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Assessment of the diagnostic value of using serum CA125 and GI-RADS system in the evaluation of adnexal masses

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Abstract

Cancer antigen 125 (CA125) is a valuable tumor marker for ovarian cancer. Gynecology Imaging Reporting and Data System (GI-RADS) is proved to be effective at identifying the adnexal masses. We investigated whether the combination of these two methods can improve the diagnostic accuracy of ovarian cancer.

We retrospectively analyzed preoperative data of 325 patients diagnosed with suspected adnexal mass, 196 patients with benign ovarian masses and 129 with malignant ovarian cancer (stage I: 34, II: 16, III: 61, IV: 18). CA125 was analyzed using the ARCHITECT system, GI-RADS was evaluated according to the International Ovarian Tumor Analysis consensus nomenclature and definitions. Sensitivities and specificities were also calculated for GI-RADS, CA125 and the combinations.

The sensitivity, specificity and accuracy of CA125, GI-RADS were 75.97%, 79.59%, 78.15%, and 90.70%, 90.82%,90.77%, the combination data were 94.79%, 96.00%,95.53%. The AUC of combined diagnostic methods was the largest and significantly better compared with each method alone, $P < .001$). For stage I-II malignancy, GI-RADS as a single method was superior to CA125.

Combined use of serum CA 125 and GI-RADS system improved the identification of adnexal masses at high risk of malignancy and could be used for clinical decision-making.

Abbreviations: AUCs = areas under curve, BI-RADS = Brest Imaging Reporting and Data System, CA125 = cancer antigen, GI-RADS = Gynecology Imaging Reporting and Data System, ROC curve = receiver operating characteristic curve.

Keywords: cancer antigen 125(CA125), combination of diagnosis, Gynecology Imaging Reporting and Data System (GI-RADS), ovarian cancer

1. Introduction

Ovarian cancer is one of the most fatal gynecologic malignancies. Usually, operative cytoreduction and platinum-based combined chemotherapy are used as the primary treatment. Although most patients can respond to standard primary treatment, 60% to 70% of patients with ovarian cancer relapse or die within 5 years after primary diagnosis.[1] As there is no effective diagnostic method to detect early ovarian cancer, most patients were investigated with advanced ovarian cancer. Patients who are detected at an early stage often have better prognosis and survival, but patients who can be diagnosed at an early stage are less than 30%.[2,3]

The level of cancer antigen 125 is usually significantly increased among most patients with ovarian cancer. And the elevated level of CA 125 closely related to the histological type and stage of ovarian cancer.[1]

With the developing of Ultrasonics these years, it offers a sensitive method for the routine detection of adnexal masses.[4,5] Indeed, ultrasonographic diagnosis is one of the important point to consider whether the patients need specialist referral or major surgery.[5–7] But because of the subjective view of the image, and recent literature has suggested that the subjective judgment may affect the correctness of the detection method, accurate preoperative differentiation of benign and malignant adnexal masses is required.[8]

The rationale of the GI-RADS classification is to be illustrated to the gynecological clinicians. In previous studies, other scoring systems or combination diagnostic system had been established for the diagnosis of malignant adnexal masses. However, most of these methods had complex scoring system for ultrasonographic findings, or even required for additional clinical and laboratory indexes combining with the ultrasonographic findings.[9] As a result, the clinicians cannot easily assess the malignancy risk immediately only by ultrasonography examination.

The International Ovarian Tumor Analysis consensus nomenclature and definitions for all tumor features evaluated by ultrasonography have improved the discrimination of adnexal masses by including quantitative assessment of morphological features.[4,10] However, the findings of the ultrasonographic report can also be confusing or even misleading for clinicians who are not majoring in Ultrasonics. Such miscommunication

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Table 1

The GI-RADS classifications.

