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SYSTEMATIC REVIEW

Diagnostic ultrasound assessment of temporomandibular joints: a systematic review and meta-analysis

[1]Fabiana Tolentino Almeida, [1]Camila Pacheco-Pereira, [1]Carlos Flores-Mir, [2]Lawrence H. Le, [2]Jacob L. Jaremko and [1]Paul W. Major

[1]School of Dentistry, University of Alberta, Edmonton, AB, Canada; [2]Radiology and Diagnostic Imaging, University of Alberta, Edmonton, AB, Canada

Objectives: The purpose of this systematic review was to determine the diagnostic capability of ultrasound to assess TMJ alterations as disc displacement (DD), joint effusion (JE) and condylar changes (CC) using 3D imaging modalities as reference standard.
Methods: Studies were gathered by searching several electronic databases and partial grey literature up to January eighth, 2018 without restrictions of language and time. The risk of bias was evaluated using the second version of Quality Assessment Tool for Diagnostic of Accuracy Studies-2 (QUADAS-2). The grading of Recommendation, Assessment, Development and Evaluation (GRADEpro system) instrument was applied to assess the level of evidence across the studies.
Results: After applying the eligibility criteria, 28 studies were identified and synthesized. All studies were methodologically acceptable presenting low applicability concerns, although none of them fulfilled all QUADAS-2 criteria. The quantitative analysis included 22 studies, 2829 joints in total. The quality of the evidence evaluated by GRADE system suggested moderate confidence in estimating the outcomes.
Conclusion: This systematic review demonstrated the ultrasound has acceptable capability to screen for DD and JE in TMD patients. For screening of condylar changes, ultrasound needs further studies using CT or CBCT as reference standard to support its use. More advanced imaging such as MRI can thereafter be used to confirm the diagnosis if deemed necessary.
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Introduction

The temporomandibular joint (TMJ) is a synovial articulation between the mandibular condyle and the glenoid fossa in the temporal bone. Temporomandibular joint disorders (TMD) constitute structural and/or functional disorders that affect TMJ, masticatory muscles and related structures. These disorders may present with clinical signs such as articular noises, TMJ pain and/or limitation in opening and closing mouth.[1]

Diagnostic imaging is an essential part of the TMD evaluation.[2] In the last two decades, several techniques have been described in the literature to assess bony and soft TMJ tissues.[3] Magnetic resonance imaging (MRI) is accepted as the reference standard for imaging diagnosis of TMD.[4] MRI has ability to evaluate soft tissue areas and inflammatory conditions; however, it has limited value to accurately diagnose osseous alterations.[5] Although MRI uses non-ionizing radiation, its downside as a TMD screening tool is related to the

Correspondence to: Dr. Fabiana Tolentino Almeida, E-mail: fabiana@ualberta.ca

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high cost, time-consuming procedure and relatively low availability. Computed tomography (CT) has been the method of choice to evaluate the contours of the cortical bone and TMD osseous alterations. A variation of CT, Cone-beam CT (CBCT), has a diagnostic accuracy comparable with CT for detecting TMD osseous changes and has the advantage of lower ionizing radiation exposure.[6,7] However, CT and CBCT poorly assess TMJ soft tissues such as the articular disk.[7,8]

Several studies have assessed ultrasound (US) to evaluate TMJ alterations.[9–13] The high-frequency source pulse emitted, and the echoes detected are accomplished by a transducer placed in contact to the patient skin acquiring the image in real time. The ultrasound frequency usually ranges from 2 MHz to 15 MHz depending on the anatomic region depth to be evaluated. For TMJ, the imaging protocol includes longitudinal and transverses scans using probes with frequencies ranging from 7.5MHz to 20MHz. As an option, static and dynamic evaluations can be performed while the mouth is closed or open. This non-ionizing imaging method is less expensive, transportable, more comfortable to the patient, and could be easily used in a dental setting.[10–14] While not in general clinical use, there are studies reporting that ultrasound has acceptable diagnostic efficacy to detect disk displacement.[15,16]

Although ultrasound assessment of TMJ disorders has been reviewed previously,[15–17] these studies only assessed disk displacement in patients without systemic diseases using MRI or arthrography as reference standard. Therefore, the purpose of this review is to systematically analyze the capability of ultrasound to detect TMJ alterations, specifically disk displacement (DD), joint effusion (JE) and condylar changes (CC) using 3D appropriate imaging modalities (MRI, CT and/or CBCT) as the reference standard.

Methods and materials

This systematic review adhered to the Preferred Reporting Items for a Systematic Reviews and Meta-Analysis of Diagnostic Test Accuracy Studies, PRISMA-DTA Checklist.[18]

Protocol and registration

This protocol was registered at PROSPERO–International Prospective Register of Systematic Reviews–under number CRD42017078836.

Study design

A systematic review of human studies was undertaken to answer the research question "For patients with TMD with or without systemic diseases, does ultrasound imaging have similar diagnostic performance as CT/CBCT or MRI to identify TMJ pathology including disk displacement, joint effusion and bony structural changes?".

Eligibility criteria

Inclusion criteria: Diagnostic studies in which the primary objective was to evaluate the diagnostic capability of 2D or 3D ultrasound imaging in assessing adults or children with TMD were included. Patients with or without systemic diseases that affected TMJ were considered. The reference standard imaging was established 3D imaging modalities (MRI, CT or CBCT). No language or time restrictions were set.

Exclusion criteria: The following exclusion criteria were applied: (1) Reviews, letters, personal opinions, book chapters, and conference abstracts; (2) studies involving in vitro with phantom or in vivo animal models; (3) studies without the reference standard comparison (MRI, CT or CBCT); (4) studies that did not provide accuracy outcome variables such as sensitivity and specificity or ROC curve.

Information sources and search strategy

Detailed individual search strategies for each of the following electronic database were performed: Cochrane, Embase, Medline, PubMed and Web of Science. A partial gray literature was accessed using Google Scholar by screening the abstracts for the first 100 results (filtered by "relevance"). The end search day, across all databases, was January 8, 2018. In addition to the electronic search, a hand search and experts' consultations were implemented, and the reference lists of the selected articles screened.

Appropriate truncation and word combinations were selected and adapted to each database search (Supplementary Material 1) using the expertise of a health sciences librarian. All references were managed by reference manager software (Refworks-COS, ProQuest, Bethesda, MD) and duplicate papers were removed.

Study selection

A two-phase selection of articles was conducted. In Phase 1, two authors (FTA and CP-P) reviewed the titles and abstracts of all the references independently. These authors selected articles that appeared to meet the inclusion criteria based on their titles and abstracts. In Phase 2, the same authors assessed the full text of all screened articles and excluded studies that did not meet the inclusion criteria. We used in this phase the Rayyan Application (Qatar Computing Research Institute, Doha, Qatar),[19] a specific tool for systematic review screening process, available at https://rayyan.qcri.org/. Disagreements between the two authors were initially resolved by consensus. The final selections were always based on the full text of the publication.

Data collection process and data extraction

One author (FTA) collected the required information from the included articles and a second author (CP-P)

crosschecked all the collected data. Once again, disagreements between them were resolved by consensus.

