REVIEW

The diagnostic utility of diffusion-weighted magnetic resonance imaging and high-resolution computed tomography for cholesteatoma: A meta-analysis

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Abstract

Objective: The purpose of this meta-analysis was to compare the efficiency of high-resolution computed tomography (HRCT) and diffusion-weighted magnetic resonance imaging (DWI) in guiding the diagnosis of middle ear cholesteatoma in clinical practice.

Materials and methods: Cochrane Library, Medline, Embase, PubMed, and Web of Science were searched for studies that evaluated the sensitivity and specificity of HRCT or DWI in detecting middle ear cholesteatoma. A random-effects model was used to calculate and summarize the pooled estimates of sensitivity, specificity, and diagnostic odds ratios. Postoperative pathological results were considered as the diagnostic gold standard for middle ear cholesteatoma.

Results: Fourteen published articles (860 patients) met the inclusion criteria. The sensitivity and specificity of DWI when diagnosing cholesteatoma (regardless of type) were 0.88 (95% confidence interval [CI], 0.80–0.93) and 0.93 (95% CI, 0.86–0.97), respectively, while those of HRCT were 0.68 (95% CI, 0.57–0.77) and 0.78 (95% CI, 0.60–0.90), respectively. Notably, the sensitivity and specificity levels of DWI were similar to those of HRCT ($p = .1178$ for sensitivity, $p = .2144$ for specificity; pair-sampled t tests). The sensitivity and specificity of DWI or HRCT for the diagnosis of primary cholesteatoma were 0.78 (95% CI, 0.65–0.88) and 0.84 (95% CI, 0.69–0.93), respectively, while that for recurrent cholesteatoma were 0.93 (95% CI, 0.61–0.99) and 0.94 (95% CI, 0.82–0.98), respectively.

Conclusion: DWI and HRCT have similar levels of high sensitivity and specificity in detecting various cholesteatomas. Also, the diagnostic efficiency of HRCT or DWI for recurrent cholesteatoma is identical to that of primary cholesteatoma. Therefore, HRCT may be used in clinical settings to reduce the use of DWI and save clinical resources.

Lay summary: Data on the use of diffusion-weighted magnetic resonance imaging and high-resolution computed tomography in the diagnosis of cholesteatoma were obtained through a literature search. They were analyzed to guide the clinical diagnosis and treatment of cholesteatoma.

Level of evidence: NA

1 | INTRODUCTION

Middle ear cholesteatoma is a typical benign lesion, which is characterized by the abnormal accumulation of keratin-producing squamous epithelium and keratin fragments in the tympanic cavity and mastoid, with or without a peripheral inflammatory reaction. Chronic discharge from the ear canal, tympanic membrane perforation, and hearing loss are the main clinical symptoms of this disease.[1] As its symptoms are progressive and relatively unnoticeable, the disease can easily be misdiagnosed, which may lead to a delayed treatment and worse prognosis. Therefore, optimizing the appropriate tests is important to obtain an accurate diagnosis. Computed tomography (CT) and magnetic resonance imaging (MRI), especially sequence high-resolution computed tomography (HRCT) and diffusion-weighted magnetic resonance imaging (DWI), are performed to diagnose cholesteatoma, and studies have shown that they have unique advantages. HRCT can highlight ossicular erosion and associated complications, such as tegmental disruption and lateral semicircular canal fistula.[2] Imaging characteristics such as intra-tympanic non-dependent soft tissue density, bone expansion and thinning, and bone erosions involving the ossicles and adjacent structures are regarded as the diagnostic bases of cholesteatoma when using HRCT.[3]

Erosion that was caused by a soft tissue mass or new lumen wall after surgery can be diagnosed as recurrent/residual cholesteatoma.[4] Meanwhile, high intensity on DWI without high intensity and contrast enhancement on T1-weighted images are the characteristics of cholesteatoma in MR images.[5] DWI can demonstrate soft tissue changes more clearly and distinguish cholesteatoma from other nonspecific tissues more efficiently than HRCT; furthermore, HRCT cannot distinguish middle ear cholesteatoma from granulation tissue (including cholesterol granulation and other soft tissue changes).[6,7] However, the reported sensitivity and specificity levels for HRCT and DWI are inconsistent although numerous studies have focused on their imaging characteristics for cholesteatoma diagnosis.

Clinicians simultaneously perform HRCT and DWI examinations when diagnosing cholesteatoma, which is a waste of time, effort, and resources. Therefore, this study presents a meta-analysis of patients with clinical suspicion of cholesteatomas to quantitatively summarize the results of similar, relevant studies and evaluate the diagnostic values of HRCT and DWI in terms of the patients' pathology results.

