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● *Clinical Note*

EVALUATION OF PRE-MALIGNANT LESIONS OF THE UTERINE CERVIX BY SHEAR WAVE ELASTOGRAPHY: A NEW DIAGNOSTIC TOOL

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Abstract—The objective of the study was to evaluate the difference in the stiffness between a healthy cervix (no pre-invasive lesions [NPILs]) and a cervix with a pre-invasive lesion (PIL). In the PIL group, we determined whether there was a difference in stiffness between the cervix with persistent low-grade lesions (>2 y, LSIL-persistent) and that with high-grade lesions (HSILs). Evaluation was performed using 2-D shear-wave elastography (SWE) in the midsagittal-plane of the uterine cervix (UC) at 0.5 cm (cervical canal, anterior and posterior cervical lips). In this prospective observational study (consecutive series), we evaluated 96 non-pregnant women: a group with PIL (LSIL-persistent, 22 cases; HSIL, 26 cases) with indications for cervical conization (48 cases) and a group without UC pathology (NPIL, 48 cases). Although we did not observe statistically significant differences (SSDs) in epidemiological characteristics, we did find an SSD in the speed and stiffness between the PIL versus NPIL groups at all evaluated depths (speed: 4.1 m/s vs 3.0 m/s, stiffness: 58.6 and 34.5kPa in the PIL and NPIL groups, respectively, $p < 0.001$). An SSD in speed and stiffness (speed: 4.9 m/s vs. 3.2 m/s, and stiffness: 76.1 and 38.0 kPa) between the HSIL (26 cases) and LSIL-persistent (22 cases) groups, respectively, was also detected ($p < 0.001$). The area under the curve of speed differentiation between a cervix with HSILs and without lesions was 73.4% (95% confidence interval [CI]: 63.1–83.7), and the best cutoff of speed was 3.25 m/s (sensitivity = 62.5%, 95% CI: 47.3–76.0), with a specificity of 75.5% (95% CI: 60.4–87.1). (E-mail: jsainz@us.es)

Keywords: **Cervical cancer, Pre-invasive lesion, Elastography, Shear wave, Transvaginal ultrasound, Diagnosis.**

INTRODUCTION

Cervical cancer remains the second leading cause of cancer death in women aged 20 to 39 (Siegel et al. 2021). The incidence of and number of deaths from cervical cancer have decreased since the implementation of widespread cervical cancer screening using cervical cytology and/or human papillomavirus (HPV) testing (Saslow et al. 2012). Although knowledge of HPV has advanced, cervical cytology remains the mainstay of cervical cancer screening. Colposcopy and cervical biopsy are the next recommended steps in patients with an altered first screening test result (Perkins et al. 2020). In recent years, there have been important advancements in the definition of colposcopy standards and terminology definitions, as well as in the generation of consensus guidelines for cancer precursors (Bornstein et al. 2012; Waxman et al. 2017; Perkins et al. 2020). Nevertheless, colposcopy still depends on the experience of the examiner, and rates of agreement between colposcopy and general histology as a single step in diagnosis range between 75% and 77% (Massad and Collins 2003), with rates of perfect agreement of 32%–37% (Petousis et al. 2018). Thus, colposcopy underdiagnoses approximately one-third of cases of high-grade pre-invasive cervical lesions (high-grade lesions [HSILs]) (Underwood et al. 2012). Performing multiple or repeated biopsies can improve these results (Underwood et al. 2012; Vallapapan et al. 2019). However, the identification capacity of colposcopy and cervical biopsy of pre-invasive or pre-malignant lesions remains limited (Adams et al. 2006; Yang et al. 2008), and the introduction of new diagnostic methods, such as sonoelastography, warrants further investigation to assess its usefulness (Yang et al. 2008).

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Shear wave elastography (SWE) is a new US technology that can quantitatively evaluate the stiffness of tissues (Ophir et al. 1991, 1999). Elasticity is a characteristic of tissues with changes during different pathological processes (trauma, inflammation, tumors), and any new formation with high stiffness is associated with a higher risk of malignancy (Wang et al. 2018). Elastography, which is also referred to as the "visual palpation method," is widely used for different organs, such as the liver and breast (Thomas et al. 2006; Ferraioli et al. 2018). Conversely, its usefulness in the evaluation of cervical uterine pathology is very limited to date (Thomas et al. 2007; Su et al. 2013; Xie et al. 2014; Bakay and Golovko 2015; Chen et al. 2020; Fu et al. 2020). In this study, we evaluated the ability of SWE to identify pre-invasive lesions of the UC before its use in cervical uterine pathology with colposcopy and cervical biopsy.

