

The Value of ESWAN in Diagnostic of Adenomyosis and Related Study about Dysmenorrheal

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Abstract

Background This **retrospective** study aimed (1) to evaluate the value of enhanced T2 star-weighted angiography (ESWAN) in diagnosis Adenomyosis(AM). And (2) to estimate the differences of focal AM patients lesion and the peripheral tissues region. And (3) analysis the correlation between the multiple indices of ESWAN and dysmenorrheal, focal AM lesion ratio.

Methods **Traditional** MRI and ESWAN were performed on seventy-two clinically–diagnosed AM patients (fifty for focal and twenty-two for diffuse AM), and fifty-six normal adult **woman**. The ESWAN indices (magnitude value, phase value, R2* value and T2* value) measured on different regions of interest (ROIs) were analyzed. Measured the focal AM lesion size and Uterine volume by tradition MRI, and using visual analogue scale(VAS) measured dysmenorrheal level.

Results The magnitude value, phase value, R2* value and T2* value of focal AM, diffuse AM, peripheral tissue in focal AM and normal myometrium were respectively 1176.20±367.70/1286.51±349.49/1139.61±426.69/1685.94±407.14, 0.0114±0.0438/0.0138±0.0182/0.0296±0.0858/0.0433±0.0869, 26.39±3.36/27.40±2.36/27.24±4.60/22.54±5.03, 39.83±5.47/37.49±3.48/38.67±7.09/43.39±8.94. The ESWAN indices by one-way ANOVA showed statistical difference with the normal myometrium and focal and diffuse AM(0.000, 0.027, 0.000, 0.002). Compared with the peripheral tissue, the focal AM indices were no statistical difference. The correlation between the dysmenorrheal level and phase value were statistical difference(0.018).

Conclusions ESWAN sequence has fractional value in diagnosis AM by different indices. And the dysmenorrheal level could react the AM feature in certain degree.

Background

Adenomyosis(AM) is a common gynecological condition that is often found in women at childbearing age, which characterized by the infiltration of the endothelial tissue of the endothelium layer into the myometrium. Due to the differences in ethnicity and diagnostic criteria, the prevalence is ranging from 5 to 70%. The disease as a heterogeneous disease can divided into diffuse or focal according to the myometrium extent of the lesion[1,2]. The diffuse AM refers to the invasion of the endometrial glands or stroma within the myometrium, and focal AM or adenomyoma implies a more circumscribed infiltration[3]. Van den Bosch T's[4] reported rare cases of cystic adenomyoma. The disease leads to chronic pelvic pain, infertility, bleeding, dysmenorrheal, metrorrhagia, dyspareunia, bulk-related symptoms, while one third of the women is asymptomatic[5-7], with multiple symptoms that negatively affect the health of women at the reproductive age. The serum CA125 level in the AM patients was greater than the normal ones, but CA125 may increase because of other ovarian cancer such as the myoma, so serum CA125 testing can be performed as the initial screening of women with AM[8]. The disease could be identified by means of non-invasive or minimally invasive techniques such as the 2D and 3D transvaginal

sonography, magnitude resonance imaging, et al[9]. Compared with the transvaginal sonography (TVS), the MRI magnitude resonance imaging (MRI) is more useful than TVS and determines the various subtypes of AM in the diagnose AM valve[10], and with a sensitivity and specificity in diagnosing AM.

Enhanced T2 star-weighted angiography (ESWAN) is a new type of multi-echo susceptibility weighted imaging (SWI) technology by GE Medical Systems, Milwaukee, WI. The SWI can well display small veins because of the different oxygenation states of hemoglobin, and the hemoglobin of different oxygenation states has different magnitude sensitivity characteristics[11]. The sequence is sensitive to magnitude sensitive substances such as blood metabolites, ferritin, calcification, et al[12], so the SWI sequence enables the detection of stroke, hemorrhage and intravascular clots, cerebral tumor and to assess bleeding-prone microangiopathy and stroke recurrences[14,15]. Compared with the conventional SWI, the ESWAN sequence can shorten scanning time and increase the signal to noise ratio (SNR), number of excitation (NEX), the contrast to noise ratio (CNR), and extremely sensitive to paramagnetic deoxygenated hemoglobin and hemosiderin[13]. With the multi-echo acquisition methods, we can obtain phase images and magnitude images message, and this images message is different from T1-weighted, T2-weighted, proton density-weighted, and diffusion weighted imaging[13,11]. Therefore, we can obtain the level of oxygenation in tissues by measuring ESWAN different indices.

