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Diagnostic accuracy of grayscale, power Doppler and contrast-enhanced ultrasound compared with contrast-enhanced MRI in the visualization of synovitis in knee osteoarthritis

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ABSTRACT

Purpose: To assess the diagnostic accuracy of grayscale (GSUS), power Doppler (PDUS) and contrast-enhanced ultrasound (CEUS) for detecting synovitis in knee osteoarthritis (OA).

Method: Patients with different degrees of radiographic knee OA were included prospectively. All underwent GSUS, PDUS, CEUS, and contrast-enhanced magnetic resonance imaging (CE-MRI), on which synovitis was assessed semi-quantitatively. Correlations of synovitis severity on ultrasound based techniques with CE-MRI were determined. Receiver operating characteristic (ROC) analysis was performed to assess diagnostic performance of GSUS, PDUS, and CEUS, for detecting synovitis, using CE-MRI as reference-standard.

Results: In the 31 patients included, synovitis scoring on GSUS and CEUS was significantly correlated ($\rho = 0.608$, $p < 0.001$ and $\rho = 0.391$, $p = 0.033$) with CE-MRI. For detecting mild synovitis, the area under the curve (AUC) was 0.781 (95 %CI 0.609−0.953) for GSUS, 0.788 (0.622−0.954) for PDUS, and 0.653 (0.452−0.853) for CEUS. Sensitivity and specificity were 0.667 (0.431−0.845) and 0.700 (0.354−0.919) for GSUS, 0.905 (0.682−0.983) and 0.500 (0.201−0.799) for PDUS, and 0.550 (0.320−0.762) and 0.700 (0.354−0.919) for CEUS, respectively. The AUC of GSUS increased to 0.862 (0.735−0.989), 0.823 (0.666−0.979), and 0.885 (0.767−1.000), when combined with PDUS, CEUS, or both, respectively. For detecting moderate synovitis, the AUC of GSUS was higher (0.882 (0.750−1.000)) and no added value of PDUS and CEUS was observed.

Conclusions: GSUS has limited overall accuracy for detecting synovitis in knee OA. When GSUS is combined with PDUS or CEUS, overall diagnostic performance improves for detecting mild synovitis, but not for moderate synovitis.

1. Introduction

Osteoarthritis (OA) is the most frequent form of arthritis and has major consequences for the individual patient and for public health. Joint inflammation, characterized by swelling of the synovium and joint effusion, also referred to as synovitis, is a key process in half of all OA patients [1]. Even in the early stages of OA, synovitis plays an important role in the perception of symptoms [2] and it is an important predictor of OA progression [3]. As the prominent role of synovitis in OA and the importance of identifying patients with synovitis for targeted anti-inflammatory treatment are increasingly recognized, the interest in imaging of synovitis in OA is growing.

The accepted reference standard for visualizing synovitis is MRI after intravenous administration of a contrast agent, also referred to as contrast-enhanced MRI (CE-MRI) [4]. CE-MRI, however, incurs high costs, long scan times, and potential health issues in high-risk patients

Abbreviations: AUC, area under the curve; BMI, body mass index; CE-MRI, contrast-enhanced MRI; CEUS, contrast-enhanced ultrasound; GSUS, grayscale ultrasound; IQR, interquartile range; KL, Kellgren & Lawrence; MRI, magnetic resonance imaging; OA, osteoarthritis; PDUS, power Doppler ultrasound; ROC, receiver operating characteristic.

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related to the use of contrast agents. Therefore, there is reluctance to implement synovitis imaging with CE-MRI routinely in clinical practice and in large clinical research studies on OA.

