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Ultrasound-Guided Vacuum-Assisted Breast Biopsy for Breast Intraductal Lesions: a Meta-Analysis of Underestimation and Pathological Nipple Discharge Cure Rates

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ABSTRACT

Background: Breast intraductal lesions present a diagnostic challenge due to the diverse spectrum of histologic changes. Vacuum-assisted biopsy (VAB) has evolved as a pivotal diagnostic and therapeutic modality. Yet, concerns about the underestimation of malignancy using VAB persist. This review examines the underestimation rates of Ultrasound-guided VAB (US-VAB) for intraductal lesions and evaluates the effectiveness of VAB in addressing pathological nipple discharge (PND).

Methods: Following PRISMA guidelines, a comprehensive search was performed across Scopus, PubMed, and Web of Science. Studies detailing the underestimation rates of intraductal breast lesions diagnosed by US-VAB and cure rates for PND post-VAB excision were selected. Statistical analysis comprised a random effects proportion meta-analysis.

Results: In this research, 31 studies were deemed eligible: 26 for underestimation and 5 for PND cure rates post-US-VAB. Quantitative synthesis focused on studies reporting data on atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS) due to limited availability for other pathologies. The pooled underestimation rate for ADH was 6.14% (95% CI: 1.59%-12.43%). The pooled underestimation rate for DCIS was 13.26% (95% CI: 6.69%-21.08%). PND's pooled cure rate post-US-VAB was 93.32% (95% CI: 82.34%-99.70%).

Conclusion: This systematic review and meta-analysis shows that US-VAB delivers low ADH underestimation rates, moderate DCIS underestimation rates, and acceptable PND cure rates in breast intraductal lesions.

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INTRODUCTION

Breast intraductal lesions have gained significant medical attention due to their diagnostic challenges and associated implications. The complexity of these lesions arises from the spectrum of detectable histologic changes, ranging from mild atypia to invasive malignancy.

Within this landscape, vacuum-assisted biopsy (VAB) has emerged as a pivotal diagnostic and therapeutic modality. Offering the advantage of extracting larger tissue volumes than traditional methods like core-needle biopsy (CNB), VAB presents the potential for more accurate diagnosis and the simultaneous benefit of therapeutic excision.[1] While VAB is recognized in sampling breast lesions, inherent concerns about underestimation of malignancy persist. Such underestimations emphasize a histologic stage shifting rather than mere false negatives.[2]

Atypical ductal hyperplasia (ADH), characterized as a "high-risk" or "B3" lesion[3], represents a prominent area of concern. ADH stands both as a precursor to invasive ductal carcinoma (IDC) and an independent risk factor for invasive breast cancer development.[4] The Second International Consensus Conference on B3 lesions advocates the surgical removal of ADH identified via percutaneous biopsy, reserving non-surgical follow-ups for unique cases following comprehensive expert consultations.[5] This recommendation stems from a clinical dilemma balancing two potential risks: undertreatment through follow-up alone versus potential overtreatment via surgical intervention.[5,6] To mitigate these uncertainties, strategies like employing larger needles and diversifying imaging guidance have been explored.[7]

Furthermore, Ductal carcinoma-in situ (DCIS) constitutes a significant proportion of breast cancer diagnoses. The main objective in treating DCIS is invasive breast cancer prevention. However, relying solely on diagnostic techniques, even advanced ones like VAB, surfaces concerns about potential untreated invasive carcinoma.[8]

VAB, while primarily employed for diagnosing intraductal lesions, has also been cited in limited reports for its potential to alleviate specific symptoms, notably pathological nipple discharge (PND).[9] Yet, contradictory research findings suggest that US-guided vacuum-assisted removal of intraductal masses may not consistently eliminate PND, calling for caution when considering it as an alternative to surgical excision.[10] This systematic review and meta-analysis aims to report the underestimation rates associated with US-VAB for intraductal lesions. Furthermore, our study also aims to detail the cure rates experienced by patients with PND post-US-VAB intervention.

METHODS

Search Strategy

To retrieve relevant publications on using US-guided VAB for diagnosing and managing intraductal lesions, we applied a comprehensive systematic search across three primary medical literature databases: Scopus, PubMed, and Web Of Science. The search was conducted in January 2023. For PubMed, our detailed search strategy was delineated as follows:

((((mammotome) OR (vacuum assisted biopsy) OR (vacuum-assisted biopsy) OR (vacuum assisted core biopsy) OR (vacuum biopsy) OR (VAB) OR (VABB) OR (VACB))) AND (("Ultrasonography"[Mesh]) OR "Ultrasonography, Mammary"[Mesh])) AND ((((((((((((intraductal) OR (intraductal breast lesion)) OR (ductal hyperplasia)) OR (usual ductal hyperplasia)) OR (UDH)) OR (atypical ductal hyperplasia)) OR (ADH)) OR (ductal carcinoma in situ)) OR (DCIS)) OR (intraductal papilloma)) OR ("Carcinoma, Intraductal, Noninfiltrating"[Mesh])) OR ("Papilloma, Intraductal"[Mesh]) OR (PND) OR (pathologic nipple discharge) OR (breast discharge) OR (pathologic breast discharge))

Subsequent searches in Scopus and Web Of Science were adapted to suit specific search functionalities of each database. All identified records were exported to the Mendeley Desktop software to manage and remove duplicates.

Selection of studies

After eliminating duplicates, two independent researchers screened the titles and abstracts of the identified studies for potential inclusion. A third author subsequently evaluated their decisions. Disagreements on study inclusion were settled through consensus during a meeting.

Studies deemed eligible met the following criteria: they were original articles detailing the underestimation rates of intraductal breast lesions diagnosed by US-guided VAB. Here, "underestimation" pertained to cases where an intraductal lesion, initially diagnosed with US-VAB, was later re-diagnosed as a more aggressive lesion upon follow-up. We also considered studies that presented cure rates for PND post-VAB excision.

Conversely, studies were excluded if they were unpublished works, conference abstracts, articles not in English, inaccessible full-text papers, or if they focused exclusively on non-intraductal breast lesions, or investigated VAB under modalities other than US.