METHODS

We conducted a prospective observational study with 110 non-pregnant women included consecutively between February 2018 and December 2019 at Valme University Hospital, Seville, Spain.

A group of patients with cervical pathology and an indication for conization as treatment and a group of patients without uterine cervical pathology were invited to participate. To participate in the study, patients had to be between 18 and 65 y old and had to give their consent to participate by means of written informed consent. The patients in both study groups were assessed, including a transvaginal ultrasound in B-mode before SWE, performed in the gynecological ultrasound unit of H. U. Valme. The ultrasound operators who performed the assessment were blinded to the status of participants. The exclusion criteria in both cohorts were age <18 y or >65 y, pregnancy, vaginal infection other than HPV or another gynecological pathology (myoma or functional or organic adnexal pathology) that would prevent direct sonographic evaluation of the UC.

Participants

Patients with a uterine cervical pre-invasive lesion (PIL). Among patients with cervical pathology (diagnosed by cytology, colposcopy and cervical biopsy) with indications for cervical conization (American Cancer Society et al. 2012; Oncoguía SEGO 2014), only cases of PILs, HSILs and low-grade invasive lesions persistent more than 2 y (LSIL-persistent) were included.

Patients belonging to this group who agreed to participate in the study underwent ultrasound evaluation and subsequently cone sectioning. Pathological analysis of the surgical section was performed. Histological lesions associated with HPV were definitively classified as "low-grade" lesions (LSILs) and "high-grade" lesions (HSILs) according to the current Lower Anogenital Squamous Terminology histopathological terminology (Richart 1973; Darragh et al. 2012; Stoler et al. 2014).

Patients with no pre-invasive lesions (NPILs)

Patients who visited the hospital for routine heath checkups constituted the control group. Those who agreed to participate in the study in a single visit were recruited. The technique to be performed was explained to the patients: a complete gynecological examination, including transvaginal ultrasound in B-mode before SWE, was performed. These patients did not undergo colposcopy.

Of the 110 initial non-pregnant women, 14 were excluded: at the beginning of the study, 6 patients (3 did not agree to participate, 1 had an adnexal lesion preventing evaluation of the cervix, 1 was pregnant and 1 did not attend the review) were excluded. Another 8 were excluded during the study: 4 in the PIL group (3 with lesions other than PILs in the definitive histological study and 1 who underwent surgery not performed at our hospital), and 4 in the NPIL group (2 with vaginal infection and 2 with incomplete 2-D SWE evaluation).

Imaging techniques

Two-dimensional SWE was performed by two operators (J.A.S., J.A.G.) with more than 5 y of experience in gynecological ultrasound and with specific training in 2-D SWE (inter-operator testing was not performed). A Toshiba Aplio 500 Platinum ultrasound scanner (Canon Medical Systems, Tochigi, Japan) with a 11C3 PVT-781VTE intracavitary transducer was used. When performing 2-D SWE, the two operators were blinded to the clinical data or results of cytology or cervical biopsy of the patients, as well as to the group to which each patient was allocated. A machine setting of a shear-wave frequency of 4 MHz and tracking of 0 was employed; this setting uses a 4-MHz push pulse and 4-MHz tracking pulse. Shear wave speed measurements were obtained using the continuous mode and the lowest frame rate setting of 1, equating to 0.4 frames/s. The elastogram map was stable for at least 3 s before speed measurements were obtained (O'Hara et al. 2019a; Castro et al. 2020).