For all included studies, the following information was extracted: study characteristics (author, year and country), sample characteristics (population studied, age range), intervention characteristics (reference standard, index test, transducer frequency, target) and outcome (sensitivity, specificity, ROC values). If the required data were not complete, attempts were made to contact the authors to retrieve the missing information.

Risk of bias and applicability

To assess the methodological quality and applicability of the included studies, the Quality Assessment Tool for Diagnostic Accuracy Studies-2 (QUADAS-2) was applied.[20] One author (FTA) and one collaborator (SC) independently evaluated the quality of each included study and scored each item as "yes", "no" or "unclear". A third author (CP-P) joined the discussion when disagreements arose.

Diagnostic accuracy measures

Sensitivity and specificity of 2D or 3D US as diagnostic tests against MRI, CT or CBCT were considered as the primary outcome measures. Positive predictive values (PPV), negative predictive values (NPV) as well as the cut off values provided by ROC curves were considered as secondary outcomes. Confidence interval at 95% was considered. Other diagnostic measures were also considered: positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR).

The diagnostic test accuracy (DTA) was evaluated based on sensitivity, specificity, LR+, LR- and DOR values. The DTA was considered excellent with LR +>10/LR–<0.1 and acceptable with LR +>3/LR–<0.3.[21] High DOR values indicated better test performance.[22] We rated sensitivity/specificity as acceptable (70–80%/80–90%) and excellent (>80%/>90%).[23]

Synthesis of results

The capability of the ultrasound to identify TMJ alterations was evaluated by diagnostic accuracy measures following the appropriate Cochrane Guidelines.[24] We generated estimates of sensitivity, specificity and their 95% confidence intervals in forest plots and hierarchical receiver operating characteristic (ROC) curve using Review Manager 5.3 (Rev-Man 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata 13.0 (StataCorp. LP 2013, Stata Statistical Software, Release 13. College Station, TX). For this quantitative analysis, we extracted the data for the true positive, true negative, false positive and false negative values for index test in each included study. In addition, these studies were clustered according to the target investigated. (Group 1) studies which assessed disk displacement (DD), (Group 2) studies which assessed condylar changes (CC) and (Group 3) studies which assessed joint effusion (JE). The studies were quantitatively analyzed by target investigated due to the diagnostic process for each TMD (DD, JE, CC).

Studies that did not provide separate data were not included in the quantitative analysis. For data not being suitable for meta-analysis a qualitative analysis was pursued.

Investigation of heterogeneity

We assessed heterogeneity by visually examining forest plots of sensitivities and specificities and ROC space for index test in all target investigated. In addition, it was considered the heterogeneity values (I^2) presented in the forest plots. From the results of I^2, the Cochrane handbook parameters were followed for interpretation as follows: 0 to 40%: might not be important; 30 to 60%: representing moderate heterogeneity; 50 to 90%: representing substantial heterogeneity; 75 to 100%: considerable heterogeneity.

Assessment of reporting bias

A funnel plot to investigate reporting bias using the statistical method suggested by Deeks et al[24] was created. Significant asymmetry ($p < 0.10$) indicates the presence of publication bias in the data.

Level of evidence

The grading of Recommendation, Assessment, Development and Evaluation (GRADEpro system) instrument recommended by Cochrane guidelines[25] was used to assess the evidence level across the studies. The quality of evidence was assessed based on the study design, risk of bias (RoB), inconsistency, indirectness, imprecision, and publication bias at the outcome level. The Grade was applied in studies with TMD patients separated by target. The quality of evidence was characterized as high, moderate, low, or very low.[26] The GRADE was assessed using the website http://gradepro.org

Results

Study selection

A flow diagram detailing the process of identification, inclusion and exclusion of the studies is shown in Figure 1. A full-text analysis was conducted on the 47 articles retrieved from the first phase of the selection process. This process led to the exclusion of 19 studies presented in Supplementary Material 2. Finally, 28 studies satisfied the inclusion criteria of this review and were selected for the qualitative synthesis..[9–14,27–48] 22 studies were quantitatively divided in groups and analyzed by a meta-analysis.[10–14,27,28,30–40,43,46–48]

Study characteristics

The included studies were published from 1997 to 2016. All articles were written in English, except one

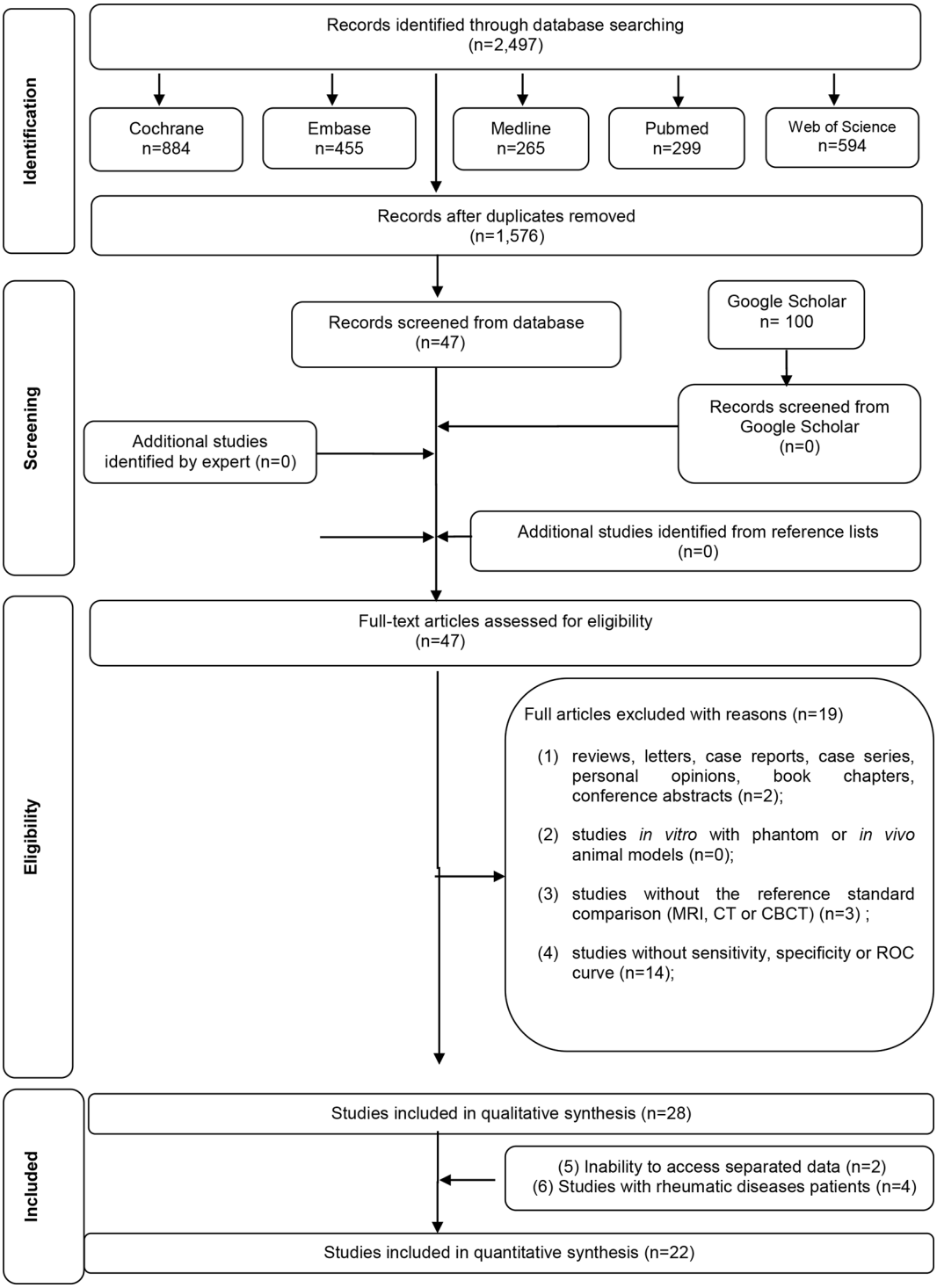

Figure 1 Flow Diagram of literature search and selection criteria adapted from PRISMA.

