Comparative Diagnostic Accuracy of Contrast-Enhanced Ultrasound and Shear Wave Elastography in Differentiating Benign and Malignant Lesions: A Network Meta-Analysis

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Background: We performed a network meta-analysis to compare the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) and shear wave elastography (SWE) in differentiating benign and malignant lesions in different body sites.

Methods: A computerized literature search of Medline, Embase, SCOPUS, and Web of Science was performed using relevant keywords. Following data extraction, we calculated sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratio (DOR) for CEUS, and SWE compared to histopathology as a reference standard. Statistical analyses were conducted by MetaDiSc (version 1.4) and R software (version 3.4.3).

Results: One hundred and fourteen studies (15,926 patients) were pooled in the final analyses. Network meta-analysis showed that CEUS had significantly higher DOR than SWE (DOR = 27.14, 95%CI [2.30, 51.97]) in breast cancer detection. However, there were no significant differences between CEUS and SWE in hepatic (DOR = -6.67, 95%CI [-15.08, 1.74]) and thyroid cancer detection (DOR = 3.79, 95%CI [-3.10, 10.68]). Interestingly, ranking analysis showed that CEUS achieved higher DOR in detecting breast and thyroid cancer, while SWE achieved higher DOR in detecting hepatic cancer. The overall DOR for CEUS in detecting renal cancer was 53.44, 95%CI [29.89, 95.56] with an AUROC of 0.95, while the overall DOR for SWE in detecting prostate cancer was 25.35, 95%CI [7.15, 89.89] with an AUROC of 0.89.

Conclusion: Both diagnostic tests showed relatively high sensitivity and specificity in detecting malignant tumors in different organs. Network meta-analysis showed that CEUS had higher diagnostic accuracy than SWE in detecting breast and thyroid cancer, while SWE had higher accuracy in detecting hepatic cancer. However, the results were not statistically significant in hepatic and thyroid malignancies. Further head-to-head comparisons are needed to confirm the optimal imaging technique to differentiate each cancer type.

Keywords: contract enhanced ultrasonography, malignant lesions benign lesions, network meta analysis, shear wave elastography, lesions
INTRODUCTION
Ultrasound (US) has been used for decades in differentiating benign and malignant lesions because of its low cost, ease of access, and non-invasiveness. For example, it belongs to the triad (physical examination, mammography and US), commonly used to assess the risk of breast cancer (1). Moreover, it can detect thyroid nodules as small as 2 mm in size and predicts malignancy based on features like irregular border, hypo-echogenicity, and calcification (2, 3). However, none of these features can individually predict malignancy and conventional US alone has shown moderate accuracy in detecting malignant lesions (4). Therefore, improvements to US technique have been sought.

The introduction of contrast agents (contrast-enhanced US/CEUS) allows for visibility of blood flow within the lesion, which improves its characterization (5). The current in-use contrast media are second-generation agents as SonoVue. These agents remain within the intravascular space, which increases their safety and allows for continuous imaging over the enhancement period (6). Several studies have reported high sensitivity and specificity for CEUS in differentiating malignant lesions with the breast, thyroid, liver and kidneys (5, 7–9). A recent meta-analysis showed no significant difference between CEUS and contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (CEMRI) in terms of the diagnostic accuracy in characterizing focal liver lesions (FLLs) (8).

Shear wave elastography (SWE) relies on the degree of lesion stiffness when subjected to external pressure. Malignant nodules have harder consistency (less elasticity) than benign ones due to the uncontrolled proliferation of cancer cells (10). Therefore, SWE has been investigated for differentiating benign and malignant nodules. Compared to conventional US, SWE is more quantitative and is less operator-dependent, allowing more effective detection of malignant tumors (11). Recent diagnostic test accuracy (DTA) studies and meta-analyses showed high sensitivity and specificity for SWE in detecting malignant lesions within the breast and hepatic tissues (11–13).

According to our knowledge, data are lacking on the direct comparison between CEUS and SWE; therefore, we performed a meta-analysis to evaluate the diagnostic accuracy of CEUS and SWE in differentiating malignant tumors in the breast, liver, thyroid, kidneys, and prostate tissues in comparison to histopathology as a reference test. Moreover, we used network meta-analysis (NMA) to compare the diagnostic accuracy of both tests in malignant tumor differentiation.

MATERIALS AND METHODS
This meta-analysis has been conducted and reported in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (The PRISMA-DTA Statement) (14); Supplementary File I.

Literature Search
We searched Medline (via PubMed), Embase, SCOPUS and Web of Science for diagnostic accuracy studies that evaluated the use of CEUS and SWE in the differentiation of malignant tumors in different body organs. The following search terms were used with different combinations in different databases: Contrast-enhanced Ultrasound OR CEUS OR Ultrasound OR SonoVue OR Shear Wave Elastography OR SWE OR Sonoelastography OR Elastosonography AND Malignant OR Cancer OR Tumor OR Benign OR Adenoma OR Adenocarcinoma OR Carcinoma OR Nodule. No search filters of any sort were used during the search. All retrieved search results from database search (including bibliographic data and abstracts) were imported into EndNote (X7) for duplicate removal and then were transferred to a Microsoft Excel Sheet for screening.

Study Screening
For a study to be eligible for inclusion, it must have matched all the following criteria: (1) Population: Patients, suspected or diagnosed with malignancy in any body organ, (2) Intervention: CEUS or SWE [no specifications by US system or probe type], (3) Comparator: Histopathology, (4) Outcomes: Sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV], and (5) Study type: Diagnostic accuracy study. Two independent authors reviewed the title and abstract of retrieved records against our eligibility criteria and classified them into: eligible, non-eligible, or requires further screening (seems to fit the inclusion criteria, but further confirmation is required). The full-text articles of the latter type were retrieved and underwent a second wave of screening. Any discrepancy between the two reviewers’ decisions was solved by a senior reviewer (with a 15-year experience in secondary analysis and evidence synthesis methods) after reviewing the debated studies in reference to the pre-specified PICO criteria.

Data Extraction and Quality Assessment
An extraction sheet (in Microsoft Excel) was formatted and pilot-tested before final extraction. The sheet was customized to extract the baseline data of the imaging device, enrolled patients, as well as the raw diagnostic data of each included study. For pilot testing, two reviewers extracted these data from 5 included studies and the datasets were matched and compared with the original studies by a third reviewer. Each set of data was extracted by two reviewers and discordant decisions were resolved by discussion. These discussions included re-examining the studies, inspecting their available additional data sources and re-evaluating the former decisions. When the discrepancies remained, a senior reviewer examined the studies and settled the differences. The extracted data included (I) baseline characteristics of enrolled participants, (II) study design, (III) diagnostic test parameters: Parameters, cutoff value and US system for SWE and contrast agent, US technique, probe and mechanical index for CEUS, and (IV) Outcome data: true positive (TP), true negative (TN), false positive (FP), and false negative (FN) values. When these values were not directly given, they were calculated from the processed data as sensitivity, specificity, PPV, and NPV, using the statistical calculator on
RevMan software (Version 5.3 for Windows). We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) score to assess the quality of included studies. It consists of 14 (yes/no/unclear) questions to assess different forms of bias within DTA studies (15).