Data Collection

For the data extraction phase, two independent researchers thoroughly examined the full text of the selected articles to gather specific details. A third researcher subsequently reviewed their collected data. In instances of disagreements, a consensus was achieved through a meeting. Key data extracted encompassed the type of US-VAB device used, pathology and count of lesions per category, cases where US-VAB underdiagnosed lesions, the timing of surgeries (whether immediate or during follow-up), follow-up duration, radiological findings, and, when available, count of patients with PND and those cured post US-VAB. A table was constructed to present these findings qualitatively.

Evaluation of methodological quality

To assess methodological quality in DTA systematic reviews, the Quality Assessment of Diagnostic Accuracy Studies 2 checklist (QUADAS-2) tool is conventionally utilized.[11] This tool is structured with 17 queries spread across four domains: patient selection, risk of bias, and applicability in both the index and reference tests, as well as the study's flow and timing. Each question can be answered with 'yes', 'no', or 'unclear'. Additionally, given the cohort-like observational nature of the included records regarding PND cure rates post-US-VAB, the JBI critical appraisal tool for cohort studies was employed to evaluate the methodological quality of these particular studies.[12]

Statistical analysis

After extracting the reported rates of underestimation and PND cure following US-VAB among the included studies, a random effects proportion meta-analysis was performed to pool the reported rates. The random effects proportion meta-analysis approach was employed due to the significant methodological heterogeneity observed across the studies. Heterogeneity was assessed using the I^2 index.[13] A value of $I^2 > 50\%$ was considered indicative of substantial heterogeneity. Confidence intervals were computed using Wilson's method. The meta-analysis was conducted utilizing the "metaprop_one" module[14], a user-made tool in STATA (Version 17.0, Stata Corp, College Station, TX). We employed the Doi plot to evaluate publication bias in the reported rates, considering its superiority for proportion meta-analysis.[15] The effect sizes displayed in the Doi plot were subjected to Freeman-Tukey transformation[16] using the “metaprop_one” module, and the Doi plot was generated using the “LFK” module in STATA.[17]

RESULTS

Literature search

Figure 1 provides an overview of the study selection process. Following the application of pre-defined search criteria, a comprehensive search yielded 115 records from PubMed, 196 documents from Web of Science, and 349 records from Scopus databases. After removing 244 duplicates, 258 studies were excluded based on predetermined criteria. Full-texts for five articles were unavailable. As a result, a total of 153 articles underwent thorough examination. Among these, 122 articles did not meet the eligibility criteria, leaving us with a final selection of 31 qualifying papers for inclusion in our study. We restricted our quantitative synthesis to studies specifically reporting ADH or DCIS pathology data due to insufficient studies available for other pathologies.

Study characteristics

Our systematic review and meta-analysis included 31 studies that examined the underestimation rate (n=26) or PND cure rate (n=5) following US-VAB for evaluating breast intraductal lesions. Table 1 summarizes the 26 studies reporting the underestimation rates of the intraductal lesions following US-VAB. The studies were conducted in various countries, including South Korea (n=13), USA (n=5), China (n=4), Italy (n=2), Canada (n=1), and Germany (n=1). Of these studies, 19 were retrospective, and 7 were prospective cohorts.

Regarding the US-VAB devices used in the studies, the Mammotome system was the most commonly employed, appearing in 21 studies. Other devices included the ATEC system and the EnCor system. The needle sizes varied among the studies, with 11G and 8G being the most frequently used. The intraductal lesions under investigation encompassed a range of pathologies, including ADH, DCIS, intraductal papillomas (IP), and usual ductal hyperplasia (UDH). Among the included studies, the most common lesion type evaluated was ADH, appearing in 18 studies, followed by DCIS in 14. The timing of surgery varied among the included studies.

In some cases, surgery was performed at follow-up evaluations ranging from a few months to years following the US-VAB procedure. Immediate surgery after US-VAB was also performed in certain studies. The radiologic findings reported in the studies, including the BI-RADS characteristics and the presence of calcifications, are summarized in Table 1.

Table 2 summarizes the five studies reporting the PND cure rates following the US-VAB procedure. These studies were conducted in various countries. Among them, 4 were retrospective cohorts, while one was prospective. The Mammotome system was the US-VAB device used in these studies. Additional information on the pathology of the included lesions and the follow-up duration can be found in Table 2.

Publication bias

To assess publication bias, we utilized the Doi plot asymmetry test evaluated by the LFK index, which revealed no asymmetry across the studies on underestimation rates of ADH (LFK index= -0.56, Figure 2) and a minor asymmetry across the studies