Despite the many advantages of MRI for a comprehensive evaluation of the osteoarthritic joint, ultrasound (US) is a suitable alternative to image the soft tissues of the knee and is therefore commonly used in clinical rheumatology practice [5]. Compared with MRI, US is more readily available, more practical, and less costly. Among the various methods that have been proposed for imaging synovitis with US, there are three methods that stand out. The most commonly used method is grayscale ultrasound (GSUS), although differentiating the synovium from joint fluid is difficult, since both synovial tissue and fluid generally appear hypoechoic on a grayscale image. In addition to GSUS, the extent of vascularization, which is expected to be increased in synovitis, can be visualized using power Doppler ultrasound (PDUS). PDUS has been shown to enhance diagnostic accuracy in conditions associated with increased vascularity such as arthritis, tendinitis, tumors, and in monitoring of healing processes [6]. Contrast-enhanced ultrasound (CEUS) constitutes a promising, relatively novel tool for imaging synovitis. CEUS makes use of contrast agents composed of microbubbles, that allow assessment of perfusion, based on enhanced ultrasound reflections in tissues where blood flow is increased. CEUS has been adopted especially in the abdomen, to be implemented on various organs such as liver, spleen, kidneys, and pancreas [7,8].

We hypothesized that ultrasound is an accurate diagnostic tool for imaging synovitis in knee OA compared with CE-MRI, and that the diagnostic performance of GSUS is potentially enhanced by PDUS and CEUS. The aim of this study was to determine the diagnostic accuracy of GSUS, PDUS and CEUS for detecting synovitis in knee osteoarthritis compared with CE-MRI as reference standard.

2. Methods

2.1. Study population

Patients were included in this prospective observational diagnostic accuracy study from the outpatient clinic of the Department of Orthopedic Surgery of Erasmus MC, University Medical Center Rotterdam, the Netherlands. Patients eligible for this study were aged over 18 years, were diagnosed with radiographic knee OA with a Kellgren & Lawrence (KL) grade of at least grade 1 and had clinical suspicion of synovitis, based on of palpable joint effusion. Exclusion criteria were: previous knee replacement surgery, knee trauma in the preceding six months, absolute and relative contra-indications to undergo MRI; pregnancy, renal insufficiency (GFR $<$ 60 mL/min/1.73m^2) and known allergy to MR or US contrast agents. The institutional ethics review board approved the study (protocol number MEC-2016−322). Both oral and written informed consent was obtained from all subjects.

2.2. MR imaging

MRI was performed using a 3 T MRI scanner (Discovery MR750, GE Healthcare, Milwaukee, WI, USA) with a dedicated 8-channel knee coil. The MRI protocol included proton density weighted and fat-saturated T2-weighted sequences in three orthogonal planes to morphologically assess the knee. For CE-MRI, we applied a 3D T1-weighted sequence with fat suppression obtained after the intravenous administration of 0.2 mmol/kg of gadoterate meglumine (Dotarem®, Guerbet, Aulnay-sous-Bois, France). This double dose of gadolinium agent was used for delayed gadolinium enhanced MRI of cartilage (dGEMRIC), the analysis of which is beyond the scope of this article.

Synovitis on CE-MR images was scored independently by two experienced musculoskeletal radiologists (EO, DH), with discrepancies resolved in consensus, using a semiquantitative scoring method described by Guermazi et al. [9] according to this method, synovitis was scored at 11 different sites throughout the knee (Table 1). At each site, the maximal thickness of the enhanced synovium was graded as follows: grade 0 if $<$2 mm, grade 1 if 2–4 mm and grade 2 if $>$4 mm. These scores were subsequently summed to generate a whole-knee synovitis score and this sum score was finally categorized into 0–4 (normal or equivocal synovitis); 5–8 (mild synovitis); 9–12 (moderate synovitis) and $\geq$13 (severe synovitis).

Table 1
Sites scored for synovitis on CE-MRI according to Guermazi et al. [9].

1. Medial parapatellar recess	7. Lateral perimeniscal
2. Lateral parapatellar recess	8. Adjacent to the anterior cruciate ligaments
3. Suprapatellar	9. Adjacent to the posterior cruciate ligaments
4. Infrapatellar	10. Baker's cysts
5. Intercondylar	11. Loose bodies
6. Medial perimeniscal	

2.3. Ultrasound imaging

Ultrasound imaging was performed on the same day, directly following the MRI examination using an ultrasound machine (LOGIQ E9, GE Healthcare, Milwaukee, WI, USA),equipped with a linear 5−15 MHz transducer (ML6−15, GE Healthcare, Milwaukee, WI, USA). US was performed by one trained examiner (SB, radiologist-in-training with 5 years' experience).

