Objective measures of adenomyosis on MRI and their diagnostic accuracy

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SYSTEMATIC REVIEW

Objective measures of adenomyosis on MRI and their diagnostic accuracy—a systematic review & meta-analysis

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Abstract

Introduction: Magnetic resonance imaging (MRI) diagnosis of adenomyosis is considered the most accurate non-invasive technique, but remains subjective, with no consensus on which diagnostic parameters are most accurate. We aimed to systematically review the literature on how adenomyosis can be objectively quantified on MRI in a scoping manner, to review the diagnostic performance of these characteristics compared with histopathological diagnosis, and to summarize correlations between measures of adenomyosis on MRI and clinical outcomes.

Material and methods: We searched databases Pubmed, Embase, and Cochrane for relevant literature up to April 2020 according to PRISMA guidelines. We included studies that objectively assessed adenomyosis on MRI, and separately assessed studies investigating the diagnostic performance of MRI vs histopathology for inclusion in a meta-analysis. The QUADAS-2 tool was used for risk of bias, with many studies showing an unclear or high risk of bias.

Results: Eighty studies were included, of which 14 assessed the diagnostic performance of individual MRI parameters, with four included in the meta-analysis of diagnostic accuracy. Common MRI parameters were: junctional zone (JZ) characteristics, such as maximum JZ thickness—pooled sensitivity 71.6% (95% CI 46.0%–88.2%), specificity 85.5% (52.3%–97.0%); JZ differential—pooled sensitivity 58.9% (95% CI 44.3%–72.1%), specificity 83.2% (95% CI 71.3%–90.8%); and JZ to myometrial ratio—pooled sensitivity 63.3% (95% CI 51.9%–73.4%), specificity 79.4% (95% CI 42.0%–95.4%); adenomyosis lesion size, uterine morphology (pooled sensitivity 42.9% (95% CI 15.9%–74.9%), specificity 87.7%, (95% CI 37.9–98.8) and changes in signal intensity—eg, presence of myometrium cysts; pooled 59.6% (95% CI 41.6%–75.4%) and specificity of 96.1% (95% CI 80.7%–99.3%). Other MRI parameters have been used for adenomyosis diagnosis, but their diagnostic performance is unknown. Few studies attempted to correlate adenomyosis MRI phenotype to clinical outcomes.

Conclusions: A wide range of objective parameters for adenomyosis exist on MRI; however, in many cases their individual diagnostic performance remains uncertain.

Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging; HIS, high signal intensity; JZ, junctional zone; LSI, low signal intensity; MRI, magnetic resonance imaging; SI, signal intensity.

JZ characteristics remain the most widely used and investigated with acceptable diagnostic accuracy. Specific research is needed into how these objective measures of adenomyosis can be correlated to clinical outcomes.

KEYWORDS
adenomyosis, diagnosis, endometriosis, magnetic resonance imaging, non-invasive imaging, uterus

1 | INTRODUCTION

Adenomyosis is a prevalent and potentially debilitating gynecological condition characterized by dysmenorrhea and heavy menstrual bleeding. Adenomyosis is thought to arise from and lead to disruptions in the uterine "junctional zone" (JZ) between the uterine endometrium and myometrium. With the advent of improving imaging techniques, adenomyosis has been more frequently diagnosed in younger, nulliparous women. Along with greatly affecting their quality of life, it is also increasingly linked to subfertility or infertility and to adverse pregnancy outcomes.[1–3] The relation between (the extent of) adenomyosis and these clinical outcomes remains largely unknown.

One barrier to elucidating the relation between adenomyosis (severity) and clinical outcomes is the accurate diagnosis of adenomyosis. Despite continuing advances in two- and three-dimensional transvaginal ultrasound imaging, MRI is generally considered to be the most consistently accurate in the diagnosis of adenomyosis;[4,5] however, there is still no accepted classification system or a set of diagnostic criteria to evaluate adenomyosis on MRI. Much has been reported about typical, atypical, direct, and indirect MRI manifestations of adenomyosis,[6,7] but the recognition of these features often still depends on the experience and expertise of the radiologist and/or gynecologist. Furthermore, it is still disputed which of the wide range of features reported is the most accurate. This makes it difficult to assess the true diagnostic accuracy of MRI for adenomyosis as different centers and physicians may use different criteria.

If adenomyosis could be noninvasively and objectively quantified (eg, on MRI), the burden of disease could be correlated with various clinical outcomes, such as symptom severity, therapy response, or fertility outcomes. Similarly, potential changes in adenomyosis could be more easily followed over a patient's lifetime, or during their menstrual cycle.[7–10] To the best of our knowledge, there is currently no comprehensive overview describing the quantitative analysis of adenomyosis on MRI.

The objectives of this review are as follows: the primary objective is to evaluate the diagnostic accuracy of MRI features for adenomyosis vs histopathology, with secondary objectives being to (a) summarize in a scoping manner how adenomyosis can be objectively quantified on MRI, and (b) how objective measures of adenomyosis on MRI have been correlated to clinical outcomes.

Key message

There are insufficient data on the diagnostic accuracy of adenomyosis MRI parameters, and their clinical relevance is equally unclear. This review provides a starting point for future studies investigating the link between adenomyosis MRI phenotype and clinical outcomes.

2 | MATERIAL AND METHODS

The full review protocol can be found on the PROSPERO database, with protocol ID CRD42020163106.

2.1 | Data sources

The search was conducted in online databases PubMed (MEDLINE), Embase, and Cochrane, and relevant articles were also screened for additional references missed in the initial search. The search was conducted using synonyms and keywords relating to adenomyosis and MRI. Full search details can be found in the Supporting Information Appendix S1.

2.2 | Main outcome measures

The outcomes of this review were the existing objective measures of adenomyosis on MRI, and their (if stated) individual diagnostic accuracy and relation to clinical outcomes.

2.3 | Study eligibility

We included studies investigating the diagnosis, evaluation or classification of adenomyosis objectively based on MRI. Studies were included regardless of study design, use of hormonal therapy, age, or clinical manifestation. Studies written in English, Dutch or French were considered for inclusion, published up to April 7, 2020.

Data reported in secondary analysis (reviews), case reports, letters to editors, conference abstracts, and protocols for ongoing

studies were excluded. We also excluded studies that only reported subjective measures of adenomyosis on MRI, eg, lesion localization, subjective signal intensity, that is, "dark" or "low", or only noting "JZ irregularity" without objectifying this (by measurement in mm).

2.3.1 | Quality assessment and risk of bias:

A risk-of-bias assessment of included studies was only carried out for the studies investigating diagnostic accuracy, using the QUADAS-II tool[11] (Tables S8–S11). Risk-of-bias summary graphs and tables were constructed using RevMan 5.3.0. It was not deemed relevant to assess the quality of the other studies investigating adenomyosis on MRI for risk of bias.

2.4 | Data collection and analysis

2.4.1 | Study selection

Study selection was conducted in Rayyan (rayyan.qcri.org) in a blinded fashion by two reviewers (CR and IR) based on title and abstract, followed by full-text assessment. If full-text was not available, contact was sought with the corresponding author of the article. The relevant articles were sorted into one or both of two groups upon full-text screening and data extraction was performed separately (Tables S1–S4):

- Studies investigating diagnostic accuracy of adenomyosis on MRI vs histopathology
- Studies evaluating adenomyosis objectively on MRI without assessing diagnostic accuracy

2.4.2 | Data collection and extraction

Data extraction was carried out independently by two reviewers (CR and IR). Data were collected pertaining to study design, study population, the type of MRI conducted, definition of adenomyosis on MRI, the diagnostic performance (if reported) of MRI parameters, as well as whether the MRI diagnosis was confirmed with histopathology. All measured MRI characteristics of adenomyosis on MRI were extracted, with a focus on objective measures. Examples of objective measures include: JZ thickness (in mm), uterine volume or length, adenomyosis lesion size (in mm, or cm^3). If clinical or treatment outcomes were mentioned (in relation to MRI characteristics), these were also reported (see Supporting Information for the full data extraction, Tables S1–S4).

