Diagnostic performance of international ovarian tumor analysis (IOTA) simple descriptors, simple rules and sassone scoring system among patients with ovarian disease in a tertiary specialty hospital*

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ABSTRACT

Background: Accessibility, cost-effectiveness and consistency in identifying pelvic masses made ultrasonography one of the first imaging modality used by clinicians in evaluating women with ovarian disease. Scoring systems to differentiate a benign or malignant lesion has been formulated for many years and the International Ovarian Tumor Analysis (IOTA) group has developed several evidenced-based algorithms for classifying adnexal diseases. This research performs prospective validation using IOTA Simple Descriptors and IOTA Simple Rules, compared with Sassone scoring system to differentiate benign and malignant disease.

Objective: To determine and compare diagnostic performance of IOTA Simple descriptors, IOTA Simple rules and Sassone Scoring System in classifying benign and malignant masses.

Study Design: A cross-sectional study was done on patients assessed to have adnexal mass or tumors either by symptoms or by physical examination and confirmed by ultrasound using two-dimensional gray-scale with Doppler studies. The classification by sonographic features was based on the IOTA Simple Descriptors, IOTA Simple Rules and Sassone Scoring System and correlated with the histopathologic result as the gold standard.

Results: A total of eighty-two cases were analyzed in the study, seventy three of which was benign. Of those with malignancy, sixty one percent belonged to ages 31-50 years old. The most common benign histopathologic diagnoses were dermoid, endometrial cyst and serous cyst, while Adenocarcinoma is the most frequent type of ovarian carcinoma. The results showed high sensitivity for IOTA simple descriptors for benign tumors at 95%. On the other hand, specificity was 85% for both IOTA Simple Rule and Sassone scoring index with low sensitivity at 58% and 44% respectively.

Conclusion: Accuracy of the different sonologic indexes ranges from 72 to 83%. Comparing IOTA Simple Rules and Sassone Score, specificity was comparable at 85%, however with lower sensitivity for Sassone Score System.

Keywords: Accuracy, Ovary, Sensitivity, Specificity, Ultrasonography

INTRODUCTION

In gynecologic clinical practice, ultrasonography (USG) is the first imaging modality performed in a female patient with symptoms of lower abdominal pain, palpable mass and / or suspected pelvic mass by physical examination.[1] Pelvic sonography is easily accessible, cost-effective, and a consistent method for identifying ovarian or adnexal masses. Transabdominal (TAS) and transvaginal sonography (TVS) are complementary technique and both are used extensively in evaluation of female reproductive tract.[2] In general, transvaginal sonography has a sensitivity and specificity of 82% and 92%, respectively[3] in identifying benign and malignant tumors. However, operator error and increased unpredictability of characteristics of ovarian tumor make a diagnosis more difficult by sonography only. To address limitations and variations in the diagnosis of ovarian masses, use of a scoring system has been advocated[4] which was popular in the last three decades. Sassone et al devised a scoring system using two-dimensional gray scale ultrasonography features to describe an ovarian lesion which on several studies showed high diagnostic value.[5] This scoring system, together with other popular scoring systems like Lerner and DePriest Scoring System has been used in the practice of gynecologic sonography since the 1990's. Thus in the early 2000, a detailed review of the literature discovered several variation in the diagnostic accuracy of these test procedures.[6] There had been reports of use of scoring systems derived from the retrospective

*Third Place, Philippine Society of Ultrasound in Obstetrics and Gynecology (PSUOG) Reseach Paper Contest, October 27, 2017, 3rd Flr. Function Room, Dr. Jose Fabella Memorial Hospital, Philippine Blood Center Compound, Diliman, Quezon City

analysis of data in a particular center does not produce such good results[7-9] when used prospectively in another center. The difference in the results may be due to, at least in part, differences in the interpretation and use of terms and definitions of the diagnostic end-points.[10]

Hence, the International Ovarian Tumor Analysis (IOTA) group instigated in the early 2000's and is currently the largest diagnostic accuracy study of its kind.[11] The aim of the consensus group was to develop an optimal "evidence-based" algorithm for the classification and management of all types of adnexal masses[11]. There are different algorithms, mathematical models with logistic regressions which were formulated and verified over the span of 15 years with the purpose of enabling the clinicians to direct patients to a subspecialist in oncology once with suspicion of ovarian malignancy and in some cases, guide them in managing benign conditions either for follow-up or immediate access to surgery.

