



# Expression and prognostic analyses of *ITGA11*, *ITGB4* and *ITGB8* in human non-small cell lung cancer

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## ABSTRACT

**Background.** Integrins play a crucial role in the regulation process of cell proliferation, migration, differentiation, tumor invasion and metastasis. *ITGA11*, *ITGB4* and *ITGB8* are three encoding genes of integrins family. Accumulative evidences have proved that abnormal expression of *ITGA11*, *ITGB4* and *ITGB8* are a common phenomenon in different malignances. However, their expression patterns and prognostic roles for patients with non-small cell lung cancer (NSCLC) have not been completely illustrated.

**Methods.** We investigated the expression patterns and prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in patients with NSCLC through using a series of databases and various datasets, including ONCOMINE, GEPIA, HPA, TCGA and GEO datasets.

**Results.** We found that the expression levels of *ITGA11* and *ITGB4* were significantly upregulated in both LUAD and LUSC, while *ITGB8* was obviously upregulated in LUSC. Additionally, higher expression level of *ITGB4* revealed a worse OS in LUAD.

**Conclusion.** Our findings suggested that *ITGA11* and *ITGB4* might have the potential ability to act as diagnostic biomarkers for both LUAD and LUSC, while *ITGB8* might serve as diagnostic biomarker for LUSC. Furthermore, *ITGB4* could serve as a potential prognostic biomarker for LUAD.

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Declarations can be found on  
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**Keywords** *ITGA11*, *ITGB4*, *ITGB8*, Non-small cell lung cancer, Expression and prognostic analysis

## INTRODUCTION

Lung cancer is the most frequent malignancy and the leading cause of cancer-related death all over the world. Five-year survival rate for lung cancer patients ranges from 4% to 17% depending on disease stage and regional differences (Hirsch et al., 2017). Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer and responsible for 85% to 90% of all lung cancer (Osmani et al., 2018). Owing to the problems in early diagnosis, patients with NSCLC are often diagnosed at advanced stage, which contributes

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a lot to the dismal prognosis (Ellis & Vandermeer, 2011; Jan et al., 2019). Thus, there is an urgent need to discover new diagnostic and prognostic biomarkers for NSCLC.

Integrins function as bridges between the extracellular matrix (ECM) and the cytoskeleton and work as radars to detect changes in the cellular microenvironment, which enables cells to react according to the external milieu (Bianconi, Unseld & Prager, 2016; Ginsberg, 2014). They play a crucial role in the regulation process of cell proliferation, migration, differentiation, tumor invasion and metastasis (Slack-Davis & Parsons, 2004). Integrins family include 24 different transmembrane, multifunctional heterodimers and are composed of an  $\alpha$  and a  $\beta$  subunit (Brakebusch et al., 2002). There are 18 different  $\alpha$  subunits and eight different  $\beta$  subunits in human body (Hynes, 1992). Recently, the effects of integrins in tumor progression have been receiving a great deal of attention.

*ITGA11* encodes integrin subunit  $\alpha 11$ , which dimerizes with  $\beta 1$  subunit and forms as a cell surface collagen receptor involved in the process of cell migration and collagen reorganization (Tiger et al., 2001). Integrin  $\alpha 11$  was overexpressed in the stroma of most head and neck squamous cell carcinomas (HNSCC) and correlated positively with alpha smooth muscle actin expression (Parajuli et al., 2017). In addition, *ITGA11* was overexpressed by cancer-associated fibroblast (CAFs) in Pancreatic Ductal Adenocarcinoma (PDAC) stroma and may serve as an interesting stromal therapeutic target (Schnittert et al., 2019). Integrin subunit  $\beta 4$ , also known as a laminin-5 receptor, is a protein encoded by *ITGB4* (Wang et al., 2012). Inhibition of *ITGB4* in glioma cells would decrease the self-renewal abilities of glioma stem cells and suppress the malignant behaviors of glioma cells in vitro and in vivo (Ma et al., 2019). Moreover, higher *ITGB4* expression level was detected in tumor than adjacent non-tumor tissues in patients with hepatocellular carcinoma (HCC). Silencing of *ITGB4* could repress cell proliferation, colony forming ability and cell invasiveness (Li et al., 2017). Integrin  $\beta 8$ , paired with  $\alpha v$  subunit, is encoded by *ITGB8*. It has been reported that *ITGB8* is upregulated in laryngeal squamous cell carcinoma (Ni et al., 2012). Additionally, the expression level of *ITGB8* can be regulated by the tumor-promoting receptor tyrosine kinase-EphB4, while knockdown of *ITGB8* may suppress migration and invasion in prostate cancer cell lines (Mertens-Walker et al., 2015). These studies have shown that *ITGA11*, *ITGB4* and *ITGB8* might be candidate biomarkers and therapeutic targets with great potential.

Recent years, there have been developed multifarious platforms, databases as well as various datasets on the web that allow cancer researchers to make in-depth bioinformatic analysis in cancer with multi omics data. Several prognostic biomarkers with great potential for NSCLC have also been identified. For instance, it has been reported that *STMN1* expression was correlated with poor OS in patients with Squamous Cell Lung Carcinoma (LUSC) and might serve as a prognostic biomarker (Bao et al., 2017). Using bioinformatics methods, Xie et al. (2019) have found that *KRT8* expression might be an independent prognostic biomarker for poor OS and PFS in Lung Adenocarcinoma (LUAD). Sun et al. (2019) have identified five genes that could predict metastasis in NSCLC and might serve as potential targets. As far as we know, bioinformatics analysis has not been applied to explore the roles of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC. Therefore, we conducted this study to

analyze the expression patterns and prognostic values of these three genes in NSCLC based on online databases, platforms and various datasets.

