RESEARCH ARTICLE

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Profiling the Expression and Prognostic Values of *FYN*, A Non-Receptor Tyrosine Kinase, in Different Histological Types of Epithelial Ovarian Cancer

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Abstract

Objective: This study was aimed at evaluating *FYN* expression among different histologic types of epithelial ovarian cancer (EOC) and its associated prognostics. **Methods:** The *FYN* expression levels using quantitative real-time PCR method were evaluated in 98 primary EOC. Receiver operating characteristic curve were used to select an optimal cut-off value for determining the presence or absence of a disease progression. **Result:** The median level of *FYN* expression varied among different EOC types, being the highest in high-grade serous carcinomas and the lowest in clear cell carcinomas (CCC). Using the cutoff *FYN* value to predict disease progression, the *FYN*-positive group had a poorer progression-free survival (PFS) compared to the *FYN*-negative group (p = 0.001). In multivariate Cox regression analysis, *FYN* expression was an independent predictor for disease progression (Hazard ratio = 2.30; 95% CI: 1.21- 4.38; p = 0.011). In subgroup analysis, *FYN* expression was significantly associated with lower PFS in early stage CCC patients (p = 0.009). **Conclusion:** *FYN* expression is variable among different types of EOC while impacting on the prognostic values in patients with early stage CCC.

Keywords: *FYN*- non-receptor tyrosine kinase protein- ovarian cancer- clear cell carcinomas- disease progression

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Introduction

Ovarian cancer is the third most common type of gynecologic cancers, but it causes the highest mortality rate. Patients commonly present an advanced stage of the disease and they are treated with a combination of surgery and chemotherapy. However, relapse of tumor is frequent and the treatment outcome at relapse is rather unfavorable. Epithelial ovarian cancer (EOC) comprises the large majority of ovarian cancer, accounting for up to 90% of cases. EOC represents a heterogenous group of tumors including a variety of differentiations (e.g., high-grade serous, low-grade serous, mucinous, endometrioid, and clear cell), with different pathogenesis and clinical behavior (Kurman et al., 2014).

FYN is a 59 kDa non-receptor tyrosine kinase protein, a member of the Src family of kinases. *FYN* phosphorylates tyrosine residue on target proteins that are involved in a variety of signaling pathways (Saito et al., 2010). *FYN* is considered as an important mediator of mitogenic signaling and regulator of cell cycle entry, cell growth and proliferation, integrin-mediated interactions, and cell-cell adhesion (Saito et al., 2010). *FYN* expression or *FYN* knockdown has been studied in many types of cancers including chronic myelogenous leukemia (CML) (Elias and Ditzel, 2015), glioblastoma multiforme, melanoma (Lu et al., 2009), breast cancer (Saito et al., 2010; Xie et al., 2016), oral squamous cell carcinoma (Lewin et al., 2010), pancreatico-biliary cancer (Lyu et al., 2018), and gastrointestinal cancer (Yu et al., 2020a; Yu et al., 2020b).

In cancers, *FYN* may play an important role in the development and progression of cancer through the involvement of apoptosis inhibition, cell proliferation, cell migration, invasion, and metastasis. *FYN* may promote anti-apoptotic activity of AKT, by phosphorylation of focal adhesion kinase (FAK) and the activation of PI3K/AKT pathway (Saito et al., 2010). *FYN* may activate ERK/MAPK signaling via RAS, resulting in increased cell motility and proliferation (Saito et al., 2010). *FYN* has a role in epithelial-mesenchymal transition (EMT), which is important for migration, invasion, and metastasis of cancer cells. In breast cancer, *FYN* was found to mediate FGF2-induced EMT through both the PI3K/AKT and ERK/MAPK pathways (Xie et al., 2016). Meanwhile, *FYN* could also induce the activity of PI3K/AKT and ERK/MAPK, suggesting that there is a crosstalk between PI3K/AKT, ERK/MAPK and *FYN* (Xie et al., 2016). In basal-type breast carcinoma, *FYN*

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contributed to mesenchymal phenotypes and metastatic potential of the tumor by enhancing NOTCH2 activation through STAT5-mediated signaling pathway (Lee et al., 2018). In gastric cancer, *FYN* may induce EMT through STAT3 pathway activation (Yu et al., 2020b). High *FYN* expression in gastric cancer was associated with lymph node metastasis, and it was an independent risk factor for poorer survival (Yu et al., 2020b). In prostatic cancer, *FYN* may bring significant contribution to metastatic ability via HGF/MET signaling pathway (Jensen et al., 2011). In colonic cancer, *FYN* is required for ARHGEF16 to promote the proliferation and migration of cancer cells (Yu et al., 2020a). *FYN* may also have an important role in treatment resistance of cancers; e.g., tamoxifen-resistant estrogen receptor-positive breast cancer, imatinib-resistant CML. On the other hand, *FYN* may serve as a potential target for cancer treatment (Saito et al., 2010; Elias and Ditzel, 2015; Yu et al., 2020b). The information regarding *FYN* expression in EOC is very limited. In an analysis of transcriptome profile in ovarian cancer cell lines, *FYN* was found to be one of the hub genes of the interaction network in cisplatin-resistant tumor (Sakhare et al., 2014). However, *FYN* expression among different types of EOC and its prognostic significance have not been well described. This study was aimed to evaluate *FYN* expression among different types of EOC and its association with the clinical outcomes.