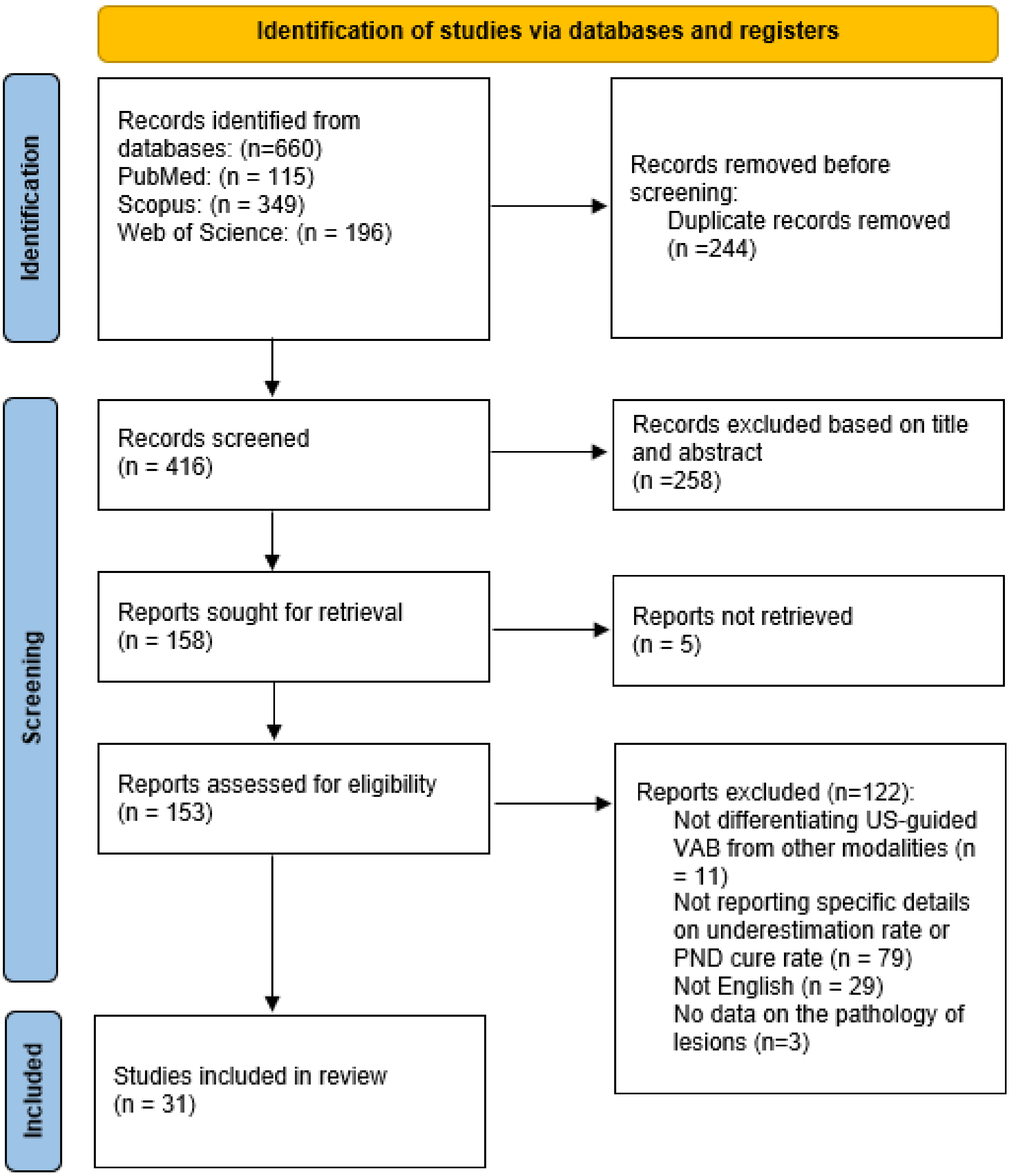

Figure 1. PRISMA flowchart showing the review process
N: number, PND: pathologic nipple discharge, PRISMA: preferred reporting items for systematic reviews and meta-analyses, VAB: vacuum-assisted biopsy, US: ultrasound

on underestimation rates of DCIS (LFK index= -1.66, Figure 3).Regarding the PND cure rate studies, no asymmetry was observed (LFK index= -0.61, Figure 4).

Quality assessment

The quality assessment of the included studies reporting underestimation was conducted using the QUADAS-2 checklist, as presented in Supplementary Table 1 and Supplementary Figure 1. In summary, the included studies raised notable concerns about the risk of bias, particularly in the domains of the "reference standard," "flow and timing," and "index test." These concerns may be attributed to variations in institutional guidelines regarding the management and follow-up of breast lesions.

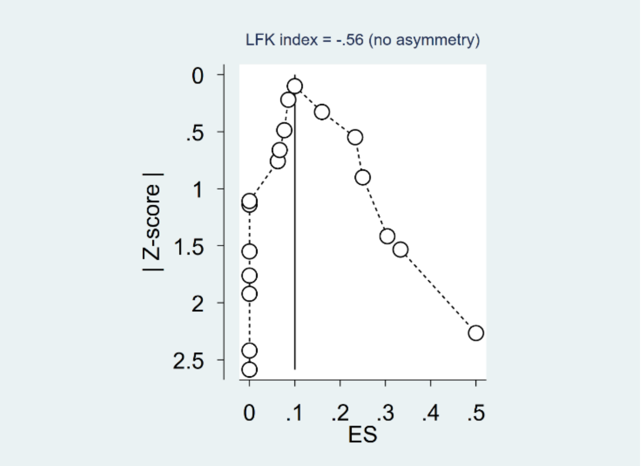

Figure 2. Doi plot asymmetry test for publication bias assessment for studies reporting underestimation rates of ADH lesions following US-VAB.
ES: effect size

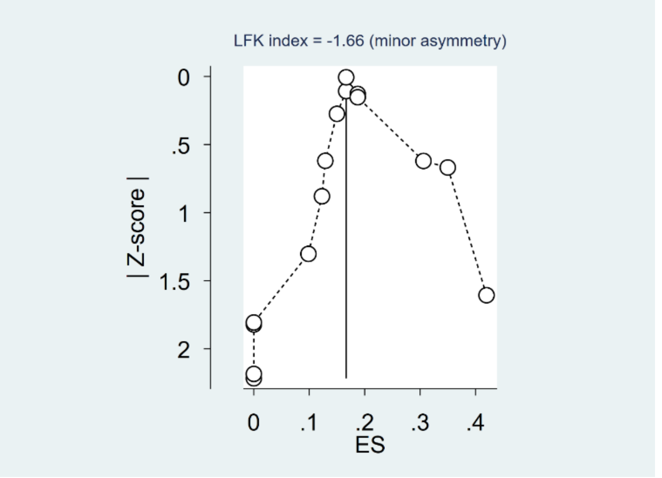

Figure 3. Doi plot asymmetry test for publication bias assessment for studies reporting underestimation rates of DCIS lesions following US-VAB.
ES: effect size

Table 1. Summary of the studies reporting underestimation rates of US-VAB procedure **(**to be continued**)**

