

Relation of Tumor Necrosis Factor Alpha and Ruptured Ectopic Pregnancy

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Abstract—Background: Ectopic pregnancy is a potentially life-threatening condition in which a fertilized ovum implants outside the uterine cavity. An ectopic pregnancy's rupture can cause serious hemorrhage, shock, and maternal morbidity. Tumor necrosis factor-alpha, a pro-inflammatory cytokine may play a role in the pathophysiology of tubal rupture, but its predictive value remains unclear. **Aim of the study:** To evaluate the level of TNF-alpha in cases of ruptured ectopic pregnancy. **Patients and methods:** Prospective observational study included 100 women diagnosed with ectopic pregnancy at Babil Teaching Hospital for Maternity and Children, Iraq, from January to August 2025. Patients were divided into two groups according to whether the pregnancy had ruptured or not, with diagnosis confirmed surgically. Serum tumor necrosis factor-alpha levels were measured using a commercial enzyme-linked immunosorbent assay kit. Clinical presentation, ultrasound findings, and laboratory data were recorded. **Results:** The mean serum level of tumor necrosis factor-alpha was significantly higher in women with ruptured ectopic pregnancy (25.6 ± 7.8 pg/mL) compared with women with unruptured ectopic pregnancy (15.3 ± 5.9 pg/mL; $p < 0.001$). Receiver operating characteristic curve showed good ability for tumor necrosis factor alpha in predicting rupture, with an area under the curve of 0.87. Using a cut-off value of 17.8 pg/mL, sensitivity was 80.1%, specificity 82.3%, positive predictive value 79.2%, negative predictive value 82.7%, and overall diagnostic accuracy 81%. **Conclusions:** Serum tumor necrosis factor-alpha levels were significantly elevated in ruptured ectopic pregnancy and demonstrate high diagnostic performance.

Keywords— TNF-alpha, Ruptured, Ruptured Ectopic Pregnancy.

I. INTRODUCTION

1. Ectopic pregnancy definition and background

Ectopic pregnancy is when a fertilized egg implants outside the uterus, most frequently in the fallopian tubes (around 97.7%). The ampulla is the most common site of implantation (80%), followed by the isthmus (12%), fimbria (5%), cornua (2%), and interstitia (2–3%). Lawani OL et al., 2019.

Abdominal pregnancies make up 1.4% of all ectopic pregnancies, while cervical and ovarian sites each make up 0.2%, making nontubal ectopic pregnancies uncommon. Some ectopic pregnancies implant in the cervix (< 1%), in previous cesarean delivery scars, or in a rudimentary uterine horn; although these may be technically in the uterus, they are not considered normal intrauterine pregnancies. (DI Gennaro D et al., 2022).

When a corpus luteum is present, around 80% of ectopic pregnancies are discovered on the same side. Gaskins LJ et al., 2018.

The pregnancy develops and obtains its blood supply from the location of aberrant implantation; the word ectopic comes from the Greek word ektopos, which means out of place. The pregnancy's growth increases the possibility of organ rupture since only the uterine cavity is intended to expand and support fetal development. Massive hemorrhage, tubal injury, or death may result from an ectopic pregnancy. (Rana P et al., 2019)

The understanding and management of ectopic pregnancy have evolved from being a near-certain fatality in the 19th century to a condition that can be managed effectively today. (Orazulike NC et al., 2018)

2. Epidemiology

Ectopic pregnancies constitute about 1-2% of all pregnancies. The incidence is influenced by factors like pelvic inflammatory disease, prior pelvic surgeries, and the use of fertility treatments, with a noted increase in developed countries due to assisted reproductive technologies. (Tulandi T et al., 2019)

Since 1970, the incidence of ectopic pregnancy in the U.S. has increased sixfold. Originally, it was 4.5 cases per 1000 pregnancies; it now accounts for 1-2% of all pregnancies. The prevalence is roughly 1 in 40 pregnancies or about 25 cases per 1000 pregnancies, as reported by the CDC. (Mann LM et al., 2020)

Similar increases in ectopic pregnancy incidents were observed globally during the same period. In Africa, estimates vary widely from 1.1% to 4.6%, based on hospital data. (Zhang S et al., 2023).

With an adjusted odds ratio of 2.9 for ectopic pregnancy, women over the age of 40 have a much greater risk. Rombauts L et al. (2018).

