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A Systematic Review On Delayed Acquisition of Post-gadolinium MRI in Meniere's Disease: Imaging of the Endolymphatic Spaces

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AL: literature review and analysis, writing the first draft and revising and approving the final draft; GK: conceptualization, literature analysis, revising the first draft and approving the final draft.

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Abstract

Objectives: To assess the clinical implications of delayed-acquisition post-gadolinium Magnetic Resonance Imaging (MRI) in identifying endolymphatic hydrops (EH) in Meniere's disease (MD).

Methods: We performed a systematic review including Medline and Embase following the PRISMA guidelines with predetermined criteria, namely MD, post-gadolinium MRI and EH; we used QUADAS-2 to assess bias.

Results: Eleven studies were included; they all used 3T MRI with 3D-FLAIR being the most common sequence. Intravenous gadolinium administration was more widely used compared to the intratympanic route. As for the timing of acquisition, 4 hours post-administration was universally used for the IV and 24 hours for the IT gadolinium. Despite patient-selection associated bias, all studies reported adequate visualisation of the endolymphatic spaces.

Conclusion: The use of delayed-acquisition MRI is increasingly supported in visualising the endolymphatic spaces in MD. While the accessibility of 3T MRI questions its wider applicability, it is a promising tool for the near future.

Keywords:

Endolymphatic Hydrops, Gadolinium, Meniere Disease, Magnetic Resonance Imaging

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Introduction

Meniere's disease (MD) is an inner ear disorder that is characterised by recurrent spontaneous episodes of a range of symptoms which can include vertigo, fluctuating low-frequency sensorineural hearing loss, tinnitus and aural fullness [1]. The prevalence of MD in the US population in 2010 was 190 per 100 000 [2]. Furthermore, it is a disease more common among adults especially for those who are in their fourth decade of life and patients usually first experience symptoms between the ages of 20 and 60 [3]. Patients initially have symptoms on one side with some patients developing bilaterality after many years [4]. The male to female ratio varies from nearly equal for both sexes to a slight female preponderance which can go up to 1:1.3 [3]. The diagnosis of MD is not always straightforward as there are no widely accepted confirmatory diagnostic tests. Patients with MD may not present with all of the classical symptoms as described above during the first encounter. Therefore, MD can only be diagnosed at a later stage when the patient already has more than one episode of disease flare-up [1-6]. Currently, most studies are using the diagnostic criteria for MD set by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria in 1995, which take into account the natural history of the disease; MD is classified as certain, definite, probable or possible [1].

The pathological hallmark of this disease is believed to be the endolymphatic hydrops (EH), which was first observed in post-mortem examination of patients with MD in 1938, without, however, a causal relationship to have ever been proven [4]. EH is the distension of the membranous labyrinth of the inner ear which can occur in both the vestibule and the cochlea [4]. This hydrops was conventionally thought to cause the symptoms experienced by the patients affected with the disorder as the sensory and neural elements of the inner ear are damaged as a result of the release of the endolymphatic fluid into the perilymph [4, 5]. Thus, visualising EH could be a potential tool in confirming the diagnosis and monitoring the progress of MD in vivo. However, EH can also be caused by trauma, viral infections, autoimmune diseases and electrolyte imbalance which can potentially confound the findings of Magnetic Resonance Imaging (MRI) [6].

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The potential to visualise the EH in vivo was first established in an animal study using post-intratympanic gadolinium MRI [7]. Since then, various projects have studied the use of MR Imaging to visualise the EH after intravenous or intratympanic administration of gadolinium [8, 9]. In an additional study, three-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) and 3D-REAL IR (three-dimensional real inversion recovery) sequences are used in post-gadolinium EH imaging as they can produce images that differentiate between the endolymphatic space and the perilymph [10]. The delayed acquisition of MRI scan post-gadolinium is also important as the perilymph is most enhanced after around 3.5 to 4.5 hours, which appears as a bright signal in the image of 3D-FLAIR [11]. Conversely, the endolymph is non-enhanced, which appears as a dark signal in the image of 3D-FLAIR [11]. This is because the perilymphatic is more permeable to the gadolinium contrast compared to the endolymphatic space and the presence of the blood-labyrinth barrier does not allow the contrast to easily enter the endolymph [10]

