects model was used to calculate Sen and Spe of DWI with corresponding 95% CIs. The pooled sensitivity and specificity were 0.86 (95% CI, 0.83–0.89) and 0.81 (95% CI, 0.77–0.84), respectively (Fig. 2). The overall PLR and NLR were 5.07 (95% CI, 3.15–8.16) and 0.17 (95% CI, 0.10–0.30), respectively (Fig. 2). The diagnostic odds ratio was 35.23 (95% CI, 17.21–72.14) (Fig. 3). The AUC was 0.916 (Fig. 4). There was statistically significant heterogeneity in Spe ($P < .001$, $I^2 = 78.0\%$), PLR ($P < .001$, $I^2 = 82\%$), and DOR ($P = .0027$, $I^2 = 61.4\%$), respectively. No threshold effect was detected.

3.5. Assessment of publication bias

The result of Deeks funnel plot asymmetry test revealed that no publication bias was observed ($P = .6$). The slope was not significant (Fig. 5), suggesting the absence of potential publication bias.

4. Discussion

Ovarian cancer is one of the most fatal cancer-related diseases among women and even frequently diagnosed in young women. On initial diagnosis, most women were diagnosed at a progressive stage. Application of new techniques for differentiating between malignant and benign ovarian lesions has a positive

Table 2**Imaging features of each studies.**

Author, year	Coil type	Company	Field (T)	Methods	<i>b</i> value	Cutoff ADC value
Zhang, P. (2012)	NA	GE	1.5T	ADC; HSI	0; 1000	1.2
Malek, M. (2014)	Phased-array pelvic coil	Siemens	3T	ADC	50; 500; 1000	1.2
Takeuchi, M. (2010)	Body-array torso coils	GE	1.5T/3.0T	ADC	0; 800	1.15
Cappabianca, S. (2013)	NA	Siemens	1.5T	HSI	0; 500; 1000	NA
Kovač, J. D. (2015)	NA	Siemens	1.5T	ADC	0; 400; 800	1.361
Low, R. N. (2009)	Phased-array torso surface coils	GE	1.5T	HSI	0; 400–500	NA
Li, W. (2012)	NA	GE	1.5T	ADC	0; 1000	1.25
Fujii, S. (2008)	Phased-array coil	Siemens	1.5T	ADC	0; 1000	NA
Fan, X. (2015)	Torso phased array coil	GE	3T	ADC	0; 500; 1000	1.063
Kierans, A. S. (2013)	Torso phased array coil	Siemens	1.5T	ADC entropy; HSI	0; 500	2.15
Takeuchi, M. (2013)	Body coil and phased-array coil	GE	1.5T/3.0T	ADC	0; 800	1.2
Zhang, H. (2013)	8-channel cardiac array coil	GE	3T	ADC	0; 700	NA

HSI: Lesions were identified as malignant with the appearance of focal areas of high signal intensity. ADC = apparent diffusion coefficient; NA = not available.

Table 3
Quality assessment.

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality score
Zhang, P. (2012)	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Malek, M. (2014)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	12
Takeuchi, M. (2010)	Yes	No	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	11
Cappabianca, S. (2013)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	12
Kovač, J. D. (2015)	Yes	No	Yes	?	Yes	Yes	Yes	Yes	Yes	?	?	Yes	Yes	Yes	10
Low, R. N. (2009)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	No	10
Li, W. (2012)	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	No	Yes	11
Fujii, S. (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	13
Fan, X. (2015)	Yes	No	Yes	?	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	No	No	9
Kierans, A. S. (2013)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	12
Takeuchi, M. (2013)	No	No	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Zhang, H. (2014)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	12

