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Effectiveness of Transvaginal Sonoelastography in Differentiation between Normal Cervix, Cervical Intraepithelial Neoplasia and Cancer Cervix

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ABSTRACT

Background: Early cervical cancer is mainly treated with surgery, whereas middle- and late-stage of cervical intraepithelial neoplasia (CIN) is mainly treated with radiotherapy. Therefore, accurate preoperative diagnosis and staging of cervical lesions are crucial to patients with cervical lesions.

Objective: The present study aimed to assess transvaginal sonoelastography in differentiation between normal cervix, CIN and cancer cervix. **Patients and methods:** A Case-control study carried out in Departments of Obstetrics & Gynecology and Radiology, Zagazig University Hospitals. Women were classified into three groups: Group A: 20 cases with normal cervix, group B: 10 cases with CIN and group C: 10 cases with cancer cervix.

Results: There was non-significant difference between studied groups as regards age and smoking. While there was significant difference regarding family history, weakened immune system, endometrial thickness and strain ratio**.**

Conclusion: Real time elastography (RTE) strain ratio (SR) of the uterine cervix, performed with a silicone ED as a reference material, seems a reliable method for distinguishing between a normal cervix and malignancy. The technique also showed promising results as a complementary investigation in diagnosing CIN.

Keywords: Sonoelastography, Transvaginal, Cervical cancer.

INTRODUCTION

Cervical cancer (CC) is among the leading causes of oncologic morbidity and mortality worldwide accounting for 6% of all cancers in women. The particular feature of CC is the possibility to detect its precursor, cervical intraepithelial neoplasia (CIN). Early intervention prevents the development of invasive forms of cancer [(1)]**.** Cancer cervix is the only gynecological cancer with clinical staging, according to FIGO. The stage is the key to the choice of treatment [(2)]**.**

Techniques as magnetic resonance imaging (MRI), diffusion-weighted MRI, dynamic contrast enhanced MRI and 18 F-fluorodeoxyglucose positron emission tomography (FDG- PET). Although superior diagnostic abilities of these techniques but not used in existing practice due to high costs, long examination time, large-scale equipment unavailability, radiation exposure, and possible adverse reactions to contrast agents [(3)]**.** Complementary to conventional ultrasound examinations, sonoelastography has been the focus of much medical research, as it is a non-invasive, widely available imaging technique. So far, sonoelastography has been intensively studied in thyroid and breast lesions, in liver and lymph node pathology [(4)]. According to the physical principle underlying the technique, there are two main types of sonoelastography: strain elastography (SE) and shear wave elastography (SWE). Both SE and SWE started to be assessed in exploring the premalignant and malignant lesions of the cervix [(5, 6)]**.** The aim of the present study was to assess the usefulness of sonoelastography in differentiation between normal cervix, CIN and cancer cervix in order to early detect malignant changes using transvaginal sonoelastography.

PATIENTS AND METHODS

A Case-control study carried out in Departments of Obstetrics & Gynecology and Radiology at Zagazig University Hospitals, Sharkia, Egypt.

Sample size:

Assuming that all cases that fulfill the inclusion and exclusion criteria included during the study period (6 months) were 3-4 cases/month, 20 cases were included as a comprehensive sample. Cases were classified into three groups: **Group A** included 20 cases with normal cervix (control), **group B** included 10 cases with CIN and **group C** that included 10 cases with cancer cervix.

Inclusion criteria: Women diagnosed or suspected to have cervical malignant changes attending at Zagazig University Hospitals with age group between 25 - 60 years.

Exclusion criteria: Pregnant women and virgin cases.

Operational Design:

All cases were subjected to full history taking including: family, obstetric, contraceptive and menstrual history. Screening for pregnancy. The concentrations of hCG and TVS were tested in our cases and all samples were negative. Complete physical examination were done including vital signs as blood pressure, temperature, heart rate and respiratory rate. Signs of pallor, cyanosis, jaundice, and lymph node enlargement were examined.

