Diagnostic accuracy of transvaginal ultrasound examination for assigning a specific diagnosis to adnexal masses: A meta-analysis

XIYA ZHANG1, XUAN MENG2, TING DOU3 and HUI SUN4

1Department of Special Inspection, Shandong Qingdao Hospital of Integrated Traditional and Western Medicine, Qingdao, Shandong 266002; 2Department of Ultrasound, Qingdao Fuwai Cardiovascular Hospital, Qingdao, Shandong 266021; 3Department of Ultrasound Medicine, The Third People's Hospital of Qingdao, Qingdao, Shandong 266041; 4Department of Special Inspection, Qingdao Women and Children's Hospital, Qingdao, Shandong 266000, P.R. China

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Correspondence to: Dr Hui Sun, Department of Special Inspection, Qingdao Women and Children's Hospital, 6 Tongfu Road, Qingdao, Shandong 266000, P.R. China
E-mail: m1028120753@163.com

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Abstract. Transvaginal ultrasound (TVUS) is a standard imaging modality for differentiating patients with benign or malignant suspected adnexal mass. To date, numerous studies have assessed the diagnostic accuracy of TVUS in various settings but with variable results. Therefore, the purpose of the present study was to perform a meta-analysis to evaluate the diagnostic accuracy of TVUS for the differentiation of adnexal masses. An electronic search in the Medline, Scopus, Cochrane and Embase databases from inception till November 2019 was carried out. Meta-analysis was performed to obtain pooled sensitivity and specificity of TVUS to distinguish malignant from benign adnexal masses. The quality assessment of diagnostic accuracy studies-2 tool was used to assess the quality of trials. A total of 41 studies with 18,391 patients were included. The pooled sensitivity and specificity of TVUS was 92% (95% CI: 90-94%) and 89% (95% CI: 85-92%), respectively. The area under the receiver operating characteristic curve was 0.96 (95% CI: 0.84-1.00). There was considerable heterogeneity with a statistically significant chi-square test (P<0.001) and I2 of 99%. Meta-regression results indicated that index test standards, patient selection bias and study design were potential sources of heterogeneity (P<0.05). The funnel plot was symmetrical and low publication bias was confirmed by an insignificant Deek's test (P=0.90). The present systematic review and meta-analysis indicated that TVUS is useful in differentiating between benign and malignant tumours among patients with suspected adnexal mass with high sensitivity and specificity.

Introduction

An adnexal tumour is defined as an enlarged structure within the adnexa of the uterus (1). It represents a spectrum of benign and malignant conditions that may originate from either gynaecological or non-gynaecological sources (2). The pathology is usually an incidental finding diagnosed during a routine clinical examination or may be present in females with any gynaecological complaint (3). Since adnexal masses may present with a wide range of symptoms, it is frequently difficult to differentiate benign tumours from other malignant lesions such as ovarian cancer (2).

Cross-sectional imaging strategies have a major role in managing patients with adnexal tumours, as they are able to consistently differentiate between benign and malignant masses affecting the fallopian tube and ovary. It is also helpful in differentiating uterine and gastrointestinal pathologies from adnexal abnormalities (1). Early and accurate diagnosis of adnexal mass is essential for formulating a treatment plan. The ability of the imaging modality to differentiate between a benign and malignant nature of a lesion further influences the decision for the requirement of expectant management (cases with no symptoms or reproductive dysfunction) or the requirement of surgery (for borderline or invasive tumours) (4). Laparoscopic observation and histopathological examination are considered the gold standard for the specific diagnosis of adnexal mass (5). However, the invasive nature of the procedure is a significant limitation for its use in routine clinical practice.

Despite several advances and technological advancements in the field of radiodiagnosis, simple transvaginal ultrasound (TVUS) has been a standard procedure for the initial diagnosis of patients with adnexal mass (6,7). Several studies have reported that TVUS may also help in discriminating between benign and malignant adnexal masses and also to make a specific diagnosis (6,7). To the best of our knowledge, there have been no systematic efforts to perform a data
Materials and methods

Inclusion criteria. All types of studies examining the diagnostic accuracy of TVUS for a specific diagnosis of an adnexal mass and comparing it with standard laparoscopic or histopathological examination as the reference standard were considered. Studies were to report on sensitivity and specificity or provide data to calculate these values. Only full-text articles were included, while unpublished data were excluded. Studies with a sample size of <10 patients and case reports were also excluded.