2.4.3 | Data synthesis and statistical analysis:

Data synthesis was done in two steps, dependent on the study design. For studies investigating diagnostic accuracy, data were synthesized narratively, and the diagnostic performance measures were summarized. We produced forest plots in Graphpad Prism 8.0 showing pairs of sensitivity and specificity together with 95% CI from each study (based on extracted data in 2 × 2 tables for each study). Summary receiver operating characteristic curves were constructed using MetaDTA. Separate forest plots and summary receiver operating characteristic curves were created for each diagnostic MRI parameter where the relevant diagnostic information was available. A pooled sensitivity and specificity for each parameter (if possible) was calculated using MetaDTA[12] using a bivariate model. Illustrative MRI images per objective parameter were taken from our center.

3 | RESULTS

3.1 | General characteristics of the studies

3.1.1 | Search results

As shown in Figure 1, a total of 80 articles were ultimately deemed eligible for inclusion in this review. Fourteen were diagnostic accuracy studies that investigated MRI vs histopathology for adenomyosis, four of which reported diagnostic accuracy data for individual MRI parameters (eg, JZ thickness >12 mm) and could be included in the meta-analysis. The remaining 66 studies were of varying study designs and did not investigate the diagnostic performance of MRI specifically, but did describe objective measures of adenomyosis on MRI, and were included to satisfy the secondary objectives of this review.

3.1.2 | Characteristics of included studies

The study characteristics and outcomes for the included studies are summarized in Supporting Information Tables S5–S7. The MRI sequences most often implemented to assess adenomyosis on MRI were T1- and T2-weighted MRI. Eight studies reported using a 3.0-Tesla coil MRI, the remaining studies used 1.0- or 1.5-Tesla coil MRI.

3.1.3 | Methodological quality of included studies

Only the studies investigating diagnostic accuracy were assessed for methodological quality. A graphical summary of the quality assessment is shown in Figure 2, as well as the assessment per included study in Figure 3. In the domain of patient selection, two studies were deemed to have a high risk of bias because of their retrospective design and/or unclear exclusion criteria.[13,14] For the index test domain (MRI), two studies had a high risk of bias, as no definition of adenomyosis before MRI evaluation was reported.[15,16] As for the reference standard domain, many studies did not clearly report if pathologists were blinded. Two studies were deemed to have a high risk of bias as in one[17] the assessment of the reference

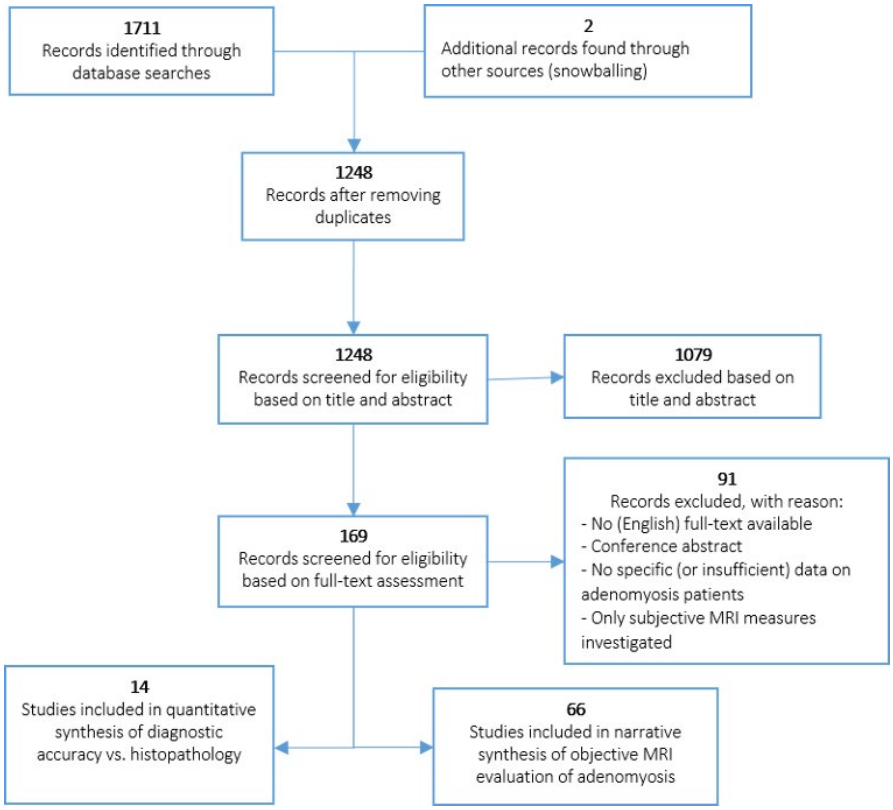


FIGURE 1 PRISMA flow diagram of study selection

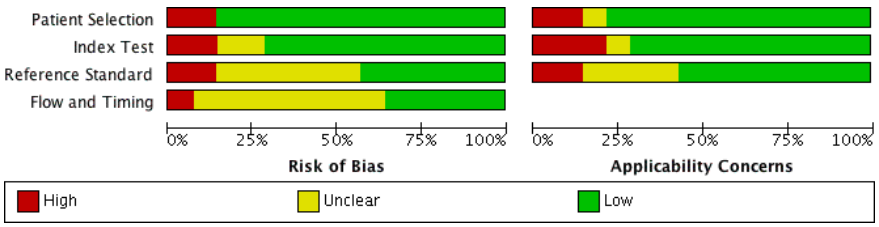


FIGURE 2 Summary graph of study quality according to the QUADAS-II tool

test was not blinded, and in the other[18] the reference diagnosis was only made based on myometrial biopsy instead of hysterectomy. For patient flow and timing, most studies did not provide enough information to assess this domain properly. Hamimi et al[14] had a high risk of bias on this domain as not all patients received the same reference standard diagnosis. Two studies[14,18] were arguably less applicable with regards to the analysis of diagnostic accuracy. Hamimi et al did not compare the index test to histopathological diagnosis in many cases, and Phillips et al only investigated the diagnostic performance of MRI in relation to adenomyomas, and not adenomyosis generally. Because of their low applicability and quality, the results of these two studies were not included in the meta-analysis. Complete details per study can be found in Supporting Information (Tables S8–S11).

3.2 | Results synthesis

We identified four common characteristics that have been used to diagnose and objectively visualize adenomyosis on MRI: JZ thickness and irregularity, adenomyosis lesion size, overall uterine morphology, and tissue signal intensity (see Table 1 for a full overview, and Table S12). The pooled diagnostic accuracy of MRI parameters can be seen in Table 2 (Figure 4).

3.2.1 | Junctional zone thickness

Thickness of JZ was the most widely reported objective measure of adenomyosis. Fifty-six studies (see Table 1 for details) reported measurement of JZ thickness in the assessment or diagnosis of adenomyosis. Studies reported differing threshold values of the JZ, with the cut-off ranging between 5 mm[10] and 15 mm,[19] with 12 mm being the most common (see Figure 4 for an example). The individual diagnostic accuracy of this value was reported in four studies (see Table 2, Figure 5 and Figures S1 and S2 for details). Most studies reported using the mean JZ diameter to assess adenomyosis, but several studies also separately noted the maximum (JZ Max, n = 1) and minimum (JZ Min, n = 5) diameter.