Author, Year	Country	Study design	US-VAB device	Intraductal lesions (N)	Underestimated (N)	Timing of surgery	F/U duration (mo)	Radiologic findings
Wang, 2018 (32)	China	Prospective cohort	7G EnCor system (EnCor MR, SenoRx)	IP (83) ADH (16)	IP (0) ADH (1)	F/U	61.26 ± 50.25 (Mean; SD) (R: 14-72)	BI-RADS characteristics (%): 3: (72.2), 4a: (17.8), 4b: (5) Calcification : 12.9%
Kim, 2020 (31)	South Korea	Retrospective cohort	Mammotome; Ethicon Endo-Surgery, Inc, Cincinnati, OH, with an 11G or 8G needle or the ATEC; Hologic, Inc, Bedford, Massachusetts system with a 9G needle	ADH (50)	ADH (8)	F/U	52.1 (Mean), (R: 18-84)	BI-RADS characteristics (%): 4b/ 4c/ 5: (28), 3/4a: (72) Calcification: 38%
Vargas, 2006 (33)	USA	Prospective cohort	Mammotome; Ethicon Endosurgery, Cincinnati, OH, with an 11G or 8G vacuum-assisted core device	ADH (3)	ADH (0)	F/U	12 (Median)	Benign clinical mammographic/ultrasound characteristics (N/S)
Quinn-Laurin, 2017 (25)	Canada	Retrospective cohort	ATEC 9G system (Hologic, Inc., Bedford, MA, USA) or Encor 7G or 10G system (Bard Biopsy Systems, Tempe, AZ, USA)	IP (42) UDH (22)	IP (0) UDH (0)	F/U	34.9 (Mean), (R: 24 - 99)	BIRADS 4 (100%), Complex cysts
Hahn, 2011 (34)	South Korea	Retrospective cohort	Mammotome; Biopsys/Ethicon Endo-Surgery, Cincinnati, OH, USA, with an 11G probe	ADH (2) DCIS (17)	ADH (1) DCIS (0)	Immediate	At least 12	BI-RADS characteristics (%): 3: (22), 4a: (47), 4b: (19), 4c: (11), 5: (1)
Li, 2020 (19)	China	Retrospective cohort	Mammotome; Devicor Medical Products, Cincinnati, USA, with 8G vacuum-assisted biopsy needle	IP (16) ADH (15)	IP (1) ADH (1)	Immediate	38 (Mean), (R: 6 - 53)	BI-RADS characteristics (%): 2: (10.6), 3: (23.5), 4a: (54.2), 4b: (8.2), 4c: (3.5)

Table 1. Summary of the studies reporting underestimation rates of US-VAB procedure(continued)

Giradi, 2021 (35)	Italy	Retrospective cohort	Vacuum suction device; FINESSE ULTRA Breast Biopsy System, Bard Biopsy, Tempe, AZ, USA with 14G needle	IP (38) ADH (35)	IP (1) ADH (3)	Immediate	At least 24	BIRDS 3 (100%)
Timple, 2015 (36)	Germany	Retrospective cohort	9G (N/S)	IP (9) ADH (23) DCIS (71)	IP (1) ADH (7) DCIS (7)	F/U	N/S	BI-RADS characteristics (%): 2: (0.8), 3: (28.5), 4: (1.7), 5a: (59.7), 5b: (9.2)
Park, 2022 (37)	South Korea	Retrospective cohort	Mammotome; Devicor Endo-Surgery, Cincinnati, OH, USA; Suros, Hologic Inc. Bedford, MA, USA with an 8–11G needle	ADH (13)	ADH (1)	F/U	At least 48	BI-RADS characteristics (%): 3: (9.9), 4a: (57.7), 4b: (26.8), 4c: (5.6) Mammographic calcification: 64.1 %
Sheng, 2020 (38)	China	Retrospective cohort	Mammotome Elite Biopsy Device with a 10G needle	DCIS (50)	DCIS (21)	Immediate	N/A	N/S
Lee, 2014 (39)	South Korea	Retrospective cohort	Mammotome, EthiconEndosurgery, Cincinnati, OH, USA, with an 8G or 11G probe	ADH (30) DCIS (122)	ADH (7) DCIS (15)	Both	At least 6	BI-RADS characteristics (%): 1/2: (0.7), 3: (57.9), 4a: (34.6), 4b: (3.4), 4c: (2.7), 5: (0.9) Calcification: 10.6%
Ye, 2013 (40)	China	Retrospective cohort	Mammotome with 11G needle	DCIS (54)	DCIS (9)	Immediate	N/A	Lesion type on mammography (%): Mass (18.4), Microcalcification (65.8) Lesion type on ultrasonography (%): Mass (61.1), Microcalcification (38.9)
Kim, 2011 (41)	South Korea	Retrospective cohort	Mammotome; Biopsys/Ethicon Endo-Surgery, Cincinnati, OH, USA, with an 8G or 11G probe	IP (5) ADH (7)	IP (0) ADH (0)	Both	36 (Median), (R: 24 - 72)	BI-RADS characteristics (%): 3: (31.5), 4: (68.5)
Kim, 2008 (42)	South Korea	Retrospective cohort	Mammotome; Biopsys/Ethicon Endo-Surgery, Cincinnati, OH, USA, with an 8G or 11G probe	ADH (4)	ADH (0)	Both	29 (Mean), (R: 24 - 48)	BI-RADS characteristics (%): 3: (12.8), 4a: (71.8), 4b: (15.4)
Kil, 2008 (43)	South Korea	Retrospective cohort	Mammotome; Ethicon Endosurgery, Cincinnati, OH, USA, with an 11G needle	IP (5)	IP (0)	Immediate	N/A	Microcalcification: 13.2%
Cassano, 2006 (44)	Italy	Prospective cohort	Hand-Held Mammotome; Ethicon Endo-Surgery, Cincinnati, OH, with 11G needle	DCIS (12)	DCIS (2)	Both	32 (Mean), (R: 28 - 42)	BI-RADS characteristics (%): 2: (7.9), 3: (55.2), 4: (34.9), 5: (2) Mammographic calcification: 50.4%

Table 1. Summary of the studies reporting underestimation rates of US-VAB procedure(continued)

