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RESEARCH ARTICLE

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Eukaryotic initiation factor 3B is overexpressed and correlates with larger tumor size, advanced FIGO stage, and shorter overall survival in epithelial ovarian cancer patients

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Abstract

Background: This study aimed to detect the eukaryotic initiation factor 3B (EIF3B) expression and explore its correlation with clinical features and prognosis in epithelial ovarian cancer (EOC) patients.

Methods: A total of 230 primary EOC patients underwent surgery treatment were retrospectively reviewed. Immunohistochemical (IHC) assay was used to determine EIF3B expression in tumor and adjacent tissue specimens of all patients. According to the total IHC score, the expression of EIF3B was classified as low expression and high expression, and the latter was further divided into 3 grades: high+, high++, and high+++ expressions. Overall survival (OS) was calculated.

Results: Eukaryotic initiation factor 3B expression was increased in tumor tissue compared with adjacent tissue. Tumor EIF3B high expression correlated with larger tumor size (>10 cm), lymphatic metastasis, and advanced International Federation of Gynecology and Obstetrics stage (FIGO) (III/IV). Besides, OS was decreased in patients with tumor EIF3B high expression compared with patients with tumor EIF3B low expression, and further analysis showed that the OS was shortest in patients with tumor EIF3B high+++ expression, followed by patients with tumor EIF3B high++ expression and patients with tumor EIF3B high + expression, and the longest in patients with tumor EIF3B low expression. Additionally, higher tumor EIF3B expression, peritoneal cytology (positive), ascites volume (>100 mL), differentiation (poor vs. well/moderate), tumor size (>10 cm), FIGO stage (III/IV vs. I/II), and cancer antigen 125 (>1000 U/mL) independently predicted shorter OS.

Conclusion: Eukaryotic initiation factor 3B exhibits a clinical value for monitoring disease progression and predicting prognosis in EOC patients.

KEYWORDS

epithelial ovarian cancer, eukaryotic initiation factor 3B, oncogenic factor, overall survival, progression

1 | INTRODUCTION

Ovarian cancer (OC) is the second most lethal gynecological cancer in women with approximately 239 000 new cases and 152 000 deaths each year worldwide.[1] As the most prevalent type of ovarian cancer, epithelial OC (EOC) accounts for over 95% of ovarian cancer cases.[2] Most of the EOC patients are diagnosed at an advanced stage (International Federation of Gynecology and Obstetrics (FIGO) stage III and IV) due to the asymptomatic nature of the disease at early stage.[2-4] At an advanced stage, although patients initially respond effectively to first-line taxane/platinum-based chemotherapies and cytoreduction, the majority of patients will develop recurrence and acquire chemoresistance with a dismal five-year relative survival rate of 29%.[2,4] Therefore, the investigation of potential biomarkers is vital for assisting disease management and prognosis improvement in EOC patients.

Eukaryotic initiation factor 3 (EIF3) is a multi-subunit complex with 13 different polypeptide subunits, which exhibits an essential role in the initial process of protein translation.[5,6] As a key scaffolding subunit in the EIF3 complex, EIF3B is reported to be involved in the tumorigenesis of several cancers such as esophageal squamous cell cancer (ESCC) and clear cell renal cell carcinoma (ccRCC).[7-11] For instance, EIF3B knockdown suppresses cell proliferation and invasion, facilitates cell apoptosis, and disrupts the cell cycle via medicating the activation of β-catenin signaling pathway in ESCC.[7] In ccRCC, EIF3B knockdown suppresses cell proliferation by interrupting the cell cycle progression and induces cell apoptosis through impairing the action of the Akt pathway.[8] Regarding the clinical value, EIF3B is associated with exacerbated clinical features and poor prognosis in multiple cancers such as ESCC, ccRCC, and gastric cancer.[7,8,11] As for EOC, a recent mechanism study displays that EIF3B inhibition attenuates cell proliferation and elevates cell apoptosis in ovarian cancer SKOV3 and HO-8910 cells.[9] However, the clinical implication of EIF3B in the development and progression of EOC is rarely reported. Therefore, this study was to detect the EIF3B expression and explore its correlation with clinical features as well as prognosis in EOC patients.

2 | MATERIALS AND METHODS

2.1 | Patients

In this retrospective study, 230 primary EOC patients who underwent surgery treatment in North China University of Science and Technology Affiliated Hospital between January 2014 and December 2018 were screened. All patients were (a) firstly diagnosed as primary EOC by histopathology, (b) age between 18 and 80 years old, and (c) the tumor tissue and adjacent tissue resected from surgery were available and eligible for immunohistochemical (IHC) assay. The following patients were excluded: (a) had incomplete clinical data at diagnosis, (b) had incomplete survival data that cannot be used for overall survival (OS) calculation, (c) history of ovarian surgery, and (d) received neoadjuvant therapy before enrollment. The Institutional Review Board of North China University of Science and Technology Affiliated Hospital approved this study, and all patients provided the written informed consents before enrollment.

