JBUON 2019; 24(6): 2336-2343
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

A meta-analysis on the diagnostic value of diffusion-weighted imaging on ovarian cancer

Guidong Dai[1]*, Kali Liang[2]*, Zhengyuan Xiao[1], Qin Yang[2], Shugen Yang[1]

[1]Department of Radiography, the Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China; [2]Department of Radiography, the Affiliated Hospital (T.C.M) of Southwest Medical University, Luzhou, Sichuan, China.

*Guidong Dai and Kali Liang contributed equally to this work.

Summary

Purpose: *This study systematically evaluated the potential influences of diffusion- weighted imaging (DWI) on the initial diagnosis, clinical decision making and diagnostic accuracy of ovarian cancer in the follow-up period.*

Methods: *Literature on the correlation between DWI and diagnosis of ovarian cancer were searched from PubMed, Embase, Cochrane Library, and Web of Science published before January 1, 2019. References in enrolled eligible literature were manually reviewed. Quality assessment on the diagnostic accuracy was performed using the QUADAS scale. Receiver operating characteristics (ROC) curve was depicted using STATA 12.0. Study heterogeneity and its sources were determined. Sensitivity (SEN), specificity (SPF), positive likelihood ratio (+LR), negative likelihood ratio (-LR) and diagnostic odds ratio (DOR) of eligible studies were calculated for depicting forest plot and summary of ROC curve (SROC). The area under the curve (AUC) was calculated.*

Results: *A total of 15 articles involving 930 ovarian cancer cases and 832 control cases were enrolled. DWI was identified to exert a certain diagnostic value on ovarian cancer. The 95%CI of the merged SEN (91%, 95%CI=84-95%), SPF (85%, 95%CI=78-90%), +LR (6.18, 95%CI=4.17-9.15) and -LR (4.05, 95%CI=3.30-4.79) were calculated using the random-effects model due to the slight heterogeneity among these studies. AUC was 0.94 (95%CI=0.91-0.96). Subgroup analysis in Asian population obtained the following results: SEN was 85% (95%CI=78-91%), SPF 83% (95%CI=72-90%), +LR 0.18 (95%CI=0.11-0.27), –LR 3.34 (95%CI=2.60-4.09) and DOR 3.34 (95%CI=2.60-4.09); AUC was 0.91 (95%CI=0.88-0.93). In Caucasian population, SEN was 96% (95%CI=83-99%), SPF 89% (95%CI=84-93%), +LR 41.36 (95%CI=5.95-287.48), –LR 0.06 (95%CI=0.02-0.18) and DOR 5.31(95%CI=3.93-6.69); AUC was 0.94 (95%CI=0.91-0.96).*

Conclusions: *This meta-analysis proved that DWI exerted a relatively high sensitivity and specificity in diagnosing ovarian cancer, especially in the Caucasian population. This conclusion still needs to be further verified in a multi-center study with a large sample size.*

Key words: *DWI, diagnostic value, ovarian cancer, meta-analysis*

Introduction

Ovarian cancer (OC) is a common tumor in gynecology, and its incidence is second only to cervical cancer and endometrial cancer in the reproductive system [1-3]. Due to the deep location of the ovaries in the pelvic cavity and occult early-stage symptoms, over 70% of OC patients are diagnosed in advanced stage accompanied by multiple metastases of the peritoneum. The mortality rate of OC is extremely high, with median survival of 18-24 months [3]. The 5-year recurrence rate of OC is up to 80%, and its cure rate for advanced cases is only 20-30%. Unfortunately, the mortality of OC

Corresponding author: Shugen Yang, BM. Department of Radiography, the Affiliated Hospital of Southwest Medical University, No.25, TaiPing Street, Jiangyang District, Luzhou, Sichan 646000, China.
Tel: +86 08303165717; Email: mriysg@126.com
Received: 24/06/2019; Accepted: 18/07/2019

This work by JBUON is licensed under a Creative Commons Attribution 4.0 International License.

remains high and stable even if the therapeutic approaches have made considerable progression [4,5]. OC genesis is a complex process involving genetic factors, estrogen levels and human papillomavirus (HPV) infection. Females with a family history of OC experience a higher onset risk of disease than those without a family history. In addition, long-term estrogen stimulation and immune hypofunction could also lead to the OC tumorigenesis [6,7]. Therefore, post-operative diagnosis of metastatic or recurrent OC as early as possible is particularly important, and imaging examinations provide direct evidence for clinical diagnosis and treatment [8]. Generally speaking, clinical significances of MRI and CT examinations after the second surgery are very limited in diagnosing small recurrent lesions or metastatic loci [9]. Diffusion-weighted imaging (DWI) can reflect the changes of water molecules in the pathological state of the tissues, which undoubtedly promotes the development of non-invasive techniques for identifying tumors [10].

DWI is a functional imaging technique in nuclear magnetic resonance. It examines the movement of water molecules to generate tissue imaging contrast [11,12]. The homogeneity of DWI is varied linearly by a pulsed field gradient. Since movement of water molecules is proportional to the magnet strength, the protons begin to process at different rates, resulting in dispersion of the phase and signal loss. The molecular motion is positively correlated with the phase loss [12,13]. DWI has been widely used in clinical examinations [14,15]. The application of DWI in pelvic tumors contributes to in-depth researches on OC [14,16].

