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Overexpression of Family with Sequence Similarity 83, Member A (FAM83A) Predicts Poor Clinical Outcomes in Lung Adenocarcinoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The aim of this study was to explore the expression levels of family with sequence similarity 83, member A (FAM83A) in lung adenocarcinoma (LUAD) and investigate its clinical prognostic value.

Material/Methods: Bioinformatics mining methods were used to predict the differential expression levels of FAM83A mRNA in LUAD and normal lung tissues based on the TCGA and Oncomine databases. Immunohistochemical staining was performed to demonstrate the FAM83A protein expression levels in 83 cases of LUAD combined with paired normal lung tissues. The correlation between clinicopathologic factors and FAM83A differential expression levels in LUAD was explored by the chi-square test. Kaplan-Meier univariate and Cox multivariate survival analyses were performed to investigate the clinical prognostic value of FAM83A expression in LUAD patients.

Results: Results from TCGA and Oncomine databases revealed that FAM83A mRNA expression level was significantly higher in LUAD than that in normal lung tissues (both $P<0.05$). Immunohistochemical findings demonstrated that the high positive rate of FAM83A in LUAD was 73.49% (61/83), while that of matched normal lung tissues was only 22.89% (19/83). Moreover, LUAD patients with FAM83A mRNA or high protein levels had dramatically lower OS times than those with FAM83A mRNA or low protein levels (All $P<0.05$). Lastly, Cox multivariate survival analysis showed that FAM83A differential expression level (low *vs.* high) was the only independent factor predicting the prognosis of LUAD patients ($P=0.001$).

Conclusions: FAM83A was overexpressed in LUAD, and FAM83A overexpression could be used as an independent factor of poor prognosis in LUAD patients.

MeSH Keywords: Lung Neoplasms • Oncogene Protein v-cbl • Prognosis

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Background

Lung cancer is the leading cause of cancer-related mortality [1]. According to the histology, lung cancer is divided into 2 main subtypes: small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC), accounting for 15% and 85% of all cases, respectively [2]. Among NSCLC, lung adenocarcinoma (LUAD) is one of the most common types of lung cancer, and is characterized by distinct cellular and molecular features, including gland and/or duct formation and/or production of significant amounts of mucus. Surgery is the standard treatment for early NSCLC [3]. Besides chemotherapy and radiotherapy, the presence of targeted drugs significantly increases the overall survival of patients with advanced NSCLC, especially for LUAD [4], but there is still a risk of recurrence in early postoperative lung cancer patients [5]. Meanwhile, chemotherapy and targeted therapies are faced with extensive drug resistance [6,7]. Thus, to understand the causes of drug resistance, establish methods of overcoming drug resistance and exploring new therapeutic targets have become important topics in the field of lung cancer.

Family with sequence similarity 83, member A (FAM83A), also known as BJ-TSA-9 [8], is located on chromosome 8, locus q24.13, and spans 27 566 base pairs. There is a promoter approximately 4000 base pairs upstream as predicted by the ElDorado tool by Genomatix. Deletions in this part of the chromosome, including the FAM83A gene, often result in Langer-Giedion syndrome [9]. Recently, some studies have found that dysregulated FAM83A is a potential biomarker in lung, prostate, and bladder cancers [8,10,11]. However, the exact expression levels of FAM83A in LUAD and its clinical prognostic value have been unknown.

Therefore, in the present study, bioinformatics methods were performed initially to predict the differential expression levels of FAM83A mRNA in LUAD and normal lung tissues through mining cancer-related databases (TCGA and Oncomine). Then, immunohistochemical staining was carried out to examine the FAM83A protein expression levels in 83 cases of LUAD combined with paired normal tissues. Moreover, the chi-square test was used to investigate the relationship between clinicopathologic parameters and differential expression levels of FAM83A protein in LUAD. Additionally, Kaplan-Meier univariate and Cox multivariate survival analyses were used to identify the prognostic value of FAM83A expression in LUAD patients.

