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Integrin Subunit beta 8 (ITGB8) Upregulation Is an Independent Predictor of Unfavorable Survival of High-Grade Serous Ovarian Carcinoma Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: *ITGB8* encodes a β subunit of integrin (integrin β8), which is upregulated in some types of cancer. In the current study, we examined the expression profile of *ITGB8* in serous ovarian cancer (SOVC) and investigated its potential as an independent prognostic indicator for overall survival (OS) and recurrence-free survival (RFS) in high-grade SOVC.

Material/Methods: A secondary study was conducted based on genomic and survival data in large online databases, including the Gene Expression Omnibus (GEO), the Human Protein Atlas (HPA), and the Cancer Genome Atlas-Ovarian cancer (TCGA-OV). Kaplan-Meier curves were generated to evaluate the association between *ITGB8* expression and OS/RFS. Univariate and multivariate analysis were performed with the Cox regression model.

Results: *ITGB8* was significantly upregulated in ovarian cancer tissues compared to that in normal ovary tissues. High-grade SOVC patients with high *ITGB8* expression had significantly shorter OS and RFS compared to their low-expression counterparts. Increased *ITGB8* expression might be an independent prognostic indicator of unfavorable OS (HR: 1.424, 95%CI: 1.228–1.653, $p<0.001$) and RFS (HR: 2.167, 95%CI: 1.507–3.114, $p<0.001$) in high-grade SOVC. DNA amplification was frequent (149/509, 29.3%) in high-grade SOVC patients and was associated with increased *ITGB8* expression compared to the copy-neutral cases.

Conclusions: *ITGB8* expression might be a valuable prognostic biomarker in high-grade SOVC, the expression of which might be regulated by its DNA copy numbers.

MeSH Keywords: Integrins • Ovarian Neoplasms • Prognosis

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Background

Integrins are a large family of heterodimeric cell-surface-adhesion transmembrane receptors that constitute 2 subunits: (α) and (β) [1]. In vertebrates, there are 18 α and 8 β subunits that can form 24 heterodimeric receptors with different binding properties and different tissue distributions [1]. Generally, integrin complexes mediate cell-cell and cell-extracellular matrix interactions [2]. Upon binding with extracellular ligands, integrins activate a series of signaling pathways related to cell cycle regulation, organization of the intracellular cytoskeleton, and movement of new receptors to the cell membrane [1,3].

Integrins have well-established regulatory effects on cancer cells, such as survival and metastasis-related signaling pathways [4]. *ITGB8* encodes a β subunit of integrin, which is upregulated in some types of cancer, such as laryngeal squamous cell carcinoma [5], lung cancer [6], prostate cancer [7] and breast cancer [8]. The αvβ8 integrin mediates the activation of latent TGF-β, which subsequently derives the epithelial-to-mesenchymal (EMT) transition of some cancers and contributes to cancer cell migration and growth [9,10]. In ovarian cancer, *ITGB8* upregulation is associated with cisplatin resistance [11].

Epithelial ovarian cancer is a group of heterogeneous diseases [12], which can generally be classified into Type I tumors and Type II tumors (>75% of cases). Type II epithelial ovarian cancer is more aggressive and includes high-grade (grade 2/3/4) serous cancer (SOVC), high-grade endometrioid, mixed mesodermal (carcinosarcoma), and undifferentiated carcinomas [13]. High-grade SOVC is the dominant form of Type II tumors, which has malignant behaviors, rapid progression, and poor prognosis [14–17]. Therefore, it is necessary to identify the potential prognostic biomarkers in this group of patients.

In this study, we performed a secondary study using genomic and survival data in large online databases to explore the expression profile of *ITGB8* in SOVC and its potential as an independent prognostic indicator for overall survival (OS) and recurrence-free survival (RFS) in high-grade SOVC.

Material and Methods

Secondary analysis of the data in the Gene Expression Omnibus (GEO)

The normalized raw data of a previous Affymetrix U133 Plus 2.0 array that investigated the gene profiling of 12 ovarian surface epithelial cells (OSE) and 12 laser capture microdissected serous papillary ovarian cancer epithelial cells (CEPIs) (GDS3592) [18] was downloaded from the GEO datasets. The data were reanalyzed to extract the expression data of *ITGB8* gene.