Materials and Methods

Study population

This study was approved by the institutional ethics committee of the Faculty of Medicine, Chiang Mai University (Study code: FAC-MED-2561-05420). The study population included women who were diagnosed with malignant epithelial tumors involving the ovary and whose tissue samples were available in the biospecimen bank project of the Department of Pathology, Faculty of Medicine, Chiang Mai University (PAT-2556-01700), between January 2014 and December 2016.

Tissue samples and information of patients

The fresh tissue of ovarian malignancy in the study was collected during the macroscopic examination and snap-frozen in liquid nitrogen. A mirror-imaged tissue block of each tissue sample was also obtained for the preparation of the histologic reference. In all cases, the pathological specimens were examined by a group of gynecologic pathologists. The histological types of EOC represented in the frozen tissue were reviewed in correlation with the histologic sections of tumors by a gynecologic pathologist (SK). The histologic types of EOC were classified based on the 2014 World Health Organization Classification (Kurman et al., 2014). EOC were further categorized as high-grade carcinomas for high-grade serous carcinomas (HGSC), clear cell carcinomas (CCC), or grade 3 for other types (i.e., endometrioid or mucinous carcinomas). Other EOC types that didn't meet the criteria for high-grade category were grouped as low-grade carcinomas. The frozen tissue samples were stored at -80°C until RNA extraction to analyze *FYN* expression.

Clinical information was obtained from medical records; it consisted of age and FIGO stage (International Federation of Gynecology and Obstetrics staging system) (Kurman et al., 2014), the status of tumor debulking (optimal versus suboptimal), and treatment information. FIGO stages were divided into early stage (stage I-II) and advanced stage (stage III-IV). Suboptimal tumor debulking was defined as the presence of maximum residual tumor greater than 1 cm after the surgical procedure. The patients who received preoperative or neoadjuvant chemotherapy were not included in the study. The follow-up outcomes recorded up until December 2019 were obtained from medical records. In the cases of patients who were followed in other hospitals after their treatment, the outcome information was obtained by directly contacting the physicians in charge of patient care. Disease progression including tumor recurrence or progressive disease was defined as the progression of cancer detected from imaging and/ or double rising of CA125.

RNA extraction and cDNA synthesis

A total RNA was extracted using RNeasy® Mini kit (QIAGEN GmbH, Germany) according to the manufacturer's recommendations. The purified total RNA was quantified using a UV spectrophotometer (Nanodrop 2000, Thermo Fisher Scientific, Waltham, MA, USA) with an assessment of the A260/230 ratio that was expected to be within the range of 1.80 to 2.30. Then, 2 µg of total RNA of each sample was converted to cDNA using a reverse transcription reagent kit (Superscript III, Invitrogen, Carlsbad, CA, USA) primed with random hexamers, according to the manufacturer's protocol.

Quantitative Real time-RT-PCR

The mRNA *FYN* expression levels in different histological groups of ovarian cancer were evaluated using the SYBR Green method (Sensifast SYBR, Invitrogen, Carlsbad, CA, USA) and the intensity of the fluorescence signal was detected by using a 7500 Real-time PCR System (Applied Biosystems, Foster City, CA). The GAPDH gene was used as an endogenous control for qRT-PCR normalization. The PCR primer sequences of *FYN* and GAPDH are displayed in Table 1. The expression levels of *FYN* were normalized with housekeeping gene GAPDH (ΔCt) and determined as $2^{-\Delta Ct}$. Each sample was tested in triplicate. Due to the lack of previously reported reference threshold for *FYN* expression, the cut-off value was determined by the clinical outcomes (disease progression).

Statistical analysis

All statistical analyses were performed using STATA version 16 (STATA Corp., Texas, USA). Kruskal-Wallis equality-of-populations rank test was used to test the significance of differences in the median values of *FYN* expression among different types of EOC. Statistical significance of the difference between two histologic types of EOC was analyzed by the Mann-Whitney test. Receiver operating characteristics (ROC) analysis was performed to calculate the area under the curve (AUC)

and to determine the best threshold for positive *FYN* expression in the prediction of disease progression, using ROC analysis with the maximum sum of sensitivity and specificity.Progression-free survival (PFS) was defined as the time from the initial treatment to the time of recurrence or progression of the disease or the time of last contact. The Kaplan-Meier analysis was used to estimate the probability and duration of PFS. Cox proportional hazards regression model was used to estimate the effect of *FYN* expression on survival outcome. Statistical significance was accepted at $P < 0.05$.

Results

Baseline characteristics of ovarian cancer patients

Among the 98 primary EOC, the mean patient age was 56.3 years (±11.8). The histologic types of 98 primary EOC included HGSC (43 cases; 43.9%), CCC (29 cases; 29.6%), endometrioid (15 cases: high-grade in 4), mucinous (9 cases: high-grade in 3), and low-grade serous carcinoma (2 cases) (Table 2). Regarding the FIGO stage, 45 (45.9%) were in early stage (stage I in 28 and stage II in 17), and 53 (54.1%) were in advanced stage (stage III in 41 and stage IV in 12). Most of HGSC presented were in advanced stage (72.1%), whereas most of CCC (58.6%) and low-grade EOC (78.9%) presented were in early stage.