2.2 | Data collection

The major clinical characteristics at diagnosis were recorded, which included age, histological subtype, peritoneal cytology, ascites volume, tumor differentiation, tumor size, lymphatic metastasis, FIGO stage, cancer antigen 125 (CA125), and carbohydrate antigen (CA199) levels were collected from database of North China University of Science and Technology Affiliated Hospital. Besides, EIF3B expression in cancer tissues (such as OC, glioma, and thyroid cancer) and the correlation of EIF3B expression with survival probability in OC patients were retrieved from Human Protein Atlas Database (https://www.proteinatlas.org) that was derived from TCGA database.

2.3 | IHC assay

The tumor tissue specimens and adjacent tissue specimens were formalin-fixed and paraffin-embedded, and all tissue specimens were cut into 4 μm sections. After the sections were deparaffinized with xylene and rehydrated with graded ethanol, the mediated antigen retrieval was performed using microwave heating. Then, the sections were blocked with 0.3% H_2O_2 for 15 minutes and incubated with 10% normal goat serum (Sigma-Aldrich) for 2 hours. Subsequently, the primary antibody rabbit monoclonal to EIF3B at 1:100 dilution (Abcam) was added to the sections, which were then incubated at 4℃ overnight. Next day, the secondary antibody goat anti-rabbit IgG H&L (HRP) at 1:1000 dilution (Abcam) was added and incubated at 37℃ for 60 min. Finally, the tissue sections were washed and treated with diaminobenzidine (DAB) (Sigma-Aldrich) followed by counterstaining with hematoxylin (Sigma-Aldrich). Of note, EIF3B-positive staining was located in the nucleoplasm and cytosol of cells (retrieved from Human Protein Atlas Database (https://www.proteinatlas.org) that was derived from TCGA database).

2.4 | EIF3B expression assessment

Nikon ECLIPSE E200 microscope (Nikon Instruments) was utilized to observe IHC staining results, and the expression of EIF3B in tissues was assessed by a semi-quantitative scoring method as previously described.[12] The intensity of positive cells was scored as 0 (negative), 1 (weakly stained), 2 (moderately stained), and 3 (strong stained). The percentage of positively stained cells (staining density) was graded as 0 (0%), 1 (1%-25%), 2 (26%-50%), 3 (51%-75%), and 4 (76%-100%). Finally, according to the IHC score (staining intensity score*staining density score), the expression of EIF3B was classified as low expression (IHC score 0-3) and high expression (IHC score 4-12) which was further

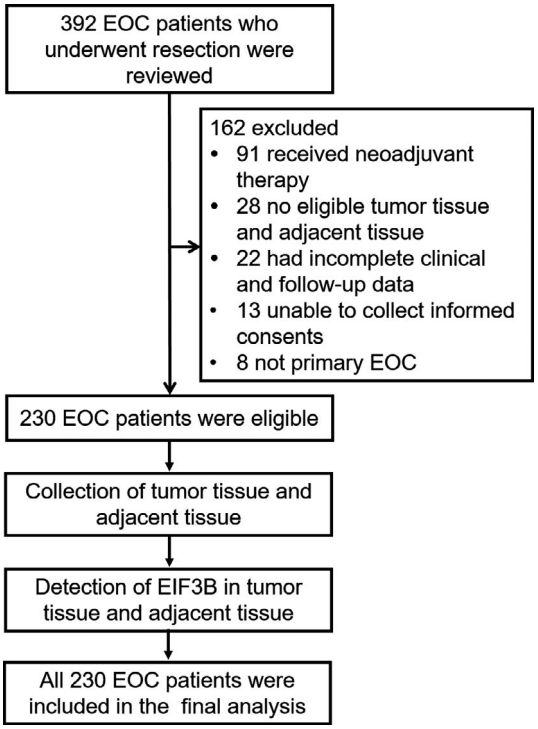

FIGURE 1 Study flow. EOC, epithelial ovarian cancer; EIF3B, eukaryotic translation initiation factor 3B

divided into 3 grades: high + expression (IHC score 4-6), high++ expression (IHC score 7-9), and high+++ expression (IHC score 10-12).[12]

2.5 | Follow-up

The survival data of patients were extracted from follow-up data. The last follow-up date was December 31, 2018, and the median duration follow-up was 30.0 months (ranging 1.0-60.0 months). Based on the survival data, the OS was calculated from the date of surgery to the date of death.

2.6 | Statistical analysis

SPSS 22.0 (IBM) was used for statistical analysis, and GraphPad Prism 7.00 (GraphPad Software) was used to plot figures. Paired-samples *t* test was used to compare the EIF3B IHC score between tumor tissue and adjacent tissue. McNemar's test was used to compare the proportions of EIF3B high expression and EIF3B low expression between tumor tissue and adjacent tissue. Student's *t* test was used to compare age between EIF3B high expression patients and EIF3B low expression patients. Chi-square test was used to compare proportions of categorical data between EIF3B high expression patients and EIF3B low expression patients. Kaplan-Meier curve was used to illuminate OS, and log-rank test was used to compare the difference of OS between two group or among four groups. Univariate and multivariate Cox's proportional hazard regression models were used to analyze the factors predicting OS $P < .05$ was considered as significant.