Methodological quality was assessed using quality assessment of diagnostic accuracy studies criteria. Quality item 1: was the spectrum of patients representative of the patients who will receive the test in practice? Quality item 2: were selection criteria clearly described? Quality item 3: is the reference standard likely to correctly classify the target condition? Quality item 4: is the time period between reference standard and index test short enough to be sure that the target condition did not change between the two test? Quality item 5: did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis? Quality item 6: did patients receive the same reference standard regardless of the index test result? Quality item 7: was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)? Quality item 8: was the execution of the index test described in sufficient detail to permit replication of the test? Quality item 9: was the execution of the reference standard described in sufficient detail to permit replication? Quality item 10: were the index test results interpreted without knowledge of the results of the reference standard? Quality item 11: were the reference standard results interpreted without knowledge of the results of the index test? Quality item 12: were the same clinical data available when test results were interpreted as would be available when the test is used in practice? Quality item 13: were uninterpretable/intermediate test results reported? Quality item 14: were withdrawals from the study explained?

effect on public health. Early-diagnosis of patients with ovarian cancer plays a critical role in improving patient outcomes and achieving better life quality. DWI as a noninvasive diagnostic technique is recently developed for distinguishing malignant tumors, determining lesion progression, and monitoring therapy responses.^[17]

A recently published research^[45] discussed the diagnosis performance of DWI in ovarian cancer, but the study focused on the difference of ADC values between benign and malignant

ovarian lesions, without clearly evaluating the diagnosis accuracy of DWI, such as specificity and sensitivity. A similar systematic review published in 2015^[41] on this topic reported the diagnosis accuracy of DWI in ovarian cancer. Since its publication, several new researches have emerged assessing DWI performance in detecting malignant ovarian cancer. Our objective was to provide an updated overview on this topic. The article included 5 of 10 studies in the previous review and also includes 2 literatures published in 2015. Although a recently published meta-analysis

