REVIEW ARTICLE

Diagnostic accuracy of diffusion weighted magnetic resonance imaging (DW-MRI) and transvaginal ultrasonography (TVUS) in assessing myometrial invasion among female patients with endometrial cancer: a systematic review and meta-analysis

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Abstract:

TVUS is the first imaging technique in determining patient with suspicious of endometrial cancer whereas the most appropriate tool for grading of endometrial cancer is MRI. Recently, DW-MRI gradually becomes a routine in grading endometrial cancer. Thus, the purpose of this study was to compare the diagnostic accuracy of transvaginal ultrasound (TVUS) and diffusion weighted magnetic resonance imaging (DW-MRI) in assessing depth of myometrial invasion in endometrial cancer. An extensive search was performed in Dimension, PubMed and Wiley Online Library guided by PRISMA. Following screening, the eligibility of the studies was checked. Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist. The search identified 7 studies (727 patients). Overall, pooled estimated sensitivity and specificity for detecting deep myometrial invasion were 79% (95% confidence interval [CI]=72%–85%) and 84% (95% CI=64%–94%) for TVUS, and 84% (95% CI=69%–92%) and 89% (95% CI=83%–93%) for DW-MRI, respectively. Low heterogeneity was found for sensitivity of TVUS but high for the specificity. For DW-MRI, the heterogeneity for specificity was low but the heterogeneity was significant for the sensitivity. In conclusion, the sensitivity and specificity of DW-MRI is higher compared to TVUS in assessing the deep myometrial invasion among women with endometrial cancer.

Keywords: Endometrial cancer, myometrial invasion, magnetic resonance imaging, transvaginal ultrasonography

1. INTRODUCTION

Endometrial cancer also called as endometrial carcinoma or corpus cancer starts when cells of the inner lining of the uterus begin to grow out of control [1]. In United States, the endometrial cancer is the most common gynecologic malignancy and the American Cancer Society predicts about 65,620 new cases will be diagnosed with this cancer and 12,590 deaths is estimated in 2020[2]. Endometrial cancer can be cured by surgery especially in the early stages[3]. The prognosis and the treatment response of patients with endometrial cancer depends on several factors such as the cell differentiation, pathological grade, cervical stromal invasion and the depth of myometrial invasion[4]. Besides early detection, presurgical evaluation of the depth of myometrial invasion is important to improve the patient treatment management[5]. There are two categories for depth of myometrial invasion which are superficial invasion (invasion depth of <50% of the myometrial thickness) and deep invasion (extension ≥50% of the myometrium).

Magnetic resonance imaging (MRI), computed tomography (CT), transvaginal ultrasound (TVUS) and positron emission tomography (PET) are the noninvasive imaging tools to assess the depth of myometrial invasion. Transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) are currently the most common imaging technique used for evaluating preoperatively the depth of myometrial infiltration (MI)[5]. In 1999, there was a meta-analyses comparing diagnostic accuracy of several imaging techniques in assessing preoperative radiological staging of myometrial infiltration and in early 2000 there was a meta-analysis conducted that assessed the role of DCE-MR(dynamic contrast enhancement) imaging in detecting the deep of myometrial invasion. As DW-MR imaging has been gradually practical in assessing myometrial invasion in last few years, there is a need for an updated systematic review and meta-analysis including this new generation imaging. The purpose of the present meta-analysis is to compare the diagnostic accuracy of TVUS and DW-MRI in detecting myometrial invasion in female patients with endometrial cancer.

2. METHODS

2.1 PRISMA

The systematic review and meta-analysis was done by referring to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[6]. All methods for inclusion/exclusion criteria, data extraction and quality assessment were specified in advance.

2.2 Data sources and searches

The following electronic databases were used in this study to search the related articles; Medline/PubMed, Dimension and Wiley Online Library. Publication years were filtered from 1st January 2011 up to 1st March 2020 in searching. Methodological filters were not performed in searching to avoid potential omission of relevant studies. The search strategy included database subject headings and text words as follows: EC or endometrial cancer, endometrial carcinoma, myometrial invasion or infiltration, ultrasound, transvaginal ultrosonography, TVUS, magnetic resonance imaging and diffused weighted image or DWI. The abstract of all relevant articles on the database were reviewed and their references were also checked for other relevant publications. Language restriction in the search was set to English.