Transvaginal sonoelastography:

Transvaginal sonoelastography was done at Radiology Department using Canon applio 1 500

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sonography machine. Elastograms acquisition and analysis were performed. A digital sonography scanner (Canon Applio 1 500) device to perform real-time tissue elastography was used for both B-mode ultrasound and elastography to assess the endometrial thickness and endometrial volume. Radiologist was blinded to the colposcopy and physical examination results. Patients were asked to empty bladder and lie in the lithotomy position. The TV ultrasound probe was put into the vagina about 1 cm away from the cervix with a disposable condom which was used to prevent cross infection. The site, shape, size, and echogenicity of the cervical lesions were recorded. Power and Color Doppler were used to assess the blood supply of the lesions. The highest sensitivity for detection of color Doppler signals was used, allowing detection of small blood flow velocities. Then, the system was turned into elastography mode to record the stiffness of the cervix and the lesions. Support of the anterior pelvic wall by the left hand and manual compression on the cervix by the right hand were done. The parameters used were as follows: frame rate M; density 2; dynamic range 4; Persistence 6; smoothing 2; frame rejection 4; noise rejection 2. On the B-mode images, the deformity was represented by color overlaid. The color scale ranges from blue to red to show the relative hardness or softness of tissue in the region of interest (ROI) as: tissue with average strain was colored in green, hard tissue was dark blue, moderately hard tissue in light blue, moderately soft tissue areas in yellow, and soft tissue areas in red. On average, 4 (range 3–6) static images and 3 (range 2–5) clips for each lesion were obtained for further assessment.

Strain ratio was obtained by measuring and dividing the mean strain of the lesion by the mean strain from the parametrial tissue, if the lesion was in the anterior cervical wall, the anterior pericervical fat was taken as the reference tissue and if the lesion was in the posterior cervical wall, the posterior pericervical fat was chosen as the reference. So, sufficient parametrial tissue was essential. The reference tissue was difficult to choose if the lesions infiltrated both sides of the pelvic wall and the value of strain ratio would be questionable. However, we think that un-infiltrated uterine myometrium could be used as a reference. Decreased compressibility of the lesion during sonoelastography means that the lesion is more malignant.

Evaluation of the elastograms:

Strain ratio was used to evaluate the hardness of the cervical tissue half-quantitatively. All the lesions were assessed by 2 independent radiologists at least 3 times, based on different static images and the average strain value was recorded as their final results. Both of the observers were blind to the physical and pathological results. Area colored in dark blue was considered to be involved. Infiltration depths of cervical cancers were measured on the sagittal view.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analyses

Data were analyzed using Microsoft Excel software then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software. According to the type of data, qualitative data were represent as number and percentage and quantitative continues group data were represent by mean ± SD. Differences between quantitative independent multiple were tested by ANOVA or Kruskall Wallis. P value was set at ≤ 0.05 for significant results &≤ 0.001 for high significant result.

RESULTS

The present study showed significant difference between studied groups as regards family history. While, there was insignificant difference regarding age and smoking (Table 1).

Table (1): Demographic data of studied cases

Data	**Group (A) (n=20)**	**Group (B) (n=20)**	**Group (C) (n=20)**	**P value**
Age	**43.9 ± 6.2**	**41.8 ± 5.5**	**42.5 ± 4.3**	**0.577**
Family History Positive Negative	 2 18	 4 6	 6 4	**0.005***
Smoker	9	4	6	**0.47**
Parity				0.013*
Primi parous (P1)	3	4	4	
Multi parous (>1)	17	6	6	

X^2: Chi Square. P>0.05: Non-significant. P<0.05: Significant

There was a significant difference between studied groups as regards weakened immune system (Figure 1).