To assess the presence and severity of EH using MR imaging, Nakashima et al have developed a grading system to categorise the EH in both vestibule and cochlea as none, mild or significant [12]. Vestibular EH is graded as none when the ratio is less than 1:3, mild when the ratio is between 1:3 and 1:2, or significant when the ratio is more than 1:2 [12]. As for cochlear EH, the grading is dependent on the displacement of the Reissner's membrane [12]. Cochlear EH is graded as none if no displacement of the Reissner's membrane can be identified, mild if the Reissner's membrane is displaced but not exceeding the space occupied by the scala vestibuli, or significant if the Reissner's membrane is displaced to the point of exceeding the scala vestibuli [12]. An alternative to this grading system is to evaluate the morphology of the saccule and compare this with the utricle to form the inversion of saccule and utricle ratio as it was noted that saccule is more commonly affected in EH compared to the utricle [13].

Despite the recent reports on delayed-acquisition post-gadolinium MRI and EH, a systematic review of the current literature with a focus on the used techniques and its clinical implications is missing. On these grounds, our objectives were to assess imaging methods that are optimal for visualising EH in patients with MD and evaluate the use of visualising EH in aiding the diagnosis of MD.

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Methods

Review Question

The topic of interest for this review is "the strength of delayed acquisition of post-gadolinium MRI in diagnosing MD". The key question that arises from this topic includes "Is visualisation of EH using post-gadolinium MR imaging adequate to diagnose MD?".

Inclusion and Exclusion Criteria

We searched for studies assessing the strengths and limitations of delayed-gadolinium MRI for detecting endolymphatic hydrops. We specifically focused on whether delayed-gadolinium MRI can detect endolymphatic hydrops and what the clinical implications of such finding are. We also documented the technical parameters used by each study with focus on the route of gadolinium administration and the delay between gadolinium administration and MRI acquisition. Table 1 demonstrates the inclusion and exclusion criteria used to perform the literature search in this review.

Search Strategy

Medline and Embase were used in the systematic search. In addition to that, the reference section listed in relevant studies were manually searched to find other potential studies that met the inclusion criteria. The literature search included the criteria: MD, post-gadolinium MRI, EH in the English language without a time limit; case reports were excluded. Preferred Reporting Items for Systematic Reviews and Metanalysis (PRISMA) was utilised for the methodology of this review [14].

Out of a total of 30 results, we ruled out 17 based on their title and abstracts. Finally, a total of 11 studies were included for review. Any duplicates that were found during the manual search were excluded from this review. The methodology of the search strategy carried out is summarised in Figure 1.

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Data Extraction

Two investigators conducted the data extraction independently. The following information was extracted from the articles that met the eligibility criteria:

- Number of patients with MD
- How the diagnosis of MD (or no MD) was set
- Type (strength of magnetic field) of scan and sequences used
- Dose and route of gadolinium
- Number of hours post-gadolinium administration that the MRI was acquired
- Items/ areas of interests assessed on the scans
- Assessment of EH and where exactly in the inner ear this was assessed
- The person(s) who carried out the assessment and whether the assessment was blinded or not (including information whether the scan assessment was performed by multiple assessors independently and in such case reports on interobserver reliability), and
- Side effects.

The data were extracted and then tabulated in the form of an Excel spreadsheet.

Assessment of bias

We used the QUADAS-2 tool to assess the bias in the included studies [15]. Due to the predominantly experimental nature of the studies, it was difficult to identify a bias tool that suited the needs of the current review; however, as we were primarily looking into diagnostic accuracy, the four domain QUADAS-2 tool was the most appropriate one. Additionally, we used screening of the studies by two independent investigators to eliminate any bias. The results of the QUADAS-2 tool are highlighted in Table 2 and Figure 2.

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Results

Characteristics of the Studies and MRI settings

The number of participants for each study varies, ranging from 6 to 68 participants; they were all diagnosed with MD using the AAO-HNS diagnostic criteria [1]. The type of scanner used for all of the studies is the 3T MRI scanner with 3D-FLAIR being the most common sequence used; 8/11 studies use 3D-FLAIR only, 1/11 study use 3D-real IR only and 2/11 studies use both 3D-FLAIR and 3D-real IR.