GSUS was performed using standardized protocols, with musculoskeletal program presets, which were kept unchanged for all examinations. GSUS was used to assess the extent of synovitis, based on joint fluid and synovial hypertrophy in the longitudinal scan plane at three locations (suprapatellar, medial and lateral), as described by Hartung et al. [10] synovial hypertrophy was defined as abnormal hypoechoic (relative to subcutaneous fat) intraarticular tissue that is non-displaceable and poorly compressible, and which may exhibit Doppler signal [11]. At the three evaluated locations, synovitis visualized by GSUS was graded semi-quantitatively, based on the joint capsule distension, with scores ranging from 0 to 3 at each site (grade 0 (absent); grade 1 (mild): small hypoechoic/anechoic line beneath joint capsule; grade 2 (moderate): joint capsule elevated parallel to joint area; grade 3 (severe): strong convex distension of the joint) [10].

PDUS was performed at the same locations as GSUS, using a frequency of 10 MHz with a pulse repetition frequency of 1.0 kHz. All settings including the color box size were standardized. PDUS activity in the synovium was scored semi-quantitatively with scores ranging from 0 to 3 at each site (grade 0: no intra-articular color signal; grade 1: up to 3 single color signals or 2 single color signals and 1 confluent color signal representing only low flow; grade 2: 1–50% of the intraarticular area filled with color signals representing clear flow; grade 3: $>$50 % of the intraarticular area filled with color signals) [10].

GSUS and PDUS scores were summed for all three locations resulting in a sum score ranging from 0 to 9 for each US technique.

The site with the highest degree of synovitis on GSUS and PDUS was imaged using CEUS (Fig. 1). CEUS was performed using 2.4 mL sulphur hexafluoride (SonoVue, Bracco, Milan, Italy), a second-generation ultrasound contrast agent, administered intravenously in the antecubital vein, followed by a saline bolus injection. The contrast inflow was imaged for 2 min. Synovial thickness on CEUS was scored semi-quantitatively, based on the maximal thickness on any slice, and graded as follows: grade 0 if $<$2 mm, grade 1 if 2–4 mm, grade 2 if 5−10 mm, grade 3 if $>$10 mm [12].

The scoring of ultrasound images was performed by two persons in consensus who were blinded to the CE-MRI scores, one radiologist-in-training with 5 years' experience (SB) and a researcher with a technical medical degree and more than 3 years' experience in musculoskeletal imaging research (BdV).