TABLE 1 Characteristics of EOC patients

Items	EOC patients (N = 230)
Age (yr), mean ± SD	57.4 ± 12.8
≤60 yr, no. (%)	134 (58.3)
>60 yr, no. (%)	96 (41.7)
Histological subtype, no. (%)	
Serous	144 (62.6)
Others	86 (37.4)
Peritoneal cytology, no. (%)	
Negative	89 (38.7)
Positive	100 (43.5)
Unknown	41 (17.8)
Ascites volume, no. (%)	
≤100 mL	81 (35.2)
>100 mL	149 (64.8)
Differentiation, no. (%)	
Well/moderate	109 (47.4)
Poor	121 (52.6)
Tumor size, no. (%)	
≤10 cm	140 (60.9)
>10 cm	90 (39.1)
Lymphatic metastasis, no. (%)	
Negative	145 (63.0)
Positive	85 (37.0)
FIGO stage, no. (%)	
I/II	80 (34.8)
III/IV	150 (65.2)
CA125, no. (%)	
≤1000 U/mL	164 (71.3)
>1000 U/mL	66 (28.7)
CA199, no. (%)	
≤37 U/mL	144 (62.6)
>37 U/mL	86 (37.4)

Abbreviations: CA125, cancer antigen 125; CA199, carbohydrate antigen 199; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.

3 | RESULTS

3.1 | Study flow

Initially, 392 EOC patients who underwent resection were reviewed, among which 162 patients were excluded (91 patients received neoadjuvant therapy; 28 patients did not have eligible tumor tissue and adjacent tissue; 22 patients had incomplete

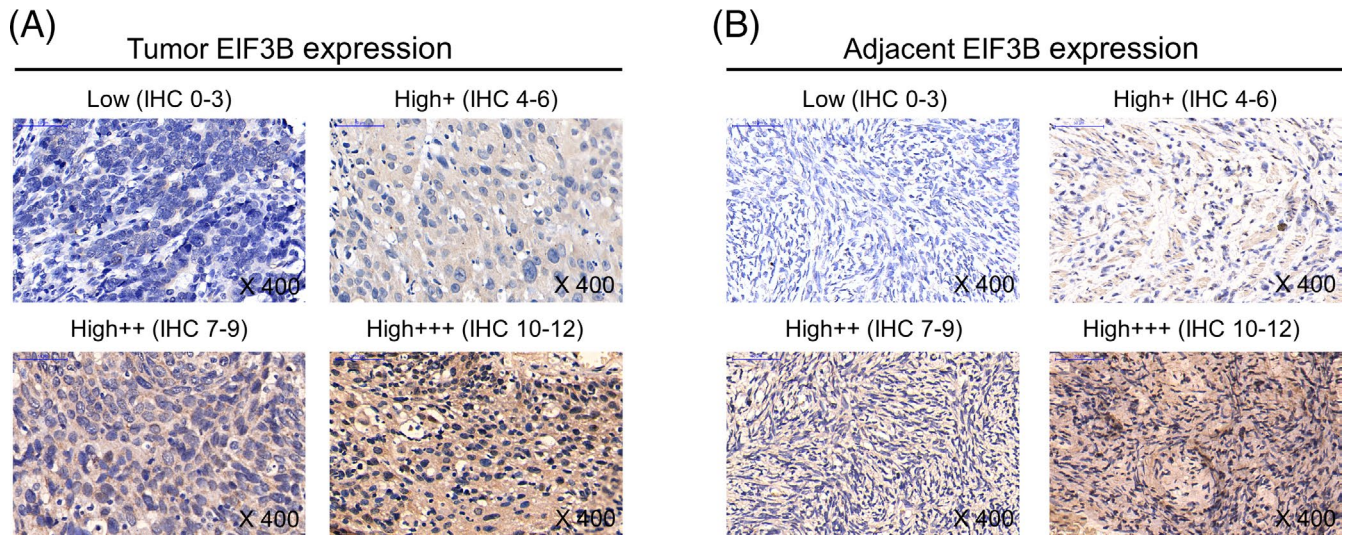

FIGURE 2 Representative IHC staining samples of EIF3B expression in tumor tissue and adjacent tissue. Representative samples of tumor tissue with EIF3B low, high+, high++, and high+++ expressions (A) and adjacent tissue with EIF3B low, high+, high++, and high+++ expressions by IHC staining (B). EIF3B, eukaryotic translation initiation factor 3B; IHC, immunohistochemical

