The Benefit of Transvaginal Elastography in Detecting Deep Endometriosis: A Feasibility Study

Nutzen der transvaginalen Elastografie bei der Erkennung der tief infiltrierenden Endometriose: Eine Machbarkeitsstudie

Authors
Anjeza Xholli[1], Ambrogio P Londero[2], Elena Cavalli[1], Umberto Scovazzi[1], Mattia Francesco Ferraro[1], Ilaria Vacca[1], Maria Giulia Schiaffino[1], Francesca Oppedisano[1], Giorgio Sirito[1], Filippo Molinari[1], Angelo Cagnacci[1, 2]

Affiliations
1 Academic Unit of Obstetrics and Gynecology, IRCCS Ospedale Policlinico San Martino, Genova, Italy
2 DINOGMI, University of Genoa, Genova, Italy

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Correspondence
Ambrogio P Londero
DINOGMI, University of Genoa, Largo Paolo Daneo 3, 16132 Genova, Italy
ambrogio.londero@gmail.com

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ABSTRACT

Objectives This study aimed to evaluate elastography features of deep infiltrating endometriosis (DIE), and to define whether this technique may discriminate lesions from surrounding non-endometriotic tissue.

Methods This was an exploratory observational study on women affected by DIE treated in a third-level academic hospital gynaecology outpatient facility between 2020 and 2021. Strain elastography (SE) was conducted via transvaginal probe. Tissue deformation of DIE and surrounding tissue was expressed as percentage tissue deformation or as subjective colour score (CS; from blue = stiff to red = soft, assigned numerical values from 0 to 3). Ratios of normal tissue/DIE were compared to ratio of normal tissue/stiffer normal tissue area.

Results Evaluations were performed on 46 DIE nodules and surrounding tissue of the uterosacral ligaments (n = 21), parametrium (n = 7), rectum (n = 14), and recto-vaginal septum (n = 4). Irrespective of location, DIE strain ratio (3.09, IQR 2.38–4.14 vs. 1.25, IQR 1.11–1.48; p < 0.001) and CS ratio (4.62, IQR 3.83–6.94 vs. 1.13, IQR 1.06–1.29; p < 0.001) was significantly higher than that of normal tissue. ROC AUC of CS ratio was higher than ROC AUC of strain ratio (99.76 %, CI.95 99.26–100 % vs. 91.35 %, CI.95 85.23–97.47 %; p = 0.007), and best ROC threshold for CS ratio was 1.82, with a sensitivity of 97.83 % (CI.95 93.48–100 %) and a specificity of 100 % (CI.95 100–100 %).

Conclusions Both strain and CS ratios accurately distinguish DIE nodules at various locations. Applications of elastography in improving the diagnosis DIE, in distinguishing different DIE lesions and in monitoring DIE evolution can be envisioned and are worthy of further evaluation.

ZUSAMMENFASSUNG

Ziel Ziel dieser Studie war es, die elastografischen Merkmale der tief infiltrierenden Endometriose (TIE) zu untersuchen und festzustellen, ob diese Technik die Läsionen von umgebendem nicht-endometriotischem Gewebe unterscheiden kann.

Methoden Dies war eine explorative Beobachtungsstudie an Frauen mit TIE, die zwischen 2020 und 2021 in einer gynäkologischen Ambulanz eines Universitätskrankenhauses der Tertiärversorgung behandelt wurden. Die Strain-Elastografie (SE) wurde über eine transvaginale Sonde durchgeführt. Die Gewebedeformation der TIE und des umgebenden Gewebes wurde als prozentuale Gewebedeformation oder als subjektive Farbscala (CS; von blau = steif bis rot = weich, mit Zahlenwerten von 0 bis 3) angegeben. Das Verhältnis Normalgewebe/TIE wurde mit dem Verhältnis Normalgewebe/steiferes normales Gewebe verglichen.

Ergebnisse Es wurden 46 TIE-Knoten und das sie umgebende Gewebe von Ligamentum sacrouterinum (n = 21), Parametrium (n = 7), Rectum (n = 14) und Septum rectovaginale (n = 4) ausgewertet. Unabhängig von der Lokalisation waren die Strain-Ratio (3,09; IQR 2,38–4,14 vs. 1,25; IQR 1,11–

1,48; p < 0,001) und CS-Ratio (4,62; IQR 3,83–6,94 vs. 1,13; IQR 1,06–1,29; p < 0,001) der TIE signifikant höher als bei Normalgewebe. Die ROC-AUC der CS-Ratio war höher als die ROC-AUC der Strain-Ratio (99,76 %; 95 % CI = 99,26–100 vs. 91,35; 95 % CI = 85,23–97,47; p = 0,007), und der optimale ROC-Schwellenwert für die CS-Ratio betrug 1,82 bei einer Sensitivität von 97,83 % (95 %CI = 93,48–100) und einer Spezifität von 100 % (95 % CI = 100–100).

