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# Correlation of Fibroblast Activation Protein Expression and Incidence of Epithelial Ovarian Cancer Recurrence

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**Abstract**

**BACKGROUND:** Ovarian cancer is one of women death causes and almost diagnosed at advanced stage which related to high recurrence rate; therefore, accurate biomarker is needed to predict recurrence rate.

**AIM:** This research purpose was to determine correlation of fibroblast activation protein (FAP) expression and epithelial ovarian cancer recurrence at H. Adam Malik Hospital Medan.

**METHODS:** This research is an analytic observational study with case control approach that will be carried out starting in May 2022 until number of samples is met. Immunohistochemical assessment for FAP expression uses Allred score because this system is simplest and has good sensitivity and specificity. The preparations were interpreted by two anatomical pathologists. The correlation between variables was carried out by Chi-square statistical test with 95% confidence interval and $p < 0.05$ was considered significant.

**RESULTS:** The analysis results using Chi-square test showed that there was a significant relationship between tissue FAP expression and ovarian cancer recurrence ($p = 0.004$). The OR value obtained was 7.429 (95% CI = 1.778–31.040), which means patients with tissue FAP expression (+) had risk of recurrent ovarian cancer 7.429 times greater than patients with tissue FAP expression (-).

**CONCLUSION:** There is a statistically significant correlation between FAP expression and epithelial ovarian cancer recurrence.

## Introduction

Ovarian cancer is one of women death causes and fifth most common cancer in women worldwide [1], [2]. GLOBOCAN statistics in 2018 reported 295,414 new cases and 184,799 deaths caused by ovarian cancer [3]. Data from Haji Adam Malik General Hospital Medan in 2009, 2010, and 2011, respectively, reported 384, 366, and 391 patients with ovarian cancer and estimated 60.3% were diagnosed at advanced stage [4].

Epithelial ovarian cancer (EOC) is most lethal gynecologic cancer and accounts for 80–90% of all ovarian cancers. EOC resulted in approximately 15,000 deaths and nearly 22,000 new cases in 2009. The high-grade serous ovarian cancer (HGSOC) subtype is most common, aggressive, and fatal type of epithelial ovarian cancer. Nearly 30% of patients die within 5 years of diagnosis. Approximately 70–85% HGSOC patients will experienced relapse at an advanced stage. A survival rate close to 90% can be achieved among ovarian cancer patients diagnosed at early stage [1], [5].

Current standard management for ovarian cancer is optimal cytoreductive surgery combined with platinum-based chemotherapy. Hennessy *et al.* in 2019 reported that despite good effects of first-line therapy, 75% of patients with advanced ovarian cancer (Stadium III or IV) experienced tumor recurrence at median 15 months after diagnosis [6]. Nearly 23% of patients experience recurrence within 6 months and 60% within 6–12 months after primary chemotherapy. Mean interval for first ovarian cancer recurrence is 18–24 months. Another literature by Luvero in 2019 stated that as many as 80% of ovarian cancer patients will experience a recurrence within 18 months [2].

In 2015, Mhawech study stated that supporting stromal tissue has been thought involved in ovarian cancer chemoresistance [7]. Tumor microenvironment (TME) has been reported to have important role in ovarian cancer tumorigenesis and one of tumor microenvironment is fibroblasts. FAP expression was not found in normal stroma. In addition, FAP also plays a role in determining tumor growth, proliferation, tumor invasion, and metastasis. Increased FAP expression presents in >90% of epithelial cancers, including breast, lung, pancreatic, colorectal, and ovarian

carcinomas and has poor prognostic value. FAP is expressed on activated stroma fibroblasts and healing tissue [8], [9], [10]. Mhawech *et al.* in 2015 reported that positive stromal FAP expression was associated with shorter recurrences in patients with similar debulking, staging, and grading operations [7]. Fauceglia *et al.*, stated that increased FAP expression was associated with chemotherapy resistance and was associated with short recurrence time in ovarian epithelial malignant tumors cases. Li *et al*. in 2020 reported that increased FAP expression is a predictor of poor prognosis in high-grade serous ovarian cancer (HGSOC) [11].

Evaluation of FAP expression has not been widely observed in epithelial ovarian cancer and this value can be used as a benchmark for determining therapeutic targets and prognostic markers. Therefore, researchers are interested in evaluating correlation of FAP expression and epithelial ovarian cancer recurrence.