Clinical follow-up outcomes were available in 87 cases of primary EOC (88.8%) with a median follow-up time of 2.58 (95% CI: 2.25-3.08) years. Progression of disease was reported in 53 patients (60.9%). The median progression free survival was 2.16 (95% CI: 1.25- 3.50) years. The patient group with disease progression represented 56.7% (30 of 53) of HGSC, 28.3% (15 of 53) of CCC, 7.5% (4 of 53) of other high-grade carcinomas, and 7.5% (4 of 53) of low-grade carcinomas

FYN expression by histologic types of ovarian carcinomas and clinical outcomes

FYN expression varied by histologic types of tumors (Figure 1). The median levels of *FYN* expression showed significant difference between groups (Kruskal-Wallis equality-of-populations rank test, $p = 0.0006$). HGSC had the highest median *FYN* expression level (0.0063; IQR: 0.0089) followed by other high-grade carcinomas (0.0034; IQR: 0.0073), -, low-grade carcinomas (0.0018; IQR: .005494), and CCC (0.0004; IQR: 0.0038). In addition, the median *FYN* expression level of HGSC was significantly higher than that of CCC (Mann-Whitney U test; $p < 0.001$) and low-grade carcinomas ($p = 0.012$). There was no significant difference in the levels of *FYN* expression between the different tumor types in the other high-grade carcinoma group and the low-grade carcinoma

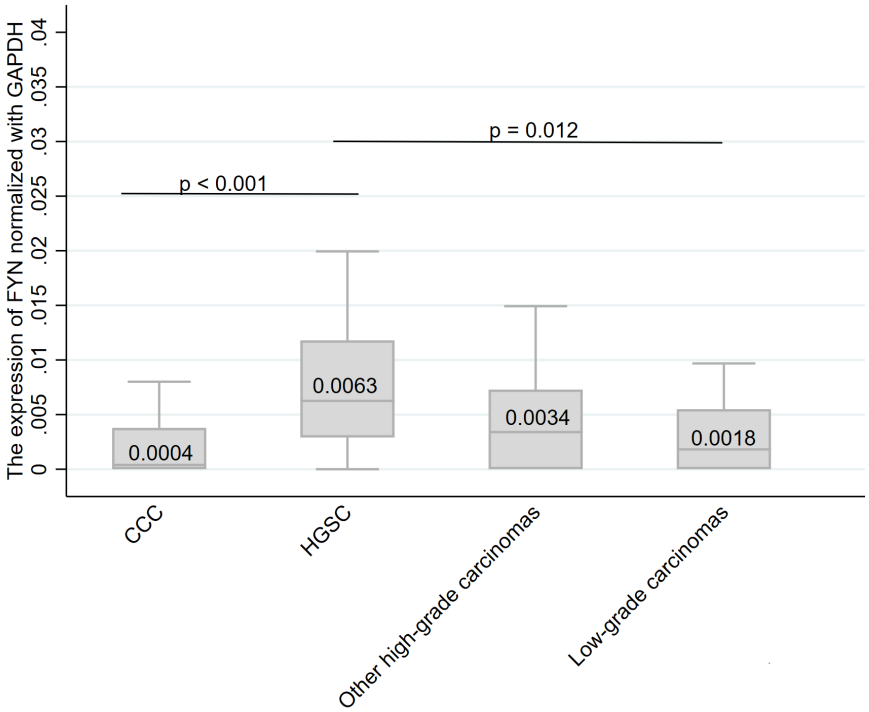

Figure 1. The Expression Levels of FYN mRNA in Differentiating Histological Subtypes of Ovarian Cancer (Kruskal-Wallis equality-of-populations rank test, p= 0.0006).

Table 1. The PCR Primer Sequences of FYN and GAPDH for This Study

Primer Name	Sequence	Tm (ºC)	Product size
FYN F	5'AAG GCT TAC CGA TCT GTC TG 3'	58	648
FYN R	5'TAT GGC ACT CTT CCT TTG GT 3'	57	
GAPDH F	5' AGC CAC ATC GCT CAG ACA CC 3'	63	204
GAPDH R	5' CCT TGA CGG TGC CAT GGA AT 3'	61	

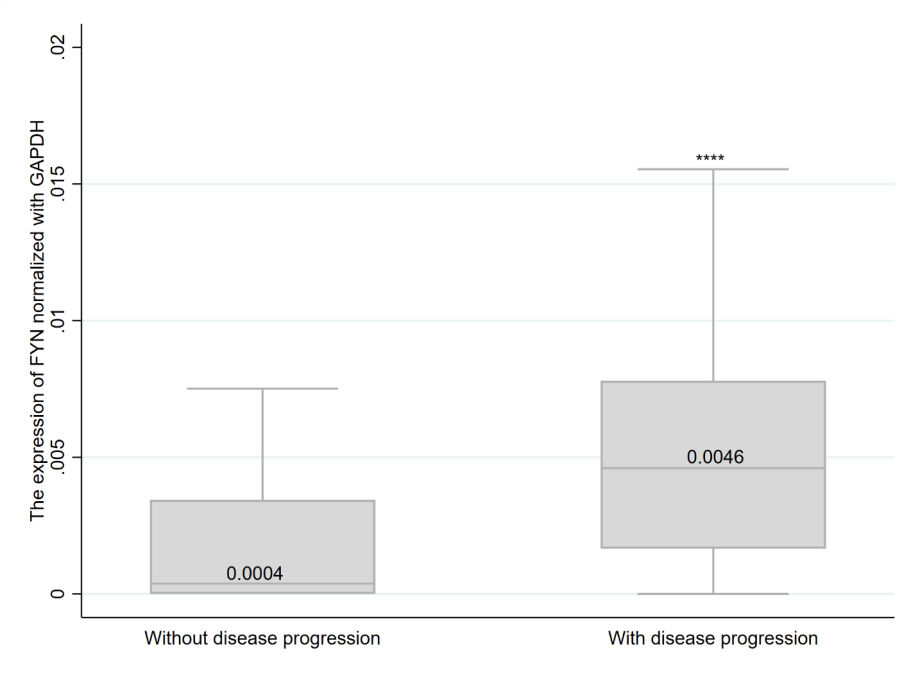

Figure 2. The Relative Expression Levels of FYN mRNA between the EOC Patient Groups with and without Disease Progression (Mann-Whitney U test, p = 0.0005).