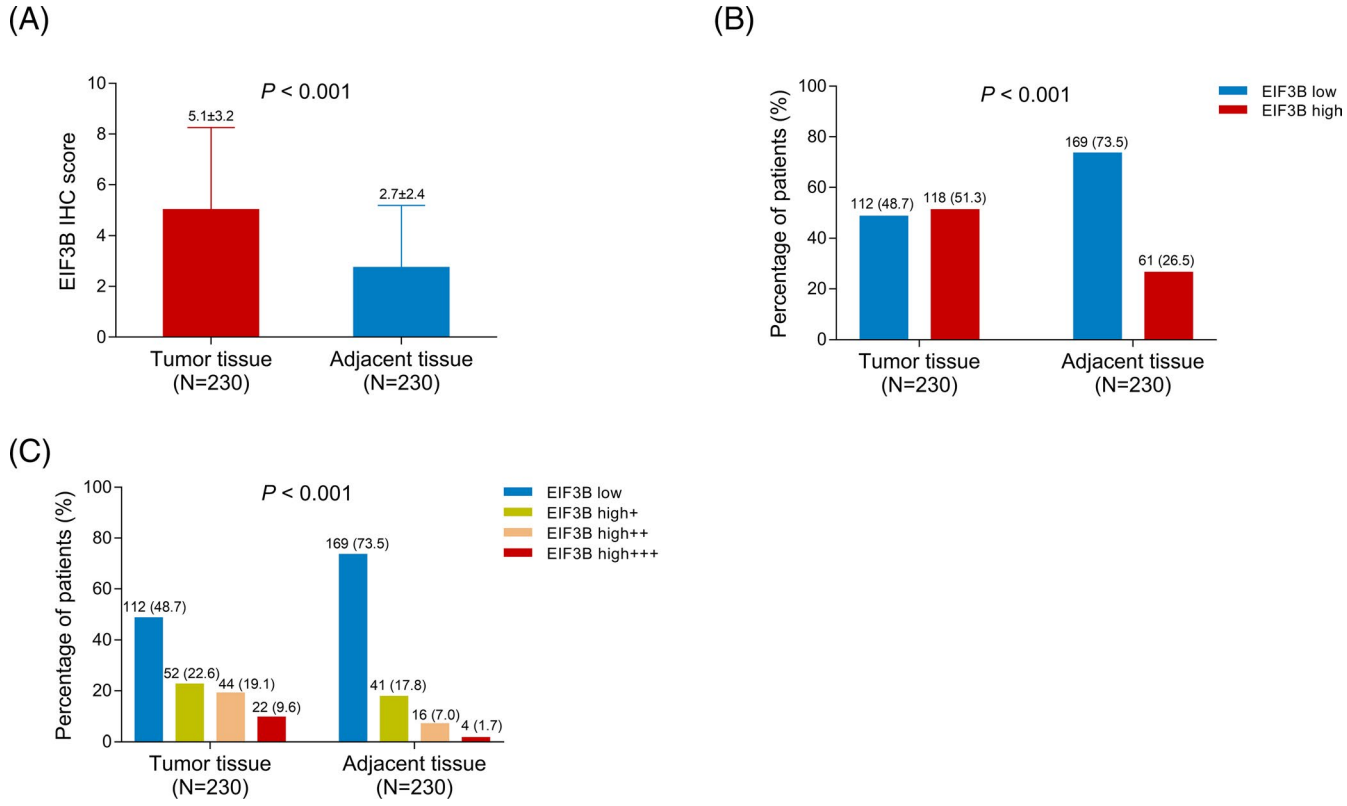

FIGURE 3 EIF3B expression in tumor tissue and adjacent tissue. Comparison of EIF3B IHC score between tumor tissue and adjacent tissue (A). Comparison of the percentage of EIF3B high expression and the percentage of EIF3B low expression between tumor tissue and adjacent tissue (B). Comparison of the percentage of EIF3B high+++ expression, the percentage of EIF3B high++ expression, the percentage of EIF3B high + expression, and the percentage of EIF3B low expression between tumor tissue and adjacent tissue (C). EIF3B, eukaryotic translation initiation factor 3B

clinical and follow-up data; 13 patients were unable to collect informed consents; 8 patients did not have primary EOC) (Figure 1). Subsequently, tumor tissue and adjacent tissue were collected from 230 eligible EOC patients to detect EIF3B expression. And all 230 EOC patients were included in the final analysis.

3.2 | Clinical features of EOC patients

The mean age of EOC patients was 57.4 ± 12.8 years (Table 1). There were 134 (58.3%) EOC patients younger than 60 years and 96 (41.7%) EOC patients older than 60 years. As for histological subtype, 144 (62.6%) and 86 (37.4%) EOC patients were with serous and other histological subtypes, respectively. Furthermore, 89 (38.7%), 100 (43.5%), and 41 (17.8%) EOC patients exhibited negative, positive, and unknown peritoneal cytology, respectively. Regarding ascites volume, 81 (35.2%) and 149 (64.8%) EOC patients had ≤100 mL and >100 mL ascites volume, respectively. In terms of differentiation, 109 (47.4%) and 121 (52.6%) EOC patients presented well/moderate and poor differentiation. In terms of tumor size and lymphatic metastasis, 140 (60.9%) and 90 (39.1%) EOC patients had ≤10 cm and >10 cm tumor size, respectively; 85 (37.0%) EOC patients exhibited lymphatic metastasis. And there were 80 (34.8%) and 150 (65.2%) EOC patients with FIGO stage I/II and FIGO stage III/IV, respectively. In addition, 164 (71.3%) and 66 (28.7%) EOC patients had ≤1000 U/mL and >1000 U/mL CA125, respectively; 144 (62.6%) and 86 (37.4%) EOC patients had ≤37 U/mL and >37 U/mL CA199, respectively.