Local estimation in Iraq found an ectopic pregnancy incidence rate of 2.217 per 1000 of the population at risk. (Yahya SA et al., 2020).

Complications of Ectopic Pregnancy

Ectopic pregnancy poses a significant risk to maternal health, particularly when it becomes ruptured and leads to hemorrhage. The complications can be acute and life-threatening, highlighting the importance of timely diagnosis and management. Complications include:

- **Collapse and Hypovolemic Shock:** When an ectopic pregnancy ruptures—most commonly in the fallopian tube—patients can experience profound intraperitoneal bleeding. This may result in dizziness, tachycardia, hypotension, and signs of peritoneal irritation, all of which

reflect potential hemorrhagic shock. (Rojas-Luengas V et al., 2019)

- Increased Risk of Future Infertility: Surgical intervention, tubal scarring, or salpingectomy can compromise future fertility. A past ectopic pregnancy also markedly elevates the probability of another ectopic event, which can further complicate reproductive outcomes. (Cirillo F et al., 2022)
- Maternal Mortality: Although modern advances in diagnostic techniques and treatment have reduced the case fatality rate, an unrecognized or untreated rupture can be fatal, especially in settings with limited resources. (Pontius E et al., 2019)
- Psychological and Emotional Impact: Beyond the physical risks, women may experience anxiety, depression, or grief following the loss of a pregnancy, surgical intervention, or concern about future fertility. (Ren N et al., 2023)

TNF-Alpha

Tumor Necrosis Factor Alpha (TNF- α) is a potent pro-inflammatory cytokine produced primarily by macrophages, T lymphocytes, natural killer cells, and certain trophoblastic/endometrial cells. (Van Loo G et al., 2023) It plays a fundamental role in:

- Inflammation and Immune Regulation: TNF- α stimulates other cytokines (e.g., IL-1, IL-6) and enhances leukocyte recruitment to areas of injury or infection. (Mitoma H et al., 2018)
- Cell Death (Apoptosis) and Survival: Depending on local Signaling, TNF- α can activate apoptosis or promote cell proliferation and survival pathways. (D'arcy MS, 2019)
- Tissue Remodeling: It can influence extracellular matrix breakdown and angiogenesis, critical processes in both normal implantation and pathological conditions. (Silva LB et al., 2019)
- Systemic Effects: Excessive TNF- α is implicated in autoimmune and inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, and sepsis. (Jang DI et al., 2021)
- In the context of recurrent miscarriage, TNF- α contributes to processes like implantation, placentation, and decidualization. However, when dysregulated, it can lead to adverse outcomes, including recurrent pregnancy loss, preterm labor, and potentially ectopic implantation. (Romanowska-Prochnicka K et al., 2021)

The Role of TNF-Alpha in Ruptured Ectopic Pregnancy

Investigations highlight those localized high levels of TNF- α within the fallopian tube may significantly contribute to tubal rupture in ectopic pregnancy. (Ma L et al., 2020)

Several mechanisms have been proposed:

- Exacerbated Inflammatory Response

Excess TNF- α can induce an intense local inflammatory milieu, damaging the tubal epithelium and smooth muscle. This inflammation weakens tubal walls, increasing the likelihood of rupture as the embryo grows.

- Promotion of Apoptotic Pathways

Regarding TNF- α is known to initiate apoptosis in trophoblastic cells and surrounding tissues. Excessive apoptosis or tissue breakdown can compromise vascular and structural integrity, thus predisposing to hemorrhage.

