Original Article

Comparison of Human Epididymis Protein 4, Cancer Antigen 125, and Ultrasound Prediction Model in Differentiating Benign from Malignant Adnexal Masses

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Abstract

Background: This study aimed to compare the diagnostic performance of carcinogenic antigen (CA) 125, (HE)-4 (Human epididymis protein 4), and ultrasound (International Ovarian Tumor Analysis [IOTA]) Simple Rules individually and to derive a composite score in the differentiating ovarian cancer from benign ovarian mass. **Subjects and Methods:** Consecutive patients (n = 100) with pelvic mass admitted during February 2018–August 2019 were included prospectively. Patients with either known case of epithelial ovarian cancer (EOC) or metastatic EOC were excluded. The primary outcome was to assess the sensitivity and specificity of CA-125, HE-4, and IOTA Simple Rules in predicting benign from malignant mass independently, while secondary outcome was derivation of a new model incorporating these variables using multivariate logistic regression analysis to predict benign from malignant lesions. Receiver operator curve (ROC) was drawn to redefine the best-performing cutoff values and difference between area under the ROC (AUROC) were compared by DeLong's method. **Results:** Out of 100 cases of adnexal mass selected, the sensitivity and specificity of CA-125 were 73.8% and 77.6%, HE-4 were 90.5% and 87.9%, and IOTA Simple Rules were 92.9% and 81.0%. CA-125, HE-4, and IOTA Simple Rules were independently associated with the likelihood of malignancy/borderline (P < 0.001). The area under the curve for the "composite score" (AUC = 0.93) was the highest and was significantly better than that of CA-125 (AUC = 0.786) (P = 0.004 using DeLong's test) and comparable with HE-4 (AUROC = 0.90; P = 0.128 using DeLong's Test). **Conclusion:** The sensitivity and specificity of HE-4 and IOTA Simple Rules for predicting malignant ovarian tumor was better than those of CA-125. The diagnostic performance of "composite score" was comparable to those of either HE-4 or IOTA Simple Rules and significantly better than CA-125.

Keywords: *Adnexal masses, HE-4, International Ovarian Tumor Analysis Simple Rules*

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Introduction

Presurgical distinction between benign and malignant tumors in a patient presenting with adnexal ovarian mass is central to determine the management and prognosis. When diagnosed in earlier stages, up to 90% of patients can be expected to have a long disease-free survival. This underscores the role of biomarkers that may not only help in prognostication but also in presurgical triaging. Various biomarkers have been evaluated so far, of which cancer antigen 125 (CA-125) is the most

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widely used tumor marker.[1] Various studies initially evaluated the role of CA-125 alone for distinguishing malignant from benign ovarian tumors. Using a cutoff of >35 U/mL for CA-125, a recent meta-analysis showed a pooled sensitivity of 80% and specificity of 75% for the diagnosis of borderline/ovarian cancer.[2] To improve the diagnostic performance, Jacob *et al*. calculated a composite "Risk of Malignancy Index" (RMI) score using ultrasound (USG) score, menopausal status, and CA-125 with a sensitivity of 85.4% and specificity of 96.9%.[3] Tingulstad *et al*.[4] formulated another score, RMI-2, using the same parameters as original RMI but with different regression coefficients and found that RMI-2 performed significantly better with a sensitivity of 80% and specificity of 92% compared to the original RMI with a sensitivity of 71% and specificity of 96%. However, CA-125 is normally expressed in a variety of epithelial cell types, and shows fluctuations with physiological conditions like pregnancy as well as benign conditions like endometriosis, and fibroid thereby limiting the specificity of CA-125-based prediction models.[5]

Human epididymis protein 4 (HE-4), member of the whey acidic protein domain family of proteins, has been shown to be highly expressed in ovarian cancer.[6,7] A recent meta-analysis showed HE-4 as a better biomarker for diagnosing ovarian cancer with a sensitivity of 78% and specificity of 86%.[8] Moore *et al*. developed the Risk of Ovarian Malignancy Algorithm (ROMA) score using HE-4, CA-125, and menopausal status.[9] ROMA score was later validated in multiple studies and found to have better discriminating abilities compared to RMI.[10,11] Later, USG prediction model developed by the International Ovarian Tumor Analysis (IOTA) showed improved diagnostic performance compared to ROMA.[12,13] In view of limitations of current "gold standards" for detecting ovarian cancer, there is an urgent need for new biomarkers with better discrimination abilities. It appears possible that using combination of USG with CA-125 and HE-4 might have better diagnostic performance in distinguishing ovarian malignancy from benign lesions. There is a paucity of studies evaluating the role of IOTA Simple Rules in combination with CA-125 and HE-4.[14,15]

This study aimed to compare the sensitivity and specificity of CA-125, HE-4, and IOTA Simple Rules individually in diagnosis of epithelial ovarian cancer (EOC) and to derive a composite score using these parameters to assess whether inclusion of HE-4 and CA-125 improves the performance of IOTA Simple Rules in the differentiating ovarian cancer from benign ovarian mass.