Secondary analysis using data from the Human Protein Atlas (HPA)

ITGB8 expression at the protein level in normal fallopian tube, ovary, and SOVC tissues was examined by checking the staining (immunohistochemistry, IHC) images in the Human Protein Atlas (HPA) (*http://www.proteinatlas.org/*) [19,20]. The protein expression score is classified as negative, low, medium, and high, which is a combination of staining intensity and fraction of stained cells.

Bioinformatic analysis of data in the Cancer Genome Atlas-ovarian cancer (TCGA-OV)

The level-3 data in TCGA-OV were obtained through the UCSC Xena Browser (*https://xenabrowser.net/*). Only patients who had not received neoadjuvant treatment were included in this study. This dataset included 562 patients with high-grade serous ovarian carcinoma (69 cases in G2, 492 cases in G3, and 1 case in G4). Gene expression profile was measured in 520 high-grade OV patients by AgilentG4502A_07_3 array; 508 out of the 520 cases had ITGB8 copy number alteration (CNAs) identified, by using Genomic Identification of Significant Targets in Cancer 2.0 (GISTIC2) method [21].

There were 516 patients with intact OS data and 65 patients had intact RFS data. Clinicopathological parameters of these patients, including age at diagnosis, clinical stage, venous invasion status, lymphatic invasion status, presence of tumor residual disease, recurrence, RFS time, survival status, and OS time were obtained for survival-related comparison.

Survival analysis using Kaplan-Meier Plotter

The difference in first progression-free survival (FPS) survival between patients with high/low *ITGB8* expression in high-grade (grade 2/3) SOVC was analyzed using the survival and genomic data in the Kaplan-Meier Plotter (*http://kmplot.com/analysis/index.php?p=service&cancer=ovar*), an online tool for genome-wide validation of survival-associated biomarkers in ovarian cancer [22]. Patients were grouped into high and low *ITGB8* expression groups according to the best cutoff.

Statistical analysis

Statistical analysis was conducted as recommended in previous studies [23–25]. In brief, GraphPad Prism 6.0 (GraphPad Inc., La Jolla, CA, USA) and SPSS 19.0 software package (SPSS Inc., Chicago, IL, USA) were used for data integration and analysis. The difference in *ITGB8* expression between different groups was compared using Welch's unequal variances *t* test. The differences in clinicopathological parameters among high-grade SOVC patients with high or low *ITGB8* expression were

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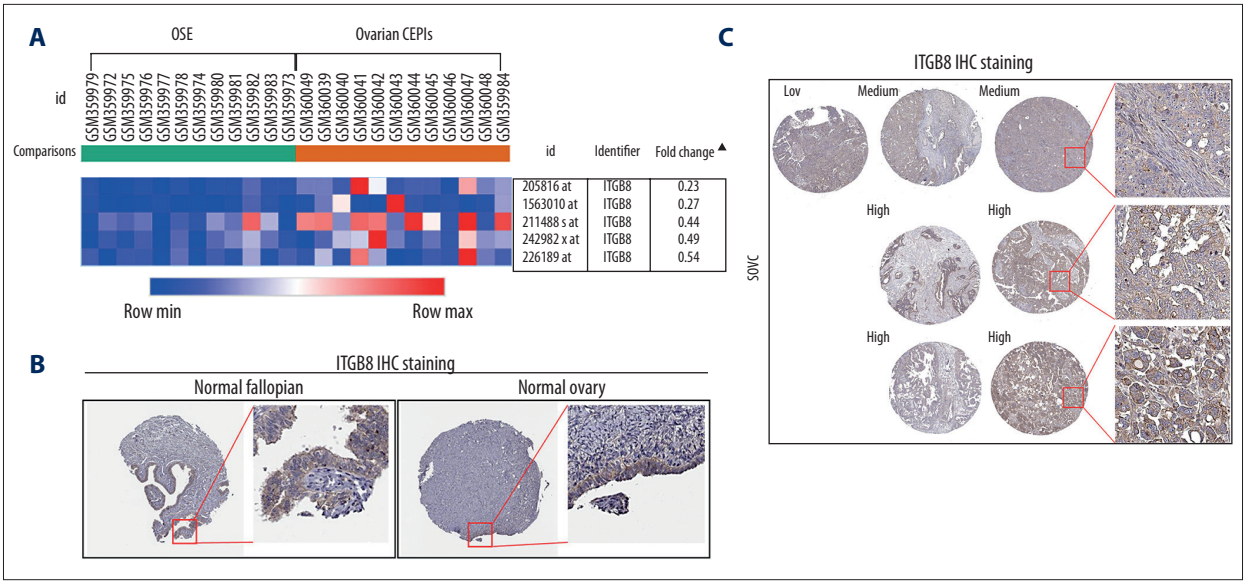