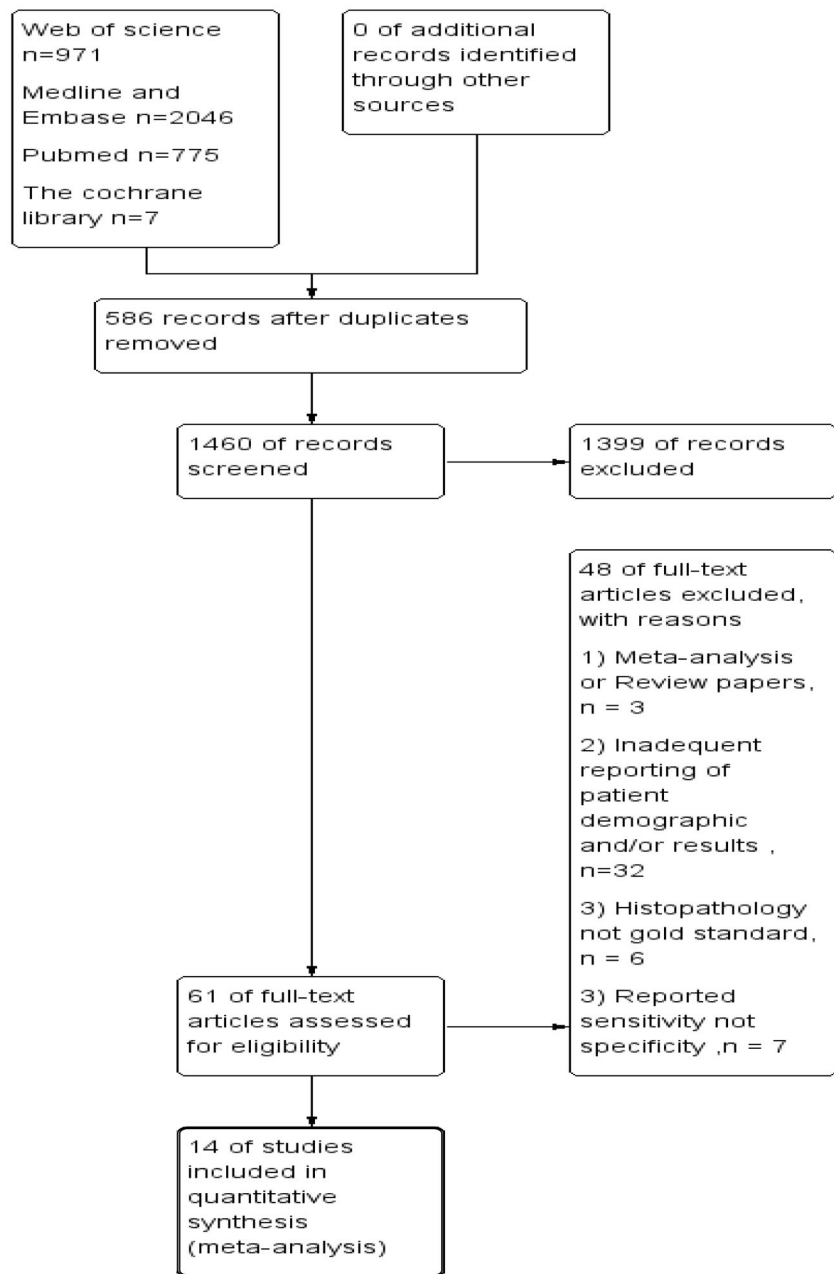## 2 | MATERIALS AND METHODS

The search terms were used: (HRCT OR magnetic resonance imaging OR diffusion magnetic resonance imaging OR diffusion-weighted magnetic resonance imaging OR diffusion-weighted imaging OR diffusion-weighted OR diffusion imaging OR DW-MRI OR diffusion MRI OR DWMRI OR MRI) AND (Cholesteatoma). We searched the Cochrane Library, Medline, Embase, PubMed, and Web of Science. I have included studies whose patients have preoperative HRCT or DWI and are diagnosed with cholesteatoma by results of the pathological examination, and whose diagnostic sensitivity and specificity of cholesteatoma by HRCT or DWI could be calculated. The following data were extracted from the included studies, including patients' information (such as age and gender), study period and interval, cohort definition, type of surgery, and CT and MRI parameters.

