

## Research Article

## Fascin Expression as Prognostic Factor for Survival in Advanced Epithelial Ovarian Carcinoma

### *Eksresi Fascin sebagai Faktor Prognostik Kesintasan pada Kanker Ovarium Jenis Epitelial Stadium Lanjut*

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#### Abstract

**Objective:** To evaluate fascin expression as a prognostic factor and its correlation with survival and clinicopathologic factors (degree of differentiation and stage) in epithelial ovarian carcinoma.

**Methods:** This study is prognostic study with historical cohort design. Fascin was analyzed in paraffin block sections of 33 advanced stage ovarian carcinoma patients using immunohistochemistry. Fascin expression was tested for its correlation with overall survival as well as with grade and stage of the cancer.

**Results:** In this study, fascin expression has no correlation with survival. In the period of 17-22 months, samples with high fascin expression had a HR of 1.59 (95% CI=0.38-6.67, p=0.449), but in the period of 17-23 months, both groups had comparable HR. In the period of more than 23 months, samples with high expression of fascin had a better HR of 0.40 (95% CI=0.04-4.38, p=0.449). No significant correlation was found between fascin expression with grade (OR=2.08, 95% CI=0.44-9.84, p=0.442) and stage (OR=2.70, 95% CI=0.39-18.96, p=0.360).

**Conclusion:** In this study, there was no correlation between fascin expression and survival, and also no correlation between fascin, grade and stage. Further study with a larger, more homogenous sample, analyzing confounding factors is needed.

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**Keywords:** advanced stage ovarian carcinoma, fascin, survival

#### Abstrak

**Tujuan:** Melakukan penilaian terhadap hubungan ekspresi fascin sebagai faktor prognostik kesintasan kanker ovarium stadium lanjut secara umum, serta hubungan antara faktor klinikopatologis (derajat diferensiasi dan stadium) pada khususnya.

**Metode:** Penelitian ini merupakan studi prognostik dengan desain kohort retrospektif. Fascin dianalisa melalui 33 sampel blok paraffin dan dilakukan pemeriksaan imunohistokimia. Data diperoleh dari status medis, wawancara dengan pasien/keluarga atau melalui telepon.

**Hasil:** Pada periode 17-22 bulan, fascin dengan ekspresi tinggi memiliki HR=1,59 (IK 95%=0,38-6,67, p=0,449), tetapi pada periode 17-23 bulan, kedua kelompok memiliki hazard rasio yang sama. Pada periode lebih dari 23 bulan, fascin dengan ekspresi tinggi memiliki HR=0,40 (IK 95%=0,04-4,38, p=0,449). Tidak terdapat korelasi bermakna antara ekspresi fascin dengan derajat diferensiasi dengan OR=2,08 (IK 95%=0,44-9,84, p=0,442) dan stadium (OR=2,70, IK 95%=0,39-18,96, p=0,360).

**Kesimpulan:** Didapatkan hasil yang tidak bermakna antara hasil ekspresi fascin yang tinggi dengan kesintasan, serta tidak terdapat korelasi bermakna antara ekspresi fascin dengan derajat diferensiasi. Diperlukan penelitian lebih lanjut dengan jumlah sampel yang lebih besar dan lebih homogen, dengan menganalisa faktor-faktor perancu yang dapat ditemui.

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**Kata kunci:** fascin, kanker ovarium stadium lanjut, kesintasan

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#### INTRODUCTION

Epithelial ovarian cancer (EOC) is the most lethal of all gynecologic malignancies, and the fifth cause of mortality. Women with organ-confined tumors have an excellent prognosis, but the majority of early stage cancer is asymptomatic, and more than two-thirds (70-75%) of patients are diagnosed with advanced disease and has often spread as diffuse small-volume tumor deposits.<sup>1</sup>