**Data Analysis**
Pairwise meta-analyses were done under the random-effects model when two or more studies investigated the same predefined research question with the same laboratory test. We extracted the sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratio (DOR) values for CEUS and SWE compared to histopathology as a reference standard. The DOR is calculated as \[(TP \times TN)/(FP \times FN)\] and defined as the odds of having a positive test result in a patient with disease compared with the odds of a positive test result in a patient without disease. Moreover, summary receiver operating characteristic (SROC) curves were constructed to examine diagnostic accuracy. All statistics were reported as absolute values with their 95% confidence interval (95% CI). A \(p\)-value < 0.05 was considered statistically significant. The Chi-square and I-square statistics were calculated in order to assess heterogeneity. Significant heterogeneity was considered to be present if the chi-square \(p\)-value was < 0.1 (as per the Cochrane Handbook for Systematic Reviews of Intervention). Data were presented into five subgroups according to cancer site: breast, liver, thyroid, kidneys, and prostate. Network meta-analyses were conducted to compare the diagnostic accuracy of CEUS vs. SWE in malignancy detection. Heterogeneity and inconsistency were checked by the \(I^2\) and the corresponding \(p\)-value. All statistical analyses were conducted on MetaDiSc (version 1.4) and R software (version 3.4.3).

**RESULTS**

**Literature Search and Study Characteristics**
Database search retrieved 5896 unique citations. Following title and abstract screening, 422 full-text articles were retrieved for further scrutiny. Finally, 114 diagnostic accuracy studies (65 on SWE and 50 on CEUS; one study by 4 assessed both modalities), reporting data from 15926 patients (5680 for CEUS and 10392 for SWE) were included in our network meta-analysis (Figure 1, Bibliographic details in Supplementary File II). According to
| References        | Country     | Study design  | Patients/Lesions (N) | Age (Years) | Male: Female | Organ     | Condition                               | Reference test/Gold standard | SWE parameters | Cutoff value (Kpa) | US system                      |
|-------------------|-------------|---------------|----------------------|-------------|--------------|-----------|-----------------------------------------|-------------------------------|----------------|-------------------|--------------------------------|
| Li et al. (16)    | China       | Prospective cohort | 276 (296 lesions) | 45.4 ± 14.7 | 100% F      | Breast    | Benign vs. malignant breast masses     | Histopathology               | SWS             | 4.39 m/sec         | S3000 US scanner (Siemens) |
| Yang et al. (17, 18) | China     | Retrospective cohort | 218 (225 lesions) | 45.3 ± 14.6 | 100% F      | Breast    | Benign vs. malignant breast masses     | Histopathology               | Emean           | 36.1 Kpa           | Acuson500 US machine (Toshiba) |
| Elmoneam et al. (13) | Egypt     | Prospective cohort | 63 (63 lesions)    | 34.7 ± 5.9  | 100% F      | Breast    | Benign vs. malignant breast masses     | Histopathology               | Emax            | 106.55 Kpa         | N/A                          |
| Kim et al. (19)   | Korea       | Retrospective cohort | 171 (177 lesions) | 45.17 ± 9.37 | 100% F      | Breast    | Small breast lesions <2cm              | Histopathology               | Emax            | 87.5 Kpa           | Aixplorer system (SuperSonic Imagine) |
| Youk et al. (20)  | Korea       | Prospective cohort | 123 (130 lesions)  | 46.7 ± 11.2 | 100% F      | Breast    | Breast cancer                          | Histopathology               | Emean           | 82.2 Kpa           | Aixplorer ultrasound system  |
| Tang et al. (21)  | China       | Prospective cohort | 98 (133 lesion)    | N/A         | 100% F      | Breast    | Benign vs. malignant breast lesion     | Histopathology Mean SWV      | 3.68 m/s        | Siemens S3000 US scanner |
| Choi et al. (22)  | Korea       | Retrospective cohort | 54 (56 lesions)    | 40.76 ± 68.07 | 100% F      | Breast    | Benign vs. malignant breast lesion     | Histopathology               | Emean           | 44.3 Kpa           | Aixplorer US system (SuperSonic Imagine) |
| Liu et al. (12)   | China       | Prospective cohort | 130 (139 lesions)  | 44.74 ± 14.7 | 100% F      | Breast    | Benign vs. malignant breast lesion     | Histopathology Max SWV       | 5.37 m/s        | Siemens Acuson S3000 ultrasound machine |
| Golatta et al. (23) | Germany  | Prospective cohort | 103 (104 lesions)  | 51 ± 18.56  | 100% F      | Breast    | Benign vs. malignant breast lesion     | Histopathology Mean SWV      | 5.18 m/s        | Siemens Medical Solutions   |
| Youk et al. (24)  | Korea       | Retrospective cohort | 324 (389 lesions)  | 46.0 ± 11.4 | 100% F      | Breast    | Benign vs. malignant breast lesion     | Histopathology Eratio        | 5.14            | Aixplorer US system (SuperSonic Imagine) |
| Ko et al. (25)    | Korea       | Retrospective cohort | 33 (34 lesions)    | 46.4 ± 7.5  | 100% F      | Breast    | Breast Non-mass lesions                | Histopathology Emean         | 41.6 Kpa        | Aixplorer US system (SuperSonic Imagine) |
| Lee et al. (26)   | Korea       | Prospective cohort | 134 (144 lesions)  | 49.1 ± 12.8 | 100% F      | Breast    | Benign vs. malignant breast lesion     | Histopathology Emax          | 147.2 Kpa       | Aixplorer US system (SuperSonic Imagine) |
| Ng et al. (27)    | Malaysia    | Prospective cohort | 152 (159 lesions)  | 52 + 20.5   | 100% F      | Breast    | Benign vs. malignant breast lesion     | Histopathology Emax          | 56.0 Kpa        | Aixplorer ultrasound system (SuperSonic Imagine) |
| Tian et al. (28)  | China       | Retrospective cohort | 210 (210 lesions)  | 43.12 ± 13.34 | 100% F | Breast    | Benign vs. malignant breast lesion     | Histopathology Emax          | 80.8 Kpa        | Aixplorer ultrasound system (SuperSonic Imagine) |