Schlussfolgerung Sowohl die Strain- als auch die CS-Ratio ermöglichen eine genaue Differenzierung von TIE-Knoten an verschiedenen Stellen. Der Einsatz der Elastografie zur Verbesserung der TIE-Diagnose, zur Unterscheidung verschiedener TIE-Läsionen und zur Überwachung der TIE-Entwicklung kann in Betracht gezogen werden und sollte weiter untersucht werden.

Introduction

Endometriosis is a common chronic inflammatory disease characterized by ectopic endometrial tissue outside the uterine cavity [1, 2, 3]. Its prevalence is roughly 5–10 % in the general female population but reaches 71–87 % in women with pelvic pain [2, 3]. Endometriosis can be characterized by superficial implants on the abdominal serous membrane or distant organs (e. g., pleura or pericardium) [3, 4, 5]. In the pelvis, endometriosis can lead to deeper lesions affecting the bladder, rectum, sigmoid tract, rectovaginal septum, parametrium and/or uterosacral ligaments [5]. These lesions are commonly aggregated under deep infiltrating endometriosis (DIE) [5, 6], which often requires extensive surgery leading to severe morbidity [7]. Several studies have now shown that transvaginal sonography (TVS) performed by an expert sonographer can be regarded as being an accurate method in defining DIE nodules and their extension, as magnetic resonance imaging (MRI) [5, 8, 9]; although, accurate diagnosis of nodules of the uterosacral ligaments and parametrium remains problematic [5]. Strain elastography (SE) measures tissue stiffness/elasticity and is commonly used to characterize lesions of the breast and other organs [10, 11]. DIE lesions are stiffer than normal surrounding tissue, but few studies have applied SE to their characterization [12, 13]. Hence, the aim of this study was to assess whether SE discriminates DIE from surrounding non-endometriotic tissue. The secondary objective was to evaluate if the capabilities of elastography in distinguishing DIE lesions differed by location.

Methods

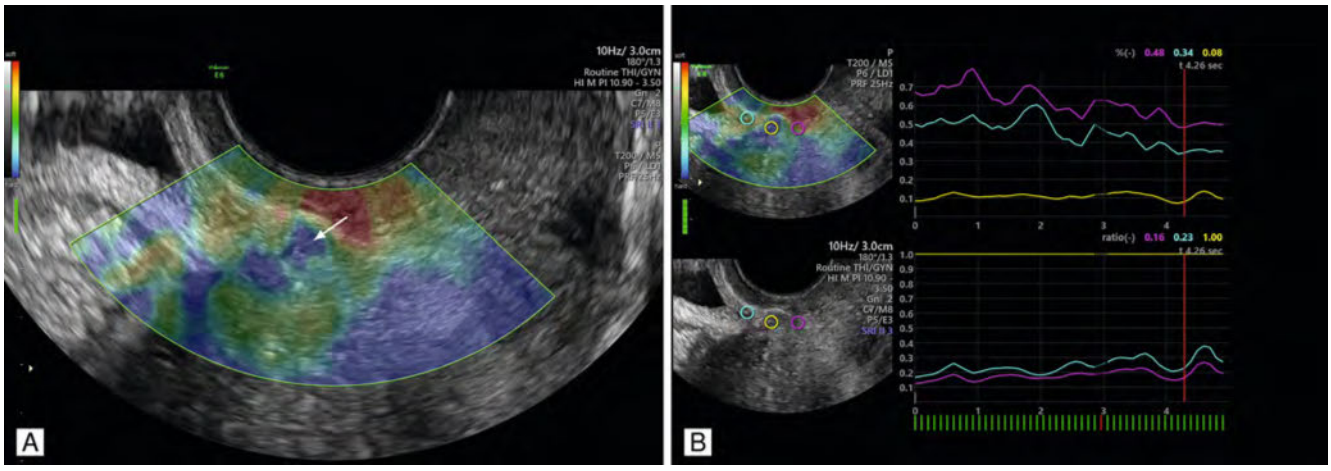
Design and participates

This observational study was conducted between October 2020 and December 2021 in a third-level academic hospital gynaecology outpatient facility. The study did not involve any intervention beyond standard clinical practice. Publication of the results was approved by the Ethics Committee of IRCCS Ospedale Policlinico San Martino, Genoa (CER Liguria n. 19/2022). Each participant signed informed written consent for the anonymous use of their data in clinical research.