in Chinese[48] and one in Korean.[34] The studies were conducted in 14 different countries (Austria, Japan, Italy, Germany, Turkey, France, China, Egypt, Norway, Korea, India, Brazil, Israel and Switzerland).

27 studies were cohort studies [10–14,27,28,31–40,43,46–48] and one was case-control design.[30] Sample size ranged from 3 to 100 patients with TMD. Those sample have patients with juvenile idiopathic arthritis (JIA),[9,44] rheumatoid

arthritis (RA) or psoriatic arthritis (PsA).[41,42] DD was assessed in 22 studies,[10–14,27,29–38,41–43,45,47,48] JE in 9,[9,36,37,40–44,46] and CC in 11 studies,[10,12,13,28,34,36,39,41,43–45] In total, 11 studies assessed more than one TMJ alteration.[10,12,13,34,36,37,41–45]

MRI was used as reference standard in 27 studies.[9–14,27–33,35–48] One of them used MRI and/or CT.[35] Only one study used CT alone[34] and none used CBCT as reference standard.

Regarding the index test, 25 studies appraised 2D US,[9–11,13,14,27–37,40–48] two-studies assessed 3D US[38,39] and one study evaluated 2D and 3D US.[12] All of these studies used extra oral ultrasound approach to evaluate TMJ. The ultrasound transducer frequency used in the studies ranged from 5 to 20 megahertz (MHz). A summary of the descriptive characteristics of the included article is given in Table 1.

Risk of bias (RoB) and applicability

None of the studies fulfilled all of the methodological quality criteria (Figure 2). The RoB of index test was scored as "unclear" for all studies due to the lack of information on the used threshold. Six studies[11,34,35,41,43,45] were evaluated as "unclear" in reference standard RoB domain. 27 studies presented low applicability concerns in all domains. Supplementary Material 3 shows the QUADAS-2 criteria for each included study.

Results of individual studies

Four studies assessed TMJ alterations in rheumatic diseases patients (JIA, RA and/or PsA)[9,41,42,44] and the results from these studies were analyzed separately from those in TMD patients. Melchiorre et al[42] and Manfredini et al[41] assessed DD with 2D US. The sensitivity/specificity were 69%/30 and 56%/73% respectively. All four studies evaluated JE using 2D US. Two of these studies assessed JE indirectly using the capsular distention measurements to discriminate joints with effusion from normal joints.[9,41] The highest sensitivity (85%) for JE assessment was seen in Manfredini et al[41] and Khirkus et al[9] described the highest specificity (70%) using a cut-off value of 1.2 mm for capsular width. The CC was evaluated by two studies.[41,44] The highest values were 67% sensitivity and 26% specificity.[41]

24 studies evaluated DD, JE and/or CC in TMD patients.[10–14,27–40,43,45–48] To improve our interpretation of the results, these studies were clustered in groups by target assessed (DD, JE and CC).

US to DD assessment

In those studies, evaluating the ability for ultrasound to detect DD in TMD patients (n = 20), a very wide range of sensitivity (from 22 to 95%) and specificity (from 16 to 100%) was present (Table 1).

Seven studies reported excellent sensitivity (>80%) and specificity (>90%).[13,32–36,48] Using 2D dynamic US with 12 MHz in 100 TMD patients (n = 200 joints), Jank et al[36] reported a sensitivity and specificity of 92% in closed-mouth evaluation. Emshoff et al investigated 2D static and dynamic US (12MHz) in three studies, they found a sensitivity ranging from 82 to 95% and specificity ranging from 92 to 96% in closed and opened-mouth.[13,32,33]

The capability of 3D US to assess DD was tested by two studies.[12,38] Landes et al reported a sonographic evaluation using 8–12.5 MHz with 53% sensitivity and 74% specificity.[38] They emphasized that 3D sonography could provide better results by using automated image enhancement and higher transducer frequency.

US to JE assessment

Five studies addressed the ultrasound capability to evaluate JE in TMD patients.[36,37,40,43,46] Using direct evaluation of the articular space to detect effusion, Jank et al[36] described excellent sensitivity (83%) and specificity (100%) and Mello et al[43] found 100% of specificity and 20% of sensitivity. Manfredini et al studied the cut-off values of the capsular distention to evaluate effusion. Ultrasound sensitivity was high (83.9%) with cut-off values less than 1.9 mm values while US specificity was high (88%) presenting cut-off greater than 2.1 mm.[40]

US to CC assessment

Nine studies assessed CC in TMD patients and the results ranged from 0 to 94% for sensitivity and from 20 to 100% for specificity.[10,12,13,28,34,36,39,43,45] In these studies, CC were considered by the presence of bone erosion,[10,12,13,28,34,36,39,44] flattening[12,28,34,39,45] and/or osteophyte[12,28,39,45] Only Gook et al[34] used CT as a reference standard for CC evaluation and the sensitivity was 87% and specificity 62%. With ultrasound showing a sensitivity of 87% and specificity of 20%, Brandlamaier et al presented that US is valuable in diagnosing the presence but insufficient in diagnosing the absence of bone erosion, flattening and/or osteophyte signs.[28] On the other hand, a sensitivity of 0% was found by other study evaluating flattening and erosion in three patients with TMD.[45]

Landes et al evaluated CC with 3D US (8–12.5 Mhz). This index test had 75% accuracy (sensitivity 70%/specificity 76%), PPV 44% and NPV 90% and concluded that 3D US is more reliable than 2D US for CC exclusion.[39]

Synthesis of results–quantitative analysis

DTA tables were constructed by target for the studies with TMD patients using the data extracted from each article (sensitivity, specificity, PPV, NPV, LR+, LR- and DOR) (Tables 2–4). Two out of 24 studies eligible for those analysis did not provide separated data to calculate DTA values.[42,48] [29,45] These authors were contacted without success.