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| References            | Country   | Study design | Patients/Lesions (N) | Age (Years)       | Male: Female | Organ | Condition                                                                 | Reference test/Gold standard | SWE parameters | Cutoff value (Kpa) | US system            |
|-----------------------|-----------|--------------|---------------------|-------------------|-------------|-------|---------------------------------------------------------------------------|-------------------------------|-----------------|-------------------|---------------------|
| Olgun et al. (29)     | Turkey    | Prospective cohort | 109 (115 lesions) | 51 + 17.5         | 0.02:1      | Breast | Benign vs. malignant breast lesion                                       | Histopathology Eratio         |                 | 4.7               | Aixplorer ultrasound system (SuperSonic Imagine) |
| Chang et al. (30)     | Korea     | Prospective cohort | 115 (133 lesions)  | 51.4 + 11.75      | 100% F      | Breast | Benign vs. malignant breast lesion                                       | Histopathology Emean          | 80.7 Kpa        | 6.07              | IU-22 (Phillips OR HDI 5000 sonography unit) |
| Yao et al. (31)       | China     | Prospective cohort | 206 (206 lesions) | 44.6 + 13.3       | 100% F      | Breast | Benign vs. malignant breast lesion                                       | Histopathology Mean SWV       | 4.22 m/s        | 6.7 Kpa           | Acuson S2000 ultrasound system (Siemens)        |
| Lee et al. (26)       | Korea     | Retrospective cohort | 139 (156 lesions)  | 43.54 ± 9.94      | 100% F      | Breast | Solid breast masses                                                      | Histopathology Emax           | 82.3 Kpa        |                  | Aixplorer ultrasound system (SuperSonic Imagine) |
| Seo et al. (32)       | Korea     | Prospective cohort | 37 (45 lesions)   | 47.4 +14.75       | 100% F      | Breast | Benign vs. malignant breast lesion                                       | Histopathology Emean          | 67.8 Kpa        |                  | Aplio 500; Toshiba                                      |
| Au et al. (33)        | Canada    | Prospective cohort | 112 (123 lesions) | 49.2 +10.7        | 100% F      | Breast | Solid breast masses                                                      | Histopathology Eratio         | 3.56            |                  | Aixplorer Multiwave V3, Supersonic Imagine       |
| Chang et al. (34)     | Korea     | Prospective cohort | 129 (150 lesions) | 47.8+8.83         | 100% F      | Breast | Benign vs. malignant solid breast lesions                                | Histopathology Emean          | 80 Kpa          |                  | Aixplorer, SuperSonic Imagine                      |
| Choi et al. (35)      | Korea     | Retrospective cohort | 113 (116 lesions) | 48.4+10           | 100% F      | Breast | Breast non-mass lesions                                                  | Histopathology Emean          | 85.1 Kpa        |                  | Aixplorer, SuperSonic Imagine                      |
| Chung et al. (36)     | Korea     | Retrospective cohort | 71 (79 lesions)   | 48+10.67          | 100% F      | Breast | Breast papillary lesions                                                  | Histopathology Emax           | 62.1 Kpa        |                  | Aixplorer, SuperSonic Imagine                      |
| Choi et al. (22)      | Korea     | Retrospective cohort | 199 (205 lesions) | 51.7 ± 13.3       | 100% F      | Breast | Benign vs. malignant solid breast lesions                                | Histopathology Emean          | 85.8 Kpa        |                  | Aixplorer, SuperSonic Imagine                      |
| Dobruch-Sobczak et al. (37) | Poland | Retrospective cohort | 76 (84 lesions) | 59.9+13           | 100% F      | Breast | Focal breast lesions                                                     | Histopathology Eav.adj.       | 68.5 Kpa        |                  | Aixplorer, SuperSonic Imagine                      |
| Guo et al. (38)       | China     | Prospective cohort | 379 (404 lesions) | N/A               | 100% F      | Breast | Focal breast lesions                                                     | Histopathology SWS            | 3.015 m/s       |                  | Siemens ACUSON S2000                                    |
| Hong et al. (39)      | Korea     | Prospective cohort | 218 (264 lesions) | 46.4+10.5         | 100% F      | Breast | Solid breast masses                                                      | Histopathology Emax           | 44.1 Kpa        |                  | N/A                                             |
| Kim et al. (40)       | China     | Retrospective cohort | 67 (67 lesions)   | 41.5+2.29         | 100% F      | Breast | Fibroadenoma vs. phylloids tumor                                          | Histopathology Emean          | 43.9 Kpa        |                  | Aixplorer, SuperSonic Imagine                      |
| Klotz et al. (41)     | France    | Retrospective cohort | 142 (167 lesions) | 57.7 +11          | 100% F      | Breast | Benign vs. malignant solid breast lesions                                | Histopathology Emax           | 106 Kpa         |                  | Aixplorer, SuperSonic Imagine                      |
| Lee et al. (42)       | Korea     | Retrospective cohort | 139 (140 lesions) | 45.5 + 10.33      | 100% F      | Breast | Complex cystic and solid breast lesions                                  | Histopathology Emax           | 108.5 Kpa       |                  | Aixplorer, SuperSonic Imagine                      |
| Li et al. (16)        | China     | Retrospective cohort | 116 (116 lesions) | 48.56+ 14.4       | 100% F      | Breast | Breast lesions BIRADS IV                                                 | Histopathology SWS            | 3.49 m/s        |                  | Siemens S3000 US machine                            |
| References          | Country | Study design                | Patients/Lesions (N) | Age (Years) | Male: Female | Organ | Condition                                      | Reference test/Gold standard | SWE parameters | Cutoff value (Kpa) | US system              |
|---------------------|---------|-----------------------------|---------------------|-------------|--------------|-------|------------------------------------------------|----------------------------|----------------|-------------------|----------------------|
| Shi et al. (43)     | China   | Prospective cohort          | 251 (279 lesions)   | 45.3 6.11.8 | 100% F       | Breast | Benign vs. malignant solid breast lesions     | Histopathology SD          |                | 8.05 Kpa           | Aixplorer, SuperSonic Imagine |
| Sim et al. (44)     | UK      | Retrospective cohort        | 52 (52 lesions)     | 67          | 100% F       | Breast | IDC                                            | Histopathology Emean       | 50 Kpa          |                   | Aixplorer, SuperSonic Imagine |
| Sim et al. (44)     | UK      | Retrospective cohort        | 52 (52 lesions)     | 67          | 100% F       | Breast | ILG                                            | Histopathology Emean       | 50 Kpa          |                   | Aixplorer, SuperSonic Imagine |
| Wu et al. (45)      | China   | Retrospective cohort        | 192 (209 lesions)   | N/A         | 100% F       | Breast | Benign vs. malignant solid breast lesions     | Histopathology N/A         | N/A             |                   | Siemens ACUSON S2000   |
| Youk et al. (20)    | Korea   | Retrospective               | 78 (79 lesions)     | 45.5 ± 11.6 | 100% F       | Breast | Benign vs. malignant solid breast lesions     | Histopathology Eratio      | 3.7             |                   | Aixplorer, SuperSonic Imagine |
| Zhang et al. (46)   | China   | Prospective cohort          | 97 (98 lesions)     | 44.74 ± 14.77 | 100% F | Breast | Small breast lesions ≤ 10 cm                  | Histopathology SWV         | 3.27 m/s        |                   | Siemens ACUSON S2000   |
| Cong et al. (47)    | China   | Prospective cohort          | 315 (326 lesions)   | 44.51 ± 11.8 | 100% F | Breast | Breast masses                                   | Histopathology SD          | 13.75           |                   | Aixplorer, SuperSonic Imagine |
| Park et al. (48, 49)| Korea   | Retrospective cohort        | 133 (156 lesions)   | 47.8 ± 12.7 | 100% F | Breast | Palpable breast masses                         | Histopathology Emax or periodic imaging surveillance |                |                   | Aixplorer, SuperSonic Imagine |
| Wang et al. (50)    | China   | Retrospective cohort        | 63 (67 lesions)     | 40.1 ± 21.2 | 100% F | Breast | Non-mass breast lesions                        | Histopathology Emax        | 81.07 Kpa        |                   | iU22 Philips           |
| Kasai et al. (51)   | Japan   | Prospective cohort          | 273 patients with chronic liver disease | 59.64 ± 14.40 | 70.98 ± 9.33 | 1:01 | Liver | HCC | Histopathology Young's Modulus | N/A | Aixplorer US system (SuperSonic Imagine S.A.) |
| Gerber et al. (52)  | Germany | Prospective cohort          | 106 (106 lesions)   | 55.5+16.74 | 3.8:1 | Liver | Characterization of solid HFLs | Histopathology and CE imaging for benign lesions | Emedian | 37.6 Kpa | Aixplorer ultrasound system (SuperSonic Imagine) |
| Özmen et al. (53)   | Turkey  | Prospective cohort          | 20 (20 lesions)     | 4.74+4     | 2.3:1 | Liver | Hemangiomata vs. malignant liver lesions | Histopathology Emean       | 23.62 Kpa        |                   | Aixplorer ultrasound system (SuperSonic Imagine) |
| Tian et al. (54)    | China   | Prospective cohort          | 221 (229 lesions)   | 48.9 ± 13.2 | 2.4:1 | Liver | Benign vs. malignant HFLs | Histopathology Emax       | 39.6 Kpa         |                   | Aixplorer, SuperSonic Imagine |
| Ahmad et al. (55)   | UK      | Prospective cohort          | 50 (1 with PSA> 20) | 69          | 100% M | Prostate | Prostate cancer | Histopathology | Shear wave velocity and Young's modulus | N/A | Aixplorer, SuperSonic Imagine |