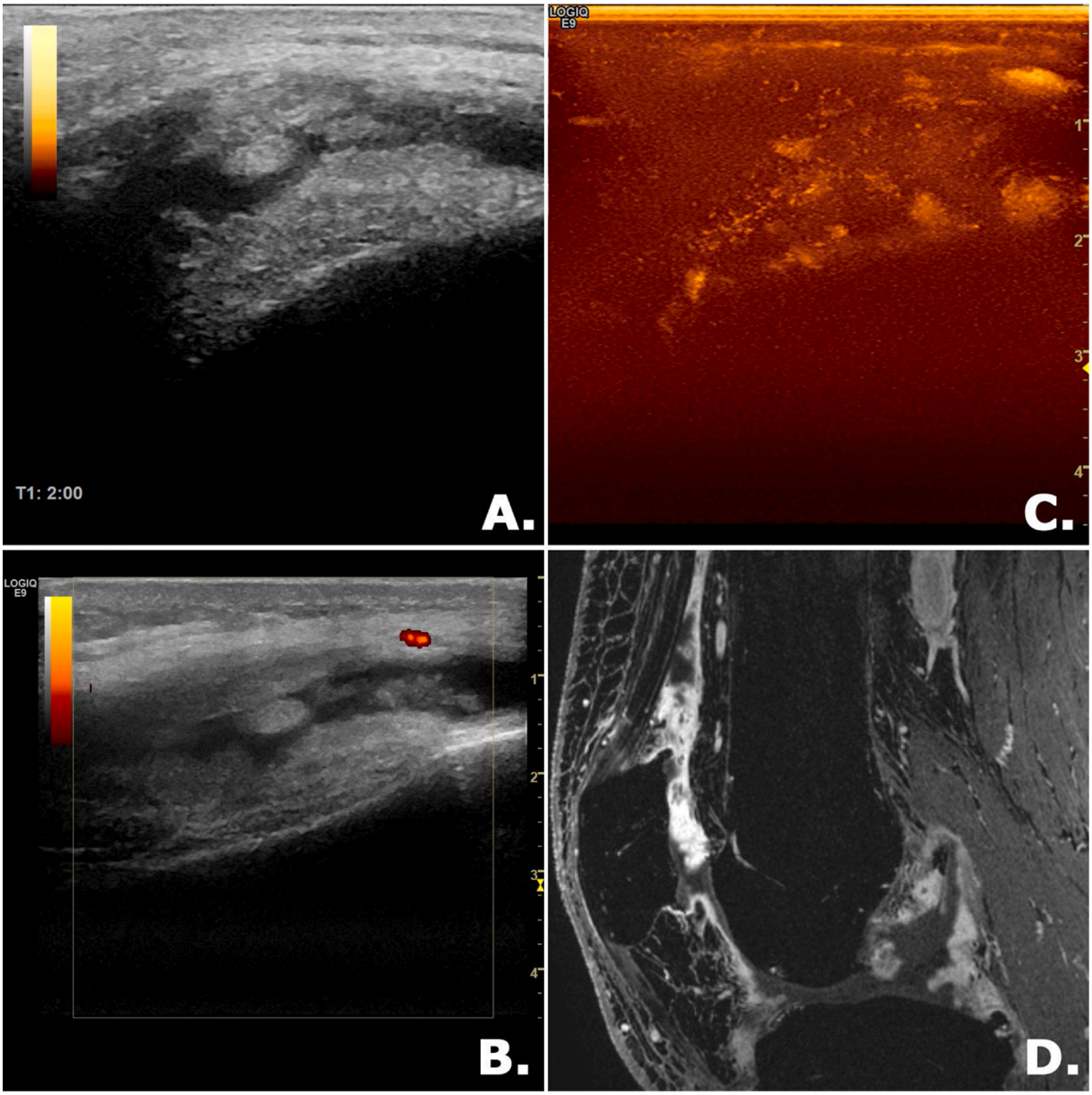

Fig. 1. US and CE-MRI findings in a representative patient with KL grade 3 radiographic OA and severe synovitis. A: longitudinal GSUS image of the suprapatellar recess, reveals convex distention of the joint capsule by synovial fluid and hyperechoic synovial tissue. B: corresponding PDUS image of same patient, revealing less than 3 color signals. C: corresponding CEUS image, depicting a summed representation of the detected contrast microbubbles. D: sagittal image from CE-MRI showing severe synovitis in the same patient.

2.4. Statistical analysis

Correlations were assessed between synovitis sum scores on GSUS, PDUS and CEUS and the whole-knee synovitis sum score on CE-MRI using Spearman's rank correlation, where <0.3 indicates little or no correlation; 0.3−0.7 moderate correlation; >0.7 strong correlation. Interobserver reliability between the two readers was assessed by calculating the intraclass correlation coefficient for summed synovitis scores and weighted Kappa statistics for each individual site and all sites pooled on CE-MRI. Receiver operating characteristic (ROC) analysis was performed to determine the diagnostic performance of GSUS, PDUS and CEUS. These were analyzed separately and combined, for the detection of synovitis with a severity of mild or higher, and moderate or higher, based on CE-MRI as the reference standard. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated along with 95 % confidence intervals. For this purpose, sum scores of GSUS, PDUS and CEUS were converted to binomial data (presence or absence). In the absence of clearly reported sum score cut-off values for any of the ultrasound techniques, Youden's index was used to define the threshold value that optimized the differentiating ability of GSUS, PDUS and CEUS [13]. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v25 (IBM Corp., Armonk, NY, USA).