3.3 | Comparison of EIF3B expression between tumor tissue and adjacent tissue

IHC was conducted to determine EIF3B expression in tumor tissue and adjacent tissue specimens. Samples of tumor EIF3B low, high+, high++, and high+++ expressions by the IHC staining were shown in Figure 2A, and samples of adjacent EIF3B low, high+, high++, and high+++ expressions by the IHC staining were displayed in Figure 2B. The EIF3B IHC score was elevated in tumor tissue compared with adjacent tissue ($P < .001$) (Figure 3A). Based on the IHC score, the expression of EIF3B was classified as low expression and high expression, and the latter was further divided into 3 grades: high+, high++, and high+++ expressions. It was observed that 112 (48.7%) and 118 (51.3%) tumor tissue exhibited EIF3B low expression and EIF3B high expression, respectively; 169 (73.5%) and 61 (26.5%) adjacent tissue exhibited EIF3B low expression and EIF3B high expression, respectively. These revealed that the percentage of EIF3B high expression and the percentage of EIF3B low expression were different between tumor tissue and adjacent tissue ($P < .001$) (Figure 3B). Furthermore, 112 (48.7%), 52 (22.6%), 44 (19.1%), and 22 (9.6%) tumor tissue exhibited EIF3B low expression, EIF3B high + expression, EIF3B high++ expression, and EIF3B high+++ expression, respectively; 169 (73.5%), 41 (17.8%), 16 (7.0%), and 4 (1.7%) adjacent tissue exhibited EIF3B low expression, EIF3B high + expression, EIF3B high++ expression, and EIF3B high+++ expression, respectively. These showed that the percentage of EIF3B low expression, the percentage of EIF3B high + expression, the percentage EIF3B high++ expression, and the percentage of EIF3B high+++ expression were all different between tumor tissue and adjacent tissue ($P < .001$) (Figure 3C). Taken together, through different statistical tests, all the findings disclosed that EIF3B was overexpressed in tumor tissue compared with adjacent tissue.

3.4 | Clinical features of EIF3B high expression patients and EIF3B low expression patients

Based on the EIF3B expression in tumor tissue, patients were divided into EIF3B high expression patients (N = 118) and EIF3B low expression patients (N = 112). The comparison of the clinical features between EIF3B high expression patients and EIF3B low expression patients disclosed that tumor size ($P < .001$) was larger, FIGO stage ($P = .026$) was advanced, and lymphatic metastasis ($P = .022$) was positive in EIF3B high expression patients compared with EIF3B low expression patients (Table 2), while no difference of mean age ($P = .070$), histological subtype ($P = .095$), peritoneal cytology ($P = .186$), ascites volume ($P = .125$), differentiation ($P = .300$), CA125 ($P = .533$), or CA199 ($P = .109$) was observed between EIF3B high expression patients and EIF3B low expression patients.

3.5 | OS in EIF3B high expression patients and EIF3B low expression patients

The OS was shorter in EOC patients with tumor EIF3B high expression compared to EOC patients with tumor EIF3B low expression ($P = .002$; Figure 4A). Furthermore, the OS was shortest in EOC patients with tumor EIF3B high+++ expression, followed by EOC patients with tumor EIF3B high++ expression and EOC patients with tumor EIF3B high + expression, and the longest in EOC patients with tumor EIF3B low expression ($P < .001$; Figure 4B).

3.6 | Analysis of factors predicting OS by univariate Cox's proportional hazard regression model

Univariate Cox's proportional hazard regression model analysis displayed that higher tumor EIF3B expression ($P < .001$, HR = 1.642), peritoneal cytology (positive) ($P = .018$, HR = 2.139), ascites volume (>100 mL) ($P < .001$, HR = 3.533), differentiation (poor vs. well/moderate) ($P = .003$, HR = 2.386), FIGO stage (III/IV vs. I/II) ($P = .018$, HR = 2.123), and CA125 (>1000 U/mL; $P = .021$, HR = 1.989) were correlated with worse OS in EOC patients (Table 3).

3.7 | Analysis of factors predicting OS by multivariate Cox's proportional hazard regression model

Multivariate Cox's proportional hazard regression model analysis exhibited that higher tumor EIF3B expression ($P = .014$, HR = 1.452), peritoneal cytology (positive) ($P < .001$, HR = 8.349), ascites volume

TABLE 2 Comparison of clinical characteristics between EIF3B high expression patients and EIF3B low expression patients

Items	EIF3B high (n = 118)	EIF3B low (n = 112)	*P* value
Age (years), mean ± SD	58.9 ± 12.8	55.9 ± 12.3	0.070
Histological subtype, no. (%)			0.095
Serous	80 (67.8)	64 (57.1)	
Others	38 (32.2)	48 (42.9)	
Peritoneal cytology, no. (%)			0.186
Negative	46 (39.0)	43 (38.4)	
Positive	56 (47.5)	44 (39.3)	
Unknown	16 (13.5)	25 (22.3)	
Ascites volume, no. (%)			0.125
≤100 mL	36 (30.5)	45 (40.2)	
>100 mL	82 (69.5)	67 (59.8)	
Differentiation, no. (%)			0.300
Well/moderate	52 (44.1)	57 (50.9)	
Poor	66 (55.9)	55 (49.1)	
Tumor size, no. (%)			<0.001
≤10 cm	58 (49.2)	82 (73.2)	
>10 cm	60 (50.8)	30 (26.8)	
Lymphatic metastasis, no. (%)			0.022
Negative	66 (55.9)	79 (70.5)	
Positive	52 (44.1)	33 (29.5)	
FIGO stage, no. (%)			0.026
I/II	33 (28.0)	47 (42.0)	
III/IV	85 (72.0)	65 (58.0)	
CA125, no. (%)			0.533
≤1000 U/mL	82 (69.5)	82 (73.2)	
>1000 U/mL	36 (30.5)	30 (26.8)	
CA199, no. (%)			0.109
≤37 U/mL	68 (57.6)	76 (67.9)	
>37 U/mL	50 (42.4)	36 (32.1)	