This article has conducted a combined analysis based on the type of examination (DWI or HRCT). And specific subgroup analysis was performed between primary cholesteatoma and recurrent cholesteatoma. For the subgroup analysis, relevant data from mixed studies were included if the necessary data were published and valuable for analysis. Sensitivity, specificity, likelihood ratio, and odds ratio were combined by a random effect model and plotted into forest plots. A summary receiver operating characteristic (SROC) curve was drawn. Statistical heterogeneity was expressed by I^2- and Q-statistics. QUADAS-2 guidelines were used to evaluate the quality of included studies, and Deek's Funnel Plot Asymmetry Tests were used to evaluate publication bias visually. Independent-sample t test and pair-sample t test were used to compare the independent and pair groups, respectively. All meta-analyses were performed using STATA16.0 (Stata Corp, College Station, TX). The 95% CI and p values were calculated, and $p < .05$ was considered statistically significant.

3 | RESULTS

The comprehensive search resulted in the identification of 1460 articles after removing duplicates. After the screening of titles and abstracts, 61 full-text articles were assessed for eligibility against the inclusion and exclusion criteria, as shown in Figure 1. Finally, 14 studies met the inclusion criteria for qualitative synthesis and meta-analysis.[3,5,8–18] The majority of studies were prospective observational

FIGURE 1 Literature search disposition.

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Web of science          0 of additional
n=971                   records identified
                        through other
Medline and             sources
Embase n=2046

Pubmed n=775

The cochrane
library n=7
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586 records after duplicates
removed
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1460 of records         1399 of records
screened                excluded
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48 of full-text
articles excluded,
with reasons

1) Meta-analysis
or Review papers,
n = 3

2) Inadequent
reporting of
patient
demographic
and/or results ,
n=32

3) Histopathology
not gold standard,
n = 6

3) Reported
sensitivity not
specificity ,n = 7
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61 of full-text
articles assessed
for eligibility
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14 of studies
included in
quantitative
synthesis
(meta-analysis)
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studies, while some were retrospective. Tables 1 and 2 present the summaries of the 14 articles, outlining the notable characteristics, findings, and performance figures of each included study. The studies were differentiated based on their DWI and HRCT sequences. Ten studies (657 patients) met the criteria for the DWI group, and five studies (203 patients) were categorized into the HRCT group. Five studies involved only first-look surgeries, and four studies involved only second-look surgeries.

The pooled diagnostic parameters for DWI and HRCT are summarized in Table 3. Among the 657 patients who underwent DWI, 396 true-positive (TP), 18 false-positive (FP), 173 true-negative (TN), and 70 false-negative (FN) patients were identified. The overall pooled sensitivity and specificity of DWI were 0.88 (95% CI, 0.80–0.93) and 0.93 (95% CI, 0.86–0.97), respectively. Among the

203 patients who underwent HRCT, 93 TP, 16 FP, 50 TN, and 44 FN patients were identified. Thus, the overall pooled sensitivity and specificity of HRCT were 0.68 (95% CI, 0.57–0.77) and 0.78 (95% CI, 0.60–0.90), respectively. Paired samples t test was conducted with four studies, in which patients underwent both HRCT and DWI. The findings showed that the sensitivity and specificity levels of DWI were similar to those of HRCT ($p = .1178$ for sensitivity, $p = .2144$ for specificity). Figure 2 depicts the forest plots of the sensitivities and specificities of DWI and HRCT separately for detecting all types of cholesteatomas. The SROC area under the curve (AUC) was 0.97 and 0.77 for diagnosing all cholesteatomas using DWI and HRCT, respectively (Figure 3). The AUC reflects the diagnostic accuracy of DWI or HRCT for cholesteatoma. Figure 3 also shows the pooled summary sensitivity and specificity values or accuracy levels as red squares and

TABLE 1 Study designs of the eligible studies.

Reference	Study Period	Study temporal direction	Surgery type	Operation-examination
Ganaha, 2011[8]	January 2006–December 2008	prospective	First- and second-look surgery	Within 3 months
Huins, 2010[9]	April 2008–September 2009	Prospective	First- and second-look surgery	Average of 3 months
Laske, 2018[10]	2011–2016.	Prospective	First- and second-look surgery	NA
Cavaliere, 2014[11]	May 2011–January 2013	Prospective	First-look surgery	Average of 29 days
Songu, 2015[3]	December 2008–February 2013	Prospective	First-look surgery	NA
Fischer, 2019[12]	November 2015–March 2018	Retrospective	First-look surgery	0–169 days
Sharifian, 2012[13]	June 2008–July 2009	Prospective	First- and second-look surgery	Within 4 months
Osman, 2017[14]	May 2015–October 2016	Prospective	Second-look surgery	Within 2–3 weeks
Foti, 2019[5]	February 2017–February 2018	Prospective	Second-look surgery	NA
De Foer B, 2010[15]	July 1, 2005–July 1, 2008	Retrospective	First- and second-look surgery	Within 2 weeks or 2 months
Garcia-Iza L, 2018[16]	January 2012–December 2014	Retrospective	First-look surgery	Average of 6.7 months
Garcia-Iza L, 2018[16]	January 2012–December 2014	Retrospective	Second-look surgery	Average of 8.7 years
Khemani S, 2011[17]	April 2008–September 2010	Prospective	Second-look surgery	Average of 59.5 days
Nash R, 2018[18]	2009–2014	Prospectively	First-look surgery	NA