Material and Methods

Bioinformatics mining

We downloaded 483 cases of LUAD and 347 cases of normal lung tissues containing FAM83A mRNA expression information from the TCGA database (*https://cancergenome.nih.gov/*). Then, RStudio software was used to analyze the differential expression levels of FAM83A mRNA between groups and draw the overall survival (OS) and disease-free survival (DFS) curves. The Oncomine database (*https://www.oncomine.org*) [12] was also screened to explore the differential expression levels of FAM83A between LUAD and normal groups. A total of 4 GEO-sourced datasets were included. Additionally, Kaplan-Meier Plotter (*http://kmplot.com/analysis/index.php?p=service&cancer=lung*) [13] was used to draw the OS and DFS curves based on the GEO data.

Collected LUAD tissues and patients' clinicopathological data

We retrospectively collected 83 cases of LUAD and matched adjacent normal lung tissues for immunohistochemical staining. All the patients had received radical surgery in the Department of Cardiovascular Surgery in our hospital from January 2006 to December 2012. The last follow-up time was June 2017. The last pathologic diagnosis of all patients was LUAD after surgery. As listed in Table 1, besides FAM83A expression levels, the corresponding clinical information of patients, including sex, age, T stage, and TNM stage, was concluded in detail. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University and informed consent was obtained from each patient.

Immunohistochemistry and judging of results

According to the manufacturer's protocol, immunohistochemistry analysis was performed to investigate the differential expression levels of FAM83A in 83 cases of LUAD and matched normal lung tissues. FAM83A monoclonal antibody (ab128245) was purchased from Abcam Corporation and its working concentration was 1: 200. The results of immunohistochemical staining were independently judged and interpreted by 2 pathologists who were double-blinded. Based on methods used in previous other studies [14–16], the immunoreaction score (IRS) was calculated from each slice, with the IRS equal to staining intensity (SI)×number of stained cells (PP). IRS scores ranged from 0 to 12. When the IRS was larger than 4, FAM83A was defined as high expression, and with IRS ≤4, FAM83A was defined as low expression.

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Table 1. Correlation between FAM83A and clinicopathological parameters of LUAD patients.

Clinicopathological parameters	Cases (n)	FAM83A expression levels		χ^2	*P* value
		Low (22)	High (61)		
Gender					
Male	42	11	31	0.004	0.947
Female	41	11	30		
Age (years)					
≤60	39	9	30	0.444	0.505
>60	44	13	31		
Histological differentiation					
Well/moderate	58	16	42	0.115	0.734
Poor	25	6	19		
Tumor size (cm)					
≤3	32	11	21	1.655	0.198
>3	51	11	40		
Tumor location					
Left lung	34	10	24	0.250	0.617
Right lung	49	12	37		
Lymph node metastasis					
No	36	11	25	0.535	0.464
Yes	47	11	36		
T stage					
T1	17	6	11	0.848	0.357
T2–T4	66	16	50		
TNM stage					
I	27	7	20	0.007	0.934
II+III+IV	56	15	41		
EGFR status					
Negative	69	16	53	2.311	0.128
Positive	14	6	8		

Statistical analysis

SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA) was used to statistically analyze the experimental data. Mean and standard deviation were used to express the quantitative data. TCGA and Oncomine data were analyzed using the independent-samples *t* test to compare the differential expression levels of FAM83A mRNA between LUAD and normal lung tissue groups. The chi-square test was used to analyze the correlation between FAM83A differential levels and clinicopathological factors of LUAD patients. Kaplan-Meier univariate and Cox multivariate survival analyses were used to verify the prognostic value of FAM83A differential levels in LUAD patients. If the *P* value was less than 0.05, the difference was considered statistically significant.