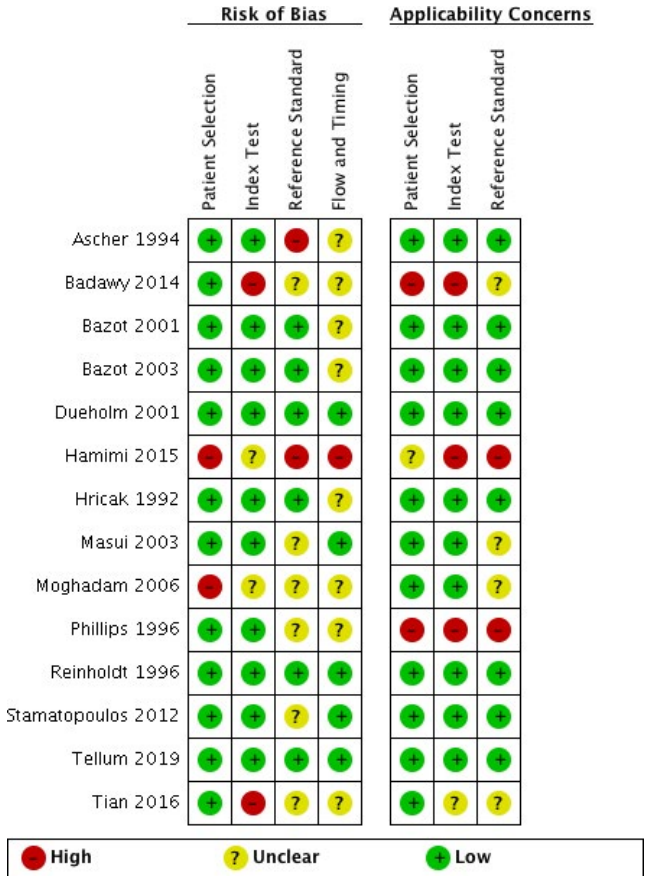


FIGURE 3 Quality assessment per included study according to the QUADAS II tool

3.2.2 | Junctional zone differential / junctional zone irregularity

Another frequently reported(n = 7 studies) quantifiable measure of adenomyosis on MRI is the JZ differential (JZ Diff). This is calculated by subtracting the JZ Min from the JZ Max, and functions as an objective measure of the irregularity of the uterine JZ, which can be a diagnostic criterion for adenomyosis (see Figure 6 for an example).

Two studies[19,20] investigated its diagnostic performance (see Table 2, Figure 7, Figures S3 and S4 for details). JZ asymmetry, measured as the difference between the anterior and posterior JZ at the same point of the uterus, was only mentioned in one study, see Figure 8.[21]

3.2.3 | Junctional zone to myometrium ratio / extent of myometrial involvement

In order to quantify the extent of invasion by adenomyosis on MRI, several studies have investigated the (maximum) ratio of JZ to normal myometrium of the uterus (n = 16 studies, see Table 1). This is thought to signify a relative increase in JZ thickness, and thereby myometrial tissue involvement. It is expressed as a percentage or ratio, with a value of 40%–50% generally thought to indicate adenomyosis (see Figure 9 for an example).

Two studies investigated the diagnostic performance of this parameter (see Table 2, Figure 7 and Supporting Information Figures S5 and S6 for details) (Figure 9).

3.2.4 | Adenomyosis lesion size

Specifically for focal type adenomyosis, the lesion size or volume was often reported as a method to quantify the extent of adenomyosis (see Figure 10 for an example, n = 27 studies, see Table 1). The adenomyosis lesion was usually identified based on an "ill-defined" low-intensity area in the myometrium on T2-weighted imaging. No studies investigated this parameter in the context of diagnostic accuracy, with most studies assessing (reduction in) lesion size as a measure of treatment response. Only one study investigated lesion size with clinical outcome, and suggested that extent of lesion volume reduction after treatment may have a direct relation with symptom reduction.[22]

In addition to elements of the JZ, another widely reported measure of adenomyosis on MRI is how it affects the uterus as a whole.

3.2.5 | Uterine morphology

The volume or size (length) of the uterus (see Figure 11 for an illustrative example) was used as an indicator for the extent of adenomyosis in 27 studies (see Table 1).

Only uterine enlargement was investigated for diagnostic accuracy (see Table 2, Figure 12, and Figures S7 and S8 for details).

Uterine wall thickness (either as a mean, or the maximum thickness) has also been reported, with 12 studies reporting this as an outcome measure (Table 1). Most studies assessed this parameter in the context of high-frequency ablation treatment. The shape of the uterus is an additional feature of adenomyosis that has been evaluated. Several studies reported homogeneous or smooth enlargement of the uterus as a defining characteristic of adenomyosis, and others looked at uterine asymmetry (as in Figures 13 and 14). Most studies evaluated this subjectively, but four studies[10,21,23,24] quantified the extent of uterine asymmetry by measuring the difference between the width of the anterior and posterior walls in the context of adenomyosis.

3.2.6 | Tissue signal intensity

A third element of adenomyosis that can be objectively characterized on MRI is the signal intensity (SI) of the affected tissue. Most studies only reported this subjectively (ie, low SI, high SI [LSI or HSI] foci in the myometrium, without further quantification). Three studies investigated the presence of HSI cysts or foci in the myometrium for their diagnostic accuracy (See Table 2, Figures 13 and 14 and Figures S9 and S10). No other parameters related to tissue signal intensity were investigated for their diagnostic accuracy.

TABLE 1 Objective measures of adenomyosis on MRI

MRI feature	Definition	Unit	Possible Stratification	Studies mentioned (ref. no.)[a]
Junctional zone parameters				
Mean JZ	Average JZ diameter	mm	<5 mm, <7 mm, <8 mm, <10 mm, <12 mm >12 mm, >15 mm	N = 56 (1–9,11–13,15–20,23–25,29–33,35–41,43–48,50,51,53–65,67,75)
JZ Max	Maximum diameter of JZ	mm	<7 mm, <10 mm, <12 mm >12 mm, >15 mm	N = 18 (1–9,11–13,15–20,23–25,29–33,35–41,43–48,50,51,53–65,67,75)
JZ Min	Minimum diameter of JZ	mm		N = 5 (5,15,29,48)
JZ Diff	As a measure of JZ irregularity Difference between maximum and minimum JZ	mm	<5 mm difference and >5 mm difference	N = 7 (5,13,15,29,48,58,63)
JZ asymmetry	Difference between anterior and posterior JZ	mm	<2 mm difference and >2 mm difference	N = 1 (30)
JZ to Myometrium Ratio	Ratio of JZ to full myometrium thickness at the same point of the uterine wall At maximum JZ, or as an average	%	>40% and <40%	N = 16 (3,11,13,15,17,21,25,29,36,41,44,48,53,58,64,76)
Adenomyosis lesion size				
Adenomyotic foci volume	Volume of adenomyotic foci in three orientations	mm^3	Diameter <40 mm 40–60 mm >60 mm	N = 27 (2,5,7,10,17,19–21,23,26–29,33,35,36,49,52,53,57,62,67,68,71)
Uterine parameters				
Uterine volume	Uterine volume measured at mid-corpus in 3 orientations	mm^3		N = 28 (5,10,16,19,24–26,28–31,37,41–44,51,52,54,56,58,59,63,66,68,70,71)
Uterine length	Measured from cervix to fundus in sagittal orientation	mm		N = 7 (23,29,32,57,71,78,80,89)
Average uterine wall thickness	Uterine wall thickness measured from endometrium to myometrium	mm		N = 12 (25,30,31,38–40,46–48,50,53,64)
Uterine asymmetry	Difference between anterior and posterior uterine wall	mm		N = 4 (30,48,50,75)
Tissue signal intensity				
Number of high signal intensity adenomyotic foci	Absolute number of visible high signal intensity myometrial foci (compared with normal myometrium) on T1 or T2 imaging	n		N = 3 (7,26,27)
Adenomyosis signal intensity ratio on T2 imaging	Signal intensity ratio of adenomyotic tissue compared with rectus muscle or normal myometrium (measured in ROI of the same size)			N = 4 (26,33,35,36)
ADC value	Apparent diffusion coefficient of adenomyotic tissue on DWI			N = 5 (14,32,33,40,69)

Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging; JZ, junctional zone.