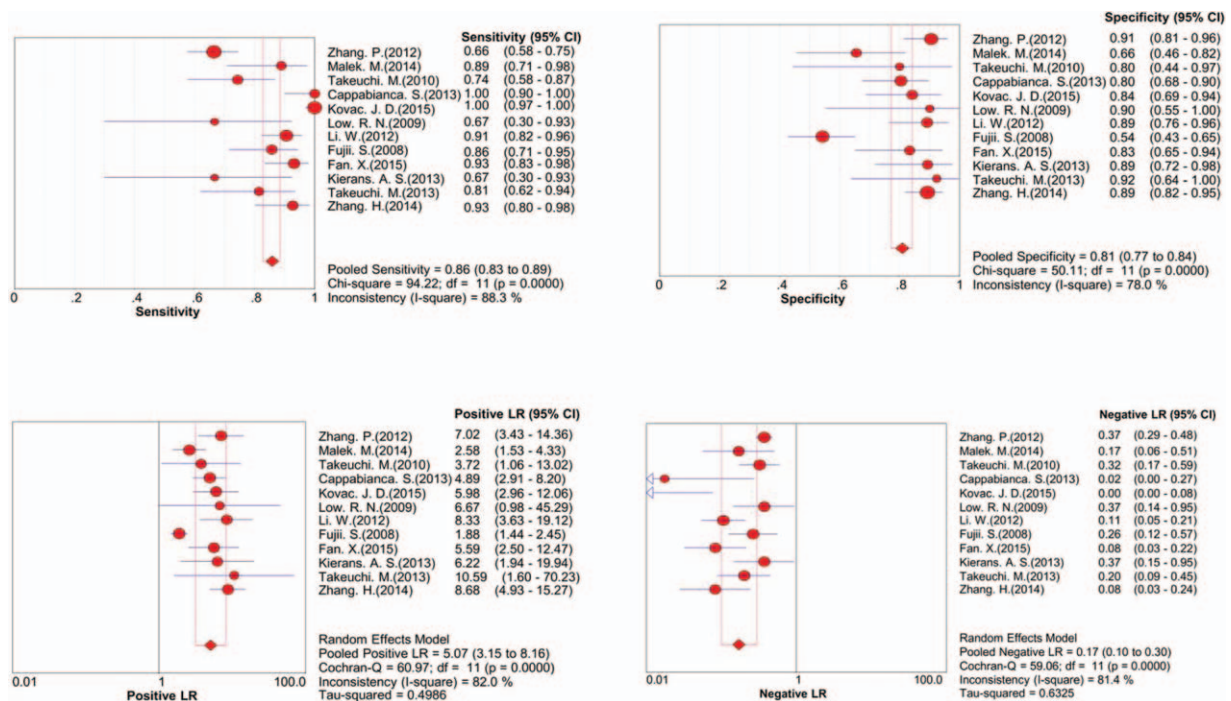


Figure 2. Forest plot of sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of DWI for detection of ovarian cancer. Solid circles represent the study-specific point estimates of sensitivity, specificity, positive LR, and negative LR. Horizontal lines indicate 95% confidence interval (CI). The diamond represents the pooled estimates and 95% CI. DWI = diffusion weighted imaging, LR = likelihood ratio.

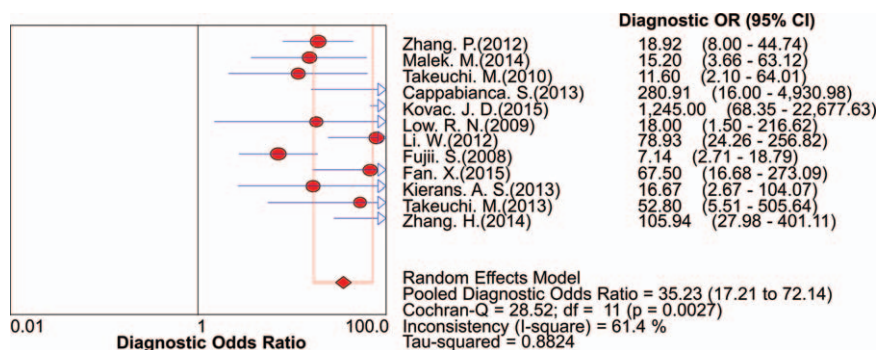


Figure 3. Forest plot of DOR of DWI for detection of ovarian cancer. Solid circles represent the study-specific DOR. Horizontal lines indicate 95% confidence interval (CI). The area of solid circles reflects the study specific weight. The diamond represents the pooled DOR and 95% CI. DOR= diagnostic odds ratio, DWI = diffusion weighted imaging.

discussed in detail Spe, Sen, NLR, PLR, DOR, SROC of DWI,^[46] some obvious shortcomings should be mentioned. First, the latest studies about DWI for diagnosing ovarian cancer were not included in their meta-analysis. Second, the included studies involved relatively narrow geographical region. Most of them were conducted in China and 4 out of 10 were published in Chinese, which might make their results less unrepresentative. Thirdly, the general QUADAS score was not favorable with most scoring less than 9 points, which would discount the credibility of results. Fourth, main characteristics of the included studies were not described in detail. The defects mentioned above have been amended in our meta-analysis, which involved global areas and scored high for study quality.

Results demonstrated that for ovarian cancer detection, DWI had both moderately high specificity (86%) and sensitivity (81%). Actually, high sensitivity and NPV of DWI indicated higher correct diagnostic rate for patients in early stages.^[47] AUC was calculated by SROC which equaled 0.9160 indicating a promising result. Significant heterogeneity existed between the 12 included studies in our analysis. We found no significant threshold effect existed through the ROC plane and first eliminated threshold effect as the source of heterogeneity.

DWI is a functional measure of tumor microenvironment with quantitatively calculated ADC values to improve diagnostic accuracy. ADC values mainly depend on extracellular/intracellular components and reflect the diffusion characteristics of water in tissues.^[33] Small ADC values demonstrate restricted diffusion which tends to indicate the presence of malignant tissue or hypercellularity.^[39] There was the presence of a significant difference of ADC values in some studies between benign and malignant masses with an optical cut-off value which showed ADC value is useful in discriminating ovarian cancer from benign masses. Sensitivity, specificity, PPV, and NPV were observed with a corresponding cut-off in each article but the 3.^[40,48,49] There was an overlap of ADC value between malignancy and benign lesions. Pathologic structures of benign tumors such as fibromas, Brenner tumors, and cystadenofibromas probably contributed to the apparent discrepancy significantly. Inside the extracellular matrix of benign fibrous tumors the presence of dense network of collagen fibers and abundant collagen-producing fibroblastic cells decreased ADC value.^[33] In addition, malignant tissues exhibited increased ADC value due to the existence of necrosis or cystic areas and fluid collection intervening papillary components.^[40]