The sample comprised all consecutive patients of 18 to 45 years of age complaining of endometriosis symptoms referred to the specialist outpatient facility during the study period with a previous or current diagnosis of DIE. Demographic and clinical data were collected for each. Presence of pain at menstruation, intermenstrual pain, and pain at intercourse was recorded [14, 15, 16]. The intensity of each type of pain was estimated individually on a 100-mm visual analogue scale (VAS) [3]. Each woman underwent standard bimanual vaginal examination to assess for the presence of stiff nodules, tenderness and mobility of pelvic organs. Transvaginal sonography was then performed by an expert qualified practitioner (A.X.). The presence of gynaecological diseases such as uterine myomas and adenomyosis was assessed using the MUSA criteria [17]. Ovarian endometriosis and DIE of the posterior and anterior compartments was diagnosed based on the IDEA consensus opinion and in accordance with recent guidelines [9, 18]. Women with a clinical and sonographic diagnosis of DIE were further evaluated by SE. Some of these women had previously received a surgical diagnosis of endometriosis, and some underwent surgery afterwards if clinically indicated [19]. When surgery was performed, endometriosis was confirmed by histology.

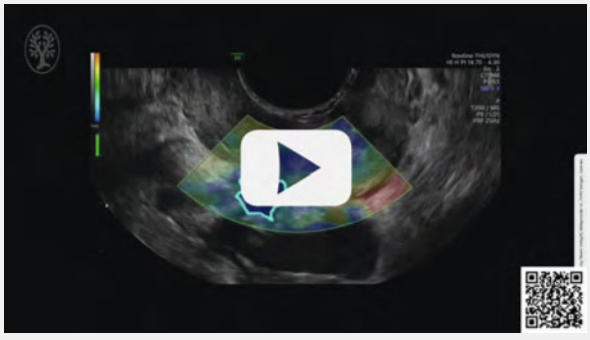
Sonographic Measurements

A sole operator performed all ultrasound assessments using a Voluson E6 General Electric (GE Medical System, Zipf, Austria) instrument. The ultrasound examinations were conducted with a transvaginal wideband 5–9 Mhz transducer and dedicated elastography software (GE Medical System, Zipf, Austria). Volume (cm3) of endometriotic nodules identified in B-mode was evaluated by the ellipsoid formula (3 main diameters × 0.5223). Tissue stiffness/elasticity was evaluated by SE, which measures tissue deformation or displacement provoked by an applied pressure [10, 12, 13]. The strain value can be depicted using colored shading superimposed on the B-mode image. The strain of different regions of interest (ROI) can be concomitantly evaluated, and the strain ratio, a measure of the discrepancy in the elasticity of different tissues, can be used to improve SE accuracy [10, 20, 21]. For image acquisition in B-mode, the vaginal probe was positioned in the region of the endometriotic nodule. Afterwards, the sonographer performed a series of approximately 5 compression-decompression cycles in the elastography modality, revealing the colored shading superimposed on the B-mode image. The compression and decompression process were achieved using sub-centimetric motions perpendicular to the axis of the endometriotic lesion. A feedback control bar in the ultrasound real-time elastography program was used to check and maintain optimal compression force (▶ **Fig. 1**). The dynamic elastography acquisition process was recorded on video, to be analyzed afterward offline (▶ **Video 1**). The offline analyst was blinded to patient data.



▶ **Fig. 1** Endometriotic nodule (white arrow) under B-mode elastography, showing colored shading superimposed on the image (Panel **A**), and example of tissue strain elastography (Panel **B**). The yellow circular region of interest (ROI) is located on the endometriotic nodule, and the other two ROIs (blue and purple) on the left and right surrounding tissue.

OP-VIDEO



▶ **Video 1** Dynamic elastography acquisition.