A better understanding of ovarian cancer is urgently needed for patients who currently present with advanced disease requiring major surgery and adjuvant chemotherapy, with the great majority experiencing recurrence. Relapse occurs in the majority of advanced stage patients after complete response to initial treatments; and at least 70-90% of these patients eventually die with drug-resistant cancers, with only 10-30% showing long-term survival. Despite many therapeutic improvements, the

development of secondary metastatic tumors that are resistant to conventional treatment remains a major cause of morbidity and mortality.<sup>1,2</sup> Tumor invasion and metastasis are the result of highly coordinated processes involving multiple intracellular and extracellular factors. Understanding the early events that enable carcinoma cell migration and invasion is an important research goal that has the potential to improve early diagnosis of aggressive tumors and stimulate new approaches towards molecular adjuvant therapies. Carcinoma cell migration is facilitated by the altered differentiation status of the epithelial cells, including changes in cell and cell matrix adhesion properties and in the organization of the actin cytoskeleton. The cytoskeleton is a complex network that includes three types of protein: actin filaments, microtubules and intermediate filaments. Changes in cytoskeletal components or associated binding proteins may be implicated in the progression and metastasis of tumors.

Fascin is a globular actin cross-linking protein that has a major function in forming parallel actin bundles in cell protrusions that are key specializations of the plasma membrane for environmental guidance and cell migration. Fascin is a highly conserved actin-bundling protein, widely expressed in mesenchymal tissues and the nervous system, and is low or absent in adult epithelium. Recent data from a number of studies have highlighted that fascin is up-regulated in many human carcinomas and in individual tissues, correlating with the clinical aggressiveness of tumors and poor patient survival. In cell culture, over-expression or depletion of fascin modulates cell migration and alters cytoskeletal organization. The identification of biomarkers to provide more effective early diagnosis of potentially aggressive tumors, or identify tumors susceptible to targeted therapies, is an important goal in clinical research.<sup>3-8</sup>

There were many studies on fascin that showed correlation between fascin and malignancy. Daponte reported that strong fascin immunoreactivity was associated with poor prognosis; patients with low fascin expression had a median survival of 36.5 months versus 32 months for high fascin expression ( $p=0.041$ ), and the median PFI was 24 versus 17.5 months, respectively ( $p=0.034$ ). Fascin expression is an independent prognostic factor for survival of advanced ovarian serous carcinoma, and may represent a novel therapeutic target for patients with aggressive forms of ovarian cancer.<sup>9</sup>

Eun et al reported that fascin expression was detected in the majority of borderline (100%, 32/32) and malignant tumors (90.5%, 67/74), but it was not seen in normal ovarian surface epithelial cells and benign tumors ( $p<0.001$ ). Fascin expression was significantly correlated with the occurrence of peritoneal metastases in the carcinomas ( $p=0.043$ ).<sup>10</sup> Fascin overexpression has an important role in invasiveness and recurrence of uroepithelial malignancy. There were significant numbers of fascin-1-positive cells (50% of the neoplastic cells) in uroepithelial carcinomas in situ ( $n=10$ ). These findings suggest an association between increased fascin-1 expression and increased invasiveness of carcinomas in the urinary bladder.<sup>11</sup>

The aim of this study is to evaluate the correlation between fascin expression, survival and clinicopathologic factors in advanced stage ovarian carcinoma. Fascin has emerged as a very interesting candidate for biomarker because its expression is low or absent in the majority of normal adult epithelium, yet up-regulation of the protein has been reported in many forms of human carcinoma. Irrespective of the tissue source of the tumor, high levels of fascin expression in primary carcinomas has been consistently correlated with a clinically aggressive phenotype and poor prognosis.<sup>9</sup>

## METHODS

This study is prognostic study with historical cohort design. Thirty-three patients with a diagnosis of advanced stage epithelial ovarian carcinoma (91% were stage III and 9% were stage IV) who received postoperative chemotherapy (TC: 175 mg/m<sup>2</sup> paclitaxel and carboplatin after calculating the area under the concentration curve) were included in this study. Due to limited sample, only 23 patients had complete cycles (6 cycles). The patients who had complete medical records were selected for further analysis. Patients were examined, diagnosed and underwent therapy in the Gynecologic Oncology Division, Obstetrics and Gynecology Department, RSCM, Jakarta.