Figure 1. *ITGB8* was significantly upregulated in ovarian carcinoma compared to normal ovary tissue. (**A**) A heatmap showing the expression profile of ITGB genes between 12 cases of OSE and 12 cases of CEPIs. Data were from GDS3592. (**B, C**) IHC staining of ITGB8 in normal fallopian tube tissues (**B, left**) and normal ovarian tissues (**B, right**) and in 7 cases of SOVC tissues (**C**). Image credit: Human Protein Atlas. IHC images were obtained from: v18.proteinatlas.org, via: *https://www.proteinatlas.org/ENSG00000105855-ITGB8/tissue/fallopian+tube#img*, *www.proteinatlas.org/ENSG00000105855-ITGB8/tissue/ovary*, and *www.proteinatlas.org/ENSG00000105855-ITGB8/pathology/tissue/ovarian+cancer#ihc*.

evaluated using the chi-squared test by two-sided Fisher's exact test. In Kaplan-Meier survival curves, patients were grouped by the optimal cutoff (Youden Index) of *ITGB8* expression in the receiver operation characteristic (ROC) curves for death and recurrence detection, respectively.

The difference between the curves was assessed using the log-rank test. The independent prognostic value of *ITGB8* expression (as a continuous variable) was assessed using the univariate and multivariate Cox regression models. $p<0.05$ was considered as significantly different.

Results

ITGB8 was significantly upregulated in ovarian carcinoma tissues compared to normal ovary tissues

Using previous RNA array data from the GEO datasets, we characterized the expression profile of *ITGB8* between 12 OSE and 12 CEPIs. The 5 probes detecting *ITGB8* expression all indicated that its expression was substantially higher in CEPIs than in OSE (Figure 1A). Since accumulating evidence suggests that high-grade SOVC arises from epithelial cells of the fallopian tube [26,27], we also analyzed ITGB8 expression at the protein level in normal fallopian tube, ovary, and in SOVC tissues, by checking the IHC staining data in the HPA. The epithelial cells of the fallopian tube (Figure 1B, left) and normal ovarian epithelial tissues (Figure 1B, right) usually had medium ITGB8 staining. In comparison, all 7 SOVC cases had ITGB8 expression, among which 4 cases had high expression and 2 cases had medium expression (Figure 1C).

ITGB8 upregulation was associated with unfavorable survival outcomes in high-grade SOVC

Using *ITGB8* expression measured by Agilent array in TCGA-OV, we did not find significant differences in *ITGB8* expression between low-grade and high-grade SOVC ($p=0.28$, Figure 2A). In high-grade SOVC, the living cases had lower *ITGB8* expression than the deceased cases, at the marginal level of significance ($p=0.083$, Figure 2B). In addition, we also observed that the cases with recurrence after primary therapy had markedly elevated *ITGB8* expression compared with those without recurrence ($p=0.02$, Figure 2C).

In high-grade SOVC patients, the high *ITGB8* expression group had significantly shorter OS and RFS

Based on survival data from TCGA, we compared the difference in survival between patients with high and low *ITGB8* expression. Results showed that the high-expression group had significantly shorter OS and RFS ($p<0.001$, Figure 3A, 3B). To verify the associations, we also examined the survival data in Kaplan-Meier Plotter. Data in this database confirmed that the high *ITGB8* expression group had significantly shorter OS