## MATERIALS AND METHODS

### ONCOMINE analysis

The expression levels of *ITGA11*, *ITGB4* and *ITGB8* and genes co-expressed with *ITGA11*, *ITGB4* and *ITGB8* were analyzed in ONCOMINE database (<https://www.oncomine.org>) (Rhodes *et al.*, 2007; Rhodes *et al.*, 2004). The cut-off of *p* value and fold change were defined as 0.01 and 2, respectively (Huang *et al.*, 2019).

### GEPIA (Gene Expression Profiling Interactive Analysis) analysis

GEPIA (<http://gepia.cancer-pku.cn/>) is an interactive web application for gene expression analysis based on 9736 tumors and 8587 normal samples from the TCGA (The Cancer Genome Atlas) and the GTEx (Genotype-Tissue Expression) databases (Tang *et al.*, 2017). The GEPIA database was used to compare mRNA levels of *ITGA11*, *ITGB4* and *ITGB8* between TCGA and GTEx databases. Meanwhile, the association among *ITGA11*, *ITGB4* and *ITGB8* in NSCLC were also analyzed in GEPIA.

### Bioinformatics analysis of data using The Cancer Genome Atlas lung cancer datasets

The level 3 data of TCGA-LUAD and TCGA-LUSC were obtained from UCSC Xena platform (<https://xenabrowser.net/datapages/>) (Goldman *et al.*, 2015) and RTCGA package (<https://rtcg.github.io/RTCGA>). The LUAD and LUSC gene expression RNAseq datasets included 524 tumor tissues and 499 tumor tissues, respectively. 502 of the LUAD patients and 492 of the 499 LUSC patients had complete survival data. The differences in overall survival (OS) of LUAD and LUSC patients with high and low expression of *ITGA11*, *ITGB4* and *ITGB8* were assessed by Kaplan–Meier curves. Meanwhile, the association between tumor stage and the expression levels of *ITGA11*, *ITGB4* and *ITGB8* were also analyzed. Clinicopathological parameters, including age at diagnosis, gender, vital status, tumor stage, smoking history and OS time, were extracted for univariate and multivariate cox regression analysis.

### Gene Expression Omnibus (GEO) microarray datasets analysis

To validate the expression profiles of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC, we collected a total of 21 datasets including tumor and non-tumor tissues of NSCLC in GEO database (<https://www.ncbi.nlm.nih.gov/geo/>). We analyzed the mRNA levels of *ITGA11*, *ITGB4* and *ITGB8* between tumor and non-tumor controls for each GEO dataset. In addition, we performed a meta-analysis based on the enrolled GEO microarray datasets.

### Immunohistochemistry analysis

The protein expression of *ITGA11*, *ITGB4* and *ITGB8* in normal lung and tumor tissues were examined using the Human Protein Atlas (HPA) (<https://www.proteinatlas.org/>) (Uhlen *et al.*, 2015; Uhlen *et al.*, 2017).

## Statistical analysis

Statistical analysis was performed on R software (3.6.1) (<https://www.r-project.org/>) and an integrated development environment RStudio (1.2.1335) (<https://rstudio.com/>). The mRNA expression of *ITGA11*, *ITGB4* and *ITGB8* between NSCLC tissues and normal controls were compared using Student's *t*-test. Data visualization was performed using an R package called “ggstatsplot” (<https://CRAN.R-project.org/package=ggstatsplot>). Kaplan–Meier curves of OS were performed in TCGA-LUAD and TCGA-LUSC raw data by setting median expression of *ITGA11*, *ITGB4* and *ITGB8* as cut-off. Statistical differences were assessed by the log-rank test. Univariate and multivariate survival analyses were performed using cox regression model, risk factors ( $p < 0.2$ ) analyzed by univariate analysis were selected for multivariate analysis.