For this procedure, ultrasound gel was placed with the help of a speculum into the vagina to improve delimitation of the contour of the cervix and the canal and to decrease pressure exerted on the cervix (Shiina et al. 2015). The evaluation of 2-D SWE was performed in the mid-sagittal plane of the UC, the cervical canal was oriented as horizontal as possible and the cervix occupied three-quarters of the image. The elastogram was 30×30 mm, and the map opacity was set to 0.3. By use of Canon technology, the accuracy of shear-wave propagation can be assessed in several ways. The elastogram speed map was set to a scale of 0.5 to 8.5 cm/s, with *blue* being indicative of softer tissues. The non-existence of peripheral *red* in the near field of the elastogram, indicative of overpressure, was confirmed, and parallel

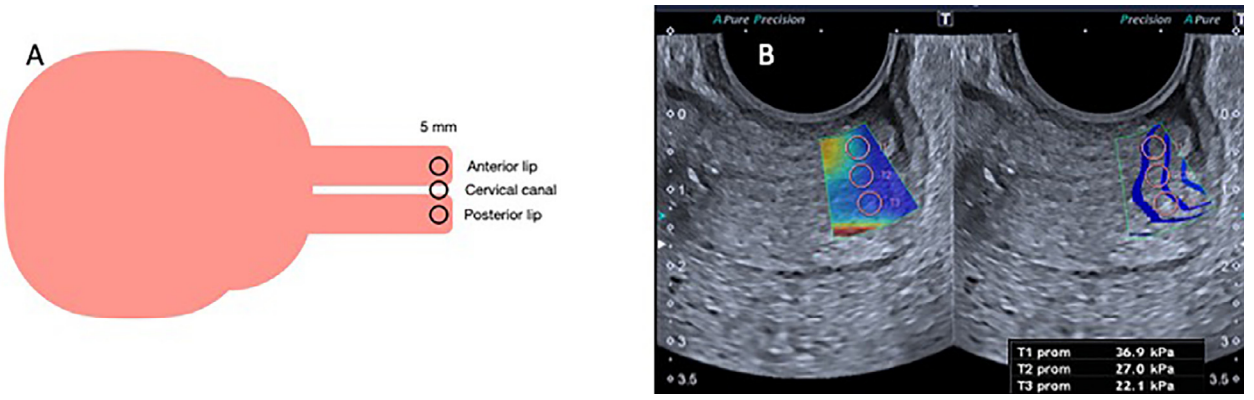

Fig. 1. Sagittal section of the uterine cervix. (a) Graphic representation of the study points in shear-wave elastography. (b) Example of evaluation of the uterine cervix by shear-wave elastography with quantitative measurement of wave propagation stiffness and speed at a 0.5-cm cervical canal.

lines in the study area in the wavefront propagation map were required. In each study area, three measurements were obtained by means of a 2-mm region of interest (Region of interest (ROI), circular study window) to calculate the mean and standard deviation of both the velocity (m/s) of propagation and the elasticity (kPa) of the tissue at 0.5 cm from the external cervical os. Measurements were taken in the anterior lip, canal and posterior lip of the cervix (Fig. 1). Quantitative measurements of the anatomical regions of the study and a qualitative assessment of the cervical regions with a color map superimposed on the B-mode ultrasound image were obtained (Fig. 1). In cases presenting irregular wavefront lines or inaccurate shear-wave propagation, we considered two accurate measurements in each region sufficient. Regions in which only one accurate measurement was obtained were removed from statistical analysis.

Statistical analysis

The statistical analysis was carried out using IBM SPSS Statistics software, Version 22 (IBM, Armonk, NY, USA). We determined the mean and standard deviation for quantitative variables and percentages for qualitative variables. Student's *t*-test was used to compare the different quantitative variables, and the χ^2-test was applied to analyze qualitative variables between different groups.

In addition, a receiver operating characteristic (ROC) curve was fitted, and the area under the ROC curve with 95% confidence interval (CI) was determined to find the cutoff of stiffness (kPa) for differentiating between a cervix with high-risk lesions (HSILs) and a cervix with no lesion. The sensitivity and specificity values were calculated. For all statistical analyses, the level of significance was set at $p < 0.05$.

To detect differences of 25% in the stiffness of the UC assessed by SWE, measured in kilopascals, as described in previous studies that evaluated the stiffness of the UC in healthy patients (Castro et al. 2020), and considering an α error of 5% and a power of 80%, we needed 45 patients per study group.