Viewing the previous literature, susceptibility weighted imaging, including ESWAN sequencing, was rarely reported in AM. SWI showed significantly more micro-hemorrhage than CT and conventional MRI[16], and according to the change of micro-hemorrhage, that will be conducive to the diagnosis AM. The uterine junctional zone (JZ) is seen as a distinct low intensity inner band in T2-weighted magnitude resonance imaging[24]. AM is likely to be related to the alterations in the endometrium myometrium junctional zone (JZ). Reinhold[17] found that the diagnostic criteria of AM is the JZ thickness more than 12mm(The normal $JZ \leq 5\text{mm}$). The change of appears to affect the oxygenation states of hemoglobin. The purpose of this study is to analyze the susceptibility-difference of AM (focal or diffuse) and normal adult woman myometrium and explore the value of ESWAN in the diagnosis of AM by analyzing the multiple indices of ESWAN. And also analyze the correlation of the degree of dysmenorrheal and the focal AM lesion ratio and the multiple indices of ESWAN.

Methods

Subjects

The research was approved by the local institutional review board, and each patients wrote informed consent before MRI procedures were conducted. Seventy-two patients with AM based on clinical pathology confirmed were chosen in the Affiliated Hospital of Weifang Medical University from December 2017 to February 2019, focal AM patients with ages ranging from 32 to 50 years old (average value: 41.8). diffuse AM patients with ages ranging from 30 to 48 years old (average value: 41.0). Fifty-six healthy adult women were selected as the control group, with ages ranging from 30 to 52 years old (average value: 41.2). All the subjects had not undergone uterus operation before MRI examination. Age

differences had no statistical significance between the focal AM, diffuse AM group and normal group. Forty-one focal AM serum CA125 levels increase, and seventeen diffuse patients serum CA125 levels increase (diagnostic criteria: CA125>35 IU/ml). And the clinical characteristics of the patients are summarized in Table 1.

MRI protocols

The experimental group and control group examinations were scanned with 3.0T MRI scanner (Signa EXCITE HDxt, GE Medical Systems, USA) equipped with an 8-channel pelvis phased array coil. The subjects were examined in supine, foot-first position. All subjects received routine MRI scanning. Axial T1WI, fat-suppressed axial T2WI, Sagittal T2WI and ESWAN sequence. The ESWAN adopted 3D gradient echo (GRE) sequencing, flow compensation, parallel imaging (ASSET) acceleration factor of 2. All scan parameters were displayed in the Table 2.

Data post-processing

All images were transferred to ADW4.5 workstation for enhanced ESWAN post-processing. According to the manufacturer's instruction manual, in post-processing, the filter width chooses 32×32 . The region of interest (ROI) were selected. The magnitude values, phase values, $R2^*$ values and $T2^*$ values were recorded respectively by two radiologists with different years of experience in pelvic imaging. The ROI measured by refers to the routine scanning sequence. The criteria of ROI selection were as follows: combined with conventional T1WI and T2WI images, the large lesion dimension was set as the ROI, where the scope of the lesion should be as large as possible; the internal areas that were necrotic or adjacent to blood vessels or bile ducts were excluded. Statistical analyses were performed to compare the results of examinations. The calculate of Uterine volume used a formula based on an ellipsoid shape: $L \times W \times AP \text{ diameter} \times 0.52$ [18]. the

focal AM volume (v): $v = 1/6 \pi \times a \times b \times c$, and a, b, and c are diameters measured in orthogonal planes on T2W images [19]. The calculate of focal AM lesion ratio was focal AM lesion size/ uterine volume.