Abbreviation: NA, not available.

the individual study values as circles. The 95% confidence region, demonstrated by the thick virtual coil, presents a two-dimensional analogy of the 95% CI of the pooled study accuracy based on the data included. The 95% prediction region, which is demonstrated by a thin dashed circle, is larger because it reflects the area in which a future study could fall with a 95% probability.

The pooled sensitivity and specificity of DWI or HRCT for diagnosing primary cholesteatoma were 0.78 (95% CI, 0.65–0.88) and 0.84 (95% CI, 0.69–0.93), respectively. Furthermore, the pooled sensitivity and specificity of DWI or HRCT for diagnosing residual or recurrent cholesteatoma were 0.93 (95% CI, 0.61–0.99) and 0.94 (95% CI, 0.82–0.98), respectively (Table 3). The sensitivity and specificity levels of either method for diagnosing primary cholesteatoma were similar to those for residual or recurrent cholesteatoma ($p = .2413$ for sensitivity, $p = .6815$ for specificity, t tests). Figure 4 shows the forest plots of the sensitivities and specificities for primary or secondary cholesteatoma detection. The SROC AUC was 0.88 for diagnosing primary cholesteatoma and 0.94 for diagnosing secondary cholesteatoma with either method (Figure 5).

Significant heterogeneity across the studies in the reported sensitivity and specificity levels of DWI in identifying cholesteatoma was observed (chi-square, $p < .05$; sensitivity, $I^2 = 77.15$; specificity, $I^2 = 52.52$), but not for the sensitivity and specificity of HRCT (Figure 2). All the 14 studies included in this meta-analysis were assessed according to the QUADAS-2 guidelines. As shown in Figure S1, three studies were of low quality. Furthermore, one study was found to have an unclear risk of bias, and 10 had a low risk of bias. According to the results of Deek's test, there was no publication bias, and the p-values for DWI and HRCT were .46 and .82, respectively (Figure S2).

4 | DISCUSSION

This study was conducted to investigate the diagnostic performance of DWI and HRCT for middle ear cholesteatoma. The meta-analysis showed that both DWI and HRCT are useful diagnostic tools for detecting cholesteatomas, and their diagnostic sensitivity and specificity were identical for various cholesteatomas. Notably, their sensitivity and specificity values when diagnosing patients who underwent second-look operations were similar to those when diagnosing patients who underwent first-look operations. In addition, the patients on whom first-look operations were performed always had primary cholesteatomas, and those on whom second-look operations were performed for residual or recurrent cholesteatomas. Therefore, patients with clinical signs of cholesteatoma recurrence should undergo DWI or HRCT for diagnostic confirmation and, in turn, avoid unnecessary surgery or delayed therapy.

An HRCT scan of the temporal bone serves as a helpful preoperative examination for middle ear cholesteatoma, as it can be used to successfully identify and record the state of the auditory ossicles, location, and extent of the disease, any erosion of the tegmentum or sinus, or a labyrinthine fistula.[6] Due to the inflammatory reaction associated with cholesteatoma, the tympanic and mastoid cavities are often observed to be filled with the soft tissue on CT scans. Therefore, accurate detection of the presence of cholesteatoma, especially recurrent or residual cholesteatoma, is not easy. In addition, since inflamed mastoid gas cells are closely related to facial nerves or soft tissue, the detection value of HRCT for a facial nerve canal rupture is suboptimal.[8] HRCT can show the structure more clearly but does not allow the differentiation between various soft tissues.[2]

In contrast, MRI has advantages in evaluating soft tissue changes and distinguishing cholesteatoma from granulation tissue, cholesterol

TABLE 2 Patient and imaging characteristics in the included studies.