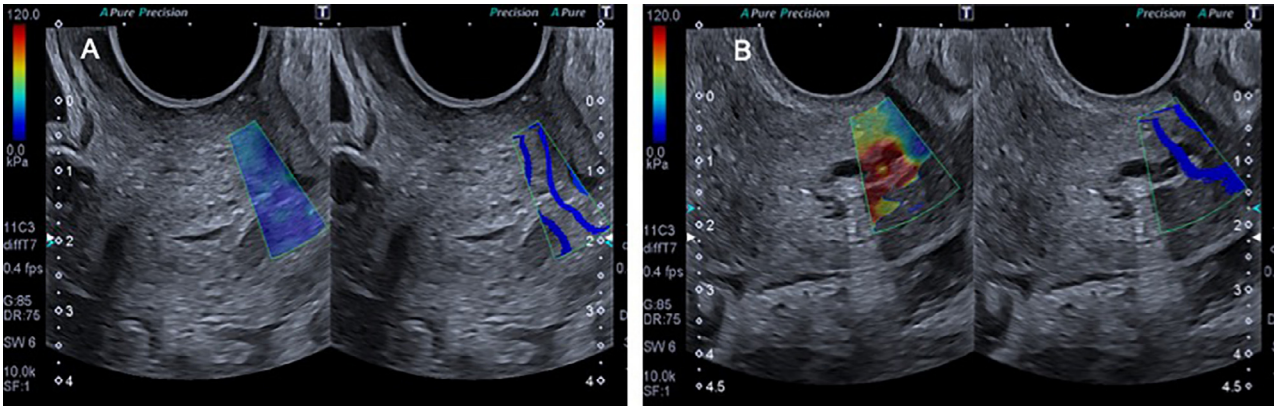

Fig. 2. (a) Uterine cervical shear-wave elastography (SWE) in the case of a healthy cervix. (b) Uterine cervical SWE in the case of a pre-invasive cervical lesion (high-grade lesions) with the presence of areas of high stiffness (*red*).

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of Valme University Hospital (1001-N-18), and informed consent was obtained from all patients.

RESULTS

Of the 110 participants enrolled in this study, 96 (48 patients with PILs and 48 patients with healthy cervices) completed the study; in both groups, 17 patients <35 years of age and 18 nulliparous patients were included. Figure 2 illustrates the subjective evaluation by 2-D SWE of a cervix without uterine cervical lesions (Fig. 2a) and of a cervix with a PIL (Fig. 2b).

The epidemiological characteristics of the patients are summarized in Table 1. No statistically significant differences (SSDs) were identified between the groups. We observed SSDs in the speed and stiffness of cervices with pre-invasive lesions compared with cervices with no cervical lesion, at all depths evaluated (Table 2). There were also SSDs between cervices with high-risk (HSIL) lesions and persistent low-risk (LSIL-persistent) cervical lesions (Table 3). However, we did not observe differences in the evaluation of uterine cervical speed and stiffness between persistent LSIL and NPIL (Table 3), evaluated by 2-D SWE. Patients with HSILs had significantly higher speed and stiffness values ($p <$ 0.001) than those with NPILs, as evaluated at the level of the cervical canal; the ROC curve is illustrated in Figure 3. The area under the ROC curve for speed was 73.4% (95% CI: 63.1−83.7), and the best cutoff for speed was 3.25 m/s, with a sensitivity of 62.5% (95% CI: 47.3−76.0) and specificity of 75.5% (95% CI: 60.4−87.1).

DISCUSSION

To our knowledge this is the first cohort study to examine the usefulness of 2-D SWE for the evaluation of pre-invasive lesions of the UC. The main finding is that the stiffness of a UC (evaluated at 0.5 cm) with a PIL is greater than that of a healthy UC (58.6 kPa vs. 34.5 kPa, $p < 0.001$). Furthermore, a cervix affected by an HSIL had greater stiffness than a cervix affected by a persistent LSIL (38.0 kPa vs. 76.1 kPa, $p < 0.001$).

The usefulness of elastography has been validated. It is broadly used in evaluating lesions suspected of being malignant in prostate, thyroid and mammary pathology, but its application is most widespread within the context of liver pathology, where it is applied to evaluate the degree of liver stiffness (fibrosis) (Ophir et al. 1991, 1999; Thomas et al. 2006; Ferraioli et al. 2018; Wang et al. 2018).