## Materials and Methods

This research is an analytic and observational study with case–control approach conducted at Department of Obstetrics and Gynecology, Faculty of Medicine, University of North Sumatra and IHC conducted at Anatomical Pathology Laboratory, Haji Adam Malik General Hospital Medan. The research will be carried out starting in May 2022 until number of samples is met.

Study population in case group were all patients who had undergone primary surgery for ovarian tumors at Haji Adam Malik General Hospital Medan and had recurrence within 1 year after last chemotherapy which met inclusion criteria, namely, paraffin ovarian tissue block taken from patients with recurrent ovarian cancer detected in 1 year after complete definitive therapy and complete debulking has been done.

Study population in control group were all patients who had undergone primary surgery for ovarian tumors at Haji Adam Malik General Hospital Medan and did not experience recurrence 1 year after last chemotherapy which met inclusion criteria, namely, paraffin block of ovarian tissue taken from ovarian cancer patients who did not experience recurrence after 1 year of complete definitive therapy and complete debulking has been done.

Patients suffering from other malignancies and preparations that could not be analyzed due to poor paraffin blocks preparation were excluded from this study. Based on sample size calculation for 2 proportions, 20 people are needed in each case and control group.

Immunohistochemical procedures were carried out at Department of Anatomical Pathology, Haji Adam Malik General Hospital Medan with VDR immunohistochemical staining. Immunohistochemical assessment for FAP expression uses Allred score because this system is simplest and has good sensitivity and specificity (Tables 1,2 and Figure 1).

**Table 1: Allred score interpretation**

| Total score | Interpretation |
|---|---|
| 0–2 | Negative |
| ≥3 | Positive |

The preparations were interpreted by two anatomical pathologists. Histopathological examination was carried out using light microscope with magnification of ×400.

**Table 2: Assessment of PS and IS**

| PS observation | PS or IS | IS observation |
|---|---|---|
| Not stained | 0 | Not stained |
| <1% of stained cells | 1 | Weak staining intensity |
| 1–10% stained cells | 2 | Moderate staining intensity |
| 11–33% stained cells | 3 | Strong staining intensity |
| 33–66% stained cells | 4 | |
| 66–100% stained cells | 5 | |

PS: Proportion score, IS: Intensity score.

Data analysis and statistical tests were carried out computerized. The study results will be presented in frequency distribution table. To analyze accuracy difference of two observers, the kappa value will be calculated, where if the kappa value is 75%, there is no significant observations difference between two observers. The correlation between variables was carried out by Chi-square statistical test with 95% confidence interval and $p < 0.05$ was considered significant.

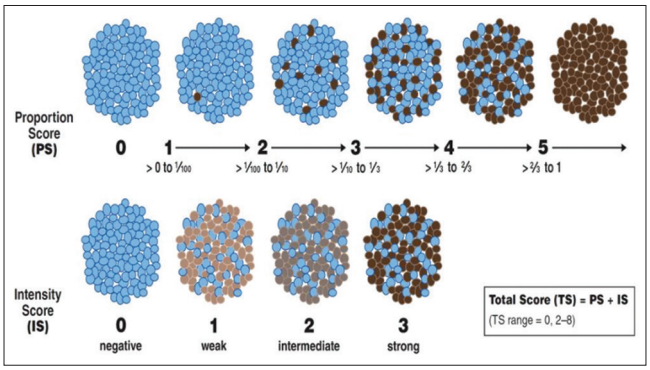


*Figure 1: Proportion score and intensity score*

## Results

This study used data slides and paraffin blocks of tissue from ovarian cancer patients who had undergone primary surgery for ovarian tumors at Haji Adam Malik General Hospital Medan. Mean recurrence duration was 7.5 months with shortest duration was 3 months and longest was 12 months (Table 3).