References	DW-MRI Protocol	DW-MRI No. of examinations	DW-MRI Sensitivity (%)	DW-MRI Specificity (%)	HRCT Protocol	HRCT No. of examinations	HRCT Sensitivity (%)	HRCT Specificity (%)	Age (y)	Male proportion (%)
Ganaha, 2011[8]	1.5-T, SE-EPI	73	69.4	92.8	High-resolution CT	73	71.19	78.57	40.9b	56.16
Huins, 2010[9]	1.5-T; turbo-spin-echo T2-weighted images HASTE	32	93	100					28b	59.38
Laske, 2018[10]	1.5-T, non-EPI	92	87.01	93.33					39.41b	67.39
Cavaliere, 2014[11]	1.5-T, not-EPI	16	91.67	100	64-slice equipment	16	58.33	50.00	32.5b	62.50
Songu, 2015[3]	1.5-T, EPI	59	85.71	90.32	64-row multisite CT scanner	59	68.97	66.67	35.8b	44.07
Fischer, 2019[12]	1.5-T, RESOLVE	50	88	96					41b	52
Sharifian, 2012[13]	1.5-T, non-EPI	35	96.2	100					34.7b	54.29
Osman, 2017[14]	1.5-T, multisession, single-shot, echo-planar imaging sequence	31	100	90	Multi-detector CT scanner 16 channel;0.5 mm collimation, 0.5 mm thickness,	31	47.6	100	27b	33.33
Foti, 2019[5]					A third-generation 384-slice dual-source CT scanner with a thickness of 0.6 mm	24	87.5	87.5	62.2b	57.89
De Foer B, 2010[15]	1.5-T, non-EPI	120	84.2	92.0					35.7b	63.33
Garcia-Iza L, 2018[16]	1.5-T, EPI and non-EPI	24	86.7	88.9					45.5 b	55.22
Garcia-Iza L, 2018[16]	1.5-T, EPI and non-EPI	43	100	100					45.5 b	55.22
Khemani S, 2011[17]	1.5-T, HASTE	38	82	90					30.6 b	68.42
Nash R, 2018[18]	1.5-T, HASTE	44	55	71					NA	NA

Abbreviations: DW, diffusion-weighted; SE, spin-echo-type; EP, echo-planar; EPI, echo planar imaging; HASTE, Half-Fourier Acquisition Single-Shot Turbo Spin-Echo Imaging; HRCT, high-resolution computed tomography; MRI, magnetic resonance imaging; NA, not available; RESOLVE, readout-segmented echo-planar.

TABLE 3 Pooled diagnostic parameters for CT and MRI for cholesteatoma.

Parameter	All Surgery types		First-look surgery (DWI OR HRCT)	Second-look surgery (DWI OR HRCT)	First- AND second-look surgery (DWI OR HRCT)
	DWI	HRCT			
No. of examinations or patients	657	203	268	167	425
No. of cholesteatoma	396	93	108	102	279
No. of studies	13	5	7	5	6
Sensitivity	0.88 (0.80, 0.93)	0.68 (0.57, 0.77)	0.78 (0.65,0.88)	0.93 (0.61, 0.99)	0.84 (0.74,0.91)
Specificity	0.93 (0.86, 0.97)	0.78 (0.60, 0.90)	0.84 (0.69, 0.93)	0.94 (0.82, 0.98)	0.93 (0.81, 0.9)
Positive likelihood ratio	13.3 (6.1, 28.9)	3.1 (1.6, 6.1)	5.0 (2.2, 11.8)	14.7 (4.9, 44.1)	12.5 (4.1, 38.2)
Negative likelihood ratio	0.13 (0.07, 0.22)	0.41 (0.30, 0.56)	0.26 (0.14, 0.47)	0.07 (0.01, 0.55)	0.17 (0.10, 0.30)
Odds ratio	106 (32, 350)	8 (3, 18)	20 (5, 80)	203 (18, 2260)	73 (16, 338)

Note: Except for the numbers of DWI and HRCT studies, values in the parentheses are 95% CI.