Table 1. Epidemiological characteristics of the study population

	Global (n = 96)			NPIL (n = 48)			PIL (n = 48)			*p* Value
Study group										
Age	39 ± 11			39 ± 13			39 ± 9			.649
BMI	23.97 ± 3.62			23.71 ± 3.54			24.23 ± 3.72			.420
Smoker	Yes	No		Yes	No		Yes	No		.054
	34 (35.4%)	62 (64.6%)		12 (25%)	36 (75%)		22 (45.8%)	26 (54.2%)		
Age group	20−34	35−49	50−65	20−34	35−49	50−65	20−34	35−49	50−65	.205
	35 (36.5%)	43 (44.8%)	18 (18.8%)	17 (35.4%)	19 (39.5%)	12 (25%)	17 (35.4%)	25 (52.1%)	6 (12.5%)	
Parity	NP	PP	MP	NP	PP	MP	NP	PP	MP	.487
	41 (42.7%)	20 (20.8%)	35 (36.5%)	18 (37.5%)	13 (27.0%)	17 (35.4%)	18 (37.5%)	12 (25%)	18 (37.5%)	
Cycle phase	Amenorrhea	First phase	Second phase	Amenorrhea	First phase	Second phase	Amenorrhea	First phase	Second phase	.086
	22 (22.9%)	41 (42.7%)	33 (34.4%)	15 (31.3%)	16 (27%)	17 (35.4%)	7 (14.6%)	25 (52.1%)	16 (33.3%)	
Menopause	Yes	No		Yes	No		Yes	No		.285
	17 (17.7%)	79 (82.3%)		11 (22.9%)	37 (77.1%)		6 (12.5%)	42 (87.5%)		
Histological lesions	Normal	LSIL−HSIL		Normal	LSIL-persistent−HSIL		LSIL-persistent	HSIL		<.0005
	48 (50%)	48 (50%)		48 (100%)	0 (0%)		22 (45.8%)	26 (54.2%)		

Data are given as mean ± SD or *n* (%).

BMI = body mass index; NP = nulliparous; PP = primiparous; MP = multiparous; PIL = patients with pre-invasive cervical lesion. NPIL = patients without pre-invasive cervical lesion; LSIL-persistent = patients with a persistent low-risk pre-invasive lesion (>2 y); HSIL = patients with a high-risk pre-invasive lesion.

Table 2. Evaluation of speed and elasticity assessed by 2-D shear-wave elastography between study groups PIL (n = 48) and NPIL (n = 48)

	Speed (m/s)			Stiffness (kPa)		
	NPIL (48)	PIL (48)	P1	NPIL (48)	PIL (48)	P2
Anterior lip	2.9 ± 1.3	3.9 ± 1.9	0.019	34.1 ± 36.0	53.8 ± 45.2	0.022
Cervical canal	3.0 ± 1.6	4.1 ± 1.7	0.001	34.5 ± 3.0	58.6 ± 41.0	0.001
Posterior lip	3.0 ± 1.0	3.3 ± 1.0	0.094	33.5 ± 3.2	38.9 ± 23.7	0.139

PIL = patients with a pre-invasive uterine cervical lesion; NPIL = patients without a pre-invasive uterine cervical lesion. P1 = evaluation of speed; P2 = evaluation of stiffness.

Data are expressed as the mean ± standard deviation.

Elastography is classified according to the principles of stress elastography (strain elastography [SE]) and wave elastography (SWE). SWE uses an ultrasonic wave to generate an artificial pulse, which propagates a transverse wave (shear wave) through tissue. When this wave passes through the tissue, its speed varies depending on the tissue's stiffness, enabling measurement of stiffness (in kPa) or propagation speed (in m/s) (Ophir et al. 1991, 1999; Wilson et al. 2000; Greenleaf et al. 2003; Parker et al. 2011; Duan et al. 2020). SWE is a quantitative method for evaluating tissue stiffness and is also an independent operator (Castro et al. 2020).

In gynecology, elastography has been used to investigate some obstetric pathologies (O'Hara et al. 2019b) to differentiate myometrial pathology (myomas vs. adenomyosis) and endometrial pathologies (polyps vs. endometrial cancer) and to guide the management of these entities (Zhang et al. 2015; Czuczwar et al. 2016, Marigliano et al. 2016; Bildaci et al. 2018). This relatively new ultrasound technique has only been applied recently for cervical uterine pathology.