Results

FAM83A was overexpressed in LUAD compared to normal lung tissues

Through mining the TCGA data, we found that FAM83A mRNA expression levels were significantly higher in LUAD than those in normal lung tissues ($P<0.05$, Figure 1A). By searching the Oncomine database, a total of 4 GEO-sourced datasets

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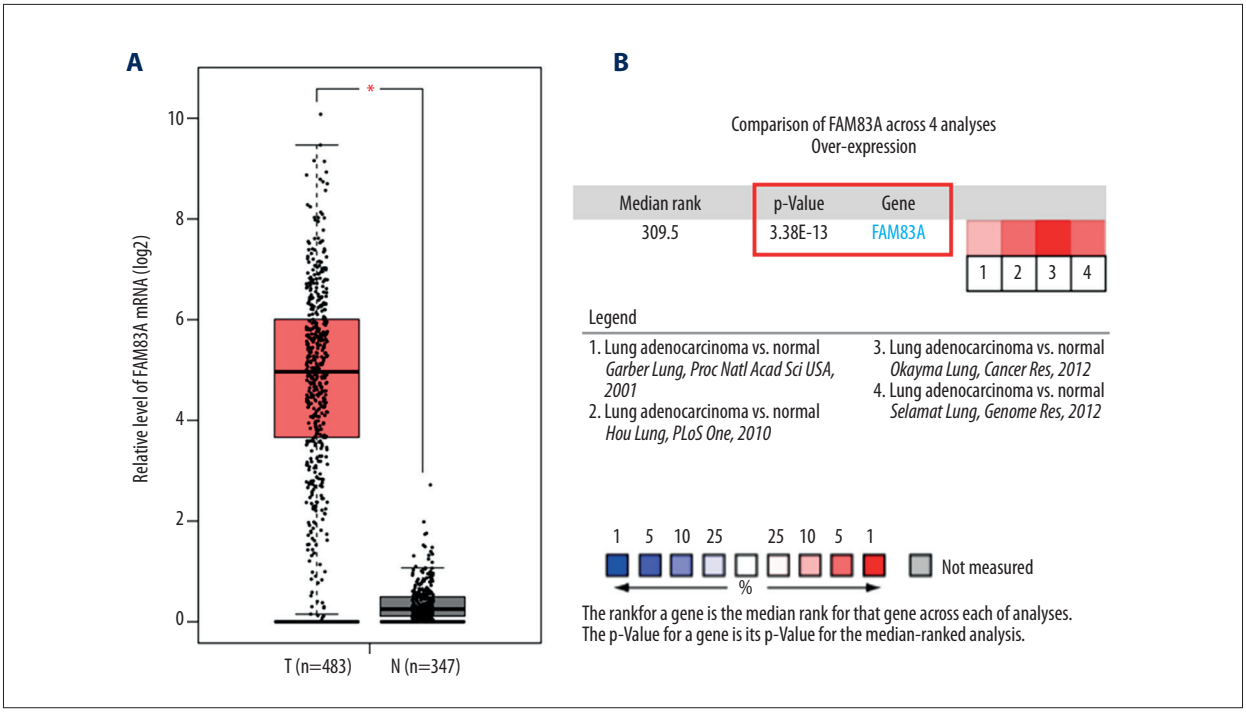

Figure 1. Overexpression of FAM83A mRNA in LUAD predicted by TCGA and Oncomine databases. (**A**) FAM83A mRNA levels in LUAD *vs.* normal lung group; (**B**) Meta-analysis of the 4 datasets on FAM83A mRNA levels in LUAD *vs.* normal lung tissue by Oncomine database.

were found. The meta-analysis revealed that FAM83A mRNA levels were dramatically higher in LUAD than in normal lung tissues (P=3.38E-13, Figure 1B). Moreover, as shown in Figure 2, results from each dataset were consistent with findings of the above meta-analysis.

Then, to confirm the above predictive results, immunohistochemistry was carried out. As shown in Figure 3A, FAM83A was positively stained in cytoplasm and cytomembrane of LUAD cells and the high positive rate of FAM83A staining in LUAD was 73.49% (61/83), while that of matched normal lung tissues was only 22.89% (19/83) (Figure 3B). Levels of FAM83A protein were remarkably higher in LUAD than those in matched normal lung tissues (χ^2=42.562, P=0.000, Table 2).

Association between FAM83A differential levels and clinicopathological factors of LUAD patients

Based on the immunohistochemical staining results, chi-square testing was done for FAM83A protein differential levels (low *vs.* high) and different subgroups of each clinicopathological factors. As shown in Table 1, there was no significant difference in FAM83A expression levels between the 2 subgroups of clinicopathological factor in LUAD patients (All P>0.05).