The classification of dysmenorrheal

Visual analogue scale (VAS) was used to evaluate the degree of dysmenorrheal. 0 point for painless, 1 point for mild pain, 2 point for moderate pain, and 3 point for severe pain. Mild dysmenorrheal pain can be tolerated, and not affect normal life; moderate and severe dysmenorrheal pain were Unbearable, moderate pain need to take analgesics, but severe pain must take town pain medication.

Statistical analysis

Statistical analyses were performed by using IBM's SPSS Statistics, ver17.0 (IBM Corp., Armonk, NY, USA). The ESWAN indices of AM (focal and diffuse) patients and normal women were analyzed by using one-way analysis of variance (ANOVA), and comparison between any two means with the three groups. The comparison of peripheral tissues and focal AM lesion were adopt paired samples t-test. Receiver

operating characteristic (ROC) analysis was performed by using MedCalc software (version 11.4.2.0) to obtain the area under the curve (AUC), sensitivity, specificity, and optimal cut-off points. The correlation of ESWAN indices, dysmenorrhea, focal AM lesion ratio were adopted Pearson correlation analysis. All the tests were two-tailed, and a P-value of <0.05 was considered to be a statistical difference.

Results

The conventional MRI and ESWAN image features of AM microhemorrhage

Some AM patients combined with microhemorrhage in lesion zone. Microhemorrhage showed small high-signal with T1-weighted and fat-suppressed T2-weighted image (Fig. a, b), and showed a low signal intensity on magnitude map (Fig. d), phase map (Fig. e) and T2* map (Fig. g), and high signal intensity on R2* map (Fig. f). The AM typical FS-T2-weighted image is demarcated low-signal intensity area, with small high-signal intensity areas, the AM lesion boundary showed unclear (Fig. c).

The ESWAN indices of AM (focal and diffuse), normal myometrium and peripheral

After the one-way ANOVA by normal myometrium, focal and diffuse AM, the ESWAN indices were statistically significant (Table 3). After comparison between any two groups, the magnitude value, phase value, R2* value and T2* value of focal AM and normal myometrium were statistically significant ($P = 0.000, 0.012, 0.000, 0.010$). The magnitude value, R2* value and T2* value of diffuse AM and normal myometrium were statistically significant ($P = 0.000, 0.000, 0.001$). But the magnitude value, phase value, R2* value and T2* value of focal and diffuse AM were not statistically significant. Compared with focal AM patients peripheral tissue, the lesion were not statistically significant in ESWAN indices (Table 4).

The efficiency of ESWAN indices in the diagnosis of AM

When focal AM and normal myometrium were differentiated, the AUC of magnitude value, phase value, R2* value and T2* value were respectively 0.836 ($P < 0.0001$), 0.709 ($P = 0.0001$), 0.749 ($P < 0.0001$), 0.636 ($P = 0.0139$). The diagnostic efficiency of magnitude value and R2* value was higher than T2* value ($P = 0.0019, P = 0.0003$), while the diagnostic efficiency of magnitude value was equivalent to R2* value ($P = 0.0986$) (Fig. 3a). When focal AM and peripheral were differentiated, the AUC of magnitude value, phase value, R2* value and T2* value were respectively 0.554 ($P = 0.3621$), 0.617 ($P = 0.0462$), 0.541 ($P = 0.4811$), 0.558 ($P = 0.3186$), there was no statistically difference in the diagnosis efficiency of T2* value ($P > 0.05$) (Fig. 3b). When diffuse AM and normal myometrium were differentiated, the AUC of magnitude value, phase value, R2* value and T2* value were respectively 0.769 ($P < 0.0001$), 0.705 ($P = 0.0004$), 0.831 ($P < 0.0001$), 0.722 ($P = 0.0001$). The diagnostic efficiency of R2* value was higher than T2* value ($P = 0.0023$), and the diagnostic efficiency of magnitude value was equivalent to T2* value ($P = 0.5461$) (Fig. 3c).