Abbreviations: CA125, cancer antigen 125; CA199, carbohydrate antigen199; EIF3B, eukaryotic translation initiation factor 3B; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.

(>100 mL) (*P* = .001, HR = 3.683), differentiation (poor vs. well/moderate) (*P* < .001, HR = 4.193), tumor size (>10 cm) (*P* < .001, HR = 7.005), FIGO stage (III/IV vs. I/II) (*P* < .001, HR = 10.034), and CA125 (>1000 U/mL; *P* = .004, HR = 2.833) were independent predictive factors for worse OS in EOC patients (Table 4).

3.8 | EIF3B expression in other cancer tissues

Data regarding EIF3B expression in other cancer tissues were retrieved from Human Protein Atlas Database (https://www.proteinatlas.org/ENSG00000106263-EIF3B/pathology) that was derived from TCGA database. It was reported that 6 (66.7%) and 3 (33.3%) ovarian cancer tissue shown EIF3B medium and high expressions; 1 (8.3%), 9 (75.0%), and 2 (16.7%) glioma cancer tissue displayed EIF3B low, medium, and high expressions, respectively; 4 (100%) thyroid cancer tissue exhibited EIF3B high expression, respectively (Table 5). The detailed EIF3B expression in other cancer tissues was displayed in Table 5.

3.9 | Correlation of EIF3B expression with survival probability in OC patients

Data regarding the correlation of EIF3B expression with survival probability in OC patients were retrieved from Human Protein Atlas Database (https://www.proteinatlas.org) that was derived from TCGA database, which observed that OC patients with EIF3B high expression displayed the trend of lower survival probability but without statistical significance (*P* = .110) (Figure S1).

4 | DISCUSSION

Epithelial ovarian cancer, a heterogeneous malignancy, consists of different histological subtypes with distinct precursor lesions, tissues of origin, molecular properties, and clinical outcomes, all of which affect prognosis and outcomes.[2,13] It remains as one of the leading causes of cancer-related deaths in females globally, despite the advances in screening, surgery, and treatment methods during the last three decades.[1] Existing routinely used biomarkers (cancer antigen 125 and human epididymal protein 4) for monitoring tumor progression of EOC lack adequate sensitivity and specificity under some circumstances.[14] Therefore, it is exceptionally urgent to explore complementary biomarkers for assisting disease management and improving prognosis of EOC.

Previous studies elucidate that EIF3B participates in the pathogenetic process of several cancers such as gastric cancer and cervical cancer.[11,15] In gastric cancer, EIF3B expression is higher in cancer tissues than that in normal tissues, and EIF3B high expression is associated with depth of tumor invasion ($T_{3\text{-}4}$), lymph node metastasis (N_1), and TNM stage (II/III/IV).[11] Another study illustrates that EIF3B expression is elevated in tumor tissue compared with paired adjacent tissue, and EIF3B high expression is correlated with advanced FIGO stage and the presence of lymph node metastasis in cervical cancer.[15] However, related study is lacking in EOC. The present study observed that EIF3B expression was elevated in tumor tissue compared with adjacent tissue, and tumor EIF3B high expression correlated with larger tumor size (>10 cm), lymphatic metastasis, and advanced FIGO stage (III/IV) in EOC patients. The possible explanations were as follows: (a) EIF3B might promote cell proliferation and invasion and inhibit cell apoptosis through triggering its downstream pathways such as β-catenin signaling pathway, caspase-3/PARP pathway, and Akt pathway, which induced the malignant