Potential prognostic value of FAM83A gene in LUAD patients

As shown in Figure 4, through mining the TCGA database and use of Kaplan-Meier Plotter, we found that LUAD patients with high levels of FAM83A mRNA had dramatically decreased OS and DFS compared to those with low levels of FAM83A mRNA (All P values <0.05, the cut-off value of FAM83A mRNA expression was set as 50%). Then, immunohistochemistry was performed to verify the predictive results. Kaplan-Meier survival analysis showed that LUAD patients with high levels of FAM83A protein had remarkably lower OS than those with low levels of FAM83A protein (P=0.002, Figure 5). Log-rank univariate survival analysis demonstrated that together with FAM83A differential levels, lymph node metastasis, T stage, TNM stage, and EGFR status were all the statistically significant parameters affecting the OS of LUAD patients (Table 3). Additionally, the above 5 factors were used in the subsequent Cox multivariate survival analysis, showing that FAM83A differential expression level (low *vs.* high) was the only independent factor predicting the prognosis of LUAD patients (P=0.001, Table 4).

Discussion

Recently, accumulating studies have found that FAM83A was overexpressed in some malignancies [17,18], including

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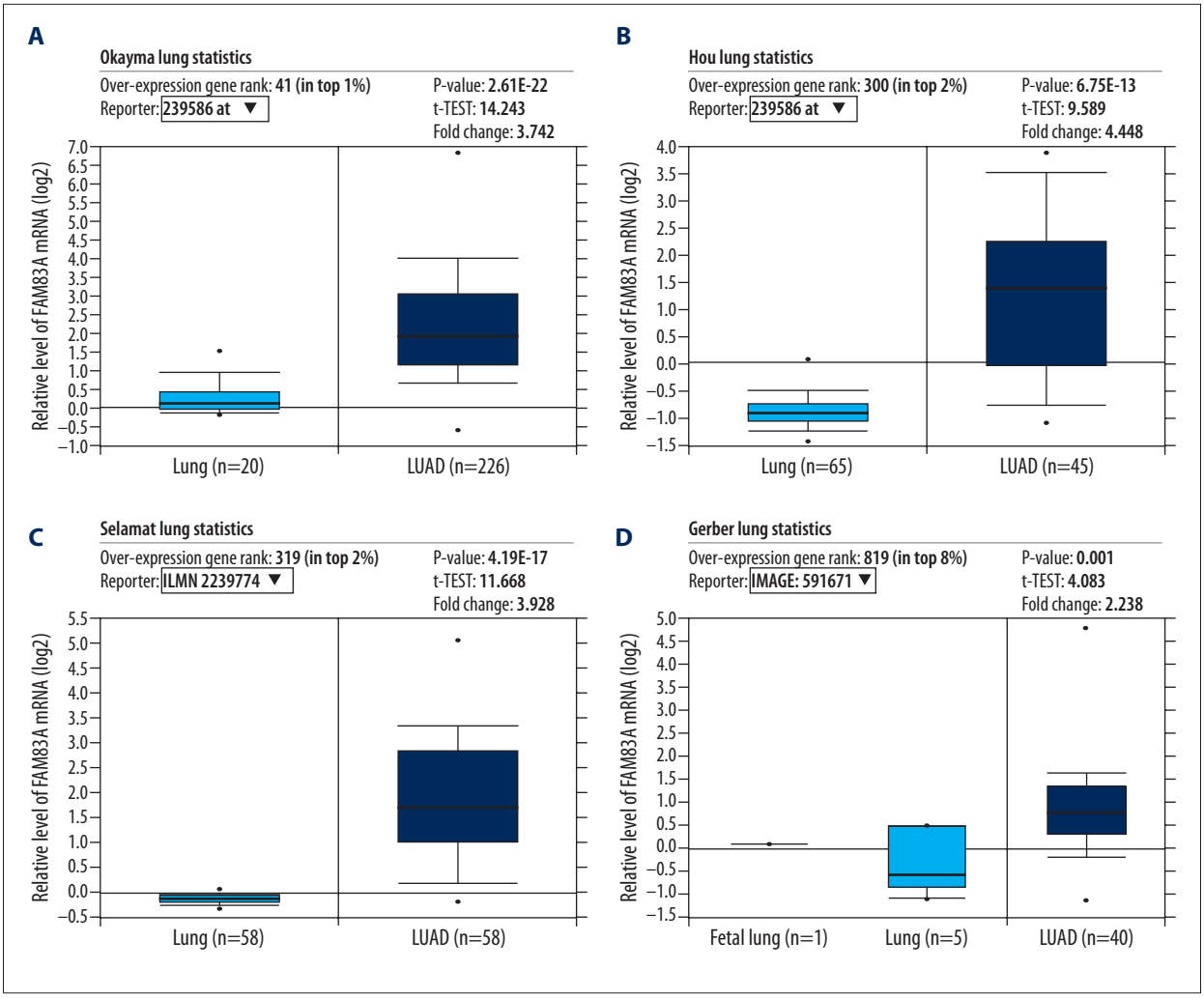