Pathological samples from paraffin-embedded tissue from each of the above patients were included in this study. Clinicopathologic information was obtained from medical records. Cancer patients were classified after a staging laparotomy; the most common initial surgical procedure consisted of abdominal hysterectomy, bilateral salphingo-oophorectomy, omentectomy, and pelvic and

paraaortic lymph node dissection. The surgery was classified as complete resection when no macroscopic tumor remained. Surgical procedures were carried out in the Division of Gynecologic Oncology, University of Indonesia. All slides were reviewed by the pathologists.

Survival analysis was performed after the patients were dichotomized according to a fascin immunohistochemistry score of  $<3$  and  $\geq 3$ . The optimal cutoff point of fascin expression based on immunohistochemistry was calculated in consideration of sensitivity and specificity of ROC curve analysis for the survival. This research started at September 2013 until October 2014, with samples being taken from 2006. At the time of analysis, 11 of the 33 patients were deceased due to their disease.

Immunohistochemical staining of ovarian tissue was performed in a commercially available automated immunostainer. The samples were fixed in 10% buffered formalin solution, embedded in paraffin blocks and cut at 4 mm sections. For fascin expression, slides were incubated for 20 minutes at room temperature with clone IM20 (Novocastra, Newcastle upon Tyne, UK) diluted to 1:300.

All slides were initially evaluated by a pathologist. During a subsequent joint evaluation, a final consensus of immune reactivity score was obtained and used for statistical analysis. Cytoplasmic immune reactivity of tumor cells was assessed in comparison with tonsil specimen, which was used as positive controls. Two aspects of immune reactivity were semi-quantitatively evaluated: the extent and the intensity of staining. Intensity was considered as "weak to moderate" when it was less than that of tonsillar tissue and "intense" when it was similar to that of the tonsil. After preliminary analysis, the pathologists involved in the evaluation of immunohistochemical staining realized that the observed differences in immunoreactivity were best represented by counting only the cellular subpopulation showing intense immunohistochemical

staining and expressing this as the HIES (highest immunohistochemical expression score). To calculate HIES, a value from 0 to 4 was assigned according to the percentage of cells showing intense staining (0: 0%, 1:  $<25\%$ , 2:  $25-50\%$ , 3:  $50-75\%$ ; 4:  $>75\%$ ).

Univariate analysis of categorical variable will be presented in percentages and frequencies. Overall survival was defined as the interval from the date of surgery to death from ovarian carcinoma or at the end of the study period on 27<sup>th</sup> October 2014. Correlation between fascin expression and survival will be tested using Kaplan Meier Method, Cox Regression and Life Table. Bivariate analysis of correlation between fascin expression and clinicopathologic characteristics, will be analysed using Fisher test. SPSS software v.22.0 for Mac was used for the statistical analysis,  $p < 0.05$  was considered to be statistically significant.

## RESULTS

We included 33 tissue samples of patients with EOC. Our sample had an average age of 49.95 years, 39.4% in the age group of 40-49 years. Only 20 patients (60.0%) had optimal debulking surgery with complete resection (no macroscopic residual disease), and 39.4% had residual tumor more than 2 cm in diameter. In terms of histologic type, 17 patients (51.5%) had serous EOC, 9/33 had clear cell carcinoma, 4/33 had endometrioid, and 3/33 had mucinous type EOC, with 6/33 patients having well differentiated tumors, and 25/33 had moderate-poor differentiated tumors.

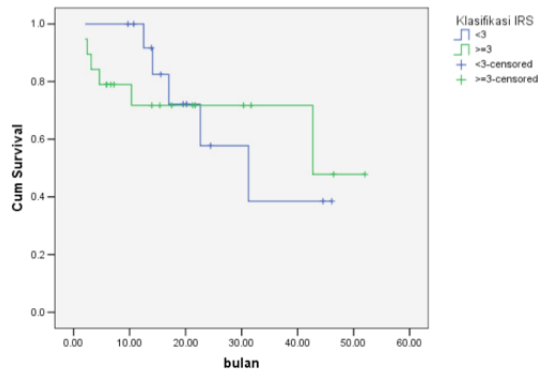
Following assessment of fascin immunoreactivity, 14 (42.4%) tumor samples were classified as having low fascin expression (immunohistochemistry score  $<3$ ) and 19 (57.6%) having high fascin expression (immunohistochemistry score  $\geq 3$ ).