The correlation with ESWAN indices, dysmenorrhea, focal AM lesion ratio

By analyzing the correlation of AM patients indicators. The degree of dysmenorrhea and phase value existed positive correlation property (Table 5). The correlation with dysmenorrhea and focal AM lesion ratio were no statistically difference ($r=0.117$, $P=0.418$).

Discussion

In clinical, AM patients often coexists with other gynecological conditions, such as the uterine leiomyoma [20]. The difference disease may not share exactly the same treatment. Therefore, it has significance for the diagnostic of AM—especially in focal AM. The ESWAN scanning can obtain multi-indices, including magnitude and phase maps, and analyze the change of local tissues' magnitude susceptibility and oxygen consumption [11,13,21]. At present, the pathogenesis of AM is still unclear and cannot be understood by only a unique theory [22], includes sex steroid hormone aberrations, inflammation, fibrosis, and neuroangiogenesis [23].

The histological basis of susceptibility-weighted imaging in AM

Enhanced T2 star weighted angiography imaging utilizes the magnitude susceptibility differences of normal tissue and lesions, paramagnetic substances, such as magnitude substances deoxyhemoglobin, hemosiderin and anti-magnetic substances calcification. These substances can change the signal intensity and phase of local tissue. In AM, hypertrophy is a characteristic histologic feature, and may reflect a compensatory mechanism or arrested maturation [24]. As is mentioned above, the AM patients especially in diffuse showed the junctional zone (JZ) broaden. The JZ feature showed the smooth muscle hyperplasia [25]. Meanwhile, compared with the normal women myometrium, utilizing electron microscopy can observe AM features including cellular hypertrophy, cytoplasmic myofilaments decreasing [26]. The microvessel density (MVD) of AM is higher than normal myometrium tissue, but vessel wall of neonatal vascular is weak and unstable, and the oxygen saturation of AM area is lower than the normal myometrium. The hypertrophy and high metabolic state can change the oxygenation state of AM area, and significantly increase the oxygen consumption. Because of the oxygen consumption increased, the deoxygenated hemoglobin of focal AM tissues will be increased. The increased deoxyhemoglobin strengthens the paramagnetic effect of focal tissue, so the AM tissue has different magnitude susceptibility with normal women myometrium. In this research we found that some AM patients accompany high signal intensity in T1-weighted magnitude resonance imaging, pathologic histology proved that these high signal in T1-weighted is micro-bleeds. The reasons of this phenomenon may endometrial invasiveness and micro-vessel density (MVD) increased, can cause small focal bleeding in T1-weighted high signal.

The comparison of ESWAN indices among AM, focal peripheral tissue, and normal tissue

In this research, this study showed that the $T2^*$ value of the AM region was lower than that of the normal women myometrium zone, while $R2^*$ value showed the opposite trend. In ESWAN sequence, $R2^*$ value represents transverse relaxation by measuring gradient recombination at different times [27].

Deoxyhemoglobin, methemoglobin, hemosiderin, ferritin and calcification were change the phase of

proton spin, and accelerates the attenuation of signal intensity. $T2^*$ value called free induction decay (FID). $T2^*$ value is the reciprocal of $R2^*$ value. We thought that the AM region blood oxygen level content were different with normal tissues. whatever it's focal or diffuse AM, the patients lesion zone cellular hypertrophy and MVD increased, so the oxygen consumption will increase. and the content of deoxyhemoglobin will increase. The oxygen consumption and deoxyhemoglobin can decrease $T2^*$ value and increase $R2^*$ value. Meanwhile. The microhemorrhage of AM tissue can decrease $T2^*$ value and increase $R2^*$ value in local tissue. Therefore, microhemorrhage is also an important factor causing $T2^*$ and $R2^*$ value differences of AM and normal tissue. The magnitude value is influenced by the deoxyhemoglobin, oxyhemoglobin, calcification, microhemorrhage, etc. meanwhile, oxygen content change will affect the magnitude value, and decrease the magnitude value in lesion tissues, showed lower signal in magnitude maps. Para-magnitude substances can produce negative phase displacement, and the phase value decreases. showed low signal in phase maps. Conversely, showed high signal. In this study, the magnitude value and phase value of focal and diffuse AM were lower than that of normal women myometrium zone. Meanwhile, the study found that T1-weighted high signal showed low signal in magnitude maps, and high signal in phase map. The change of MRI signal proved the view about microhemorrhage of local AM tissues. Meanwhile, the level of oxygen content in the AM will also influence the magnitude value, and decrease the magnitude value. The para-magnitude substance creates a negative offset of proton and decreases phase value, so the phase value in focal AM is lower than normal women. but there was no statistical difference in diffuse AM patients, the reason may be influenced by the lesion form and the sample content size.