The endometriotic nodule was well characterized under SE as a homogenous blue area distinct from surrounding tissue. Three ROIs (circular areas of 7.06 mm2), placed at an equal distance from the probe, were: the endometriotic nodule, the surrounding non-endometriotic tissue on the left of the nodule, and the surrounding non-endometriotic tissue on the right (▶ **Fig. 1**). The strains and the colour scores were computed at optimal compression. For each of the three ROIs, the SE software provided the numerical value of the strain as the percentage of tissue deformation. The CS (purple/blue as low elasticity, yellow/green as intermediate, and red as high) was also coded as follows: from 0 = blue/purple to 3.0 = red [20, 21]. The mean value of three measurements was used. Raw values for strain and CS were used to calculate the respective ratios. Strain or CS ratio of the endometriotic nodule was defined as the ratio between the mean of the two non-endometriotic tissue ROIs as the nominator, divided by the value obtained from the endometriotic nodule ROI as the denominator. The resulting value was compared to the strain or CS ratio of the non-endometriotic tissue; this was calculated as the ratio between the mean of the two non-endometriotic tissue ROIs as the nominator, and the minimum value between the two ROIs from surrounding non-endometriotic tissue as the denominator. This yielded ratios with a scale starting from 1, and progressively increasing values that correspond to tissue of greater consistency.

Sample size assessment

The sample size was calculated according to preliminary data collected from six patients to find any difference in strain ratio for different DIE locations paired with normal tissue using a nonparametric test. The target sample size was therefore 4 pairs, sufficient to detect differences in the median strain ratio between endometriosis and normal tissue in every DIE assessed, with power 80 % and a 0.05 significance level on two-sided testing.

Data analysis

Data were analyzed using the statistical package R [22] (version 3.6.3; R Core Team (2020). Kolmogorov–Smirnov was used to test the normal distribution of data. A Wilcoxon test or t-test was applied to the continuous variables, as appropriate (the endometriotic lesion and the paired normal tissue were tested using a paired test). Dichotomic variables were tested using the chi-squared or Fisher's exact test. Continuous data are presented as the median and interquartile range (IQR) or mean and standard deviation. Categorical variables are expressed as frequencies, absolute values, and percentages. Intra-operator variability was assessed via the intraclass correlation coefficient (ICC) and its 95 % confidence interval (CI.95). The performance of strain and CS ratios in determining the presence of an endometriotic nodule was evaluated by generating the receiver operating characteristic (ROC) curves. ROC curves are presented with their area under the curve (AUC) and relative CI.95. The DeLong test was used to compare AUCs of different ROC curves. For all analyses, a two-tailed p-value < 0.05 was considered significant.

Results

Population

The study examined 46 DIE nodules from 32 women. Mean age at diagnosis was 37.31 ± 8.43 years. ▶ **Table 1** shows the characteristics of participants. 18.7 % of them had had a surgical diagnosis of endometriosis within the previous 24 months. A subsequent histological evaluation of the nodule detected at sonography was obtained in 32.1 % of the nodules.

▶ **Table 1** Characteristics of the population.

Women's background characteristics and therapy	
Women (n.)	32
Age (years)	37.31 (± 8.43)
Nulliparity	31.25 % (10/32)
Actual surgery	34.38 % (11/32)
Previous surgery	18.75 % (6/32)
Medical therapy	34.38 % (11/32)
▪ Progesterone	28.12 % (9/32)
▪ COC	6.25 % (2/32)
Women's symptoms	
Dysmenorrhea	68.75 % (22/32)
▪ Dysmenorrhea VAS	5 (0–8)
Ovulation pain	37.5 % (12/32)
▪ Ovulation pain VAS	0 (0–5)
Chronic pelvic pain	62.5 % (20/32)
▪ Chronic pelvic pain VAS	3.5 (0–6.25)
Dyspareunia	46.88 % (15/32)
▪ Dyspareunia VAS	0 (0–7.25)
Dyschezia	25 % (8/32)
▪ Dyschezia VAS	0 (0–1)
Back pain	43.75 % (14/32)
▪ Back pain VAS	0 (0–5.25)
Inguinal pain	9.38 % (3/32)
Endometriotic nodules characteristics	
Number	46
Volume (cm^3)	0.62 (0.35–1.01)
Nodules per women	1 (1–2)
Locations	
▪ Uterosacral ligaments	45.65 % (21/46)
▪ Parametrium	15.22 % (7/46)
▪ Rectum	30.43 % (14/46)
▪ Recto-vaginal septum	8.7 % (4/46)

Acronyms: COC = Combined oral contraceptives; VAS = Visual Analogue Scale.