[a]Reference numbers refer to the full reference list of the included studies as reported in Supporting Information Appendix S2.

Three studies[25–27] attempted to quantify the extent of adenomyosis by reporting the absolute number of HSI foci (on T2 imaging) in the myometrium (as shown in Figure 15). No cut-off value regarding the number of HSI foci has been described, with the majority of studies denoting their presence as stand-alone evidence of adenomyosis.

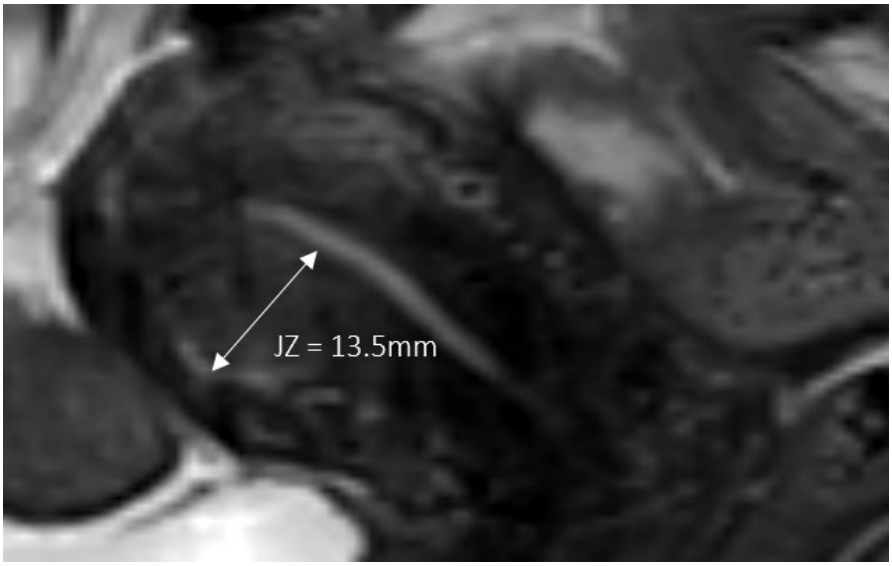
Four studies[22,26,28,29] described a method to quantify the SI of adenomyotic tissue further, on T2 imaging. In these studies the

TABLE 2 Pooled diagnostic accuracy of individual MRI parameters for adenomyosis

Adenomyosis MRI feature	Number of studies investigating diagnostic accuracy (n)	Pooled sensitivity (%, 95% CI)	Pooled specificity (%, 95% CI)
JZ thickness >12 mm	4	71.6 (46.0–88.2)	85.5 (52.3–97)
JZ differential >5 mm	2	58.2 (44.3–72.1)	83.2 (71.3–90.8)
JZ to myometrium ratio >40%	2	63.3 (51.9–73.4)	79.4 (42.0–95.4)
Enlarged uterus	2	42.9 (15.9–74.9)	87.7 (37.9–98.8)
Myometrial cysts	3	59.6 (41.6–75.4)	96.1 (80.7–99.3)

Abbreviation: JZ, junctional zone.

FIGURE 4 Sagittal T2 W MRI showing the junctional zone (JZ) with a diameter of >12 mm



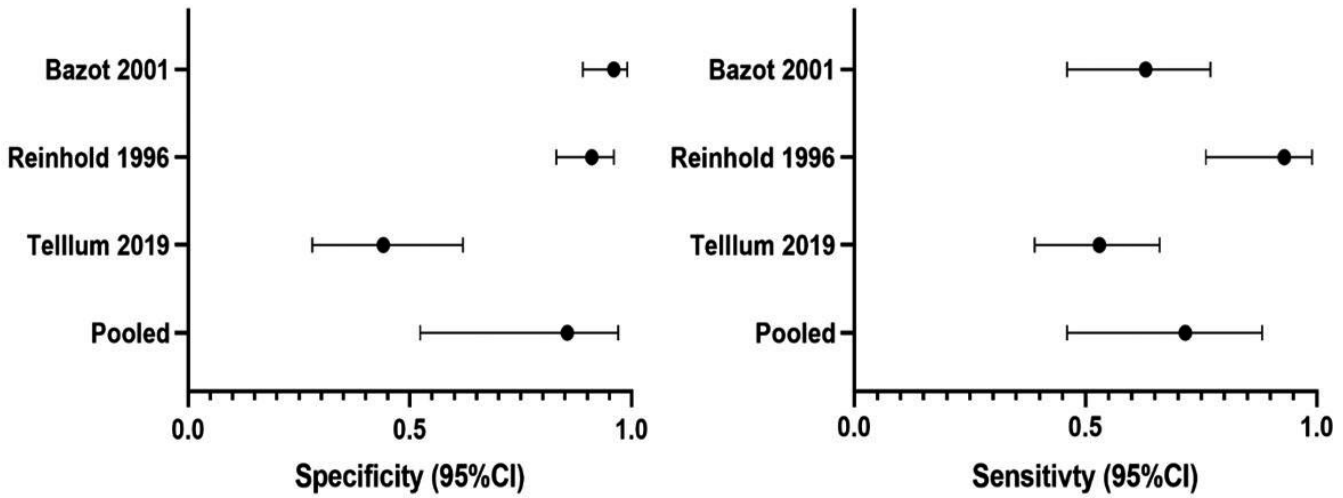


FIGURE 5 Diagnostic performance of junctional zone >12 mm on MRI vs histopathology

relative SI ratio of adenomyotic tissue was compared with that of apparently normal myometrium, or rectus muscle, and given an absolute value (see Figure 16 for a visualization). This ratio has not been investigated for diagnostic accuracy.

3.2.7 | Tissue diffusion characteristics

Finally, five studies (see Table 1) used diffusion-weighted imaging (DWI) to characterize adenomyosis, and attempted to quantify this.