Our quantitative analysis included 2829 joints (1533 in DD, 554 in JE and 742 in CC assessment). Measures of the diagnostic test accuracy such as sensitivity and specificity of each included study in the quantitative

Table 1 Summary of descriptive characteristics of included studies

Study characteristics		*Sample characteristics*		*Intervention characteristics*				*Outcomes*	
Study/Year	*Country*	*Population studied (N = patients)*	*Age range (y)*	*Reference standard*	*Index test (US)*	*Transducer frequency (MHz)*	*Target*	*Sensitivity (%)*	*Specificity (%)*
Emshoff et al., 1997	Austria	TMD (17)	16–60	MRI	2D static/dynamic	7.5	DD	Static CM/OM: 50/13 Dynamic CM/OM: 39/13	71/70 100/95
Hayashi et al., 2001	Japan	TMD (18)	8–12	MRI and/or CT	2D dynamic	8 or 10	DD	83	96
Jank et al., 2001	Austria	TMD (66)	13–78	MRI	2D static	12	DD	CM: 78 OM: 61	CM: 78 OM: 95
Emshoff et al., 2002 a	Austria	TMD (64)	17–65	MRI	2D dynamic	12	DD	82	95
Emshoff et al., 2002 b	Austria	TMD (29)	19–62	MRI	2D static	12	DD	CM: 90 OM: 95	CM: 94 OM: 91
Brandlmaier et al., 2003 a	Austria	TMD (48)	17–67	MRI	2D static	12.5	DD	82	85
Tognini et al., 2005	Italy	TMD (41)	ND	MRI	2D static/dynamic	8–20	DD	65	80
Landes et al., 2006 a	Germany	TMD (53)	14–77	MRI	3D static	8–12.5	DD	53	74
Cakir-Ozkan et al., 2010	Turkey	TMD (28)	16–51	MRI	2D static/dynamic	12	DD	CM: 57 OM: 64	CM: 78 OM: 71
Dupuy-Bonafe et al.,2012	France	TMD (40) controls (20)	21–59 21–29	MRI	2D static/dynamic	5–12	DD	CM: 22 OM: 0	CM; 96 OM: 98
Yang et al., 2012	China	TMD (35)	37.3 mean	MRI	2D static	12	DD	82	94
Razek et al., 2015	Egypt	TMD (20)	15–57	MRI	2D static/dynamic	12	DD	79	72
Manfredini et al., 2003	Italy	TMD (69)	ND	MRI	2D static/dynamic	8–20	JE	83	73
Tognini et al., 2003	Italy	TMD (44)	ND	MRI	2D static/dynamic	8–15	JE	75	76
Kirkhus et al., 2016	Norway	JIA (55)	<18	MRI	2D static	12–18	JE	72	70
Brandlamaier et al., 2003 b	Austria	TMD (40)	16–78	MRI	2D static	12.5	CC	87	20
Landes et al., 2006 b	Germany	TMD (53)	14–77	MRI	3D static	8–12.5	CC	70	76
Melchiorre et al., 2003	Italy	RA (22), PsA (11)	30–81	MRI	2D static/dynamic	7.5	DD JE	69 70	30 75
Kaya et al., 2010	Turkey	TMD (52)	28.3 mean	MRI	2D static/dynamic	7.5	DD JE	91 53	16 63
Gook et al., 2008	Korean	TMD (20)	ND	CT	2D static	12	DD CC	95 87	90 62
Sinha et al., 2012	India	TMD (3)	ND	MRI	2D dynamic	10	DD CC	33 0	100 100
Emshoff et al., 2003	Austria	TMD (48)	15–72	MRI	2D dynamic	12	DD CC	95 83	91 63
Habashi et al., 2015	Israel	TMD (39)	18–77	MRI	2D static/dynamic	5–17	DD CC	74 36	84 83
Landes et al., 2007	Germany	TMD (33)	14–77	MRI	2D/3D static	8–12	DD CC	2D: 58 3D: 60 2D: 69 3D: 69	63 68 74 78

(Continued)

Table 1 (Continued)

Study characteristics		*Sample characteristics*		*Intervention characteristics*				*Outcomes*	
Study/Year	*Country*	*Population studied (N = patients)*	*Age range (y)*	*Reference standard*	*Index test (US)*	*Transducer frequency (MHz)*	*Target*	*Sensitivity (%)*	*Specificity (%)*
Muller et al., 2009	Switzerland	JIA (30)	2–16	MRI	2D static/dynamic	12	JE CC	33*	82*
Jank et al., 2005	Austria	TMD (100)	≥16	MRI	2D dynamic	12	CM/OM: DD JE CC	92/86 81 94	92/91 100 100
Manfredini et al.,2005	Italy	TMD/RA/PsA (68)	43.4 mean age	MRI	2D static/dynamic	8–20	DD JE CC	56 85 67	73 66 26
Mello et al., 2011	Brazil	TMD (38)	16–65	MRI	2D static	12.5	CM/OM: DD JE CC	83/0 20 15	100/100 100 87

AC, accuracy; CC, condylar change; CM, closed mouth; CT, computed tomography; DD, disk displacement; JE, joint effusion; JIA, juvenile idiopathic arthritis; MHz, megahertz; MRI, magnetic resonance imaging; ND, not described; OM, open mouth; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TMD, temporomandibular joint disorder; US, ultrasound; y, year; 2D, two dimensional; 3D, three dimensional; CM, closed mouth;
*separate data not available.

analysis and summary sensitivity/specificity for each TMD are shown in Figure 3. In general, ultrasound sensitivity and specificity varied substantially, from 22 to 95% and 16 to 100%, respectively. Figure 4 shows the ROC curve for each group.

For DD assessment in TMD patients (n = 17), 70% of the included studies presented DTA values considered excellent or acceptable[10,13,14,27,30,32–36,47,48] and 30% reported poor values.[11,12,31,37,38] Regarding PPV and NPV, the studies from Jank et al[36] and Emshoff et al[13] reported the highest values respectively. Additionally, the highest DOR values were observed in these two studies (Table 2).

For JE assessment, the additional analyses were done in five studies.[36,37,40,43,46] Jank et al[36] and Mello et al[43] described excellent LR+, LR- and DOR values (Table 3). Also, from eight studies used for CC assessment additional analyses,[10,12,13,28,34,36,38,39,43] only one[36] reported LR values (LR+ ∞, LR- 0.06) and DOR (∞) excellent for DTA. This study provided the highest PPV (100%) value and the best NPV (95%) was seen in Gook et al article[34] (Table 4).

High heterogeneity (I^2 ranging from 83.35 to 96.12) was observed between the studies included in the meta-analysis (Figure 3).

Risk of bias across studies

The main methodological limitations were related to the lack of clear information in reporting QUADAS domain 2 item 2 addressing/reporting the use of a threshold. The potential bias is related to the fact that the threshold may influence the interpretation of the index test results. Additionally, QUADAS domain 4 item 1, exploring the interval between index test(s) and reference standard, were scored as "unclear" as no information on the timing between the examinations reported in some studies. Figure 2 details RoB and applicability concerns across included studies.

The Deeks funnel plot showed p-value = 0.39 for DD, 0.49 for JE and 0.65 for CC (Figure 5). This high asymmetry in the data suggests possible publication bias.

Additional analysis–level of evidence

Overall, the quality of the evidence evaluated by GRADE system was determined to be moderate. It suggested moderate confidence in estimating the outcomes. The indirectness factor was judged as serious due to the different parameters used in the index test studied and unclear information regarding images interpretation expertise (Supplementary Material 4).