Abbreviations: CT, computed tomography; DWI, diffusion-weighted magnetic resonance imaging; HRCT, high-resolution computed tomography; MRI, magnetic resonance imaging.
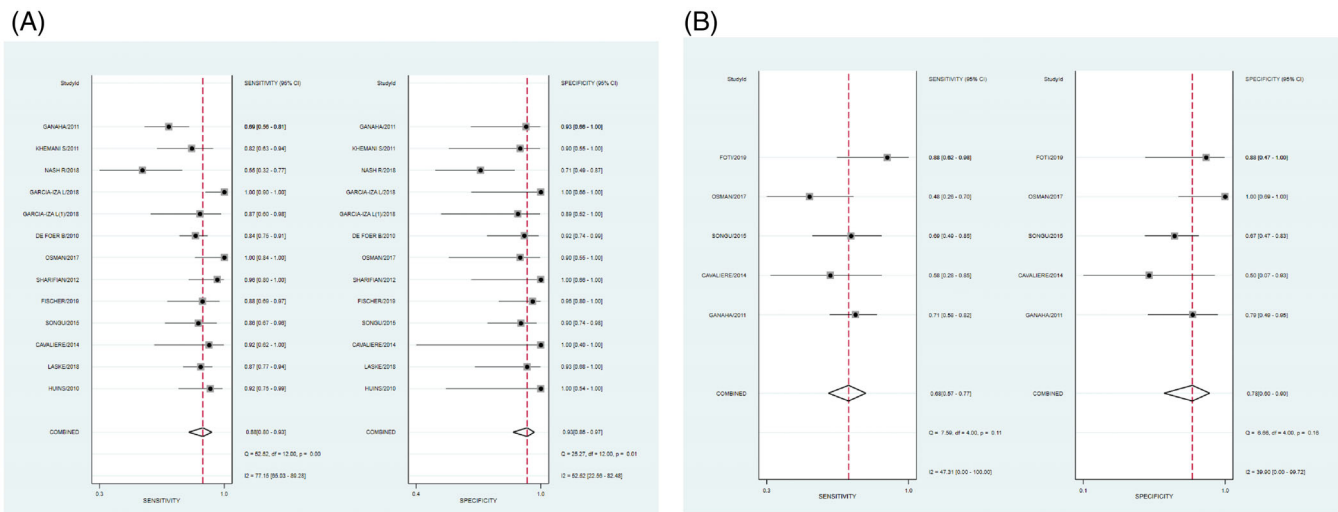

FIGURE 2 Sensitivity and specificity of DWI and HRCT in the diagnosis of all cholesteatomas. (A) The forest plot shows the pooled results of the analysis of DWI sensitivity and specificity. (B) The forest plot shows the pooled results of the analysis of HRCT sensitivity and specificity. DWI, diffusion-weighted magnetic resonance imaging; HRCT, high-resolution computed tomography.

granuloma, and other nonspecific tissues.[7] Cholesteatoma is slightly hypointense relative to the brain on T1-weighted images and hyperintense on T2-weighted images in MRI.[19] DWI is important for diagnosing cholesteatomas, especially postoperative cholesteatomas.[20,21] However, standard clinical DWI sequences have some significant limitations, such as the low image quality and production of relatively thick image sections with distorted shapes due to the artifacts at the skull base.[22,23] The use of DWI and echo planar imaging (EPI) or non-EPI DWI makes cholesteatoma diagnosis more accurate.[24,25]

In the present meta-analysis, the number of HRCT studies considered was approximately one-third of the DWI studies, primarily because many HRCT diagnoses of cholesteatoma are indirect; thus, studies consider the intraoperative cholesteatoma invasion of surrounding tissue in comparison to preoperative HRCT imaging. Pathology results are not the gold standard in these studies. HRCT is widely