This study analyzed the relevant literature on reporting the application of DWI in diagnosing OC and our aim was to evaluate the diagnostic value of DWI in OC.

Table 1. Characteristics and methodology assessment of individual studies included in the meta-analysis

First author, year	*Country*	*Ethnicity*	*Design*	*Reference standard*	*No. of lesions*	*Age (y)*	*Case*	*Control*	*TP*	*FP*	*FN*	*TN*	*QUADAS score*
Michielsen, 2017	Belgium	Caucasian	Retrospective	Histopathology	NA	61	50	44	47	1	3	43	12
Michielsen, 2016	Belgium	Caucasian	Retrospective	Histopathology	NA	63	48	3	47	2	1	1	11
Kovac, 2015	Serbia	Caucasian	Retrospective	Histopathology	162	60.6	124	38	124	6	0	32	10
Fan, 2015	China	Asian	Retrospective	Histopathology	88	46.7	58	30	54	5	4	25	9
Malek, 2014	Iran	Asian	Retrospective	Histopathology	56	36.5	27	29	24	10	3	19	12
Zhang, 2014	China	Asian	Prospective	Histopathology	144	NA	41	103	38	11	3	92	12
Cappabianca, 2013	Italy	Caucasian	Retrospective	Histopathology	91	NA	35	56	35	11	0	45	12
Kierans, 2013	USA	Caucasian	Retrospective	Histopathology	37	NA	9	28	6	3	3	25	12
Takeuchi, 2013	Japan	Asian	Retrospective	Histopathology	40	55	27	13	22	1	5	12	11
Michielsen, 2013	Belgium	Caucasian	Retrospective	Histopathology	NA	61.9	208	267	189	24	19	243	10
Zhang, 2012	China	Asian	Retrospective	Histopathology	202	56.5	128	74	85	7	43	67	13
Li, 2012	China	Asian	Retrospective	Histopathology	131	NA	85	46	77	5	8	41	11
Takeuchi, 2010	Japan	Asian	Retrospective	Histopathology	49	59	39	10	29	2	10	8	11
Low, 2009	USA	Caucasian	Retrospective	Histopathology	19	NA	9	10	6	1	3	9	10
Fujii, 2008	Japan	Asian	Retrospective	Histopathology	123	52	42	81	36	37	6	44	13

NA: not available, QUADAS: quality assessment of diagnostic accuracy studies

Methods

Literature search

Literature on the correlation between DWI and the diagnosis of OC were searched from PubMed, Embase, Cochrane Library and Web of Science published before January 1, 2019. Keywords were as follows: "diffusion weighted imaging", "DWI" and "ovarian cancer" and "diagnosis", "detection". References of enrolled eligible literature were manually reviewed. Keywords were adjusted in each database and mainly divided into three parts: target disease, evaluated trials and diagnostic accuracy.

Inclusion and exclusion criteria

Published literature on the diagnostic value of DWI in OC was searched. Inclusion criteria were applied as follows: (1) Publication in English language; (2) Literature reporting the diagnostic value of DWI in OC; (3) Prospective or retrospective study; (4) Sample size ≥ 20 cases; (5) DWI was performed for each subject; (6) Complete or latest data were enrolled if data were overlapping; and (7) True positive (TP), false positive (FP), true negative (TN) and false negative (FN) were directly provided or relative data were provided to calculate these parameters.

Exclusion criteria were applied as follows: (1) Literature on evaluating OC only; (2) Other examinations rather than DWI; (3) Abstracts, reviews, reports, and low-quality literature.

Data extraction

Data acquisition was independently carried out by two reviewers, and a third reviewer was responsible for re-evaluating disagreements. Baseline data acquisition included: first author, study type, sample size, year of publication, region, examinations, outcome parameters.

Evaluation of QUADAS

The enrolled literature consisted of diagnostic trials. Diagnostic quality was evaluated by the QUADAS scale, with 71% (11/14) as the boundary to distinguish high from low scores [17].

Statistics

Statistical analyses were performed using Stata software (version 12.0, Stata Corporation, College Sta-