Compared with the focal AM patients lesion and peripheral tissue, the ESWAN indices were no statistically difference. In focal AM lesion, some patients have T1-weighted high signal, and magnitude map and phase map showed low signal. These microhemorrhage can decrease the magnitude value, the result consistent with the research, but there was no statistically difference.

The correlation with ESWAN indices, dysmenorrheal, focal AM lesion ratio

VRS is a common analytical pain intensity rating method at present. AM patients often accompanied with dysmenorrheal, and the course of disease is often progressive aggravation, The degree of dysmenorrheal of AM is divided into four levels by experienced clinical doctors in department of gynaecology. the sensitivity of phase value to measure the change of iron content is higher than other ESWAN indices.

Our study had several limitations. First, the AM patients(especially in diffuse AM patients) in our study relatively less might lead to the bias in the results. Second, the verbal rating scale indexes about AM patients may exist in bias because of the patients subjectivity. Third, the VRS of the degree of dysmenorrheal have subjective differences

Conclusions

ESWAN sequence has fractional value in the diagnosis of AM. However, about the correlation between the serum CA125 and the degree of dysmenorrheal and focal AM lesion ratio, and the multiple indices of ESWAN need further study.

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Tables

Table 1: Clinical characteristic

	Number
focal / diffuse /normal	50/22/56
focal age	32~50(average value: 41.8)
diffuse age	30~48(average value: 41.0)
normal age	30~52(average value: 41.2)
the degree of dysmenorrheal	0:8/1:24/2:30/3:10
CA125	116.16±105.26
T1-weighted high signal(focal/diffuse)	64%/50%

Table 2: Protocols of MR sequences

	Axial T1WI	Axial fat-suppressed T2WI	Sagittal T2WI	ESWAN
TR/TE (ms)	900/10.2	2760/68	3960/114	49.8/4.5
slice thickness(mm)	5.0	5.0	5.0	2.0
slice interval(mm)	1.0	1.0	1.0	0.0
FOV(mm ²)	360×360	360×360	360×360	400×400
Matrix	320×192	320×192	320×192	320 × 288
echo interval(mm)				5.9
flip angle				20°
Bandwidth(MHz)	50.00	41.67	41.67	31.25

Table 3: Comparison of ESWAN indices between normal myometrium, focal and diffuse AM

	Magnitude value	Phase value	R2* (Hz)	T2* (ms)
focal AM	1139.51±426.69	0.0296±0.0858	27.24±4.60	38.67±7.09
diffuse AM	1286.51±349.49	0.0138±0.0182	27.40±2.36	37.49±3.48
myometrium	1685.94±407.14	0.0433±0.0869	22.54±5.03	43.39±8.94
F	25.004	3.733	16.966	6.759
P	0.000	0.027	0.000	0.002

Note: one-way ANOVA, $P < 0.05$ was statistically significant.

Table 4: Comparison of ESWAN indices between focal AM and peripheral

	Magnitude value	Phase value	R2* (Hz)	T2* (ms)
focal AM	1176.20±367.70	0.0114±0.0438	26.39±3.36	39.83±5.47
peripheral	1139.61±426.69	0.0296±0.0858	27.24±4.60	38.67±7.09
t	0.459	-1.336	-1.109	0.915
p	0.647	0.185	0.297	0.362

Note: paired samples t-test, $P < 0.05$ was statistically significant.