Currently, pattern recognition using subjective assessment of ultrasound images is the best way of characterizing ovarian pathology[12]. Many adnexal masses exhibit a typical sonologic appearance and are easily classified even by inexperienced sonologists. Using this idea, the IOTA group established in 2013 "Simple Rules" on a clearly defined ultrasound features, with no risk estimates unlike the mathematical logistic models, and tumors are classified as benign, malignant or unclassified.[13] The "Simple Rules" consists of five malignancy features (M-features) and five benign features (B-features) with the corresponding ultrasound images (Figure 1). It is classified as malignant if at least one or more M-feature is present and no of the B-features are present; and classified as benign if one or more B-feature is present and no M-feature is present. If no B- or M-features are present, or if both B- and M-features are present, then the mass was labeled as unclassified.

Another learning point in the IOTA study is the use of "Easy or Simple Descriptors", for example in typical dermoid or typical endometriomas, or even in late ovarian cancers which also has very characteristic ultrasound features[14]. Simple descriptors described four benign features and two malignant features exhibiting characteristics which were very typical for such types, whether classified as benign or malignant.

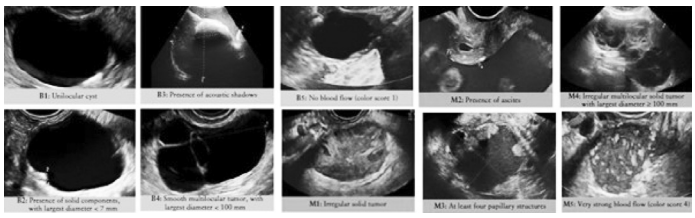

Figure 1. IOTA simple rules

Source: Ultrasound Obstet Gynecol 2013; 41; 9-20; Published online in Wiley online library DOI 101.1002/bo.12323. Improving Strategies for diagnosing ovarian cancer: a summary of the International Ovarian Tumor Analysis (IOTA) studies. Kaijser, J., Bourne, T., Valentins, L., Sayasheh, A., Van Holsbeke, C., Vergote, I., Testa, AC, Franchii, D. Van Calster, B., Timmerman, D.

Significance of the Study

Prior to the commencement of the fellowship training program in OB-Gyn Ultrasound, this institution used the Sassone scoring index in classifying benign and malignant ovarian masses. And in the early 2015, in compliance to the Standardization of contents of OB-Gyn Ultrasound Reports as set by Philippine Society of Ultrasound in Obstetrics and Gynecology (PSUOG) Boards, they recommended the use of IOTA classification in ultrasound reports as part of the evaluation of adnexal / ovarian masses for all its accredited Fellowship Training Institutions. Therefore, this study was focused on the diagnostic performance of the IOTA Simple Descriptors and IOTA Simple Rules in classifying ovarian pathology in our institution. It is expected to improve accuracy in the diagnosis of ovarian pathologies with the primary end-point of aiding our clinicians in their pursuit of ensuing optimal management for our patients.

General objective: To determine the diagnostic performance of different sonologic index in classifying benign and malignant masses.

Specific objectives:

1. To evaluate the diagnostic performance of IOTA Simple descriptors, IOTA Simple rules and Sassone Scoring System in detecting benign and malignant masses using histopathology as the reference standard.
2. To compare diagnostic performance of IOTA Simple rules and Sassone Scoring Index in classifying benign and malignant masses.

MATERIALS AND METHODS

A. Setting and Subjects

The subjects of this study included all the patients with an ultrasound finding of Ovarian New Growth and/or Ovarian Mass by ultrasound and subsequently underwent surgical intervention in this institution.