**Table 3: Ovarian epithelial cancer frequency distribution based on demographic characteristics**

| Demographic characteristics | Ovarian cancer | |
|---|---|---|
| | Recurrence | Without recurrence |
| Age, years old | | |
| Mean (SD) | 54.7 (11.06) | 48.75 (11.63) |
| Median (Min–Max) | 55 (34–73) | 54 (24–74) |
| <30, n (%) | 0 | 1 (5) |
| 30–39, n (%) | 2 (10) | 3 (15) |
| 40–49, n (%) | 6 (30) | 4 (20) |
| ≥50, n (%) | 12 (60) | 12 (60) |
| Parity, n (%) | | |
| Virgo/nulliparous | 6 (30) | 8 (40) |
| Primiparous | 3 (15) | 2 (10) |
| Multiparous | 7 (35) | 10 (50) |
| Grandemultiparous | 4 (20) | 0 |
| BMI, n (%) | | |
| Underweight | 2 (10) | 2 (10) |
| Normal | 5 (25) | 8 (40) |
| Overweight | 7 (35) | 7 (35) |
| Obese | 6 (30) | 3 (15) |
| Menopause status, n (%) | | |
| No | 7 (35) | 10 (50) |
| Yes | 13 (65) | 10 (50) |
| Clinical stadium, n (%) | | |
| Stadium I | 2 (10) | 4 (20) |
| Stadium II | 3 (15) | 2 (10) |
| Stadium III | 14 (70) | 13 (65) |
| Stadium IV | 1 (5) | 1 (5) |
| Grading, n (%) | | |
| Low grade | 17 (85) | 13 (65) |
| High grade | 3 (15) | 7 (35) |
| Histopathology types, n (%) | | |
| Serous | 17 (85) | 13 (65) |
| Mucinous | 0 | 2 (10) |
| Endometrioid | 2 (10) | 4 (20) |
| Clear cell | 1 (5) | 1 (5) |
| Recurrence duration, months | | |
| Mean (SD) | 7.5 (2.98) | - |
| Median (Min–Max) | 8 (3 – 12) | |

BMI: Body mass index, FAP: Fibroblast activation protein, SD: Standard deviation.

By using Fischer's Exact test, there is a significant relationship between FAP expression and histopathological grading of epithelial ovarian cancer (p = 0.01) (Table 4).

**Table 4: Correlation of FAP expression and histopathological grading of epithelial ovarian cancer**

| FAP Expression | Histopathological grading | | p |
|---|---|---|---|
| | High grade | Low grade | |
| Expression (+) | 21 (87) | 2 (13) | 0.01* |
| Expression (-) | 9 (58.8) | 8 (41.2) | |

*Fischer's exact. FAP: Fibroblast activation protein.

Using Mann–Whitney test, there is a significant relationship between FAP expression and histopathological cell types of ovarian cancer (p = 0.066) (Table 5 and Figure 2).

**Table 5: Correlation of FAP expression and histopathological cell types of ovarian cancer**

| FAP expression | Cell types | | | | p |
|---|---|---|---|---|---|
| | Clear cell | Endometrioid | Musinosum | Serous | |
| Expression (+) | 1 (4.3) | 1 (4.3) | 1 (4.3) | 20 (87) | 0.047* |
| Expression (-) | 1 (5.9) | 5 (29.4) | 1 (5.9) | 10 (58.8) | |

*Mann–Whitney. FAP: Fibroblast activation protein.

The analysis results using Fischer's exact test showed that there was a significant relationship between tissue FAP expression and ovarian cancer stadium (p = 0.030). The OR value obtained was 5.926 (95% CI = 1.267–27.714), which means that patients with tissue FAP expression (+) at risk for Stadium III and IV 5.926 times greater than patients with tissue FAP expression (-) (Table 6 and Figure 3).

### *Correlation of FAP expression and ovarian cancer recurrence*

Of 20 ovarian cancer patients with recurrent ovarian cancer, 16 (80%) patients had positive FAP expression. Meanwhile, of 20 ovarian cancer patients who did not experience recurrence, only 7 (35%) patients had positive FAP expressions. The analysis results using Chi-square test showed that there was a significant relationship between tissue FAP expression and ovarian cancer recurrence (p = 0.004). The OR value obtained was 7.429 (95% CI = 1.778–31.040), which means patients with tissue FAP expression (+) had risk of recurrent ovarian cancer 7.429 times greater than patients with tissue FAP expression (-) (Table 7 and Figure 4).