3. Results

Thirty-one patients (14 females and 17 males; mean age 58 years) were included in this study. In one patient, CEUS was not acquired due to temporary license problems on the ultrasound machine, therefore, analyses on CEUS were performed in 30 patients. Baseline characteristics are shown in Table 2.

Table 2
Baseline patient characteristics.

Characteristic	
Sex	Male: n = 14 Female: n = 17
Mean age, y (range)	58 (33–81)
Mean BMI, Kg/m2 (range)	27.5 (20.6–39.9)
Symptomatic knee	Left: n = 15 Right: n = 16
Mean Knee injury and Osteoarthritis Outcome Score (KOOS), pain subscale (95 % CI)	51.7 (42.8−60.6)
Radiographic OA severity (K&L grade)	Grade 0: n = 0 Grade 1: n = 6 Grade 2: n = 8 Grade 3: n = 8 Grade 4: n = 7

3.1. Imaging findings

On CE-MRI, 10 (32.3 %) patients had no synovitis, while 9 (29.0 %), 7 (22.6 %) and 5 (16.1 %) had mild, moderate and severe synovitis, respectively. We found good interobserver reliability for the summed synovitis score on CE-MRI, with an ICC of 0.81 (95 % CI 0.64−0.90). The weighted Kappa value per individual site was variable and ranged from 0.22 to 0.78, whereas interobserver reliability for all sites pooled was moderate (weighted Kappa 0.56; 95 %CI 0.47−0.64). With GSUS, the median sum score over the 3 locations assessed, was 4 (IQR 3–5, range 1–8), while for PDUS the median sum score was 2 (IQR 2−3, range 0–6). With CEUS, 16 of 30 patients (53.3 %) were scored with grade 0, 6 (20.0 %) with grade 1 (slight thickening), 7 (23.3 %) with grade 2 (moderate), and 1 (3.3 %) with grade 3. Table 3 describes the distribution of KL grades and ultrasound sum scores per grade of synovitis severity based on CE-MRI. Fig. 1 shows an example of US and CE-MRI findings in a representative patient.

3.2. Correlation between US and CE-MRI

A moderate, statistically significant, correlation was observed between the GSUS sum score and CE-MRI whole-knee sum score (Spearman's $\rho = 0.608$, $p < 0.001$). The correlation between PDUS sum score and CE-MRI whole-knee sum score was weak ($\rho = 0.299$, $p = 0.102$) and not statistically significant, whereas the correlation between CEUS sum score and CE-MRI sum score was moderate and statistically significant ($\rho = 0.391$, $p < 0.033$).

3.3. Receiver operating characteristic (ROC) analysis

Table 4 describes the results of the receiver operating characteristic (ROC) analysis for the detection of synovitis with a severity of mild or higher, and moderate or higher, based on CE-MRI. When the ultrasound techniques were analyzed separately, the areas under the curve (AUC) were 0.781 for GSUS, 0.788 for PDUS, and 0.653 for CEUS, for the detection of synovitis with a severity of mild or higher. The sensitivity of GSUS was moderate (0.667) similar to the specificity (0.700) (Table 4). PDUS showed a high sensitivity (0.905) but a substantially lower specificity (0.500), CEUS demonstrated moderate sensitivity (0.550) and specificity (0.700).

When combinations of ultrasound techniques were analyzed, the AUC of GSUS increased from 0.781 to 0.862 when it was combined with PDUS and to 0.823 when it was combined with CEUS, largely explained by substantially increased specificity. When all three US techniques were combined, the AUC was 0.885 with a substantially higher sensitivity (0.909) and NPV (0.938) than for the combinations of two techniques. However, the specificity (0.789) was substantially lower than for two techniques combined, as was the PPV (0.714).