Discussion

The number of affected people with TMJ alterations or TMD has been growing. A recent meta-analysis showed that one in 6 children and adolescents have clinical signs of TMD.[49] Some studies suggested that the prevalence of TMD in adults range from 1 to 75% and approximately 33% of the adults have at least one symptom.[50–52] There is evidence that the TMD signs or symptoms could be more common in the adult population than it is reported.[52] However, TMD prevalence in the adult population is a subject under debate, due to the heterogeneity in the diagnostic criteria used and the modality of patients' recruitment. Recently, the Research Diagnostic Criteria for TMD (RDC/TMD) was reviewed and a new Diagnostic Criteria (DC/TMD) was proposed.[2] In

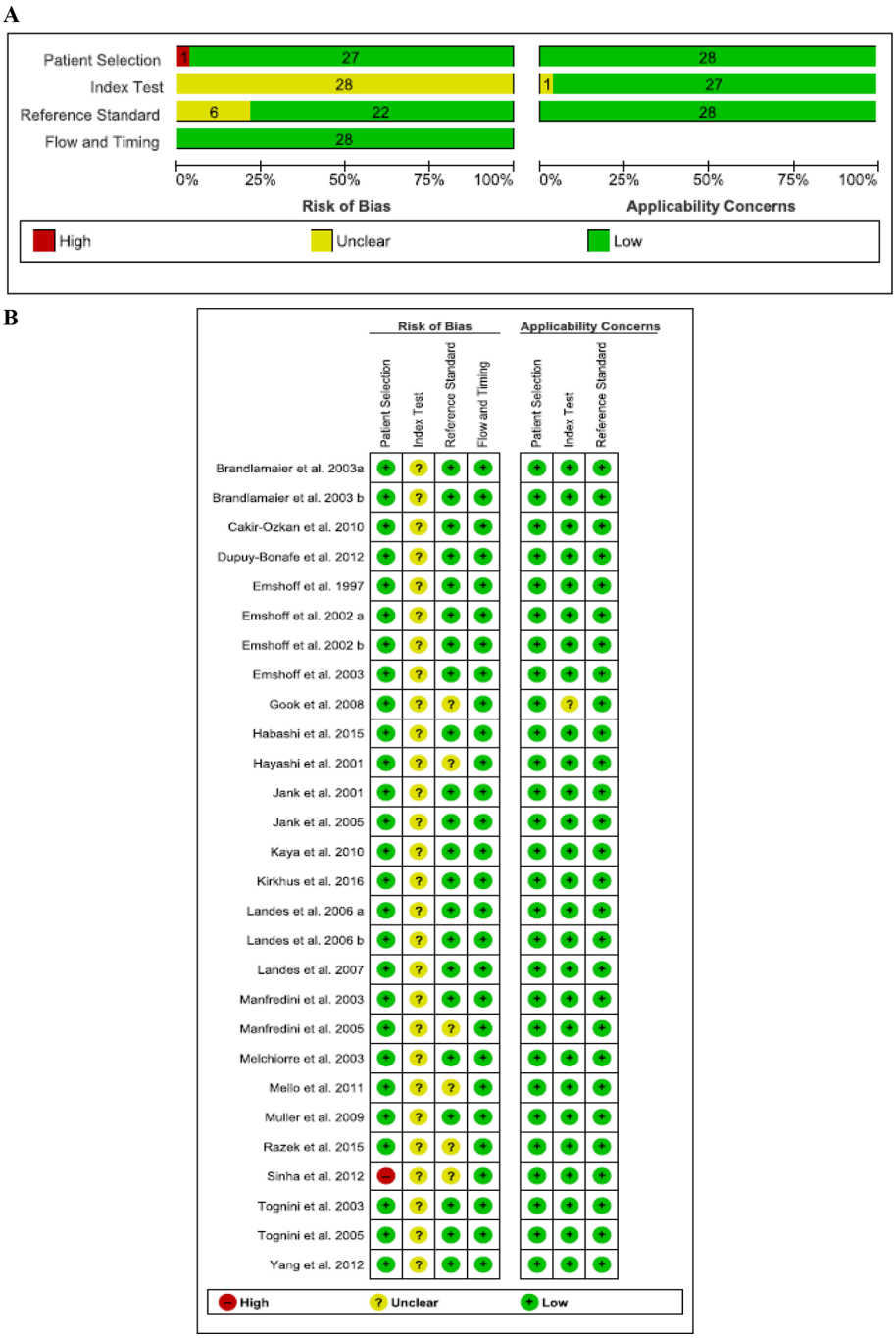

Figure 2 Risk of bias and applicability concerns graph: review authors' judgments about each domain presented as percentages across included studies. (A) Risk of bias graph; (B) Risk of bias summary.

this context, the diagnostic imaging plays an important role in improving TMD detection.

This systematic review investigated the available evidence on the diagnostic capability of ultrasound to assess TMJ alterations (DD, JE and CC). It is important to emphasize that multiple imaging modalities such as panoramic radiography, CBCT, CT and MRI have been used, with some limitations, to assess those TMJ alterations. Conventional imaging techniques as panoramic radiography are not useful to detect the first stages of the alterations just providing two-dimensional images.[3,4] CT and CBCT are not used as screening method due to ionizing radiation and they are not able to detect articular disk alterations.[8] Currently, although MRI is the method of choice to TMD evaluation, its limited accessibility, somewhat limited assessment of osseous changes, high-cost, and there are limitations related to claustrophobic patients and patients using metal devices

Table 2 Diagnostic test accuracy, measurements for US in DD assessment of TMD patients

Author, Year	*Sample size (N joints)*	*Prevalence (%)*[a]	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*[a]	*NPV (%)*[a]	*LR+*[a]	***LR–***[a]	*DOR*[a]
Emshoff et al,1997	33	78	50	71	86	27	1.75	0.70	2.45
Hayashi et al, 2001	36	33	83	95	90	92	20.0	0.17	117.6
Jank et al, 2001	132	65	78	77	87	64	3.5	0.28	12.5
Emshoff et al, 2002a	128	21	81	95	81	95	16.45	0.19	81.0
Emshoff et al, 2002b	116	54	92	92	93	90	12.1	0.08	151.2
Emshoff et al, 2003	96	44	95	90	89	96	10.1	0.05	202.0
Brandlmaier et al, 2003a	192	46	82	85	82	85	5.2	0.21	25.33
Tognini et al, 2005	82	50	65	80	77	70	3.37	0.42	7.97
Jank et al, 2005	200	69	92	92	96	83	11.4	0.08	142.5
Landes et al, 2006a	105	44	61	62	58	66	1.62	0.61	2.63
Landes et al, 2007	66	45	63	47	50	60	1.2	0.7	1.52
Gook et al, 2008	40	50	95	90	90	94	9.5	0.05	190
Kaya et al,2010	52	88	91	16	89	20	1.09	0.52	2.08
Dupuy-Bonafe et al, 2012	98	40	22	96	81	64	6.52	0.80	8.02
Yang et al, 2012	40	57	82	94	95	80	14.04	0.18	78
Razek et al, 2015	39	71	78	72	88	57	2.88	0.29	9.93
Habashi et al, 2015	78	38	74	83	73	83	4.4	0.31	13.9

DOR, diagnostic odds ratio; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value;
[a]when the data is not available, the authors calculated data from information available in the article.

with ferromagnetic properties.[3] Moreover, dynamic MRI is hard to be acquired and have lower image quality than static images. Therefore, as ultrasound has merits such as low-cost, accessibility due to mobile units, non-invasive and non-ionizing radiation, it could be considered a screening method.[15] For this reason, it is important to investigate its diagnostic capability.