Subjects and Methods

This prospective cohort study was conducted in the department of obstetrics and gynecology at a tertiary care referral hospital from February 2018 to August 2019. Before the collection of biological samples and surgery, all patients or their authorized representatives were required to give informed consent. The study protocol was approved by the Institute Ethics Committee (Ref. AIIMS/IEC/18/117).

Inclusion criteria

Consecutive patients diagnosed with an ovarian cyst or pelvic mass who were scheduled to undergo surgery for removal of the mass were eligible for enrolment.

Exclusion criteria

Patients who had undergone surgical debulking or chemotherapy previously for EOC and those known to have malignancies secondarily involving the ovary were excluded from the study.

Examination and investigations

All patients underwent detailed medical history and general physical examination including breast, thyroid examination, per abdomen, per speculum, per vaginal, per rectal examination. All the patients underwent USG (Siemens, 3.5 MHz probe) abdomen and pelvis as per IOTA Simple Rules for staging and resectability. On USG examination, sonographic morphology of the adnexal masses was characterized by two-dimensional real-time and color Doppler USG. Demographic data of the patients such as age, tumor marker levels, if available, and sonographic features of the adnexal masses used in the IOTA Simple Rules and RMI scoring were prospectively recorded in the research forms and stored in the computerized database. The IOTA Simple Rules to characterize whether the features were benign (B) or malignant (M) were based on the descriptions proposed by Timmerman *et al*.[13] If one or more M-features applied in the absence of a B-feature, the mass was categorized as malignant. If one or more B-features applied in the absence of an M-feature, the mass was categorized as benign. If both M-rules and B-features applied or no rule applied, the mass was categorized as inconclusive.

Ten milliliters of venous blood were drawn in serum vials BD® vacutainer preoperatively and allowed to stand in room temperature for 1 h. It was then centrifuged at 3000 rpm for 10 min that would separate the serum and it was stored in aliquots at − 80°C. Subsequently, serum levels of CA-125 and HE-4 levels were determined by enzyme-linked immunosorbent assay.[16]

The definite diagnoses of the adnexal masses, used as a gold standard, were based on pathological reports.

All masses were classified into two groups: Benign or malignant. Masses with pathological diagnosis of borderline tumors were classified as malignant.

Treatment

All patients underwent primary debulking surgery or TAH/TLH/TRH+BSO (open/laparoscopic/robotic ovariotomy/cystectomy or USG-guided biopsy) as per provisional diagnosis. Staging was done intraoperatively and specimens were sent for histopathological examination.

Outcomes

The primary endpoint of the clinical study was to classify patients with a pelvic mass into malignant versus benign using the serum biomarkers CA-125 and HE-4, and to determine the accuracy of these classifications. The secondary outcome was derivation of a new model incorporating variables with ability to independently predict the outcome (benign versus malignant) and compare its sensitivity and specificity with those of the individual variables.

The primary outcome was prediction of benign versus malignant ovarian tumors and assess relative usefulness of all CA-125, HE-4, and IOTA Simple Rules based on sensitivity and specificity. The secondary outcome was derivation of a new model incorporating these three variables in differentiating benign and malignant ovarian masses.

Statistical analysis

Independent *t*-test was used to compare continuous normally distributed variables, while Mann–Whitney *U*-test was used for continuous nonparametric variables. Chi-square test was used for comparing categorical variables. Receiver operator curve (ROC) was drawn to redefine the best-performing cutoff values (using Youden's index) for each biomarker and difference between area under the ROC (AUROC) were compared by DeLong's method using the package Proc.[17] In addition, we assessed sensitivity, specificity, and positive and negative predictive values for each biomarker by applying the test-specific cutoff values. Multivariate logistic regression analysis with backward elimination was done for deriving the best predictors (covariates), the binary outcome being benign disease or ovarian cancer. A coefficient (i.e., weighting characteristic) for each variable as well as a model constant was determined. The statistical analysis was done using Statistical Package for Social Sciences 23 version (IBM, Chicago, IL, USA) software and "*r*" statistics. Graphs were prepared using GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA). A variable with a two-tailed $P < 0.05$ was considered significant.

