

# Elevated serum CA 19-9 level, combined with D-dimer, could detect the presence of ruptured ovarian endometriosis

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## Research

**Keywords:** CA19-9, D-dimer, CA-125, Biomarker, Ruptured ovarian endometriosis

**DOI:** <https://doi.org/10.21203/rs.3.rs-34066/v1>

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# Abstract

**Background:** Ovarian endometriosis (OE) is a common type of endometrioma, which is a benign disease of gynecology. For the diagnosis of OE, ultrasonography is a very effective and straightforward. OE rupture is rare, and there is still a lack of a non-invasive and effective method for diagnosis. Elevated serum CA19-9 or CA-125 levels are typically applied as biomarkers for malignancy, besides, the CA-125 and CA19-9 levels have been recommended as a useful marker for the diagnosis of endometriosis. We aimed to clarify the clinical importance of serum CA19-9, CA-125 level, and plasma D-dimer (D-D) for detecting spontaneously ruptured ovarian endometriosis.

**Results:** Among the 21 patients of rupture OE, 16 with a history of detected pelvic cysts, 19 claimed sudden onset of lower abdominal pain, however, only 6 patients detected fluid accumulation in the cul-de-sac by ultrasound. For the serological investigation, the serum CA19-9 was significantly elevated in the ruptured OE group ( $343.09 \pm 367.67$  U/ml vs.  $36.84 \pm 40.01$  U/ml,  $P < 0.0001$ ). D-D was also abnormally elevated in the ruptured OE group ( $3.39 \pm 4.90$  mg/L vs.  $0.43 \pm 0.29$  mg/L,  $P < 0.0001$ ). The AUC value for the combined CA19-9 and D-D was 0.975 (95% CI, 0.939 - 0.993), with the highest specificity of 96.69, and sensitivity of 85.71.

**Conclusion:** The combination of serum CA19-9 and plasma D-D levels could serve as an effective biomarker to identify patients with spontaneously ruptured ovarian endometriosis pre-operatively in the context of clinical assessment.

## Background

Endometriosis, widely considered estrogen-dependent, is defined as the presence of active endometrial glands and stroma tissue outside of the uterus. Endometriosis usually causes chronic inflammation and infertility (1-3). In women of reproductive age, the incidence rate of endometriosis is 5–10%, and for infertile women, the prevalence of endometriosis may be as high as 50% (4, 5). Ovarian endometriosis (OE) is a common type of endometrioma. Jenkins et al. reported that the incidence of OE is as high as 17–44% in patients with endometriosis (6).

Elevated serum CA19-9 or CA-125 levels are typically applied as biomarkers for malignancy. CA19-9 was initially reported as an antigen associated with colorectal carcinoma and used as a biomarker for potential metastasis and malignant tumors (7). Lately, it was reported that the combination of CA19-9 and CEA, CA72-4, CA-125, and Ferritin could be used to diagnose colorectal cancer, appraise the tumor status and even evaluate the therapeutic effect (8). Besides, in advanced cases of ovarian malignancy, the level of CA 19-9 was also reportedly elevated (9). CA-125, another high molecular weight glycoprotein, is used as the first-line screen for ovarian cancer (10, 11). More recently, reports showed that the Symptom Index, along with CA-125 and HE4, had good performance statistics for predicting cancer in women with pelvic masses, and yielded acceptable specificity with higher sensitivity (12).

For the diagnosis of OE, ultrasonography is a very effective and straightforward (13); besides, the CA-125 and CA19-9 levels have been recommended as a useful marker for the diagnosis of endometriosis(14-16). However, OE rupture is rare, and there is still a lack of a non-invasive and effective method for diagnosis. Use of just ultrasonography could not confirm a ruptured OE. Moreover, the symptoms of OE are relatively non-specific, when compared with other gynecological acute abdominal diseases.

Some cases reported the phenomenon of extremely elevated serum CA 19-9 or CA-125 level in patients with ruptured OE (17-20); however, few studies focused on the diagnostic efficiency of ruptured OE in relationship to abnormally elevated CA-125 or CA19-9 levels(21). It is essential to discriminate ruptured benign OE—which showed an extremely higher expression of CA19-9 or CA-125—from malignant ovarian tumors (22) to eliminate patients' anxiety and, more importantly, guide the optimal surgical approach.