Parker, 2001 (45)	USA	Prospective cohort	Hand-Held Mammotome with 11G needle	ADH (3) DCIS (1)	ADH (0) DCIS (0)	Immediate	N/A	BI-RADS characteristics (%): 3: (43.5), 4: (47.6), 5: (8.9)
Cho, 2009 (46)	South Korea	Prospective cohort	Mammotome; Biopsys/Ethicon Endo-Surgery, Cincinnati, OH, USA, with an 11G probe	ADH (4) DCIS (16)	ADH (1) DCIS (3)	Both	N/S	BI-RADS characteristics (%): 3: (2.7), 4a: (56), 4b: (30.7), 4c: (5.3), 5: (5.3)
Bae, 2015 (47)	South Korea	Retrospective cohort	Mammotome; Ethicon Endo-Surgery, Inc, Cincinnati, OH, with an 11G or 8G needle	ADH (2) DCIS (31)	ADH (0) DCIS (4)	Immediate	N/A	BI-RADS characteristics (%): 4a: (50.9), 4b: (27.1), 4c: (17), 5: (5)
March, 2003 (26)	USA	Prospective cohort	Mammotome; Ethicon Endo-Surgery, Cincinnati, OH, USA, with an 11G probe	ADH (1) DCIS (1)	ADH (0) DCIS (0)	Immediate	N/A	Calcification: 8.8%
Graham, 2017 (48)	USA	Prospective cohort	IntactR device (known as the Breast Lesion Excision System)	DCIS (8)	DCIS (0)	Both	66 (Median), (R: 24 - 96)	BI-RADS characteristics (%): 4: (88), 5: (12)
Cho, 2005 (49)	South Korea	Retrospective cohort	Mammotome; Ethicon Endo-Surgery, Cincinnati, OH, USA, with an 11G probe	ADH (10) DCIS (20)	ADH (1) DCIS (7)	Immediate	N/A	BI-RADS characteristics (%): 4a: (18.2), 4b: (54.5), 5: (27.3) Calcification: 36.4 %
Youk, 2012 (27)	South Korea	Retrospective cohort	Mammotome; Ethicon Endosurgery, Cincinnati, OH, with an 11G or 8G probe	ADH (3)	ADH (1)	Immediate	N/A	BI-RADS characteristics (%): 4a: (66.6), 4b: (33.3)
Grady, 2005 (50)	USA	Retrospective cohort	Hand-Held Mammotome Ethicon Endo-Surgery with a 1G or 8G probe	ADH (47)	ADH (6)	Immediate	N/A	BIRDS 3-5 (N/S)
Kim, 2012 (51)	South Korea	Retrospective cohort	Mammotome; Ethicon Endosurgery, Cincinnati, OH, with an 11G or 8G vacuum-assisted device	DCIS (209)	DCIS (64)	Immediate	N/A	BI-RADS characteristics (%): 3: (0.4), 4a: (27.1), 4b: (28.1), 4c: (13.8), 5: (22.3) Mammographic microcalcification : 37.4 %
Suh, 2012 (24)	South Korea	Retrospective cohort	Mammotome; Ethicon Endosurgery, Cincinnati, OH, with an 11G or 8G vacuum-assisted device	DCIS (56)	DCIS (9)	Immediate	N/A	BI-RADS characteristics (%): 3: (3.5), 4a: (28.6), 4b: (16.1), 4c: (30.4), 5: (21.4) Mammographic microcalcification : 76.4 % Ultrasonographic microcalcification : 66.1 %

ADH: atypical ductal hyperplasia, BI-RADS: Breast imaging-reporting and data system, DCIS: ductal carcinoma in situ, F/U: follow-up, G: gauge, IP: intraductal papilloma, mo: months, N/A: not applicable, N/S: not specified, N: number, R: range, SD: standard deviation, UDH: usual ductal hyperplasia, US-VAB: ultrasound-guided vacuum-assisted biopsy

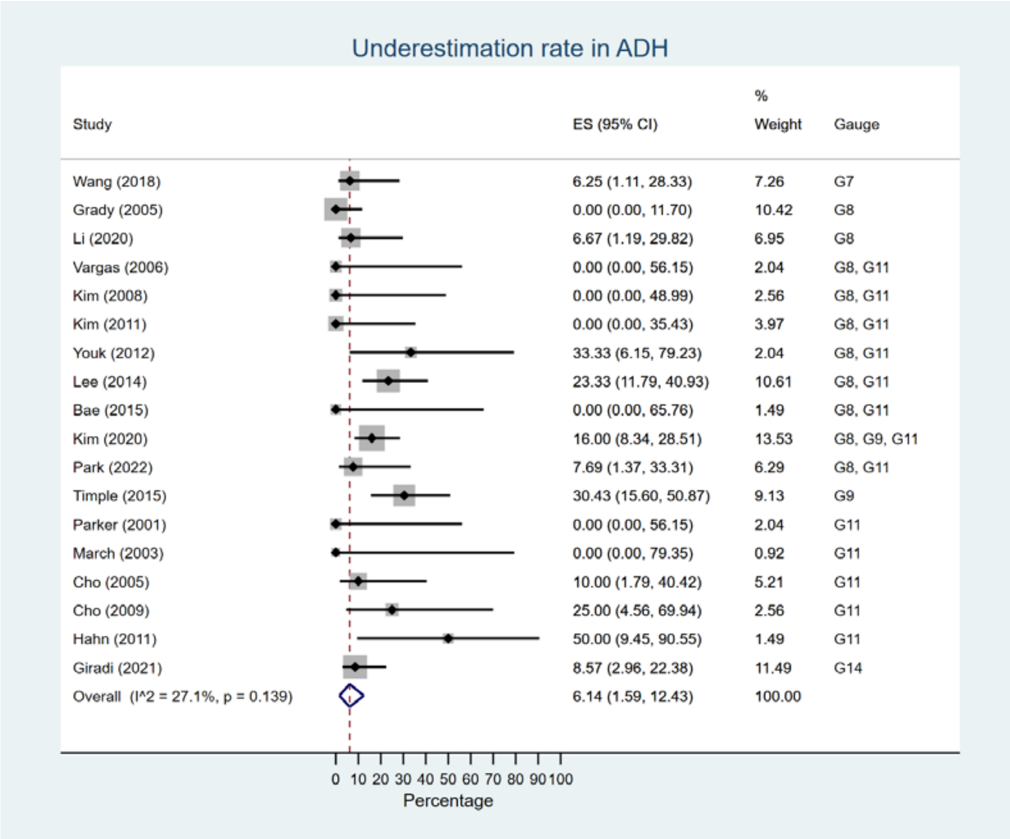

Figure 5. Forest plot of the random effects proportion meta-analysis of the pooled underestimation rates in patients with ADH undergoing US-VAB. CI: confidence interval, ES: effect size, G: gauge

Figure 6 presents the forest plot of the random effects proportion meta-analysis of the pooled underestimation rates in patients with DCIS undergoing US-VAB. According to the included studies, the pooled underestimation rate was 13.26% (95% CI: 6.69%-21.08%). The meta-analysis revealed a moderate to high heterogeneity among the reported rates (I^2=72.2%). Given the significant heterogeneity, a univariate meta-regression analysis was performed to explore the potential impact of the needle gauge. However, this analysis did not explain the observed heterogeneity.