The cutoff point was determined from the sensitivity and specificity analysis and ROC curve analysis to survival. We found that the cutoff IRS

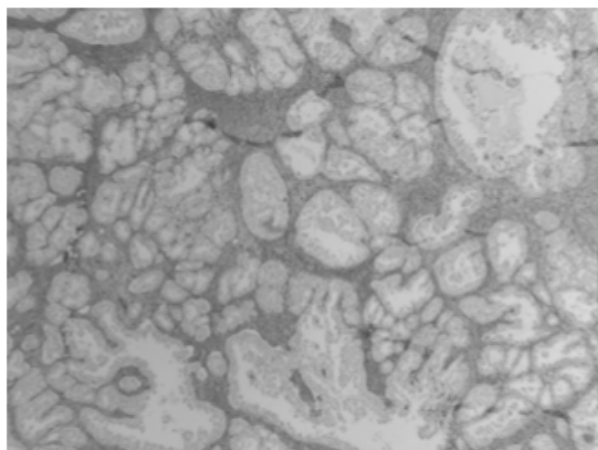
**Table 1.** Correlation between Fascin Expression and Survival

Time	Variable	Coefficient	SE	Wald	df	value p	HR	95% CI	
								Min	Max
0-17 months	Fascin $\geq 3$	0.461	0.733	0.396	1	0.529	1.59	0.38	6.67
>23 months	Fascin $\geq 3$	-0.929	1.229	0.572	1	0.449	0.39	0.04	4.39

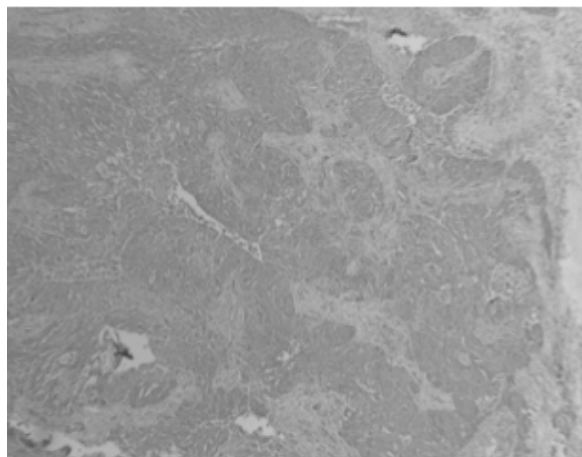
score was 3 with sensitivity of 54.5% and specificity of 40.9% with AUC=0.450 (95% CI=0.240-0.661).



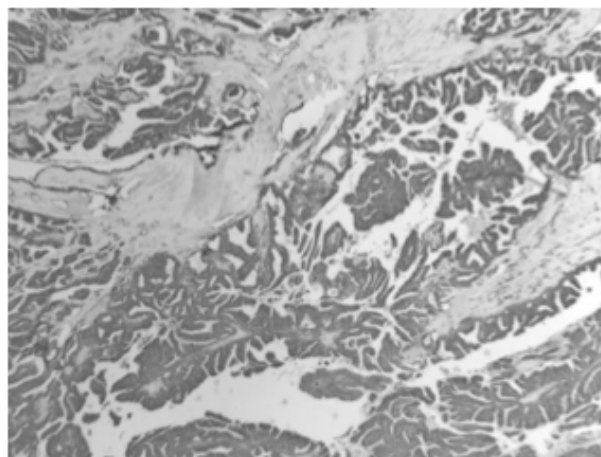
**Figure 1.** Kaplan Meier Curve Associated with Fascin Expression



**Figure 2A.** Clear cell carcinoma with immunostaining for fascin. Note low cytoplasmic staining, negative intensity. IRS score : 0



**Figure 2B.** Serous adenocarcinoma with immunostaining for fascin. Note moderate cytoplasmic staining, moderate intensity, IRS score : 8



**Figure 2C.** Serous adenocarcinoma grade 1 with immunostaining for fascin. Note strong cytoplasmic staining, strong intensity, IRS score : 5.5