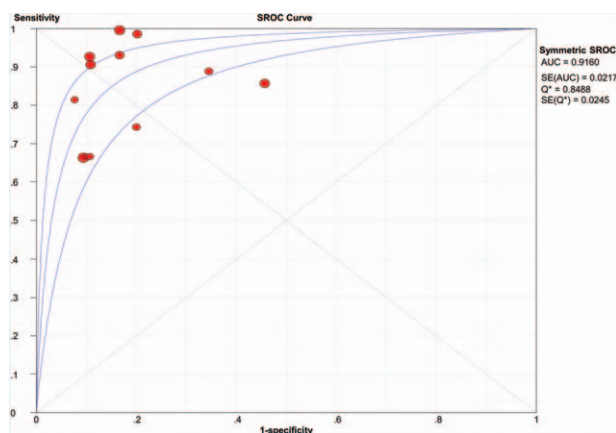


Figure 4. The summary receiver operating characteristic (SROC) curve and Q* index of diagnostic performance of DWI in evaluation of ovarian cancer. Solid circles represent each study included in the meta-analysis. The size of each study is indicated by the size of the solid circle. The regression SROC curves summarize the overall diagnostic accuracy. DWI = diffusion weighted imaging.

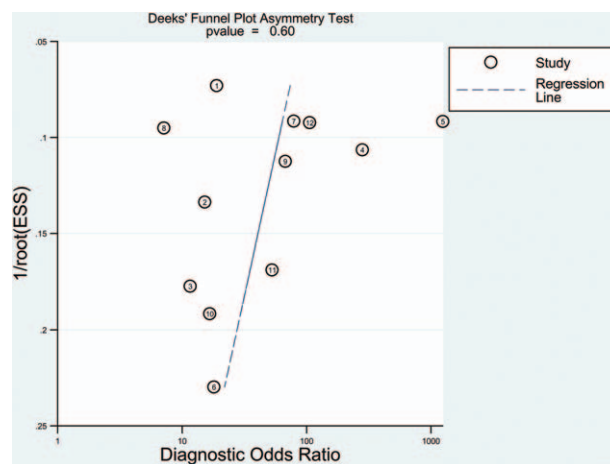


Figure 5. Funnel graph to assess risk of publication bias among included studies. The funnel graph plots the log of the diagnostic odds ratio (DOR) against the standard error of the log of the DOR (an indicator of sample size). Solid circles represent each study in the meta-analysis. Regression line is shown.

Meanwhile, we searched 2 articles on DWI for differentiating borderline from malignant ovarian lesions.^[50,51] Histologically, borderline ovarian lesions are characterized by both benign and malignant masses, thus in this review they were excluded in order to avoid increasing the uncertainty of analysis results.

Notwithstanding, some limitations of the meta-analysis also should be acknowledged. First, only a small number of studies were included in the final meta-analysis because many studies were excluded based on eligibility criteria and may not be qualified to evaluate the diagnostic accuracy. All included studies were published in English which may have negated some of the gray literature. Second, MRI protocols for diagnosis of ovarian cancer were not standardized. Not all the studies used similar DWI parameters, such as *b*-value and magnet field strength among the studies. Studies used 1.5 T or 3 T and *b* value varied from 400 to 1500. Standardization of DWI protocol for ovarian cancer across the multicenter studies is recommended. Finally, the considerable overlap of ADC between cancer and noncancerous tissue made it difficult to determine a cutoff value which might be a source of statistical heterogeneity.^[52]

In conclusion, DWI as an accurate noninvasive imaging method is a useful tool for diagnosis of ovarian cancer. Still, further prospective researches are required to build the value of DWI for diagnosis of ovarian cancer.

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