This retrospective study evaluated abnormally elevated serum CA-125 and CA 19-9 levels, and plasma levels of D-dimer (D-D) to provide an easy way for the noninvasively diagnose ruptured OE and help guide surgical planning.

## Results

### Measurement of clinical data in in the experimental and control groups

A total of 173 patients with OE were identified and retrospectively examined. Among these, 21 patients had spontaneously ruptured OE and were considered the experimental group. Of experimental group patients, seven were classified as early stage (I–II), and 15 exhibited advanced disease (III–IV). The 152 unruptured OE cases were defined as the control group; in this group, 59 patients were classified as early stage, while 93 exhibited advanced stage disease.

Both groups were similar in age. In the spontaneously ruptured (experimental) group, the mean age was  $33.0 \pm 7.3$ , while in the control group, the mean age was  $32.2 \pm 6.9$ . The measurement of CA-125, CA19-9, D-D, FIB, CA-153, and CA-724 levels in the experimental and control groups are shown in Table 1.

In the experimental group, the level of CA-125 was significantly elevated compared to the control group ( $852.51 \pm 1002.71$  U/ml vs.  $70.53 \pm 64.49$  U/ml,  $P < 0.0001$ ). The level of CA19-9 was also significantly elevated in the experimental group ( $343.09 \pm 367.67$  U/ml) compared to the control group [ $36.84 \pm 40.01$  U/ml ( $P < 0.0001$ )].

We also measured the expression of D-D and FIB routinely before surgery. For the experimental group, both D-D level and FIB were remarkably increased compared with the control group. To be specific, the experimental group D-D value was  $3.39 \pm 4.90$  mg/L vs.  $0.43 \pm 0.29$  mg/L in the control group ( $P < 0.0001$ ). Meanwhile, the level of FIB was  $6.42 \pm 6.44$  g/L in the experimental group and  $2.55 \pm 0.58$  g/L in the control group ( $P < 0.0001$ ).

### The difference of CA-125, CA19-9 levels, and plasma D-D in the experimental and control groups

We subdivided the experimental group into unilateral and bilateral cases. This group was also subdivided into early and advanced disease groups. We then analyzed the levels of CA-125, CA19-9, and D-D according to the various subgroups.

Our results showed no difference in CA-125 levels between the unilateral and bilateral subgroups ( $884.92 \pm 1039.83$  U/ml vs.  $658.00 \pm 892.96$  U/ml  $P=0.796$ ), with similar results for CA19-9 level ( $369.18 \pm 386.250$  U/ml vs.  $186.52 \pm 202.10$  U/ml,  $P=0.503$ ). For plasma D-D, there was no difference between the unilateral and bilateral subgroups ( $3.56 \pm 5.238$  mg/L vs.  $2.40 \pm 2.19$  mg/L,  $P=0.51$ ) (the results were shown in table 2).

When we compared patients with early versus advanced stage disease, we detected no differences in the levels of CA-125, CA19-9, or D-D. To be specific, the level of CA-125 was  $960.08 \pm 907.93$  U/ml (experimental) vs.  $786.31 \pm 1087.37$  U/ml (control;  $P=0.962$ ), CA19-9 was  $427.65 \pm 519.979$  U/ml (experimental) vs.  $291.05 \pm 244.72$  U/ml (control;  $P=0.271$ ), D-D was  $4.27 \pm 5.918$  mg/L (experimental) vs.  $1.98 \pm 2.177$  mg/L (control;  $P=0.242$ ) between the two groups (the results were shown in table 2).