2.3 Study selection and data collection

In order to exclude clearly unrelated articles, the title and abstracts identified by the searches was screened first by two reviewers. For instance, those that not strictly associated to the topic under review will be excluded. The reference lists of selected articles also were screened for search completion. Then, relevant full texts were obtained to recognize possibly eligible studies and the same reviewers independently reviewed the full text for inclusion criteria. The following inclusion criteria were applied to the full text:

- Type of studies: Prospective or retrospective cohort studies
- Type of participants: Adult women with biopsy-proven primary adenocarcinoma of the endometrium, undergoing preoperative detection of deep myometrial invasion prior to surgery. Patients with any stage of the disease were included.
- Target condition: Presurgical detection of deep myometrial invasion in primary endometrial adenocarcinoma
- Index test(s): TVUS and DW-MRI (DWI without referring to fusion with other sequences) were regarded as index tests because these tests are usually used to assess depth of myometrial invasion in patient with endometrial cancer. In addition, other index tests that are usually detecting myometrial invasion were also included.
- Types of outcome: The primary outcomes were sensitivity (SEN), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV), and their respective 95% confidence intervals.
- Reference Standard: Pathological assessment of the presence of deep myometrial invasion on the uterus removed at surgery

Disagreements that were generated in the process of study selection were resolved by consensus. The Patients, Intervention, Comparator, Outcomes, Study Design (PICOS) criteria were used for describing the studies include.

2.4 Risk of bias in individual studies

Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) is a tool that used to assess the quality of the studies and this tool had been adapted in this study. There are four domains in the QUADAS-2 format: 1) patient selection, 2) index test, 3) reference standards, 4) flow and timing. The possibility of bias and concerns about applicability were evaluated in each domain (the latter not applying to the 4th domain) and graded as low, high or unclear risk. The outcomes of quality assessment were used for descriptive purposes to explore potential sources of heterogeneity and to provide an assessment of the overall quality of the included studies.

The quality of methodology was evaluated independently by the two reviewers, using a standard form with quality assessment criteria and a flow diagram; discussion had been done to resolve the disagreements.

2.5 Statistical analysis

Information on diagnostic accuracy of both TVUS and DW-MRI from each primary study was extracted. All studies had a reference standard patient (at least 50% of myometrial invasion according to surgical pathological data) and all considered as positives. The primary outcome was reported in term of pooled specificity, sensitivity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) and of diagnostic odds ratio (DOR), together with their 95% confidence intervals (CI). P-value based on the likelihood ratio test were provided (α=0.05, two-sided). LR+ and LR- were applied to characterize the clinical utility of test and to assess the post-test probability of disease. Weak evidence was provided when value of LR is 0.2-5.0 for either ruling out or approving the disease. Moderate evidence was achieved when the LR is 5.0-10.0 and 0.1-0.2. For LR >10 or <0.1, this value provided strong evidence to either rule out or confirm the disease.

Heterogeneity for sensitivity and specificity were explored graphically thru constructing forest plots of sensitivity and specificity of each primary study. Then, they were plotted in the hierarchical summary receiver operating characteristic (HSROC) space, the latter to identify whether any heterogeneity could be attributable to an implicit threshold effect. Besides, HSROC curves for each technique were plotted to illustrate relationship between sensitivity and specificity. Means of a test on the Q statistic and I2 index were calculated to assess the presence of heterogeneity. A p-value <0.1 points to heterogeneity.

The I2 index was measured to define the percentage of overall variation across studies that are due to heterogeneity rather than chance. The I2 value of 25%, 50% and 75% would be considered to specify low, moderate and high heterogeneity, respectively. Comparison of effect of the TVUS and DW-MRI for detecting deep myometrial invasion was done using the bivariate method. All analyses were performed using Meta-analytical Integration of Diagnostic Accuracy Studies (MIDAS) and (METANDI) commands in STATA version 13.0.