This was a cross sectional study from January to December 2016, which specifically determines the diagnostic accuracy parameters using Ultrasound following the standards specified by the IOTA study.

The inclusion criteria consisted of all women seen and evaluated by the section of Ultrasound, intervened in the institution and with the specimen submitted for histopathologic evaluation. The exclusion criteria were the following: seen by the section but was not intervened,

underwent operation but specimen not evaluated for histopathology, underwent operation but procedure was abandoned because of surgical difficulty, and those who failed to give consent for inclusion in the research.

B. Sample size computation

Using simple random sampling drawn without replacement from possible cases of ONG cases over the two year period of 80 cases per year (for both Benign and Malignant) with 75% accuracy compatible with histopathology reports. Using the following assumptions: The margin of error is plus or minus 4% or 0.04. The confidence level is 95% or 0.95. Alpha is equal to one minus the confidence level. Thus, alpha = 1 - 0.95 = 0.05. The critical standard score is the value for which the cumulative probability is 1 - alpha/2 = 1 - 0.05/2 = 0.975. The distribution of standard scores has a mean of 0 and a standard deviation of 1. We use the following entries: Value = 0.975; Mean = 0; and Standard deviation = 1. And finally, we assume that the population proportion p is equal to its past value over the previous 2 years. That value is 0.75. Given these inputs, we can find the smallest sample size n that will provide the required margin of error.

$n = [(z^2 * p * q) + ME^2] / [ME^2 + z^2 * p * q / N]$
$n = [(1.96)^2 * 0.75 * 0.25 + 0.0016] / [0.0016 + (1.96)^2 * 0.75 * 0.25 /80]$
$n = 68.$

C. Data Collection

Prior to conducting this study, the research was reviewed by the Department and Section Research Committee following the standard set by the Research and Ethics Review Committee of the institution. All eligible patients signed the informed consent forms prior to examination and a data collection tool was used. The patients were examined using Transvaginal and/or Transabdominal probe by one fellow-in-training and the findings was confirmed by an accredited sonologist of PSUOG to decrease inter-observer variability. When a transvaginal scan was considered inappropriate (e.g. no previous sexual encounters, patient who failed to give consent, huge pelvoabdominal mass that cannot properly classify or assess the mass), a transrectal ultrasound and/or transabdominal ultrasound was used instead. Ultrasound examination was focused on the Ovarian Pathology. The machine used was Samsung WS80A following the standard setting for two-dimensional evaluation. For color flow analysis in IOTA classification, the setting used was frequency of at least 5MHz, Pulse Repetition Frequency (PRF) 0.3-0.9 kHz, wall filter 30-50 Hz, and power Doppler gain was reduced until all color artifacts disappeared, to elicit maximum sensitivity even for low velocity flow.

All women were scanned on lithotomy position with an empty bladder. The uterus was scanned longitudinally and transversely. On assessment of the ovarian masses / tumors, a stepwise approach was adopted. Initially, ovarian masses are classified using Simple Descriptors and if not applicable, proceeded to use IOTA Simple Rules and Sassone scoring index.

Surgical treatment options were based on the pre-operative and intra-operative evaluation of the attending clinicians. Pathologists were blinded on the sonologic findings of each cases submitted. Only patients with complete and final histopathologic diagnosis were included in the final analysis. All ovarian tumors were classified using the World Health Organization (WHO) histological classification 2013 with the borderline tumors included in the malignant category.

D. Statistical Analysis

Data were described using frequency counts and percentages. Chi-square was used to determine significant difference in the distribution of discrete variables. 95% confidence intervals were computed for variables which showed significance at 0.05 confidence level. Accuracy parameters that were computed were as follows: Sensitivity, Specificity, Positive and Negative Predictive Value, Positive and Negative Likelihood Ratio and Area under the curve (AUC) using the 2x2 table and the diagnostic performance were computed using histopathologic results as the gold standard. Data were encoded in Excel and calculated using standard formulas and EpiInfo Software Version 3.5.1 (by Division of Health Informatics & Surveillance (DHIS), Center for Surveillance, Epidemiology & Laboratory Services (CSELS). A result was determined as statistically significant if the p-value of each respective test was <0.05.