**Table 2.** Correlation between Fascin Expression and Grading

		Moderate-poor differentiation		Well differentiation		p-value	OR (95% CI)
		n	%	n	%		
IRS Score	Positive ( $\geq 3$ )	15	78.9	4	21.1	0.442	2.08 (0.44-9.84)
	Negative ( $< 3$ )	9	64.3	5	35.7		

**Table 3.** Correlation between Fascin Expression and Stage

		Stage 4		Stage 3		p-value	OR (95% CI)
		n	%	n	%		
IRS Score	Positive ( $\geq 3.75$ )	3	23.1	10	76.9	0.360	2.70 (0.39-18.96)
	Negative ( $< 3.75$ )	2	10.0	18	90.0		
IRS Score	Positive ( $\geq 3$ )	3	15.8	16	84.2	1.000	1.13 (0.16-7.82)
	Negative ( $< 3$ )	2	14.3	12	85.7		

Among 33 samples, 11 patients were deceased due to their disease, and 22 (64.7%) were still alive at the end of the study. There were cutoff points in the period of 17 months and 22 months. In the period of month 17-22, samples with high fascin expression had a HR of 1.59 (95% CI=0.38-6.67,  $p=0.449$ ), but in the period of month 17-23 both groups had comparable HR. In the period of more than 23 months, group with high fascin expression had a better HR of 0.40 (95% CI=0.04-4.38,  $p=0.449$ ). This is presented in Figure 1 and Table 1.

The sensitivity and specificity analysis and ROC curve analysis for tumor grading showed an optimal cutoff point for fascin expression to be  $\geq 3$  with sensitivity of 62.5% and specificity of 55.6%, AUC=0.525 (95% CI=0.307-0.744);  $p=0.824$ . The proportion of samples with high fascin expression and moderate-poor differentiation was 78.9%, compared with the well differentiated being only 21.1%. Meanwhile, proportion of samples with low fascin expression and moderate-poor differentiation was 64.3%, compared with those that are well differentiated being only 35.7%.

The ROC curve analysis for the staging, had an optimal cutoff point of 3.75 with sensitivity and specificity of 60% and 64.2%, with AUC of 0.607 (95% CI=0.329-0.885,  $p=0.451$ ). High fascin expression in stage four EOC was 23.1%, compared with stage three EOC which was 76.9%. Meanwhile, low fascin expression in stage four EOC was only 10%, while in stage three EOC was 90%.

## DISCUSSION

Ovarian cancer is the most common cause of gynecological cancer-related mortality. Patients with this disease generally undergo surgery followed by platinum-taxane chemotherapy (TC), with additional chemotherapy at occurrence of relapse. Although the prognosis for patients with advanced cancer is poor, with a five-year survival of only 30-40%, there is a wide range of outcomes for individual patients. Clinicopathological variables such as staging, grading, histological type, debulking status, and response to chemotherapy continue to provide the basis on which treatment decisions are made for individual patients. Additional biomarkers in cancer tissues need to be extensively evaluated to improve individualized therapy for patients.<sup>9</sup>

Fascin has emerged as a prognostic marker in some carcinomas. In this study, we examined ovarian neoplasms to confirm the presence of any correlation between fascin expression and established clinicopathologic parameters.<sup>12</sup>

Fascin is a 55 kDa globular protein that organizes F-actin into well-organized, tightly packed parallel bundles in vitro and in cells. Fascin have been well conserved in animal evolution: homologues are present in *Drosophila*, echinoderms and the platyhelminth *Schmidtea mediterranea*. Vertebrate genomes encode three forms of fascin: fascin-1, which is widely expressed by mesenchymal tissues and in the nervous system; fascin-2, which is expressed by retinal photoreceptor cells; and fascin-3, which is testis-specific. The focus of this article is on fascin-1 (also known as fascin), which contributes to the organization of two major forms of actin-based structures: cortical cell protrusions that mediate cell interactions and migration, and cytoplasmic microfilament bundles that contribute to cell architecture and to intracellular movements.<sup>13</sup>