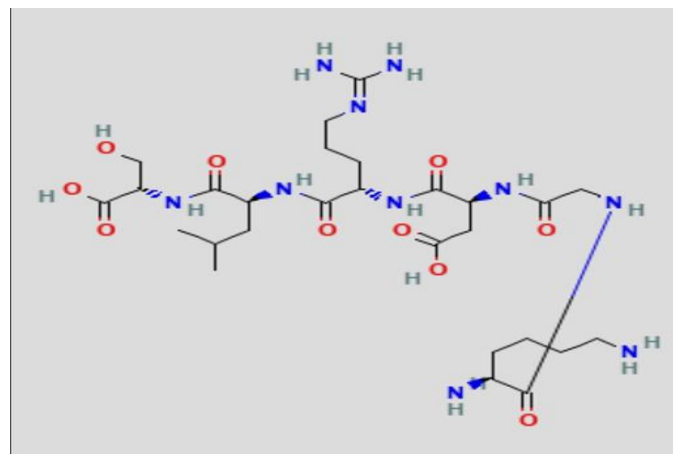


Figure 1.1: Biochemical structure of TNF

- Angiogenic Dysregulation

Tumor necrosis factor alpha can affect blood vessel growth in both pro-angiogenic and anti-angiogenic directions. In ectopic pregnancies, unbalanced angiogenesis could yield fragile vasculature prone to bleeding and rupture. (Zatecka J et al., 2022)

Justification of the study

Clarifying the relation of TNF- α in cases of ruptured ectopic pregnancy is promising for improving early risk stratification, patient counseling, and potentially introducing novel therapeutic strategies may reduce tubal damage and maternal morbidity.

II. PATIENTS AND METHODS

2.1. Study Design

Prospective observational study

2.2. Study Setting

The study was conducted at Babil Teaching Hospital for Maternity and Children, Iraq, over an eight-month period, from January 2025 to August 2025. Data collection was conducted prospectively after obtaining approval from the Iraqi Board of Medical Specializations / Scientific Council of Gynecology and Obstetrics.

The study included a total of one hundred women diagnosed with ectopic pregnancy that were divided into two groups:

- Case group: fifty women with ruptured ectopic pregnancy
- Control group: fifty women with unruptured ectopic pregnancy

In all cases and controls the definitive diagnosis (ruptured or unruptured) was confirmed during surgical intervention

2.3. Ethical approval

1- The study protocol was approved by the Iraqi Board of Medical Specializations / Scientific Council of Gynecology and Obstetrics.

2-Administrative approval were granted from Babil Teaching Hospital for Maternity and Children.

3-. Verbel consent was obtained from all the patients during data collection and blood sampling

4- Data and information of the participants were kept confidential.

2.4. Inclusion Criteria

1. Women diagnosed with ectopic pregnancy and treated surgically according to senior gynaecologist decision.
2. 18-40 years age group.

2.5. Exclusion Criteria

1. Patients with chronic inflammatory or autoimmune diseases including rheumatoid arthritis, inflammatory bowel disease, and sepsis.
2. Patients with acute infections or sepsis.
3. Women with known chronic diseases (diabetes, hypertension).
4. Patients on immunosuppressive or anti-inflammatory therapy within the last 3 months.

2.6. Data Collection

A paper questionnaire (Appendix) was used to collect the required data. The collected information included:

1. History: age, gravidity, parity, menstrual history, past medical and surgical history, risk factors for ectopic pregnancy, and presenting symptoms.
2. Examination: vital signs, abdominal examination findings, pelvic examination findings.
3. Laboratory investigations: complete blood count, blood group and Rh typing, serum TNF- α levels.
4. Imaging: transvaginal or transabdominal ultrasound findings. Using SAMSUNG USS-HS6NL40/WR (Korea, 2021)
5. Intraoperative findings: ruptured or unruptured ectopic pregnancy

2.7. Sample Collection

A venous blood sample (5 mL) was collected from each patient prior to any blood transfusion or postoperative anti-inflammatory therapy. Serum was separated by centrifugation and stored at -20°C until analysis.

Serum TNF- α levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Elabscience® Human TNF- α [Tumor Necrosis Factor Alpha] ELISA Kit), following the manufacturer's protocol.

The assay is based on the sandwich ELISA principle. The kit was not available at the hospital and was provided by the researcher. concentrations were expressed in picograms per milliliter (pg/mL).

After completing the data collection in the paper questionnaires all the patients' data was transformed into a Microsoft excel work sheet and sent for further statistical analysis.

2.8. Statistical Analysis

Data analysis was done using Statistical Package for Social Sciences (SPSS) version 27 for Microsoft® Windows 11, results were presented in simple measures of frequency, percentage, mean, range and standard deviation and illustrated as tablets and figures.

Associations were tested using the independent samples t-test for continues variables and chi-square test or fisher's exact test for associations between categorical variables. A p-value < 0.05 was considered statistically significant.