Table 5: the correlation with ESWAN indices and CA125, focal AM lesion ratio, dysmenorrheal

ESWAN	focal AM lesion ratio		dysmenorrheal	
	r	P	r	P
Magnitude	0.149	0.213	-0.099	0.408
phase	0.028	0.813	0.279	0.018
R2*	-0.099	0.406	0.004	0.973
T2*	-0.001	0.993	0.028	0.817

Note: Pearson correlation analysis, $P < 0.05$ was statistically significant.

Abbreviations

AM: adenomyosis

MRI: magnitude resonance imaging

ESWAN: enhanced T2 star-weighted angiography

T1WI: T1-weighted imaging

T2WI: T2-weighted imaging

ROI: region of interest

ROC: receiver operating characteristic

AUC: area under the curve

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Affiliated Hospital of Weifang Medical University and all participants gave witnessed informed consent.

Consent for publication

The informed consent provisions and protocols were reviewed and approved by the Institutional Review Board of the Affiliated Hospital of Weifang Medical University.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no competing interests.

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Authors' contributions

X-ZW and C-SC guaranteed the integrity of the entire study. Q-CC carried out the study design and concepts. Z-YW and F-L carried out the literature research and data acquisition. J-YX, S-SG and J-GL carried out the data analysis. Q-CC prepared the manuscript. X-ZW and C-SC reviewed and edited the manuscript. All the authors approved the final manuscript.

Acknowledgements

Not applicable.