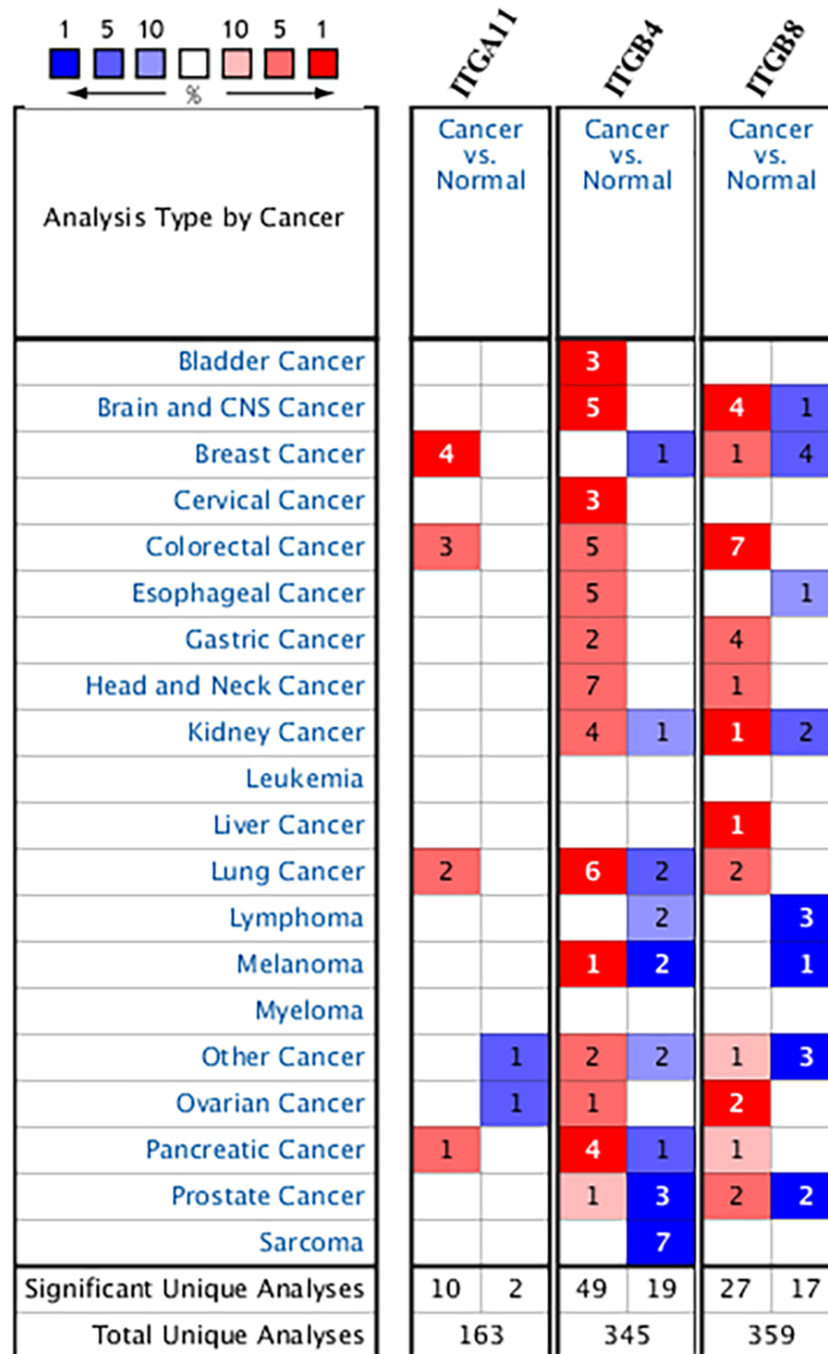
For GEO datasets analysis, mean (M) and standard deviation (SD) were calculated for each NSCLC tumor and normal control group. In addition, an R package called “meta” was used in R to perform a comprehensive meta-analysis (Schwarzer, 2007). The Q test and  $I^2$  statistic were calculated to assess the heterogeneity among the enrolled studies. If  $p < 0.05$  or  $I^2 > 50\%$ , a random effects model would be selected. Sensitivity analysis was conducted to explore whether a specific study played a crucial influence in significant heterogeneity. Finally, the publication bias was examined through funnel plots and Egger's test (Egger *et al.*, 1997). Once there was a publication bias, the “fill and trim” method would be selected to adjust for the bias (Duval & Tweedie, 2000).  $p < 0.05$  deemed statistically significant.

## RESULTS

### The expression levels of *ITGA11*, *ITGB4* and *ITGB8* in patients with non-small cell lung cancer

Using ONCOMINE database, we investigated the transcription levels of *ITGA11*, *ITGB4* and *ITGB8* in lung cancer vs. normal samples. ONCOMINE analysis revealed that the mRNA expression of *ITGA11*, *ITGB4* and *ITGB8* were obviously overexpressed in NSCLC tissues in ten datasets (Fig. 1). These datasets were summarized in Table 1. The GEPIA analysis results also suggested that the expression levels of *ITGA11* and *ITGB4* were significantly higher in both LUAD and LUSC than that in normal tissues, while the expression level of *ITGB8* was only significantly upregulated in LUSC tissues (Fig. 2). Furthermore, we analyzed *ITGA11*, *ITGB4* and *ITGB8* mRNA expression level in both lung cancer and normal tissues using the TCGA-LUAD and TCGA-LUSC original data. The results revealed that the expression levels of *ITGA11*, *ITGB4* and *ITGB8* were all significantly upregulated in tumor tissues compared with normal tissues (Fig. S1).

To further explore the protein expression of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC, we analyzed the IHC images using the Human Protein Atlas (HPA) database. As shown in Fig. 3, the protein expression of *ITGA11* and *ITGB4* were upregulated in both LUAD and LUSC cancer tissues compared with normal lung tissues (Figs. 3A–3C and 3D–3F). In comparison, the protein expression of *ITGB8* was obviously upregulated in LUSC with medium staining, but not in LUAD (Figs. 3G–3I).

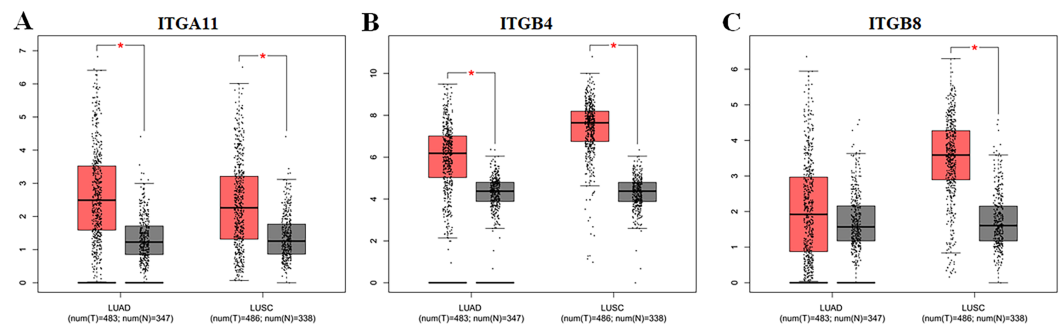


**Figure 1** The transcription levels of ITGA11, ITGB4 and ITGB8 in different cancers compared with normal tissues in the ONCOMINE database. Cell color is determined by the best gene rank percentile for the analysis within the cell.