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| References          | Country        | Study design | Patients/Lesions (N) | Age (Years) | Male: Female | Organ          | Condition           | Reference test/Gold standard | SWE parameters | Cutoff value (Kpa) | US system                  |
|---------------------|----------------|--------------|---------------------|-------------|--------------|----------------|---------------------|-----------------------------|----------------|-------------------|-----------------------------|
| Boehm et al. (56)   | Germany        | Prospective cohort | 60 patients with suspected prostate cancer | N/A         | 100% M       | Prostate       | Prostate cancer     | histopathology             | Young's Modulus | 50 Kpa            | TRUS Aixplorer             |
| Porsch et al. (57)  | Germany        | Prospective cohort | 69 (794 samples)    | 65+8        | 100% M       | Prostate       | Prostate cancer     | Histopathology             | Young's Modulus | 48 Kpa            | SuperSonic Imagine Ultrasound System AIXPLORER |
| Woo et al. (58)     | Korea          | Prospective cohort | 87 (87 lesions)     | 66 ± 9.0    | 100% M       | Prostate       | Prostate cancer     | Histopathology             | Young's Modulus | 43.9 Kpa          | SuperSonic Imagine             |
| Correas et al. (59) | France         | Prospective cohort | 184 (1040 samples)  | 65.1 6.7.6  | 100% M       | Prostate       | Prostate cancer     | Histopathology             | Young's Modulus | 35 Kpa            | SuperSonic Imagine             |
| Glybochko et al. (60)| Russia        | Prospective cohort | 302 (134 with suspected PC, 120 with confirmed PC and 48 healthy men) | N/A         | 100% M       | Prostate       | Prostate cancer     | Histopathology             | Young's Modulus | 50 Kpa            | Super Sonic Imagine             |
| Zhang et al. (61, 62)| China         | Prospective cohort | 59 (71 lesions)     | 50.5 ± 9.1  | 0.4:1        | Thyroid        | Benign vs. malignant thyroid nodules <10mm | Histopathology             | Shear wave velocity | 2.910 m/s | Acuson S2000 Siemens VTQ |
| Azzì et al. (63)    | USA            | Prospective cohort | 676 (707 lesions)   | 51.2+15     | 0.2:1        | Thyroid        | Thyroid cancer      | Histopathology             | Shear wave velocity | 3.54 m/s | Virtual Touch IQ Software on the Siemens ACU-SON S3000 US |
| Liu et al. (12)     | China          | Prospective cohort | 271 (331 lesions)   | 45.9 ± 13.4 | 0.32         | Thyroid        | Malignant thyroid node | Histopathology             | SHE mean | 39.3 Kpa          | SuperSonic Imagine             |
| Wang et al. (64)    | China          | Prospective cohort | 322 (322 nodules)   | 50.5 ± 12.6 | 0.3:1        | Thyroid        | Malignant thyroid node | Histopathology             | Elastic modulous and SWS | 3.52 m/s | Aplio500, Toshiba Medical Systems |
| Duan et al. (65)    | China          | Prospective cohort | 118 (137 lesions)   | 45.9 ± 13.4 | 0.6:1        | Thyroid        | Malignant thyroid node | Histopathology             | SHE mean | 34.5               | Aplio; Supersonic Imagine |
| Liu et al. (66)     | China          | Prospective cohort | 238 (254 lesions)   | 50.9 ± 11.9 | 0.3:1        | Thyroid        | Malignant thyroid node | Histopathology             | SWS       | 2.78 m/s          | N/A                                  |
| Liu et al. (67)     | China          | Retrospective cohort | 227 (313 lesions)   | 46.14 ± 9.70 | 0.2:1        | Thyroid        | Malignant thyroid node | Histopathology             | Emax       | 51.95 Kpa         | N/A                                  |
| Kim et al. (68)     | Korea          | Retrospective cohort | 99 (99 lesions)     | 45.7+13     | N/A          | Thyroid        | Malignant thyroid node | Histopathology             | Emean     | 62 Kpa            | Aplio US system (SuperSonic Imagine) |
| Deng et al. (69)    | China          | Prospective cohort | 146 (175 nodules)   | 46.36 ± 12.5 | 0.4:1        | Thyroid        | Malignant thyroid node | Histopathology             | SWS       | 2.59 m/s          | Siemens Acuson S2000 US machine |
| Baig et al. (70)    | China          | Prospective cohort | 122 (163 nodules)   | 53 ± 13.7   | 0.2:1        | Thyroid        | Malignant thyroid node | Histopathology             | Emax       | 67.3 Kpa          | Aplio, Supersonic Imagine |
| Dobrusch-Sobczak et al. (71) | Poland     | Prospective cohort | 119 (169 lesions)   | 49.2+14     | 0.3:1        | Thyroid        | Characterization of thyroid nodules | Histopathology | Emean     | 30.5 Kpa          | Aplio, SuperSonic Imagine |

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the QUADAS score, 25 (21.5%), 30 (25.8%), 22 (18.9%), 23 (19.8%), and 16 (13.8%) studies scored 10, 11, 12, 13, and 14, respectively. The baseline data of enrolled participants, as well as the characteristics of the used US systems for SWE and CEUS tests are illustrated in Tables 1, 2, respectively.

### Outcomes of Pair-Wise Meta-Analysis

#### Breast Cancer

Detailed figures for pairwise meta-analysis in all five organs are illustrated in Supplementary File III. The pooled sensitivity, specificity, positive LR, and negative LR for CEUS in detection of breast malignant lesions were 0.89 (95% CI, 0.85, 0.92), 0.85 (95% CI, 0.81, 0.89), 6.13 (95% CI, 4.70, 8.01), and 0.12 (95% CI, 0.07, 0.21), respectively. The pooled DOR was 49.66 (95% CI, 29.42, 83.82) and the area under the receiving-operating characteristic (AUROC) curve was 0.92, Figure 2A. No heterogeneity was observed for sensitivity (p = 0.15) or specificity (p = 0.95).

For SWE, the pooled sensitivity, specificity, positive LR, and negative LR were 0.84 (95% CI, 0.83, 0.86), 0.86 (95% CI, 0.85, 0.87), 7.12 (95% CI, 5.54, 9.15), and 0.18 (95% CI, 0.15, 0.22), respectively. The pooled DOR was 46.22 (95% CI, 31.33, 68.18) with an AUROC of 0.93, Figure 2B. Significant heterogeneity was observed for sensitivity (p < 0.0001) and specificity (p < 0.0001).

#### Hepatic Cancer

The pooled sensitivity, specificity, positive LR, and negative LR for CEUS in differentiating malignant hepatic lesions were 0.78 (95% CI, 0.76, 0.81), 0.89 (95% CI, 0.87, 0.91), 6.51 (95% CI, 3.90, 10.85), and 0.13 (95% CI, 0.06, 0.25), respectively. The overall DOR was 57.94 (95% CI, 24.78, 135.45) with an AUROC of 0.95, Figure 3A. The included studies were heterogeneous in the estimates of sensitivity (p < 0.0001) and specificity (p < 0.0001).

For SWE, the pooled sensitivity, specificity, positive LR, and negative LR were 0.82 (95% CI, 0.77, 0.87), 0.83 (95% CI, 0.76, 0.89), 4.30 (95% CI, 2.85, 6.48), and 0.29 (95% CI, 0.12, 0.71), respectively. The overall DOR was 14.46 (95% CI, 4.09, 51.04) with an AUROC of 0.90, Figure 3B. The included studies were heterogeneous in the estimates of sensitivity (p < 0.0009) and specificity (p < 0.0001).