Figures

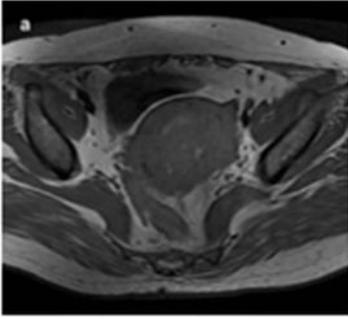


Fig. a: The Axial T1-weighted imaging

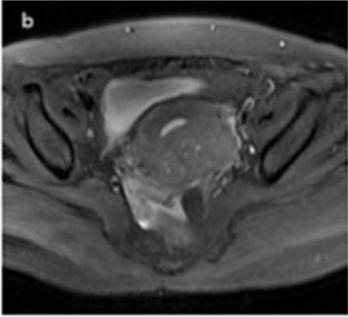


Fig. b: The Axial fat-suppressed T2-weighted imaging

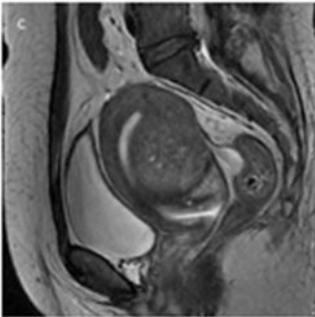


Fig. c: The sagittal of T2-weighted imaging

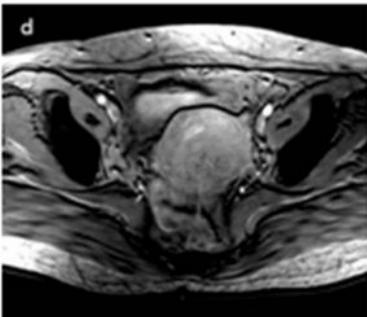


Fig. d: the information magnitude map

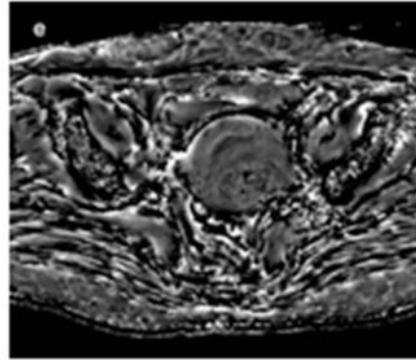


Fig. e: the information phase map

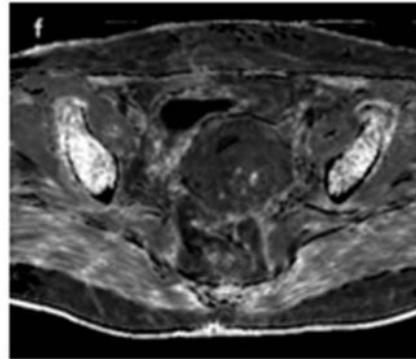


Fig. f: the information R2*map

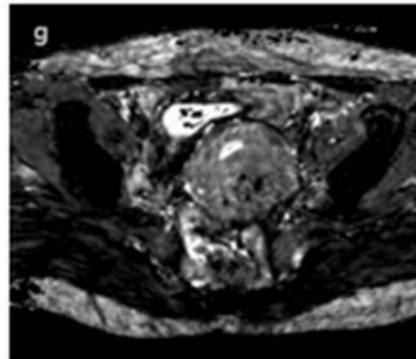


Fig. g: the information T2*map

Figure 1

a: The Axial T1-weighted imaging. b: The Axial fat-suppressed T2-weighted imaging. c: The sagittal of T2-weighted imaging. d: the information magnitude map. e: the information phase map. f: the information R2*map. g: the information T2*map.

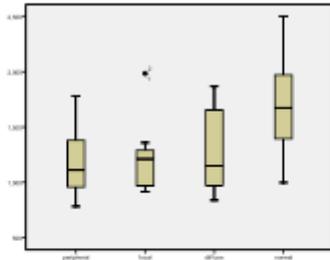


Fig 2a: The comparison of magnitude value

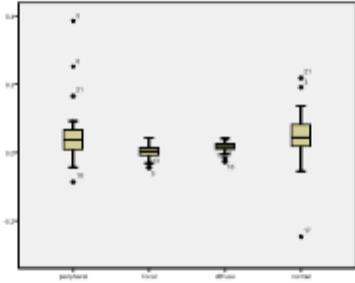


Fig 2b: The comparison of phase value

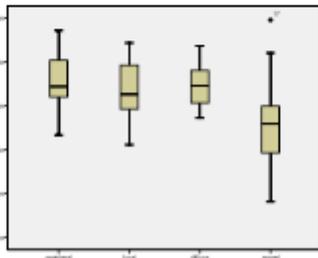


Fig 2c: The comparison of R2* value

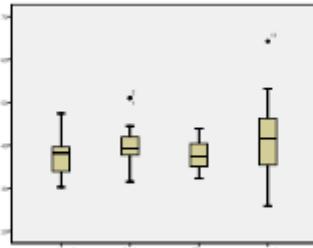


Fig 2d: The comparison of T2* value

Figure 2

2a: The comparison of magnitude value. 2b: The comparison of phase value. 2c: The comparison of R2* value. 2d: The comparison of T2* value

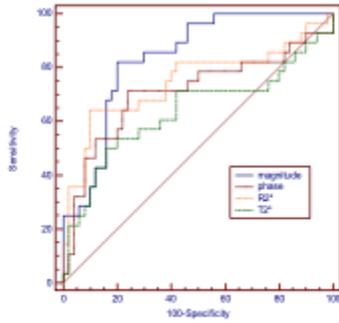


Fig. 3a: The ROC curves of ESWAN indices between focal and normal women

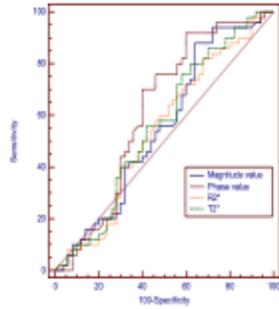


Fig. 3b: The ROC curves of ESWAN indices between focal and peripheral women

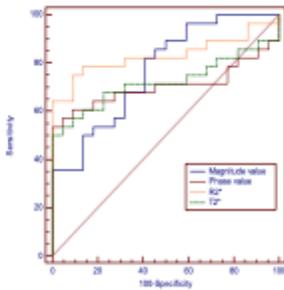


Fig. 3c: The ROC curves of ESWAN indices between diffuse and normal women

Figure 3

3a: The ROC curves of ESWAN indices between focal and normal women. 3b: The ROC curves of ESWAN indices between focal and peripheral women. 3c: The ROC curves of ESWAN indices between diffuse and normal women.