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Diagnostic Value of Serum D-Dimer Level for Tubo-Ovarian Abscess: A Cross-Sectional Pilot Study

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Abstract

Aim of this study is to investigate the diagnostic role of serum D-dimer levels for tubo-ovarian abscess (TOA). Patients diagnosed with TOA (n = 36) and matched controls with ovarian cysts (n = 39) were collected prospectively. Patients in the 2 groups were compared on the basis of size of TOA or cyst, demographic characteristics, and serum D-dimer levels. Baseline characteristics of both groups were comparable. Mean D-dimer levels were significantly higher ($P < .0001$) in patients with TOA (1870.6 ± 2401.7 ng/mL) when compared to adnexal cyst group (164.4 ± 81.1 ng/mL). D-Dimer had a diagnostic value of 99.9%, specificity of 100.0%, and sensitivity of 97.4% based on a cutoff value 314 ng/mL for predicting TOA. In conclusion, serum D-dimer level was significantly elevated in women with TOA compared with benign adnexal cysts. Thus, this inexpensive, feasible, and reproducible marker can be used for differential diagnosis of TOA.

Keywords

pelvic inflammatory disease, tubo-ovarian abscess, D-dimer, ovarian cyst

Introduction

A tubo-ovarian abscess (TOA) is an inflammatory mass involving the fallopian tube, ovary, and, occasionally, other adjacent pelvic organs (eg, bowel and bladder).[1] Tubo-ovarian abscesses most frequently result from upper genital tract infection, usually pelvic inflammatory disease (PID). A TOA may also arise from local spread of infection associated with uncontrolled inflammatory diseases of the bowel, appendicitis, and adnexal surgery or, occasionally, from hematologic spread.

Pelvic inflammatory disease represents a spectrum of clinical disease, from endometritis to fatal intra-abdominal sepsis. There are multiple gold standards (clinical examination, laboratory tests, imaging techniques, and laparoscopy) in use to establish the diagnosis. Many diagnostic markers were investigated such as the density of the plasma cell infiltrate correlated with the clinical severity of disease or inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[2,3] But none of them was found adequate alone. Furthermore, none of these tests is highly specific and sensitive. However, D-dimer was also described as a new diagnostic marker.[4,5]

D-Dimer is one of the major fibrin degradation products, which is generated by fibrin monomers of activated factor XIII crosslinks. Elevated plasma concentrations of D-dimer designates recent or ongoing intravascular blood coagulation and such high levels were demonstrated in many clinical conditions such as arterial and venous thromboembolic disease, disseminated intravascular coagulation, malignancy, renal, and liver diseases.[6-10]

The aim of this study was to compare serum D-dimer levels of patients with TOA and matched controls with ovarian cysts and to investigate the accuracy of serum D-dimer levels for the diagnosis of TOA.

Materials and Methods

This study was conducted at Department of Obstetrics and Gynecology, Izmir Katip Celebi University Ataturk Training and Research Hospital between October 2012 and August

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2013. The study was approved by local ethics committee, and all women gave written informed consent.

Inclusion criteria were (1) ultrasonographically confirmed pelvic mass (ovarian cyst or TOA), (2) lack of thromboembolic diseases, and (3) pelvic pain requiring hospitalization. A total of 75 patients were prospectively collected. The patients were grouped as adnexal cyst group (n = 39) and TOA group (n = 36). Tubo-ovarian abscess was diagnosed clinically by detecting cervical motion tenderness or uterine or adnexal tenderness in the presence of lower abdominal or pelvic pain and also presence of 1 or more of the following findings: fever (38°C or more), leukocyte count of more than 10.000/mL, and ESR of more than 15 mm/h in addition to adnexal mass detected by ultrasonography.[11] Blood samples were taken from all patients on admission to detect serum D-dimer levels using the kit, HemosIL HS D-dimer (Instrumentation Laboratories, Lexington, Massachusetts). Demographic characteristics such as age, body mass index (BMI), parity, marital status, and contraceptive use were recorded.

The patients in TOA group initially presenting positive peritoneal signs underwent laparatomy. However, hemodynamically stable patients with no signs of ruptured TOA (acute abdomen and sepsis) were initially treated with a second-generation cephalosporin combined with clindamycin plus gentamicin. Failure criteria for medical treatment were emergence of positive peritoneal signs or the persistence of high fever after 72 hours of antibiotic therapy. According to these criteria, 10 (27.8%) of the 36 patients in TOA group underwent surgery, whereas 26 (72.2%) patients were medically treated.