#### Thyroid Cancer

The pooled sensitivity, specificity, positive LR, and negative LR for CEUS in detecting malignant thyroid nodules were 0.81 (95% CI, 0.78, 0.84), 0.88 (95% CI, 0.86, 0.90), 6.01 (95% CI, 3.88, 9.31), and 0.23 (95% CI, 0.17, 0.31), respectively. The overall DOR was 28.54 (95% CI, 16.79, 48.51) with an AUROC of 0.91, Figure 4A. Significant heterogeneity was observed for sensitivity (p = 0.001) and specificity (p < 0.0001).

For SWE, the pooled sensitivity, specificity, positive LR, and negative LR were 0.67 (95% CI, 0.64, 0.69), 0.77 (95% CI, 0.76, 0.79), 3.50 (95% CI, 2.93, 4.18), and 0.33 (95% CI, 0.25, 0.45), respectively. The overall DOR was 11.17 (95% CI, 8.04, 15.51) with an AUROC of 0.84, Figure 4B. Significant
### TABLE 2 | Baseline characteristics of enrolled patients and criteria of the used CEUS system.

| References | Country | Study design | Organ | Condition | Patients/ Lesions (N) | Age (Years) Mean ± SD | Male: Female | Contrast agent | Reference test | US technique | Mechanical index | Probe |
|------------|---------|--------------|-------|-----------|----------------------|------------------------|--------------|---------------|---------------|--------------|-----------------|-------|
| Bertolotto et al. (5) | Italy | Retrospective | Kidney | Indeterminate renal masses with equivocal enhancement on CT | 47 (30 HP) | 65 ± 13 | 4.75:1 | 2.4 mL SonoVue | Histopathology | Pulse inversion harmonic imaging Cadence contrast pulse sequencing | 0.05-0.21 | Convex array (C5–1) & (4C1) & (C5–2 HDI) & (CA430E) |
| Cai et al. (77) | China | Prospective cohort | Kidney | Benign vs. malignant renal masses | 73 (73 lesions) | 56.36 ± 12.2 | 1.6:1 | 1.0–1.8 mL SonoVue | Histopathology and follow up data | Acuson Sequoia 512, Siemens, | 0.21–0.23 | 4C1-S convex probe 1–4 MHz |
| Chang et al. (30) | USA | Prospective cohort | Kidney | Renal solid and cystic lesions | 44 (23 HP lesions) | 56 ± 14 | 0.7:1 | Sonazoid | Histopathology and follow up data | Siemens Acuson Sequoia 512 | 0.19 | 4C1 abdominal transducer |
| Chen et al. (78, 79) | China | Prospective cohort | Kidney | RCC vs. AML | 99 (102 lesions) | 56.6 ± 16.5 | 2:01 | 1.2 mL of SonoVue | Histopathology | Acuson S2000 (contrast pulse sequencing) | N/A | N/A |
| Chen et al. (90) | China | Prospective cohort | Kidney | Complex cystic renal masses | 59 (71 lesions) | 49.6 ± 14.25 | 2.9:1 | 2.4 mL of SonoVue | Histopathology and follow up data | Coded phase inversion harmonic imaging (Logiq 9 scanner GE Healthcare) | 0.07–0.10 | 3.5C (2.5–5.0 MHz) and 4C (1.0–4.0 MHz) convex transducers |
| Defortescu et al. (81) | France | Prospective cohort | Kidney | Complex renal cysts | 47 (47 lesions) | 46 ± 9.75 | 1:8:1 | 1.2 mL SonoVue | Histopathology and follow up data | Acuson S2000-Siemens – 10 | 0.06-0.1 | Convex probe 3-4.5 MHz |
| Li et al. (16) | China | Retrospective | Kidney | RCC vs. AML | 411 (429 lesions) | 54.12 ± 12.57 | 1.9:1 | 1.2 mL SonoVue | Histopathology | E9 system (GE Healthcare) | 0.11 | C1-5, 1-5 MHz |
| Li et al. (82) | China | Retrospective | Kidney | Solid Renal Masses | 91 (100 lesions) | 62.0 ± 15.6 | 2.6:1 | 1.0–1.2 mL SonoVue | Histopathology | Acuson Sequoia 512 scanner | <0.2 | 4V1 vector transducer, 1-4 MHz |
| Lu et al. (83) | China | Retrospective | Kidney | RCC vs. AML | 189 (189 lesions) | 47.3 ± 20.7 | 1.6:1 | 1.2 mL SonoVue | Histopathology | LOGIC E9 | <0.1 | C1–5, 1.5 MHz |
| Nicolau et al. (64) | Spain | Prospective cohort | Kidney | Indeterminate renal masses by CT | 72 (83 nodules) | 64.9 ± 14.5 | 1.9:1 | 2.4 mL of SonoVue | Histopathology and follow up data | Cadence contrast pulse sequencing technology (CPS) | <0.2 | 4C1 convex array probe |
| Tian et al. (28) | China | Prospective cohort | Kidney | Renal SOL | 367 (373 lesions) | N/A | N/A | 1.2 mL SonoVue | Histopathology | ACUSON S2000 Ultrasound System | N/A | N/A |

(Continued)
| References          | Country | Study design | Organ       | Condition                                  | Patients/ Lesions (N) | Age (Years) | Male: Female | Contrast agent | Reference test | US technique                           | Mechanical index | Probe       |
|---------------------|---------|--------------|-------------|--------------------------------------------|-----------------------|-------------|--------------|----------------|----------------|----------------------------------------|-----------------|-------------|
| Wei et al. (88)     | China   | Retrospective | Kidney      | Benign vs. malignant solid renal masses    | 118 (118 lesions)     | 53.5 ± 12.6 | 1.6:1        | SonoVue        | Histopathology | Contrast pulse sequence, Sequoia 512 ultrasound system (Siemens) | 0.18–0.20       | 4C1, 3–4 MHz |
| Yong et al. (89)    | Singapore | Retrospective | Kidney      | Undetermined renal masses                  | 63 (74 nodules)       | 62.4 ± 14.5 | 1.6:1        | SonoVue        | Histopathology | Apio500, Toshiba Medical Systems AND iU22, Philips Healthcare | N/A             | N/A         |
| Zhang et al. (90)   | China   | Prospective cohort | Kidney      | Benign vs. malignant thyroid nodules       | 148 (157 lesions)     | 45.4 ± 10.5 | N/A          | SonoVue        | Histopathology | Contrast pulse sequence (CPS) imaging, Acuson, Sequoia 512 Encompass | 0.20–0.23       | 15L8w probe (8–14 MHz) |
| Myamoto et al. (91) | Japan   | Prospective cohort | Breast      | Focal breast lesions                      | 127 (127 lesions)     | 48.5 ± 12.3 | 1:1          | SonoVue        | Histopathology | ApioXG, Toshiba AND, 0.1–0.4 Hitachi-Aloka AND Logiq E9, GE | Broadband linear phased-array transducer | 3–9-MHz linear transducer |
| Xia et al. (92)     | China   | Retrospective | Breast      | Papillary breast lesions                  | 50 (52 lesions)       | 51 ±13.57   | 1:1          | SonoVue        | Histopathology | Pulse-inversion harmonic technique with iU22-Philips | 0.06            | 9–3-MHz line transducer |
| Xiao et al. (93)    | China   | Prospective cohort | Breast      | Subcentimeter breast lesions              | 203 (209 lesions)     | 47±15.25    | 1:1          | SonoVue        | Histopathology | Sequoia; Siemens Medical Solutions | N/A             | 10 MHz transducer |
| Yuan et al. (94)    | China   | Prospective cohort | Breast      | Breast tumors                             | 216 (216 lesions)     | 46 ± 12     | 1:1          | SonoVue        | Histopathology | (tissue harmonic grayscale imaging) LOGIQ 7 or E9 US | N/A             | N/A         |
| Aubé et al. (95)    | France  | Prospective cohort | Liver       | Diagnosis of HCC (<3-cm)                  | 381 (54.4 lesions)    | 62 ± 9.69   | 4.6:1        | SonoVue        | Histopathology | LOGIQ E9, GE                                 | N/A             | 1–6 MHz curved probe |
| Beyer et al. (96)   | Germany | Retrospective | Liver       | Benign vs. malignant liver nodules        | 83 (83 lesions)       | 59.8 ±10    | 2.6:1        | SonoVue        | Histopathology | LOGIQ E9, GE                                 | N/A             | D multilrequency (2.5–5 MHz) convex probes |
| Corvino et al. (97) | Italy   | Prospective cohort | Liver       | Cystic and cystlike liver lesions         | 48 (50 lesions)       | 65±15       | 0.9:1        | SonoVue        | Histopathology | MyLab 70 Twice scanner (Esaote) | N/A             | Convex or linear probes with a frequency of 2–5 MHz |
| Feng et al. (98)    | China   | Retrospective | Liver       | HCC differentiation                       | 271 (374 lesions)     | 49.25 ± 17  | 3.9:1.0      | SonoVue        | Histopathology | IU22 system (Philips)               | <0.1            | Convex or linear probes with a frequency of 5–2 MHz convex transducer (CS-2). |
| Iwamoto et al. (99) | Japan   | Retrospective | Liver       | Macroscopic HCC                           | 77 (79 lesions)       | 70 ± 9      | 2.7:1        | SonoVue        | Histopathology | LOGIQ 7 or E9 US | (tissue harmonic grayscale imaging) | 0.2–0.3          | Convex or linear probes with a frequency of 2–5 MHz or 4–9 MHz |