Search strategy. An extensive and systematic electronic search was performed in the Medline, Scopus, Cochrane Library and Embase databases. Both medical subject headings along with free text terms were utilized for the literature search. The search terms used were as follows: ‘Validation studies’, ‘adnexal mass’, ‘pattern recognition’, ‘transvaginal ultrasonography’, ‘benign adnexal mass’, ‘malignant adnexal mass’, ‘gynaecological disorders’, ‘sensitivity’, ‘specificity’, ‘diagnosis’, ‘adnexal lesions’ and ‘diagnostic accuracy studies’. The time limit for the search was from inception to November 2019 without any language restriction. Reference lists of primary studies were hand-searched to find any missed articles for inclusion in the review.

Selection of studies. Primary screening of title, keywords and abstracts was performed by two authors independently (XZ and XM). Full-text articles of the relevant entries were retrieved. These were further screened independently by the two authors (XZ and XM) for final inclusion in the review. Agreement between the two authors in making decisions related to inclusion or exclusion of studies was found to be excellent with a kappa value of 0.82. Disagreements during the selection of studies were resolved by consulting the third author (TD).

Data extraction and management. The primary investigator (XZ) performed data extraction using a data-extraction form. The following details were extracted: Study setting, study design, inclusion and exclusion criteria, reference standards, index test, total participants, comorbidities, mean age, sensitivity and specificity values. The extracted data were entered into STATA software. They were double-checked for correct entry by comparing the data in the review and the study reports. The following outcome measures were analysed in the review: Sensitivity, specificity, diagnostic odds ratio (DOR), likelihood ratio positive (LRP) and likelihood ratio negative (LRN).

Risk of bias assessment. The risk of bias for all of the included studies was assessed by two authors (XZ and XM) independently using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (8). Studies were rated for patient selection bias, conduct and interpretation of index test and reference standard, as well as time interval (i.e. flow and timing) of the outcome assessments. The studies were graded as having low, high or unclear risk of bias for each domain.

Statistical analysis. The final estimate of sensitivity, specificity, LRN, LRP and DOR for TVUS was obtained using the bivariate meta-analysis method. The summary receiver operator characteristic curve was constructed from which area under the curve (AUC) was obtained. An AUC value closer to 1 was indicative of a better diagnostic value.

Forest plots were used to graphically represent the study-specific and pooled estimates of sensitivity and specificity. The clinical value of the TVUS was determined by the LR scattergram. The probability of a patient having a benign or malignant adnexal mass was tested using the Fagan plot. Heterogeneity was assessed graphically using bivariate boxplots and tested using the chi-square test and I² statistic. The source of heterogeneity was explored with meta-regression using study-related covariates such as the study design, year of publication, sample size, study region and quality-related factors. Publication bias was tested using Deek's test and graphically depicted by a funnel plot. The analysis was performed using the ‘metandi’ command package in STATA 14.2 software (StataCorp).

Results

Selection of studies. After database screening, a total of 2,442 records were retrieved, of which 927 records were from Medline, 813 from Scopus, 590 from Embase and 112 from the Cochrane library (Fig. 1). After the first stage of screening, 243 relevant studies were retained. The full text of these studies was examined against the eligibility criteria. In total, 41 studies with 18,391 participants satisfying the inclusion criteria were included in the present review (9-49).

Characteristics of included studies. The characteristics of the included studies are described in Table I. Of the included studies, 35 were prospective studies. Most of the studies were performed in high-income European countries such as the United Kingdom, Italy, Belgium and Spain. The average age of the participants ranged from 33.3 to 53.3 years. The sample size of the studies varied from 37 to 2,403 patients. All of the included studies used laparoscopy or laparotomy with histopathology as the reference standard for comparing the diagnostic accuracy of TVUS. The time interval between TVUS and the reference standard varied from 24 h to 12 weeks.

Risk of bias. The assessment of the risk of bias among the included studies is presented in Fig. 2. Of the studies, 90% had a low risk of bias for ‘selection bias’. Furthermore, out of the 41 studies, 26 had a low risk of bias for ‘conduct and interpretation of index test’. All of the studies had a low risk of bias for the ‘conduct of reference standards test and interpretation’. A total of 32 studies had a low risk of bias concerning ‘flow and interval between index and reference standard test’ among the patients.

Diagnostic performance of TVUS. Analysis of data from the 41 studies provided a pooled sensitivity and specificity of
TVUS for differentiating benign and malignant adnexal mass of 92% (95% CI: 90-94%) and 89% (95% CI: 85-92%), respectively (Fig. 3). The DOR was 97 (95% CI: 65-147). The LRP was 8.3 (95% CI: 6.1-11.3) and the LRN was 0.09 (0.06-0.12). The upper right quadrant in the LR scatter diagram was occupied by these values, indicating that the TVUS may be used for confirmation only (Fig. 4). The AUC was 0.96 (95% CI: 0.84-1.00) (Fig. 5), indicating a high diagnostic value. TVUS for adnexal mass had a good clinical value, as Fagan’s nomogram had a significantly different post-test probability (positive, 80%; negative, 4%) compared to the pre-test probability (28%) (Fig. 6).