Receiver operating characteristic (ROC) curve was used to assess the ability of serum TNF- α for predicting rupture, and the area under the curve (AUC) was calculated. The optimal cut-off value and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using Youden's index.

III. RESULTS

Table 3.1 showed the demographic and clinical characteristics of the participants. The mean age of women in the ruptured group was 29.4 ± 5.8 years, compared with 27.8 ± 6.1 years in the unruptured group. Most patients in both groups were between 25–34 years (56% in ruptured vs. 60% in unruptured). Age difference was statistically not significant ($P=0.781$)

Gravidity and parity were comparable between the groups, with no statistically significant differences ($p > 0.05$).

TABLE 3.1: Demographic and clinical characteristics of participants (n = 100)

Variable	Ruptured (n = 50)	Unruptured (n = 50)	p-value
Age group (years)			
18–24	12 (24%)	11 (22%)	0.781
25–34	28 (56%)	30 (60%)	
>35	10 (20%)	9 (18%)	
Mean $\pm$ SD	29.4 ± 5.8	27.8 ± 6.1	
Gravidity	1-5	1-5	0.422
Parity	0-3	0-3	0.667

Table 3.2 showed that the distribution of risk factors and past history did not differ significantly between groups. A history of previous ectopic pregnancy was found in 12% of ruptured and 8% of unruptured cases.

Pelvic inflammatory disease was more frequently reported among the ruptured cases (28%) compared with unruptured cases (16%), but this difference was not statistically significant ($p = 0.11$). Previous pelvic or abdominal surgery, use of infertility treatment, and smoking status showed no significant differences between the two group with P values above the significant level of ($p > 0.05$).

TABLE 3.2: Risk factors and past history

Variable	Ruptured (n = 50)	Unruptured (n = 50)	p-value
Previous ectopic pregnancy	6 (12%)	4 (8%)	0.57
History of pelvic inflammatory disease	14 (28%)	8 (16%)	0.11
Previous pelvic surgery	18 (36%)	12 (24%)	0.15
Use of infertility treatment	5 (10%)	7 (14%)	0.56
Smoking status (current or former)	8 (16%)	6 (12%)	0.57

Abdominal pain was the most common symptom in 96% of ruptured EP and 84% of unruptured cases with no significant difference ($P = 0.06$).

Vaginal spotting occurred in 70% of ruptured and 62% of unruptured cases with no significant difference ($P=0.29$).

Shock on presentation, defined as systolic blood pressure <90 mmHg, was significantly more common in ruptured cases (18%) and was absent in unruptured cases ($p < 0.001$).

Abdominal tenderness was present in 86% of ruptured and 80% of unruptured cases with no significant difference ($P=0.17$).

Pelvic mass was palpable in 62% of ruptured EP cases and 54% of non-ruptured EP cases with no significant difference ($P=0.35$).

Ultrasound examination showed that free peritoneal fluid was significantly more common in ruptured cases (78%) compared with unruptured cases (30%) ($p < 0.001$). Adnexal masses were detected in both groups at high frequencies (88% vs. 94%, $p = 0.47$). As shown in table 3.3.

TABLE 3.3: Clinical presentation, physical examination and investigation in ruptured and unruptured ectopic pregnancy.

Variable	Ruptured (n = 50)	Unruptured (n = 50)	p-value
Abdominal pain	48 (96%)	42 (84%)	0.06
Vaginal spotting	35 (70%)	31 (62%)	0.29
Shock at presentation (SBP <90 mmHg)	9 (18%)	0 (0%)	<0.001
Abdominal tenderness	43 (86%)	40 (80%)	0.17
Bimanual exam			
Pelvic mass	31 (62%)	27 (54%)	0.35
Ultrasound			
free peritoneal fluid present	39 (78%)	15 (30%)	<0.001
Adnexal mass visualized	44 (88%)	47 (94%)	0.47

The mean serum TNF- α concentration was significantly higher in the ruptured group (25.6 ± 7.8 pg/mL; range 12.0–42.0) compared with the unruptured group (15.3 ± 5.9 pg/mL; range 6.0–28.0), with a highly significant difference ($p < 0.001$). as shown in table 3.4. and figure 3.1.

TABLE 3.4: Serum TNF- α levels in ruptured vs unruptured ectopic pregnancy.