(Continued)
| References     | Country | Study design | Organ | Condition | Patients/Lesions (N) | Age (Years) | Male: Female | Contrast agent | Reference test | US technique | Mechanical index | Probe                  |
|---------------|---------|--------------|-------|-----------|---------------------|-------------|-------------|---------------|----------------|--------------|------------------|-----------------------|
| Kobayashi et al. (100) | Japan | Retrospective | Liver | NS-HCC | 85 (85 lesions) | 66 + 13.75 | 2.9:1 | 0.015 ml/kg Sonazoid | Histopathology | Wide-band pulse-inversion harmonic imaging (HI VISION Ascendus (Hitachi)) | 0.16-0.2 | Microconvex probe (EUP-C715, 3.5 MHz) |
| Kobayashi et al. (101) | Japan | Retrospective | Liver | Liver metastasis | 98 (148 lesions) | 66.46 ± 11.2 | 1.7:1 | 0.0075 ml/kg Sonazoid | Histopathology | SSA 770 A or 790 A US 0.17-0.27 system (Toshiba) | 3.75-MHz convex probe | Convex array probe (frequency: 3.5-5 MHz) |
| Liu et al. (12) | China | Prospective cohort | Liver | Hyperechoic HFL | 102 (135 lesions) | 51.4 ± 12.5 | 2.8:1 | 1.5 mL of SonoVue | Histopathology | GE Logiq9 color Doppler ultrasonography | 0.11 | Convex array 2-4 MHz, 4C1 transducer AND 2-5-MHz broadband curvilinear probe |
| Quaia et al. (102) | Italy | Retrospective | Liver | Benign vs. malignant liver lesions in cirrhotic patients | 46 (55 lesions) | 55 ± 10 | 0.8:1 | 2.4 mL SonoVue | Histopathology | GE Logiq E9 AND Siemens Acuson S2000 AND Toshiba Aplio 500 | N/A | N/A |
| Sandrose et al. (103) | USA | Retrospective | Liver | CT undetermined HFL | 78 (163 lesions) | 61.8 ± 15.25 | 1.1:1 | 1.2 ml bolus of SonoVue | Histopathology and PET/CT followup | Pulse inversion harmonic imaging (GE LOGIQ 9E) | N/A | N/A |
| Schellhaas et al. (104) | Germany | Prospective cohort | Liver | HCC by CEUS and ESCULAP | 100 (100 lesions) | 66.1 ± 7.17 | 5.7:1 | 1.5 ml SonoVue | Histology and imaging | GE Logiq E9 AND Siemens Acuson S2000 AND Toshiba Aplio 500 | N/A | N/A |
| Tada et al. (105) | Japan | Prospective cohort | Liver | Macroscopic HCC 99 (99 lesions) | 67.8 ± 10.4 | 2.7:1 | 0.015 ml/kg Sonazoid | Histopathology | Wideband harmonic imaging (Aplio 501, 2.0–4.0 MHz) | (0.18–0.28) | 5-MHz convex transducer 1.4 and 5.3 MHz |
| Thakur et al. (106) | India | Prospective cohort | Liver | HCC | 50 (50 lesions) | 52 + 14.25 | 1.4:1 | 2.4 ml SonoVue | Histopathology, CT and MRI | Philips iU22, LOGIQ E9, Aplio 500 | N/A | N/A |
| Wang et al. (64) | Germany | Prospective cohort | Liver | Superficial HFL | 27 (27 lesions) | N/A | 2.4:1 | 2.4 ml SonoVue | Histopathology, one patient by MRI | Philips iU22, LOGIQ E9, Aplio 500 | N/A | N/A |
| Wu et al. (107) | China | Prospective cohort | Liver | Focal hepatic lesions | 46 (55 lesions) | 46.5 + 15.2 | 1.2:1 | 2.4 mL dose of SonoVue | Histopathology, OECT and MRI | Philips iU22 US system 0.06 | 3C2 multi-frequency convex probe | N/A |
| Yin et al. (108) | China | Prospective cohort | Liver | Cholangiocarcinoma vs. inflammatory lesions | 40 (40 lesions) | 58.7 + 9.701 | 1.4:1 | 1.5 mL of SonoVue | Histopathology | LOGIQ E9 (GE Healthcare) | <0.1 | C5-1, 2.0-4.0 MHz |
| Zhang et al. (109) | China | Prospective cohort | Liver | Benign vs. malignant liver lesions | 156 (176 lesions) | 50.7 + 16.25 | 1.9:1 | 2.4 mL of SonoVue | Histopathology | Acuson 82000 ultrasound system Siemens | N/A | 4C1 convex array probe; frequency 2.0-4.0 MHz |