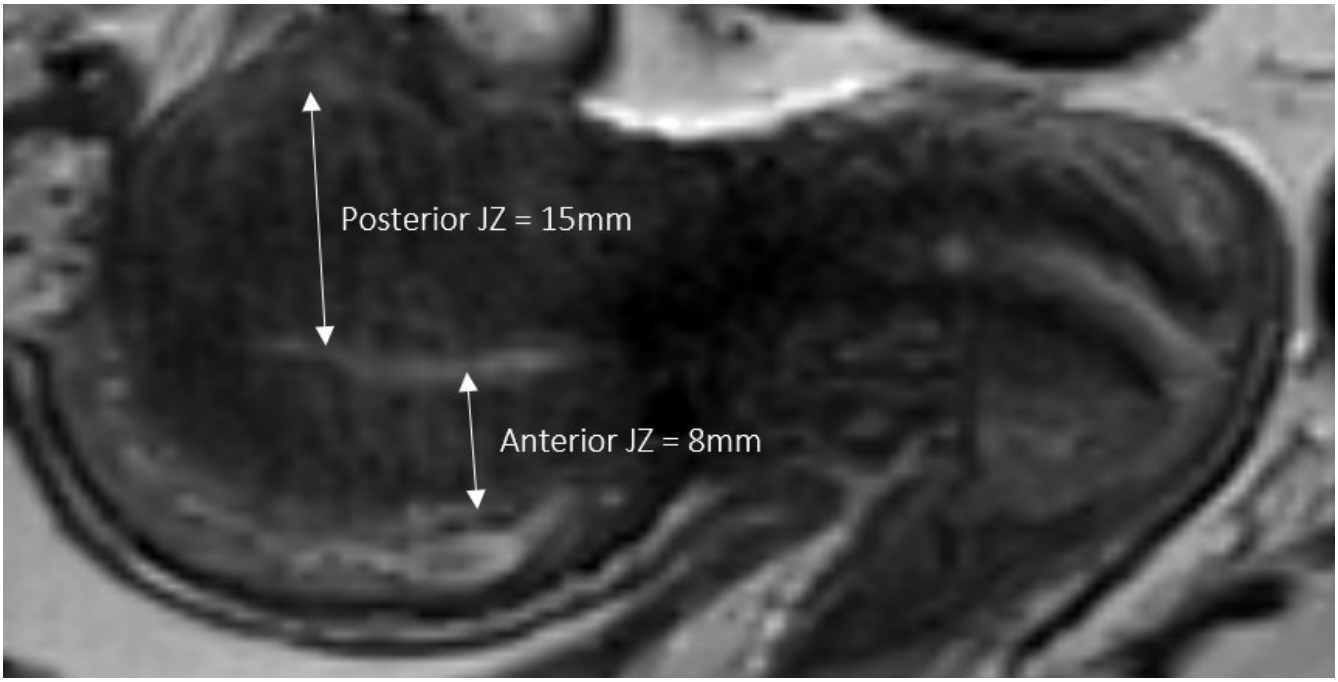


FIGURE 6 Sagittal T2 W MRI showing junctional zone (JZ) and myometrial (M) thickness. The JZ to myometrium ratio here is 0.8 (80%)

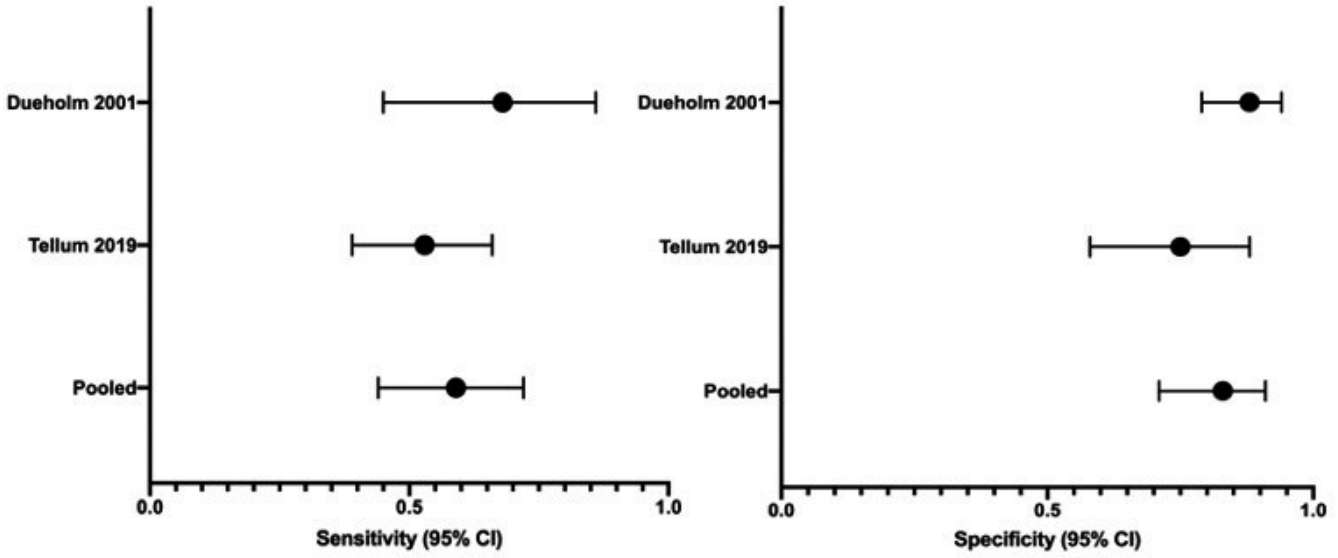


FIGURE 7 Diagnostic performance of junctional zone differential >5 mm on MRI vs histopathology

In these studies, the apparent diffusion coefficient (ADC) was measured for adenomyotic tissue compared with healthy uterus tissue, or other types of lesions (fibroids, sarcomas).[30] DWI allows visualization of water diffusion characteristics of different types of tissue, of which ADC is a quantitative measure.[31,32] Tian et al[16] investigated the added value of adenomyosis DWI and ADC values, and found it significantly improved the diagnostic accuracy compared with conventional MRI sequences (95.7% vs 89.1%, respectively). Similarly, Kilickesmez et al[33] found that JZ tissue in adenomyosis patients had significantly different ADC values compared with JZ tissue in healthy patients (albeit not compared with histopathological diagnosis).

3.2.8 | Correlation with clinical outcomes

The JZ thickness was most often investigated in relation to clinical outcomes. Several studies (n = 8) used (reduction in) JZ thickness as a measure of therapy response, but relatively few studies investigated (change in) JZ thickness and other clinical outcomes. Those that did, reported conflicting results.[34–37] Froeling et al[39] and Fukunishi et al[38,39] could not find a direct relation between JZ thickness and symptom reduction or severity. Conversely, four other studies did report a direct association between duration and severity of dysmenorrhea and JZ thickness.[36,37,40,41] An increase of average JZ

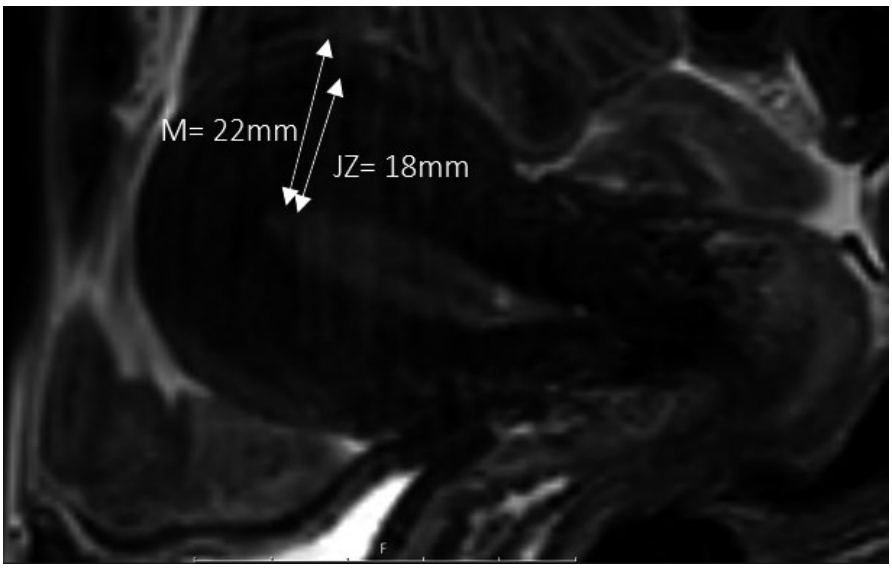


FIGURE 8 Sagittal T2 W MRI showing junctional zone (JZ) asymmetry of the anterior and posterior walls, with a JZ differential (JZ Diff) >5 mm