Results

A total of 100 patients were included in the study. The mean age of the study cohort was 41.65 ± 15.4 years and 29 (29%) patients were postmenopausal. Most common symptom was abdominal pain, noted in 94% followed by Anorexia/weight loss in 26% of patients. The baseline characteristics are shown in Table 1. Staging laparotomy was done in 63% of patients, ovariotomy in 12%, cystectomy in 9%, hysterectomy with bilateral salpingo-oophorectomy, and USG-guided biopsy in 8% each. SUPON histopathological examination, 34 (34%) had malignant, 8 (8%) had borderline, and the rest had benign lesions. The details of the histopathological findings are shown in Table 2.

For analysis, borderline histopathological findings were grouped under malignancy. The best-performing cutoff for the CA-125 and HE-4 in our cohort was re-calculated to be 67.9 and 394.5, respectively. The diagnostic performance of HE-4 was significantly better than those of CA-125. The AUROC for CA-125 and HE-4 for predicting borderline/malignant versus benign mass was 0.79 (95% confidence interval [CI]: 0.68–0.89) and 0.90 (95% CI: 0.82–0.97), respectively (*P* value for comparison 0.02 using DeLong's method) [Figure 1a-c]. The sensitivity and specificity of HE-4 and IOTA Simple Rules for predicting malignant ovarian tumor were similar and both were better than those of CA-125.

Subgroup comparison of sensitivity and specificity showed that the diagnostic performance of individual criterion was better in postmenopausal women compared to premenopausal. This was especially for CA-125, whose sensitivity improved to 86.7% (59%–98%) in postmenopausal compared to 66.7% (46%–83%) in premenopausal women. The details of comparison of sensitivity, specificity, positive predictive values (PPVs), and negative predictive values in the whole cohort are presented in Table 3.

Logistic regression with backward elimination analysis revealed that CA-125, HE-4, and IOTA Simple Rules were all significantly ($P < 0.001$) and independently associated with the likelihood of malignancy/borderline. Age, parity, and menopausal status were not associated with the likelihood of malignancy [Table 2]. The composite score was thus defined as follows:

The best-performing cutoffs for the "composite score" in our cohort were calculated to be 0.47. The sensitivity of "composite score" at this cutoff was 85.7% (71%–95%) whereas its specificity was 94.8% (86%–99%) for predicting borderline/malignant masses. PPV

Table 1: Demographic variables, tumor markers, and International Ovarian Tumor Analysis Simple Rules in final diagnosis

All parameters	Diagnosis based upon histopathology			*P*
	Benign (*n*=58), *n* (%)	Borderline (*n*=8), *n* (%)	Malignant (*n*=34), *n* (%)	
Age (years)	42.50±14.32	43.38±18.59	39.79±14.58	0.612[a]
Parity				
P0	9 (15.5)	1 (12.5)	5 (14.7)	0.947[b]
P1	4 (6.9)	0	3 (8.8)	
P2	14 (24.1)	3 (37.5)	6 (17.6)	
≥P3	31 (53.4)	4 (50.0)	20 (58.8)	
Age at menarche (years)	12.71±1.14	12.50±1.20	12.74±0.93	0.852[a]
Postmenopausal	19 (32.8)	2 (25.0)	8 (23.5)	0.621[c]
Clinical impression				
Malignant	26 (44.8)	4 (50.0)	20 (58.8)	0.476[b]
Benign	32 (55.2)	4 (50.0)	14 (41.2)	
CA-125***	337.41±2014.54	240.78±252.09	452.51±924.28	<0.001[a]
HE4***	329.31±418.54	959.60±683.32	955.16±607.68	<0.001[a]
Simple rules***				
B-rule	47 (81.0)	0	3 (8.8)	<0.001[b]
M-rule	11 (18.9)	0	31 (91.1)	
USG findings				
Multi-locularity	38 (65.5)	7 (87.5)	27 (79.4)	0.21
Papillary projections	1 (1.7)	4 (50.0)	19 (55.9)	<0.001
Septations	45 (77.6)	8 (100)	29 (85.3)	0.25
Ascites	5 (8.6)	3 (37.5)	22 (64.7)	<0.001
Solid mass	5 (8.6)	4 (50.0)	20 (58.8)	<0.001