There was considerable heterogeneity with a statistically significant chi-square test result ($P<0.001$) and an $I^2$ value of 99%. As indicated in the bivariate box plot (Fig. 7), 4 studies were outside the circle, demonstrating a possibility of inter-study heterogeneity. Meta-regression for assessing the source of heterogeneity suggested that the selection domain, standards of index test conduct and study design...
| First author | Year | Study design | Country | Type of Gold standard comparator | Mean age (years) | Time interval between index test and reference standard (years) | Sample size | Type of diagnostic modality | Sample size diagnosis modalities |
|-------------|------|--------------|---------|---------------------------------|----------------|---------------------------------------------------------------|-------------|---------------------------|---------------------------------|
| Alcázar     | 2013 | Prospective  | Spain   | Subjective assessment by TVUS   | 42.1 (9)       | 3 weeks                                                       | 340         | Simple TVUS-based rules   | 1.958                           |
| Daemen      | 2011 | Prospective  | UK      | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 247         | Simple TVUS-based rules   | 1.958                           |
| Ruiz de Gauna | 2015 | Prospective  | Spain   | Simple TVUS-based rules         | 43.6 (11)      | 3 weeks                                                       | 122         | Simple TVUS-based rules   | 1.958                           |
| Fathallah   | 2010 | Prospective  | Italy   | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 2148        | Simple TVUS-based rules   | 1.958                           |
| Granberg    | 1990 | Prospective  | Sweden  | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 180         | Simple TVUS-based rules   | 1.958                           |
| Guerriero   | 2010 | Prospective  | Italy   | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 2148        | Simple TVUS-based rules   | 1.958                           |
| Hartmann    | 2015 | Prospective  | France  | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 110         | Simple TVUS-based rules   | 1.958                           |
| Jain        | 1993 | Prospective  | Japan   | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 82          | Simple TVUS-based rules   | 1.958                           |
| Jain        | 1994 | Prospective  | Japan   | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 49          | Simple TVUS-based rules   | 1.958                           |
| Komatsu     | 1996 | Prospective  | Poland  | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 226         | Simple TVUS-based rules   | 1.958                           |
| Kratel      | 2013 | Prospective  | Poland  | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 1320        | Simple TVUS-based rules   | 1.958                           |
| Lucidarme   | 2000 | Prospective  | Italy   | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 226         | Simple TVUS-based rules   | 1.958                           |
| Mansoński   | 2002 | Prospective  | Poland  | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 318         | Simple TVUS-based rules   | 1.958                           |
| Nunes       | 2013 | Prospective  | USA     | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 202         | Simple TVUS-based rules   | 1.958                           |
| Radosa      | 2014 | Prospective  | USA     | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 1520        | Simple TVUS-based rules   | 1.958                           |
| Romagnolo   | 2006 | Prospective  | Italy   | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 226         | Simple TVUS-based rules   | 1.958                           |
| Roman       | 1997 | Prospective  | USA     | Subjective assessment by TVUS   | 43.6 (11)      | 3 weeks                                                       | 226         | Simple TVUS-based rules   | 1.958                           |
| First author and year | Country          | Study design     | Sample size | Type of diagnostic modality | Gold standard comparator | Time interval between index test and reference standard | Mean age (years) | (Refs.) |
|-----------------------|------------------|------------------|-------------|-----------------------------|--------------------------|-------------------------------------------------------|-----------------|---------|
| Salle 1995            | France           | Prospective      | 91          | Subjective assessment by TVUS| Histopathology           | Not specified                                        | Not specified   | (28)    |
| Sayasneh 2013         | United Kingdom   | Prospective      | 255         | 2D grayscale TVUS            | Histopathology           | 120 days                                              | 46              | (29)    |
| Sayasneh 2015         | United Kingdom   | Prospective      | 313         | 2D grayscale TVUS            | Histopathology           | Not specified                                        | 47              | (30)    |
| Shetty 2017           | India            | Prospective      | 136         | Pattern recognition by TVUS | Histopathology           | Not specified                                        | 40.5            | (31)    |
| Shetty 2019           | India            | Prospective      | 183         | IOTA Simple rules using TVUS | Histopathology           | 12 weeks                                              | 37.5            | (32)    |
| Silvestre 2015        | Brazil           | Prospective      | 75          | IOTA Simple rules using TVUS | Histopathology           | 7 days                                                | Not specified   | (33)    |
| Sohaib 2005           | United Kingdom   | Prospective      | 72          | Subjective assessment by grayscale TVUS | Histopathology           | Not specified                                        | 53              | (34)    |
| Sokalska 2009         | Nine European centers | Retrospective  | 860        | Grayscale TVUS              | Histopathology           | Not specified                                        | 37              | (35)    |
| Stein 1995            | USA              | Prospective      | 160         | Grayscale TVUS              | Histopathology           | Not specified                                        | 114 patients were premenopausal (mean, 33 years; range, 13-53), 39 were perimenopausal or postmenopausal (mean, 57; range, 44-80) and eight had undergone hysterectomy (mean, 44 years; range, 33-61) | (36)    |
| Strigini 1996         | Italy            | Prospective      | 109         | TVUS                        | Laparotomy and histopathology | 1 week                                               | Median, 43      | (37)    |
| Tantipalakorn 2014    | Thailand         | Prospective      | 398         | IOTA simple rules using TVUS | Pathological or operative findings | 24 h                                                 | 42.4            | (38)    |
| First author and year | Country | Study design | Sample size | Type of diagnostic modality | Gold standard comparator | Time interval between index test and reference standard | Mean age (years) | (Refs.) |
|-----------------------|---------|--------------|-------------|-----------------------------|--------------------------|-------------------------------------------------|----------------|---------|
| Testa 2014            | 18 centres in six countries (Sweden, Belgium, Italy, Poland, Spain and Czech Republic) | Prospective | 2,403 | IOTA Logistic regression model using TVUS | Histopathology | 120 days | Not specified | (39) |
| Timmerman 1999        | Belgium | Prospective | 300 | TVUS | Histopathology | Not specified | Premenopausal (mean age, 40; range, 22-57); postmenopausal (mean age, 65; range, 47-93) | (40) |
| Timmerman 2010        | 19 centres in eight European countries | Prospective | 1,501 | IOTA Simple rules using TVUS | Histopathology | 120 days | 46 | (41) |
| Utrilla-Layna 2015    | Spain   | Prospective | 367 | Pattern recognition by TVUS | Histopathology | Not specified | 46.5 | (42) |
| Valentin 1999         | Sweden  | Prospective | 173 | TVUS | Histopathology | 8 days | 98 were premenopausal (median age, 37.5; range, 18-54), 70 were postmenopausal (median age, 66; range, 51-88; median 15 years past menopause with a range of 1-44 years), four had undergone hysterectomy (median age, 51.5; range, 44-66) | (43) |
| Valentin 2009         | Nine European US centres | Prospective | 534 | TVUS | Histopathology | 120 days | 48.8 | (44) |
| Van Calster 2007      | Nine European US centres | Prospective | 809 | TVUS | Histopathology | Not specified | 49 | (45) |
were statistically significant sources of heterogeneity (P<0.05; Fig. 8). The funnel plot for assessing the publication bias was symmetrical and the low publication bias was confirmed by non-significant Deek's test (P=0.90 Fig. 9).