Disc displacement

The most data about DTA of ultrasound from this study was provided by studies that assessed DD. Regarding this TMD, 70% of the studies showed excellent or acceptable DTA of ultrasound. These studies used different methodologies to evaluate DD and the disc in ultrasound images ranged from hyperechoic to hypoechoic. Most likely, because the challenge of viewing the disk due to the surrounding bone structures, the variation in ultrasound technical characteristics and the absence of a standardized US protocol for TMJ evaluation.[53] Ultrasound was tested using different frequencies (ranging from 7.5 to 20MHz) and dynamic and static imaging were investigated in closed and/or open-mouth. In our review, excellent and acceptable DTA values for DD assessment were found in studies using dynamic and/or static US. The meta-analysis of Su et al found higher diagnostic values of the combined static and dynamic examinations than static examination alone.[17] Other systematic review addressing this subject applied meta-regression to determine if the clinical heterogeneity could influence diagnostic accuracy. The influence of the different types of ultrasound on diagnostic efficacy was minimal. However, it is relevant to question the meta-regression statistical power due to few studies using dynamic and 3D US.[15]

The majority of studies addressed 2D US and a wide variation in accuracy values was observed in our review. A disadvantage of the 2D US is that an incorrect transducer angulation could easily cause the correctly positioned disk to disappear from the sonographic picture and could be the main reason for false-negative results. Moreover, one of the major shortcomings of the 2D US is the technique limitation to detect DD laterally or medially.[29,54,55]

Effusion

ultrasound has been used to detect synovitis and effusion in several joints. It is accurate to detect intra articular fluids in larger joints.[56] With the technologies progress in the last years, attempts are made to study effusion in small joints using the ultrasound. The hallmark of JE in large joints is the distention of the joint capsule and due to the lack of literature on this specific issue in TMJ, the diagnostic criteria is not well established. The presence of effusion using MRI is depicted as hyperintense signal within articular space. In ultrasound evaluation, effusion may be detected by direct visualization as a hypoechoic area within the articular space or by indirect measurement of the capsular distention. In our results, just five studies investigated effusion in TMD patients, while three of them presented acceptable or excellent DTA values..[36,43,46] Manfredini et al, [40] using indirect visualization of effusion, showed higher sensitivity (83%) and specificity (73.7%) with 1.9 mm of capsular distention. Jank et al[36] studied 200 joints and

Table 3 Diagnostic test accuracy, measurements for US in JE assessment of TMD patients.

Author, Year	*Sample Size (N joints)*	*Prevalence %)*[a]	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*[a]	*NPV (%)*[a]	*LR+*[a]	*LR–*[a]	*DOR*[a]
Manfredini et al, 2003	138	44	83	73	59	80	1.7	0.3	5.67
Tognini et al, 2003	88	46	75	76	73	78	3.2	0.3	9.50
Jank et al,2005	200	29	83	100	100	93	∞	0.18	∞
Kaya et al, 2010	52	57	53	63	66	50	1.4	0.73	1.92
Mello et al, 2011	76	6	20	100	100	94	∞	0.8	∞

DOR, diagnostic odds ratio; LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value;
[a]when the data is not available, the authors calculated data from information available in the article

Table 4 Diagnostic test accuracy, measurements for US in CC assessment of TMD patients

Author, Year	*Sample Size (N joints)*	*Prevalence (%)*[a]	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*[a]	*NPV (%)*[a]	*LR+*[a]	*LR–*[a]	*DOR*[a]
Emshoffet al 2003	48	18	83	62	34	94	2.24	0.26	8.62
Brandlmaier et al, 2003b	80	87	87	20	88	18	1.08	0.64	1.69
Jank et al, 2005	200	95	94	100	100	45	∞	0.06	∞
Landes et al, 2006b	106	21	69	75	44	90	2.8	0.4	6.68
Landes et al, 2007	66	24	68	75	45	88	2.6	0.4	6.19
Gook et al, 2008	40	20	87	62	36	95	2.33	0.20	10.92
Mello et al, 2011	76	17	15	87	20	83	1.2	0.96	1.18
Habashi et al, 2015	78	50	36	82	66	56	2.0	0.78	2.56

DOR, diagnostic odds ratio; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value;
[a]when the data is not available, the authors calculated data from information available in the study.

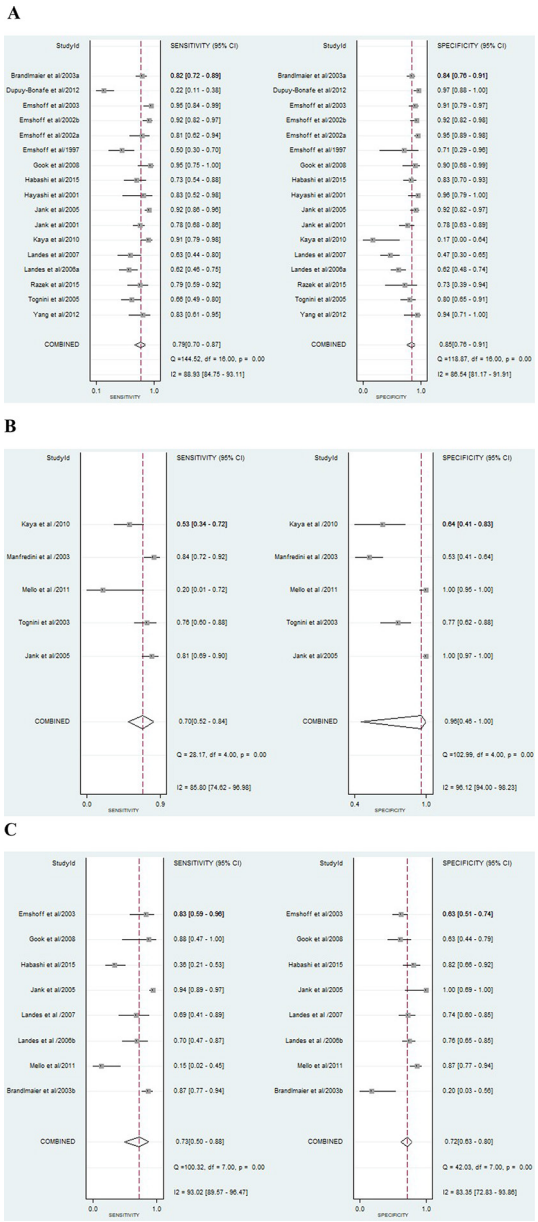

Figure 3 Forest plot with the diagnostic test accuracy (DTA) of each study (sensitivity, specificity and 95% confidence interval) and heterogeneity assessment. (A) Forest plot with the diagnostic test accuracy (DTA) for US to DD assessment; (B) Forest plot with the diagnostic test accuracy (DTA) for US to JE assessment; (C) Forest plot with the diagnostic test accuracy (DTA) for US to CC assessment.

found the same sensitivity (83%) presented by Manfredini et al[40] and higher values for specificity (100%). The threshold used to evaluate JE was not detailed in Jank et al study. Standardized parameters to detect JE was further encouraged by all those studies and are reinforced by our results. At the moment, as there is no clarified classification system for effusion diagnosis by ultrasound, the comparison between the reference standard MRI and US could be not reliable.