***Significant at $P<0.05$, [a]Kruskal–Wallis test, [b]Fisher's exact test, [c]Chi-squared test. CA-125: Cancer antigen 125, HE4: Human epididymis protein 4, USG: Ultrasonography

Table 2: Histopathological findings in our study

Benign (*n*=58), *n* (%)	Borderline (*n*=8), *n* (%)	Malignancy (*n*=34), *n* (%)
Serous cystadenoma: 20 (34.5)	Borderline mucinous tumor: 5 (62.5)	High-grade serous cystadenocarcinoma: 11 (32.3)
Mucinous cystadenoma: 9 (15.5)	Borderline serous tumor: 3 (37.5)	Mucinous adenocarcinoma: 9 (26.5)
Endometrioma: 9 (15.5)		Papillary serous adenocarcinoma: 6 (17.6)
Mature cystic teratoma: 4 (6.9)		Adenocarcinoma: 5 (14.7)
Granulomatous inflammation: 2 (3.4)		Endometrioid carcinoma of ovary: 2 (5.9)
Sex cord-stromal tumor: 2 (3.4)		Liposarcoma: 1 (2.9)
Paraovarian cyst: 2 (3.4)		
Fibroid: 2 (3.4)		
Corpus albicans: 1 (1.7)		
Hemorrhagic corpus luteum: 1 (1.7)		
Edematous ovary: 1 (1.7)		
Fibroma: 1 (1.7)		
Dermoid cyst: 1 (1.7)		
Spindle cell tumor: 1 (1.7)		
Tubal ectopic: 1 (1.7)		
Benign cystic epithelial lesion: 1 (1.7)		

was determined to 92.3% (79%–98%) and negative predictive value was calculated to be 90.2% (80%–96%) making its diagnostic accuracy as 91.3% (84%–96%). While HE-4 and IOTA Simple Rules had slightly higher sensitivity compared to the "composite score," the latter had better specificity and PPV compared to the former.

The area under the curve (AUC) for the "composite score" (AUC = 0.93) was the highest. Comparison of AUROC revealed that the diagnostic performance of "composite score" was significantly better than that of CA-125 (AUC = 0.786) (P = 0.004 using DeLong's test) and was insignificantly higher than HE-4 (AUROC = 0.90; P = 0.128 using DeLong's test). As observed for

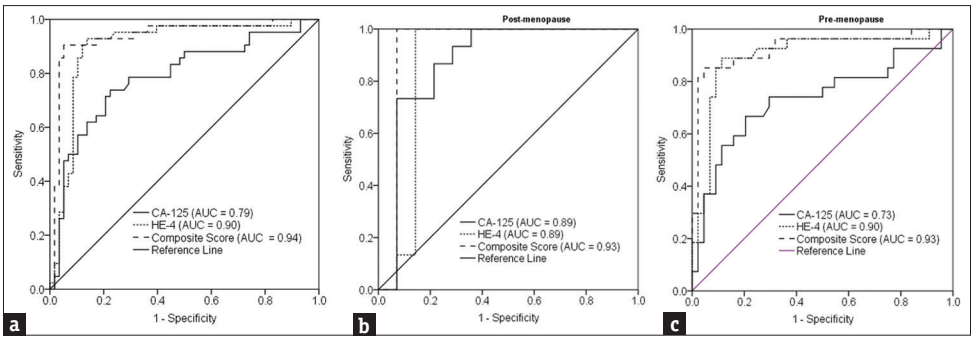

Figure 1: (a-c) ROC curve analysis showing diagnostic performance of individual criteria in predicting borderline/malignant versus benign adnexal masses in premenopausal, postmenopausal and all patients. AUC: Area under the curve, HE: Human epididymis protein 4, CA: Cancer antigen

Table 3: Comparison of the diagnostic performance of various predictors in predicting borderline/malignant versus benign in premenopausal, postmenopausal, and in all patients