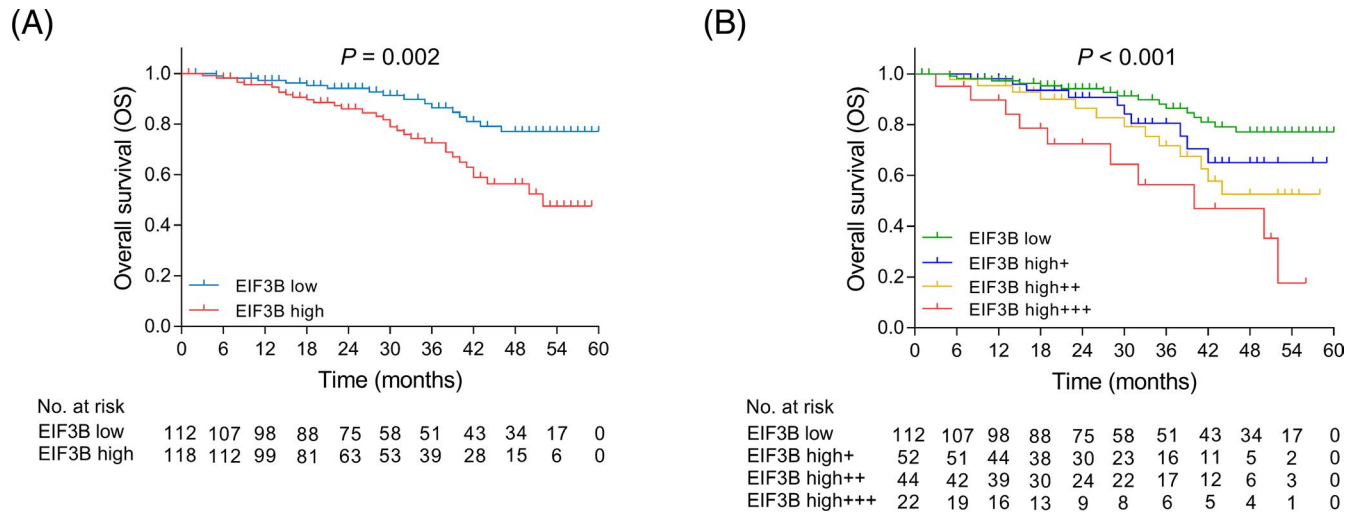

FIGURE 4 Correlation of EIF3B expression with OS in EOC patients. Comparison of OS between patients with EIF3B high expression and patients with EIF3B low expression (A). Comparison of OS among patients with EIF3B high+++ expression, EIF3B high++ expression, EIF3B high expression, and EIF3B low expression, respectively (B). OS, overall survival; EIF3B, eukaryotic translation initiation factor 3B; EOC, epithelial ovarian cancer

TABLE 3 Univariate Cox's proportional hazard regression model analysis of factors predicting OS

	Univariate Cox's regression model			
			95% CI	
Items	*P* value	HR	Lower	Higher
Higher EIF3B expression[a]	<.001	1.642	1.278	2.109
Age (>60 yr)	.212	1.434	0.814	2.524
Histological subtype (serous)	.639	1.149	0.642	2.056
Peritoneal cytology (positive)	.018	2.139	1.142	4.006
Ascites volume (>100 mL)	<.001	3.533	1.819	6.860
Differentiation (poor vs. well/moderate)	.003	2.386	1.338	4.257
Tumor size (>10 cm)	.053	1.753	0.992	3.097
FIGO stage (III/IV vs. I/II)	.018	2.123	1.140	3.953
CA125 (>1000 U/mL)	.021	1.989	1.112	3.559

Abbreviations: CA125, cancer antigen 125; CI, confidence interval; EIF3B, eukaryotic translation initiation factor 3B; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; OS, overall survival.

[a]In the univariate Cox's regression model, EIF3B expression was coded as: low expression = 1, higher + expression=2, higher++ expression = 3, and higher+++ = 4.

TABLE 4 Multivariate Cox's proportional hazard regression model analysis of factors predicting OS

	Multivariate Cox's regression model			
			95% CI	
Items	*P* value	HR	Lower	Higher
Higher EIF3B expression[a]	.014	1.452	1.080	1.953
Age (>60 yr)	.797	0.910	0.442	1.873
Histological subtype (serous)	.529	0.807	0.413	1.575
Peritoneal cytology (positive)	<.001	8.349	3.871	18.007
Ascites volume (>100 mL)	.001	3.683	1.718	7.898
Differentiation (poor vs. well/moderate)	<.001	4.193	2.043	8.609
Tumor size (>10 cm)	<.001	7.005	3.169	15.485
FIGO stage (III/IV vs. I/II)	<.001	10.034	3.352	30.037
CA125 (>1000 U/mL)	.004	2.833	1.391	5.767

Abbreviations: CA125, cancer antigen 125; CI, confidence interval; EIF3B, eukaryotic translation initiation factor 3B; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; OS, overall survival.

[a]In the multivariate Cox's regression model, EIF3B expression was coded as: low expression = 1, higher + expression = 2, higher++ expression = 3, and higher+++ = 4.

transformation of cells, tumor growth, and tumor progression.[7,10,16] Thereby, tumor EIF3B high expression was associated with larger tumor size and advanced FIGO stage in EOC. (b) EIF3B might facilitate cell migration and invasion by activating critical processes of cell activities such as epithelial-to-mesenchymal transition, which led to tumor cells migration to distal sites.[8] Thereby, tumor EIF3B high expression was associated with lymphatic metastasis and advanced FIGO stage in EOC.