As for the route of gadolinium administration, most of the studies use IV only (8/11) with the rest being IT only (2/11) and both IV and IT (1/11). The dose of gadolinium used for the IV route varies from 0.1 mmol/kg (6/11) to 0.2 mmol/kg (3/11) whereas the dose for the IT route ranges from 5-fold dilution (1/11) to 8-fold dilution (2/11). In terms of the time of acquisition of MRI post-gadolinium, 4 hours is the most widely used (8/11) for the IV route. As for the IT route, 24 hours is used (3/11). Shi et al and Sano et al used multiple times of acquisition, which include 3 hours, 6 hours and 12 hours for Shi et al and 10 minutes for Sano et al [22, 24]. Additionally, Attye et al [20] reported an acquisition time of between 4.5 and 5.5. hours. Table 3 demonstrates the number of patients and the imaging techniques used in each study.

Radiological assessment and findings

Table 4 outlines the structures that were visualised in the MR images, measurements that were used to evaluate EH and the persons who evaluated the scans for each study. EH of both the vestibuli and cochlea were evaluated for almost all of the studies (9/11) with two studies only evaluated the vestibular EH. All of the studies that investigated cochlear EH determined its presence by observing if there are any dilatation of the cochlear duct. As for vestibular EH, the cut-off values for VES/vestibule ratio include 33.3% (7/11), 45% (1/11) and 50% (2/11). Additionally, Attye et al also

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described the use of SURI technique (Saccule to Utricle Ratio Inversion) to determine the presence of EH in the vestibule [13, 20].

As for the number of radiologists/persons who evaluated the scans for each study, 6/11 had 2 persons evaluated the scans, 3/11 had only one person evaluated the scans and 2/11 did not mention who evaluated the scans. 8/11 studies state that the evaluators were blinded to clinical data while the rest (3/11) did not mention any form of blinding.

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Discussion

Main findings

This is, to our knowledge, the first review to assess the potential strengths and biases associated with the evaluation of EH using the delayed gadolinium MRI, as well as the clinical applicability of such technique. We include a series of main findings of both radiological and clinical significance. Firstly, all studies used the 3T MRI scanner with 3D-FLAIR being the most commonly used MRI sequence to assess EH. Secondly, the IV route of administering gadolinium was overall found to be more ubiquitous than the IT route. Thirdly, all studies used some form of semi-quantitative grading systems in their assessment of EH. As for the timing of acquisition of MRI, 4 hours appeared to be the most commonly used for IV gadolinium. In contrast, 24 hours is more commonly used for IT gadolinium. Moreover, most of the studies included experienced radiologists for assessing EH of both the vestibule and cochlea who were blinded to clinical data. Despite the relatively small number of so far carried out studies, the used protocols appear grossly uniform with only minor modifications.

However, we identified bias mostly in the patient selection but also in the methodology of scan assessment (lack of independent or blind review in some studies); to overcome these limitations further studies to strengthen the evidence of utilising MRI for diagnostic purposes in MD will be required.

Technical considerations and clinical implications

There are several explanations why certain parameters were used more frequently in these studies. Firstly, 3D-FLAIR was used more frequently than 3D-real IR as it is more sensitive to gadolinium contrast and no post-imaging processing is required [10]. Additionally, administering gadolinium through the IV route provides a shorter acquisition time than the IT route and allows for visualising of both the inner ears [10]. As for the dose of gadolinium used, it is dependent on the optimisation of the imaging sequence. Lower concentrations are needed for heavily T2-weighted 3D-FLAIR, which makes it more ideal in the clinical settings as it could reduce any concerns about potential side effects of gadolinium on the patients [22]. There are multiple semi-quantitative grading systems used in these

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studies which demonstrates the lack of standardisation in assessing EH. Therefore, the objectivity of determining EH on MRI scans is difficult to examine.

Additionally, all published studies have used 3T MRI, which, although more accessible than in the past in many places, still is not widely available. There are no studies utilizing a weaker magnetic field; thus, delayed acquisition post-gadolinium MRI for identifying EH is not possible in many areas. This limits its applicability but also restricts the set-up of future studies.

With respect to the clinical implication of the available studies, while the endolymphatic spaces can well be visualized, it remains unclear to what extent the presence or absence of EH can confirm or exclude the diagnosis of MD. Attye et al recently showed that EH can be related to sensorineural hearing loss rather than the presence of MD itself [20]. While the endolymphatic spaces are well visualized, the diagnosis of MD cannot be set based on purely radiological grounds. While MRI can facilitate the diagnosis, MD still remains predominantly a clinical diagnosis.