Classification	Diagnosis	Morphological details	Risk of malignancy, %	Clinical management
GI-RADS 1	Definitive benign	Normal ovaries identified and no adnexal mass seen	0	NA
GI-RADS 2	Very probably benign	Classic appearance of functional origin cyst (e.g. follicle, corpus luteum, or hemorrhagic cyst)	<1	Assumed to be functional; requires follow-up by sonography
GI-RADS 3	Probably benign	Classic appearance of common benign neoplasms of the ovary (e.g. teratoma, endometrioma, or paraovarian cyst)	1–4	Assumed to persist over me; surgery required (preferably laparoscopy)
GI-RADS 4	Probably malignant	Adnexal lesion not included in GI-RADS 1–3, and with 1–2 morphological findings suggestive of malignancy	5-20	Appropriate additional imaging techniques (computed tomography or magnetic resonance imaging); surgical management
GI-RADS 5	Very probably malignant	Adnexal masses with ≥3 morphological findings suggestive of malignancy	>20	Appropriate additional imaging techniques (computed tomography or magnetic resonance imaging); surgical management

Thick papillary projections, thick septations, solid areas and/or ascites, defined according to IOTA criteria12, and vascularization within solid areas, papillary projections or central area of a solid tumor on color or power Doppler assessment5. Est. prob., estimated probability.

GI-RADS = Gynecology Imaging Reporting and Data System, NA = not applicable.

between the sonographer and the clinician often lead to unwarranted concern or interventions.[11] An approach has been taken to enable structured reporting of adnexal masses. In 2009, Amor et al,[12] developed the Gynecology Imaging Reporting and Data System (GI-RADS), which was based on the Brest Imaging Reporting and Data System (BI-RADS) classification. Prospective multicenter studies of GI-RADS were published in 2011 and 2017, respectively.[13,14] These studies found GI-RADS to be effective at identifying the malignant risk of adnexal masses.

This study aims to assess whether the test of CA125 leads to comparable clinical results in combination with GI-RADS. Thus, we can find a more valuable method in diagnosing ovarian cancer.

2. Materials and methods

A retrospective study was conducted for 325 patients diagnosed with suspected adnexal mass and received surgery at West China Second University Hospital, Chengdu, China, between September 1, 2016, and September 30, 2017. And all these patients were contacted by telephone to obtain verbal informed consent, and for children who were under 18 years old, we had obtained special consent from these children's guardians. The inclusion criteria were a primary clinical diagnosis of adnexal mass, and CA125 as well as ultrasonic data available before surgery, pathological data after surgery for final diagnosis. Patients with a history of gynecologic or other malignant tumors were excluded. The present study was approved by the Ethics Committee of Ethics Committee of the West China Medical School of Sichuan University.

All serum samples had been obtained preoperatively when they came to our hospital at the very start, and then the samples were stored at −70 °C. CA125 were analyzed using the ARCHITECT system [Abbott, ARCHITECT, Abbott Park, IL] according to the manufacturers' instructions. According to FIGO staging and previous reports,[15] we chose 35 U/ml as the cut-off of CA125.

Patients who received examination were evaluated by either transvaginal ultrasonography in the lithotomy position or transabdominal ultrasonography in the horizontal position (for maiden). Ultrasonography was performed using IU22 digital scanner (Philips Healthcare, Bothell, WA) and Voluson 730 machine (GE Medical Systems, Zipf, Austria) according to scanning protocol which was advanced determined.[12] Two independent sonographers who were attending doctors and experienced in the diagnosis of gynecologic conditions present in each examination. The images were evaluated and recorded by both sonographers, who were masked to the pathology results around the whole examination. If the scores were discordant, a third sonographer provided the consensus.

As shown in Table 1, morphological features which were considered suspicious malignant adnexal mass included thick wall and septum, solid papillary projection, solid areas, presence of ascites, and central blood flow.[16] Only central blood flow was used in the analysis of tumors that exhibited both peripheral and central blood flow. The GI-RADS method classifies adnexal masses into one of five categories that provide an estimate of malignancy risk and state how the lesion should be managed (Table 1).[12] The final results are determined by GI-RADS that provides an effective means of assessing the likelihood of malignancy.[12–14,16]

Final diagnosis was established through histological examination. We obtain accurate pathological diagnosis of tissue by surgery or biopsy. All patients were operated on by experienced gynecological surgeons. Pathological diagnosis and staging of tumors in accordance with WHO and FIGO criteria,[17] and in our study, borderline tumors were also included in the category of malignant tumors. STARD guidelines were followed for designing and conducting the study.[18]