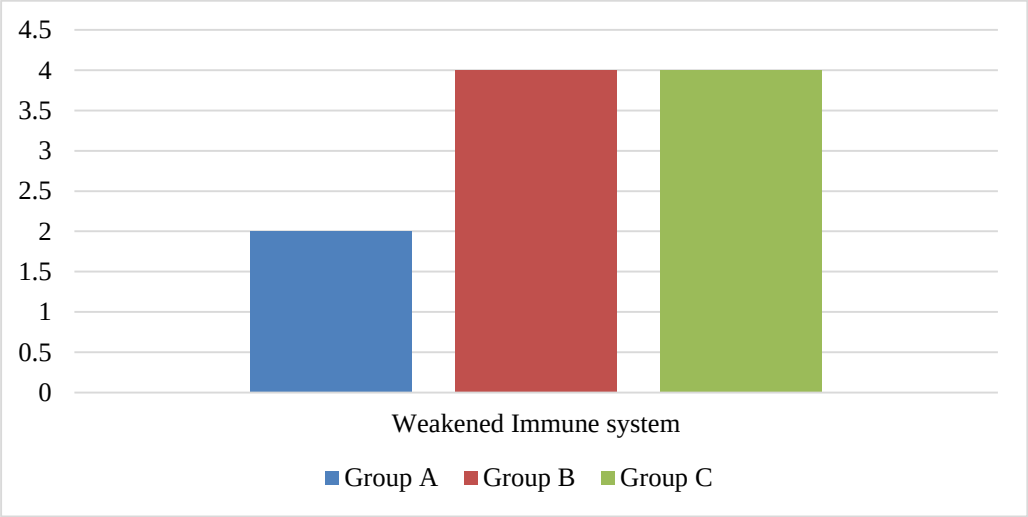

Figure (1): Comorbidities among studied case

There was a significant difference between studied groups as regards endometrial thickness (Figure 2).

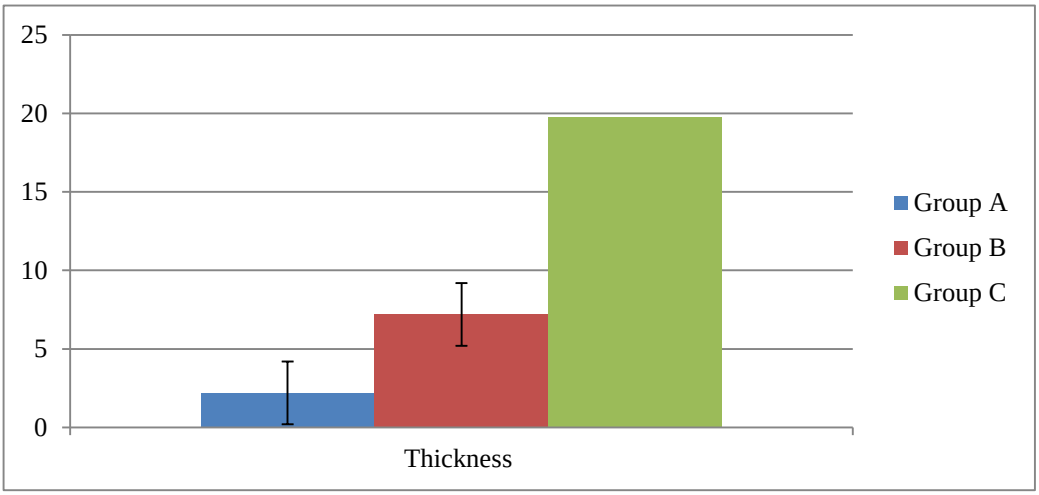

Figure (2): Histopathological diagnosis in group B and C

There were significant difference between studied groups as regards strain ratio (Figure 3).