PND cure rate

Figure 7 presents the forest plot of the random effects proportion meta-analysis of the pooled cure rates among patients with PND following US-VAB. According to the included studies, the pooled cure rate was 93.32% (95% CI: 82.34%-99.70%). The meta-analysis revealed a moderate to high heterogeneity among the reported rates (I^2=74.5%).

DISCUSSION

This systematic review and meta-analysis synthesized evidence from 31 studies investigating underestimation rates following US-VAB for breast intraductal lesions and PND cure rates after US-VAB treatment. Our findings suggest that US-VAB is associated with relatively low underestimation rates for ADH diagnoses and moderate underestimation rates for DCIS. Additionally, US-VAB achieved high PND cure rates in patients with breast intraductal lesions.

At present, the most commonly employed biopsy techniques in breast procedures include VAB and CNB.[18,19] VAB offers simplicity, precision, and a lower incidence of complications. As per the available literature, VAB demonstrates a sensitivity ranging from 85% to 97% and a false negative rate within the range of 0% to 9%.[20] Huang *et al.* demonstrated that when compared to CNB, VAB exhibits superior diagnostic performance in terms of DCIS underestimation rates. This improvement is attributed primarily to VAB's capacity to harvest a larger volume of breast tissue.[21]

The assessment of the underestimation rate of vacuum-assisted biopsy and its potential as a substitute for surgical excision has been a focal point of active research, encompassing numerous original and review studies that investigate the underestimation rates and efficacy of these procedures across various types of breast lesions.

Table 2. Summary of the studies reporting PND cure rates following US-VAB procedure

Author, year	Country	Study design	US-VAB device	PND (N)	The cure rate (%)	Pathology	F/U duration (mo)
Dennis, 2000 (9)	USA	Retrospective cohort	Mammotome; Biopsys/Ethicon Endo-Surgery, Cincinnati, OH, USA, with an 11G probe	38	97.37	Papillary lesion	13 (Mean)
Govindarajulu,2006 (29)vvgo	UK	Prospective cohort	Hand-Held Mammotome; Ethicon Endosurgery, Johnson & Johnson Company with an 11G probe	77	94.8	Benign ductal papilloma (n=33), Fibrocystic disease of epithelial hyperplasia of the usual type with ductal dilation (n=19), Chronic inflammatory disease or periductal mastitis (n=24), ADH (n=1), Malignant (n=4)	16 (Mean)
Youk, 2012 (27)	South Korea	Retrospective cohort	Mammotome; Ethicon Endosurgery, Cincinnati, OH, with an 11G or 8G probe	4	100	N/A	32.2 ± 7.4 (Mean± SD), (R: 24 - 49)
Chang, 2009 (10)	South Korea	Retrospective cohort	Mammotome; Ethicon Endosurgery, Cincinnati, OH, with an 11G probe	36	69.44	Cured cases: Fibrocystic change (n=7)/ Papilloma (n=17)/ Fibroadenoma (n=1)	25 (Mean), (R: 13 - 24)
Torres-Tabanera, 2008 (28)	Spain	Retrospective cohort	Mammotome; Biopsys/Ethicon Endo-Surgery, Cincinnati, OH, USA, with an 11G needle	41	95.12	Cured cases: IP (n=30), Dilated duct with papillomatous projections (n=11), Ductal ectasia with no papillary lesion (n=3), Nonspecific benign (n=1)	6 (for all patients)

ADH: atypical ductal hyperplasia, F/U: follow-up, G: gauge, IP: intraductal papilloma, N/A: not applicable, N: number, PND: pathologic nipple discharge, R: range, SD: standard deviation, US-VAB: ultrasound-guided vacuum-assisted biopsy

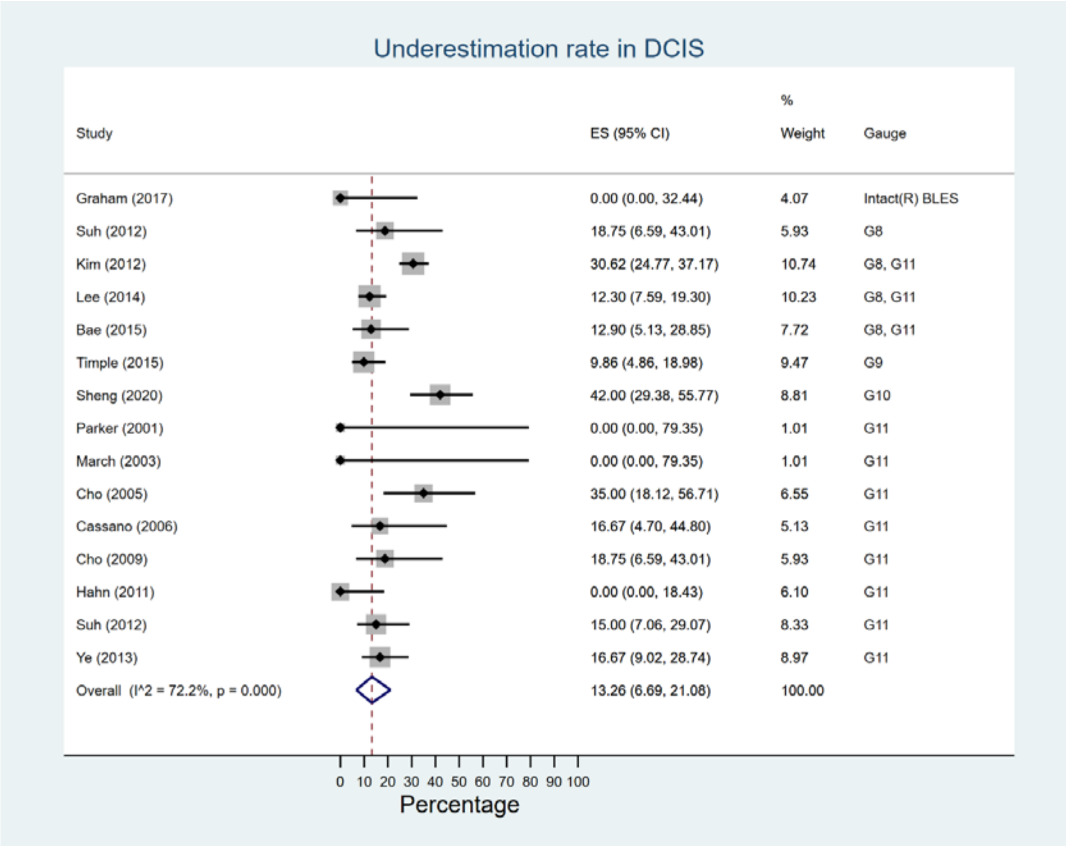

Fig. 6. Forest plot of the random effects proportion meta-analysis of the pooled underestimation rates in patients with DCIS undergoing US-VAB.
CI: confidence interval, ES: effect size, G: gauge