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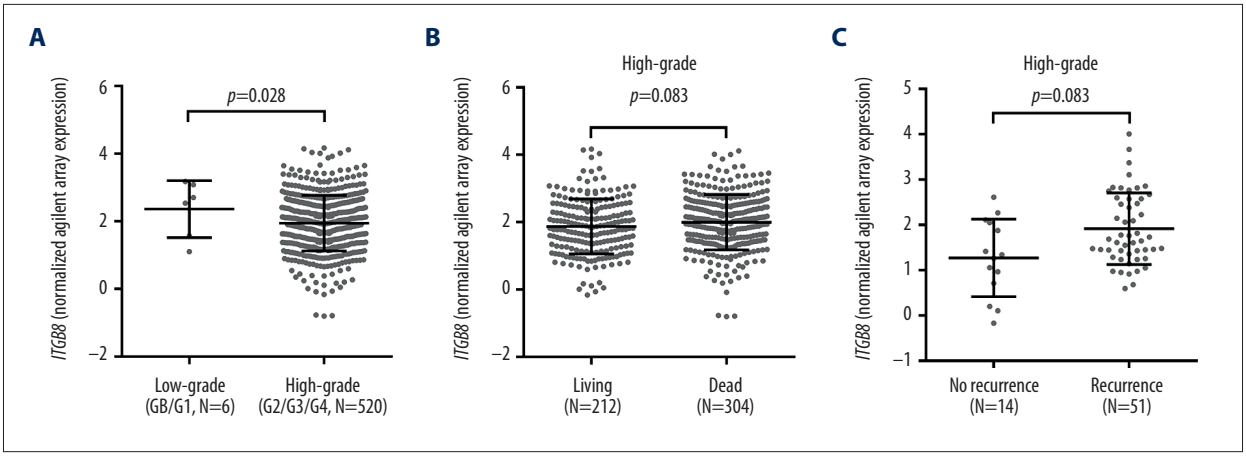

Figure 2. *ITGB8* upregulation was associated with unfavorable survival outcomes in high-grade SOVC. (**A–C**) Compassion of *ITGB8* genes between the high-grade (G3/G4) and low-grade (GB/G1/G2) SOVC patients (**A**), between the dead and living patients (**B**), and between the cases with or without recurrence after primary therapy (**C**). GB: The tissue is considered borderline cancerous. G1 – Well-differentiated; G2 – Moderately differentiated; G3 to G4 – Poorly differentiated or undifferentiated.