3. RESULT AND DISCUSSION

3.1 Search result

The search of Dimension, PubMed and Wiley Online Library databases provided a total 201 citations. After removal of duplicate records, 144 citations were remained. Of these, 133 were discarded because it was clear from the title and abstract that they did not meet the criteria. The remaining 11 papers were examined. Finally, 4 studies[5], [7]–[9] were excluded because these articles did not meet inclusion criteria and the remaining 7 studies[10]–[16]were included in the review and meta-analysis. There were no additional related studies were found from references cited in the articles included in the review. Figure 1 below is a flowchart summarizing literature identification and selection.

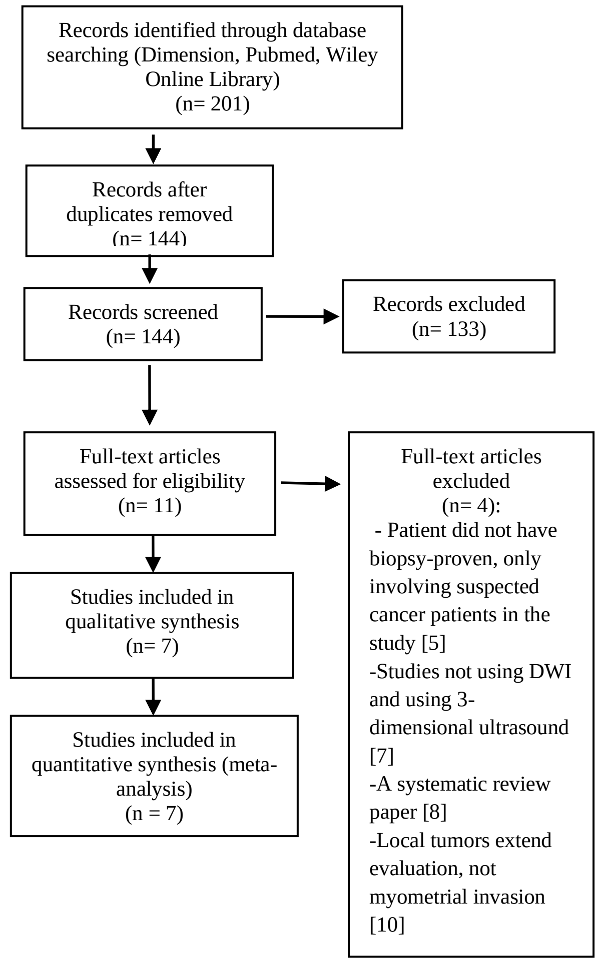


Figure 1: Flow chart summarizing literature identification and selection.

3.2 Characteristics of included studies

A total of 7 studies published between January 2012 to December 2017 reporting on 727 patients were included in the final analyses. Among these 727 women, 287 had deep myometrial invasion. Mean patients' age were reported in 6 out of 7 studies and ranged from 31-89 years. Two of the studies were retrospective studies and the remaining were prospective studies. Three studies used TVUS to assess the depth of myometrial invasion and another three studies used DW-MRI to detect the myometrial invasion. Only one study evaluates the depth of myometrial invasion using both TVUS and DW-MRI on the same patients. Table 1 shows PICOS features of studies included. All of the studies were based on the radiologist's or physician's impression.

The technical aspects of MR protocols are described in Table 2. Two studies used 3T MR and another two studies used 1.5T. All studies were used surface coil. Two studies [11], [16]performed fused T2 and DW imaging to interpret DW and the remaining two interpret DW imaging alone (one at

1.5T and one at 3T). No adverse events were reported during MR examinations. Concerning possible drawbacks for MR imaging, only one study described benign pathology found at MR examination.

For TVUS, one of the four studies[12] used objective measurement, Gordon's approach to assess myometrial invasion. In 3 studies [10], [13], [14]myometrial invasion assessment was based on the examiner's subjective impression. The major patient features in these studies are not provided. There was no patient underwent oncological therapy between TVUS and surgery.