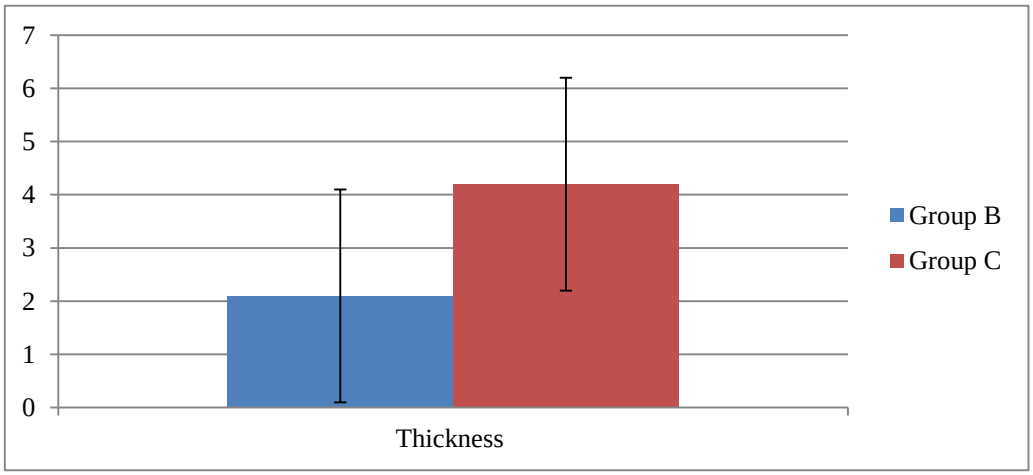

Figure (3): Strain ratio of endometrial lesions in group B and group C

The semi-quantitative assessment of the cervix, by using strain ratio (SR) that implies the selection on the elastographic image of two ROIs, one representing the area to be analyzed [cervical tissue (cervical lesion) = A] and the second being used as reference (B). The ratio between the strain of the reference and the strain of the cervix (B/A), thus providing numeric results (Figures 4, 5 & 6).

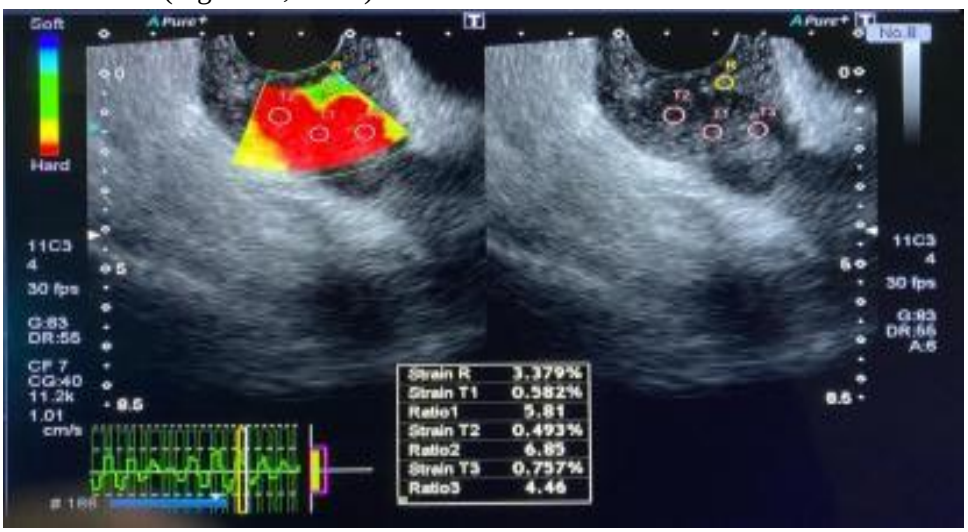

Figure (4): A case of 40 years old P4+0,(4VD), diabetic, presented with contact bleeding, HPE showing squamous cell carcinoma (R = reference; T1 = analyzed cervical tissue among the studied cases).