Strengths and limitations of the included studies

There are several limitations of the studies that are included in this review. Firstly, the sample size of each study is small due to the low prevalence of MD; additionally, the included studies did not comment on the power of the enrolled cohorts. The small sample size makes it more difficult to validate the effectiveness of these imaging techniques in identifying EH and its relation to MD. Secondly, some studies only had one radiologist evaluating the scans, which methodologically questions the robustness and the reliability of the measurements. Moreover, some of the studies did not mention any form of blinding, which may lead to biases when it comes to the interpretation of scans in patients with MD. Additionally, the majority of these studies did not use healthy controls with no inner ear pathologies to make comparisons with patients diagnosed with MD.

We used the QUADAS-2 tool to identify and highlight these limitations to include accurate data and meaningful conclusions that help with the clinical significance of such imaging techniques. According to the QUADAS-2 tool, patient selection appeared to be at high risk of bias for most of the studies as the patients are not randomly selected; some studies did not include all of the patients recruited in the

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results due to various reasons. Additionally, there is a high risk of bias for the index test domain of the QUADAS-2 tool for 6 out of 11 studies in the review.

Bullet point summary

- Delayed acquisition of post-gadolinium Magnetic Resonance Imaging (MRI) appears accurate in visualising the endolymphatic spaces, improving our understanding of the inner ear and particularly Meniere's disease.
- While intratympanic gadolinium can also be used, intravenous administration with MRI acquisition four hours later seems to be the preferred and most practical option.
- The use of 3T MRI is the preferred strength of magnetic field; however, as 3T MRI scanners are not widely available, yet, the applicability of such technique is currently limited. Future developments should overcome this issue.

Conclusion

Recent advances in MRI techniques have enabled us to identify EH on delayed acquisition post-gadolinium MR imaging; this carries the potential in aiding the diagnosis of MD and also guide the clinicians to decide on optimal treatment. However, these techniques need to be more thoroughly validated before they can be widely used in the management of patients with MD; the availability of a 3T MRI scanner could also be an issue. We identified bias in most of the included studies; thus, future studies including larger number of patients and control groups should help with further improving this developing and promising technique.

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Table 1: Inclusion and exclusion criteria

	Inclusion	**Exclusion**
Patient demographics	Diagnosed with MD based on the AAO-HNS diagnostic criteria [1].	Non-MD patients
Imaging techniques	Post-gadolinium MR imaging through intravenous or intratympanic routes.	Other imaging techniques.
Items visualised	EH	Other items that are not related to EH.

MD: Meniere's disease; EH: endolymphatic hydrops

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Table 2: Results of QUADAS-2 assessment [15]

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Yoshida et al [16]	X	X	—	✓	✓	✓	—
Barath et al [17]	X	✓	—	✓	✓	✓	—
Sepahdari et al [18]	X	✓	—	✓	✓	✓	—
Tagaya et al [19]	X	X	—	✓	✓	✓	—
Attye et al [20]	✓	✓	—	✓	✓	✓	—
Attye et al [13]	✓	✓	—	✓	✓	✓	—
Claes et al [21]	X	X	—	✓	✓	✓	—
Sano et al [22]	X	X	—	✓	✓	✓	—
Pakdaman et al [23]	X	✓	—	✓	✓	✓	—
Shi et al [24]	X	X	—	✓	✓	✓	—
Naganawa et al [25]	X	X	—	✓	✓	✓	—

✓ Low Risk X High Risk — Unclear Risk

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Table 3: Number of patients and imaging techniques used for each study

Studies	**Number of patients with MD (n)**	**MR Sequences**	**Dose of gadolinium administered (mmol/kg)**	**Route of gadolinium administered (Intravenous (IV)/ Intratympanic (IT)**	**Time between gadolinium and MRI**
Yoshida et al [16]	42	3D-FLAIR	0.1	IV	4 hours
Barath et al [17]	53	3D-real IR	0.1	IV	4 hours
Sepahdari et al [18]	11	3D-FLAIR	0.2	IV	4 hours
Tagaya et al [19]	12	3D-FLAIR and 3D-real IR	0.2	IV	4 hours
Attye et al [20]	20	3D-FLAIR	0.1	IV	Between 4.5 and 5.5 hours
Attye et al [13]	30	3D-FLAIR	0.1	IV	4 hours
Claes et al [21]	12	3D-FLAIR	Eight-fold dilution	IT	24 hours
Sano et al [22]	6	3D-FLAIR	0.1	IV	10 minutes, 4 hours
Pakdaman et al [23]	32	3D-FLAIR	0.2	IV	4 hours