Group	Mean $\pm$ SD (pg/mL)	Range (pg/mL)	p-value
Ruptured EP (n = 50)	25.6 ± 7.8	12.0 – 42.0	<0.001
Unruptured EP (n = 50)	15.3 ± 5.9	6.0 – 28.0	

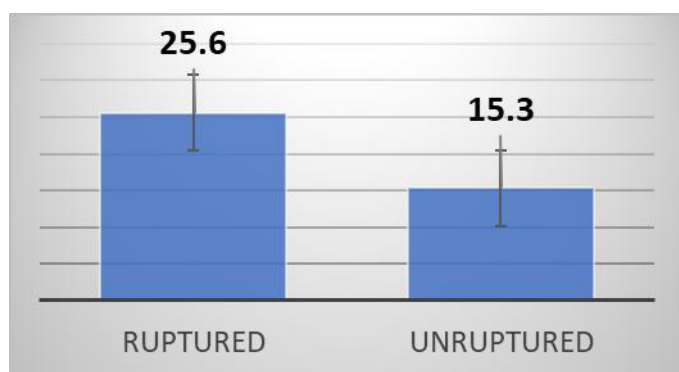


Figure 3.1: Serum TNF- α levels comparison.

The receiver operating characteristic (ROC) curve analysis showed an area under the curve (AUC) of 0.87, which indicates that serum TNF- α had a good discriminatory ability between the two groups.

The optimal cut-off value of TNF- α was identified at 17.8 pg/mL using Youden's index. At this threshold, the test achieved a sensitivity of 80.1%. The specificity was 82.3%. The positive predictive value (PPV) was 79.2%. the negative predictive value (NPV) was 82.7%.

The overall diagnostic accuracy of the test was 81%, confirming that TNF- α is a reliable predictor of rupture in EP. As shown in table 3.5. and figure 3.2.

TABLE 3.5: Diagnostic utility of serum TNF- α for predicting rupture EP.

Parameter	Value
Area under the curve (AUC)	0.87
Optimal cut-off (pg/mL)	17.8
Sensitivity (%)	80.1
Specificity (%)	82.3
Positive predictive value (PPV) (%)	79.2
Negative predictive value (NPV) (%)	82.7
Diagnostic accuracy (%)	81

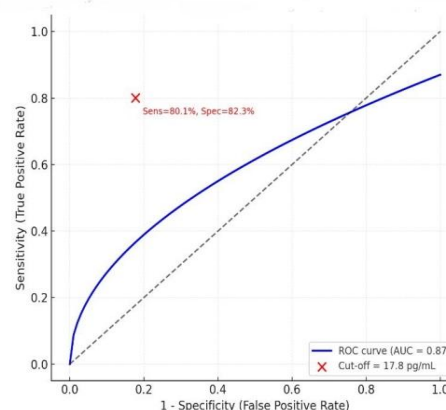


Figure 3.2: ROC curve of serum TNF- α in predicting rupture.

IV. DISCUSSION

This study showed that the mean age of women with ruptured ectopic pregnancy (EP) was 29.4 ± 5.8 years, slightly higher than the 27.8 ± 6.1 years observed in the unruptured group reflecting the typical reproductive age at risk for EP. This is consistent with a study by (Chate MT et al., 2017). where the highest incidence of tubal pregnancy occurred in women aged 21–25 years, with a higher frequency in multiparous women.

Gravidity and parity were comparable between groups, indicating that reproductive history alone may not predict rupture risk, a meta-analysis by (Xu C et al., 2023). concluded that risk factors such as age, parity, prior ectopic, PID, infertility, β hCG, gestational age had conflicting associations with rupture with lack of reliable “universal” predictors.

Regarding risk factors, including prior ectopic pregnancy, pelvic inflammatory disease (PID), previous pelvic surgery, infertility treatment, and smoking, did not significantly differ between groups. this is consistent with a study by (Goksedef BP et al., 2011). on 232 ectopic pregnancy (EP) cases of which 88 (37.9%) were ruptured and 144 (62.1%) were

unruptured found no significant associations with IUD use, smoking, prior ectopic pregnancy, pelvic inflammatory disease, or endometriosis.