(Continued)
| References       | Country     | Study design  | Organ          | Condition                  | Patients/Lesions (N) | Age (Years) Mean ± SD | Male: Female | Contrast agent     | Reference test  | US technique                       | Mechanical index | Probe                          |
|------------------|-------------|---------------|----------------|-----------------|-------------------------|-------------------------|---------------|-------------------|----------------|-----------------------------------|------------------|----------------------------------|
| Takahashi et al. | Japan       | Prospective   | Liver          | HFL < 30 mm     | 56 (67 lesions)         | 65.8 ± 10.1            | 2.5:1         | 0.0075 mL/kg SonoVue | Histopathology | SSA-790A ultrasound system (Aplio) | (0.20–0.25)      | 3.75 MHz convex probe            |
| Taimr et al.     | Canada      | Prospective   | Liver          | Liver metastasis| 89 (89 lesions)        | 31–87                  | 1.6:1         | 1.5–2.4 mL SonoVue | Histopathology | Contrast-tuned imaging Hitachi 900 and Hitachi Premier | N/A              | 2.5–5.0 MHz probe                 |
| Cantisani et al. | Italy       | Prospective   | Thyroid        | Thyroid nodules | 48 (53 lesions)        | 49.4 ± 8.75            | 2.7:1         | 4.8 mL SonoVue    | Histopathology | MyLab 70Avx, Esaote              | N/A              | Linear probe (7–12 MHz) (N:36)   |
| Deng et al.      | China       | Prospective   | Thyroid        | Malignant thyroid nodule | 146 (175 nodules) | 46.36 ± 12.5           | 0.4:1         | 2.4 mL of the SonoVue | Histopathology | Siemens Acuson S2000 US machine | 0.1              | 9L4, 5.0 MHz to 14.0 MHz          |
| Diao et al.      | China       | Prospective   | Thyroid        | Benign vs. malignant thyroid nodules | 77 (87 lesions) | 52.4 ± 17.2            | N/A           | 1.5 mL SonoVue    | Histopathology | Siemens Acuson S2000 US          | 0.06–0.1         | 5- to 14-MHz linear array transducer (9L4) |
| Giusti et al.    | Italy       | Prospective   | Thyroid        | Benign vs. malignant thyroid nodules | 63 (HP in 38 lesions) | 55.9 ± 14.7            | 0.2:1         | 4.8 mL of SonoVue | Histopathology | MyLab 70 US scanner              | N/A              | 7.5-MHz linear probe             |
| Jiang et al.     | China       | Prospective   | Thyroid        | Benign vs. malignant calcified thyroid nodules | 122 (122 nodules) | 46 ± 12                | 0.4:1         | 2.4 mL of the SonoVue | Histopathology | Contrast pulse sequencing (CPS) (ACUSON Sequoia 512) | 0.32             | 15L8w high-frequency linear transducer |
| Wu et al.        | China       | Retrospective | Thyroid        | Benign vs. malignant thyroid nodules | 133 lesions       | 46.3 ± 10              | 0.5:1         | 1.2 mL SonoVue    | Histopathology | ESAOTE MyLab 90 X-vision          | 0.05–0.07        | LA22 (3-9 MHz) linear-array probe |
| Zhang et al.     | China       | Prospective   | Thyroid        | Benign vs. malignant thyroid nodules | 70 (200 lesions) | 49.6 ± 12.8            | 0.3:1         | 2.0 mL SonoVue    | Histopathology | Acuson S2000                   | <0.10            | 9-MHz transducer                  |
| Zhang et al.     | China       | Prospective   | Thyroid        | Benign vs. malignant thyroid nodules | 246 (319 patients) | 46.1 ± 15.2            | 0.5:1         | 2.4 mL SonoVue    | Histopathology | Contrast pulsed sequencing (CPS) Siemens Acuson S2000 | N/A              | L4 transducer                     |
| Zhang et al.     | China       | Prospective   | Thyroid        | Benign vs. malignant thyroid nodules | 111 (145 nodules) | 48 ± 13.45             | 0.2:1         | 1.6 mL SonoVue    | Histopathology | Contrast-tuned imaging N/A Mylab Twice Esaote | LA22 transducer (3–9 MHz) |
| Zhou et al.      | China       | Prospective   | Thyroid        | Benign vs. malignant thyroid nodules | 161 (167 lesions) | 44.14 ± 12.01          | 0.4:1         | 2.4 mL SonoVue    | Histopathology | DC-8EXP; Mindray                   | 0.15             | L12-3E transducer                  |
heterogeneity was observed for sensitivity ($p < 0.0001$) and specificity ($p < 0.0001$).

Renal Cancer
The sensitivity of CEUS ranged from 0.71 to 0.98 with a pooled sensitivity of 0.87 (95% CI, 0.85, 0.88). Specificity ranged from 0.50 to 0.97 with a pooled specificity of 0.84 (95% CI, 0.82, 0.87). The pooled positive and negative LRs were 5.55 (95% CI, 3.74, 8.22) and 0.12 (95% CI, 0.07, 0.19), respectively. The overall DOR was 53.44 (95% CI, 29.89, 95.56) with an AUROC of 0.95, **Figure 5A**. Significant heterogeneity
was observed for sensitivity ($p < 0.0001$) and specificity ($p < 0.0001$).

**Prostate Cancer**

The sensitivity of SWE ranged from 0.42 to 0.96 with a pooled sensitivity of 84% (95% CI, 0.80, 0.87). Specificity ranged from 0.70 to 0.95 with a pooled specificity of 0.84 (95% CI, 0.82, 0.86). The pooled positive and negative LRs were 4.59 (95% CI, 2.68, 7.87) and 0.18 (95% CI, 0.07, 0.44), respectively. The overall DOR was 25.35 (95% CI, 7.15, 89.89) with an AUROC of 0.89 (Figure 5A). Significant heterogeneity was observed for sensitivity ($p < 0.0001$) and specificity ($p < 0.0001$) (Figure 5B).
Table 3 summarizes the diagnostic results for both tests in different cancer sites.

Outcomes of Network Meta-Analysis

Corresponding network plots and forest plots of network meta-analysis between CEUS and SWE are shown in Figure 6. In breast cancer, NMA showed that CEUS was associated with significantly higher DOR than SWE (DOR = 27.14, 95% CI [2.30, 51.97], p = 0.011). While NMA showed no significant difference between CEUS and SWE in detecting hepatic (DOR = −6.67, 95% CI [-15.08, 1.74], p = 0.61) and thyroid malignant lesions (DOR = 3.79, 95% CI [-3.10, 10.68], p = 0.58). No significant heterogeneity or inconsistency were observed between the pooled studies for breast (I² = 10%, p = 0.30) and hepatic cancer (I² = 20%, p = 0.21). While a p-value of 0.05 indicated significant heterogeneity among the studies of thyroid cancer; therefore, the random-effects model was employed.

Ranking Diagnostic Tests

According to Glas et al. (116), the DOR is considered as an indicator of ranking of competing diagnostic tests. According to our results, CEUS achieved the highest DOR in detecting breast and thyroid malignant lesions, while SWE achieved the highest DOR in detecting hepatic malignant lesions.

DISCUSSION

This meta-analysis of DTA studies provides a comprehensive assessment and comparison of the diagnostic accuracy of two US modalities in differentiating malignant tumors in different body organs. It showed relatively high sensitivity (between 78 and 89%) and specificity (between 84 and 89%) for CEUS in identifying malignant lesions in the breast, liver, thyroid and kidneys. Moreover, it demonstrated relatively high sensitivity (between 82 and 84%) and specificity (between 83 and 86%) for SWE in differentiating malignant tumors within the breast, liver