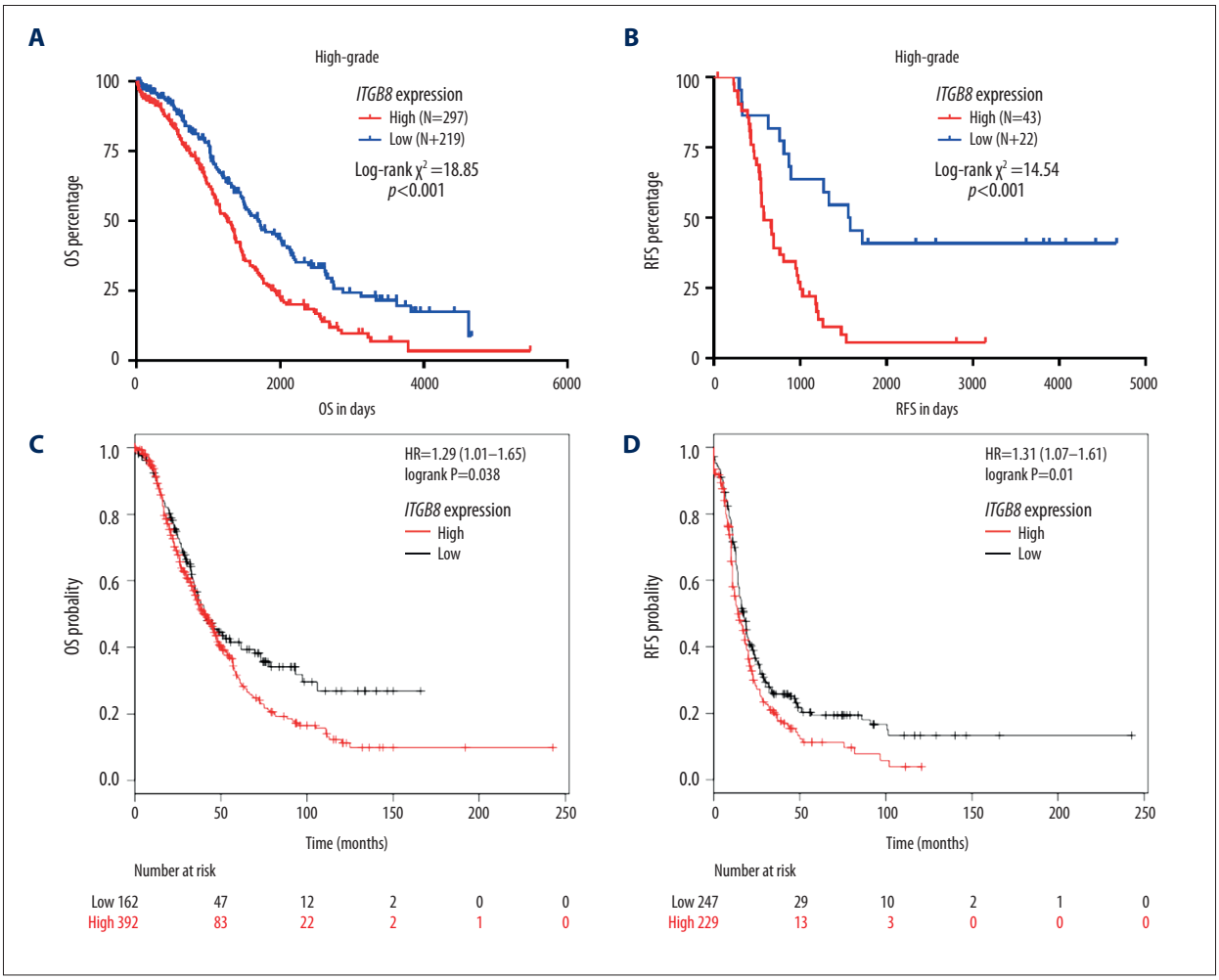

Figure 3. High *ITGB8* expression was associated with significantly shorter OS and RFS in high-grade SOVC. (**A, B**) Kaplan-Meier curves of OS (**A**) and RFS (**B**) in high-grade SOVC patients. Data were from TCGA-OV. (**C, D**) Kaplan-Meier curves of OS and PFS in high-grade SOVC patients. Data were from Kaplan-Meier Plotter.

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Table 1. The association between *ITGB8* expression and the clinicopathological parameters in high-grade SOVC.

Parameters		ITGB8 expression		*p* Value
		High (N=297)	Low (N=219)	
Age (Mean ±SD)		60.02±11.73	59.34±11.19	0.51
Clinical stage	I/II	21	20	0.42
	III/IV	273	199	
	Null	3	0	
The presence of venous invasion	No	35	30	0.50
	Yes	49	32	
	Null	213	157	
The presence of lymphatic invasion	No	39	36	0.24
	Yes	77	49	
	Null	181	134	
The presence of tumor residual disease	No	9	5	0.99
	Yes	21	10	
	Null	267	204	
Recurrence status	With recurrence	5	9	0.76
	Without recurrence	22	29	
	Null	270	181	
Living Status	Living	110	102	0.03
	Dead	187	117	

Null – data were not available.

(HR: 1.29, 95%CI: 1.01–1.65, p=0.038, Figure 3C) and first progression-free survival (PFS) (HR: 1.31, 95%CI: 1.07–1.61, p=0.01, Figure 3D).

ITGB8 expression independently predicted poor OS and RFS of high-grade SOVC

The association between *ITGB8* expression and the clinicopathological parameters in high-grade SOVC patients are summarized in Table 1. Chi-square analysis showed that the high-expression group had a high proportion of death compared to the low-expression group (p<0.03) (Table 1). No significant difference was observed in other parameters (Table 1). Then, the independent prognostic value of *ITGB8* expression was analyzed using univariate and multivariate analysis. In univariate analysis, older age, advanced clinical stages (III/IV), and increased *ITGB8* expression were risk factors of unfavorable OS, while only increased *ITGB8* expression was a risk factor of unfavorable RFS (HR: 2.167, 95%CI: 1.507–3.114, p<0.001) (Table 2). Multivariate analysis showed that elevated *ITGB8* expression was independently associated with shorter OS (HR: 1.424, 95%CI: 1.228–1.653, p<0.001) after adjustment for other risk factors.

ITGB8 expression was related to its CNA status

By checking the DNA CNA status in the patients with quantified *ITGB8* expression, we also examined the correlation between *ITGB8* DNA CNAs and its RNA expression. Data showed that DNA amplification was frequent in high-grade SOVC patients (149/509, 29.3%) (Figure 4A). In addition, the group with *ITGB8* amplification had significantly higher *ITGB8* expression compared to the group with neutral *ITGB8* copy number (p<0.001, Figure 4B). In comparison, the group with *ITGB8* deletion had markedly lower *ITGB8* expression compared to the group with neutral *ITGB8* copy number (p<0.001, Figure 4B).