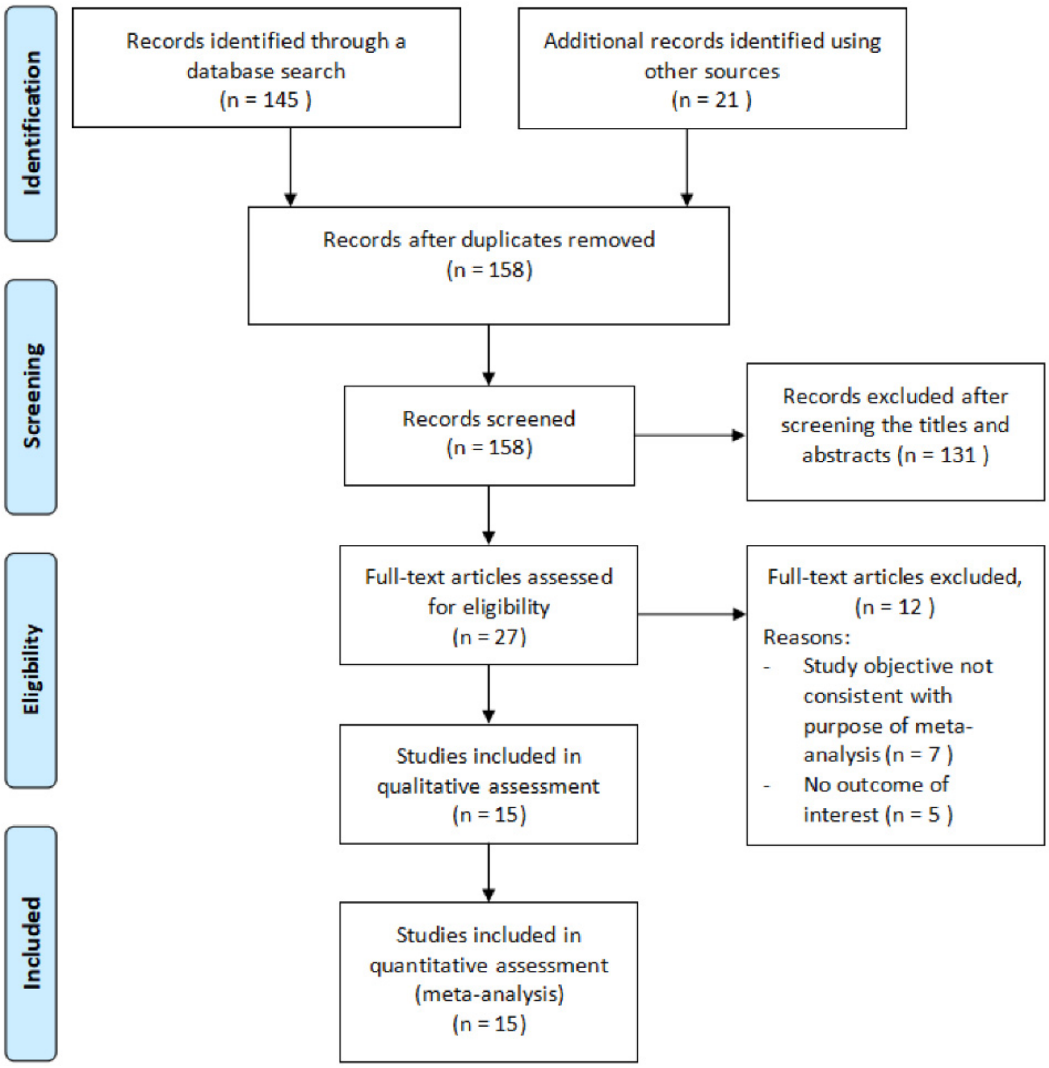

Figure 1. Flow diagram of the selection process.

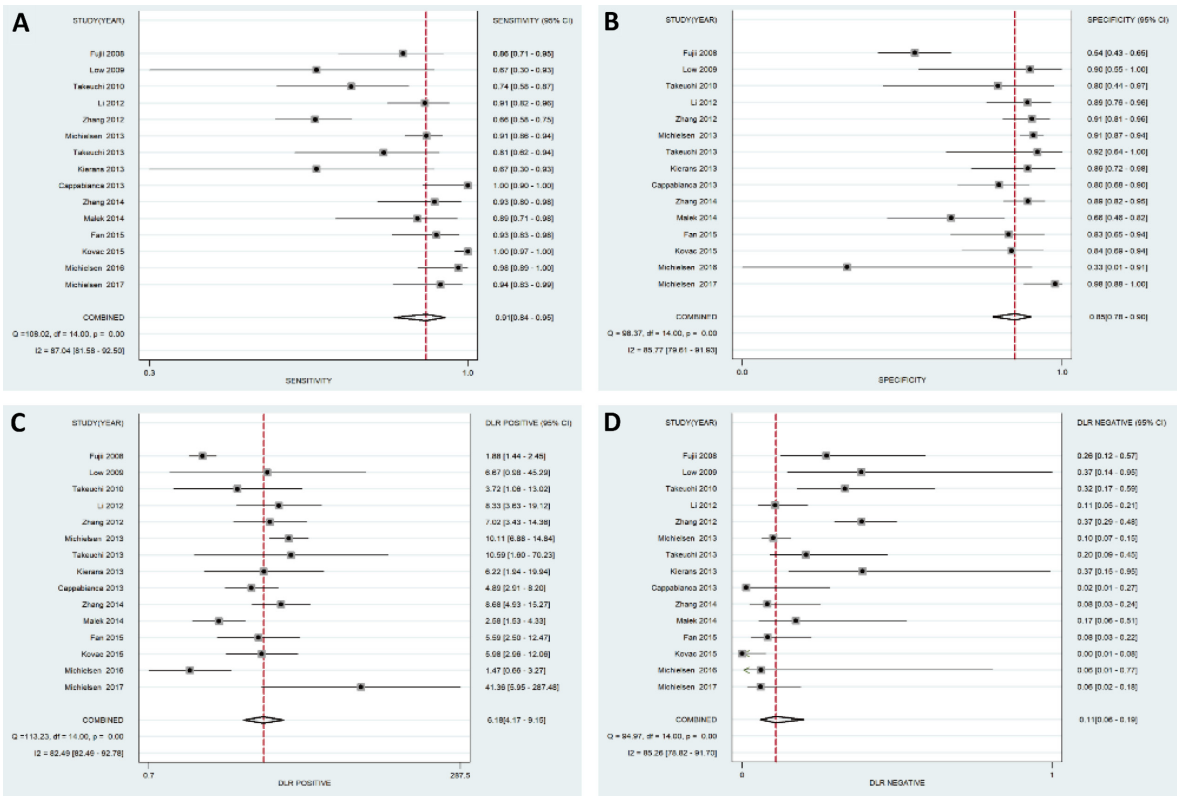

Figure 2. Forest plots of sensitivity **(A)**, specificity **(B)**, positive predictive value **(C)** and negative predictive value **(D)** by diffusion-weighted imaging as a diagnostic technique for ovarian cancer including both Asian and Caucasian populations in the studies included for meta-analysis. Each solid circle represents an eligible study. The size of the solid circle reflects the sample size of each eligible study. Error bars represent 95% CI.