Criteria	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Whole cohort (*n*=100)					
CA-125 (cutoff: 67.9 by ROC)	0.79 (0.68–0.89)	73.8 (58–86)	77.6 (65–87)	70.5 (54–83)	80.4 (68–90)
HE4 (cutoff: 394.5 by ROC)	0.90 (0.82–0.97)	90.5 (77–97)	87.9 (77–95)	84.4 (71–94)	93 (82–98)
Simple rules	NA	92.9 (81–99)	81.0 (69–90)	78 (64–88)	94.0 (83–99)
"Composite Score" (cutoff: 0.47 by ROC)	0.94 (0.86–0.99)	85.7 (71–95)	94.8 (86–99)	92.3 (79–98)	90.2 (80–96)
Premenopausal (*n*=71)					
CA-125	0.73 (0.60–0.86)	66.7 (46–83)	77.3 (62–89)	64 (44–81)	79.1 (64–90)
HE4	0.90 (0.81–0.98)	88.9 (71–98)	88.6 (75–96)	83 (64–94)	93 (81–99)
Simple rule	NA	89 (71–98)	84.1 (70–93)	77.4 (59–90)	92.5 (80–98)
"Composite score"	0.93 (0.85–0.99)	81.5 (62–94)	95.5 (85–99)	92 (73–99)	89.4 (77–96)
Postmenopausal (*n*=29)					
CA-125	0.88 (0.73–1.0)	86.7 (59–98)	78.6 (49–95)	81.3 (54–96)	84.6 (55–98)
HE4	0.87 (0.69–1.0)	93.3 (68–100)	85.7 (57–98)	87.5 (62–98)	92.3 (64–100)
Simple rule*	-	-	-	-	-
"Composite score"	0.93 (0.79–1.0)	93.3 (68–100)	92.9 (66–100)	93.3 (68–100)	93 (66–100)

*Could not be calculated as one of the values in the column was zero. ROC: Receiver operator curve, AUROC: Area under ROC curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, CA: Carcinogenic antigen, HE4: Human epididymis protein 4, NA: Not available

previous criteria, "composite score" performed better in postmenopausal compared to premenopausal women. Details are shown in Table 3 and Figure 1a-c.

Discussion

In this study, the sensitivity and specificity of HE-4 and IOTA Simple Rules for predicting malignant ovarian tumor were similar and both were better than those of CA-125. "Composite score" had better specificity and PPV compared to HE-4 and IOTA Simple Rules. The AUROC was highest for "composite score" and significantly higher than that of CA-125. However, the AUROC of HE-4, IOTA Simple Rules, and the "composite score" were comparable. Individual criterions performed better in postmenopausal compared to premenopausal women, especially for CA-125.

Most women with suspected ovarian mass will undergo an USG prior to surgery, and USG prediction models developed by IOTA have shown improved diagnostic performance compared to ROMA.[12] There are few studies on the role of combination of USG with CA-125 and HE-4. In a study on 414 women with adnexal masses, Wilailak *et al*. noted that combining USG with HE-4 had better sensitivity for detecting ovarian cancer compared to CA-125-containing algorithms. HE-4 +USG improved the classification of cancer by 8.8% and benign by 15.9% when compared with ROMA.[14] However, Gentry-Maharaj *et al*. could not demonstrate any added advantage of combining HE-4 to USG + CA-125 compared to USG + CA-125.[15] In our study, although the AUROC was highest for the new score using combination of IOTA Simple Rules, CA-125, and HE-4 (composite score), it was comparable if not slightly better than either HE-4 or IOTA Simple Rules. Also, the PPV of the new "composite score" was better than both HE-4 and IOTA Simple Rules. However,

the "composite score" performed significantly better than CA-125 alone. It is likely that a "ceiling effect" is achieved once the sensitivity and specificity approximate 90%, which is common for any diagnostic test following a sigmoid-shaped curve.

The sensitivity, specificity, and cutoffs of CA-125 and HE-4, as expected for any diagnostic test, vary with different studies and patient population. Using a cutoff of >35 U/mL for CA-125, a recent meta-analysis of 17 studies showed a pooled sensitivity of 0.80 (95% CI, 0.76–0.82) and specificity of 0.75 (95% CI, 0.73–0.77) for the diagnosis of borderline/ovarian cancer irrespective of menopausal status, similar to our study.[2] In our study, however, the best-performing cutoff for CA-125 was obtained as 67.9 U/mL. Consistent with previous studies,[18,19] the diagnostic performance of CA-125 was significantly better in postmenopausal women with a sensitivity of 86.7% compared to premenopausal (66.7%) women in our study. The cutoff of 35 U/mL yielded a higher sensitivity of 90% at the cost of lower specificity of 55% resulting in higher false positives. Xu *et al*. showed that at cutoff of 60 U/mL, the specificity of CA-125 increased without any significant loss of sensitivity in premenopausal women.[20] Similarly, in another study in postmenopausal women, a higher cutoff (>71 U/mL) for CA-125 resulted in a sensitivity of 89% and specificity of 96%.[21] We noted similar sensitivity (86.7%), but lower specificity of 78.6% in postmenopausal women. The lower specificity of CA-125 in our study may be due to higher proportion of premenopausal women with elevated serum CA-125 level in common benign gynecologic disorders. Ahmed and Abdou[22] in their study involving 140 cases (62 as malignant masses and 78 as benign masses) noted that CA 125 ≥35 IU/mL predicted ovarian malignancy with a sensitivity of 91.9%, specificity of 53.8%, and accuracy of 70.7%. Raising the cutoff to 67.5 IU/mL resulted in decreased sensitivity of 83.9% and increased specificity of 80.7% with accuracy of 82.1%.