Table 2. Histologic Distribution of 98 Cases in the Study

Histologic types	Number of cases	%
High-grade carcinomas	79	80.61
Serous	43	43.87
Clear cell	29	29.6
Endometrioid	4	4.08
Mucinous	3	3.06
Low-grade carcinomas	19	19.39
Endometrioid	11	11.22
Serous	2	2.05
Mucinous	6	6.12
Total	98	100

group.

Based on the outcome status (with versus without disease progression), the patient group with disease progression had a significantly higher median level of *FYN* expression compared to the patient group without progression (Mann-Whitney U test, p = 0.0005) (Figure 2).

Receiver operating characteristic curve analysis was performed to determine the threshold value with optimal sensitivity and specificity for discriminating between the EOC patient group with disease progression and the group without progression. The cutoff value of 0.003397 was chosen, with an AUC value of 0.736 (95% CI; 0.630 - 0.824), a sensitivity of 71.70%, and a specificity of 73.53% with a likelihood ratio of 2.70 for distinguishing both patient groups (Figure 3). The optimal cutoff values for predicting disease progression in each histologic type of EOC are presented in Table 3.

The cutoff value of each histologic group was comparable to the overall cutoff value. Using the overall threshold *FYN* expression levels (0.003397), the positive predictive value was 69.8% (95% CI, 55.7% - 81.7%) while the negative predictive value was 73.5% (95% CI, 55.6% - 87.1%) for predicting disease progression. The highest rate of *FYN* expression was observed in HGSC (68.4%, 26 of 38), followed by CCC (41.4%, 12 of 28), low-grade carcinomas (40.0%, 6 of 15), and other high-grade carcinomas (33.3%, 2 of 6).

The analysis of progression-free survival (PFS) among EOC patients revealed that the *FYN*-positive group had poorer PFS outcome compared to the *FYN*-negative group (log-rank test; p = 0.0012) (Figure 4). Further analysis of PFS in each histologic group was performed, significant survival difference of *FYN* expression status was observed among the CCC patient group (log rank test, p = 0.005). (Figure 5 A-D).

The Cox regression analysis for variables that may be associated with disease progression is shown in Table 4, including histologic type, age, *FYN* expression, FIGO stage, and debulking status. The multivariate Cox

Table 3. The Optimal Cutoff Values for Predicting Disease Progression in Different Histologic Groups of EOC

Histologic Subtype	Optimal cutoff value	Sensitivity (%)	Specificity (%)	AUC (95% CI)
High-grade serous carcinomas	0.0035	75.86	62.5	0.6681 (0.502 - 0.820)
Clear cell carcinomas	0.00348	73.33	92.31	0.797 (0.590 - 0.917)
Other high-grade carcinomas	0.00339	50	50	0.5625 (0.118 - 0.882)
Low-grade carcinomas	0.00329	75	63.64	0.6591 (0.384 - 0.882)

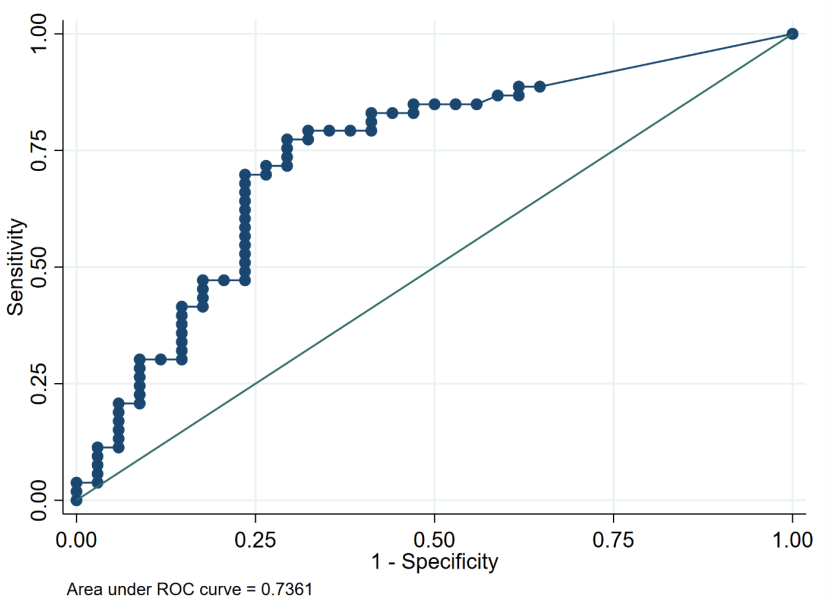

Figure 3. The ROC Curve Analysis of FYN Expression for Prediction of Disease Progression in EOC Patients.

regression showed that FIGO stage, histologic type, and *FYN* expression were independent predictors for disease progression.

We further analyzed whether *FYN* expression could predict disease progression or PFS in different histologic groups of EOC with an early or an advanced stage. In the group of early stage CCC patients, *FYN*-positive patients had a lower PFS than *FYN*-negative patients (log rank test; p = 0.0086) (Figure 6A). However, no significant difference in survival by *FYN* expression was observed among patients with an advanced stage CCC (p = 0.586) (Figure 6A). Using *FYN* expression as a predictor for disease progression in CCC patients, the *FYN* expression had a high performance with a sensitivity of 91.7% (95% CI: 61.5% - 99.8%), a specificity of 75.0% (95% CI: 47.6% - 92.7%), a positive predictive value of 73.3% (95% CI: 44.9% - 92.2%), and a negative predictive value of 92.3% (95% CI: 64.0% - 99.8%).