used before cholesteatoma operations. Since it has good spatial resolution and can detect typical manifestations of middle ear cholesteatoma,[26] the scope of lesion invasion is shown well. In many hospitals, surgeons advocate preoperative HRCT for all patients with clinically suspected cholesteatoma because it can be used to locate and estimate the lesion extent, especially in complex areas, such as facial recesses and tympanic sinuses. Surgeons can make better surgical plans and reduce the occurrence of postoperative residue under HRCT guidance.[16] HRCT can also help distinguish cholesteatoma from the granulation tissue of chronic otitis media based on changes in the tympanic and ossicular chains, Eustachian tube orifice,[27,28] and an inverted U- or C-shaped enlargement of the Eustachian tube. The enlarged boundary of the Eustachian tube that was caused by granulation tends to be blurred and wedge-shaped.
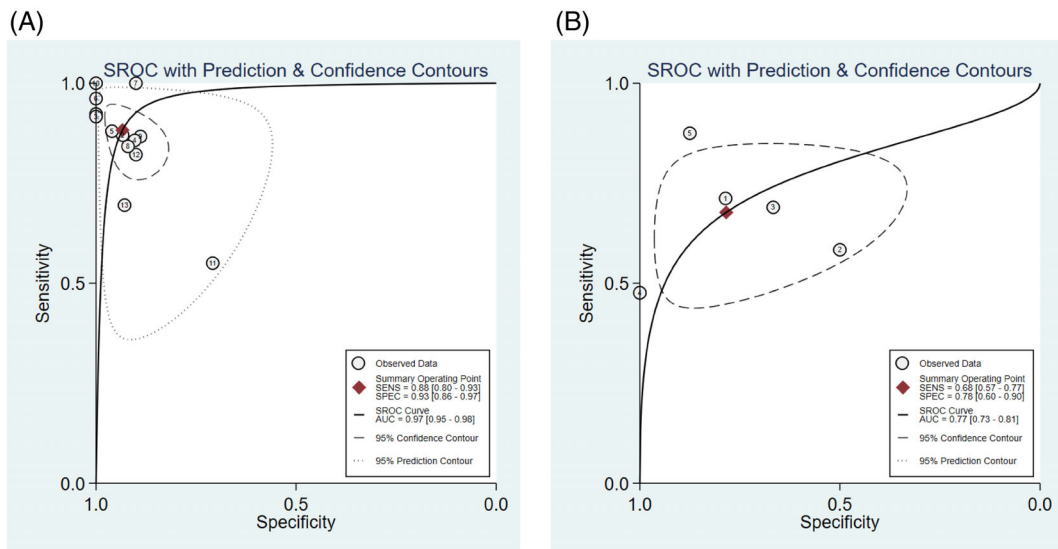
FIGURE 3 SROC curves for DWI or HRCT in the diagnosis of all cholesteatomas. (A) The graph shows the SROC curve for DWI in diagnosing all cholesteatomas. (B) The graph shows the SROC curve for HRCT in diagnosing all cholesteatomas. DWI, diffusion-weighted magnetic resonance imaging; HRCT, high-resolution computed tomography; SROC, summary receiver operating characteristic.
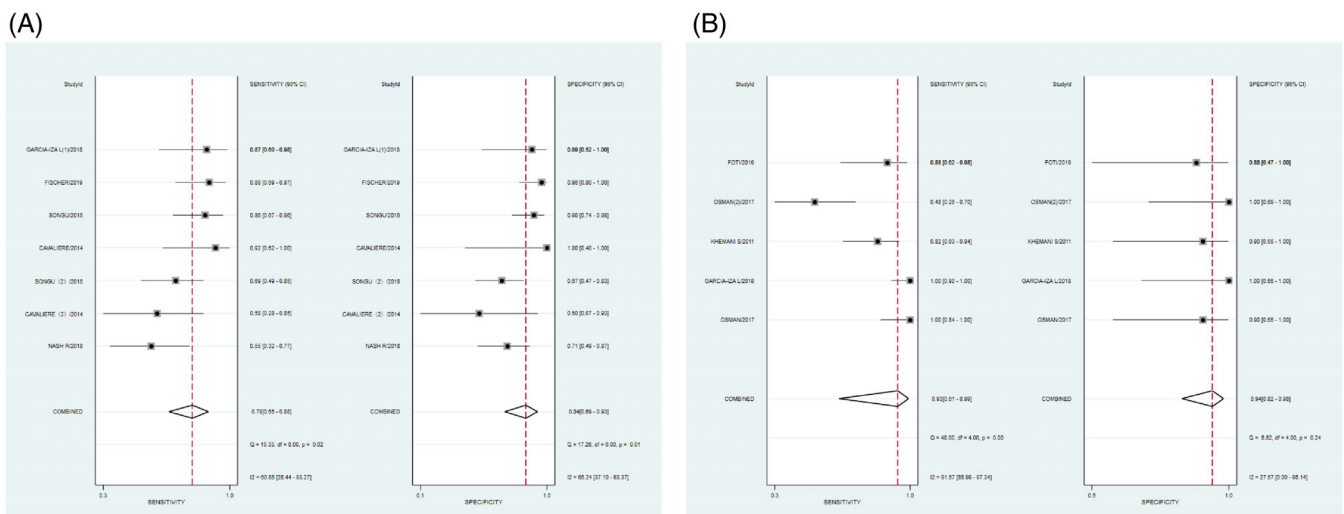

FIGURE 4 Sensitivity and specificity of DWI or HRCT for first- and second-look surgery cholesteatomas. (A) Forest plot shows the pooled analysis results of the sensitivity and specificity for first-look surgery cholesteatomas. (B) Forest plot shows the pooled analysis results of the sensitivity and specificity for second-look surgery cholesteatomas. DWI, diffusion-weighted magnetic resonance imaging; HRCT, high-resolution computed tomography.