The data were analyzed using SPSS version 23.0 (IBM, Armonk, NY). We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR−) of the CA125 single, GI-RADS single, as well as the combination of the both for identifying adnexal masses at high risk of malignancy. Continuous variables were described by the mean ± standard deviation. An independent sample t test was used to compare continuous variables. The χ^2 and Fisher exact tests were used for the univariate analysis of categorical variables. Logistic regression was applied in the multivariate analysis. Two-tailed P values of less than .05 were considered to be statistically significant. The relationship between the sensitivity and specificity of single diagnosis or combined diagnosis is reflected by measuring the areas under curve (AUCs), which can summarize the inherent capacity of a test to distinguish disease or not. The better the test, the closer the AUCs to 1, and the poor the test, the closer the

Table 2

CA125 and GI-RADS related to histology in ultrasonographically adnexal tumors.

Histology	n	CA125		GI-RADS	
		CA125<35 U/ml	CA125≥35 U/ml	GI-RADS2–3	GI-RADS4–5
Malignant	129				
Granulosa cell tumor	5	1	4	1	4
Immature teratoma	9	3	6	2	7
Yolk sac tumor	6	0	6	0	6
Asexual cell tumor	3	1	2	0	3
Serous adenocarcinoma	35	8	27	1	34
Mucous adenocarcinoma	9	3	6	2	7
Clear-cell adenocarcinoma	10	0	10	1	9
Endometrioid adenocarcinoma	5	2	3	2	3
Cystadenocarcinoma	10	6	4	3	7
Carcinosarcoma	1	0	1	0	1
Squamous-cell carcinoma	1	1	0	0	1
Spindle cell tumor	1	0	1	0	1
Mixed carcinoma	34	6	28	0	34
Benign	196				
Endometrioma	61	40	21	47	14
Serous cystadenoma	3	3	0	3	0
Mucinous Cystadenoma	17	16	1	16	1
Mature teratoma	103	90	13	102	1
Brenner tumor	1	1	0	1	0
Fibroma	9	4	5	8	1
Theca cell tumor	2	2	0	1	1

GI-RADS = Gynecology Imaging Reporting and Data System, CA125 = Cancer antigen, n = Number.

AUCs to 0.5,[19,20] and the statistical significance of the AUCs is compared by calculating the *P* value.

3. Results

The 325 women were included in our study who were diagnosed as adnexal masses in our hospital. The 129 cases were malignant, 196 cases were benign. As showed in Table 2, the malignant cases were verified by pathological diagnosis. All 29 adnexal masses classified as GI-RADS 5 were verified as malignant. We summarized the general characteristics of the patients as showed in Table 3, The mean age was 40 (range, 6–85) years old. The 85 (26%) women were postmenopausal and 240 (74%) were premenopausal. The 260 (80%) patients had prior sexual activity and 65 (20%) were virgo-intacta. The 75 (23%) patients had bilateral tumors and 250 (77%) had unilateral tumor. In malignant patients, 50 (39%) patients were in an early stage (I-II) and 79 (61%) women were in advanced stage (III-IV). Malignant tumors were more likely to occur in postmenopausal women (47.3%) than in premenopausal women (12.2%) ($P < .001$), patients with malignant tumors were older than patients with benign tumors ($P < .001$). Additionally, bilateral tumors were more often diagnosed as malignant than unilateral ones ($P = .008$).

Table 3

General characteristics of the patients (n = 325).

Characteristic	Final diagnosis		P	GI-RADS		P	CA125 (U/ml)		P
	Benign	Malignant		2–3	4–5		<35	≥35	
Age			<.001			<.001			<.001
<39	145	31		137	40		126	50	
≥39	51	98		53	95		61	88	
Postmenopausal			<.001			<.001			.308
No	172	68		168	72		149	91	
Yes	24	61		22	63		38	47	
Sex experience			.091			=.008			=.007
No	45	20		47	18		41	24	
Yes	151	109		143	117		146	114	
Bilateral involvement			=.008			=.041			<.001
No	161	89		154	96		167	83	
Yes	35	40		36	39		20	55	
FIGO									
I-II		50			43			30	
III-IV		79			74			68	

Values are given as number or number (percentage), unless indicated otherwise. Statistical comparisons with χ^2 test, unless indicated otherwise.
Values are given as mean ± standard deviation, unless indicated otherwise. Statistical comparison with independent *t* test.
GI-RADS = Gynecology Imaging Reporting and Data System, CA125 = Cancer antigen.