RESULTS

A total of 352 cases were referred and seen by the Section of OB-Gyn Ultrasound for pelvic ultrasound to assess the adnexa due varied signs and symptoms from January to December 2016. More than 60 percent was secondary to palpable mass on physical examination, followed by complaint of abdominal or hypogastric pain (32%) and the rest were asymptomatic. Only 29.8% of the referred case (105 cases) underwent surgery and was included in the analysis (Figure 2). Seventy-three percent of those who underwent surgical intervention has as pre-operative clinical evaluation of benign disease compared 26.7% of malignant disease. Of the 105 cases, 23 cases were excluded because of incomplete or unavailability of the final histopathology report, thus only 82 cases were included in the computation of diagnostic performance.

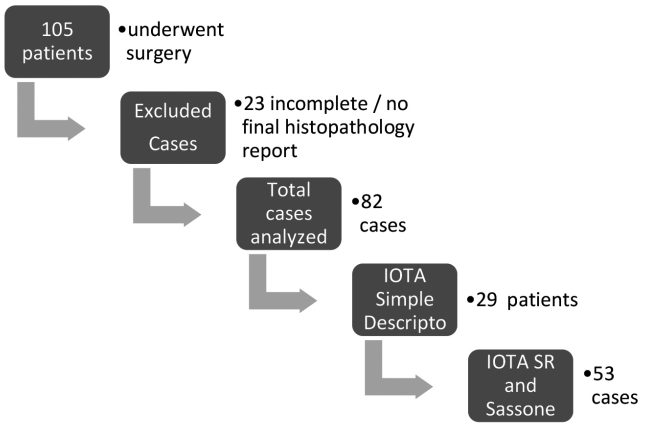

Figure 2. Flow chart of inclusion of cases in the analysis of data

Twenty nine of which used pattern-recognition using IOTA Simple Descriptors and the remaining 53 cases were evaluated using both the IOTA Simple Rules and Sassone scoring Index.

Table 1 described the profile of the patients included in the study. The mean age of participants was 39 years old (SD ±11.2), 67% belonging to age range of 31 to 50 years old. Fifty six percent were gravida 1-3 and 24% were nulligravid.

Table 2 summarized the histologic findings of all the cases and was stratified based on age and gravidity. Of the 82 cases sent for histopathology, 73% was benign and 22 % was malignant. Malignancy was high in the premenopausal age (ages 31 to 50) at 61%. Four cases (4.8%) has no identified pathology by histology but with ultrasound findings of ovarian cysts.

Exploring the results on histopathologic types for benign tumors, (Table 3a) dermoid and endometrial cyst accounted for about 47% followed by serous cyst/ cystadenoma at 12%. Table3b showed the 18 cases of malignancy determined by histopathology. Ten cases are epithelial type (six cases of Mucinous cystadenocarcinoma, three cases of Endometriod adenocarcinoma, and one case of Papillary carcinoma) and one sex-cord tumor.

Table 4 showed analysis of the ultrasound finding of the six cases of Mucinous Tumor with Low malignant potential or commonly identified as borderline tumors. All the borderline tumors were classified as benign by Sassone scoring index. However, 2 out of 6 (33%) of these borderline tumors were classified as malignant when using the IOTA nomenclature.