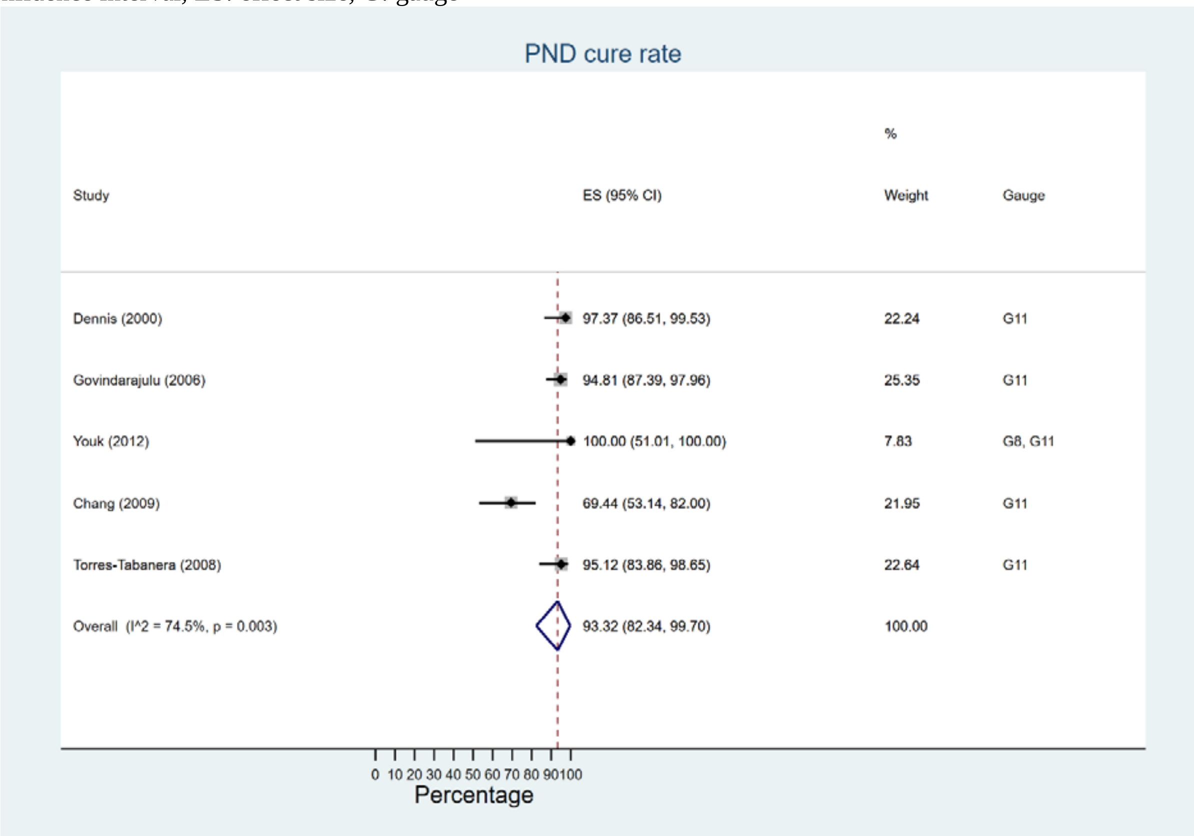

Figure 7. Forest plot of the random effects proportion meta-analysis of the pooled cure rates among patients with PND following US-VAB. CI: confidence interval, ES: effect size, G: gauge, PND: pathologic nipple discharge

The present meta-analysis specifically focused on ultrasound-guided vacuum-assisted breast biopsy (US-VAB) and exclusively on intraductal lesions. In contrast to Lu *et al.*, who noted concerns of underestimation in high-risk lesions identified via VAB, particularly breast DCIS, recommending surgical biopsy for accurate diagnosis[18], our study found a lower pooled underestimation rate of 6.14% for ADH. This is substantially lower than the 20.90% reported by Yu *et al.*[22] Moreover, Huang *et al.* reported lower DCIS underestimation rates of 11.05%[21], which differs from our reported rate of 13.26%. These variations may be attributed to differences in methodology and sample size.

The key distinction of our study lies in its incorporation of newer original studies and its specific focus on ultrasound-assisted biopsy, unlike previous analyses. This inclusion reflects the recent advancements in breast biopsy technology and techniques, which could explain the discrepancies in underestimation rates between our study and earlier research. Additionally, our study's concentration on US-VAB might have allowed for a more detailed and focused analysis of intraductal lesions, contributing to the nuanced understanding of underestimation rates in this context.

Furthermore, while Shen *et al.* emphasized the role of factors such as operator experience and biopsy modalities in influencing outcomes[23], our study did not find needle gauge to be a significant source of heterogeneity. This suggests that other factors, potentially related to the advancements in ultrasound technology and operator proficiency with newer equipment, might play a more pivotal role in the outcomes of US-VAB.

Regarding the biopsy technique, Suh *et al.* discovered that the underestimation rate of invasive carcinoma in cases where DCIS was present during US-guided core biopsies was notably higher with 14-gauge ACNB than with 8- or 11-gauge VAB. This disparity in underestimation rates remains consistent across various lesion types on US. Future research endeavors should consider delving deeper into these aspects.[24]

The consistency between the reported studies highlights the efficacy of US-VAB as a therapeutic approach, allowing breast conservation in appropriate patients. For instance, some surveys used the role of ultrasound-guided vacuum-assisted excision to remove small papilloma and complex cystic lesions with a slight chance of underestimation and recurrence.[19,25] However, March *et al.* evaluated the effects of using a VAB technique to remove all ultrasonographic evidence of breast lesions. The study discovered a substantial probability of remaining lesions that were not seen during the operation following surgery or follow-up imaging. Indeed, heterogeneity among studies was moderate/high in both analyses.[26] As discussed above, differences in lesion characteristics, US-VAB technical factors, and surgical timing likely contributed to the heterogeneity.