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**Table 1** The transcription levels of *ITGA11*, *ITGB4* and *ITGB8* between lung cancer and normal samples in ONCOMINE database.

Gene ID	Types of lung cancer vs. normal	Fold change	P value	t-Test	References
<i>ITGA11</i>	Lung Adenocarcinoma vs. Normal	2.047	6.79E-16	10.685	<i>Selamat et al. (2012)</i>
	Lung Adenocarcinoma vs. Normal	2.968	7.47E-09	7.945	<i>Okayama et al (2012)</i>
<i>ITGB4</i>	Squamous Cell Lung Carcinoma vs. Normal	2.867	1.32E-05	8.706	<i>Wachi et al. (2005)</i>
	Squamous Cell Lung Carcinoma vs. Normal	3.505	5.33E-06	6.406	<i>Garber et al. (2001)</i>
	Squamous Cell Lung Carcinoma vs. Normal	2.637	4.64E-10	7.458	<i>Talbot et al. (2005)</i>
	Squamous Cell Lung Carcinoma vs. Normal	6.818	5.21E-04	3.57	<i>Bhattacharjee et al. (2001)</i>
	Lung Adenocarcinoma vs. Normal	2.99	1.17E-14	9.575	<i>Selamat et al. (2012)</i>
	Squamous Cell Lung Carcinoma vs. Normal	3.591	8.92E-10	8.599	<i>Hou et al. (2010)</i>
<i>ITGB8</i>	Squamous Cell Lung Carcinoma vs. Normal	2.455	1.95E-05	5.627	<i>Garber et al. (2001)</i>
	Squamous Cell Lung Carcinoma vs. Normal	2.876	1.26E-07	6.484	<i>Hou et al. (2010)</i>

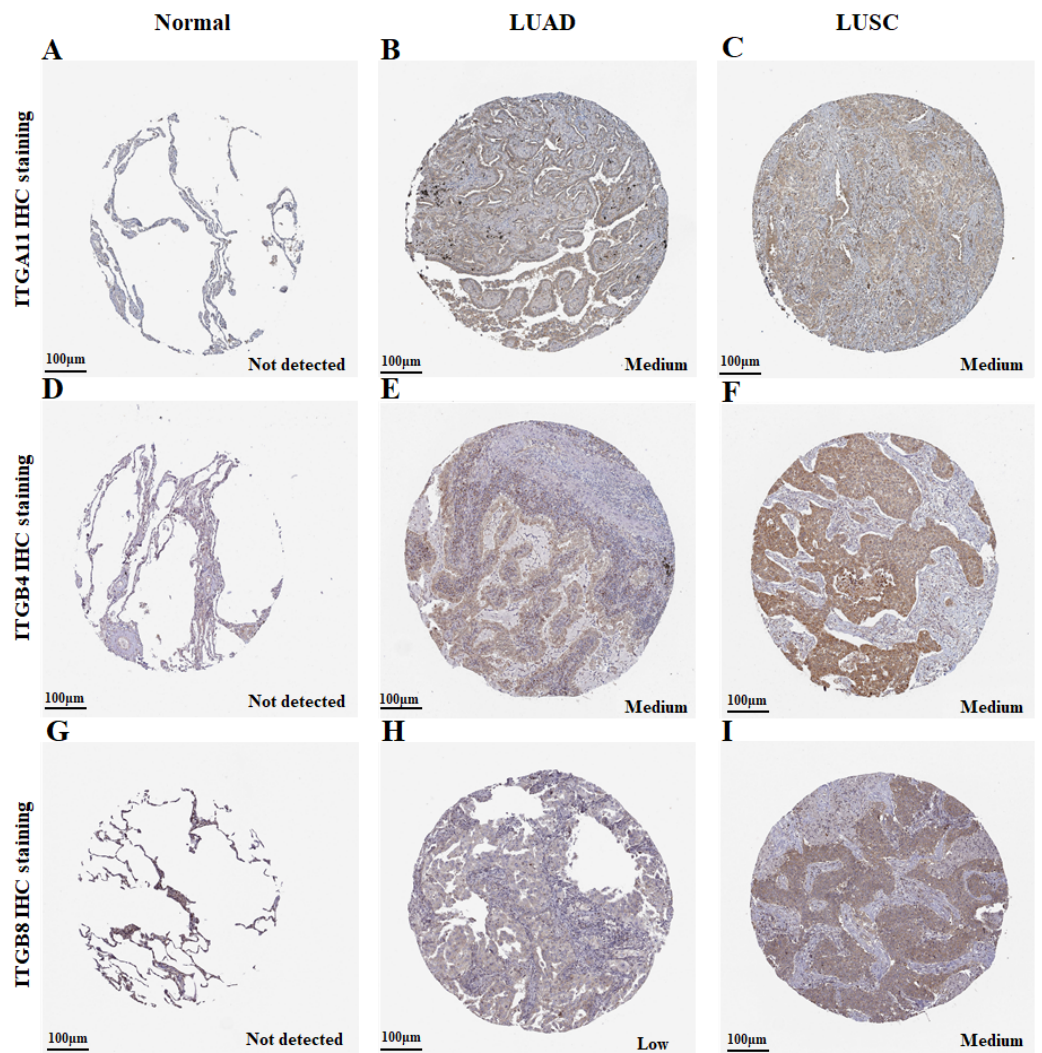
**Figure 2** The expression levels of *ITGA11* (A), *ITGB4* (B) and *ITGB8* (C) between NSCLC tissues and normal tissues in GEPIA. \*Indicate that the results are statistically significant.