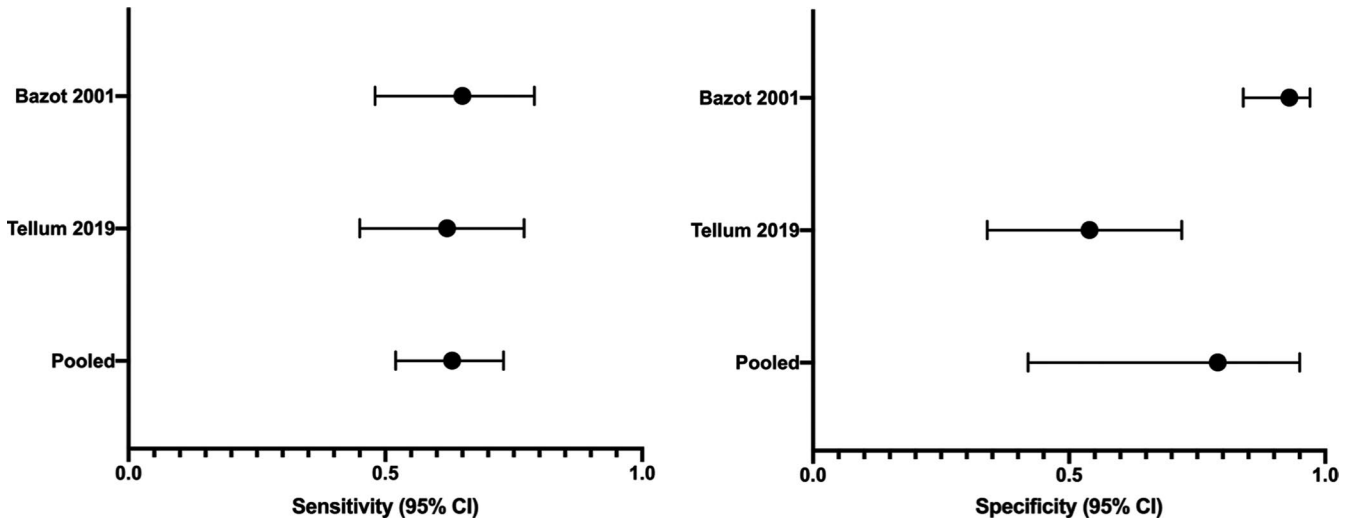


FIGURE 9 Diagnostic performance of junctional zone to myometrium ratio >40% on MRI vs Histopathology

thickness with age, suggesting a relation with higher incidence of adenomyosis in older women, has also been reported.[35,41,42] Kunz et al[42] and Kissler et al[34] investigated JZ thickness in the context of uterine dysperistalsis-associated infertility but did not find a significant relation. Further studies[23,24,43,44] evaluated JZ thickness in the context of endometriosis phenotypes, whereby Larsen et al[23] reported an increased mean JZ in conjunction with endometriosis severity. Chapron et al refuted this, however.[44]

Uterine size and morphology have also been correlated to clinical outcomes (see Table 1) with uterine volume sometimes used in the context of symptom reduction. Generally, uterine size was directly associated with severity of adenomyosis symptoms.[37]

Furthermore, several studies attempted to correlate tissue signal intensity with therapy response.[25,26,34,47] Keserci et al[22] suggested that a lower adenomyosis SI ratio vs normal myometrium was associated with more symptom reduction after therapy.

4 | DISCUSSION

Generally, adenomyosis can be diagnosed and quantified on MRI by looking at four characteristics: JZ thickness and (ir)regularity, adenomyosis lesion size, uterine morphology, and (relative) myometrial signal intensity. We are unable to suggest from our results which single MRI parameter is most accurate as a diagnostic criterion because of a lack of data; however, JZ thickness is the most widely used. Most reported diagnostic adenomyosis MRI parameters have in fact not been verified vs the reference standard of histopathology. Only a small number of studies investigated the correlation between MRI phenotype and clinical outcome, with conflicting results.

This is the first review to specifically investigate how adenomyosis can be objectively quantified on MRI and to summarize the diagnostic potential of individual MRI parameters up to now. Previous similar reviews have looked at the use of MRI in the diagnosis and

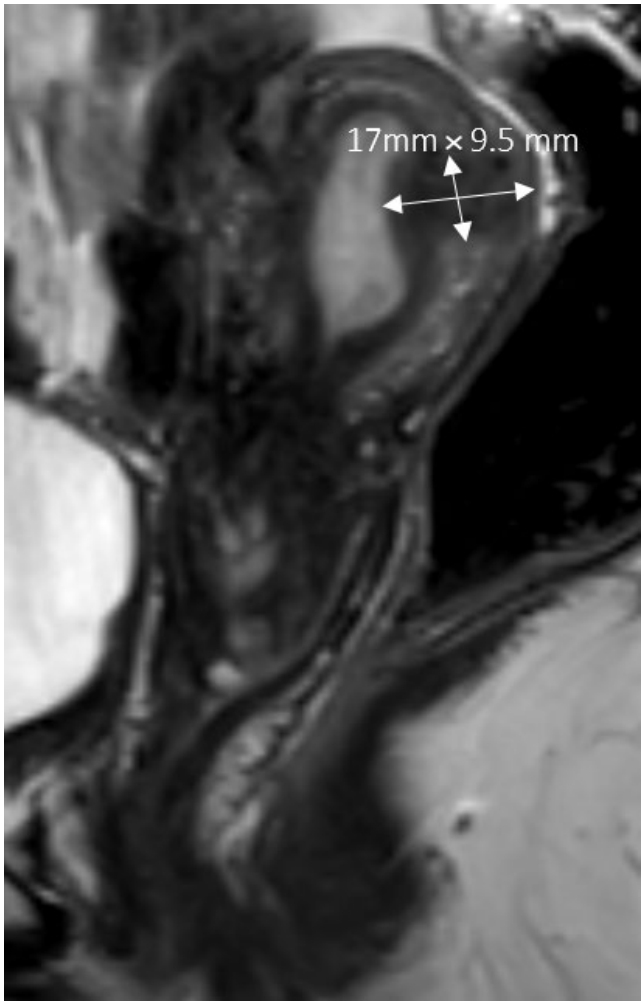


FIGURE 10 Sagittal T2 W MRI showing a focal adenomyosis lesion in the posterior uterine wall

classification of adenomyosis in general, or the JZ separately.[5,48] Munro et al[5] and Kobayashi et al[48] reviewed the existing classification systems for adenomyosis on imaging and histology and attempted to correlate MRI findings to clinical outcomes. As with our review, the classification systems and diagnostic criteria were shown to vary widely, and few studies correlated clinical outcomes in adenomyosis to MRI phenotype. This was also noted by Gordts et al,[49] highlighting a need for standardized classification and diagnosis of adenomyosis. It has been postulated that adenomyosis phenotype may not be able to be reliably correlated to clinical outcomes,[5] and it should be noted that imaging alone may not be the final answer in defining adenomyosis phenotypes. More knowledge of the (epi) genetic profile of adenomyosis, in combination with well-defined and detailed imaging, will likely provide a definitive characterization of the disease in future. Several studies have summarized the relation of JZ thickness generally to various clinical outcomes.[50,51] These studies reported a significant relation between JZ thickness and outcomes such as infertility or menstrual phase; however, it is unknown how this may translate to adenomyosis patients. Of the studies included in this review, it could be suggested that JZ thickness is correlated to symptom severity, treatment response, infertility, and age.