Transvaginal elastography

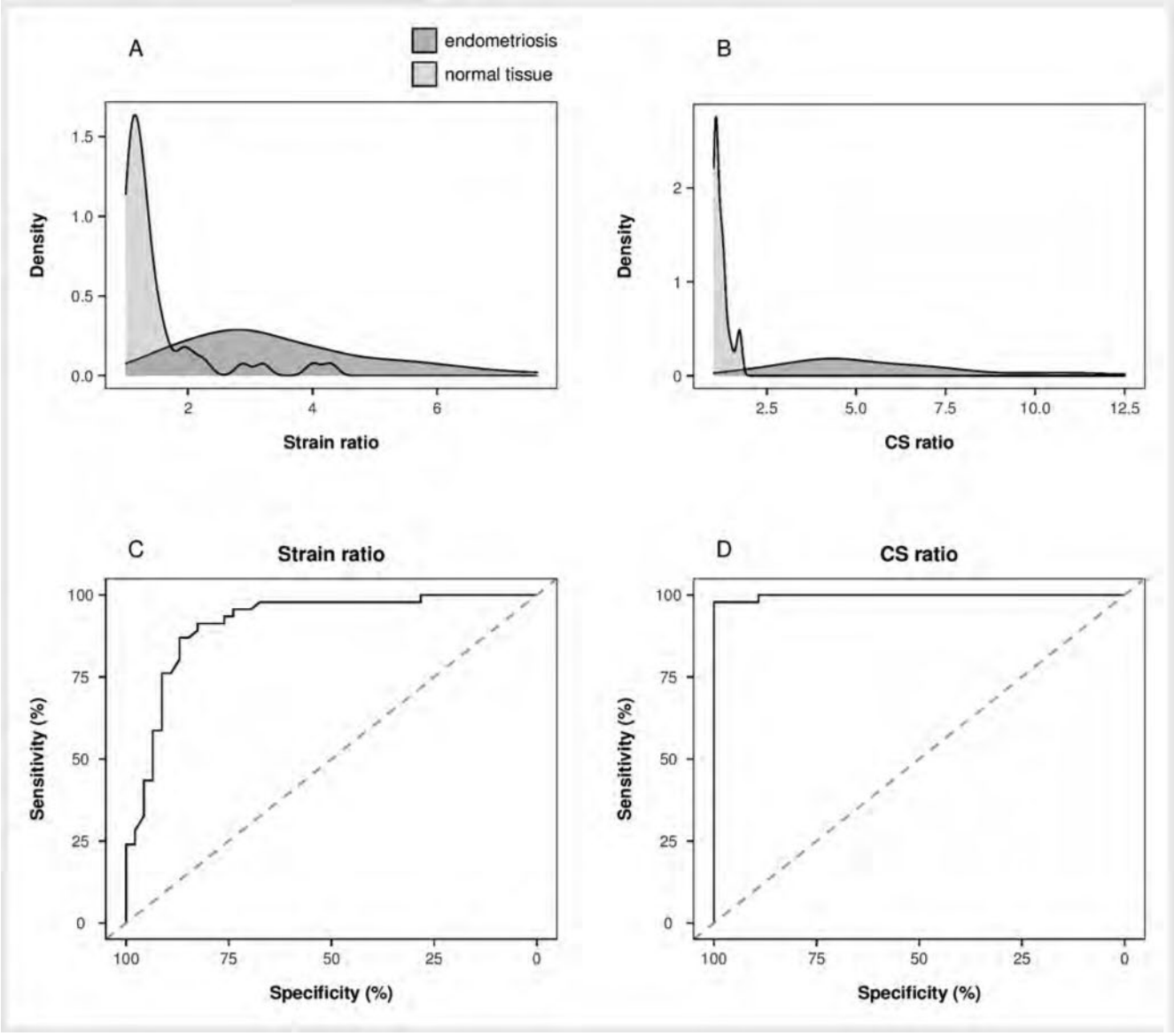
In a preliminary assessment of 6 nodules in 6 different subjects, the intra-operator variability for strain ratio was 0.841 (CI.95 0.516–0.966), and for CS ratio it was 0.925 (CI.95 0.816–0.980).