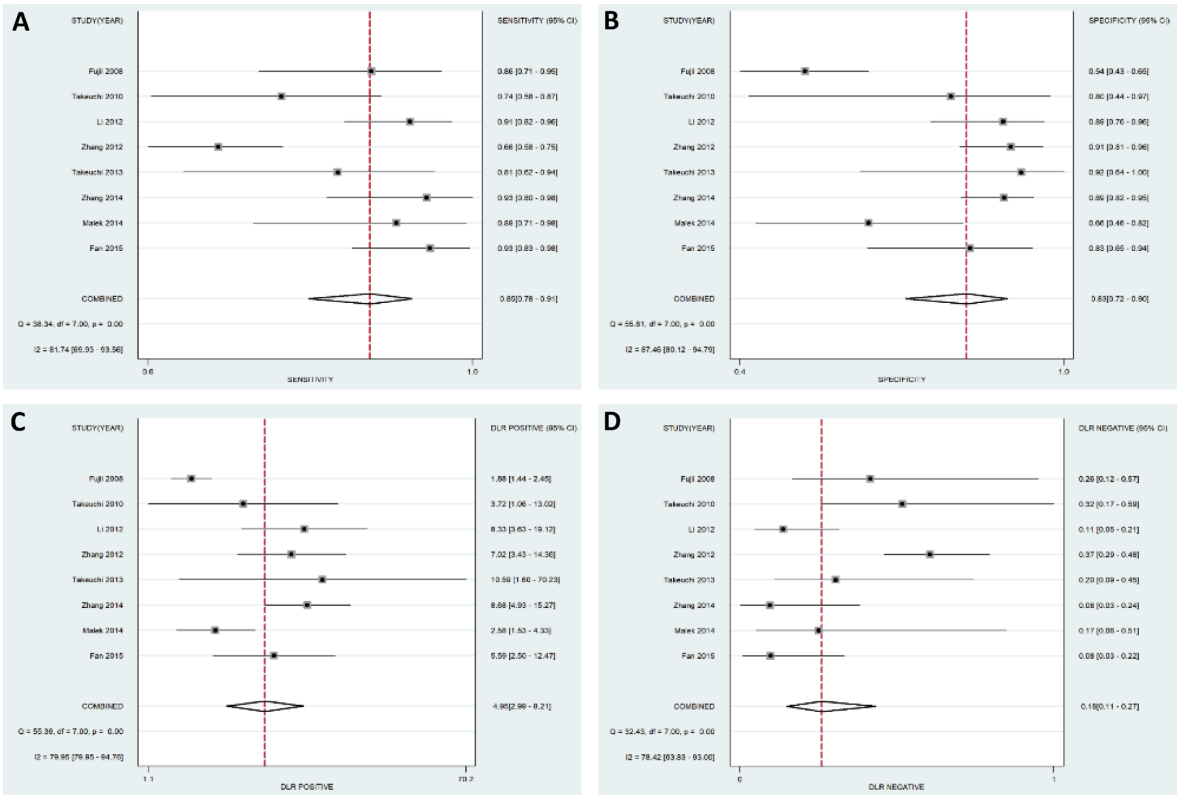

Figure 3. Forest plots of sensitivity **(A)**, specificity **(B)**, positive predictive value **(C)** and negative predictive value **(D)** by diffusion-weighted imaging as a diagnostic technique for ovarian cancer in Asian population. Each solid circle represents an eligible study. The size of the solid circle reflects the sample size of each eligible study. Error bars represent 95% CI.