Cell motility is one of the defining characteristics of invasive tumors, enabling tumor cells to migrate into adjacent tissues or through the basement membranes and extracellular matrices. The initial step in cell migration is the protrusion of the cell membrane. This is driven by localized actin polymerization. Reorganization of the actin cytoskeleton is the primary mechanism of cell motility and is essential for most types of cell migration. Invasive tumor cells have been demonstrated to present dysregulated cell motility in response to extracellular signals from growth factors and cytokines.<sup>14</sup>

A key structural requirement for cell protrusion is the need for a rigid cytoskeletal structure to support the localized extension of the plasma membrane with its characteristic morphology. This is achieved in finger-like protrusions by a central, unipolar bundle of filamentous actin (F-actin) and in lamellipodial protrusions by radial, rib-like actin bundles that are integrated with a dendritic meshwork of microfilaments. Fascin-1 is known to be the core actin bundling protein of dendrites, microspikes, filopodia, and lamellipodial ribs, and to be concentrated in cell protrusions during cell migration. Fascin-1 contributes to the formation of various actin-based cellular structures.<sup>13,15,16</sup> Among those, and critical in cancer cell biology, are the cellular surface protrusions that mediate cell

movement. In vitro studies, based on transfection experiments, have shown that elevated levels of fascin increased the speed of cell migration and emphasized the association between fascin expression and motility of transformed cells.<sup>15</sup>

Metastatic and invasive tumor cells often exhibit changes in cell morphology, disruption of cell-cell contacts, degradation of ECM and increase in cell migration, which result from rearrangements of the cytoskeletal microfilaments. Reorganization of the actin cytoskeleton is regulated by the action of actin crosslinking proteins. Fascin expression is either low or absent in adult epithelia and is often up-regulated in several types of epithelial cancers including breast, ovarian, skin, pancreatic, liver, esophageal squamous cell, urothelial carcinoma, glioblastoma and cervical cancer.<sup>3,14,17-19</sup>

A number of prior studies have shown that fascin up-regulation is associated with a more aggressive and metastatic phenotype in epithelial cancers. Several correlative studies have demonstrated the tumor promoting function of fascin, its role in tumor development and/or progression of ovarian cancer is yet to be comprehensively investigated. Meta-analyses demonstrate that there is strong evidence that fascin-1 protein is associated with an up to two-and-a-half-fold increased risk of mortality in breast, colorectal, and esophageal carcinomas. At present, there is little evidence that fascin-1 is associated with mortality for gastric and lung carcinomas. Fascin-1 is correlated with an increased risk of disease progression in breast and colorectal carcinomas, but not in lung carcinoma. Strong evidence for association of fascin-1 with increased risk of lymph node metastasis has been observed for colorectal and gastric carcinomas, but not for lung and esophageal carcinomas. Fascin-1 protein was also associated with a greater than 70% increased risk of distant metastasis in colorectal, gastric, and esophageal carcinomas, although the statistical evidence for association with esophageal carcinoma metastasis was weak. Pooled analysis of all carcinomas within our dataset provides strong evidence that fascin-1 may carry the potential as a novel biomarker for early identification of aggressive and metastatic tumors. These data will assist rational decision-making for focusing ongoing efforts investigating fascin-1 as a biomarker for the most relevant carcinoma.<sup>20</sup>

In general, fascin overexpression has been associated with invasive, high-grade tumors. Recently,

however, Yamaguchi et al have reported over-expression of fascin and up-regulation of fascin mRNA in intraductal papillary mucinous neoplasms of pancreas that correlated with increasing histologic grade (adenoma, borderline neoplasm, and carcinoma with or without invasion) suggesting fascin up-regulation as an early event in the pathogenesis of pancreatic mucinous intraductal papillary neoplasms.<sup>21</sup> Down regulation of fascin has been shown to have inhibitory effects on the migration, proliferation, and invasiveness of esophageal squamous cell carcinoma cell lines, suggesting that fascin contributes to tumor progression and could possibly be a therapeutic molecular target.<sup>22</sup>