Elastography of DIE nodules and surrounding tissue is depicted in ▶ **Fig. 1**. The strain ratio of DIE nodules (3.09, IQR 2.38–4.14) was significantly higher than that of normal tissue (1.25, IQR 1.11–1.48) ($p < 0.001$). Similarly, the CS ratio of DIE nodules was significantly higher (4.62, IQR 3.83–6.94) than that of normal tissue (1.13, IQR 1.06–1.29) ($p < 0.001$). The distributions of strain and CS ratios of DIE nodules was well distinguished from those of normal tissue (▶ **Fig. 2**). ROC plots present strain and CS ratio accuracy in defining DIE implants (▶ **Fig. 2**); the best threshold for strain ratio ROC was 1.68, with a sensitivity of 91.3 % (CI.95 82.61–97.83 %) and a specificity of 82.61 % (CI.95 71.74–93.48 %), while the best threshold for CS ratio ROC was 1.82, with a sensitivity of 97.83 % (CI.95 93.48–100 %) and a specificity of 100 % (CI.95 100–100 %). CS ratio AUC (99.76 %, CI.95 99.26–100 %) was higher than strain ratio AUC (91.35 %, CI.95 85.23–97.47 %) ($p = 0.007$).

Strain ratio and CS ratio of different DIE locations

Strain ratio and CS ratio were not significantly different among the different DIE locations. Similarly, the difference between endometriosis and normal tissue strain and CS ratios was consistently shown in all the locations investigated, even though, for a low number of cases in the recto-vaginal septum, it did not reach statistical significance (▶ **Table 2**). Strain and CS ratios of nodules with histological diagnosis of endometriosis were also calculated separately. Data were not different from those obtained when considering all nodules (▶ **Table 2**).

The accuracy of the strain and CS ratios in distinguishing endometriotic nodules in different locations was evaluated by ROC plots (▶ **Fig. 3**). Data were similar among locations. At the uterosacral ligaments, the strain ratio AUC was 89.91 % (CI.95 81.49–98.33 %) and the CS ratio AUC 100 % (CI.95 100–100 %), the difference between the two being significant ($p = 0.019$). At the parametrium, the strain ratio AUC was 90.99 % (CI.95 82.6–99.39 %) and the CS ratio AUC 100 % (CI.95 100–100 %), the difference between the two being significant ($p = 0.036$). At the rectum, the strain ratio AUC was 92.31 % (CI.95 85.46–99.16 %) and the CS ratio AUC 99.22 % (CI.95 97.57–100 %), the difference between the two being close to significant ($p = 0.056$). At the recto-vaginal septum, the strain ratio AUC was 96.2 % (CI.95 90.77–100 %) while the CS ratio AUC was 100 % (CI.95 100–100 %); this difference was not significant, probably due to the limited number of cases in the sample ($p = 0.169$). Separate ROC curves for DIE nodules confirmed by histology were also calculated. Data were comparable to those reported for all nodules considered together (**Supplemental Figure 1**).



▶ **Fig. 2** Distribution of strain ratio (panel **A**) and color score (CS) ratio (Panel **B**) values in endometriosis versus normal tissue. ROC plot showing accuracy of strain ratio (Panel **C**) and CS ratio (Panel **D**) values in distinguishing endometriosis nodule from non-endometriotic tissue.

Discussion

Principal findings

At SE analysis, strain and CS ratios for DIE lesions and normal tissue were significantly different, irrespective of nodule location. The accuracy of discriminating endometriotic tissue from normal tissue was high in all areas examined.

Results in the context of what is known

The value of tissue stiffness obtained by SE is variable and operator dependent [23, 24]. Accordingly, it is not feasible to appropriately define absolute stiffness by this method. Usually, the stiffness ratio of sites of interest and adjacent tissue is more appropriate to eliminate inter-operator variability, as the compression and decompression exerted by the operator similarly affect the two areas [10, 25, 26]. In this study, the stiffness ratio of two areas of the same tissue surrounding the nodule was compared with the stiffness of the nodule. DIE nodules were always stiffer than surrounding tissue, and the ratio of non-endometriotic/DIE nodule was consistently above 1. We aimed to evaluate whether SE analysis expressed in this way can be used to differentiate DIE from surrounding tissue. To achieve this goal, we calculated the normal tissue ratio as the ratio between the mean stiffness of the two areas surrounding the nodule as the numerator, divided by the value of the stiffer area of the two. In this case too, the ratio was consistently above 1. It emerged that the distribution of both strain and CS ratios of DIE nodules was markedly different from those of surrounding tissue. Cut-off values differentiating nodule from surrounding tissue were similar for strain and CS ratios, and both showed high sensitivity and specificity. For CS ratio, a cut-off value of 1.82 was associated with sensitivity and specificity close

▶ **Table 2** Strain ratio and CS ratio divided by location and tissue type (endometriosis/normal tissue). Analysis on nodules confirmed by histological diagnosis is also separately reported.