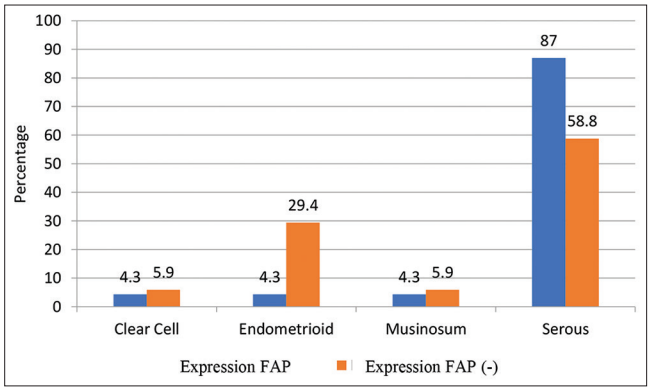


*Figure 2: Histogram graph of ovarian cancer tissue fibroblast activation protein expression based on histopathological cell type*

**Table 6: Correlation of FAP expression and ovarian cancer stadium**

| FAP expression | Ovarian cancer | | p* | OR |
|---|---|---|---|---|
| | Stadium III and IV | Stadium I and II | | 95% IK |
| Expression (+) | 20 (69) | 3 (27.3) | 0.030 | 5.926 |
| Expression (-) | 9 (31) | 8 (72.7) | | 1.267–27.714 |

*Fischer's exact. FAP: Fibroblast activation protein.

## Discussions

The analysis results using Chi-square test showed that there was a significant relationship between tissue FAP expression and ovarian cancer recurrence (p = 0.004). The OR value obtained was 7.429 (95% CI = 1.778–31.040), which means that ovarian cancer patients with tissue FAP expression (+) had risk of recurrence 7.429 times greater than patients with tissue FAP expression (-).

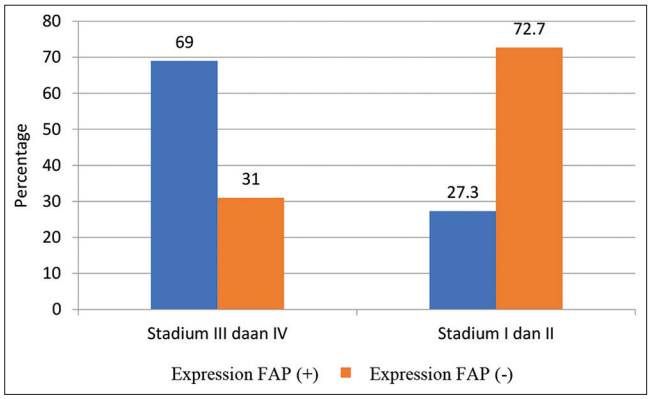


*Figure 3: Histogram graph of ovarian cancer tissue fibroblast activation protein expression based on ovarian cancer stadium*

Fibroblast activation protein-α (FAP) is Type II transmembrane glycoprotein which is member of serine protease family. FAP is minimally expressed by fibroblasts under normal circumstances, but highly expressed by activated fibroblasts in epithelial tumor stroma. High FAP expression is associated with poor survival, high recurrence rates, and advanced stadium of several cancers, including oral squamous cell carcinoma, ovarian cancer, pancreatic ductal adenocarcinoma, and non-small cell lung cancer (NSCLC) [12].

**Table 7: Correlation of FAP expression and ovarian cancer recurrence**

| FAP expression | Ovarian cancer | | p* | OR |
|---|---|---|---|---|
| | Recurrence (n=20) | Without recurrence (n=20) | | 95% IK |
| Expression (+) | 16 (80) | 7 (35) | 0.004 | 7.429 |
| Expression (-) | 4 (20) | 13 (65) | | 1.778–31.040 |

*Chi-square. FAP: Fibroblast activation protein.

Several studies reported benefits of FAP in predicting prognosis and therapy response. It is reported that FAP expression is an independent predictor of platinum resistance and overall survival, which suggests that FAP expression can be used in clinical practice to identify patients who at risk for platinum resistance and poor prognosis [3], [7].