Table 4

Statistics of CA 125 in 325 women.

Final diagnosis	N of tumors classified as: CA125≥35 U/ml	CA125<35 U/ml	Total
Malignant	98	31	129
Benign	40	156	196
Total	138	187	325

CA125 = Cancer antigen, N = Number.

We collected the data of CA125 serum concentration before surgery. Of the 325 women, the level of CA125 serum concentration was significantly higher in malignant cases compared with benign cases as showed in Table 4, but the results indicated that there was no value in diagnosing the stage of ovarian cancer by CA125 serum concentration ($P = .059$) as showed in Table 5. The mean time from obtaining CA125 until surgery of patients with benign masses were both 3 days (CA125 < 35U/ml and CA125 ≥ 35U/ml), the mean time from obtaining CA125 until surgery of patients with malignant masses were both 9 days (CA125 < 35U/ml and CA125 ≥ 35U/ml). And there was no significant difference between them ($P = .877$ and .655, respectively).

The sensitivity for the CA125 serum concentration in predicting malignancy was 75.97% (95% CI, 67.50–82.86%), specificity was 79.59% (95% CI, 73.13–84.86%), positive predictive value (PPV) was 71.01% (95% CI, 62.58–78.26%), negative predictive value (NPV) was 83.42% (95% CI, 77.14–88.30%), positive likelihood ratio (LR+) was 3.72 (95% CI, 2.78–4.99), negative likelihood ratio (LR−) was 0.30 (95% CI, 0.22–0.41), accuracy rate was 78.15%, respectively (Table 6).

Then we collected the GI-RADS data. The results indicated that no benign tumors were classified as GI-RADS 5, but 18 benign tumors were classified as GI-RADS 4 all because of ascites. In total, 190 of the 325 cases were classified as GI-RADS 2–3, but, actually, 178 of these cases were confirmed as benign tumors diagnosed by pathologists. And of the 135 patients classified as GI-RADS 4–5, 18 were benign and 117 were malignantly diagnosed by pathologists (Table 7). Furthermore, as shown in Table 8, the results indicated the value of distinguishing the stage of ovarian cancer by GI-RADS ($P = .003$). The mean time from obtaining sonograms until surgery of patients with benign masses were 9 and 3 days respectively (GI-RADS 2–3 and GI-RADS 4–5), the mean time from obtaining sonograms until surgery of patients with malignant masses were 8.5 and 10 days, respectively (GI-RADS 2–3 and GI-RADS 4–5). Similarly, with the results of CA125, there was no significant difference between them ($P = .055$ and .871, respectively).

Table 5

FIGO stage according to CA125 serum concentration.

stage	N of tumors classified as: CA125≥35U/ml	CA125<35U/ml	Total
I-II	30	20	50
III-IV	68	11	79
Total	98	31	129

$P = .059$.
CA125 = Cancer antigen, N = Number.

Table 6

Diagnosis according to CA125 serum concentration.

Final diagnosis	n	CA125 (U/ml) Mean ± SD	Median	Range
Malignant	129	744.02 ± 1711.41	122.4	5.2–12000
Benign	196	31.11 ± 41.01	18.6	3.7–358.3

$P < .001$.
CA125 = Cancer antigen, SD = Standard deviation, n = Number.

Table 7

Statistics of GI-RADS in 325 women.

Final diagnosis	N of tumors classified as: GI-RADS 4–5	GI-RADS 2–3	Total
Malignant	117	12	129
Benign	18	178	196
Total	135	190	325

GI-RADS = Gynecology Imaging Reporting and Data System, N = Number.

The sensitivity for the GI-RADS in predicting malignancy was 90.70% (95% CI, 83.98–94.89%), specificity was 90.82% (95% CI, 85.65–94.31%), positive predictive value (PPV) was 90.91% (95% CI, 79.48–91.69%), negative predictive value (NPV) was 93.68%(95% CI, 88.97–96.54%), positive likelihood ratio (LR +) was 9.88 (95% CI, 6.35–15.39), negative likelihood ratio (LR−) was 0.10 (95% CI, 0.06–0.18), accuracy rate was 90.77%, respectively (Table 7).