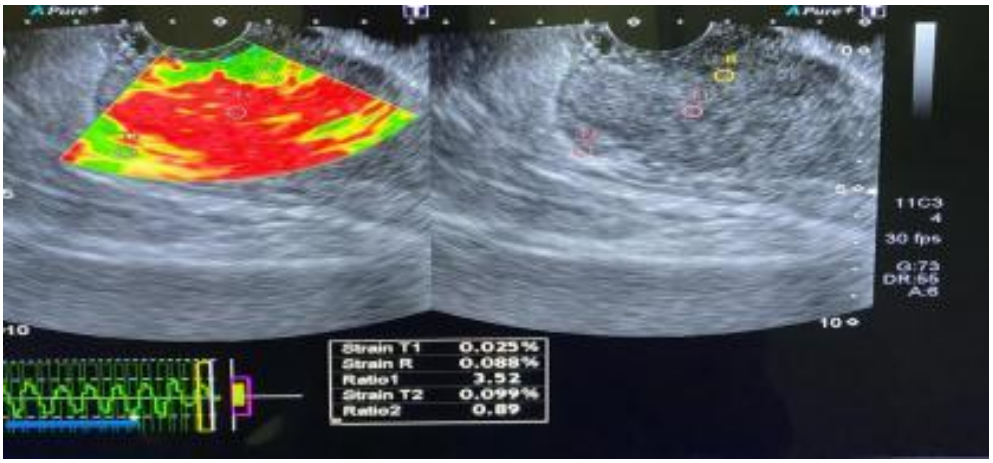

Figure (5): A case of 59 years old P6+1, (6VD), presented with offensive vaginal discharge and passage of necrotic tissue from vagina, HPE showing invasive poorly differentiated carcinoma.

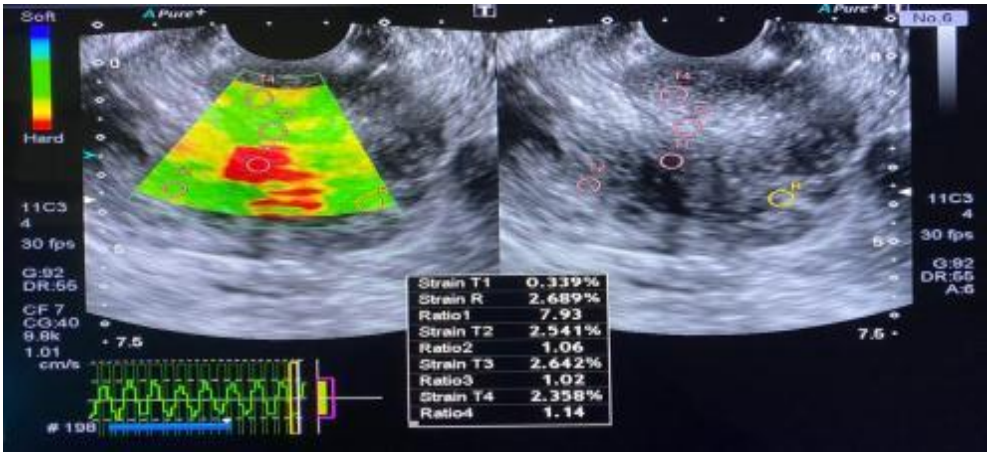

Figure (6): A case of 56 years old p3+2 (3VD), diabetic and hypertensive, presented with contact bleeding and vaginal discharge, HPE showing squamous cell carcinoma.

Diagnostic value of transvaginal elastography for CIN with cut off that was 2.1 ± 0.25, sensitivity was 72.72%, specificity was 78.94%, and accuracy was 76.67% (Table 2). While, for cervix cancer, the cut off was 3.25, sensitivity was 87.2%, specificity was 94.1% and AUC was 0.878 (Table 3).