The Med Calc ver 9.3 software was used for the statistical analysis. Data are presented as means ± standard deviations and percentages. The normality of the continuous variable distribution was assessed with Kolmogorov-Smirnov test. A chi-square analysis was used to analyze categorical variables, Student *t* test was used for normally distributed variables, and the Mann-Whitney *U* test was used for abnormally distributed variables. Relative risks with 95% confidence intervals were calculated. A *P* value <.05 was considered to indicate statistical significance. A receiver–operating characteristic (ROC) curve was used to evaluate cutoff, sensitivity, and specificity values.

Results

The mean age of patients in adnexal cyst group was 37.4 ± 12.1 versus 35.7 ± 8.9 years in TOA group as shown in Table 1 ($P = .70$). Moreover, other baseline demographic characteristics were similar between the 2 groups except for marital status and contraceptive use. Intrauterine device use as a contraceptive method in patients with TOA was 3-fold higher than those women with adnexal cyst ($P = .001$). Furthermore, there was statistically significant difference regarding serum D-dimer levels between patients with TOA (1870.6 ± 2401.7 ng/mL) and adnexal cyst (164.4 ± 81.1 ng/mL; $P < .0001$; Table 1).

The D-dimer values were then analyzed to predict sensitivity and specificity. The results were plotted on an ROC curve (Figure 1). D-Dimer had a diagnostic value of 99.9%, specificity of 100.0%, and sensitivity of 97.4% based on a cutoff value of 314 ng/mL for predicting TOA ($P < .0001$, area under curve [AUC]: 99.9).

Table 1. Demographic and Clinical Characteristics of the Groups.[a]

	Adnexal Cyst Group (n = 39)	TOA Group (n = 36)	*P* Value
Age, year	37.4 ± 12.1	35.7 ± 8.9	.70
Body mass index, kg/m^2	25.1 ± 5.0	24.7 ± 4.6	.70
Parity, n	1.1 ± 1.1	1.4 ± 1.0	.31
Marital status, n			.02
Single	8 (20.5)	1 (2.8)	
Married	31 (79.5)	35 (97.2)	
Mean diameter of cyst, cm	5.6 ± 2.0	5.7 ± 2.0	.74
Contraceptive use, n			.001
None	17 (54.8)	11 (31.4)	
Condom	8 (25.8)	2 (5.7)	
Intrauterine device	6 (19.4)	22 (62.9)	
D-Dimer, ng/mL	164.4 ± 81.1	1870.6 ± 2401.7	<.0001
Requiring surgery, n	12 (30.8)	10 (27.8)	.80

Abbreviation: TOA, tubo-ovarian abscess.
[a]Values are mean ± standard deviation or number (%).

Table 2 shows the comparison of patients who underwent surgery (surgery subgroup) or received only medical therapy (nonsurgery subgroup) in TOA group. Of the 36 patients, 10 (27.8%) underwent surgery initially or after appearance of positive peritoneal signs or failure of medical treatment. Although mean serum D-dimer level of patients in surgery subgroup (2024.7 ± 2989.4 ng/mL) was higher than those of nonsurgery subgroup (1803.2 ± 2200.3), the difference was not statistically significant ($P = .39$). However, BMI of patients in surgery subgroup was statistically significantly higher ($P = .004$) than patients in nonsurgery subgroup. Moreover, the D-dimer values were reanalyzed to predict sensitivity and specificity in order to make the clinical decision regarding treatment of TOA. The results were plotted on a ROC curve (Figure 2). D-Dimer had a diagnostic value of 59%, with a sensitivity of 57.6% and specificity of 80.3% based on a cutoff value of 1037 ng/mL for making clinical decision ($P = .39$, AUC = 59.0%).

Discussion

The aim of this study was to show diagnostic value of serum D-dimer level for TOA, which is an inflammatory mass involving the fallopian tube, ovary, and occasionally, other adjacent pelvic organs. Findings indicated that serum D-dimer level was a highly specific and sensitive diagnostic predictor of TOA. However, in the discrimination of surgery decision, serum D-dimer level cannot be used as a convenient marker.

Threshold of suspicion for the diagnosis of PID should be low, since a delay in treatment might cause long-term