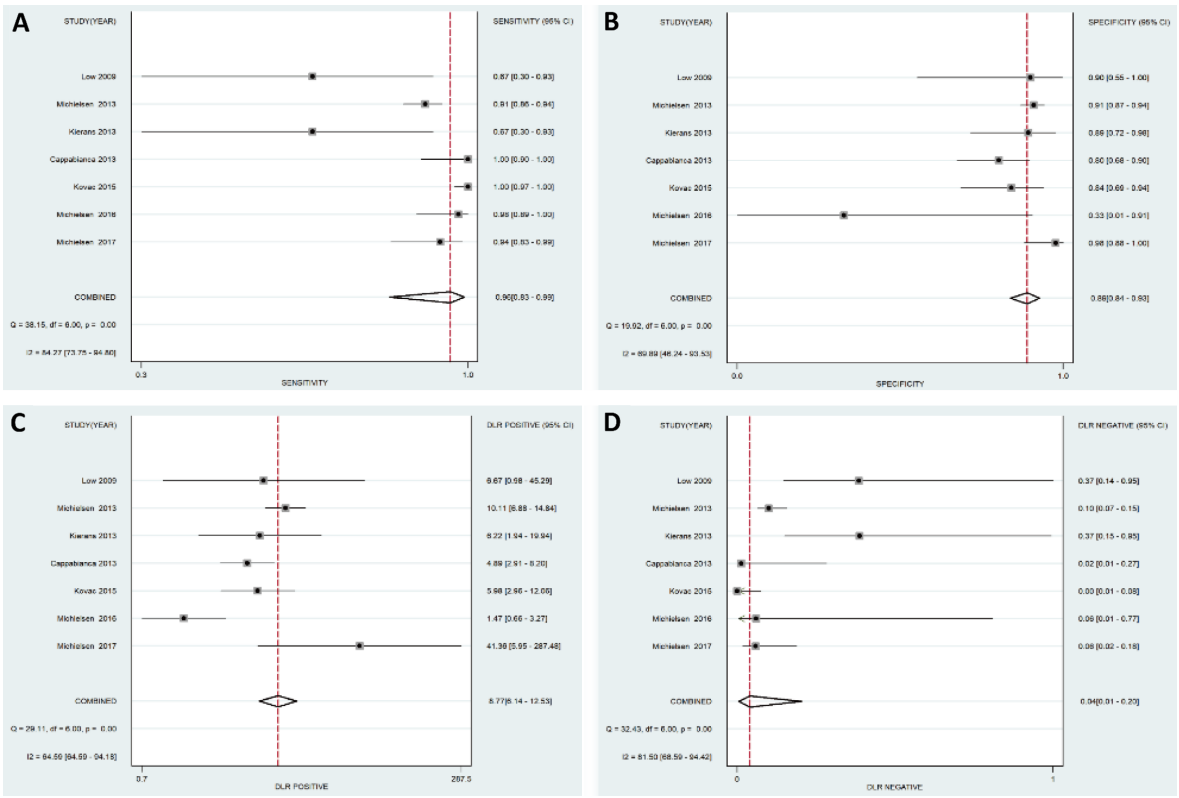

Figure 4. Forest plots of sensitivity **(A)**, specificity **(B)**, positive predictive value **(C)** and negative predictive value **(D)** by diffusion-weighted imaging as a diagnostic technique for ovarian cancer in Caucasian population. Each solid circle represents an eligible study. The size of the solid circle reflects the sample size of each eligible study. Error bars represent 95% CI.

tion, TX, USA). P<0.05 was considered statistically significant. Fixed-effect model was used when I^2<50% and p>0.1; Otherwise, the random-effects model was used. SEN, SPF, +LR, -LR and DOR were calculated. SROC was used for calculating AUC. Deek's funnel was drawn for evaluating the publication bias.

Results

Characteristics of the studies

A total of 15 articles involving 930 ovarian cancer cases and 832 control cases were enrolled [18-20]. Baseline characteristics and prognostic parameters are displayed in Table 1 [21-32]. The searching and selection process is depicted in Figure 1. The enrolled literature graded over 11 points of QUADAS score suggested that it was of high quality.

Quantitative synthesis results

This study came to the conclusion that DWI elevates the diagnostic efficacy of OC. Here, I^2=82.04% of the merged SEN and the random-effects model was utilized. The merged SEN was calculated as 91% (95%CI=84-95%). Also, if I^2=85.77% of the merged SPF we also used the random-effects model for analysis. The merge SPF was 85% (95%CI=78-90%). The merged +LR (6.18, 95%CI=4.17-9.15) and -LR (4.05, 95%CI=3.30-4.79) were calculated (Figure 2). The merged DOR was 4.05 (95%CI=3.30-4.79, Figure 5A). After depicting SROC, AUC was 0.94 (95%CI=0.91-0.96, Figure 6A).

Subgroup analysis in Asian population obtained the following results: SEN was 85% (95%CI=78-91), SPF was 83% (95%CI=72-90), +LR was 0.18 (95%CI=0.11-0.27), -LR was 3.34 (95%CI=2.60-4.09) and DOR was 3.34 (95%CI=2.60-4.09); AUC was 0.91 (95%CI=0.88-0.93) (Figure 3, 5B and 6B).

In Caucasian population, SEN was 96% (95%CI=83-99), SPF was 89% (95%CI=84-93), +LR was 41.36 (95%CI=5.95-287.48), -LR was 0.06 (95%CI=0.02-0.18) and DOR was 5.31(95%CI=3.93-6.69); AUC was 0.94 (95%CI=0.91-0.96) (Figure 4, 5C and 6C).

Test of heterogeneity

ROC curve was not in the shoulder-brachial distribution, suggesting that there was no heterogeneity due to threshold effects. Heterogeneity judgment caused by non-threshold effect was evaluated by DOR forest map. DOR on the individual