Condylar changes

The ultrasound capability to assess hard tissues is a subject under controversy in the literature.[10,13,28] Only one study out of eight included in the DTA table showed an excellent capability to assess condylar erosion reporting 94% of sensitivity and 100% of specificity.[36] It is important to discuss that ten of the studies addressing CC in this systematic review used MRI as the reference standard. Since MRI has limitations to assess bone alterations as erosion, flattening and osteophyte, the results of these studies could have been misinterpreted. Brandlmaier discussed in his study that many of CC diagnosed with ultrasound could be not visible in MRI images.[28] Using CT as the reference standard and 2D static US, Gook et al found 87% for US sensitivity and 62% to specificity when evaluating condyle flattening and erosion.[34] These results allow us to affirm that the diagnostic capability of US to assess CC should be more explored using CT or CBCT as the reference standard.

Overall, there is a very wide variation in sensitivity and specificity of ultrasound for each type of pathology across a variety of included studies. This variation could be related to the parameters established to diagnose the presence or absence of the TMD such as diagnostic criteria for disc displacement. On the other hand, some of this variability could be due to technical factors such as the transducer frequency used, probe design, methods of examination and the diagnostic ability of the sonographer and image reader. High-resolution transducers (≥12 MHz) have shown a better visualization of the TMJ structures with better results than low-resolution devices.[10,33] Ultrasound requires an experienced reader for image interpretation.[57] Technical factors such as the type of gel or standoff pad used to scan the patient, contact pressure and probe angle could influence the quality of US image and its interpretation. In general, the included studies in this review did not provide detailed and replicable information about these parameters. Also, the visualization of the disc, articular space and condyle with US could be challenging due to the anatomic configuration of the TMJ, especially the medial part of the joint. The extraoral ultrasound approach used by the included studies in the current systematic review presented challenges to acquire the images externally through the zygomatic process and temporal bone. Recently, Katzberg et al described the first trans-oral ultrasound approach using an intraoral probe and images were acquired with adequate anatomic depth. The condyle and sub condylar space were visible in 100% of the joints and the disc was visible in 70%.[53] For researches, could be a promising approach to improving the limitations caused by the difficulty of imaging structures behind bone and air.

3D US

On its acquisition process, the tissue block is obtained and slicing in several plans which allow multiplanar views (sagittal, coronal and axial) of a joint portion

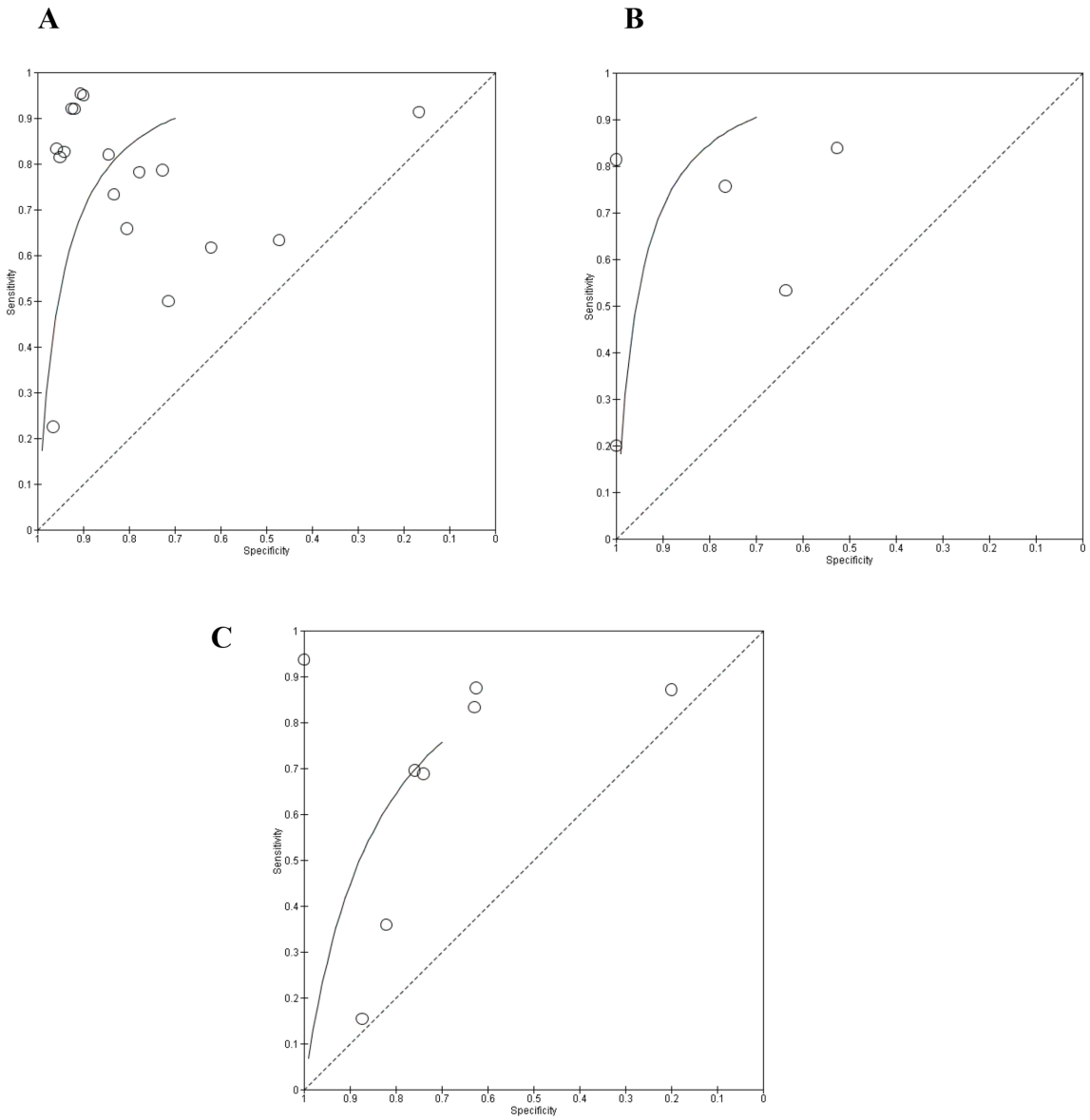

Figure 4 Receiver operating characteristic (ROC) curves for each group. (A) ROC curve for US to DD assessment; (B) ROC curve for US to JE assessment; (C): ROC curve for US to CC assessment.

and favor the interpretation. In our study, three papers from the same group tested the performance of 3D US to assess TMD.[12,38,39] One of them, compared 2D *vs* 3D US and the 3D one presented better results, maybe due to the better viewing.[12] All those papers discussed that the main advantage of using 3D US was to obtain a complete overview of the articular disk and condyle. They also discussed that the 3D US performance could be improved by applying automated imaging enhancement. 3D ultrasound have been currently used in some areas of medicine and new technologies to improve those image analyses have been tested.[58,59] Hareendranathan et al proposed a technique for semiautomatic segmentation of echogenic structures from 3D US applied to hip dysplasia. The study showed that it is a fast and reliable method to delineate the surface and shape of the structures aiding in more accurate diagnosis of the evaluated area. They emphasized the technique could be applied for any 3D US.[58] As the current approach to evaluate TMD by ultrasound is a challenging, this type of technology applied to the image could be an opportunity for further studies.