### **Serum CA-125 and CA19-9 levels in the experimental and control groups**

We then explored the difference between CA-125 and CA19-9 levels in patients with different stages of unruptured OE, and differences between the unilateral and bilateral subgroups. Both levels of CA-125 and CA19-9 were much higher in the bilateral group compared to the unilateral group; however, the difference of CA-125 showed no significant difference ( $89.90 \pm 67.56$  U/ml vs.  $58.91 \pm 59.99$  U/ml  $P=0.095$ ), as showed in Table 3. Meanwhile, the level of CA19-9 was significantly higher in the bilateral group versus the unilateral group ( $47.09 \pm 51.72$  U/ml vs.  $30.69 \pm 29.60$  U/ml,  $P=0.036$ ).

The levels of CA-125 and CA19-9 were higher in patients with advanced stage vs. early stage disease. As shown in Table 3, the difference in CA-125 levels was significant ( $80.00 \pm 77.45$  U/ml vs.  $55.59 \pm 30.71$  U/ml,  $P=0.004$ ), while there was no significant difference in the CA19-9 levels ( $42.99 \pm 44.64$  U/ml vs.  $27.13 \pm 29.16$  U/ml  $P=0.093$ ).

### **Performance of serum concentration of CA-125, CA 19-9, and D-D in identifying the spontaneously ruptured OE.**

Finally, we applied a ROC curve to assess the importance of serum levels of CA-125, CA 19-9, and D-dimer for differentiating patients with spontaneously ruptured OE. The results were shown in Figure 1A, Table 4, and Supplementary Table 1.

The area under the curve (AUC) showed a statistically significant difference from the null hypothesis (AUC of 0.5), except for OE diameter (shown in Figure 1B and Table 4). To be specific, the AUC for CA-125 was 0.912 (95% CI, 0.859–0.950), while the sensitivity was 85.71, with a specificity of 85.53. The AUC for CA19-9 was 0.918 (95% CI, 0.867–0.955), with sensitivity and specificity of 80.95% and 94.08%, respectively. Besides, the AUC for D-D was 0.924 (95% CI, 0.874–0.959), with a sensitivity and specificity of 85.71% and 81.46%, respectively. The cut-off values of CA-125, CA19-9, and D-D were calculated as

108.1, 95.13, and 0.6, respectively, using MedCal version 19.05. Furthermore, we found the AUC value for the combination of CA19-9 and D-D was 0.975 (95% CI, 0.939–0.993), with the highest specificity of 96.69, and LR+ of 25.89 and LR– of 0.15, while the sensitivity was 85.71. The AUC for the diameter of OE was 0.514 (95% CI, 0.436–0.591), with a sensitivity of 66.67%, and a specificity of 21.33.

We then compared the ROC curves for each marker alone and in combination. The AUC value for CA-125 was G1, the AUC value for CA19-9 was G2, and the AUC value for D-D was G3. The AUC curve of the combined CA-125 and CA19-9, CA-125 and D-D, and CA19-9 and D-D were named G4, G5, and G6, respectively. We concluded that the AUC value for the combined CA19-9 and D-D was significantly higher compared to the AUC value of CA-199, CA-125, and D-D alone, respectively (S Table 1).

## Discussion

OE is a very common ovarian cyst in women of reproductive age, with patients often showing symptoms as secondary dysmenorrhea, dyspareunia, and even infertility. While endometriosis rupture is uncommon, it has not attracted enough attention. To our best knowledge, few studies have attempted to discriminate ruptured endometriosis from other conditions (21, 23). OE rupture could cause acute abdominal pain—even severe peritonitis—and over the long run, might cause adhesions and systemic disturbances which can decrease ovarian function (24). In this study, we found that the serum CA19-9 level, along with the D-D level, or CA-125 level along with the D-D level, could non-invasively indicate a preoperative diagnosis of spontaneously ruptured endometriosis.