Discussion

Previous studies showed that the dysregulation of integrin family members is common in ovarian cancer and plays an important role in the pathological development of this disease [28,29]. For example, integrin α2β1 upregulation enhances spheroid disaggregation and proteolysis responsible for the peritoneal dissemination of ovarian cancer [30]. Integrin β3 inhibits tumor progression and reduce metastasis in patients

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Table 2. Univariate and multivariate analysis of OS/RFS in high-grade SOVC.

Parameters	Univariate analysis				Multivariate analysis			
	p	HR	95%CI		*p*	HR	95%CI	
			Lower	Upper			Lower	Upper
OS								
Age	<0.001	1.025	1.014	1.035	<0.001	1.023	1.012	1.033
Clinical stage: III/IV *vs.* I/II	0.006	2.438	1.297	4.582	0.010	2.300	1.223	4.325
Venous invasion: No *vs.* Yes	0.959	0.986	0.588	1.654				
Lymphatic invasion: No *vs.* Yes	0.070	0.668	0.431	1.033				
Tumor residual disease: Yes *vs.* No	0.155	2.899	0.669	12.566				
ITGB8 expression	<0.001	1.458	1.255	1.694	<0.001	1.424	1.228	1.653
RFS								
Age	0.479	1.010	0.982	1.039				
Clinical stage: III/IV *vs.* I/II	0.136	0.212	0.028	1.632				
Tumor residual disease: Yes *vs.* No	0.192	5.213	0.436	62.330				
ITGB8 expression	<0.001	2.167	1.507	3.114				