Inflammatory arthritis

We found just four papers addressing ultrasound for TMJ alterations in rheumatic disease population,[9,41,42,44] too few to construct a meaningful DTA table, forest plot or ROC curve and to draw conclusions. Besides that, these papers studied different rheumatic diseases with their own prevalence and TMD etiopathogenesis, which could lead to misinterpretation if combined. A recent

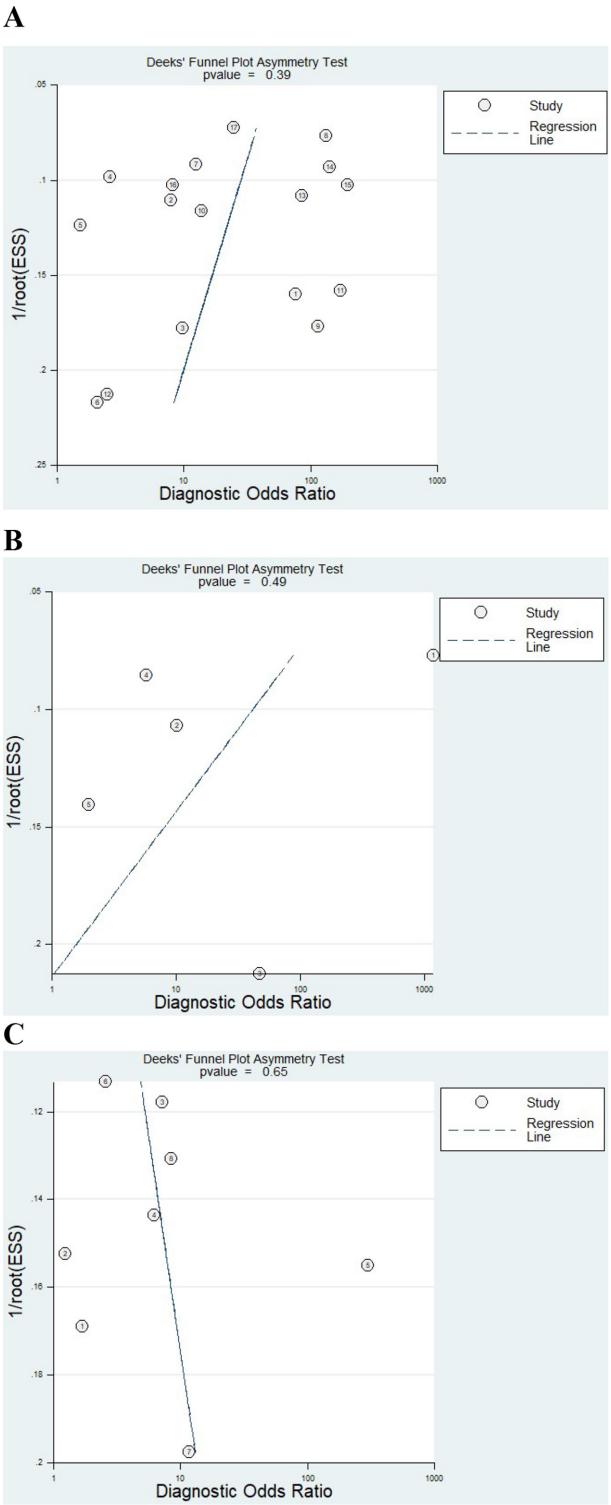

Figure 5 Publication bias assessment. Deeks' funnel plot with superimposed regression line. (A) Deeks' funnel plot for US to DD assessment; (B) Deeks' funnel plot for US to JE assessment; (C) Deeks' funnel plot for US to CC assessment.

review investigated the performance of US compared to MRI in JIA patients and found a wide variation in the sensitivity (0–72%) and specificity ranging from 70 to 83%. Furthermore, they found that in JIA patients, dynamic US improves sensitivity and specificity compared to static US.[60]

Summary of evidence

Based on this review results, the diagnostic ability for ultrasound to diagnose TMJ pathology varied widely from poor to excellent, depending on factors which are not clearly delineated in the various reports. In summary, the present synthesis showed US has a moderate diagnostic capability to assess DD and JE, which justify its use in clinical practice for these purposes. We cannot fully assess its diagnostic capability to CC assessment since only one study presented acceptable DTA values. Overall, the specificity and NPV of ultrasound seemed slightly higher than sensitivity and PPV values for each type of TMJ alteration. Clinically, these indicated that ultrasound is better to exclude than to confirm TMD. In this case, MRI should be used to confirm TMD detected by US. Therefore, ultrasound may contribute to clinical examination as an initial screening tool as has already been proposed in some medical areas. More advanced imaging can follow. That way the expensive resources are used more efficiently.

For the future studies, a 3D US dynamic approach with high-resolution transducer should be considered to verify if the reliability of the examination would increase. To DD assessment, the clinical significance of the disc movement patterns and its position abnormalities should be taken into account in further studies. Also, researchers are encouraged to address the diagnostic capability of US to CC assessment using appropriate reference standard. Despite the large studies in this field and the improvement of the ultrasound imaging in the last years, it is still necessary to standardize the TMD assessment by ultrasound. Possibly, studies stablishing the normal parameters of ultrasound TMJ evaluation could contribute to the standardization.

Limitations

Some limitations of this review should be considered. First, some papers did not describe the thresholds to determine the presence of DD, JE or CC. Second, six papers did not provide information about the blind interpretation of the reference standard results. These two limitations may influence the test performance estimation and DTA values presenting here could be affected.

Despite the summary of sensitivity/specificity were provided by the presented forest plots, caution should be exercised while interpreting these pooled results. First, positive and negative predictive values may vary with disease prevalence. Second, high heterogeneity and potential biases inherent to the included studies could have magnified pooled accuracy. Finally, the combined

approach does not take into account the possibility of different test thresholds in the studies.

The forest plot shows a large range of accuracy values, this could be due to the studies criteria to select participants or the criteria used to acquire and to evaluate the images. There was a large number of studies from the same group. 16 studies belong to three research groups (Frankfurt University-Germany, University of Pisa-Italy and University of Innsbruck-Austria).[12–14,27,28,31–33,36,38–42,46,47] Despite this, the results vary between the studies of the same group and no standardization or protocol are observed for TMD assessment by US.

Conclusion

This systematic review suggests that ultrasound may have clinically acceptable capability to screen for disk displacement and joint effusion in TMD patients. For screening of condylar changes, ultrasound needs further studies using CT or CBCT as the reference standard to support its use. More advanced imaging such as MRI can be used after a positive screening with ultrasound to confirm the TMD diagnosis if deemed necessary.

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Conflict of interest

The authors declare that they have no conflict of interest.

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