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Shi et al [24]	6	3D-FLAIR and 3D-real IR	5-fold dilution	IT	3 hours, 6 hours,12 hours, 24 hours
Naganawa et al [25]	10	3D-FLAIR	8-fold dilution (IT); 0.1 mmol/kg (IV)	IT and IV	24 hours (IT), 4 hours (IV)

All studies were performed in a 3T MRI scanner

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Table 4: Outline of items visualised on the scan, assessments used to identify EH, person who assessed the scans and whether the assessors are blinded or not for each study

Studies	**Number of patients with MD (n)**	**Strength of magnetic filed**	**MR Sequence (s)**	**Dose of gadolinium administered (mmol/kg)**	**Route of gadolinium administered (Intravenous (IV)/ Intratympanic (IT)**	**Time between gadolinium and MRI**
Yoshida et al [16]	42	3T MRI	3D-FLAIR	0.1	IV	4 hours
Barath et al [17]	53	3T MRI	3D-real IR	0.1	IV	4 hours
Sepahdari et al [18]	11	3T MRI	3D-FLAIR	0.2	IV	4 hours
Tagaya et al [19]	12	3T MRI	3D-FLAIR and 3D-real IR	0.2	IV	4 hours
Attye et al [20]	20	3T MRI	3D-FLAIR	0.1	IV	Between 4.5 and 5.5 hours
Attye et al [13]	30	3T MRI	3D-FLAIR	0.1	IV	4 hours
Claes et al [21]	12	3T MRI	3D-FLAIR	Eight-fold dilution	IT	24 hours
Sano et al [22]	6	3T MRI	3D-FLAIR	0.1	IV	10 minutes, 4 hours
Pakdaman et al [23]	32	3T MRI	3D-FLAIR	0.2	IV	4 hours
Shi et al [24]	6	3T MRI	3D-FLAIR and 3D-real IR	5-fold dilution	IT	3 hours, 6 hours,12 hours, 24 hours
Naganawa et al [25]	10	3T MRI	3D-FLAIR	8-fold dilution (IT); 0.1	IT and IV	24 hours (IT), 4 hours

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				mmol/kg (IV)		(IV)