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### Confirmation of the expression profiles of *ITGA11*, *ITGB4* and *ITGB8* in non-small cell lung cancer using GEO datasets

We also performed a data-mining analysis to investigate the differences in the expression levels of *ITGA11*, *ITGB4* and *ITGB8* between tumor and normal tissues in NSCLC using GEO datasets. The main characteristics of the enrolled GEO studies were described in [Table S1](#). The results were shown in [Fig. 4](#) and [Figs. S2–S4](#). As illustrated in [Fig. 4A](#) and [Fig. S2D](#), the expression level of *ITGB4* was significantly increased in tissues from patients with LUAD (SMD: 0.94; 95% CI [0.65–1.24];  $p < 0.01$ ) as well as LUSC (SMD: 1.37; 95% CI [0.71–2.04];  $p < 0.01$ ) compared to the normal tissues. The heterogeneity was apparent for LUAD ( $I^2 = 80\%$ ;  $p < 0.01$ ) and LUSC ( $I^2 = 89\%$ ;  $p < 0.01$ ). The following sensitivity analysis demonstrated that no study was found to have a vital influence in the enrolled studies ([Fig. 4B](#) and [Figs. S3D](#)). In addition, we didn't find evidence of publication bias based on the funnel plot and the Egger's test ([Fig. 4C](#),  $p = 0.7759$ ). However, the [Figs. S4D](#) indicated publication bias (Egger's test,  $p = 0.04729$ ). Therefore, we used the fill and trim method to adjust for the bias. The adjusted random effects model result showed that *ITGB4* was also significantly upregulated in LUSC tissues (SMD: 0.77; 95% CI [0.03–1.52];  $p = 0.04$ ).





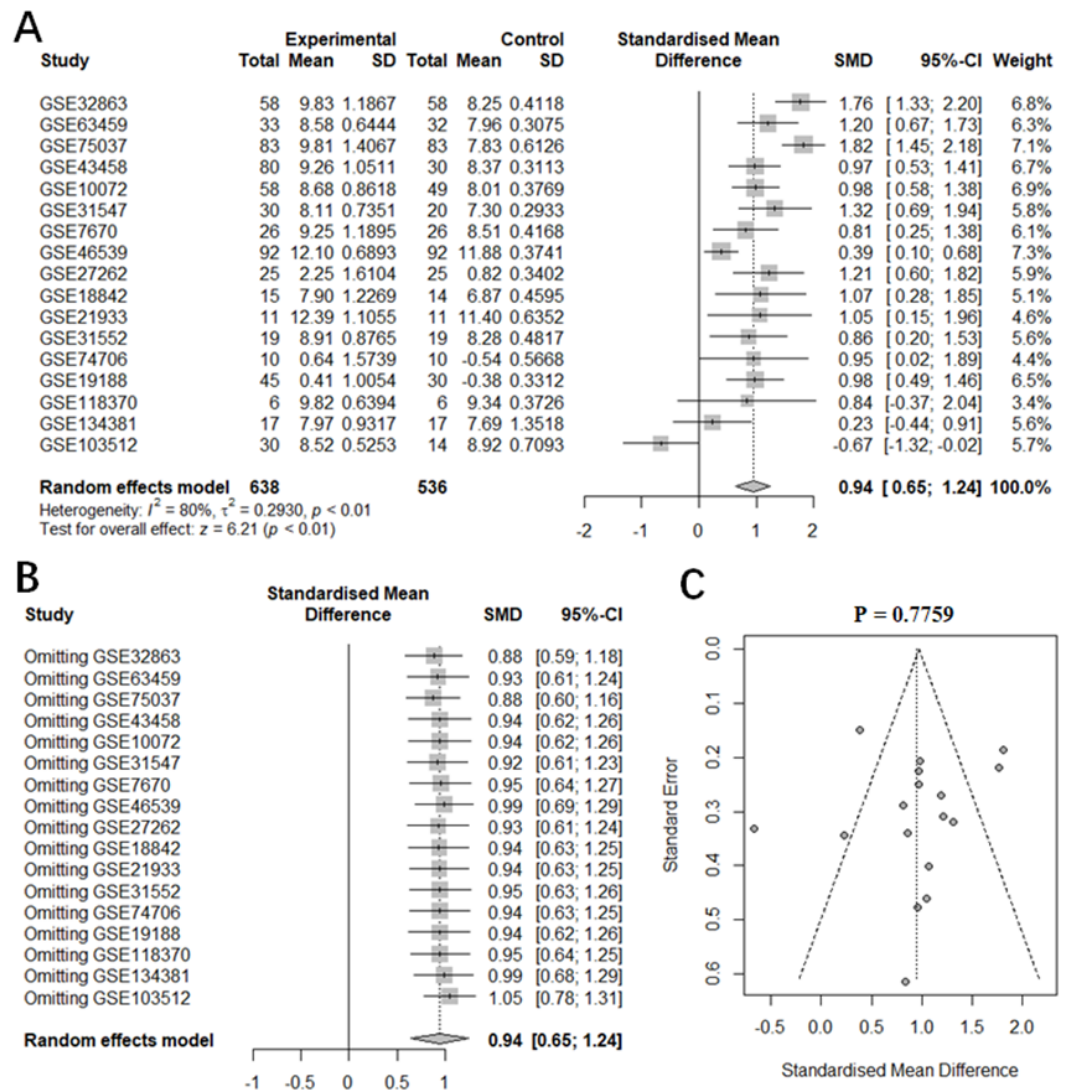
**Figure 3** Immunohistochemistry analysis for ITGA11, ITGB4 and ITGB8 in NSCLC (HPA database). (A–F) The protein expression of ITGA11 and ITGB4 were significantly higher in both LUAD and LUSC tissues compared with the normal lung, respectively. (G–I) The protein expression level of ITGB8 was significantly higher in LUSC tissues compared with the normal lung.