Table 1: Characteristics of included patients and studies according to PICOS.

Study	Study design	No. of patient	No. ≥50 % MI	Age (years) Mean	Min -max	Obser-vers TVUS	Obser-vers DW -MRI
(Savelli et al., 2012)	Pro-	155	76	63	32 -88	Multi-ple	NA
(Hori et al.,2013)	Pro-	71	19	58	31 -82	NA	Multi-ple
(Ørtoft et al., 2013)	Pro-	156	66	66	32 -88	Multi-ple	NA
(Christensen et al., 2016)	Pro-	110	47	69	32 -85	Single	NA
(Angioli et al., 2016)	Pro-	79	27	53	47 -78	Multi-ple	Multi-ple
(Rodrı et al., 2016)	Retro-	98	39	NA	NA	NA	Single
(Guo et al., 2017)	Retro-	58	13	60	45 -78	NA	Single

Pro-, Prospective; Retro-, Retrospective

Table 2: Technical characteristics of the MR protocols used in the included studies.

Study	Tesla	Mark b value	Thick-ness (mm)	FOV (mm)	Matrix	T2-fused
(Hori et al., 2013)	3.0	1,000	4	200	96 x 96	Yes
(Rodrı et al., 2016)	1.5	800	-	-	-	No
(Rodrı et al., 2016)	1.5	800	-	-	-	No
(Guo et al., 2017)	3.0	-	-	200	256 x 320	Yes

3.3 Methodological quality of included studies

Figure 2 shows the evaluation of the risk of bias and concerns regarding the applicability of the selected studies. Concerning the risk of bias and patient selection domain, only one study[15] did not report patient selection criteria. This study was considered as risk bias since it did not avoid inappropriate exclusion criteria. Three TVUS studies sufficiently described the method of index test and how it interpreted or performed while one study was unclear [14]. For DW-MRI, two studies unclearly described the method of index test and how it interpreted or performed [14], [15]. However, another two studies adequately described them [11], [16]. Same threshold was adopted (≥50% of myometrial thickness) to define the deep myometrial invasion.

For the domain reference standard, all studies were unclear to describe the reference standard and one study was undertaken as low bias [16]. However, all these studies reported that the observers were blinded to imaging results. Regarding the flow and timing domain, only three studies report the interval between TVUS [12], [13]or MRI [16] and surgery, the rest of the studies did not report the information.

For patient selection, one study[15] concerned that included patient did not match the review question. For index test domain, also one study[13] unclearly reported whether there was concern that the TVUS, its conduct differ from the review question of the study. Concerning the reference standard domain of applicability, all studies were in low risk of bias.

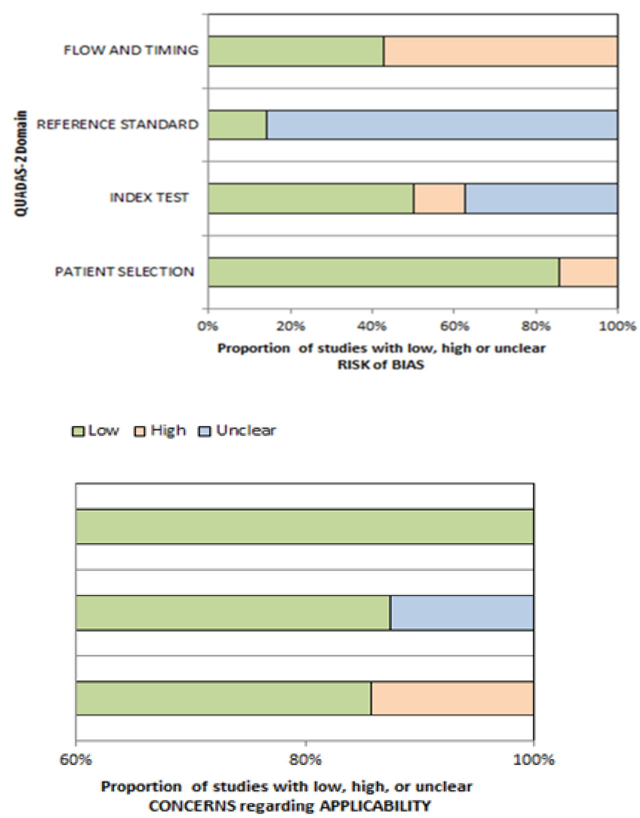


Figure 2 : Quality assessmentof all studies included in the meta-analysis, according to QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) criteria.