Table 5 showed analysis of 29 cases using IOTA Simple Descriptors with Benign features revealing high sensitivity but low specificity (95 and 43%, respectively) an accuracy rate of 82.75%. The most common histopathologic diagnosis identified using Simple Descriptors were dermoid cyst at 51% followed by endometrial/endometriotic cyst at 34%. However, three cases (10%) identified with

Table 1 : Baseline characteristics of patients

Age (Mean ± SD) 39 ± 11.2 years	N	Percentile
≤ 20 years old	5	4.8
21-30 years old	15	14.3
31-40 years old	34	32.4
41-50 years old	37	35.2
more than 50 years old	14	13.3
Gravida		
Nulligravid	25	23.8
1-3	59	56.2
≥ 3	21	20.0

Table 2: Profile of patient by histology stratified by age and gravidity

	Benign	Percent	Malignant	Percent
Diagnosis by Pathology*	60	73.17	18	21.95
Age				
≤ 20 years old	3	5.00	2	11.11
21-30 years old	8	13.33	2	11.11
31-40 years old	24	40.00	4	22.22
41-50 years old	18	30.00	7	38.89
more than 50 years old	7	11.67	3	16.67
Gravida				
Nulligravid	11	18.33	7	38.89
1-3	37	61.67	7	38.89
≥ 3	12	20.00	4	22.22

Table 3. Histology of the included cases

	n	Percent
A. Benign		
Mature cystic teratoma/Dermoid	21	25.61
Endometriotic cyst/ endometrial cyst	18	21.95
Serous cyst/cystadenoma	10	12.2
Mucinous cyst/cystadenoma	9	10.98
Others: Paratubal	1	1.22
Fibrothecoma with degeneration	1	1.22
B. Malignant		
Carcinoma/Adenocarcinoma	11	13.41
Mucinous Low Malignant Potential	6	7.32
Others: GI mass- spiral cell tumor	1	1.22

Table 4. Profile of Cases with Findings of Mucinous with Low Malignant Potential

	Age	Gravida	Ultrasound Result	
			IOTA	Sassone
Case 1	53	G5	Malignant	Benign
Case 2	56	G0	Unclassified	Benign
Case 3	44	G6	Benign	Benign
Case 4	40	G2	Benign	Benign
Case 5	16	G0	Malignant	Benign
Case 6	20	G2	Benign	Benign

Table 5. Evaluation of ovarian cyst/tumors using IOTA Simple Descriptors (Benign Features)

		95% C.I.
Sensitivity	**95.45%**	77.16 to 99. 88%
Specificity	**42.86%**	9.90 to 81.59%
Accuracy	**82.75%**	
AUC	**0.69**	0.49 to 0.85
Positive Likelihood Ratio	**1.67**	0.87 to 3.19
Negative Likelihood Ratio	**0.11**	0.01 to 0.86
Disease Prevalence	**75.86%**	56.46 to 89.70%
Positive Predictive Value	**84.00%**	73.31 to 90.94%
Negative Predictive Value	**75.00%**	26.92 to 96.07%

Table 6. Diagnostic performance of IOTA Simple Rule (SR) and Sassone Scoring S

	SR	95% C.I.	Sassone	95% C.I.
Sensitivity	**57.89%**	33.50 % to 79.75 %	**44.44%**	21.53% to 69.24%
Specificity	**85.29%**	68.94% to 95.05%	**85.71%**	69.74% to 95.19%
Accuracy	**75.47%**		**71.69%**	
AUC	**0.72**	0.58 to 0.83	**0.65**	0.51 to 0.78
Positive Likelihood Ratio	**3.94**	1.61 to 9.64	**3.11**	1.19 to 8.14
Negative Likelihood Ratio	**0.49**	0.29 to 0.85	**0.65**	0.42 to 1.00
Disease Prevalence	**35.85%**	23.14% to 50.20%	**33.96%**	21.52% to 48.27%
Positive Predictive Value	**68.75%**	47.32% to 84.35%	**61.54%**	37.94% to 80.72%
Negative Predictive Value	**78.38%**	67.75% to 86.22%	**75.00%**	66.01% to 82.25%

ovarian cyst by ultrasound has no identified pathology by histopathology.

Table 6 showed the diagnostic performance of two indices for 53 cases. The specificity of Simple Rule (SR) and Sassone Scoring were comparable at 85%. On the contrary, the sensitivity of Sassone was lower (44%) compared to SR (58%). The predictive values and likelihood ratios was not statistically significant for both Indices.