For the detection of moderate or severe synovitis, the AUC for GSUS was 0.882, while the AUCs for PDUS and CEUS were substantially lower, 0.592 and 0.708, respectively. The sensitivity of GSUS was moderate (0.750) while specificity was very high (0.947). The trend for PDUS was opposite (sensitivity 0.917; specificity 0.316), while CEUS demonstrated moderate sensitivity (0.727) and specificity (0.684). The combination of PDUS with GSUS did not increase diagnostic performance compared to GSUS alone, whereas the addition of CEUS increased the AUC marginally (0.882 to 0.895), with increased sensitivity and NPV, but decreased specificity and PPV. Finally, combining all three ultrasound techniques resulted in a sensitivity of 0.909, but specificity was substantially lower than for GSUS alone or combined with either PDUS or CEUS.

Table 3
Distribution of KL grade and ultrasound sum scores per grade of synovitis severity based on CE-MRI.

Synovitis severity on CE-MRI	Median KL (IQR)	Median GSUS sum score (IQR)	Median PDUS sum score (IQR)	Median CEUS sum score (IQR)
No synovitis (sum score 0−4) (n = 10)	2 (1−2)	3.0 (1.8−4)	1.5 (1−2.3)	0 (0−1)
Mild synovitis (sum score 5−8) (n = 9)	3 (1−3.5)	3.0 (3−4)	3.0 (2−4)	0 (0−1.5)
Moderate synovitis (sum score 9−12) (n = 7)	3 (2−4)	5.0 (3−8)	3.0 (2−3)	1.0 (0−2)
Severe synovitis (sum score ≥13) (n = 5, CEUS n = 4)	3 (3−4)	5.0 (5−7)	2.0 (1−4.5)	2.0 (0.5−2)

4. Discussion

This study demonstrated that, even under optimized conditions, the combination of GSUS, PDUS and CEUS shows only limited overall diagnostic accuracy for the assessment of synovitis compared to CE-MRI as the gold standard. We found that GSUS showed the highest overall diagnostic performance compared to PDUS and CEUS when analyzed separately. Nevertheless, although GSUS has high PPV, it has limited sensitivity, specificity, and NPV for the detection of synovitis with a severity of mild or higher based on CE-MRI. Thus, the application of GSUS alone for detection of mild synovitis is insufficient, and, accordingly, our results indicate that adding PDUS or CEUS increases overall diagnostic performance for detecting mild synovitis. From a practical perspective, the application of CEUS involves the intravenous administration of a contrast agent, which results in longer examination times and higher costs. Since the addition of CEUS to GSUS/PDUS only increased sensitivity and NPV, but substantially decreased specificity and PPV, we believe that CEUS is less likely to be useful in most clinical practices.

For the detection of synovitis with a severity of moderate or higher, no added value of PDUS and CEUS was observed compared to GSUS alone. The increased sensitivity associated with the combination of GSUS and CEUS or all three ultrasound techniques combined was accompanied by a greater reduction in specificity.

Synovitis plays a key role in pain perception in OA patients [14] and has been identified as an important factor for OA progression [3]. Therefore, according to recent insights, identifying patients with synovitis through imaging is crucial in order to initiate targeted anti-inflammatory therapy and prevent progression of OA [15]. Ideally, the diagnosis of synovitis is made at an early stage of OA before structural joint damage is evident on radiography, and when the severity of synovitis may be still mild. However, large-scale evaluation of OA patients with the reference standard for synovitis imaging, CE-MRI, is not feasible since CE-MRI requires the use of a gadolinium-based contrast agent and a long scan time and incurs high costs. Because ultrasound theoretically remains an attractive alternative to CE-MRI that is more

Table 4
Results of receiver operating characteristic (ROC) analysis and diagnostic performance statistics.