3.4 Diagnostic performance of TVUS and DW-MRI in detecting deep myometrial invasion

Individual results of TVUS and DW-MRI are shown in chronological order on the forest plots in Figure 3.

Overall, pooled sensitivity, specificity, LR+, and LR− of TVUS for detecting deep myometrial invasion were 79% (95% confidence interval [CI]=72%–85%), 84% (95% CI=64%–94%), 5.03 (95% CI=1.90–13.29), and 0.25 (95% CI=0.16–0.38), respectively. Low heterogeneity was establish for sensitivity (I^2=32.24%; Cochran Q=4.43; p=0.22). However, high heterogeneity was found for specificity (I^2=80.12%; Cochran Q=15.16; p=0.00). On the other hand, pooled sensitivity, specificity, LR+, and LR− of DW-MRI for detecting deep myometrial invasion were 84% (95% CI=69%–92%), 89% (95% CI=83%–93%), 7.60 (95% CI=4.64-12.43), and 0.18 (95% CI=0.09–0.38), respectively. Significant heterogeneity was found for sensitivity (I^2=59.27%; Cochran Q=7.36; p=0.06) but low heterogeneity was achieved for specificity (I^2=20.93%; Cochran Q=3.79; p=0.28) in DW-MRI.

The Figure 4 shows the summary point with a 95% prediction region and 95% confidence region. It can be observed that both techniques have wider prediction contour than the confidence contour respectively. The region of confidence is plotted from the CI around the summary point and shows that, the 'real value' would be estimated to be inside the region 95% of the time. Furthermore, the prediction region is wider compared to the region of confidence because it goes more than the improbability in the presented data. Besides, TVUS has wider area under the curve for HSROC curve than the DW-MRI. However, DW-MRI has higher DOR compared to the TVUS (41.75 and 20.45 respectively) but the LR shows moderately increase of the probability of the disease. The specificity of detection of myometrial invasion was greater in TVUS but lower in DW-MRI. Fagan nomograms (Figure 5) show that a positive test for TVUS and DW-MRI increases significantly the pretest probability deep myometrial invasion, from 12% to 41% in case of TVUS and from 12% to 51% in case of DW-MRI, while a negative test significantly decreases the pretest probability, from 12% to 3% in case of TVUS and from12% to 1% in case of MRI.

Aside from the stage, the depth of myometrial invasion is acknowledged as one of the most crucial prognostic aspects in endometrium carcinoma and for management and surgical staging[17]. Preoperative information might impact on the treatment plan[18].

In the present meta-analysis, the pooled diagnostic accuracy of TVUS and DW-MRI has been compared and evaluated in detecting deep myometrial invasion among adult women with endometrial carcinoma undergoing surgical staging. This analysis shows that DW-MRI has higher diagnostic performance compared to TVUS with the sensitivity and specificity of 84% and 89% respectively. However, there is no substantial significant difference was observed between them which TVUS has slightly lower sensitivity and specificity (79% and 84% respectively). In addition, it was found that the values of LR+ (5.03 and 7.60 using TVUS and DW-MRI, respectively) and LR- (0.25 and 0.18 using TVUS and DW-MRI, respectively) were essentially between within the range of moderates estimates for both confirming and ruling out the disease.