Regarding clinical presentation abdominal pain was the most frequent symptom in both ruptured (96%) and unruptured (84%) EP, Vaginal spotting and abdominal tenderness were common but did not differ significantly between groups, indicating that these clinical features alone are insufficient to predict rupture. this is consistent with (Ranji GG et al., 2018). study. While a study by (Li PC et al., 2022). found that women presenting with abdominal pain, higher parity, and low preoperative hemoglobin should be considered at risk for ruptured ectopic pregnancy.

During this study shock on presentation (SBP <90 mmHg) occurred exclusively in ruptured cases (18%, $p < 0.001$), (Moustakli E et al., 2025). study also mentioned that shock is occurs in rupture EP.

Ultrasound findings of free peritoneal fluid were significantly higher in ruptured cases (78% vs. 30%, $p < 0.001$), supporting the role of ultrasonography in the early detection of rupture. (Lee R et al., 2018)

This study found significantly elevated serum TNF- α levels in ruptured EP (25.6 ± 7.8 pg/mL) compared to unruptured EP (15.3 ± 5.9 pg/mL; $p < 0.001$). ROC analysis demonstrated a good discriminatory ability of TNF- α for predicting rupture, with an AUC of 0.87. Using a cut-off of 17.8 pg/mL, sensitivity and specificity were 80.1% and 82.3%, respectively, and the overall diagnostic accuracy was 81%. These findings suggest that serum TNF- α could serve as a reliable biomarker for identifying patients at high risk of rupture, potentially aiding in earlier intervention and improving maternal outcomes.

A study by (Sadovsky et al., 1991). found that tumour necrosis factor alpha is elevated in the peritoneal fluid from women with ruptured ectopic pregnancies, they measured TNF α in peritoneal fluid (not serum) and found that 68% of ruptured EP had peritoneal TNF $\alpha > 40$ units/ml vs 21% in unruptured/intrauterine pregnancies ($p < 0.05$). They suggested that rupture triggers a local peritoneal inflammatory reaction, likely due to exposure of peritoneum to trophoblastic/fetal tissue and blood, leading to macrophage activation.

A study by (Chali TJ and Mahdi N). In Bent Al Huda Hospital, Thi-Qar, found that serum levels of cytokines IL1RA, IL6, IL8, TNF- α , and INF- α were significantly higher in women with EP compared with intrauterine pregnancies. They suggest that elevated pro-inflammatory cytokines, particularly IL1RA, IL6, IL8, TNF- α , and INF- α , may play a role in the pathogenesis of ectopic pregnancy, but did not evaluate its role in prediction of rupture.

Another study by (Rajendiran S et al., 2016). also measured serum inflammatory cytokines (IL 6 and IL 8) in women with tubal EP (ruptured and non ruptured), intrauterine miscarriage, and normal pregnancies. They found significantly elevated IL 6 in EP compared to other groups, suggesting inflammatory cytokines may have diagnostic relevance in EP.

The current study findings suggest a strong association between systemic inflammatory response and tubal rupture. TNF- α , a pro-inflammatory cytokine, is known to mediate

tissue damage and vascular permeability which may explain its higher levels in ruptured cases.

Other studies have investigated the role of other inflammatory markers, (Seyfettinoglu S et al., 2023). study found that the neutrophil to lymphocyte ratio (NLR) was significantly associated with histopathologically confirmed tubal rupture they suggested NLR should be considered in EP management.

Study (Abdulla et al., 2025). in Al-Elwiya Maternity Teaching Hospital in Baghdad found that ruptured EP showed significantly higher lymphocyte counts and lower neutrophil-to-lymphocyte ratios (NLR) compared with unruptured cases ($p = 0.015$ and <0.001 , respectively). They also found increased mean platelet volume (MPV, $P = 0.002$) and markedly lower platelet-to-lymphocyte ratios (PLR, $P < 0.0001$). PLR demonstrated strong predictive ability for tubal rupture, with an area under the curve (AUC) of 0.815; at a cutoff of 88.65, sensitivity was 90% and specificity 85%. NLR showed moderate predictive performance with an AUC of 0.750.

V. CONCLUSIONS

Serum TNF- α levels were significantly higher in ruptured EP compared to unruptured cases, indicating a strong association between systemic inflammation and tubal rupture.

Serum TNF- α demonstrated high diagnostic performance (AUC = 0.87; accuracy = 81%), TNF- α may serve as a reliable biomarker for predicting rupture in EP.

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