Accuracy is measured by the area under the ROC curve. Figures 3a and 3b showed the Receiver-operating characteristic (ROC) for Sassone scoring index and IOTA Simple Rule showing an area under the curve (AUC) of 0.65 and 0.72, respectively.

Figure 3. Computing for Receiver operator curve

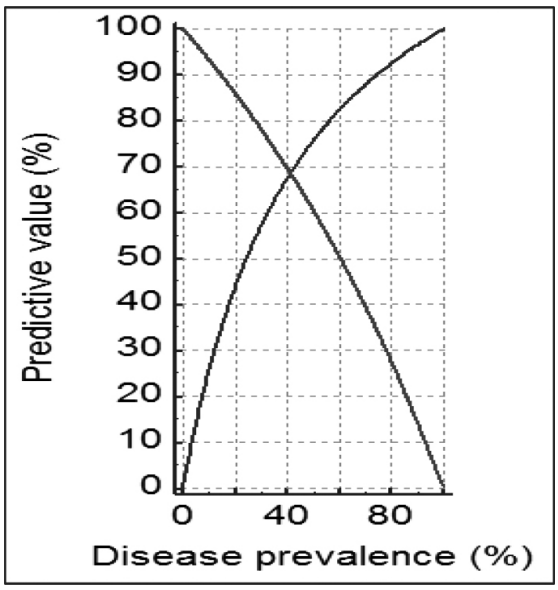

Figure 3A: Receiver operating characteristic (ROC) for Sassone score; AUC= 0.65

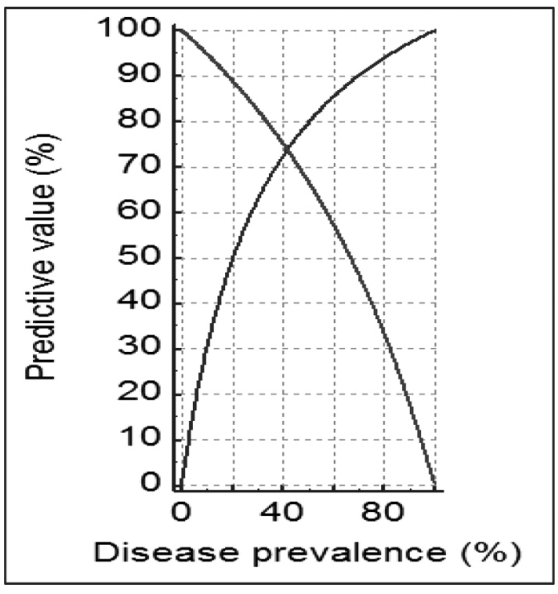

Figure 3B: Receiver operating characteristic (ROC) for IOTA Simple Rules; AUC=0.72

DISCUSSION

Symptoms of hypogastric pain, palpable mass or suspected pelvic by physical examination is the most common presentation for patients with adnexal condition such as ovarian cyst or adnexal mass. In this study, more than 60% of the cases presented with palpable mass, followed by hypogastric pain. Risk factors for ovarian pathology, particularly carcinoma in general includes age more than 50, inherited gene mutation, estrogen replacement therapy, early menarche and late menopause, fertility treatment drugs, smoking and currently, polycystic ovarian syndrome has been linked to this entity.[9,10,12] Predisposition to Ovarian carcinoma for age greater than 50 was not shown in this study and this findings were contrasting to the study published by Testa et al[15] wherein the prevalence was highest in postmenopausal patients (age 50 and above) at 57%, and only 28% are premenopausal. The disparity may be due the limited number of postmenopausal women included in the study which was only 12% of the total number of participants.

Of the 82 cases sent for analysis, 73% was benign and 22 % was malignant. This distribution was almost similar to the findings of Ameye et al[16], wherein 74% were benign and 26% were malignant. However, in our study, 4 cases (or 5%) have no identified pathology by histology but with ovarian cysts or tumors by sonologic evaluation.