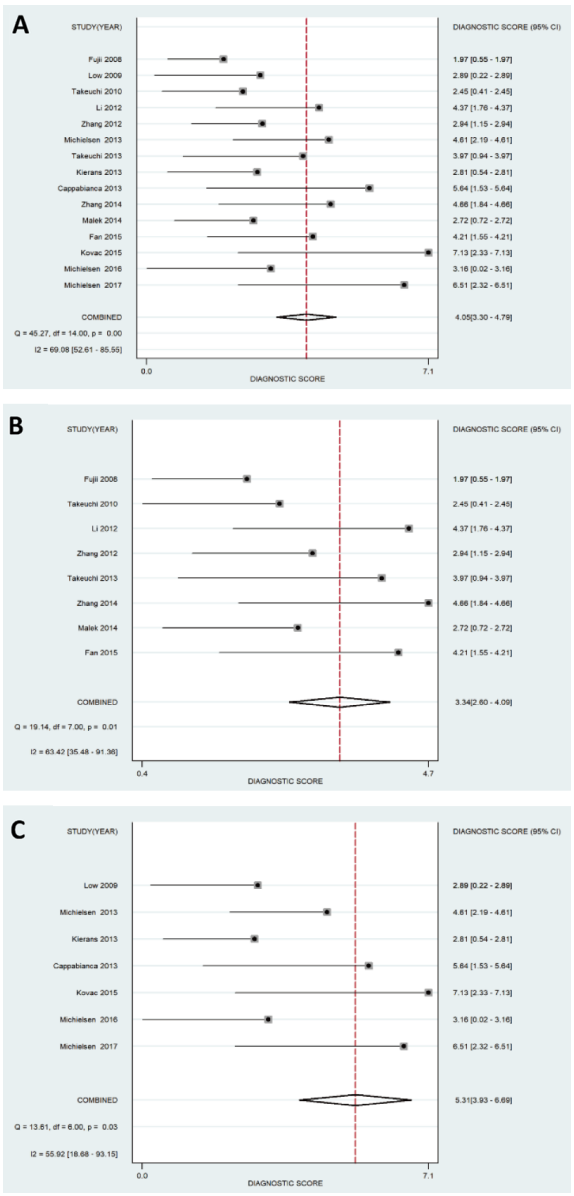

Figure 5. Forest plots of diagnostic score by diffusion-weighted imaging as a diagnostic technique for ovarian cancer in the studies included for meta-analysis. **A:** All studies showed that DOR was 4.05 (95% CI:3.30-4.79); **B:** Asian population. The results showed that DOR was 3.34 (95% CI:2.60-4.09); **C:** Caucasian population. The results showed that DOR was 5.3 (95% CI:3.93-6.69); Each solid circle represents an eligible study. The size of the solid circle reflects the sample size of each eligible study. Error bars represent 95% CI.

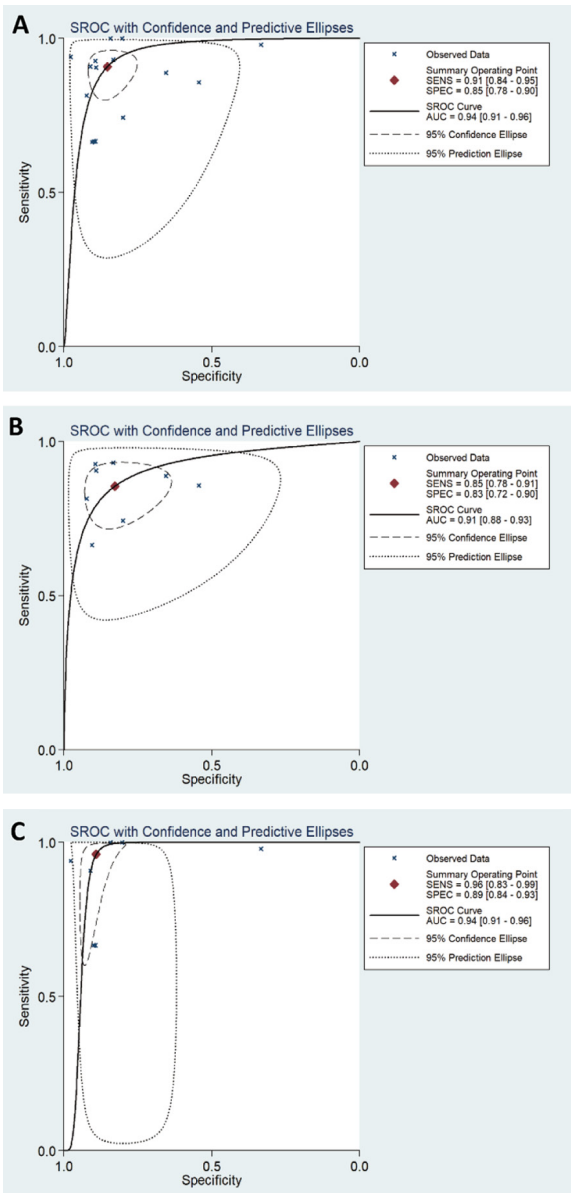

Figure 6. Summary of receiver operating characteristic curves (sROC) from the hierarchical summary ROC model generated from the studies that found that diffusion-weighted imaging as a diagnostic technique for ovarian cancer. **A:** All studies. The results showed that AUC was 0.94 (95% CI:0.91-0.96). **B:** Asian population. The results showed that AUC was 0.91 (95% CI:0.88-0.93); **C:** Caucasian population. The results showed that AUC was 0.94 (95% CI:0.91-0.96). Each solid circle represents an eligible study. The size of the solid circle represents the sample size of each eligible study. The regression curve summarizes the overall diagnostic efficiency.

study and the merged DOR were not distributed along the same straight line, indicating heterogeneity in the enrolled literature (Figure 6).

Publication bias

Publication bias in this study was assessed by depicting Deek's funnel. The systematic shape of the funnel diagram indicated no significant publication bias (p=0.462).