Strain elastography has been employed by different studies to differentiate benign from malignant cervical pathology. Lu et al. (2014) used SE to identify a cutoff point of 4.52 for malignancy (strain ratio; sensitivity = 90.9%, specificity = 90.0%, positive predictive value = 90.5% and negative predictive value = 90.9%). In addition, Sun et al. (2012) reported a stress ratio of malignant lesions of 8.19 versus 2.81 for benign lesions, and Xu et al. (2020) used SE imaging to assess the response of locally advanced cervical cancer to chemoradiotherapy. Ma et al. (2017) used this technique to evaluate parametrial infiltration in cases of cervical cancer, with good results. Therefore, it seems clear that SE can help in identifying and managing malignant cervical pathology.

We propose the use of 2-D SWE in the assessment of pre-invasive lesions of the UC; to this end, we used SWE instead of SE because the latter has limitations (Molina et al. 2012; O'Hara et al. 2019a). For example, O'Hara et al. (2019a) reported difficulty in standardizing this technique for the UC and found that the rigidity of the UC can be evaluated using SWE, in addition to publishing the reliability of this technique for cervical evaluation (O'Hara et al. 2019c). Thus, before carrying out this work, our group determined that SWE has adequate inter-observer and intra-observer variability with respect to the UC, which is normal in the presence of injury (Moga et al 2018).

There are only two studies to date on the evaluation of cervical stiffness in the presence of pre-malignant or malignant cervical pathology using SWE. Initially, Su et al (2013) used SWE to observe that invasive lesions of the cervix exhibit a mean speed of 3.41 m/s versus 2.11 m/s for the healthy cervix. Fu et al (2020) also recently reported differences in the rigidity of the UC in the presence of invasive lesions compared with the healthy cervix using SWE (speed of 2.9 m/s vs. 1.5, $p < 0.035$). In the present study, we used 2-D SWE evaluation of cervical stiffness at 0.5 cm to identify differences in stiffness between the healthy cervix and the cervix with pre-invasive lesions (more rigid) (34.5 kPa vs. 58.5 kPa, $p < 0.001$); because we did not observe differences between the healthy cervix and persistent low-grade pre-invasive lesions, this technique was only affective for high-grade pre-invasive lesions (34.5 and 38.0 kPa, $p < 0.080$). We also detected greater stiffness with high-grade pre-invasive lesions than persistent low-grade pre-invasive lesions (76.1 kPa vs. 38.0 kPa, $p < 0.001$), as well as a greater difference in stiffness at the level of the cervical canal than the anterior and posterior lip between a cervix with pre-invasive lesions and a healthy cervix. This observation can be justified by the origin of pre-invasive cervical pathology that begins at this level (Richart 1973; Darragh et al. 2012; Stoler et al. 2014).

Initially, we observed a cutoff point of 3.25 m/s for identifying areas affected by a high-grade pre-invasive lesion. This cutoff point for high-grade pre-invasive lesions agrees with those reported by other authors for cervical cancer (2.9 m/s according to Fu et al. [2020] and 3.4 m/s according to Su et al. [2013]). Although it is still limited and its use must be confirmed with studies specially designed for this purpose, this approach may help in improving the clinical management of pre-invasive cervical lesions, which is currently based on

Table 3. Evaluation of speed and elasticity assessed by 2-D shear-wave elastography between patient groups

	Speed (m/s)						Stiffness (kPa)					
	LSIL-persistent(n = 22)	HSIL(n = 26)	NPIL(n = 48)	P1	P2	P3	LSIL-persistent(n = 22)	HSIL(n= 26)	NPIL(n = 48)	P4	P5	P6
Anterior lip	3.1 ± 1.5	4.5 ± 1.9	2.9 ± 1.3	0.007	0.593	<0.0005	35.2 ± 32.2	69.6 ± 49.0	34.1 ± 36.0	0.006	0.479	<0.0005
Cervical canal	3.2 ± 1.3	4.9 ± 1.7	3.0 ± 1.6	0.001	0.102	<0.0005	38.0 ± 27.4	76.1 ± 42.8	34.5 ± 3.0	0.001	0.080	<0.0005
Posterior lip	3.0 ± 0.8	3.5 ± 1.2	3.0 ± 1.0	0.131	0.241	0.023	33.0 ± 15.2	44.1 ± 28.5	33.5 ± 3.2	0.241	0.335	0.030