CA19-9 was initially discovered as an antigen in colorectal carcinoma cells, and was found to be elevated in patients with malignant tumors, including colorectal carcinoma, [gastric cancer](#), [ovarian clear cell carcinoma](#)(9, 25, 26). CA-125, another high molecular weight glycoprotein, has been used as the first-line screen for ovarian cancer and applied as a biomarker for endometrial cancer (27) and breast cancer(28). Both CA-125 and CA19-9 levels could be abnormally elevated in patients with benign tumors (29). It widely accepted that the serum CA-125 level is a classic marker for the diagnosis of endometriosis (16, 30, 31). Moreover, elevated levels of CA19-9 in combination with CA-125, have also been examined for the evaluation of endometriosis severity. In 2002, Tatsuya Harada et al. found that serum CA19-9 levels were significantly higher in patients with endometriosis compared to patients without endometriosis. They also found that the increased serum CA19-9 levels correlated with endometriosis severity (15). Zehra Kurdoglu et al. claimed that serum CA19-9 was a valuable marker for diagnosing endometriosis, and could be used to identify patients with severe endometriosis when used with CA-125 (14). On the other hand, some studies claimed that patients with endometriosis had significantly higher levels of CA-125; however, these studies found that CA19-9 alone—or even in combination with CA-125—could not be used as biomarkers to discriminate between patients with or without endometriosis(32, 33).

More recently, some cases with unusually high serum levels of CA 19-9 or CA-125 in benign ovarian tumors were reported. In 2011, Yu-Hsin Huang reviewed the medical records of 11 patients with ruptured ovarian endometriotic cysts and found that four out of the six patients exhibited elevated CA-125 levels.

Moreover, one case showed an extremely elevated level which was higher than 2000 IU/mL (18). One year later, researchers found that patients with ruptured OEs showed serum CA-125 levels that were markedly elevated at 9391 IU/ml (17). Hitoshi Kurata reported a 23-year-old woman who suffered from ruptured OE with elevated concentrations of CA-125 (9537 IU/ml) and CA19-9 (15,653 IU/ml) (19). To our best knowledge, the last study was published in 2015. Here, Dai et al. found that serum CA-125 and CA19-9 were significantly increased in patients with spontaneously ruptured OE. They suggested CA-125 combined with CA19-9 showed better sensitivity and specificity for diagnosing spontaneous OE rupture (21).

It might be that, for patients with ruptured OE, the levels of CA 19-9 or CA-125 are unusually elevated. Because spontaneous OE rupture is rare, extremely high serum levels of CA 19-9 or CA-125 could indicate the presence of malignant ovarian tumors. It is essential to discriminate ruptured benign OE, which shows extremely high expressions of CA19-9 or CA-125 from malignant ovarian tumors so as to reduce patients' anxiety and guide surgical planning.

In this study, we focused on the phenomenon that patients with spontaneously ruptured OE showed unusually higher expression of both CA19-9 and CA-125. We found that the serum CA19-9 and CA-125 levels were significantly elevated in the ruptured OE group compared with the unruptured (control) OE group. However, in cases of ruptured endometriosis, we detected no difference in the level of either CA-125 or CA19-9 between subgroups of patients with early or advanced stage disease. We concluded the combination of CA-125 and CA19-9 could distinguish spontaneously ruptured OE from the unruptured group, the AUC for CA19-9 combined with CA-125 was 0.945 (95% CI, 0.899–0.974), with a sensitivity and specificity of 90.45% and 87.5%, respectively. Our results are in accordance with the findings which stated that the AUC value for the combined biomarkers of CA-125 and CA19-9 was 0.992 (95% CI, 0.981–1.000)(21).

At the same time, we focused on elevated serum D-D levels in patients with ruptured OE. D-D is a secondary product of polymerized fibrin that is degraded by plasmin after the process of blood coagulation. High plasma D-D levels usually indicate fibrinolytic activity. Early in 2003(34), Hiroshi Fujiwara reported a case with ruptured OE with rapid elevation in serum D-D. By applying immunohistochemical staining, they found that deposition of D-D in the endometriotic cyst wall and assumed the rapid elevation of serum D-D was a result of peritoneal absorption of cyst fluid from the ruptured OE which contains fibrin-degraded products, including D-D. In 2015, Kei Tanaka et al. (23) focused on the association between the elevated expression of D-D and the rupture of ovarian endometriotic cysts. They examined 22 cases of endometriotic cysts. Of these, six cases were ruptured, while 16 cases underwent planned surgery. They clarified that the elevated plasma D-D levels were associated with endometriotic cyst rupture, which was in accordance with our results. However, they found no difference in serum levels of CA-125 between patients with ruptured and unruptured cysts ( $163.6 \pm 126.4$  U/ml vs.  $86.1 \pm 87.5$  U/ml,  $P=0.12$ ). The authors did not measure the level of CA19-9. We assumed the contradictory result in regard to the level of CA-125 might be caused by the limited cases in their study.