Several studies illuminated that upregulation of EIF3B is associated with poor prognosis in cervical cancer and non-small cell lung cancer.[15,16] For instance, cervical cancer patients with EIF3B high expression present shorter disease-free survival (DFS) and OS

TABLE 5 EIF3B expression in cancer tissues[a]

	Number of tissues	EIF3B expression		
		Low, no. (%)	Medium, no. (%)	High, no. (%)
Ovarian cancer	9	0 (0.0)	6 (66.7)	3 (33.3)
Glioma	12	1 (8.3)	9 (75.0)	2 (16.7)
Thyroid cancer	4	0 (0.0)	0 (0.0)	4 (100.0)
Lung cancer	12	2 (16.7)	9 (75.0)	1 (8.3)
Colorectal cancer	10	0 (0.0)	7 (70.0)	3 (30.0)
Head and neck cancer	4	0 (0.0)	3 (75.0)	1 (25.0)
Stomach cancer	10	2 (20.0)	8 (80.0)	0 (0.0)
Liver cancer	11	0 (0.0)	9 (81.8)	2 (18.2)
Carcinoid	4	0 (0.0)	2 (50.0)	2 (50.0)
Pancreatic cancer	12	0 (0.0)	4 (33.3)	8 (66.7)
Renal cancer	12	0 (0.0)	9 (75.0)	3 (25.0)
Urothelial cancer	12	0 (0.0)	11 (91.7)	1 (8.3)
Prostate cancer	9	1 (11.1)	8 (88.9)	0 (0.0)
Testis cancer	11	0 (0.0)	8 (72.7)	3 (27.3)
Breast cancer	11	0 (0.0)	10 (90.9)	1 (9.1)
Cervical cancer	11	1 (9.1)	6 (54.5)	4 (36.4)
Endometrial cancer	10	0 (0.0)	4 (40.0)	6 (60.0)
Melanoma cancer	11	0 (0.0)	8 (72.7)	3 (27.3)
Skin cancer	11	0 (0.0)	7 (63.6)	4 (36.4)
Lymphoma	8	1 (12.5)	3 (37.5)	4 (50.0)

[a]Data retrieved from Human Protein Atlas Database (https://www.proteinatlas.org/ENSG00000106263-EIF3B/pathology) that was derived from TCGA database.

compared to those with EIF3B low expression.[15] In non–small-cell lung cancer, EIF3B high expression is an independent predictive factor for shorter DFS and OS.[16] However, there is currently no study about the correlation of EIF3B expression with prognosis in EOC patients. In the present study, we found that EOC patients with tumor EIF3B high expression had shorter OS compared to EOC patients with tumor EIF3B low expression, and the higher tumor EIF3B expression, the shorter OS. Besides, higher tumor EIF3B expression was an independent predictive factor for shorter OS in EOC. Herein, we proposed several reasons: (a) EIF3B might increase the proliferation and invasion and decrease the apoptosis of EOC cancer cells by mediating the downstream pathways; thereby, tumor EIF3B high expression was associated with larger tumor size (>10 cm) and advanced FIGO stage (III/IV), which led to poor OS in EOC patients.[10,16] (b) EIF3B might promote the metastasis of EOC cancer cells to distal sites, which might result in disease recurrence; it might induce drug resistance and the subsequent poor treatment outcomes, thereby resulted in shorter OS in EOC patients.[16] However, these speculations needed further validation. In addition, from Human Protein Atlas Database (https://www.proteinatlas.org) that was derived from TCGA database, we retrieved information about the correlation of EIF3B with survival probability in ovarian cancer patients and found that OC patients with EIF3B high expression displayed the trend of lower survival probability but without statistical significance. The discrepancies from our findings were likely to be explained by that in the Human Protein Atlas Database, RNA sequencing was used to detect EIF3B mRNA expression, and EIF3B was divided into EIF3B low/high based on EIF3B median expression, while in our study, IHC assay and semi-quantitative scoring method were used to classify different grade of EIF3B expressions. Collectively, EIF3B displayed the potential as a biomarker for assisting tumor management and prognosis surveillance of EOC. However, the value of IHC-detected EIF3B in improving the sensitivity and specificity of CA125 (commonly clinically applied serum biomarker via quantitative detection) in the diagnosis of EOC was not accessible due to the following reasons: (a) To evaluate the sensitivity and specificity of EIF3B, healthy controls must be included; however, in our study, only EOC patients were recruited. (b) EIF3B expression in tumor tissues and adjacent tissues was determined by IHC assay and semi-quantitative scoring method, which was not suitable for assessing the sensitivity and specificity.

Several limitations must be taken into consideration in the present study. Firstly, since the present study was a retrospective study, and most of the patients were from other regions of China, it was difficult to obtain precise DFS data. Hence, the present study mainly selected patients with complete OS data during the follow-up. As for DFS, it was not selected as screening criteria since most of the patients' DFS data were lost. Secondly, the sample size was relatively small, which might decrease the statistic power. Thereby, further study with large sample size needed to verify our finding. Thirdly, the mechanism of EIF3B on development and progression of EOC was not investigated in the present study. Thereby, future relevant experiments should be carried out. Lastly, the present study was conducted in the primary EOC patients; hence, the prognostic value of EIF3B in secondary EOC patients remained unclear.

To conclude, EIF3B is overexpressed in tumor tissue and tumor EIF3B high expression correlates with larger tumor size, advanced FIGO stage, and poor OS in EOC patients. These findings suggest that EIF3B may serve as an indicator for monitoring disease progression and predicting prognosis in EOC patients.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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