Kabukcuoglu et al studied fascin expression in ovarian tumors (serous, endometrioid, clear, mucinous, mixed, and transitional) and found various degrees of epithelial staining in 20% of cystadenoma, 62% of borderline tumors, and 64% of invasive epithelial ovarian tumors.<sup>19,23</sup> Hu et al have also shown increased expression of fascin in cell cultures derived from stage IV ovarian tumors versus cell cultures derived from stage II-III ovarian tumors. They also shown that the expression of fascin in ovarian tumor cell cultures is significantly associated with their ability to grow and spread intraperitoneally after intraperitoneal inoculation, supporting the role of fascin in ovarian tumor metastasis.<sup>19</sup> It was also observed that there was increased expression of fascin in paraffin-embedded sections from borderline ovarian tumors, whereas they did not see any expression of fascin in benign ovarian epithelium. Fascin up-regulation in human breast cancer cell lines has been associated with HER-2 overexpression, which is associated with poor prognosis in breast cancer. HER-2 is often positive in serous ovarian tumors as well, and its association with fascin up-regulation can be a subject for further investigation.<sup>22</sup>

In our study, we characterized fascin protein expression in a series of advanced stage epithelial ovarian carcinoma by immunohistochemistry. Figure 1 shows that survival in groups with fascin expression  $\geq 3$  and fascin expression  $< 3$  crossed in the periode of 17 months to 22 months. Between 0-17 months, subject with fascin expression  $\geq 3$  has worse HR of 1.59 (95% CI=0.38-6.67, p=0.449). However, between 17-23 months, both of the group have same hazard. After 23 months, higher fascin expression had a better hazard with HR of 0.40 (95% CI=0.04-4.38).

Previous studies have implicated fascin as a novel biomarker for human carcinomas and aggressive tumor behavior. In our study, statistically these findings were not significant and it could be due to the heterogeneity and limited sample of this research.

In tissues with positive expression of fascin, up to 78.9% had moderate-poor differentiation, which was higher than those that are well differentiated, which was 21.1%. Statistically this is not significant, but the difference between positive and negative fascin expression is clinically significant. Positive expression of fascin in stage 4 EOC is 23.1%, compared with stage 4 in the negative expression group, which was only 10%. Nevertheless, this was not statistically significant.

The cadherin family of trans membrane glycoproteins is important for cellular adhesion in epithelial cells. It is known that E-cadherins mediate homotypic adhesions in epithelial tissues and serve to keep the epithelial cells together.<sup>24</sup> Ying et al suggested that fascin and cadherin binding sites within  $\beta$ -catenin overlaps; and that, in vitro, fascin and cadherins compete for binding to  $\beta$ -catenin in transformed epithelial cell systems.<sup>25</sup> Yamashiro et al observed that transfection of the fascin gene leads to cell-to-cell contact disorganization and increased cell motility by inducing the emission of microspikes on apical surfaces and on the extended lamellipodia on basolateral surfaces. Some of these changes are due to the downregulation and altered cytoplasmic distribution of the E-cadherin based adhesion complex induced by fascin over expression.<sup>26</sup> E-cadherin is the key functional component of adherent junctions between epithelial cells. Downregulation of E-cadherin in several types of human neoplasms usually correlates with poor tumor differentiation, more advanced disease stage, lymph node metastases, and poor survival rates. A relationship between fascin and E-cadherin has been documented, where cytoplasmic accumulation of fascin leads to a loss of cell-to-cell adhesion by disruption of the E-cadherin adhesion system.<sup>24</sup> This agrees with findings of Okada et al who showed that increased immunoreactivity for fascin had a tendency to disrupt membranous immunoreactivity for E-cadherin. Therefore, it may be postulated that the altered expression of E-cadherin is involved in fascin mediated cell motility.<sup>27</sup>

## CONCLUSION

In conclusion, we have found an association between fascin expression and survival, as well as clinicopathologic properties (grade and stage) in epithelial ovarian cancer. However, the association was not statistically significant. Confounding bias (sample is heterogenous) and sample bias (small number of sample) could be the reason why these results were not significant. Further studies with a larger, more homogenous sample, with analysis of the confounding factors are required.

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