In this study, for the ruptured endometriosis group, the D-D levels were remarkably increased compared to the control group. The AUC for the D-D was 0.924 (95% CI, 0.874–0.959), with sensitivity and specificity of 85.71% and 81.46%, respectively. To our knowledge, this is the first assertion that the combination of CA19-9 and D-D could be used as the most useful biomarker for the diagnosis of spontaneously ruptured OE (21, 23). Our results showed that the AUC value for the combined CA19-9 and D-D was 0.975 (95% CI, 0.939–0.993), with the highest specificity of 96.69, and LR+ of 25.89 and LR- of 0.15, while the sensitivity was 85.71. We found no difference as respect to OE diameter between patients with spontaneously ruptured OE and the control group ( $7.50 \pm 3.33$  U/ml vs.  $7.07 \pm 2.09$  U/ml,  $P=0.16$ ), which indicated a discrepancy from prior literature (21). We assumed that the rupture of OE cysts might be related to the diameter of the cyst and other factors such as external forces. Moreover, the different outcomes also might because of the limited number of spontaneously ruptured OE we collected.

## Conclusion

In conclusion, the combination of serum CA-199 and plasma D-D levels can be applied as a useful marker to identify patients with spontaneously ruptured OE pre-operatively. This might emerge as an easier way of determining if emergency surgery is required and to plan the appropriate surgical approach. However, we did not find a difference in OE diameter between patients with spontaneously ruptured OE and the control group. Besides the application of serum CA19-9 level and CA-125 levels alone; surgeons should consider plasma D-D levels to estimate the presence or absence of ruptured OE. Our study was obviously limited by its retrospective design; in the future, a multi-center study featuring a larger sample size should be considered to clarify our conclusions.

## Methods

### Patients

The Ethics Committee of the First Affiliated Hospital of Xi'an Jiao Tong University approved our study. All the patients recruited either underwent laparotomy or laparoscopy. The revised classification made in the year 1985 by the American Society for Reproductive Medicine (ASRM), was applied to diagnose and classify the patients.

The inclusion criteria were: (i) aged 21–45 years, (ii) underwent surgery via either laparotomy or laparoscopic procedure. Exclusion criteria were: (i) patients with suspected malignant ovarian or other tumors, (ii) patients with a diagnosis of myoma, adenomyosis, or pelvic inflammatory disease, (iii) patients with a history of deep venous thrombosis of the lower limbs.

### Tumor marker test and coagulation function test

Venous blood samples were collected from all patients before surgery and tested for serum CA-125, CA19-9, CA72-4, and CA153. Blood coagulation, including plasma D-D, FIB, was also tested before surgery. Serum CA19-9 and CA-125 levels were measured using a Roche electro-chemiluminescence

immunoassay (Roche Co., COBAS e 602, Mannheim, Germany) with the CA19-9 test Kit (Roche Co., YZB/GER 5395-2014) and CA-125 test Kit (Roche Co., YZB/GER 1568-2015), following manufacturer's instructions. The normal reference value of CA19-9 were 0–39 U/ml, and the normal reference range for CA-125 was 0–35 U/ml, with above the upper limit considered positive. The detection of D-D was performed by Latex immunoturbidimetry (SYSMEXM, CS-5100, Tokyo, Japan) using a D-D test kit (SEKISUI Co., GS1-128) following the manufacturer's instructions. The normal reference value of D-D was 0–1.0 mg/L.