**Discussion**

Several imaging modalities are available for making a specific diagnosis among patients with adnexal mass (50). However, these modalities cannot replace histopathology or biopsy as the gold standard for diagnosis. Imaging modalities still have a major role in clinical practice as these are non-invasive and are able to significantly reduce the diagnostic delay and complications associated with invasive diagnostic techniques (51). Since TVUS is a widely used imaging tool for adnexal masses, it is important to evaluate the diagnostic accuracy of this modality in differentiating between benign and malignant adnexal mass.

In total, 41 studies with 18,391 participants met the eligibility criteria of the review. The majority of the included studies were prospective studies. Most of them were performed in high-income countries such as the United Kingdom, the USA, Italy and Sweden. The overall quality of evidence was high, as most of the studies had a low risk of bias for all of the four domains of the QUADAS tool.

The diagnostic accuracy of TVUS for differentiating benign and malignant adnexal masses has not been evaluated in any previous reviews, to the best of our knowledge. In the present first meta-analysis, the pooled estimate of the sensitivity of TVUS was 92% and the pooled specificity was 89% with a high diagnostic performance (AUC=0.96). This diagnostic accuracy almost reached that of other biomarkers and algorithms such as CA-125, human epididymis protein 4, Risk of Malignancy Index and the Risk of Ovarian Malignancy Algorithm (52-56).