Discussion

OC is a challenging gynecological tumor. Typical symptoms of OC are occult in early stage and gradually become apparent during advanced stages. Females should be vigilant about abdominal pain, bloating, increased abdominal circumference, loss of appetite, and a sense of satiety more than 12 times per month [1-3]. Therefore, early diagnosis,

precise treatment and recurrence prevention of OC have been well concerned [7,8]. Recent studies have identified the diagnostic potential of DWI in multiple types of diseases, which markedly elevates the diagnostic efficacy of OC [16]. Diagnostic efficacy of DWI on OC, as well as its sensitivity and specificity, should be well explored to enhance the clinical outcomes of OC patients.

DWI examination can quantitatively evaluate tissue structure and cell component, and it accurately determines the lesion location, size and nature as well as the chemotherapy outcomes [10-12]. DWI provides evidence for clinical diagnosis and complements morphology and biochemical examinations [13]. DWI images are generated based on the degree of molecular motion limitation and attenuation, which indirectly reflects the microstructure. Two factors greatly influence DWI: The first is the diffusion sensitivity factor (b value), the magnetic diffusion gradient [14,15]. The more attenuated the image is at a given position, the greater diffusion there is in the direction of the diffusion gradient. The second factor is the strength of the diffusion gradient [13-15]. DWI exerts a certain clinical importance in diagnosing OC.

DWI differentiates benign and malignant tumors according to the biological metabolism of tumor cells. The working principle of DWI is essentially different from that of CT and MRI. DWI detects small recurrent or metastasis lesions earlier, thus improving the early-stage diagnostic rate [15,16]. Nevertheless, DWI examination is expensive and could not be applied as a routine examination item for diagnosis or follow-up [14,15]. This study focused on searching the most optimal method for diagnosing OC with the highest sensitivity and specificity. Our results identified that DWI exerted certain advantages in diagnosing OC. A total of 15 articles involving 930 ovarian cancer cases and 832 control cases were enrolled. DWI was identified to exert a certain diagnostic value on OC. The data revealed that the merge SEN was 91%, SPF 85%, +LR 6.18, -LR 4.05 and AUC 0.94. Subgroup analysis in Asian population obtained the following results: SEN was 85%, SPF 83%, +LR 0.18, -LR 3.34, DOR 3.34 and AUC 0.91. In Caucasian population, SEN was 96%, SPF 89%, +LR 41.36, -LR 0.06, DOR 5.31 and AUC 0.94.

Some limitations should be noteworthy. Firstly, the gold standard for diagnosing OC remained different in the enrolled literature, which may influence the accuracy of our results. Secondly, we did not explore the in-depth correlation between DWI and CA125 level, tumor location and tumor size of recurrent lesions owing to the limited sample size. Thirdly, pathogenic factors vary a lot in different ethnicities and may result in differences in diagnosis. This study only focused on the Asian and Caucasian populations. We were unclear whether the diagnostic potential of DWI in OC is different in other populations. Fourthly, unpublished literature and those published in other languages (English language was limited here) could lead to publication biases.

To sum up, this study identified accurate diagnostic potential in OC. However, this conclusion still needs to be further validated in a multi-center study with a large sample size. Gene-environment impact on diagnosing OC should also be fully explored.

Conclusions

This meta-analysis proved that DWI exerted a relatively high sensitivity and specificity in diagnosing OC, especially in Caucasian population.

Conflict of interests

The authors declare no conflict of interests.

References

1. Yao N, Yu L, Zhu B, Gan HY, Guo BQ. LncRNA GIHCG promotes development of ovarian cancer by regulating microRNA-429. Eur Rev Med Pharmacol Sci 2018;22:8127-34.
2. Gupta KK, Gupta VK, Naumann RW. Ovarian cancer: screening and future directions. Int J Gynecol Cancer 2019;29:195-200.
3. Vlad C, Dina C, Kubelac P, Vlad D, Pop B, Achimas CP. Expression of toll-like receptors in ovarian cancer. JBUON 2018;23:1725-31.
4. Antonijevic A, Rancic N, Ilic M, Tiodorovic B, Stojanovic M, Stefanovic J. Incidence and mortality trends of ovarian cancer in central Serbia. JBUON 2017;22:508-12.
5. Liu MC, Tewari KS. Anti-angiogenesis therapy, synthetic lethality, and checkpoint inhibition in ovarian cancer: state of the science and novel combinations. Drugs Context 2018;7:212558.
6. Kotoula V, Lakis S, Tikas I et al. Pathogenic BRCA1 mutations may be necessary but not sufficient for tissue genomic heterogeneity: Deep sequencing data from ovarian cancer patients. Gynecol Oncol 2019;152:375-86.