	AUC (ROC)	Cut-off based on Youden's index	Sensitivity	Specificity	PPV	NPV	FP	TP	TN	FN
Mild, moderate, or severe synovitis										
GSUS	0.781 (0.609−0.953)	4	0.667 (0.431−0.845)	0.700 (0.354−0.919)	0.824 (0.558−0.953)	0.500 (0.240−0.760)	3	14	7	7
PDUS	0.788 (0.622−0.954)	2	0.905 (0.682−0.983)	0.500 (0.201−0.799)	0.792 (0.573−0.921)	0.714 (0.303−0.949)	5	19	5	2
CEUS	0.653 (0.452−0.853)	1	0.550 (0.320−0.762)	0.700 (0.354−0.919)	0.786 (0.488−0.943)	0.438 (0.208−0.694)	3	11	7	9
GSUS + PDUS	0.862 (0.735−0.989)	7	0.619 (0.387−0.810)	1.000 (0.655−1.000)	1.000 (0.717−1.000)	0.556 (0.313−0.776)	0	13	10	8
GSUS + CEUS	0.823 (0.666−0.979)	5	0.650 (0.409−0.837)	0.900 (0.541−0.994)	0.929 (0.642−0.996)	0.563 (0.306−0.792)	1	13	9	7
GSUS + PDUS + CEUS	0.885 (0.767−1.000	7	0.909 (0.571−0.995)	0.789 (0.539−0.930)	0.714 (0.420−0.904)	0.938 (0.677−0.997)	1	15	9	5
Moderate or severe synovitis										
GSUS	0.882 (0.750−1.000)	5	0.750 (0.428−0.933)	0.947 (0.719−0.997)	0.900 (0.541−0.995)	0.857 (0.626−0.962)	1	9	18	3
PDUS	0.592 (0.387−0.797)	2	0.917 (0.598−0.996)	0.316 (0.136−0.565)	0.458 (0.262−0.668)	0.857 (0.420−0.992)	13	11	6	1
CEUS	0.708 (0.510−0906)	1	0.727 (0.393−0.927)	0.684 (0.435−0.864)	0.571 (0.296−0.812)	0.813 (0.537−0.950)	6	8	13	3
GSUS + PDUS	0.787 (0.621−0.953)	7	0.667 (0.354−0.887)	0.737 (0.486−0.899)	0.615 (0.322−0.849)	0.778 (0.519−0.926)	5	8	14	4
GSUS + CEUS	0.895 (0.770−1.000)	5	0.909 (0.571−0.995)	0.789 (0.539−0.930)	0.714 (0.420−0.904)	0.938 (0.677−0.997)	4	10	15	1
GSUS + PDUS + CEUS	0.844 (0.706−0.983)	7	0.909 (0.571−0.995)	0.684 (0.435−0.864)	0.625 (0.359−0.837)	0.929 (0.642−0.996)	6	10	13	1

readily available, less costly and faster, further study is needed to better understand and improve upon the reasons for its limited diagnostic accuracy demonstrated in this study. One previous study by Song et al. [16] evaluated GSUS, PDUS and CEUS in comparison with CE-MRI in a population of 36 patients with painful knee OA. In their study, only the superior and lateral recess were systematically evaluated, MRI was performed on a low-field dedicated extremity scanner precluding the assessment of obese patients, 4.8 mL instead of 2.4 mL sulphur hexafluoride was used for CEUS, the focus of analysis was mainly on sensitivity and percentage positive findings, and no combinations of ultrasound techniques were evaluated [16]. Our finding that PDUS has higher sensitivity than GSUS, with an opposite trend for specificity, is in agreement with their study.

In a study among patients with rheumatoid arthritis, Rednic et al. [17] found that synovial thickness measured with CEUS might be related to the "active" state of synovitis. Our finding that CEUS and CE-MRI only correlated moderately in OA patients may point towards a higher degree of "active" synovitis in rheumatoid arthritis.