Table (2): Diagnostic value of transvaginal elastography for CIN

	Cutoff (m/s)	Sensitivity	Specificity	AUC
Diagnostic value of transvaginal elastography	2.1±0.25	87.2	94.1	0.878

Table (3): Diagnostic value of transvaginal elastography for cancer cervix

	Cutoff (m/s)	Sensitivity	Specificity	AUC
Diagnostic value of transvaginal elastography	3.25	87.2	94.1	0.878

DISCUSSION

Despite extensive screening for the known precursors of cervical carcinoma, this lesion is still the most common malignant uterine neoplasm, causing 30% of all gynecologic cancer deaths. The peak incidence of the disease is between the ages of 45 and 55, a decade earlier than endometrial carcinoma. Patients are often asymptomatic, with bleeding or leucorrhea occurring in less than one-third [(7)]. Nevertheless, the fact that nowadays approximately one-third of all cervical cancers are found at stage I and about one-third at stage II is due to regular gynecological check-ups including cytology, colposcopy and palpation. The prognosis is largely limited by the volume of the primary tumor and the stage of the disease [(8)].

Treatment of patients with cervical cancer is determined primarily by stage according to the FIG0 classification, which is based on visual inspection, palpatory findings and surgical staging. The literature however indicates a high rate of inaccuracy in clinical evaluation: only 20-30% of stage-I, 44-75% of stage-II and 50-94% of stage-III disease are detected [(9)]. Most errors are linked to the wrong interpretation of parametrial features with understaging of early parametrial involvement and overstaging in cases of peritumoral inflammatory reactions. In order to improve pretreatment staging, new imaging techniques have been employed. Among these techniques transvaginal sonography (TVS) seems to be the most promising method as it is non-invasive and low cost, and allows prompt visualization of the uterine cervix and paracervical tissue [(10)].

Our study aimed to assess the usefulness of sonoelastography in differentiation between normal cervix, CIN and cancer cervix in order to early detect malignant changes. Our study cleared that there was significant difference between studied groups as regards family history, and insignificant difference as regards age and smoking. This is in contrast to results reported by **Ho *et al.*** [(11)] who found that various smoking measures were positively associated with CIN2 and CIN3 cases when compared to CIN1 cases.

Our study reported that there was significant difference between studied groups concerning DM. **Chen *et al.*** [(12)] indicated that diabetes could predict poor overall survival and recurrence-free survival in cervical cancer. Therefore, the systematic review and meta-analysis suggested that diabetes is an important prognostic factor in patients with cervical cancer, and it is associated with the poor survival of cervical cancer patients.

Our study reported that there was significant difference between studied groups as regards parity. **Muñoz *et al.*** [(13)] pooled data from eight case-control studies on invasive cervical carcinoma (ICC) and two on in-situ carcinoma (ISC) from four continents. 1465 patients with squamous-cell ICCs, 211 with ISCs, 124 with adenocarcinomas or adenosquamous ICCs, and 255 control women and all positive for HPV DNA by PCR-based assays, were analysed. They showed that nulliparous women were at lower risk of squamous-cell carcinoma of the cervix than parous ones, and among parous women, a clear trend towards increasing risk with increasing number of full-term pregnancies emerged. The strength of the association was, however, greatly affected by the model used. The age-adjusted odds ratio for women who reported seven or more full-term pregnancies, compared to none, was 8:3, whereas in the fully adjusted model, the corresponding odds ratio was 3:8.

Our study illustrated that there were, 3 cases with FIGO Ib, 7 cases with FIGO III, 1 case with CIN II and 9 cases with CIN III. **Dudea *et al.*** [(14)] showed that a total of 79 participants (mean age of 42.48 years) were enrolled. Of these, 39 patients had benign cervical findings; 32 were diagnosed with CIN [10 cases with CIN I (31.25%), 6 with CIN 2 (18.75%) and 16 with CIN 3 (50%)] and in 8 patients CC was detected, all of which were squamous cell carcinomas (cancer in situ – 1 case, IA stage – 3 cases, IB stage – 1 cases, IIA stage –1 case, IIIA – 1 and stage IIIB – 1 case according to FIGO classification).