7. Kobayashi Y, Banno K, Kunitomi H, Tominaga E, Aoki D. Current state and outlook for drug repositioning anticipated in the field of ovarian cancer. J Gynecol Oncol 2019;30:e10.
8. Dong X, Men X, Zhang W, Lei P. Advances in tumor markers of ovarian cancer for early diagnosis. Indian J Cancer 2014;51 (Suppl 3):e72-6.
9. Togashi K. Ovarian cancer: the clinical role of US, CT, and MRI. Eur Radiol 2003;13 (Suppl 4):L87-104.
10. Takeuchi M, Matsuzaki K, Harada M. Evaluating Myometrial Invasion in Endometrial Cancer: Comparison of Reduced Field-of-view Diffusion-weighted Imaging and Dynamic Contrast-enhanced MR Imaging. Magn Reson Med Sci 2018;17:28-34.
11. Usuda K, Funazaki A, Maeda R et al. Economic Benefits and Diagnostic Quality of Diffusion-Weighted Magnetic Resonance Imaging for Primary Lung Cancer. Ann Thorac Cardiovasc Surg 2017;23:275-80.
12. Ota T, Hori M, Onishi H et al. Preoperative staging of endometrial cancer using reduced field-of-view diffusion-weighted imaging: a preliminary study. Eur Radiol 2017;27:5225-35.
13. Tang L, Zhou XJ. Diffusion MRI of cancer: From low to high b-values. J Magn Reson Imaging 2019;49:23-40.
14. Leibfarth S, Winter RM, Lyng H, Zips D, Thorwarth D. Potentials and challenges of diffusion-weighted magnetic resonance imaging in radiotherapy. Clin Transl Radiat Oncol 2018;13:29-37.
15. Ueno YR, Tamada T, Takahashi S et al. Computed Diffusion-Weighted Imaging in Prostate Cancer: Basics, Advantages, Cautions, and Future Prospects. Korean J Radiol 2018;19:832-7.
16. Whittaker CS, Coady A, Culver L, Rustin G, Padwick M, Padhani AR. Diffusion-weighted MR imaging of female pelvic tumors: a pictorial review. Radiographics 2009;29:759-774, 774-778.
17. McGuinness LA, Warren-Gash C, Moorhouse LR, Thomas SL. The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: A systematic review. Pharmacoepidemiol Drug Saf 2019;28:244-55.
18. Michielsen K, Dresen R, Vanslembrouck R et al. Diagnostic value of whole body diffusion-weighted MRI compared to computed tomography for pre-operative assessment of patients suspected for ovarian cancer. Eur J Cancer 2017;83:88-98.
19. Michielsen KLM, Vergote I, Dresen R et al. Whole-body diffusion-weighted magnetic resonance imaging in the diagnosis of recurrent ovarian cancer: a clinical feasibility study. Br J Radiol 2016;89:20160468.
20. Michielsen K, Vergote I, Op De Beeck K et al. Whole-body MRI with diffusion-weighted sequence for staging of patients with suspected ovarian cancer: a clinical feasibility study in comparison to CT and FDG-PET/CT. Eur Radiol 2014;24:889-901.
21. Zhang P, Cui Y, Li W, Ren G, Chu C, Wu X. Diagnostic accuracy of diffusion-weighted imaging with conventional MR imaging for differentiating complex solid and cystic ovarian tumors at 1.5T. World J Surg Oncol 2012;10:237.
22. Malek M, Pourashraf M, Mousavi AS et al. Differentiation of Benign from Malignant Adnexal Masses by Functional 3 Tesla MRI Techniques: Diffusion-Weighted Imaging and Time-Intensity Curves of Dynamic Contrast-Enhanced MRI. Asian Pac J Cancer Prev 2015;16:3407-12.
23. Takeuchi M, Matsuzaki K, Nishitani H. Diffusion-weighted magnetic resonance imaging of ovarian tumors: differentiation of benign and malignant solid components of ovarian masses. J Comput Assist Tomogr 2010;34:173-6.
24. Cappabianca S, Iaselli F, Reginelli A et al. Value of diffusion-weighted magnetic resonance imaging in the characterization of complex adnexal masses. Tumori 2013;99:210-7.
25. Kovac JD, Terzic M, Mirkovic M, Banko B, Dikic-Rom A, Maksimovic R. Endometrioid adenocarcinoma of the ovary: MRI findings with emphasis on diffusion-weighted imaging for the differentiation of ovarian tumors. Acta Radiol 2016;57:758-66.
26. Low RN, Sebrechts CP, Barone RM, Muller W. Diffusion-weighted MRI of peritoneal tumors: comparison with conventional MRI and surgical and histopathologic findings--a feasibility study. AJR Am J Roentgenol 2009;193:461-70.
27. Li W, Chu C, Cui Y, Zhang P, Zhu M. Diffusion-weighted MRI: a useful technique to discriminate benign versus malignant ovarian surface epithelial tumors with solid and cystic components. Abdom Imaging 2012;37:897-903.
28. Fujii S, Kakite S, Nishihara K et al. Diagnostic accuracy of diffusion-weighted imaging in differentiating benign from malignant ovarian lesions. J Magn Reson Imaging 2008;28:1149-56.
29. Fan X, Zhang H, Meng S, Zhang J, Zhang C. Role of diffusion-weighted magnetic resonance imaging in differentiating malignancies from benign ovarian tumors. Int J Clin Exp Med 2015;8:19928-37.
30. Kierans AS, Bennett GL, Mussi TC et al. Characterization of malignancy of adnexal lesions using ADC entropy: comparison with mean ADC and qualitative DWI assessment. J Magn Reson Imaging 2013;37:164-71.
31. Takeuchi M, Matsuzaki K, Harada M. Ovarian adenofibromas and cystadenofibromas: magnetic resonance imaging findings including diffusion-weighted imaging. Acta Radiol 2013;54:231-6.
32. Zhang H, Zhang GF, He ZY, Li ZY, Zhang GX. Prospective evaluation of 3T MRI findings for primary adnexal lesions and comparison with the final histological diagnosis. Arch Gynecol Obstet 2014;289:357-64.