The clinical value of our findings is accentuated by its revelation of the nominal underestimation rates associated with US-VAB for intraductal breast lesions, in stark contrast to the higher underestimation rates often linked with CNB. While our analysis could not directly compare US-VAB and CNB, the evidence distinctly suggests that US-VAB holds a substantial advantage in accuracy, a factor critical for optimal clinical decision-making, particularly in treating intraductal lesions.

This interpretation is bolstered by pertinent literature. A meta-analysis by Brennan *et al.* (2011) notably identifies a high underestimation rate of 26% in DCIS diagnosed through CNB, indicating a significant likelihood of failing to detect invasive breast cancer.[27] This is complemented by the findings of Ciatto *et al.* (2007), who elucidate the difficulties in accurately determining malignancy via breast core needle biopsy.[28]

A study by Badan *et al.* (2016) further corroborates this perspective, demonstrating that biopsy techniques involving more extensive removal of the lesion typically exhibit lower underestimation rates.[29] This is a key aspect of US-VAB, which frequently involves significant lesion removal, similar to surgical methods. The criticality of comprehensive lesion excision is further reinforced by Destounis *et al.* (2011), who examined pathological underestimation rates across various gauge sizes of breast needle core biopsies[30], and by Sydnor *et al.* (2007), who found core-needle biopsy underestimating the presence of breast carcinoma in papillary lesions.[31]

In light of these findings, US-VAB emerges as a highly advantageous technique in breast lesion management. Its minimally invasive nature, compatibility with office-based settings, and absence of radiation exposure make it an especially appealing option in an era increasingly focused on patient-centered, minimally invasive treatment approaches.

Another area of interest in the present meta-analysis was the cure rate for PND in patients with intraductal lesions presenting with PND due to its importance in clinical practice. The present study found a PND cure rate of 93.32% following US-VAB treatment of breast intraductal lesions. Several studies showed that the use of US-VAB was associated with the satisfactory treatment of PND without any particular complications.[9,10,32–34] However, among the included studies, the study by Chang *et al.* stands out due to its notably lower cure rate of 69% for PND in patients with single benign intraductal masses presenting with PND.[10] This figure contrasts sharply with the near-complete cure rates documented in other studies, thus positioning Chang *et al.*'s work as a potential outlier in this meta-analysis, which is in line with the visual inspection of the figures of our meta-analysis. The divergence observed in this study's outcomes could be attributed to several factors, including variations in the methods employed for vacuum-assisted biopsy, the distinct pathology of the lesions examined, and a longer follow-up period compared to other studies. This longer follow-up duration raises critical questions about the long-term efficacy of vacuum-assisted excision as an alternative to surgical intervention. Consequently, the observed discrepancy underscores the need for additional research, particularly studies with extended follow-up periods, to thoroughly evaluate the long-term stability of PND cure rates post vacuum-assisted biopsy in patients with PND.

The predominance of the Mammotome system in our reviewed studies underscores its widespread adoption in US-VAB. These findings align with the work of Ding *et al.*, who recognized the Mammotome system for its precision and reduced complication rates.[35] Yet, the presence of other systems, like ATEC and EnCor, suggests that there is room for further comparative studies to discern the optimal strategy for various breast intraductal lesions.

The mentioned attitude is consistent with the findings of Govindarajulu *et al.*, who highlighted the success of the Mammotome system in achieving high PND cure rates. However, the heterogeneity in this result suggests variability across studies, possibly due to different follow-up durations, surgical practices post-US-VAB, or even varying definitions of cure among studies.[34]

Two key factors that may impact US-VAB's performance are the experience level of the radiologist and the specific biopsy system used. The mammotome system was most common among the included studies, particularly the 8G and 11G models. However, some studies employed the EnCor or ATEK system, and no specific system was reported.[25,35,36] Comparisons of different biopsy devices would be informative. Thus, radiologist experience likely contributes to diagnostic accuracy and should be considered in future studies.[23]

Overall, different US-VAB protocols, patient flow, and study designs are considered to be the source of bias in our study. However, publication bias had minimal impact on our meta-analysis results.

Limitations

There are some limitations to this review that should be considered when interpreting the results. First, a significant between-study heterogeneity was detected for the DCIS and PND analyses, which may affect the reliability of these pooled estimates. Subgroup analyses by potential sources of heterogeneity could be explored in future meta-analyses with larger sample sizes. Furthermore, in keeping with the inherent nature of meta-analyses, this study is susceptible to limitations that may introduce bias into the reported effect sizes of the included studies. As elucidated in the quality assessment section, certain concerns arose regarding deviations from optimal methodology within the 31 included studies. These deviations pertained to aspects such as patient selection, study flow, and reference tests, potentially introducing bias that could lead to an overestimation or underestimation of the genuine efficacy of US-VAB in some of the studies. For instance, most studies included were observational designs prone to bias. Quasi-randomized or randomized controlled trials are needed to establish US-VAB's efficacy better. However, randomized studies pose ethical concerns about assigning patients to surgical excision rather than US-VAB. Finally, the quantitative synthesis was restricted to studies reporting data on ADH or DCIS pathology due to insufficient studies for other pathologies.

CONCLUSION

In conclusion, this meta-analysis found that US-VAB is associated with low ADH and moderate DCIS underestimation rates and high PND cure rates for breast intraductal lesions. While further research is necessary to substantiate and expand upon our findings, the present evidence indicates that ultrasound-guided vacuum-assisted biopsy (US-VAB) is a suitable diagnostic and therapeutic modality for most common intraductal breast lesions, characterized by its comparatively low rate of underestimation. Surgical excision is required for only a limited subset of patients. It is crucial, however, to exercise careful patient selection, implement routine screening, and adopt conservative strategies for high-risk individuals to minimize the risk of underestimating malignant conditions. Future high-quality research is imperative, particularly focusing on the determinants of underestimation, the effect of utilization of various devices and operator experience on success rates, and on obtaining extensive long-term follow-up data from a broader patient cohort with intraductal lesions.

CONFLICT OF INTERESTS

The authors declare the absence of any known financial conflicts of interest or personal relationships that could have influenced the work presented in this paper.

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