Histopathology of the benign diseases showed that dermoid and endometrial cyst accounted for 47% of all benign tumors which was also similar to the findings published in the study of Ameye[16], and Yabek et al[17]. In a study published by Calen, M. in 2009[18], approximately 80% of the cases dermoid cysts occur in patients between 20 and 30 years of age and represent about 18-20% of all benign ovarian tumours[18], which was also similar to the findings of this study. In the published study of Granberg et al and Aslam et al, epithelial carcinoma accounted to about 85-90% of all ovarian cancers[3,11] and with the results showing 90% of the malignant type of carcinoma.

Borderline tumors i.e. Mucinous with Low Malignant Potential (LMP) falls under a separate classification from malignancy and its pathophysiology were different from ovarian cancer because it does not grow into the stroma of the ovarian tissue. Thus 2003, World Health Organization (WHO) separated LMP from carcinomas and classified as borderline tumors. LMP when compared to other ovarian cancers of any type has an excellent prognosis[20]. In the analysis of our data set, LMP were included and analyzed under the malignancy type/category. A study of Cormio[20] et al showed up to 63% of patients with LMP appeared on the ultrasound as a cyst with papillae inside, but without solid patterns, septa or any other sign of complexity. Ultrasound images may also appear as unilocular cyst with solid papillary projections arising from the inner wall and with a positive ovarian crescent sign which are all features of a benign ovarian masses[17]. Other images showed a multilocular nodule, or simple anechoic cysts without any papillae, and up to 30% as cysts with septa[17,20]. Comparing the result of our study, Sassone scoring index classified 100% of LMP cases as benign. However by IOTA nomenclature, 33% of LMP were classified as malignant. The discrepancy in histology and ultrasound appearance is secondary to its non-specific sonologic appearance and sometimes consistent with benign features. For these six cases, the presence of papillae or thick septa was not considered as sensitive sonographic markers for borderline tumors.

Diagnostic performance of IOTA Simple descriptors showed high sensitivity but low specificity with an accuracy rate of 82.75%. All cases used in the analysis used the benign features category only, with the dermoid cyst accounting for 51% of the case followed by endometrial/ endometriotic cyst at 34%. However, using IOTA simple descriptors with benign features, three cases has no identified pathology by histology but was identified as ovarian cyst with benign features.

To measure for the diagnostic performance of IOTA Simple Rules and Sassone scoring index, a total of 53 cases were included. The specificity of IOTA Simple Rule (SR) and Sassone scoring was comparable at 85%. On the contrary, the sensitivity of Sassone was lower (44%) compared to SR (58%). In the study published in by Testa et al[15] , both showed comparable specificity at 87% (95%CI 83.5-90.7) with high sensitivity at 92.5% (95% CI 89.6-94.6). Another study by Nunez et al[21] yielded both high sensitivity and specificity at 97 and 99%, respectively. Sassone scoring study by Shende et al[22], on the other hand showed almost similar specificity to the result of this study at 88%.

One factor that may have caused the low sensitivity of our result may be attributed to low sample size included in the analysis. Another factor to consider which resulted in low sensitivity was the high number of cases in false-negatives. The inclusion of Borderline (LMP) tumors as part malignancy cases may have caused the increased in false-negative cases.

CONCLUSION

The diagnostic performance of IOTA Simple Descriptors showed high sensivity but low specificity for identifying benign types of tumors. On the other hand, IOTA Simple Rules and Sassone Scoring Index showed high specificity but low sensivity for categorizing malignant ovarian masses. Accuracy of the methods ranges from 72 to 83%.

Comparing IOTA Simple Rules and Sassone Score, specificity was comparable at 85%, but lower sensitivity for Sassone Score at 44%. Accuracy as measured by area under the ROC curve (AUC) was higher for IOTA Simple rules at 0.72.

RECOMMENDATIONS

1. External validation with higher sample size is commended.
2. Continuous training of operators/personnel may assist in decreasing errors in classification (either false-negatives or false-positives) and improving accuracy and increasing over-all diagnostic performance of any sonologic evaluation.
3. Usefulness of Sassone or other scoring index for adnexal masses should be further evaluated. ■

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