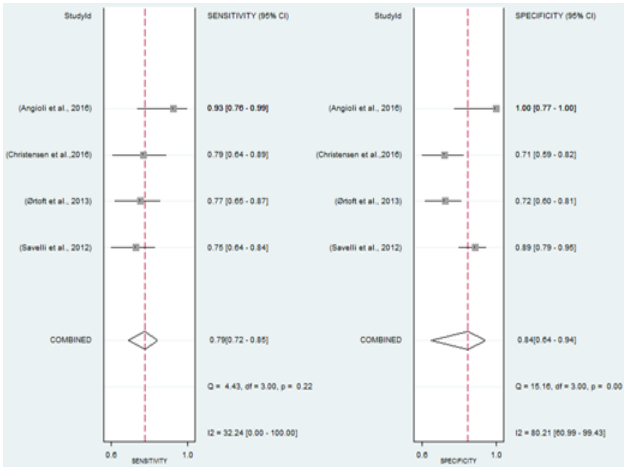
According to Sundar et al., (2017)[19], in some guidelines, MRI is currently suggested for preoperative imaging. Thus, these outcomes might be of clinical relevance. The heterogeneity of the studies was studied through this meta-analysis and high heterogeneity was observed for specificity of TVUS. In contrast, low heterogeneity was found for the specificity in DW-MRI. In term of sensitivity, the heterogeneity was significant for DW-MRI but not for TVUS. The possible explanation of this heterogeneity is the different technical aspects and approaches used in each of the study.

DW-MRI and TVUS play important role in detecting the depth of myometrial invasion. This review provides an idea of the methodological quality of studies using DW-MRI and TVUS in detecting the deep myometrial invasion. However this meta-analysis only included small number of studies. Therefore, the efficacy of these imaging in evaluating myometrial invasion should be further investigated in the future in larger scale of studies.

Some limitations had been recognized from this meta-analysis. Firstly, there are limited numbers of studies and sample size reported in this systematic review. This make the possibility to observe all potential sources of heterogeneity is not allowed. In addition, the technical aspects of the DW-MRI are different in every study as well as the TVUS which used different approaches in each study. Moreover, from the meta-analytic point of view, it is appropriate to review the studies that directly compared the diagnostic accuracy of both imaging on the same set of women. This method will lessen the risk of bias as the heterogeneity among studies that cannot be adequately controlled. This has been done in only one study [14]. From the current study, the DW-MRI technique was superior to the TVUS technique.

The low- and high-risk patients for deep myometrial invasion were involved in the most of the studies. This made the applicability of both techniques affected as preoperative evaluation is suitable in patients with preoperative histological records representing potential low risk. Hence, the overestimate of diagnostic accuracy for detecting the depth of myometrial invasion cannot be ruled out, because of the involvement of high-risk patients. This could also enlighten the heterogeneity observed among studies for pooled specificity.

(A)



(B)

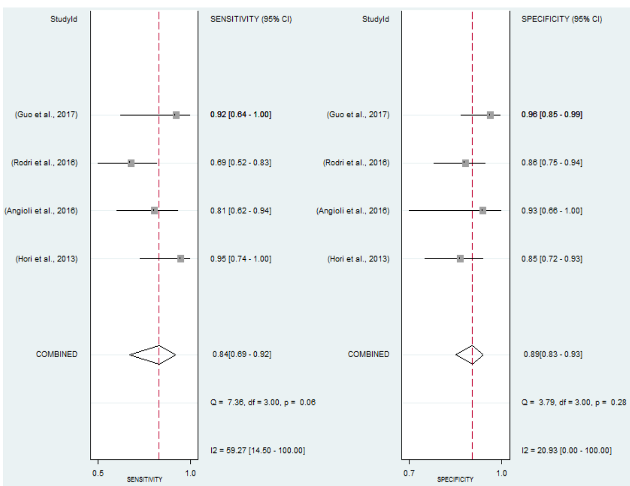
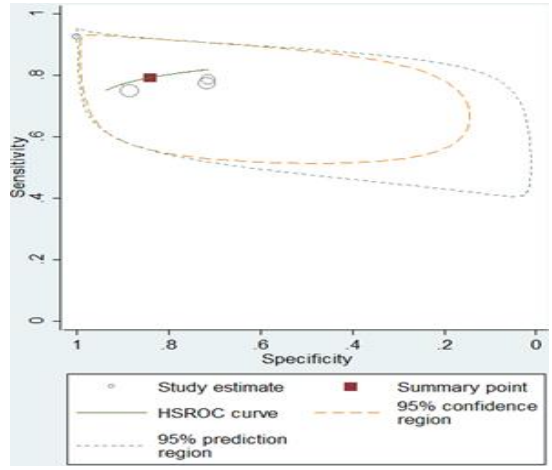