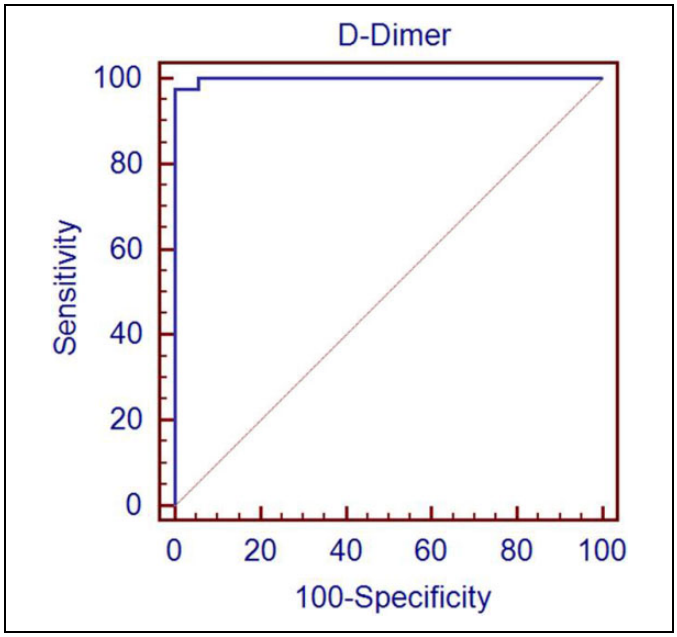

Figure 1. Receiver–operating characteristic (ROC) curves for D-dimer used to make the clinical decision regarding diagnosis of a tubo-ovarian abscess (the areas under the ROC was 99.9).

complications. As PID is a polymicrobial infection (including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*), broad-spectrum antibiotic coverage is indicated particularly for those with severe disease requiring hospitalization. Indications for hospitalization and parenteral antibiotics are pregnancy, lack of response or tolerance to oral medications, nonadherence to therapy, inability to take oral medications due to nausea and vomiting, severe clinical illness (high fever, nausea, vomiting, and severe abdominal pain), complicated PID with pelvic abscess (including TOA), possible need for surgical intervention, or diagnostic exploration for alternative etiology (eg, appendicitis).[11]

Diagnosis of PID can be difficult because of the wide variation in the symptoms and signs, ranging from minimal or mild symptoms to severe pain in the pelvis. Clinical diagnosis alone has only 87% sensitivity and 50% specificity.[12] Therefore, identifying biological markers that are useful for early diagnosis and correlating their expression with the severity of PID could provide significant benefits to patients having PID.

Noninvasive diagnostic tests for PID include general laboratory studies looking for signs of inflammation, culture testing and microscopy of cervical or vaginal secretions, and imaging studies. But according to meta-analysis, there was no single test or combination that was both sensitive and specific for the diagnosis of PID.[13]

C-reactive protein, first and most commonly used biomarker in daily practice for diagnosis of PID, has overall sensitivity and specificity of 74% and 67%, respectively, using a cutoff level of 2.0 mg/dL.[14] Although sensitive, nonspecific nature of CRP limits its clinical use. Thus, it is necessary to identify biological markers that could be used for early diagnosis and

Table 2. Demographic and Clinical Characteristics of the TOA Group According to Therapy.[a]

	Surgery Subgroup (n = 10)	Nonsurgery Subgroup (n = 26)	*P* Value
Age, year	35.2 ± 9.9	35.9 ± 8.7	.81
Body mass index, kg/m^2	28.2 ± 3.6	23.3 ± 4.3	.004
Parity, n	1.7 ± 1.2	1.3 ± 0.9	.42
Marital status, n			.27
Single	1 (20.5)	–	
Married	9 (90.0)	26 (100.0)	
Mean diameter of cyst, cm	6.7 ± 2.0	5.4 ± 1.9	.06
Contraceptive use, n			.65
None	3 (30.0)	8 (30.8)	
Condom	–	2 (7.7)	
Intrauterine device, n	7 (70.0)	16 (61.5)	
D-Dimer, ng/mL	2024.7 ± 2989.4	1803.2 ± 2200.3	.39

Abbreviation: TOA, tubo-ovarian abscess.
[a]Values are mean ± standard deviation or number (%).

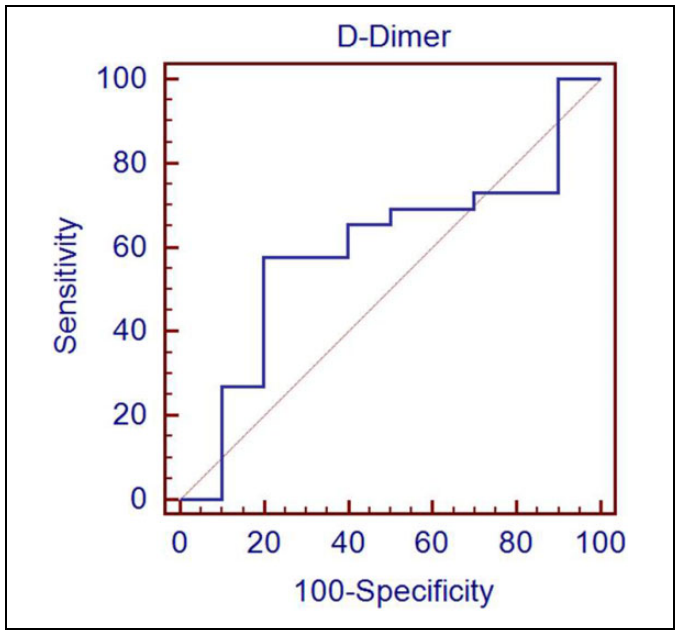

Figure 2. Receiver–operating characteristic (ROC) curves for D-dimer used to make the clinical decision regarding treatment of a tubo-ovarian abscess (the areas under the ROC was 59.0).