## **Statistical methods**

Data were examined using the Statistical Package for the Social Sciences software package (SPSS Statistics ver. 17.0). Levels of serum CA19-9, CA-125, and D-D were treated as continuous data and are expressed as means with standard deviations (SDs). The ages of the patients and the diameter of the OE were also continuous data and were expressed as means with SDs. An unpaired t-test was used to compare individual markers between the ruptured and control groups. To clarify the importance of serum levels of CA-125, CA19-9, and D-D for the identification of ruptured endometriosis, a receiver operating characteristic (ROC) curve analysis was applied. The sensitivity, specificity, and positive and negative predictive values were calculated using the SPSS Statistics version 17.0. Further, the cutoff value depended on the Youden index of each marker and was assessed using area under the ROC curve (AUC) as determined by MedCal software, version 19.05. *P* values less than 0.05 were considered statistically significant.

## **Abbreviations**

OE: Ovarian endometriosis; D-D: D-dimer; AUC: Area under the curve; ASRM: American Society for Reproductive Medicine; SDs: Standard deviations; ROC: Receiver operating characteristic

## **Declarations**

### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

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

### **Competing interests**

The authors declare that they have no competing interests.

## Funding

This work was supported by the Shaanxi Provincial Collaborative Technology Innovation Plan (2017XT-026, 2017ZDXM-SF-068, 2017ZDJC-11, 2018XT-002, 2019QYPY-138). None of the funding bodies had any part in the design of the study and interpretation of data.

## Authors' contributions

QL, TS and LZ devised the conceptual idea. KZ, YW and PY executed the work, TS wrote the manuscript. LG, WJ and XF critically reviewed the manuscript. All authors contributed to the revision of the manuscript and approved its final version.

## Acknowledgements

The authors wish to thank the participating infertile women as well as all doctors, nurses and laboratory staff employed at the First Affiliated Hospital, Xi'an Jiaotong University.

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## Tables

**Table 1. Analysis of clinical value in the ruptured OE group and control group.**

	Ruptured OE	Unruptured OE	P
Numbers of patients	21	152	
Age	33.0±7.3	32.2 ±6.9	NS
CA-125 (U/ml) (mean ± SD)	852.50±1002.70	70.53±64.49	0.0001
D-dimer	3.40±4.90	0.43 ± 0.29	0.0001
FIB	6.41±6.44	2.54±0.58	0.0001
CA19-9 (U/ml) (mean ± SD)	343.09±367.67	36.84±40.01	0.0001
CA-724(ng/ml) (mean ± SD)	13.13±16.80	6.80±11.71	0.034
CA-153 (ng/ml) (mean ± SD)	22.91 ± 13.40	11.51 ± 8.03	0.0001
Diameter (cm) (mean ± SD)	7.51 ±3.33	7.07 ±2.09	0.16

**Table 2. Level of CA-125, CA19-9 and D-dimer in the ruptured OE group**

Side of occurrence	CA-125 (U/ml) (mean ± SD)	CA19-9 (U/ml) (mean ± SD)	D-dimer (mean ± SD)
Unilateral	884.92±1039.83	369.18±386.25	3.56±5.24
Bilateral	658.00±892.96	186.52±202.10	2.40±2.19
P	0.796	0.503	0.51
Stage			
Minimal to mild(I-II)	960.08±907.93	427.65±519.98	1.98 ± 2.18
Moderate to severe (III-IV)	786.31±1087.37	291.05±244.72	4.27 ± 5.92
P	0.962	0.271	0.242

**Table 3. Level of CA-125 and CA19-9 in the unruptured OE group**

Side of occurrence	CA-125 (U/ml) (mean ± SD)	CA19-9 (U/ml) (mean ± SD)
Unilateral	58.91±59.99	30.69±29.60
Bilateral	89.89±67.56	47.09±51.72
P	0.095	0.036
Stage		
Minimal to mild(I-II)	55.59± 30.71	27.13± 29.16
Moderate to severe (III-IV)	80.00±77.45	43.00±44.64
P	0.004	0.093

**Table 4. Performance of serum concentration of CA-125, CA19-9 and D-dimer in distinguishing the ruptured ovarian endometriosis**