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**TABLE 3 | Summary of the results of pooled sensitivity, specificity, positive, and negative likelihood ratios for SWE and CEUS in different cancers.**

| Cancer             | Test   | Sensitivity (95% CI) | Specificity (95% CI) | +ve LR (95% CI) | -ve LR (95% CI) | DOR (95% CI) | AUROC (95% CI) |
|--------------------|--------|----------------------|----------------------|-----------------|-----------------|--------------|---------------|
| Breast cancer      | SWE    | 0.84 (0.83, 0.86)    | 0.86 (0.85, 0.87)    | 7.12 (5.54, 9.15)| 0.18 (0.15, 0.22)| 46.22 (31.33, 68.18)| 0.93          |
|                    | CEUS   | 0.89 (0.85, 0.92)    | 0.85 (0.81, 0.89)    | 6.13 (4.70, 8.01)| 0.12 (0.07, 0.21)| 49.66 (29.42, 83.82)| 0.92          |
| Hepatic cancer     | SWE    | 0.82 (0.77, 0.87)    | 0.83 (0.76, 0.89)    | 4.30 (2.85, 6.48)| 0.29 (0.12, 0.71)| 14.46 (4.09, 51.04)| 0.90          |
|                    | CEUS   | 0.78 (0.76, 0.81)    | 0.89 (0.87, 0.91)    | 6.51 (3.90, 10.88)| 0.13 (0.06, 0.25)| 57.94 (24.78, 135.45)| 0.95          |
| Thyroid cancer     | SWE    | 0.67 (0.64, 0.69)    | 0.77 (0.76, 0.79)    | 3.50 (2.93, 4.18)| 0.33 (0.25, 0.45)| 11.17 (8.04, 15.51)| 0.84          |
|                    | CEUS   | 0.81 (0.78, 0.84)    | 0.88 (0.86, 0.90)    | 6.01 (3.88, 9.31)| 0.23 (0.17, 0.31)| 28.54 (16.79, 48.51)| 0.91          |
| Renal carcinoma    | CEUS   | 0.87 (0.85, 0.88)    | 0.84 (0.82, 0.87)    | 5.55 (3.74, 8.22)| 0.12 (0.07, 0.19)| 53.44 (29.59, 95.56)| 0.95          |
| Prostate cancer    | SWE    | 84% (0.80, 0.87)     | 0.84 (0.82, 0.86)    | 4.59 (2.68, 7.87)| 0.18 (0.07, 0.44)| 25.35 (9.15, 89.89)| 0.89          |

AUROC, Area under the receiving-operating curve; CEUS, contrast-enhanced ultrasound; DOR, Diagnostic odds ratio; LR, Likelihood ratio; SWE, Shear wave elastography.

**FIGURE 6 | Network plots showing direct evidence between Contrast Enhanced Ultrasound and Shear Weight Elastography in (A) breast cancer, (B) hepatic cancer, and (C) thyroid cancer. Also, forest plots of network meta-analysis between Contrast Enhanced Ultrasound and Shear Weight Elastography vs. histopathology in (A) breast cancer, (B) hepatic cancer, and (C) thyroid cancer. (D) Forest plot CEUS vs. SWE of breast cancer. (E) Forest plot CEUS vs. SWE of hepatic cancer. (F) Forest plot CEUS vs. SWE of thyroid cancer.**

**DISCUSSION**

This meta-analysis of DTA studies provides a comprehensive assessment and comparison of the diagnostic accuracy of two US modalities in differentiating malignant tumors in different body organs. It showed relatively high sensitivity (between 78 and 89%) and specificity (between 84 and 89%) for CEUS in identifying malignant lesions in the breast, liver, thyroid and kidneys. Moreover, it demonstrated relatively high sensitivity (between 82 and 84%) and specificity (between 83 and 86%) for SWE in differentiating malignant tumors within the breast, liver...
and prostate. However, it had relatively lower sensitivity (67%) and specificity (77%) in identifying malignant nodules within the thyroid gland.

Our results support some recent practice guidelines that endorse the use of CEUS and SWE in differentiating malignant lesions within the liver and the breast (117, 118). Moreover, it provides new data on a comparison that can impact the clinical practice. Through NMA, we compared the diagnostic accuracy of CEUS and SWE in three organs (where data on both tests were available in the literature). Our network and ranking analysis showed that CEUS was more accurate than SWE in differentiating breast and thyroid lesions (although the difference was not significant in thyroid malignancy according to NMA). On the other hand, SWE ranked higher in terms of diagnostic accuracy in differentiating hepatic malignant lesions (although the difference was not significant according to NMA).

Our results are in agreement with a former meta-analysis by Sadigh et al. that showed high sensitivity and specificity for SWE in differentiating breast malignant lesions [88 and 83% in comparison to 84 and 86% in our analysis; (11)]. However, our sensitivity and specificity results are quite lower than those obtained by Liu et al. in a meta-analysis on SWE accuracy in differentiating thyroid malignancy [sensitivity 81% and specificity 84%; (12)]. Likewise, another meta-analysis reported high sensitivity and specificity (93 and 90%, respectively) for CEUS in identifying hepatic malignant lesions (119). The observed discrepancy between our findings and those of the aforementioned meta-analyses may be attributed to the different sample size (being larger in our analysis) or the lesional characteristics of enrolled patients (being easier to identify in the studies included in the other meta-analysis i.e., less depth and clear contrast from the surrounding tissue).

Interestingly, a meta-analysis by Guang et al. showed comparable diagnostic accuracy for SonoVue-enhanced US with contrast-enhanced computed tomography and magnetic resonance imaging (8). Moreover, CEUS has other advantages over these modalities as ease of access, lack of radiation exposure or nephrotoxic materials; limitations that affect the use of CT and MRI in several diagnostic applications (120, 121). It is also fair to recognize that both tests have limitations as well. For example, SWE suffers from operator-dependency and manual compression, while the adverse effects of the contrast agent is a concern with CEUS use. Further technical improvements with both modalities would further enhance their clinical potential.

**Strength Points**

This NMA directly compares the diagnostic accuracies of CEUS and SWE in different cancer sites and using different analytic approaches as pairwise, network and ranking pooled analyses. Therefore, it provides a holistic evaluation of the comparison of both techniques in different body organs. We performed a thorough literature search and retrieved a large number of studies (relatively large sample size), which adds to the validity and generalizability of our findings. Unlike former reviews that retrieved a small number of studies and focused on one test in one organ, we aimed to provide a comprehensive assessment of both tests in different organs and a high quality comparison whenever suitable data were provided.

**Limitations and Future Research Implications**

Our meta-analysis has some limitations. First, the observed heterogeneity in the majority of our outcomes may be due to differences in study design and patient characteristics. Second, we could not examine the effects of lesion characteristics, such as size and depth on the diagnostic accuracy of both tests due to lack of data. Third, many of the included studies did not mention whether the results of CEUS or SWE were interpreted with blinding to the findings of histopathology or not. Future studies should report diagnostic accuracy data based on the size and depth of the lesions to allow more detailed analysis. Moreover, they should adhere to the Standards for Reporting of Diagnostic Accuracy “STRAD” checklist in reporting their methods and findings to allow a more thorough critical appraisal.

**CONCLUSION**

Both diagnostic tests (CEUS and SWE) showed relatively high sensitivity and specificity in detecting malignant tumors in different organs; CEUS had higher diagnostic accuracy than SWE in detecting breast and thyroid cancer, while SWE had higher accuracy in detecting hepatic cancer (the differences in the latter two cancer types were not statistically significant). These results endorse the use of both tests for malignancy detection and rank their accuracy in different organs. Future studies should provide more data to allow characterization of both tests in lesions of different size or depth.

**AUTHOR CONTRIBUTIONS**

YS developed the concept, designed the study, and prepared the manuscript. RH acquired the data, controlled quality of the work, analyzed the data, and prepared the manuscript. LJ acquired the data. YX analyzed the data. YG acquired the data. HR acquired the data and conducted the analysis. ZW analyzed the data. YG prepared the manuscript.

**FUNDING**

This work was supported by funding from National Natural Science Foundation of China. Award Number 31300137 received by RH.

**ACKNOWLEDGMENTS**

We are extremely thankful to authors of all the included papers for proving suitable data for analysis.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00102/full#supplementary-material

- Supplementary File I | PRISMA checklist for systematic reviews/meta-analysis.
- Supplementary File II | Bibliographic Information of Included Studies.
- Supplementary File III | Additional Pairwise Meta-analysis Figures.
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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