In the other types of EOC, no significant difference of PFS was observed in the subgroups of early stage and advanced stage patients; this included HGSC (p = 0.847 for early stage and p = 0.659 for advanced stage), other high-grade carcinomas (p = 0.225 for early stage and p = 0.157 for advanced stage), and low-grade carcinomas (p = 0.613 for early stage and p = 0.317 for advanced stage).

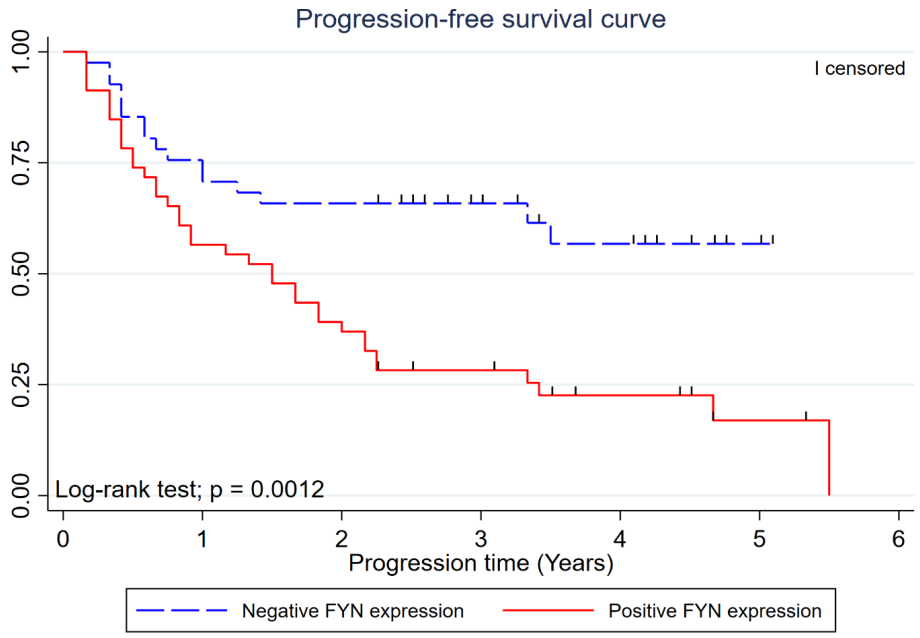

Figure 4. Kaplan-Meier Progression-Free Survival Plot of EOC Patients Stratified by FYN Expression Status (log-rank test; p = 0.0012)