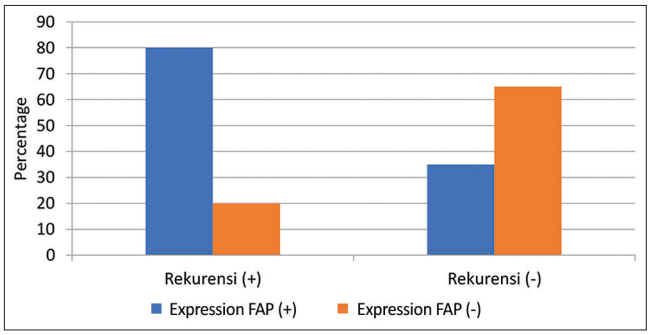


*Figure 4: Histogram graph of ovarian cancer tissue fibroblast activation protein expression based on recurrence incidence*

Mhawech *et al*. reported that positive stromal FAP expression was associated with shorter recurrences duration in patients with similar debulking, staging, and grading surgery [7]. Fauceglia *et al*. suggested that increased FAP expression was associated with chemotherapy resistance and shorter recurrence duration in ovarian epithelial malignant tumors [13]. Li *et al.* in 2020 reported that increased FAP expression is predictor of poor prognosis in high-grade serous ovarian cancer (HGSOC). Increased FAP expression in malignant ovarian tumors is associated with disease progression, lymph node metastases, latent distant metastases, and FIGO grading. However, FAP expression did not showed significant correlation with other clinicopathological factors, such as patient age, tumor size, and tumor location [5], [8], [14].

Tumorigenesis process is stimulated both paracrine and autocrine by growth factors and cytokines such as VEGF, TGF-β, PDGF, bFGF, and IL-10. The presence of growth factors, ECM remodeling, and neovascularization induction will increase tumor growth, progression, and metastasis, including reactive stroma. Reactive stroma or better known as desmoplastic stroma will be associated with poor prognosis, immunosuppression of tumor microenvironment, and cause tumor cells chemoresistance, especially epithelial ovarian cancer [14], [15].

Fibroblast activation protein alpha (FAP) is overexpressed by fibroblasts in tumor microenvironment. Stromal FAP (+) was associated with more rapid recurrence compared to stromal FAP (-) (p = 0.0247). In 21.8% of tumors, FAP protein was expressed by tumor epithelium and FAP mRNA was higher expressed in tumors than in normal tissues (p = 0.003). *In vitro*, FAP addition to EOC cells induced 10–12% increase in cell viability with and without cisplatin. FAP expression in EOC is associated with worse clinical outcome [7].

Activation of host stromal microenvironment, commonly referred as "reactive stroma," is an important component of carcinoma development in various cancers. The reactive stroma in cancer has similarities biology of wound healing process in normal tissue, in that stromal cells exhibit increased production of extracellular matrix (ECM) components, growth factors, and matrix remodeling enzymes to create tumor microenvironment that supports survival, proliferation, and invasion of cancer cells [16], [17].

Increased FAP expression is believed to cause epithelial ovarian cancer recurrence after chemotherapy. High-grade serous ovarian cancer (HGSOC) is most common histologic type of epithelial ovarian cancer, based on FAP location in HGSOC tissue, FAP may be a positive potent cell surface receptor. FAP has high expression in HGSOC patients in Chinese (>60%) and other ethnic (>50%) populations. High level of FAP expression is associated with poor prognosis of HGSOC through fibronetin-1 (FN1) pathway [16].

FAP Expression by tumor stroma triggers tumor cell invasion through its gelatinase activity and increases tumor cell proliferation and migration. *In vivo* model, stromal FAP expression was associated with increased tumor incidence, growth, and microvascular density. Proliferation of CaOV3 cells increased 8.9% when cultured with FAP (p > 0.02). In addition, in presence of cisplatin and FAP, CaOV3 cells were significantly more proliferative than when incubated with cisplatin alone (p > 0.02). SiRNA inhibition of FAP resulted in 10% reduction in EOC cell proliferation [13], [18].

Finally, this study is consistent with other studies that reported FAP expression was an independent predictor factor to determine therapy chemoresistance, especially platinum-based chemotherapy and also to determine poor prognostic factor of ovarian epithelial malignant tumor. The higher FAP expression, the more reactive stroma involved in tumor microenvironment. This reactive stroma will affect chemotherapy response and caused rapid recurrence after therapy. Changes of tumor stroma will control chemoresistance and improve chemotherapy response, one of which is targeting by anti-FAP therapy;

therefore, anti-FAP through various mechanisms can provide a better response to chemotherapy [2], [19], [20].

## Conclusion

There is a statistically significant correlation between FAP expression and epithelial ovarian cancer recurrence. FAP can be used as a routine examination to assess prognosis and recurrence of epithelial ovarian cancer.

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