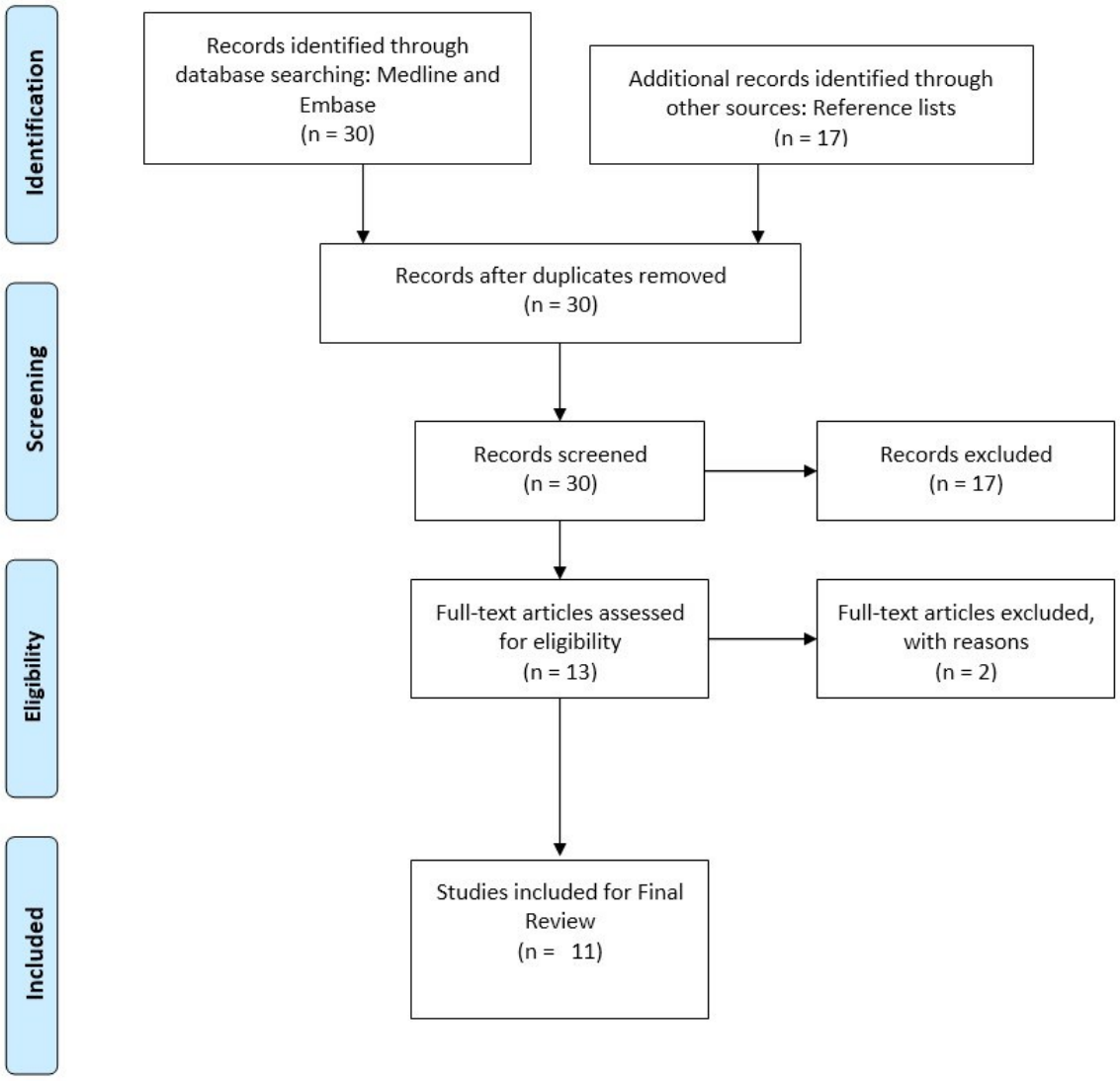

Figure 1: Flow diagram adapted from PRISMA 2009 [14]

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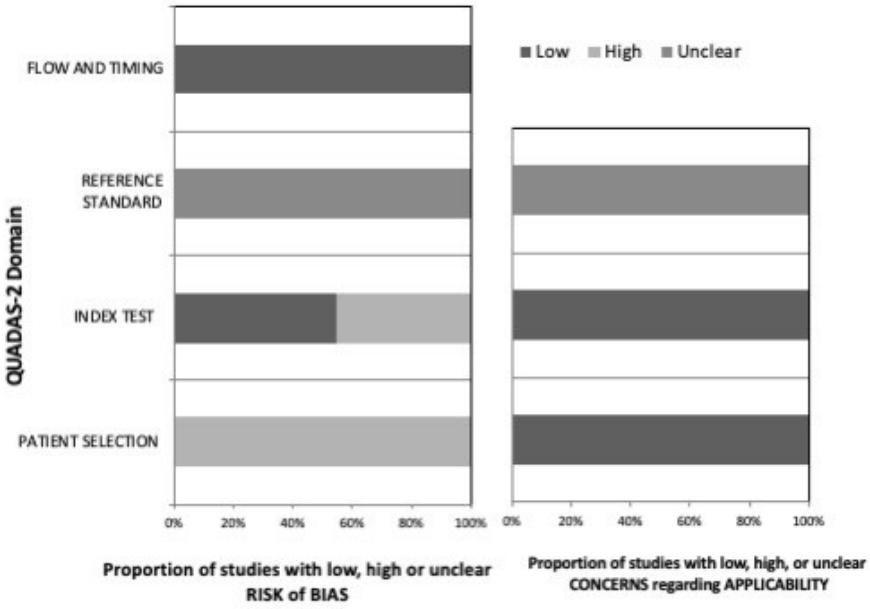

Figure 2: Graph illustrating the proportion of studies with low, high or unclear risk of bias and concerns regarding applicability using the QUADAS-2 tool [15]

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