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The analysis results of *ITGA11* and *ITGB8* mRNA levels in LUAD and LUSC were the same as the above results (Figs. S2–S4). The separate analyses of the expression levels of *ITGA11*, *ITGB4* and *ITGB8* in LUAD and LUSC tissues compared with normal tissues for each GEO dataset were presented in the Figs. S5 and S6.

### The prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in non-small cell lung cancer

By using GEPIA, we investigated the prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC. The survival curves revealed that high expression level of *ITGB4* could indicate a poor OS in LUAD ( $p < 0.001$ ; Fig. 5B), while *ITGA11* and *ITGB8* were not related with OS



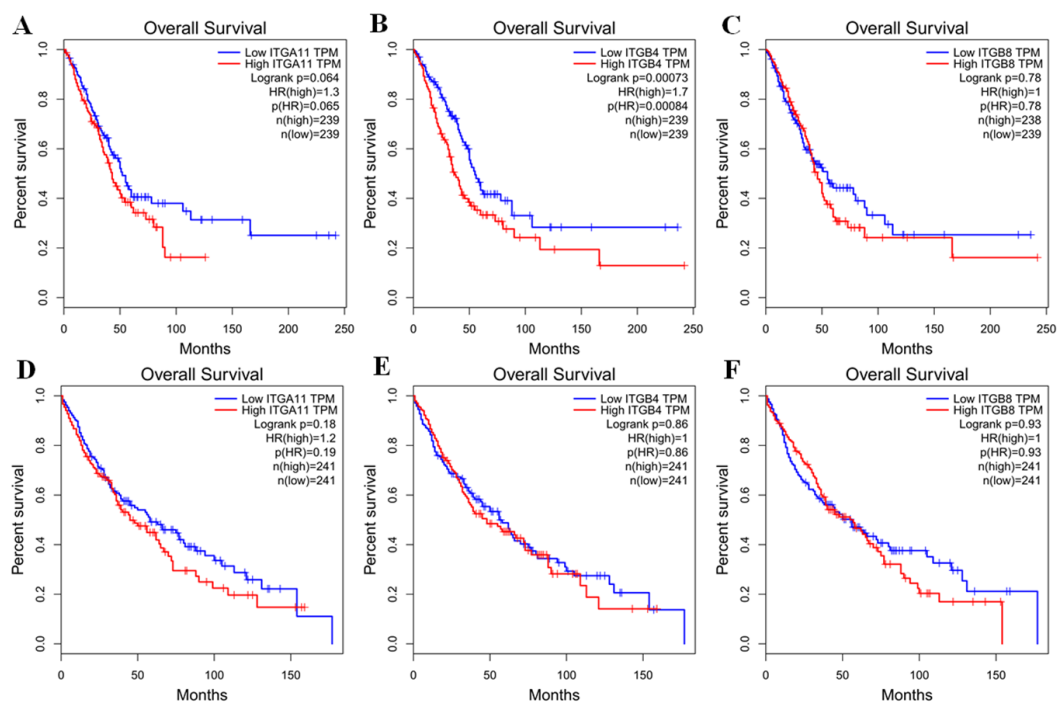
**Figure 4** Meta-analysis of *ITGB4* expression in LUAD tissues compared with normal controls based on GEO datasets. (A) Forest plot of SMD comparing *ITGB4* expression in LUAD tissues with normal controls from the enrolled GEO datasets. (B) Sensitivity analysis of the enrolled GEO datasets. (C) The evaluation of the publication bias of the enrolled GEO datasets (Egger's test,  $p = 0.7759$ ).

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in LUAD ( $p = 0.064$  and  $p = 0.78$ , respectively, Figs. 5A and 5C). In comparison, there were no obvious associations between the expression levels of *ITAG11*, *ITGB4* and *ITGB8* and LUSC (Figs. 5D–5F). Moreover, using the TCGA original data, we performed survival analysis to validate these associations. The results were consistent with GEPIA analysis (Fig. S7).

Next, we performed cox regression analysis to further assess and validate the prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC based on TCGA original data. The univariate cox analysis indicated that high *ITGB4* expression and advanced stages were significantly correlated with worse OS in LUAD (Table 2). Meanwhile, multivariate cox





**Figure 5** Kaplan–Meier survival curves of overall survival (OS) in LUAD and LUSC (GEPIA database). Survival curves of OS based on the high and low expression of *ITGA11*, *ITGB4* and *ITGB8* in LUAD (A–C) and LUSC (D–F), respectively.

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analysis confirmed that high *ITGB4* expression was an independent prognostic biomarker for patients with LUAD (HR: 1.417; 95%CI [1.042–1.926];  $p = 0.026$ ; Table 2). In addition, no significant results were found with other genes in the OS of LUAD and LUSC (Table 2). These results were consistent with that analyzed by GEPIA. Furthermore, we investigated the correlation between tumor stage and the expression levels of *ITGA11*, *ITGB4* and *ITGB8* (Fig. S8). The results showed that there was a significant correlation between tumor stage and mRNA expression of *ITGB8* in LUSC (Fig. S8F).