Imaging of the uterine anatomy and function has progressed rapidly over the last few decades, with sophisticated functional imaging of the uterus becoming more common. This is leading to new insights into different aspects of uterine function such as uterine movement, blood flow and structural and functional changes during the menstrual cycle.[52,53] Techniques employed now include DWI, blood oxygenation function studies, and cine-MRI.[54–56] More recently, the use of diffusion tensor imaging has also been explored in uterine and gynecological disorders like endometriosis, malignancies, and uterine

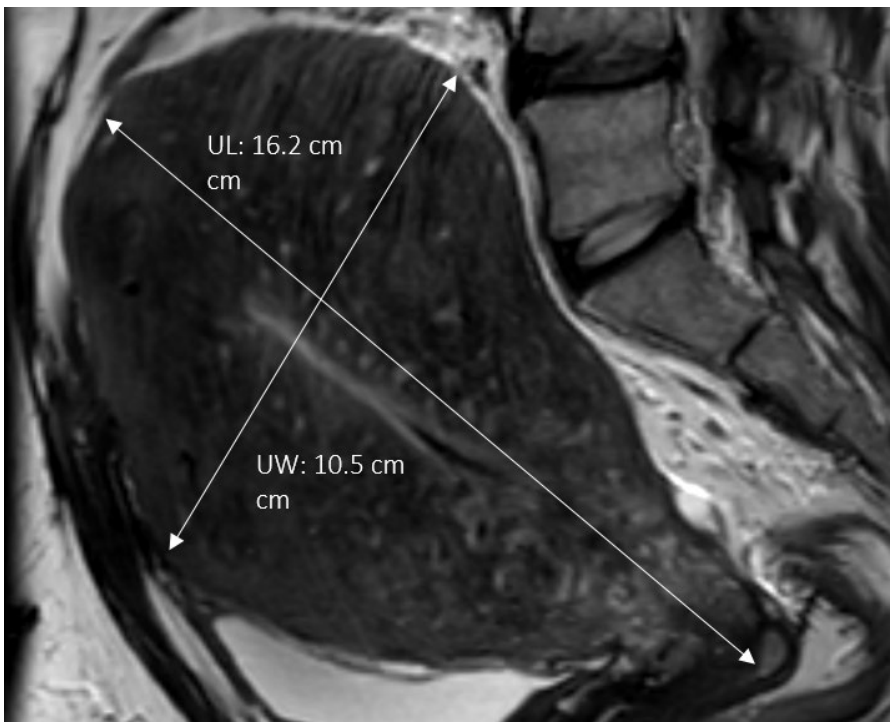


FIGURE 11 Sagittal T2 W MRI showing an enlarged, diffusely adenomyotic uterus, with a uterine length (UL) of 16.2 cm and a uterine width (UW) of 10.5 cm

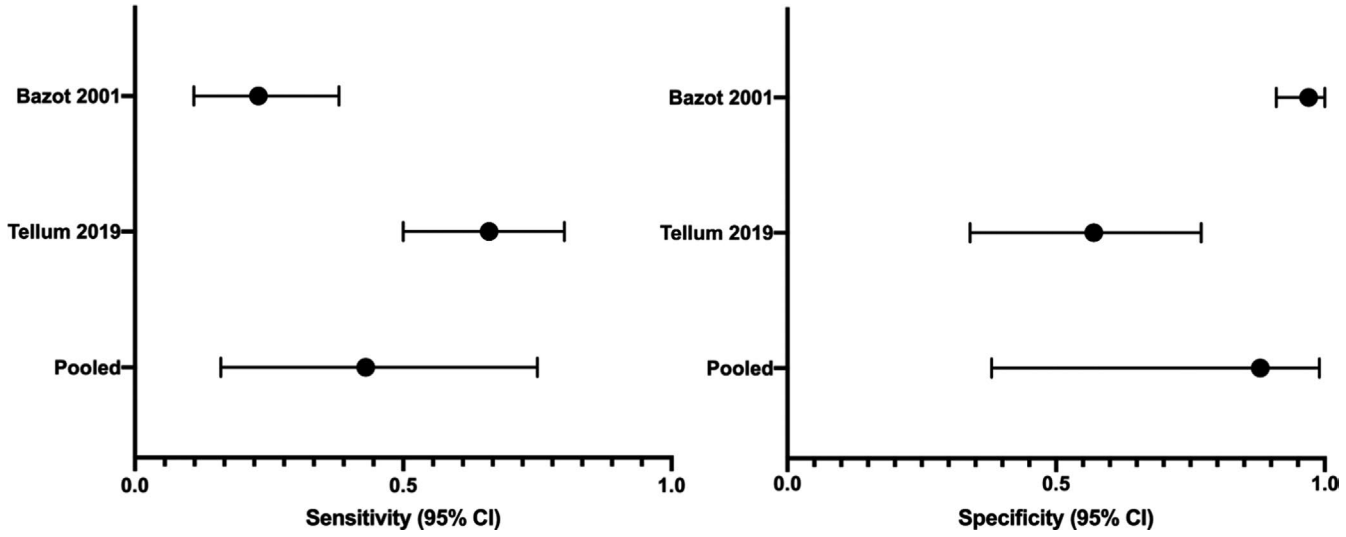


FIGURE 12 Diagnostic performance of uterine enlargement on MRI vs histopathology

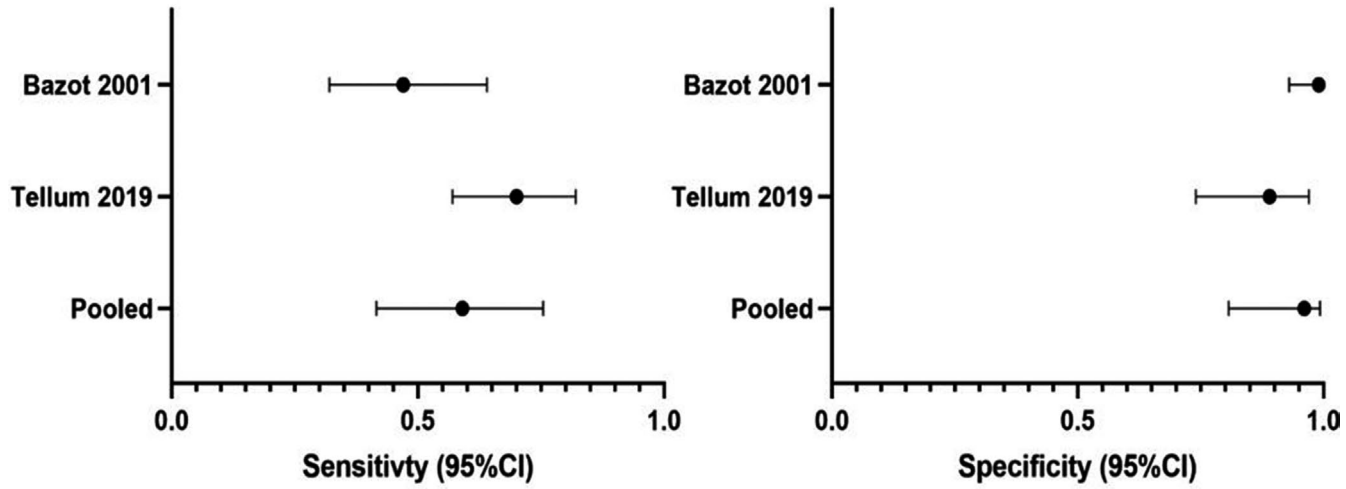


FIGURE 13 Sagittal T2 W MRI showing clear posterior and anterior wall asymmetry due to focal adenomyosis (and several leiomyomas)

fibroids, suggesting great potential in the use of these techniques in gynecological conditions.[57,58] Their diagnostic potential remains to be definitively evaluated; however, the one study that investigated diffusion tensor imaging for its diagnostic potential showed superior accuracy over conventional MRI.[16]

There are several limitations which may impact our results. First, despite their benefits, our broad inclusion criteria inevitably led to a heterogeneous selection of study designs and populations. This makes it difficult to apply the MRI parameters presented to specific patient groups (ie premenopausal or postmenopausal, symptomatic or asymptomatic, with or without concomitant fibroids or endometriosis etc.). Furthermore, many studies did not report on the specific diagnostic performance of individual parameters, meaning we could only include a small number of studies in our quantitative analysis. Studies that did report on individual MRI parameters also showed varied quality and results, leading to broad confidence intervals in our pooled analysis. As a result, we were not able to answer one of the objectives of our review; namely, which individual parameter is most accurate.