## Figures

	AUC	AUC CI)	(95% Youden index J	Cut off value	Sensitivity (%)	Specificity (%)	+LR	-LR	P Value
CA-125	0.912	0.859 - 0.950	0.7124	108.1	85.71	85.53	5.92	0.17	<0.0001
CA19-9	0.918	0.867 - 0.955	0.7503	95.13	80.95	94.08	13.67	0.2	<0.0001
D-dimer	0.924	0.874 - 0.959	0.6717	0.6	85.71	81.46	4.62	0.18	<0.0001
CA-125+CA19-9	0.945	0.899 - 0.974	0.7798	-	90.48	87.5	7.24	0.11	<0.0001
CA-125+D-dimer	0.964	0.924 - 0.986	0.7789	-	90.48	87.42	7.19	0.11	<0.0001
CA19-9+D-dimer	0.975	0.939 - 0.993	0.824	-	85.71	96.69	25.89	0.15	<0.0001
Diameter	0.514	0.436 to 0.591	0.1200	5.7	66.67	21.33	-	-	0.8510

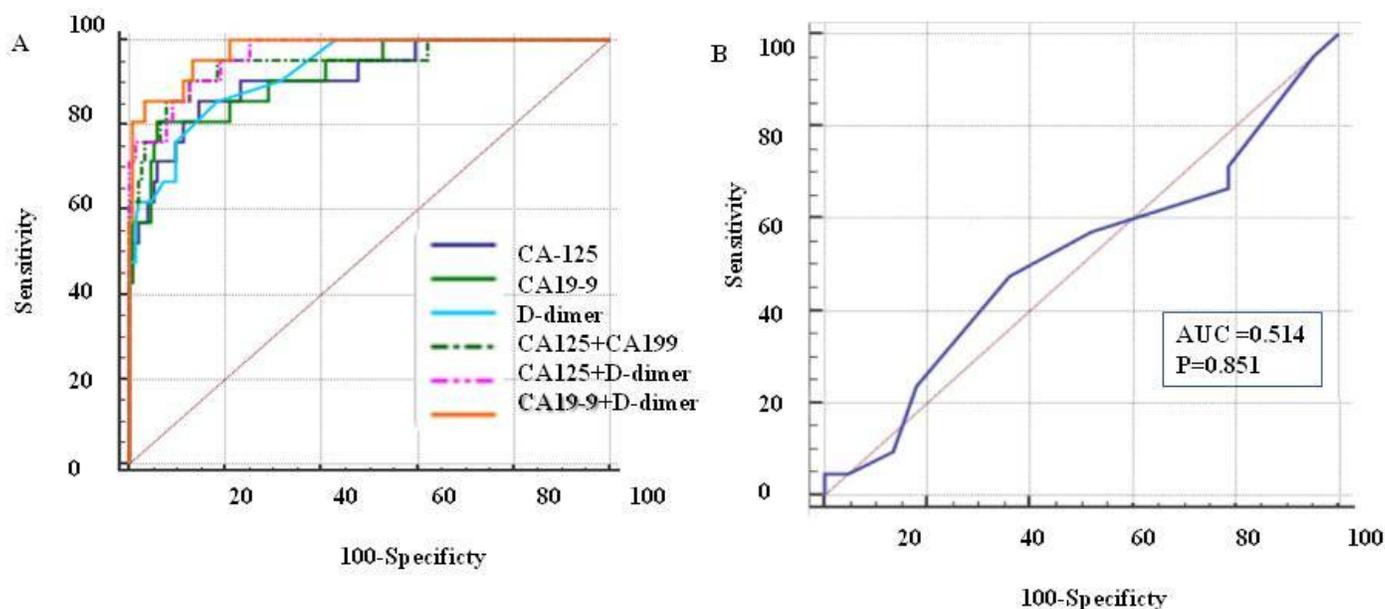


Figure 1 Shuang, et al.

## Figure 1

A. Receiver operating characteristics curve for identification of ruptured OE for CA-125, CA 19-9, D-dimer, CA-125 combined with CA19-9, CA-125 combined with D-dimer, CA19-9 combined with D-dimer respectively. B. Receiver operating characteristics curve for identification of ruptured OE for cyst diameter.

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