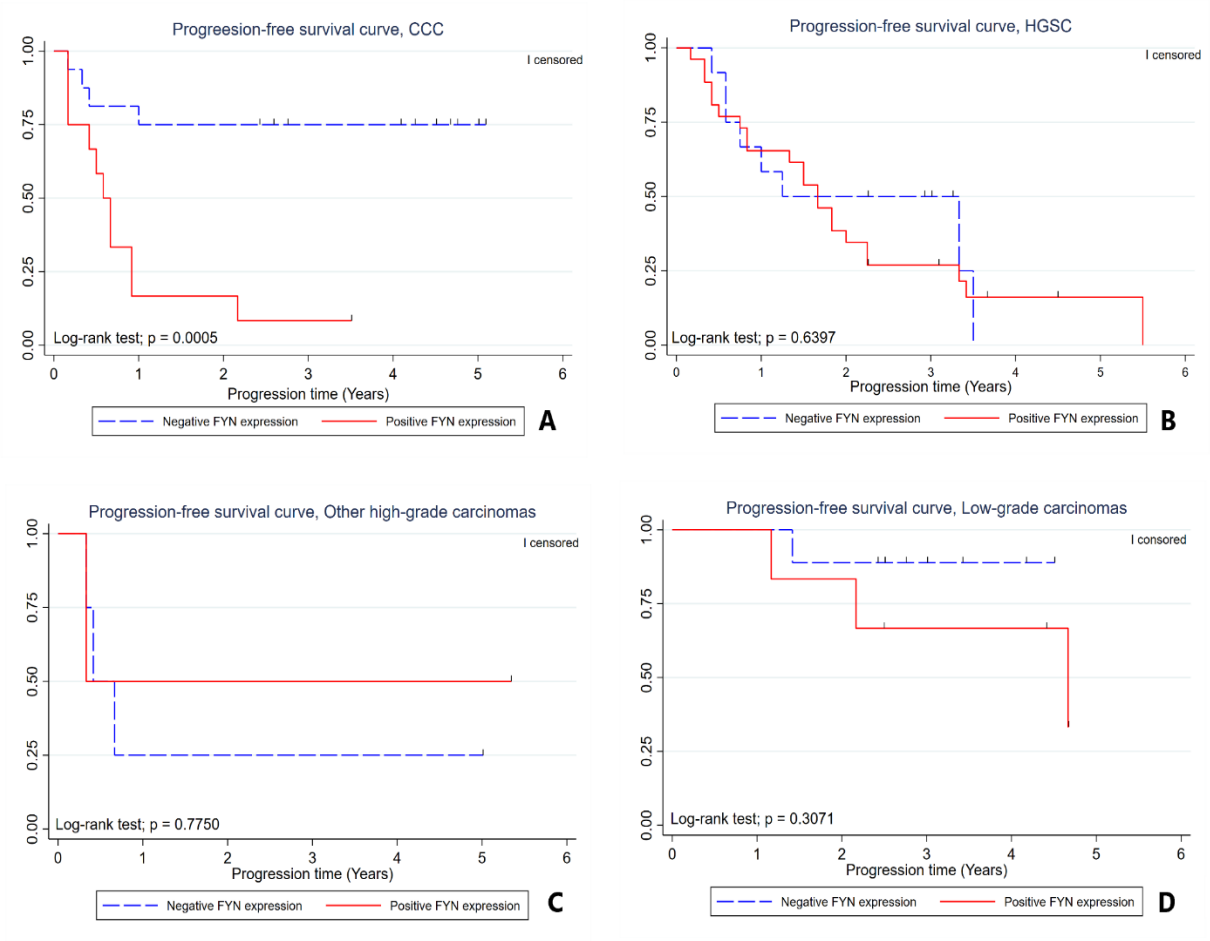

Figure 5. Kaplan-Meier Progression-Free Survival Plots of Patients with Different Types of EOC stratified by FYN expression status. A, clear cell carcinomas (CCC); B, high-grade serous carcinomas (HGSC); C, other high-grade carcinomas; D, low-grade carcinomas

Table 4. Analysis for Variables Predicting Disease Progression in EOC Patients

Factor	Univariate Cox regression		MultivariateCox regression	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI) (Adjusted)	P-value
Histologic types				
Low-grade carcinomas	Reference		Reference	
High-grade serous carcinoma	3.88 (1.36- 11.08)	0.011	1.68 (0.57- 4.92)	0.344
Clear cell carcinoma	2.69 (0.89-8.13)	0.079	5.52 (1.68-18.09)	0.005
Other high-grade carcinomas	2.98 (0.74- 11.98)	0.124	3.12 (0.75- 12.86)	0.115
Age at diagnosis (years)				
≤50 years	Reference		Reference	
>50 years	0.48 (0.27 - 0.86)	0.013	0.50 (0.30 - 0.10)	0.049
FYN expression				
Negative	Reference		Reference	
Positive	2.54 (1.41- 4.60)	0.002	2.30 (1.21 - 4.38)	0.011
FIGO stage				
Early Stage (I & II)	Reference		Reference	
Advance stage (III & VI)	4.61 (2.35 - 9.02)	<0.001	4.39 (1.90 - 10.16)	0.001
Status of tumor debulking				
Optimal	Reference		Reference	
Suboptimal	2.55 (1.47- 4.43)	0.001	1.72 (0.88 - 3.36)	0.108