Few studies corrected for the influence of the menstrual cycle. Evaluation of the JZ can be problematic as its thickness changes during the menstrual cycle and is affected by hormonal therapy, making it difficult to distinguish between "normal" JZ and adenomyotic foci.[6] This thought has been echoed in previous reviews bringing the reliability of only JZ evaluation as a diagnostic marker for adenomyosis into question.[4,20] It is debatable how much adenomyotic tissue in the JZ responds to these hormonal stimuli,[6] but it is accepted that MRI diagnosis should take place in the proliferative phase of the menstrual cycle to minimize hormonal influence. Furthermore, only eight studies used 3.0-T MRI, with the majority using 1.5-T coils, which impacts overall image quality and thus diagnostic potential.

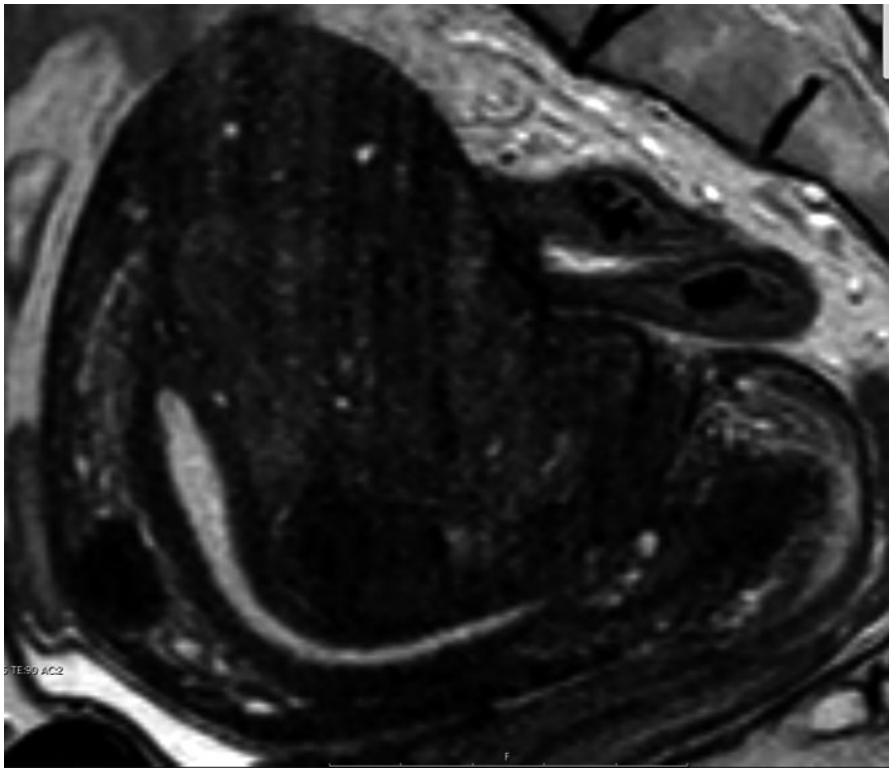


FIGURE 14 Diagnostic performance of presence of myometrial cysts on MRI vs Histopathology

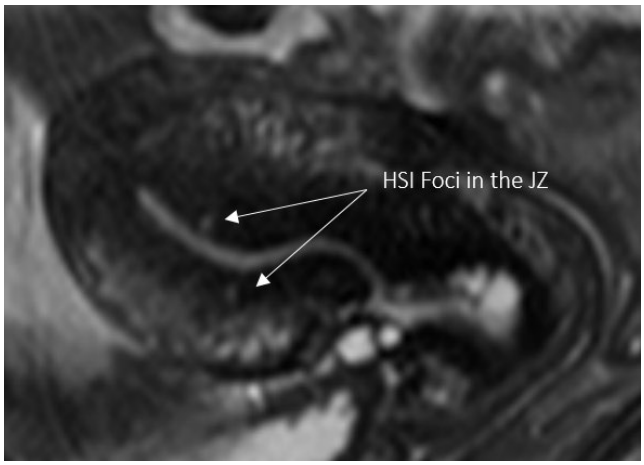


FIGURE 15 Sagittal T2 W MRI showing subtle high signal intensity (HSI) foci in the junctional zone (JZ)

Another noteworthy issue is that included studies used different definitions of adenomyosis. Although the definitions used were often similar, exact criteria and cut-off values varied. This difference persisted in recent studies, which confirms a lack of consensus regarding diagnostic criteria for adenomyosis on MRI. The histopathological definition used for adenomyosis was similarly often not clearly defined.

Despite these limitations, we do believe that the results of our review are clinically relevant and highlight future research opportunities. Our inability to comprehensively summarize the clinical impact of adenomyosis on MRI serves to highlight the need for studies that specifically investigate this correlation. If the MRI phenotype of adenomyosis can be definitively linked to certain clinical outcomes (fertility, treatment response, symptom severity) this would be of great value for both clinicians and patients. The overview provided here can form the basis for such research, and thereby aid in the creation of an objective, accurate, clinically applicable, and commonly accepted classification system of adenomyosis. The development of a (patient-specific) diagnostic tool or predictive algorithm based on individual MRI parameters could also be facilitated by the results presented here.

5 | CONCLUSION

This review has identified three main characteristics that can be quantified on MRI to visualize the extent of adenomyosis. These characteristics are also of generally acceptable diagnostic accuracy and can be used to differentiate adenomyosis on MRI from other uterine lesions and disorders. Knowledge of these parameters can form the basis for much-needed research into how adenomyosis severity on MRI can be related to clinical outcomes and aid in the development of an objective diagnostic tool for adenomyosis. More research into the characterization of adenomyosis using MRI techniques is needed be able to fully characterize adenomyosis objectively and be sure of the diagnostic accuracy of these imaging modalities.

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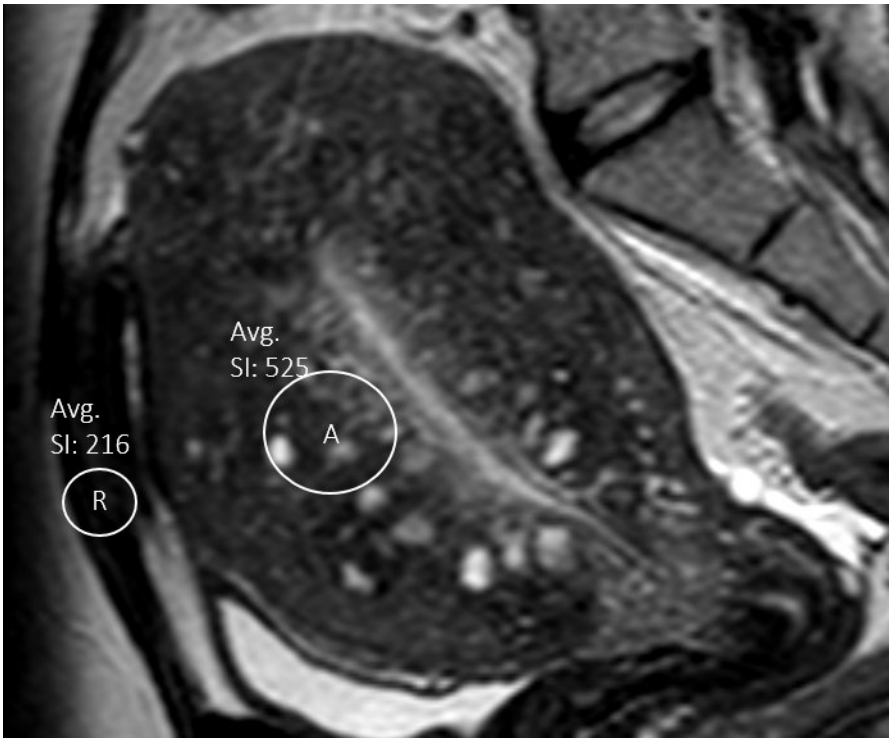

FIGURE 16 Sagittal T2 W MRI showing an example of adenomyosis tissue (A) signal intensity (SI) vs that of the rectus muscle (R)

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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