In the LR scatter diagram, LRP and LRN occupied the left lower quadrant, indicating that the TVUS should be used as the test for confirmation only and not for exclusion. The clinical value of TVUS for adnexal mass was also good, as Fagan's nomogram indicated a significant increase in the post-test probability compared to the pre-test probability. However, while inferring these results, one must consider the quality and differences in methodology of the included studies, which may have influenced the study results. Hence, an analysis of inter-study heterogeneity amongst the included studies was also performed. The present analysis indicated significant inter-study heterogeneity with a significant chi-square test result and I² statistic. On further exploration of the source of heterogeneity via meta-regression, it was indicated that the study design, publication year and quality-associated characteristics had a significant influence on the inter-study variability. Deek's test and the funnel plot indicated that there was no significant publication bias among the studies reporting on the diagnostic accuracy of TVUS.

The present study has the following strengths. A comprehensive review was performed by including 41 studies with 18,391 patients to evaluate the diagnostic accuracy of TVUS in differentiating adnexal masses. To the best of our knowledge, the present study was the first to provide pooled estimates for the specific diagnosis of adnexal mass using TVUS. Furthermore, publication bias was determined to be
Figure 3. Forest plot indicating the pooled sensitivity and specificity for transvaginal ultrasound. A point estimate and 95% CI of each individual study is presented by a square and horizontal lines, respectively. Diamonds indicate combined sensitivity and specificity with the red line indicating the combined point estimate.

Figure 4. Likelihood ratio scatter diagram providing a summary matrix of the positive and negative likelihood ratio of TVUS for diagnosing adnexal masses. The scatter diagram suggested that TVUS is useful only for confirming the diagnosis of adnexal masses (when positive). LRN, likelihood ratio negative; LRP, likelihood ratio positive; LLQ, left lower quadrant; LUQ, left upper quadrant; RLQ, right lower quadrant; RUQ, right upper quadrant; TVUS, transvaginal ultrasound.
Figure 5. SROC with pooled estimates of SENS and SPEC and AUC for transvaginal ultrasound in the diagnosis of adnexal masses. An AUC value closer to 1 is indicative of a better diagnostic value. SROC, summary receiver operator characteristic curve; AUC, area under the curve; SENS, sensitivity; SPEC, specificity.

Figure 6. Fagan nomogram for calculating post-test probabilities of the disease from the LR of the test result. The straight line drawn from the patient's pre-test probability of the disease through the LR of the test result points to the post-test probability of the disease. LR, likelihood ratio; Prob, probability; Pos, positive; Neg, negative.

Figure 7. Bivariate boxplot of the sensitivity and specificity in the included studies. The inner oval region represents the median distribution of the data points and the outer oval represents the 95% confidence boundary. Studies outside this grey area are considered as outliers. LOGIT_SENS, logit sensitivity; LOGIT_SPEC, logit specificity.

Figure 8. Meta-regression plot for different variables to explore sources of heterogeneity in the meta-analysis. Point estimates are depicted by red circles and 95% CIs are depicted by horizontal lines for each variable. Statistically significant results are marked by asterisks. *P<0.05; **P<0.01.

Figure 9. Deek's funnel plot for assessing publication bias in the included studies with super-imposed regression line. The statistically insignificant P-value (0.90) for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias. ESS, effective sample size.
insignificant, which adds credibility to the results obtained in the present review. However, the present study also has certain limitations. First, certain studies had a high risk of bias, which may have influenced the pooled estimates. Furthermore, there was significant inter-study heterogeneity in the review. This limits the study's ability to interpret the pooled results. However, it was attempted to overcome this limitation by exploring the potential source of heterogeneity among the included studies by a meta-regression analysis.

Despite these limitations, the present study provided valuable insight regarding the diagnostic accuracy of non-invasive techniques for differentiating benign and malignant adnexal masses. While TVUS had good sensitivity and specificity, it can only almost reach the SnNout triage test criteria for sensitivity. It cannot meet the SpPin criteria for the specificity of a diagnostic test (57). This means that TVUS can rule out an adnexal mass to be free from malignancy but cannot differentiate benign and malignant with utmost certainty based on radiological evidence. These results are in line with the international guidelines for the diagnosis of adnexal masses, which suggests TVUS as a first-line imaging modality to rule out malignancies such as ovarian cancer (6). However, it is not a replacement for laparoscopic surgery and biopsy, which is still the gold standard for the differentiation of adnexal masses.

In conclusion, the present study indicated that TVUS may be a useful imaging modality for differentiating between benign and malignant tumour among patients with adnexal mass with high sensitivity and specificity. TVUS may be employed as an efficient and rapid screening tool for suspected adnexal masses to rule out malignancy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

XZ designed the study. XZ, XM, TD and HS were involved in literature search and data interpretation. XM and TD were responsible for the data analysis. XZ prepared the manuscript. HS edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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