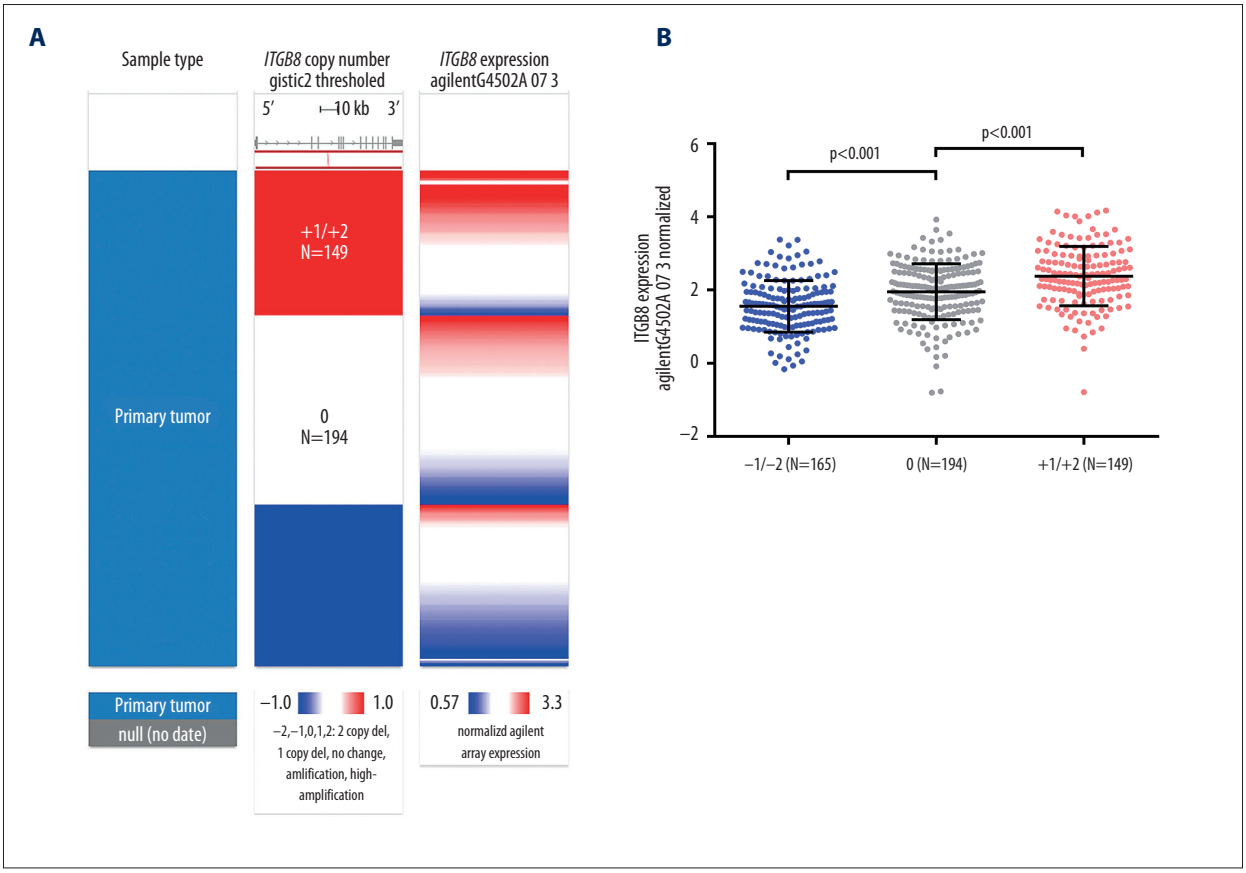

Figure 4. *ITGB8* expression was related to its CNA status. (**A**) A heatmap showing the correlation between *ITGB8* CNAs and its RNA expression. (**B**) Comparison of *ITGB8* expression among the groups with different CNA status. CNAs were defined as homozygous deletion (–2), heterozygous loss (–1), copy-neutral (0), low-level copy gain (+1), high-level amplification (+2).

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with ovarian cancer [31]. Fibrillar type I collagen facilitates the invasion of aggressive ovarian cancer cells via modulating integrin β1 and PTEN-mediated PI3K/Akt signaling pathway [32]. Inhibition integrin α5 inhibits the peritoneal dissemination of ovarian cancer cells [33]. Some integrin subunits also might be potential prognostic markers of ovarian cancer. For instance, *ITGB3* downregulation is associated with shorter OS in patients with advanced SOVC [31,34].

The analysis in the current study revealed that *ITGB8* expression was substantially elevated in ovarian cancer tissues compared to that in normal ovarian tissues. In addition, we demonstrated that elevated *ITGB8* expression was independently associated with shorter OS (HR: 1.424, 95%CI: 1.228–1.653, $p<0.001$) and RFS (HR: 2.167, 95%CI: 1.507–3.114, $p<0.001$) in high-grade SOVC. These findings reveal the potential clinical value of *ITGB8* expression as a prognostic indicator in high-grade SOVC.

Previous studies showed that integrin β8 is an important mediator of latent TGF-β signaling pathways via regulating the liberation of active TGF-β from its latent complex [35–37]. TGFβs have been reported to promote cell migration in development and cancer, including SOVC [38,39]. In lung cancer cell lines, *ITGB8* silencing induces cell cycle arrest and reduces the adhesion and invasion abilities of cancer cells [6]. A recent study showed that in glioblastoma multiforme (GBM), integrin β8 is an essential regulator of cell invasiveness during malignant progression via enhancing TGF-β signaling [35]. TGF-β activation induces a dose- and time-dependent upregulation of urokinase-type plasminogen activator (uPA) in highly invasive human ovarian cancer cell lines and results in cell invasion [40]. TGF-β can also modulate ovarian cancer invasion by upregulating cancer-associated fibroblasts (CAF)-derived versican in the tumor microenvironment [41]. These findings might help to explain the potential contribution of *ITGB8* upregulation to the poor survival in high-grade SOVC.

The exact mechanisms regulating *ITGB8* expression in cancer cells remain obscure. A recent study reported that miR-93 directly targets *ITGB8* and reduces its expression in human renal cancer cells [42]. miR-142-3p directly binds to *ITGB8* and negatively regulates its expression in glioma cells [43]. In SOVC cells, the expression of *ITGB8* is suppressed by miR-199-3p [11]. All these known mechanisms are epigenetic regulations. In this study, by examining the correlation between *ITGB8* DNA copy number data and its RNA expression, we found that DNA amplification was frequent and was associated with increased *ITGB8* expression in high-grade SOVC patients. Therefore, we infer that DNA amplification might also contribute to aberrantly expressed *ITGB8* in high-grade SOVC.

Conclusions

ITGB8 might be a valuable prognostic biomarker in high-grade SOVC, the expression of which might be regulated by its DNA copy numbers.

Conflicts of interest

None.

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