LSIL-persistent = patients with a persistent low-risk pre-invasive lesion (>2 y); HSIL = patients with a high-risk pre-invasive lesion; NPIL = patients without pre-invasive uterine cervical lesion (n = 48); P1 = evaluation of speed between LSIL-persistent and HSIL; P2 = evaluation of speed between LSIL-persistent and NPIL; P3 = evaluation of speed between HSIL and NPIL; P4 = evaluation of stiffness between LSIL-persistent and HSIL; P5 = evaluation of stiffness between LSIL-persistent and NPIL; P6 = evaluation of stiffness between HIL-persistent and NPIL.

Data are expressed as the mean ± standard deviation.

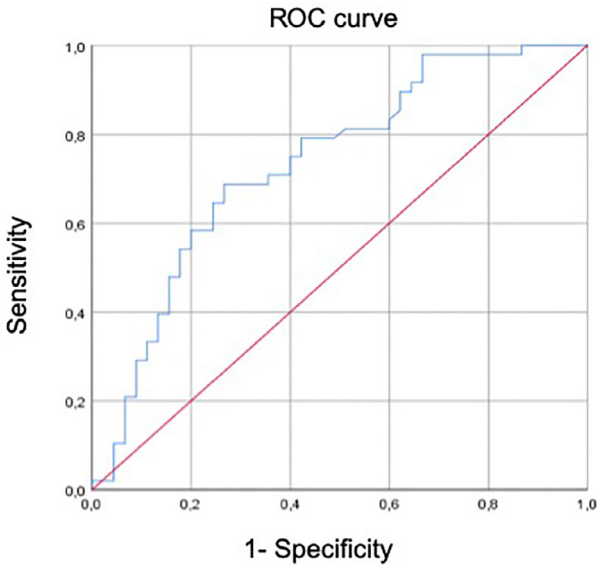

Fig. 3. Receiver operating characteristic (ROC) curve for speed (m/s) shear-wave elastography (SWE) in the differentiation a cervix with high-grade invasive lesions (HSILs) from a healthy cervix (NPIL) (evaluation at 0.5 cm of the cervical canal). The area under the ROC curve was 73.4% (95% confidence interval [CI]: 63.1−83.7). The cutoff for a speed of 3.25 m/s had a sensitivity of 62.5% (95% CI: 47.3−76.0) and a specificity of 75.5% (95% CI: 60.4−87.1).

cytology and colposcopy; indeed, its ability to identify pre-invasive or pre-malignant lesions is limited (Adams et al. 2006; Yang et al. 2008).

Changes of increased cervical stiffness in cases of a PIL that we observed by means of SWE from the anatomopathological viewpoint are justified by the histological changes to the UC with HPV infection (Reid 1993; Massad and Collins 2003; Darragh et al. 2012; Stoler et al. 2014; Waxman et al. 2017). Our data allow for studying pre-invasive cervical lesions, as current evaluation by colposcopy and biopsy has limitations, and stiffness assessment using 2-D SWE can help to identify areas of the UC for analysis.

Our study also has limitations. Although we evaluated the cervix exclusively in the horizontal position, we believe that 2-D SWE evaluation should also be performed in other positions (posterior, vertical and angulated) (O'Hara et al. 2019a), as evaluation of stiffness or speed with 2-D SWE might differ in these positions. Inter-operator testing was not performed in this work. In addition, the sample size was limited and calculated only to identify differences in stiffness between a healthy cervix and a cervix with a PIL but not to evaluate other variables. Last, we did not include cases of benign cervical pathology, and we did not adjust the assessment by age and parity of the patients.

CONCLUSIONS

When evaluated by 2-D SWE, uterine cervical stiffness in the presence of pre-invasive lesions is greater than that of a healthy UC. Furthermore, a cervix affected by a high-grade PIL has greater rigidity than a cervix affected by a persistent low-grade pre-invasive lesion.

CONFLICT OF INTEREST DISCLOSURE

The authors declare no competing interests.

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