A) All endometriotic nodules	Uterosacral ligaments (21)	Parametrium (7)	Rectum (14)	Recto-vaginal septum (4)
Strain ratio endometriosis	3.09 (2.10–4.00)	3.00 (2.42–3.50)	3.47 (2.64–4.83)	3.75 (3.08–4.38)
Strain ratio normal tissue	1.16 (1.07–1.32)	1.24 (1.17–1.26)	1.34 (1.15–1.56)	1.82 (1.44–2.65)
p-value (*)	< 0.001	0.016	0.003	0.125
CS ratio endometriosis	5.17 (4.50–7.75)	3.83 (2.56–6.00)	4.50 (3.80–6.94)	4.00 (3.34–5.38)
CS ratio normal tissue	1.10 (1.05–1.26)	1.11 (1.07–1.16)	1.22 (1.09–1.30)	1.52 (1.36–1.64)
p-value (*)	< 0.001	0.016	0.001	0.125
B) Nodules with histology	Uterosacral ligaments (6)	Parametrium (3)	Rectum (5)	Recto-vaginal septum (1)
Strain endometriosis	3.34 (2.14–4.00)	3.00 (2.50–3.46)	3.83 (2.67–4.30)	–
Strain control	1.30 (1.10–1.61)	1.24 (1.12–1.25)	1.15 (1.07–1.33)	–
p-value (*)	< 0.001	0.016	0.003	–
CS endometriosis	4.69 (4.50–9.09)	6.25 (4.44–9.38)	4.50 (4.50–7.00)	–
CS control	1.18 (1.07–1.28)	1.17 (1.13–1.21)	1.17 (1.13–1.27)	–
p-value (*)	< 0.001	0.016	0.001	–

(*) Differences between endometriosis and normal tissue in each location (paired Wilcoxon test).
Acronyms: CS = color score.

to 100 %. Results were similar for any location of DIE, as previously reported for shear-wave elastography [27]. Similar results were obtained when considering DIE nodules with a histological diagnosis separately.

Clinical implications

SE has previously been applied to DIE in Douglas's cul-de-sac. Although greater tissue stiffness was found in women with DIE, no attempt was performed to evaluate the sensitivity of this technique [12]. In a recent article, share wave elastography proved to be capable of detecting DIE nodules [27]. Share-wave elastography is more reproducible than SE and gives an absolute tissue stiffness value. However, we demonstrate herein that SE detects DIE, from surrounding non-endometriotic tissue, with high sensitivity and specificity when appropriate ROIs are used for calculating strain or CS ratio. In particular, the distribution curves of strain and CS ratios of normal versus endometriotic tissue had minimal if any superimposition. In normal tissue the curve was narrow, while in DIE it was broader and flatter, indicating a large variability of DIE nodule stiffness, probably due to the different proportions of fibrotic tissue [27].