### Co-expression and correlation analyses of *ITGA11*, *ITGB4* and *ITGB8* in non-small cell lung cancer

The co-expression analysis was conducted using ONCOMINE database. Based on Hou Lung dataset (Hou *et al.*, 2010), we analyzed genes that were co-expressed with *ITGA11*, the result showed that *ITGA11* was co-expressed with *COL10A1*, *THBS2*, *SULF1*, *CTRHC1*, *GREM1*, *C5orf46*, *COL11A1*, *NOX4* (Fig. S9A). The Bild Lung dataset indicated that *ITGB4* was co-expressed with *LAD1*, *SFN*, *FXYD3*, *KRT19*, *DSG2*, *JUP*, *DSP*, *PERP* (Bild *et al.*, 2006) (Fig. S9B). Based on Yamagata Lung dataset (Yamagata *et al.*, 2003), we analyzed genes that were co-expressed with *ITGB8*, the result showed that *ITGB8* was co-expressed with *ERC2*, *PDE6D*, *C17orf99*, *SNRNP27*, *C1orf61*, *GATA1*, *PPP2R2B*, *CCK*, *CRYBA1*, *APBA3*, *CYP3A4*, *UROS* (Fig. S9C).

**Table 2** Univariate and multivariate cox analysis of OS in LUAD and LUSC. Smoking history: 1. life-long non-smoker; 2. current smoker; 3. current reformed smoker (for >15 years); 4. Current reformed smoker (for ≤ 15 years); 5. current reformed smoker (duration not specified).

Characteristics	Univariate analysis			Multivariate analysis		
	p value	HR	95%CI	p value	HR	95%CI
<b>LUAD-OS</b>						
Gender	0.745	1.050	0.784-1.405			
Male vs. Female						
Age	0.229	1.198	0.892-1.610			
>65 vs. ≤65						
Smoking history	0.530	0.875	0.578-1.325			
2/3/4/5 vs. 1						
Clinical stage	0	2.466	1.786–3.404	0	2.329	1.682–3.226
III/IV vs. I/II						
ITGA11 expression	0.076	1.306	0.973–1.753	0.361	1.153	0.849–1.566
High vs. Low						
ITGB4 expression	0.002	1.575	1.175–2.112	0.026	1.417	1.042–1.926
High vs. Low						
ITGB8 expression	0.925	0.986	0.737–1.320			
High vs. Low						
<b>LUSC-OS</b>						
Gender	0.179	1.251	0.902–1.736	0.177	1.253	0.903–1.739
Male vs. Female						
Age	0.124	1.253	0.940–1.670	0.049	1.343	1.001–1.803
>65 vs. ≤65						
Smoking history	0.430	0.698	0.286–1.704			
2/3/4/5 vs. 1						
Clinical stage	0.002	1.655	1.199–2.284	0.002	1.665	1.204–2.301
III/IV vs. I/II						
ITGA11 expression	0.385	1.128	0.860–1.479			
High vs. Low						
ITGB4 expression	0.388	1.127	0.859–1.479			
High vs. Low						
ITGB8 expression	0.875	0.978	0.746–1.283			
High vs. Low						

By using GEPIA, we investigated the association among *ITGA11*, *ITGB4* and *ITGB8* in NSCLC based on Pearson correlation analysis. The results indicated that there was no correlation between *ITGA11* and *ITGB4* ( $R = -0.018$ ;  $p > 0.05$ ) (Fig. S10A). Also, there was scarcely any correlation between *ITGA11* and *ITGB8* ( $R = 0.069$ ;  $p < 0.05$ ) (Fig. S10B). In addition, a weak positive correlation was found between *ITGB8* and *ITGB4* ( $R = 0.32$ ;  $p < 0.05$ ) (Fig. S10C).

## DISCUSSION

Numerous studies have suggested that *ITGA11*, *ITGB4* and *ITGB8* are involved in migration, epithelial-mesenchymal transition, invasion, and metastasis in different cancers (Gan et al., 2018; Huang et al., 2017; Kitajiri et al., 2002; Li et al., 2017). The

aberrant expression of *ITGA11*, *ITGB4*, and *ITGB8* have been reported in many cancers (*Grossman et al., 2000; Mertens-Walker et al., 2015; Parajuli et al., 2017; Tagliabue et al., 1998*). Regrettably, the expression profiles and prognostic roles of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC are still not clear. Thus, we conducted this study to explore the expression patterns and prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in NSCLC.

It has been reported that *ITGA11* could serve as an important stromal factor in NSCLC, which can enhance tumorigenicity of human non-small cell lung cancer cells by regulating IGF2 expression in fibroblasts (*Zhu et al., 2007*). Moreover, in carcinoma-associated fibroblasts (CAFs), *ITGA11* signaling pathway may play an important role in carcinoma-associated fibroblasts (CAFs), which means Integrin  $\alpha 11\beta 1$  can promote tumor growth and metastatic potential of NSCLC cells by regulating cancer stromal stiffness (*Navab et al., 2016*). These results suggested that *ITGA11* might play an important role for NSCLC. In our study, ONCOMINE analysis showed that mRNA expression level of *ITGA11* was highly expressed in Lung Adenocarcinoma compared with that in normal controls. GEPIA revealed that the expression level of *ITGA11* was obviously higher in both LUAD and LUSC than that in normal tissues. In addition, we also downloaded TCGA original data, GEO datasets, and protein expression data from HPA to validate *ITGA11* expression profile, the results were consistent with the GEPIA analysis results. These results indicated that *ITGA11* might be a diagnostic biomarker for patients with LUAD and LUSC. Furthermore, we investigated the association between the expression level of *ITGA11* and OS in LUAD and LUSC using GEPIA and cox regression analysis. However, the results showed *ITGA11* expression had no prognostic role in terms of OS in LUAD and LUSC.