Similar to previous studies, we found HE-4 to be a better biomarker compared to CA-125 in diagnosing ovarian carcinoma with a sensitivity and specificity of 90.5% (77–97) and 87.9% (77–95), respectively, albeit at a higher cutoff of 394.5 pg/mL than previously described,[23] with almost similar diagnostic ability in both pre- and postmenopausal women.[24] The cutoff values for HE-4 have shown variation in different studies ranging from 70 to 150 pm.[25] The higher cutoff for HE-4 obtained in our study could be because of differences in the study population. We included patients with mass undergoing surgery from a tertiary care hospital with advanced stage of disease as evident from significantly (7 times) higher mean HE-4 levels (955.16 ± 607.68 pg/mL) in patients with malignant ovarian cancer. Even in those with benign tumors, the mean HE-4 level was 329.3 pg/mL compared to previous studies.[26] Our results are in accordance with those reported by Sandri MT *et al*. in which the mean values in those with ovarian carcinoma were 869.84 compared to 44.23 in benign ovarian masses obtaining a sensitivity of 83.1 (95% CI 76.4–88.6) at a predefined specificity of 90% and prespecified cutoff of 70 pg/mL.[26] Contrary to ours, Braicu *et al*. noted the mean values of HE-4 in benign and malignant ovarian masses as 54.52 U/mL and 51.61 U/mL, respectively27. Ahmed et al. noted that serum HE-4 concentration ≥150 pmol/L predicted ovarian malignancy with sensitivity and specificity of 83.9% and 70.5%, respectively. They concluded that HE-4 was more accurate than CA-125 (76.4% vs. 70.7%) for predicting malignant ovarian masses.[27]

In a study by Garg *et al*., the sensitivity for the detection of malignancy in cases where IOTA Simple Rules were applicable was 91.66% and specificity was 84.84%.[28] Another study by Auekitrungrueng *et al*.[29] concluded that the sensitivity and specificity of IOTA rules (83.8% and 92.0%, respectively) were significantly higher than RMI (77.2% and 86.8%, respectively) and RMI-2 (82.1% and 82.6%, respectively). The sensitivity of IOTA in our study was found to be 91.2% (76–98) whereas its specificity was calculated to be 81% (69–90).

Several studies in the past have tried to find the most accurate methods in various combinations for early diagnosis of malignancy in patients with adnexal mass. Multi-marker tests have been shown to improve performance for ovarian cancer diagnosis compared to CA125 or HE-4 alone.[30,31] However, there is no consensus in the conclusions, and some are even contradictory. This is important especially where women undergo surgery for an ovarian cyst or pelvic mass in a community hospital by a gynecologist or a general surgeon. Stiekema *et al*. found that HE-4 performed so well on its own at distinguishing between benign and malignant masses that the addition of USG characteristics did not provide any extra benefit.[32] However, they noted that the presence of intra-abdominal metastasis on computed tomography-scan improved the discriminative potential of HE-4. The findings of our study are in accordance with those reported by Stiekema *et al*.[32] Future studies are required to support our findings and to assess whether the addition of USG findings either in sequential manner or together with other biomarkers may improve the diagnostic performance and might help in formulation of newer diagnostic algorithms.

Strengths and limitations

Our study is limited by small sample size from a single tertiary care center experience. The main strength of our study was to evaluate a composite score for predicting ovarian malignancy. However, to validate the "composite score" in different cohorts, large multicenter studies are required to confirm our findings. The possibility of selection bias may also be a limitation as only the patients scheduled for surgery were recruited.

Conclusion

The sensitivity and specificity of HE-4 and IOTA Simple Rules for predicting malignant ovarian tumor were similar and both were better than those of CA-125. The diagnostic performance of "composite score" was comparable to those of either HE-4 or IOTA Simple Rules and significantly better than CA-125. "Composite score" had better specificity and PPV compared to HE-4 and IOTA Simple Rules.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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