Of the 325 women whose tumor diameter had been measured, 29 (9%) were classified as GI-RADS 2, 161 (50%) as GI-RADS 3, 120 (37%) as GI-RADS 4 and 15 (4%) as GI-RADS 5. There were no significant differences of diameters between tumors in the group of GI-RADS 2 and 3 or between tumors in the group of GI-RADS 4 and 5, but diameters of tumors in the group of GI-RADS 2 and 3 were significantly smaller than that in the group of GI-RADS 4 and 5 (Table 9).

Table 8

FIGO stage according to GI-RADS.

Stage	N of tumors classified as: GI-RADS 4–5	GI-RADS 2–3	Total
I-II	41	9	50
III-IV	77	2	79
Total	118	11	129

$P = .003$.
GI-RADS = Gynecology Imaging Reporting and Data System, N = Number.

Table 9

Tumor volume according to Gynecologic Imaging Report and Data System (GI-RADS).

	n	Tumor diameter (cm) Mean ± SD	Median	Range
GI-RADS 2[a]	29	8.17 ± 5.46	7	3–25
GI-RADS 3[b]	161	7.39 ± 4.04	7	3–30
GI-RADS 4[c]	120	12.41 ± 6.71	10	3–40
GI-RADS 5[d]	15	13.33 ± 4.01	13	8–20

a vs b: $P = .46379662$.
a vs c: $P = .00077690$.
a vs d: $P = .00104139$.
b vs c: $P = .00000000$.
b vs d: $P = .00004201$.
c vs d: $P = .44927717$.
GI-RADS = Gynecology Imaging Reporting and Data System, n = Number, SD = Standard deviation.

Table 10

Statistics of combined diagnosis.

	Malignant	Benign
CA125+/ GI-RADS 4–5	91	6
CA125+/ GI-RADS 2–3	7	34
CA125-/ GI-RADS 4–5	26	12
CA125-/ GI-RADS 2–3	5	144

GI-RADS = Gynecology Imaging Reporting and Data System, CA125 = Cancer antigen.

Then we combined the results of GI-RADS and CA125 for more accurate diagnosis. Among the 325 patients who received the both examinations (Table 10), we could see 91 cases were identified with GI-RADS 4–5 and CA125 ≥35 U/ml, 5 cases were identified with GI-RADS 2–3 and CA125 <35 U/ml in the malignant patients. And 6 cases were identified with GI-RADS 4–5 and CA125 ≥35 U/ml, and 144 cases were identified with GI-RADS 2–3 and CA125 <35 U/ml in the benign patient. We found the sensitivity of the combined analysis in predicting malignancy was 94.79% (95% CI, 87.70–98.07%), specificity was 96.00% (95% CI, 91.11–98.36%), positive predictive value (PPV) was 93.81%(95% CI, 86.50–97.46%), negative predictive value (NPV) was 96.64% (95% CI, 91.94–98.76%), positive likelihood ratio (LR+) was 15.17 (95% CI, 6.98–32.98), negative likelihood ratio (LR−) was 0.03 (95% CI, 0.01–0.08), accuracy rate was 95.53%, respectively. Compared with diagnosis of GI-RADS or CA125 single, the combined analysis of CA125 and GI-RADS was significantly superior to any single method.

For obtaining the Receiver operating characteristic (ROC) curve, we calculated the regression equation with two-regression analysis ($y = 2.911 \times \text{RADS} + 0.011 \times \text{CA125} - 11.391$) to get the result just as shown in Figure 1. Moreover, AUC for both CA125 and GI-RADS (0.931) was significantly higher in comparison to CA125 (0.893) or GI-RADS (0.835) alone in patients ($P < .001$).

4. Discussion

Ovarian cancer is the principal cause of death among all gynecological malignancies in women,[17,18,21] and it is often detected at advanced stage. Thus, we are badly in need of an effective method which can provide better accuracy for the diagnosis of ovarian cancer. But so far, the diagnosis of tumor marker, imaging or clinical examination are not satisfactory.[22,23] The purpose of this study was to evaluate the accuracy of the combination of serum CA 125 and GI-RADS in the evaluation of ovarian malignant tumors.