*ITGB4* was found to have a strong positive correlation with tumor size ( $p = 0.01$ ) and tumor nuclear grade ( $p < 0.01$ ) in early breast cancer (*Diaz et al., 2005*). Furthermore, it is reported that *ITGB4* could promote the invasion and metastasis of tumor cells through a series of processes (*Stewart & O'Connor, 2015*). These results imply us that *ITGB4* might also play a crucial role in NSCLC. In our report, ONCOMINE and GEPIA analysis revealed that the expression level of *ITGB4* was significantly upregulated in LUAD and LUSC. Additionally, we confirmed this expression feature by analysis TCGA original data and GEO datasets. The protein level was also consistent with the mRNA expression level. Taken together, these results implied that *ITGB4* expression could act as a diagnostic biomarker for patients with LUAD and LUSC. Moreover, the survival curve showed that high *ITGB4* expression was strong correlated with inferior OS in LUAD. The following univariate cox and multivariate cox regression analysis confirmed that high *ITGB4* expression level was an independent prognostic biomarker for poor OS in LUAD.

It has been reported that *ITGB8* could mediate the activation of latent TGF- $\beta$ , which subsequently derives the epithelial-to-mesenchymal (EMT) transition of some cancers and contributes to cancer cell migration and growth (*Mu et al., 2002; Pozzi & Zent, 2011*). Furthermore, *ITGB8* was significantly upregulated in ovarian cancer tissues compared with that in normal ovary tissues (*He et al., 2018*). Moreover, It has been reported that *ITGB8* silencing could suppress the metastatic potential of human lung cancer cell lines A549 and PC (*Xu & Wu, 2012*). These studies suggested that *ITGB8* might play an important role in NSCLC. In our study, we found that the mRNA expression level of *ITGB8* was highly

overexpressed in LUSC both in ONCOMINE and GEPIA analysis. This expression feature was successfully validated by analyzing the TCGA original data and GEO datasets. These results suggested that *ITGB8* might act as a diagnostic biomarker in LUSC. It was worth mentioning that there was no significant correlation in *ITGB8* expression level between LUAD and normal tissues by GEPIA analysis. However, the expression feature was not showed when we analyzed the TCGA original data and GEO datasets. This may due to the lack of normal controls in TCGA datasets and the differences in enrolled participants in GEO datasets. Future large-scale studies are required to assess and validate this expression pattern. In addition, we explored the association between the expression level of *ITGB8* and OS in LUAD and LUSC using GEPIA and cox regression analysis. the results showed *ITGB8* expression had no prognostic role in terms of OS in LUAD and LUSC. Furthermore, we found that there was a strong correlation between *ITGB8* expression level and tumor stage in LUSC.

The potential limitations of our study need to be noted. First, the biological mechanisms of these three candidate markers in LUAD and LUSC are still unknown. Second, although this study had a comprehensive analysis based on several databases such as TCGA and GEO, traditional in-house experimental studies including enough specimens are required to further validate our findings.

## CONCLUSIONS

In summary, we systematically analyzed the expression patterns and prognostic values of *ITGA11*, *ITGB4* and *ITGB8* in patients with LUAD and LUSC by conducting a bioinformatics analysis based on several web platforms and various datasets. Our results indicated that *ITGA11* and *ITGB4* might act as diagnostic biomarkers for both LUAD and LUSC, while *ITGB8* may serve as diagnostic biomarker for LUSC. Furthermore, *ITGB4* might serve as a potential prognostic biomarker for LUAD. We hope our findings will enrich the knowledge of diagnostic and therapy designs for patients with NSCLC.

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## ADDITIONAL INFORMATION AND DECLARATIONS

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## Competing Interests

The authors declare there are no competing interests.

## Author Contributions

- Pancheng Wu and Yanyu Wang conceived and designed the experiments, performed the experiments, analyzed the data, authored or reviewed drafts of the paper, approved the final draft.
- Yijun Wu, Ziqi Jia and Yang Song analyzed the data, prepared figures and/or tables, approved the final draft.
- Naixin Liang conceived and designed the experiments, authored or reviewed drafts of the paper, approved the final draft.

## Data Availability

The following information was supplied regarding data availability:

The TCGA-LUAD and TCGA-LUSC raw data is available at UCSC Zena (available at <https://xenabrowser.net/datapages/>).

NCBI GEO datasets: [GSE32863](#), [GSE63459](#), [GSE75037](#), [GSE43458](#), [GSE10072](#), [GSE31547](#), [GSE7670](#), [GSE46539](#), [GSE27262](#), [GSE18842](#), [GSE21933](#), [GSE31552](#), [GSE74706](#), [GSE19188](#), [GSE118370](#), [GSE134381](#), [GSE103512](#), [GSE2088](#), [GSE12428](#), [GSE33479](#) and [GSE30219](#).

The raw code is available in a [Supplementary Files](#).

## Supplemental Information

Supplemental information for this article can be found online at <http://dx.doi.org/10.7717/peerj.8299#supplemental-information>.

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