Figure 3: Forest plot for sensitivity and specificity for each study and pooled sensitivity and specificity for (A) TVUS and (B) DW-MRI

(A)



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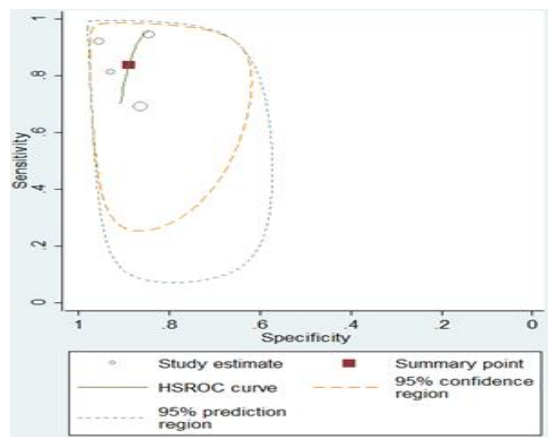
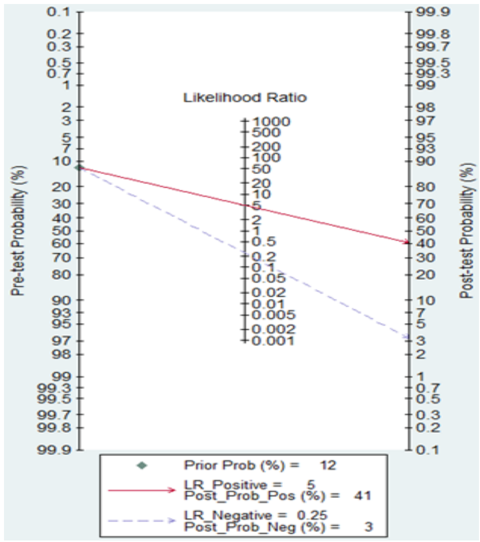


Figure 4: HSROC curve for (A) TVUS and (B) DW-MRI

(A)



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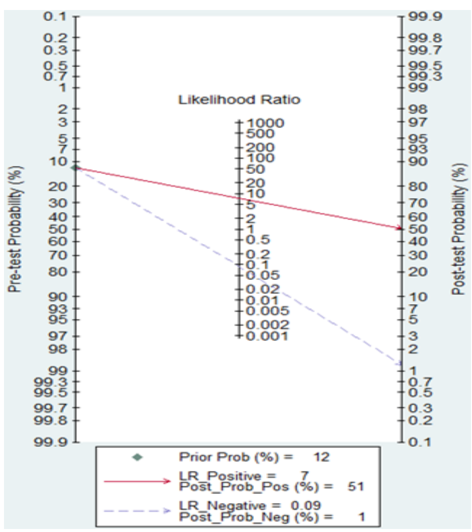

Figure 5: Fagan nomograms showing how pre-test probability change when the test is performed (post-test probability) depending on a positive or negative result for (A) TVUS and (B) DW-MRI

4. CONCLUSION

In conclusion, this systematic review and meta-analysis revealed that DW-MRI is superior to the TVUS imaging in measuring the deep myometrial invasion in preoperative endometrial cancer and the sensitivity and specificity of DW-MRI are slightly higher compared to the TVUS imaging. However, the difference observed was not statistically significant. Taking into account the time consuming and high cost of MRI, TVUS may have a role as the first imaging in measuring the depth of myometrial invasion among adult women with endometrial cancer. Whenever there is limited resources in a clinical settings, TVUS should be considered worthy to evaluate the depth of myometrial invasion.

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