Our study revealed that there was significant difference between studied groups regarding strain ratio. **Dudea-Simon *et al.*** [(4)] showed that mean SR value was, as follows: 0.89 in group 1, 1.42 in group 2 and 1.75 in group 3. However, 2 outlying values were noted in group 3 (0.71 and 0.85), which had been attributed to patients diagnosed with CC complicated with hemorrhagic necrosis. After excluding the outliers, mean SR was 2.07 for group 3. Student's T test revealed significant difference between mean SR of groups 1 and 2. Comparison of initial data by the Mann-Whitney U test indicated significant difference between mean SR of groups 1 and 3, but no difference between groups 2 and 3. After the exclusion of outlying values in group 3,

analysis indicated significant difference between groups 2 and 3. **Lu *et al.* [14]** showed that the strain ratios of benign lesions (range, 0.62–4.50) and malignant lesions were different and showed high statistical significance. The challenge in using SR is the choice of reference tissue to which the cervix is reported. The parameters' stiffness might vary from one patient to another; the uterine body's strain may also differ as a result of the presence of pathological processes (leiomyomas or adenomyosis) and hormonal- or age-dependent changes. The ratio of normal to abnormal cervical tissue might be relative, since tumor margins cannot be certainly delimited on an ultrasonographic image **[4].**

Our study showed that in group B, there were none with score 1, 2, 3 and 5, while there were 8 cases with score 4. In group C, there were none with score 1, 2, 3 and 4, while there were 9 cases with score 5 in the elasticity score. **Lu *et al.* [14]** showed that according to the color maps of their strain images, 34 of the 40 benign lesions (85%) had a score of 1 to 3, and 6 (15%) had a score of 4 or 5 (including calcified cervical leiomyoma lesions). Of the 44 malignant lesions, 36 (81.8%) had a score of 4 or 5, and 8 (13.6%) had a score of 2 or 3 (including cervical cancer with a cystic changes and others).

Our study showed that in regard to diagnostic value of transvaginal elastography in case of CIN, the cut off was 2.1 ± 0.25, sensitivity was 72.72%, specificity was 78.94% and accuracy was 76.67%.

Our study showed that as regards diagnostic value of transvaginal elastography in case of cancer cervix the cut off value was 3.25 ± 0.25, sensitivity was 90%, specificity was 85%, and accuracy was 86.67%. **Lu *et al.* [14]** showed that the AUC was 0.905 (95% confidence interval, 0.845–0.991), and the best cut off point for the strain ratio was 4.525. The sensitivity, specificity, accuracy, PPV, and NPV of the strain ratio in the differential diagnosis of cervical lesions were 90.9%, 90.0%, 90.5%, 90.9%, and 90.0%, respectively.

The results of our study demonstrated that the strain ratio could quantitatively distinguish benign from malignant cervical lesions. **Dudea-Simon *et al.* [4]** showed that when comparing groups 1 and 3, AUC was 0.966 with a 95% CI (0.914-1.000). The best cut off point of SR was 1.42, with a sensitivity of 100% and a specificity of 94.9%. For Groups 1 and 2, AUC was 0.752 with a 95% CI (0.629-0.876). For the cut-off value of 1.03, sensitivity and specificity were 75% and 74% respectivelt. The AUC for groups 2 and 3 was 0.797, 95% CI (0.648- 0.946) and the cut-off point was established at 1.51, with a sensitivity of 100% and a specificity of 65%.

Certain limitations of this study need to be addressed. All imaging examinations were performed by a single observer and intra- and interobserver reproducibility studies have not been carried out. The small number of subjects, especially for the CC group, is another limitation. It is debatable if by repeating the experiment on another equipment from another manufacturer, the cut-off values would remain the same. Another limitation of the method irrespective of the ultrasound system used, the assessment of stiffness is compromised in cases of CC complicated with hemorrhagic necrosis. Also, transvaginal sonoelastography mode is not found in all ultrasound devices and found only in highly specialized centers and most of cases came advanced so its value as screening tool is limited.