Strengths and limitations

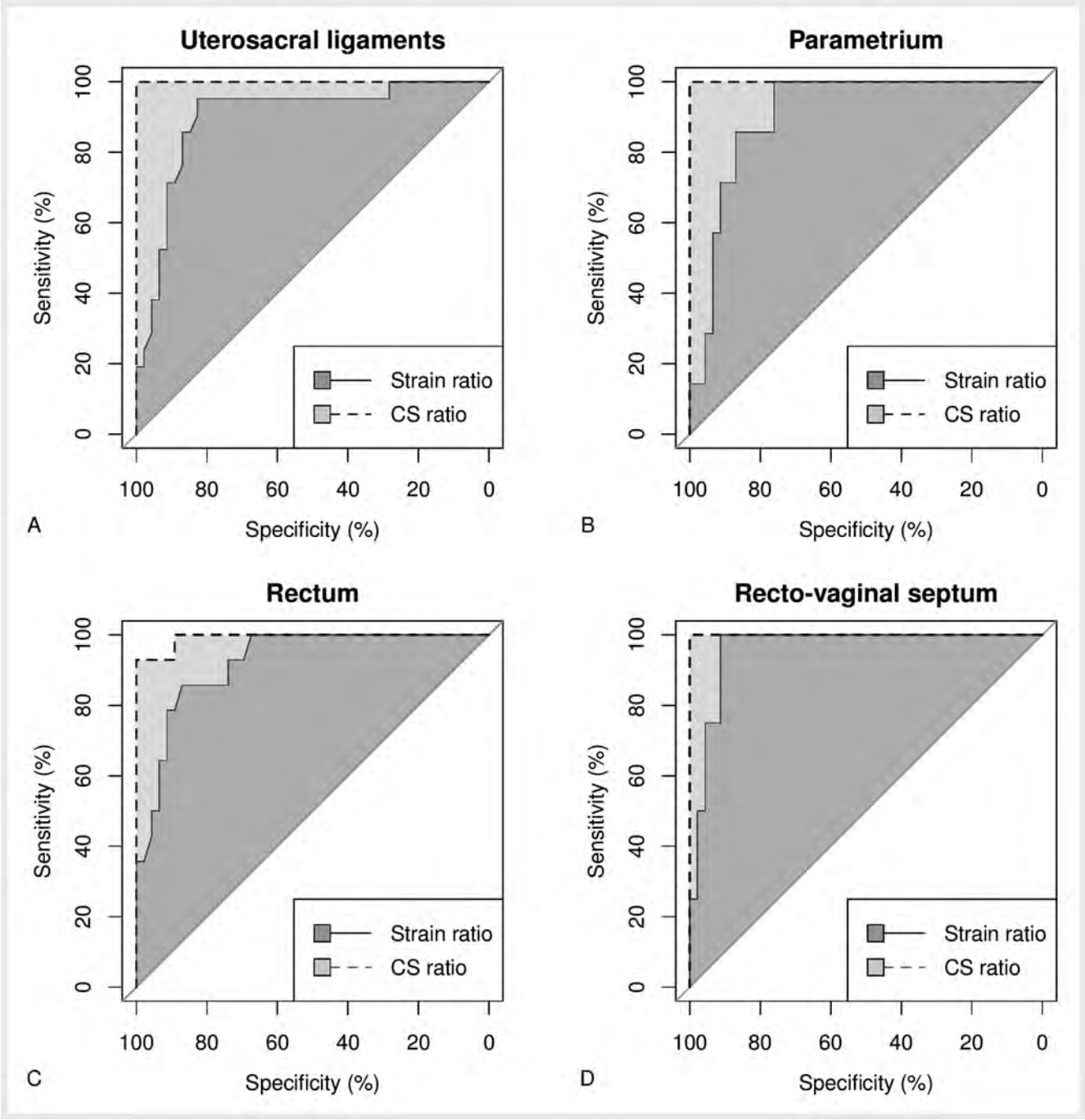
One of the limitations of this study is that SE is operator-dependent. To minimize this bias, we used three different strategies: a single experienced operator performed all the elastography evaluations; strain values were analyzed at optimal tissue compression, as indicated by the elastography software; strain or CS values were not considered as an absolute value but as the ratio of ROIs values. Yet, we acknowledge that the inter-observer reproducibility of our analysis needs to be tested in further studies. Some women had undergone surgery before our evaluation and post-surgical scars may have modified tissue stiffness. We did not observe relevant differences between women with and without a previous surgery, but the number of subjects was limited, and additional studies are necessary to investigate this possible confounding. Elastography was applied after nodule identification, and in this condition, both strain and CS ratios discriminated nodules from normal tissue. It remains to be seen whether elastography may help less-skilled sonographers to distinguish DIE from surrounding tissue, becoming an additional tool for achieving an accurate diagnosis of DIE.

Research implications

Prospective studies should help determine whether our method is a sensitive and specific tool for diagnosing DIE, particularly in areas where ultrasonography is less accurate, such as the uterosacral ligaments and the parametrium [5]. The stiffness of DIE nodules varies widely, and whether these differences are related to a different DIE composition is suggestive but unproven. A different stiffness may identify an active DIE, which can be more symptomatic and responsive to medical treatment.

Conclusions

SE expressed as both strain and CS ratio highly accurately distinguishes DIE nodules at various locations from surrounding non-endometriotic tissue. Pending validation and reproducibility testing of our findings by prospective studies, elastography may represent an important tool for diagnosing DIE and possibly monitoring its evolution either spontaneous or in response to treatment.



▶ **Fig. 3** ROC plots show the accuracy of strain and color score (CS) ratios in identifying endometriotic nodules in different locations.

Conflict of Interest

The authors declare that they have no conflict of interest.

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