correlate their expression levels with the severity of PID.[15] Sensitivity and specificity of recently investigated biomarkers are as follows: 84.4% and 81.4% for pentraxin 3,[16] 76.6% and 57.1% for neutrophil gelatinase-associated lipocalin,[17] 92.2% and 42.9% for Gas6 and sAxl, plasma growth arrest-specific 6 and its soluble tyrosine kinase receptor,[18] 82.3% and 60.0% for osteopontin,[19] and 76.6% and 65.0% for the matrix metalloproteinase 9.[20] Moreover, plasma stromal cell-derived factor 1α level is elevated in patients with PID.[21]

The D-dimer test indicates whether or not there is activation of the fibrinolytic system. Since D-dimer is generated from cross-linked fibrin, but not from fibrinogen, an elevated plasma concentration of D-dimer indicates recent or ongoing intravascular blood coagulation.[22] In the first study, Franchi et al demonstrated that D-dimer level was a useful parameter, which appears to correlate with the severity of PID.[4] In that study, patients were therefore divided into 3 groups, namely, women being treated only by medical therapy, women undergoing conservative surgery, and women undergoing destructive surgery. They demonstrated that D-dimer values were altered in severe PID forms and the median of D-dimer values in the 3 groups was significantly different. In particular, for patients who underwent destructive surgery, it was more than double that of medically treated patients.

In a study conducted by Patrelli et al, patients with TOA were divided into 3 groups as medical therapy only, conservative surgery, and destructive surgery (surgical procedures that impaired fertility) group.[5] Data from the 3 groups were compared with respect to general and medical history data, clinical signs on admission, laboratory tests, and ultrasound findings. The CRP and D-dimer values most likely correlated with disease severity. Ultrasound evidence of ovaritis generally led to medical therapy. Conversely, when sonography revealed pyosalpinx or TOAs, surgery was performed. They concluded that clinical presentation is fundamental in diagnostic counseling but should be supplemented with further laboratory tests to detect inflammation and sonograms. However, CRP and D-dimer levels appear indicative of the need for surgical treatment. In our study, we could not detect such a statistically significant level in clinical management decision by means of D-dimer level. It might be due to our limited number of surgery subgroup patients in the TOA group.

D-Dimer levels were searched for many purposes. In a case report, acute elevation in plasma D-dimer level was found to be associated with rupture of ovarian endometriotic cyst.[23] In another study, plasma D-dimer levels were used to help discriminate between patients with benign and malignant tumors.[24] They concluded that D-dimer alone differentiated malignant from benign ovarian tumors and also improved differentiation when combined with CA-125. In a previous study, a high preoperative plasma D-dimer level was associated with shorter postoperative survival, and the presence of vascular invasion was associated with higher preoperative D-dimer levels.[25] Moreover, in our previous case with extended pelvic abscesses confirmed at operation, the patient had extremely elevated preoperative serum D-dimer level (10 500 ng/mL).[26]

There are some limitations in the present study such as the limited number of patients underwent surgery for TOA. The data collected from surgery group might be improved in further studies. The lack of data in adnexal cyst group management is another limitation of current study. Also, clinical condition of patients at admission requiring medical therapy but not urgent surgical interventions might lead to different serum D-dimer levels in TOA therapy subgroups.

In conclusion, serum D-dimer level is a very sensitive and specific marker in order to detect TOA. Thus, this inexpensive, feasible, and reproducible marker can be used for differential diagnosis of TOA. However, its use in making clinical decision for medical or surgical treatment of TOA needs further investigations.

Authors' Note

Bulent Yilmaz contributed to conceiving the study design and writing the article. Burcu Kasap contributed to writing and drafting the article. Mustafa Demir contributed to data collection and critical revision of the article. Kemal Gungorduk carried out statistical analyses and drafted the article. Sefa Kelekci conceived design and data collection. Recep Sutcu analyzed the biochemical biomarkers and contributed to critical revision of the article. This study was exhibited as a poster presentation at Ovarian Club III Congress, Novotel Tour Eiffel Hotel, Paris, November 14-16, 2013.

Declaration of Conflicting Interests

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