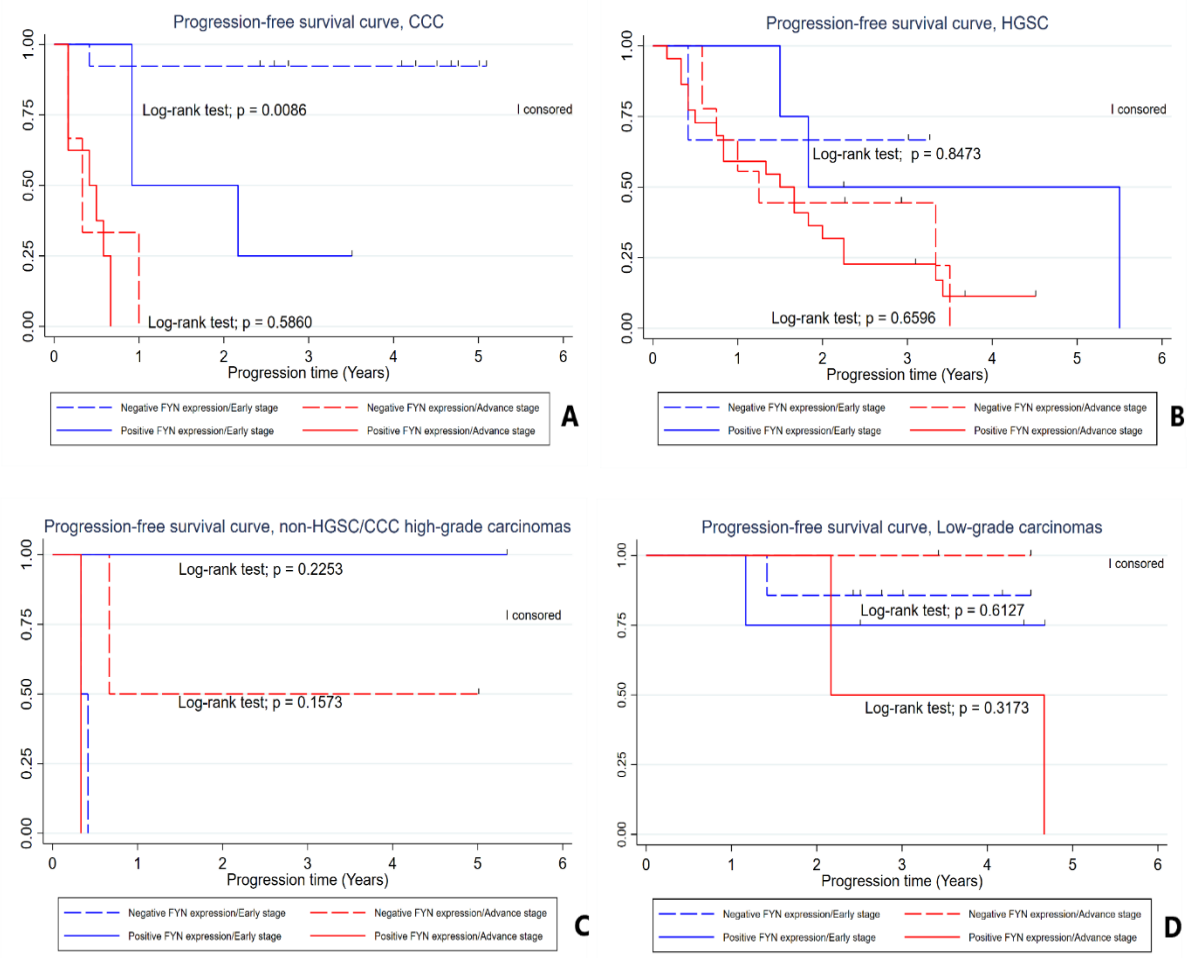

Figure 6. Kaplan-Meier Progression-Free Survival Plots of Patients with Different Types of EOC Stratified by FYN Expression and FIGO Stage. A, clear cell carcinomas (CCC); B, high-grade serous carcinomas (HGSC); C, other high-grade carcinomas; D, low-grade carcinomas

Discussion

EOC is heterogeneous. HGSC comprises the majority of EOC (up to 70%). While CCC represents only 12% of EOC in North America, this type of cancer is more common among Asian countries, accounting for up to 27% of EOC in Japan, notably (Takahashi et al., 2020). In terms of frequency of CCC, the data in this study closely match against what is observed in the Eastern populations. Although different types of EOC are treated with a similar regimen/policy, CCC is well recognized for its particularly poor prognosis in advanced stage patients (Jin et al., 2014; Takahashi et al., 2020). The prognosis of CCC was poorer than that of HGSC among the patients with an advanced stage or with recurrent disease, at least partly due to chemoresistance of CCC (Iida et al., 2021). A development of new therapeutic strategies for CCC is needed (Takahashi et al., 2020). Studies on therapies targeting angiogenic pathways, PIK/AKT/mTOR pathway, immune checkpoints, or MAPK pathway are currently under evaluation (Iida et al., 2021).

Among different histologic groups of EOC, HGSC represents the type with the highest median level of *FYN* expression, whereas CCC had the lowest. Other high-grade carcinomas (endometrioid/mucinous) and low-grade carcinomas produced values that were intermediate between HGSC and CCC. The explanation for such differences remains to be elucidated, but it is well recognized that molecular pathogenesis of each type of EOC is different.

Between HGSC and CCC, there are rather striking differences in molecular pathogenesis. The most important molecular genetic alteration in HGSC is TP53 mutation, which is detected in over 95% of cases and occurs early in the carcinogenesis steps (Yamulla et al., 2020). In contrast, TP53 mutation is present in only 18% of CCC (Friedlander et al., 2016). In CCC, mutations of ARID1A and PIK3CA represent the two most important genetic alterations, each having been identified in 50% of cases (Iida et al., 2021). The frequency of PIK3CA mutation in CCC is more frequent than in the other types of EOC (Friedlander et al., 2016), and PIK3CA mutation is even rare in HGSC (Yamulla et al., 2020). Although it is not clear how TP53 mutation in HGSC could link to *FYN* expression, TP53 mutation is associated with genetic instability and with some increased amplification of multiple oncogenes (Donehower et al., 2019). The p53 status can also affect MAPK signaling pathway (Stramucci et al., 2018), which interacts with *FYN* expression (Xie et al., 2016). Wild-type p53 could induce a negative feedback on

p38MAPK expression, whereas mutant p53 could increase p38MAPK expression, which affects cell proliferation and survival (Stramucci et al., 2018). Given that CCC has a higher rate of PIK3CA mutation than that of other types of EOC, it is possible that oncogenic signaling pathways other than PIK3K pathway are necessary for high *FYN* expression in EOC.

In this study, *FYN* expression status was an independent predictor of poor PFS in EOC patients, in addition to the well-established parameter, namely the FIGO stages. Clear cell histology was also found to be another independent prognostic predictor. The prognostic impact of *FYN* expression was demonstrated in patients with early-stage CCC. The information in this study may be considered preliminarily, and further investigations are needed to confirm the significance of *FYN* expression in early-stage CCC.

In a previous comparative analysis of transcriptome profile in ovarian cancer cell lines, between cisplatin-resistant cell line (OVCAR3) and that with drug-sensitive (SKOV3), *FYN* and ERRB2 (HER2) were found to be the two hub genes of the interaction network in the potential pathway of drug resistance (Kim et al., 2011). A recent study in patients with HGSC reported a significant decrease in phosphorylation of multiple tyrosine kinases, including *FYN*, in the cases with excellent response to neoadjuvant chemotherapy (n=10) compared to those with a poor response (n=10) (Lee et al., 2020). In our study, all patients with early-stage CCC had received post-operative adjuvant chemotherapy, but *FYN* expression was associated with tumor recurrence in this patient group. This finding may raise some possible involvement of *FYN* in the resistance to chemotherapy of CCC cells. However, there was no significant association between *FYN* expression and the clinical outcome of the patients with advanced stage CCC; this was also the case with other types of FOC.

The limitation in the study included a rather small number of cases. The mechanism of *FYN* involvement in the clinical behavior of EOC also remains to be clarified. In this study, *FYN* expression may contribute to the increased aggressiveness of ovarian EOC, specifically CCC type. If the postulation that *FYN* can increase the aggressiveness of CCC is true, there may be a possibility for combining therapy targeting *FYN* with standard chemotherapy for the prevention of recurrence in patients with early-stage CCC. Future study in a larger population would further verify the role of *FYN* expression in ovarian EOC.