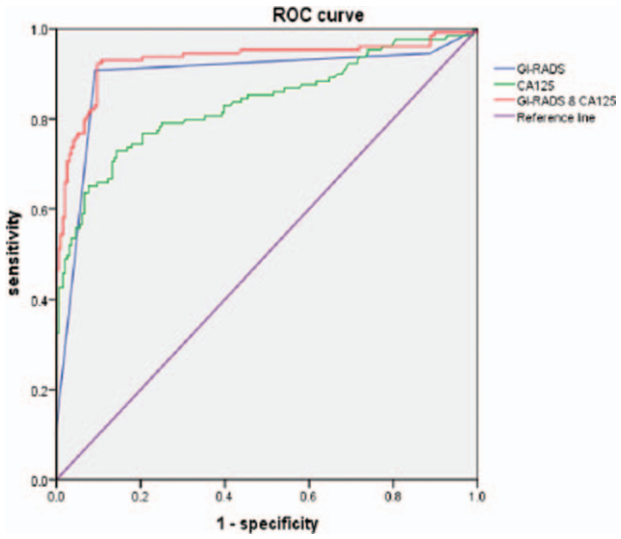

Figure 1. ROC curves of CA125, GI-RADS and combination of two diagnostic methods assessment for distinguishing malignant and benign ovarian masses.

As reported in the literature, serum CA 125 acted as a dominant method of detecting the risk of malignancy in patients with pelvic masses.[24] Our study confirmed that the concentration of serum CA125 in ovarian cancer patients differed from benign gynecologic diseases. Patients with ovarian cancer generally show higher level of CA125. But only relying on the CA125 did not show very accurate diagnosis and predictive value, so we combined a new diagnostic method with CA125.

With the developing of ultrasonics these years, it offered a more sensitive method for the routine detection of adnexal masses.[4,5] However, subjectivity was the unavoidable disadvantages of ultrasound. As a result, the Gynecology Imaging Reporting and Data System (GI-RADS) has been taken as an approach to enable structure reporting of adnexal masses these years.[12–14]

In our study, GI-RADS had high sensitivity and specificity in predicting the malignance of adnexal masses, and patients with advanced ovarian cancer presented with higher scores. But its positive or negative likelihood ratio was not very ideal. Furthermore, although ovarian fibroma usually could be difficult to classify because it often exhibited features which were suggestive of malignancy, relying on the judgment of the experienced sonologists, we could obtain more accurate results to reduce misdiagnosis rate. Among the false-positive masses, it showed the difficulty in classifying endometrioma because of its obvious pelvic effusion.

Finally, we combined CA125 with GI-RADS for the diagnosis of the ovarian cancer. Each index showed that combined diagnosis was better than any diagnostic method alone. In our study, combined diagnosis improved the accuracy of the diagnosis of ovarian tumors, the results of which were similar with the published literatures.[24–26]

As the morbidity of adnexal masses increases these years, clinicians should have a more accurate method to determine what kind of patients are at high risk of ovarian cancer. Our study shows that the combined diagnosis of CA125 and GI- RADS can improve the accurate discrimination between ovarian cancer and benign adnexal masses. These results suggest that this method can provide a better preoperative diagnosis for gynecologists.

Notwithstanding, there were some limitations in our study: the higher incidence of malignant tumors comparing to the general population is a possible selection bias, which may affect the estimation of sensitivity and specificity, but the results of PPV, NPV, LR+ and LR− are not affected by disease incidence. Another possible bias is that doctors who do ultrasound are experts with years of experience, it will potentially affect diagnostic performance.[27,28] Furthermore, as patients in our hospital usually did the preoperative examinations only a few days before the surgery, time from obtaining sonograms or CA125 until surgery were mostly within one month, the value of exploring the appropriate time for preoperative diagnostic examinations is limited. Finally, the cohort was small and derived from only one hospital, which could have bias related to different regions. Therefore, large-scale and multicenter studies are required in the future. Combined use of serum CA 125 and GI-RADS system improved the identification of adnexal masses

at high risk of malignancy and could be used for clinical decision-making.

Author contributions

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