CONCLUSIONS

RTE SR of the uterine cervix, performed with a silicone ED as a reference material, seemed a reliable method for distinguishing between a normal cervix and malignancy. The technique also showed promising results as a complementary investigation in diagnosing CIN. However, SR becomes inoperant in cases of cancer complicated with hemorrhagic necrosis. Larger studies are required to confirm the observations in this paper, as well as to evaluate CIN according to severity. We recommend further studies to assess the efficacy of using transvaginal sonoelastography as a screening tool of CIN and cancer cervix. Also, further studies to compare between transvaginal sonoelastography and MRI regarding sensitivity and specificity in cancer cervix.

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Author contribution: Authors contributed equally in the study.

REFERENCES

1. **Ferlay J, Soerjomataram I, Ervik M (2012):** Cancer incidence and mortality worldwide. International Agency for Research on Cancer, 11 (2): 11-15.
2. **Kashyap N, Krishnan N, Kaur S *et al.* (2019):** Risk factors of cervical cancer: a case-control study. Asia-Pacific Journal of Oncology Nursing, 6(3): 308-312.
3. **Xu G, Feng L, Yao M *et al.* (2014):** A new 5-grading score in the diagnosis of prostate cancer with real-time elastography. Int J Clin Exp Pathol., 7 (7): 4128–4135.
4. **Dudea-Simon M, Burde A, Ciortea R *et al.* (2020):** Usefulness of real time elastography strain ratio in the assessment of cervical intraepithelial neoplasia and cervical cancer using a reference material. Medical Ultrasonography, 22 (2): 145-151.
5. **Dudea S, Giurgiu C, Dumitriu D *et al.* (2011):** Value of ultrasound elastography in the diagnosis and management of prostate carcinoma. Med Ultrason, 13: 45–53.
6. **Aksoy D, Yildiz S, Atasoy B *et al.* (2021):** Effect of Quantitative and Semi-quantitative Elastography Methods for the Management of Borderline Lesions on Ultrasonography. Current Medical Imaging, 17 (6):

767-774.

7. **Liao J, Fisher C, Madeleine M (2019):** Gynaecologic cancers and solid organ transplantation. American Journal of Transplantation, 19 (5): 1266-1277.
8. **Warnares G (2017):** Prevalence of Human Immunodeficiency Virus (HIV) and Sexually Transmitted Infections (STIs) among Women Working in Entertainment Venues in Jayapura-Papua, Indonesia. International Journal of Gynecology & Obstetrics, 12 (3): 12-15.
9. **Lee S, Atri M (2019):** 2018 FIGO staging system for uterine cervical cancer: enter cross-sectional imaging. Radiology, 292 (1): 15-24.
10. **Hayatullah G, Song J, Mirwais A (2018):** Hysteroscopy Assessment of Endometrial Pathology with Endometrial Thickness Cut-Off Value 5 mm in Postmenopausal Women with Vaginal Bleeding. International Journal Science Inventions Today, 7 (1): 89-107.
11. **Ho G, Kadish A, Burk R *et al.* (2004)** HPV 16 and cigarette smoking as risk factors for high-grade cervical intra-epithelial neoplasia. Int J Cancer, 78: 281–285.
12. **Chen S, Tao M, Zhao L *et al.* (2017):** The association between diabetes/hyperglycemia and the prognosis of cervical cancer patients: A systematic review and meta-analysis. Medicine, 96 (40): 12-15.
13. **Muñoz N, Franceschi S, Bosetti C *et al.* (2002):** Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. The Lancet, 359 (9312): 1093–1101.
14. **Lu R, Xiao Y, Liu M *et al.* (2014):** Ultrasound Elastography in the Differential Diagnosis of Benign and Malignant Cervical Lesions. Journal of Ultrasound in Medicine, 33 (4): 667–671.