MRI has good resolution density and is sensitive to mucosal hypertrophy and effusion. Moreover, DWI is highly valued for diagnosing middle ear cholesteatoma[29,30] which has a high signal intensity.[23] Compared to traditional MRI, various DWI sequences considerably improved in the diagnosis of cholesteatoma and provided a variation of conventional MRI sequences that use the principle of molecular diffusion or Brownian motion to generate contrast. In this context, molecular diffusion mainly refers to the random movement of water molecules and is restricted under some pathological conditions. Particularly, the keratin fragments in cholesteatoma limit water spread and result in high signal intensity, whereas mucosal edema, fibrosis, and scars or granulation tissue do not limit water spread and thus produce low-intensity signals.[12] In the present study, the diagnostic sensitivities and specificities of HRCT and DWI for cholesteatomas in patients who underwent primary- or second-look surgery were high. The sensitivity and specificity of DWI or HRCT for diagnosing recurrent or residual cholesteatoma were 0.93 (CI, 0.61–0.99) and 0.94 (CI, 0.82–0.98), respectively, which were consistent with those of DWI for recurrent or residual cholesteatoma.[31,32]

The results of this study showed that HRCT and DWI have similar capabilities in diagnosing cholesteatoma. Since the cost of HRCT is
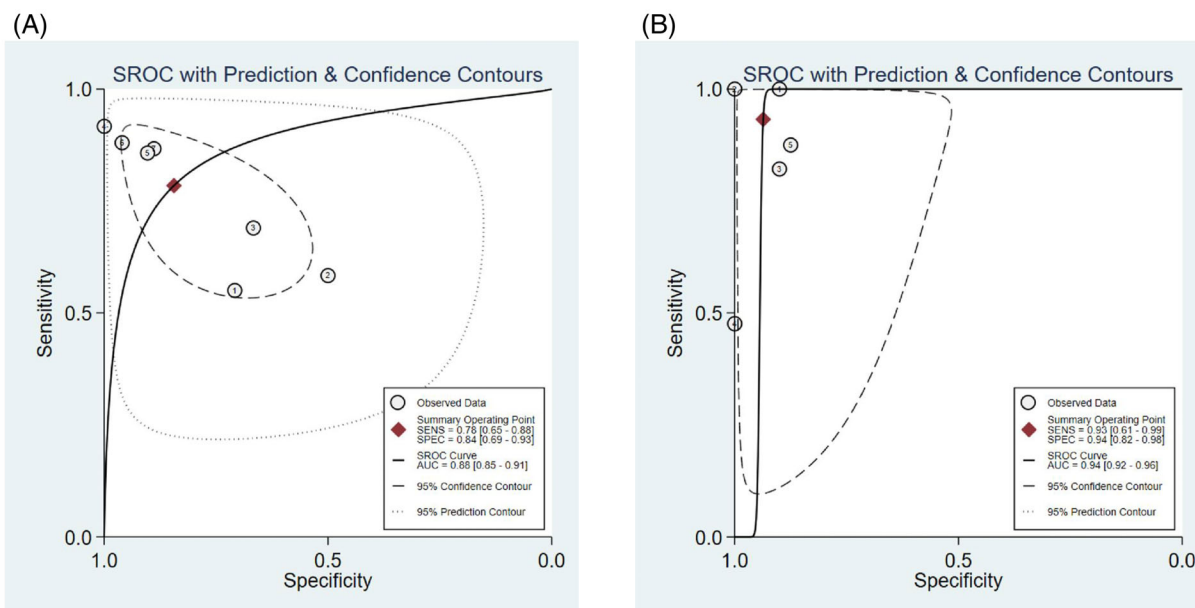
FIGURE 5 Graphs showing the SROC curves of DWI or HRCT in diagnosing first- and second-look surgery cholesteatomas. (A) SROC curve for DWI or HRCT in diagnosing first-look surgery cholesteatomas. (B) SROC curve for DWI or HRCT in diagnosing second-look surgery cholesteatomas. DWI, diffusion-weighted magnetic resonance imaging; HRCT, high-resolution computed tomography; SROC, summary receiver operating characteristic.

much lower than that of DWI, HRCT may be used instead of DWI in diagnosing cholesteatoma to save clinical resources.

4.1 | Limitations

This study has two limitations. First, an insufficient number of papers on HRCT for diagnosing cholesteatoma was considered. Second, the different DWI sequences were not analyzed and compared separately.

5 | CONCLUSION

Both DWI and HRCT have good and similar sensitivity and specificity levels for diagnosing various cholesteatomas. In addition, the diagnostic ability of HRCT or DWI for recurrent cholesteatoma is identical to primary cholesteatoma.

FINANCIAL DISCLOSURE
All authors have no competing financial interests to declare.

CONFLICT OF INTEREST STATEMENT
The research was conducted without any commercial relationship that could be construed as a potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.