In conclusions, expression of *FYN* varied among different histologic types of EOC, with the highest expression level in HGSC. There was a correlation between *FYN* expression and disease progression in EOC patients, particularly with CCC histology. The prognostic value of *FYN* expression was identified in early stage CCC patients.

Author Contribution Statement

WD., conceptualized and designed the study, conducted data collection, analyzed and interpreted the data, wrote the first draft of the manuscript; SK., conducted data collection, analyzed and interpreted the data, and critically reviewed the manuscript for important intellectual content; PS., analyzed and interpreted the data, and critically reviewed the manuscript for important intellectual content; SL., administered the project, analyzed and interpreted the data, and critically reviewed the manuscript for important intellectual content. All authors reviewed the results and approved the final version of the manuscript.

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General

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Scientific Approval

This manuscript is not part of an approved student thesis or was approved by any scientific body.

Ethical Approval

This study was approved by the institutional ethics committee of the Faculty of Medicine, Chiang Mai University (Study code: FAC-MED-2561-05420).

Availability of data

All data generated or analysed in this study are included in this manuscript. The primary data can be obtained from the corresponding authors.

Conflict of interest

The authors have no conflict of interest to declare.

References

Donehower LA, Soussi T, Korkut A, et al (2019). Integrated Analysis of TP53 Gene and Pathway Alterations in The Cancer Genome Atlas. *Cell Rep*, **28**, 1370-84 e5.

Elias D, Ditzel HJ (2015). *FYN* is an important molecule in cancer pathogenesis and drug resistance. *Pharmacol Res*, **100**, 250-4.

Friedlander ML, Russell K, Millis S, et al (2016). Molecular Profiling of Clear Cell Ovarian Cancers: Identifying Potential Treatment Targets for Clinical Trials. *Int J Gynecol Cancer*, **26**, 648-54.

Iida Y, Okamoto A, Hollis RL, et al (2021). Clear cell carcinoma of the ovary: a clinical and molecular perspective. *Int J Gynecol Cancer*, **31**, 605-16.

Jensen AR, Saito YD, Liao CH, et al (2011). *FYN* Is Downstream of the HGF/MET Signaling Axis and Affects Cellular Shape and Tropism in PC3 Cells. *Clin Cancer Res*, **17**, 3112-22.

Jin Y, Li Y, Pan L (2014). The target therapy of ovarian clear cell carcinoma. *Onco Targets Ther*, **7**, 1647-52.

Kim TM, Ha SA, Kim HK, et al (2011). Gene expression signatures associated with the in vitro resistance to two tyrosine kinase inhibitors, nilotinib and imatinib. *Blood Cancer J*, **1**, e32.

Kurman RJ, International Agency for Research on Cancer., World Health Organization. 2014. WHO classification of tumours of female reproductive organs, Lyon, International Agency for Research on Cancer.

Lee GH, Yoo KC, An Y, et al (2018). *FYN* promotes mesenchymal phenotypes of basal type breast cancer cells through STAT5/NOTCH2 signaling node. *Oncogene*, **37**, 1857-68.
Lee S, Zhao L, Rojas C, et al (2020). Molecular Analysis of Clinically Defined Subsets of High-Grade Serous Ovarian Cancer. *Cell Rep*, **31**, 107502.
Lewin B, Siu A, Baker C, et al (2010). Expression of *FYN* kinase modulates EMT in oral cancer cells. *Anticancer Res*, **30**, 2591-6.
Lu KV, Zhu S, Cvrljevic A, et al (2009). *FYN* and SRC are effectors of oncogenic epidermal growth factor receptor signaling in glioblastoma patients. *Cancer Res*, **69**, 6889-98.
Lyu SC, Han DD, Li XL, et al (2018). *FYN* knockdown inhibits migration and invasion in cholangiocarcinoma through the activated AMPK/mTOR signaling pathway. *Oncol Lett*, **15**, 2085-90.
Saito YD, Jensen AR, Salgia R, et al (2010). *FYN*: a novel molecular target in cancer. *Cancer*, **116**, 1629-37.
Sakhare SS, Rao GG, Mandape SN, et al (2014). Transcriptome profile of OVCAR3 cisplatin-resistant ovarian cancer cell line. *BMC Bioinformatics*, **15**.
Stramucci L, Pranteda A, Bossi G (2018). Insights of Crosstalk between p53 Protein and the MKK3/MKK6/p38 MAPK Signaling Pathway in Cancer. *Cancers (Basel)*, **10**.
Takahashi K, Takenaka M, Kawabata A, et al (2020). Rethinking of treatment strategies and clinical management in ovarian clear cell carcinoma. *Int J Clin Oncol*, **25**, 425-31.
Xie YG, Yu Y, Hou LK, et al (2016). *FYN* promotes breast cancer progression through epithelial-mesenchymal transition. *Oncol Rep*, **36**, 1000-6.
Yamulla RJ, Nalubola S, Flesken-Nikitin A, et al (2020). Most Commonly Mutated Genes in High-Grade Serous Ovarian Carcinoma Are Nonessential for Ovarian Surface Epithelial Stem Cell Transformation. *Cell Rep*, **32**, 108086.
Yu B, Xu L, Chen L, et al (2020a). *FYN* is required for ARHGEF16 to promote proliferation and migration in colon cancer cells. *Cell Death Dis*, **11**, 652.
Yu J, Zhou Z, Wei Z, et al (2020b). *FYN* promotes gastric cancer metastasis by activating STAT3-mediated epithelial-mesenchymal transition. *Transl Oncol*, **13**, 100841.