All patients included in this study had clinical signs of synovitis, with palpable effusion documented on clinical examination. Although this was an inclusion criterion for our study, not all patients showed synovitis on CE-MRI. As many as 11 out of 31 patients were classified as having no or equivocal synovitis on CE-MRI (sum score 0−4). This may be explained by a high false-positive rate of detecting effusion on clinical examination, as well as the fact that imaging for this study was not performed at the time of the clinical diagnosis of synovitis. Moreover, OA is characterized by so-called "flare-ups", sudden and temporary increases in symptoms along with exacerbations of synovitis [18,19], and it is possible that the degree of synovitis at the time of imaging was lower than during clinical examination. However, since our analyses focused on comparison of imaging techniques within the same patient exactly at the same time point, we expect that this will not have affected our results.

Overall, our study showed that US, in any combination of the evaluated US techniques, is inferior to CE-MRI for the assessment of synovitis in knee OA. The most plausible explanation for this, is the intrinsic difference between US as a 2D imaging tool that only assesses distinct superficial knee joint areas, and MRI that provides a comprehensive 3D visualization of all areas in the knee. In addition, pressure applied on the skin might also affect the assessment in US imaging, where areas of synovitis could be displaced outside of the imaging plane, although in our study we applied minimal pressure. Finally, using CE-MRI, the enhanced synovium can be clearly distinguished from joint effusion, which in our experience is more difficult with US.

The strengths of our study are that we included patients with all severities of radiographic OA (KL grade 1–4), and that we were able to perform a comprehensive range of ultrasound and MRI techniques, including two different contrast-enhanced methods with two different contrast agents on the same day, within a few hours, in as many as 30 patients. Another strength of our study is that we used standardized protocols for the ultrasound acquisition, although we realize that adapted protocols might be more suitable for specific patient groups, e.g. the use of a curved US transducer in patients with a very high BMI. The main limitation of this study is the small sample size from the perspective of statistical analysis, resulting in a small number of patients in each category of synovitis severity, and large measures of variability associated with US grades and diagnostic performance statistics. The low number of subjects per KL grade also precluded subgroup analysis by severity of radiographic OA. However, due to the extensive imaging protocol with two contrast administrations, a larger number of subjects was not feasible. In view of the limited statistical power, our results suggests that, if a sonographic diagnosis of synovitis is necessary, the individual sonographic techniques may only be used complementarily and not as alternatives.

Specifically for CEUS, another limitation was that we were only able to assess one location within the knee for one contrast injection. Furthermore, we did not always detect synovitis with CEUS in cases which were diagnosed with synovitis using GSUS and CE-MRI, although the assumption is that the microbubbles flow through inflamed tissue with increased vascularity. Factors that may possibly account for this are low flow, small size of the vessels and obesity. Another limitation is that we used a double dose of gadolinium contrast agent for the purpose of dGEMRIC, but we believe that this did not affect appearance of synovitis on CE-MRI compared to a single dose of gadolinium. A final limitation is that the scoring of all ultrasound images was performed during the same session, whereas for CE-MRI this was performed independently.

In conclusion, ultrasound has only limited accuracy in detecting synovitis in knee osteoarthritis compared to CE-MRI. When GSUS is combined with PDUS or CEUS, overall diagnostic performance is improved for detecting synovitis with a severity of mild or higher, but not for synovitis with severity of moderate or higher. From a practical perspective, GSUS is most feasibly combined with PDUS, whereas CEUS is less likely to be useful in most clinical practices.

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CRediT authorship contribution statement

Bas A. de Vries: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Stephan J. Breda:** Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Duncan E. Meuffels:** Data curation, Methodology, Writing - review & editing. **David F. Hanff:** Formal analysis, Writing - review & editing. **M.G. Myriam Hunink:** Formal analysis, Investigation, Validation, Writing - review & editing. **Gabriel P. Krestin:** Conceptualization, Funding acquisition, Writing - review & editing. **Edwin H.G. Oei:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors reported no declarations of interest.

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