Figure 2. Four datasets on FAM83A mRNA levels in LUAD *vs.* normal lung tissue by Oncomine database. The GSE number of each dataset was listed as follows: (**A**) *Okayama Lung* (GEO: GSE31210); (**B**) *Hou Lung* (GEO: GSE19188); (**C**) *Selamat Lung* (GEO: GSE32863); (**D**) *Garber Lung* (GEO: GSE3398).

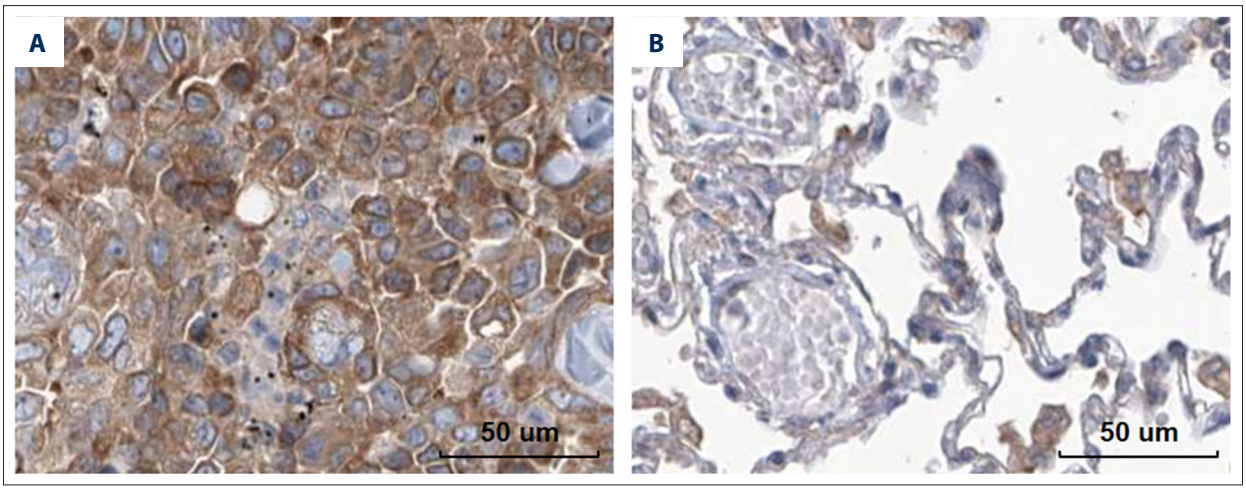

Figure 3. FAM83A protein levels in 83 cases of LUAD and matched adjacent normal lung tissues by immunohistochemical staining. (**A**) High expression of FAM83A in LUAD; (**B**) Low expression of FAM83A in matched normal lung tissue. Bar=50 um.

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Table 2. Overexpression of FAM83A in 83 cases of LUAD tissues.

Tissues	FAM83A expression levels (Cases, %)		χ^2	*P*
	Low	High		
LUAD	22 (26.51)	61 (73.49)	42.562	0.000
Matched normal tissues	64 (77.11)	19 (22.89)		

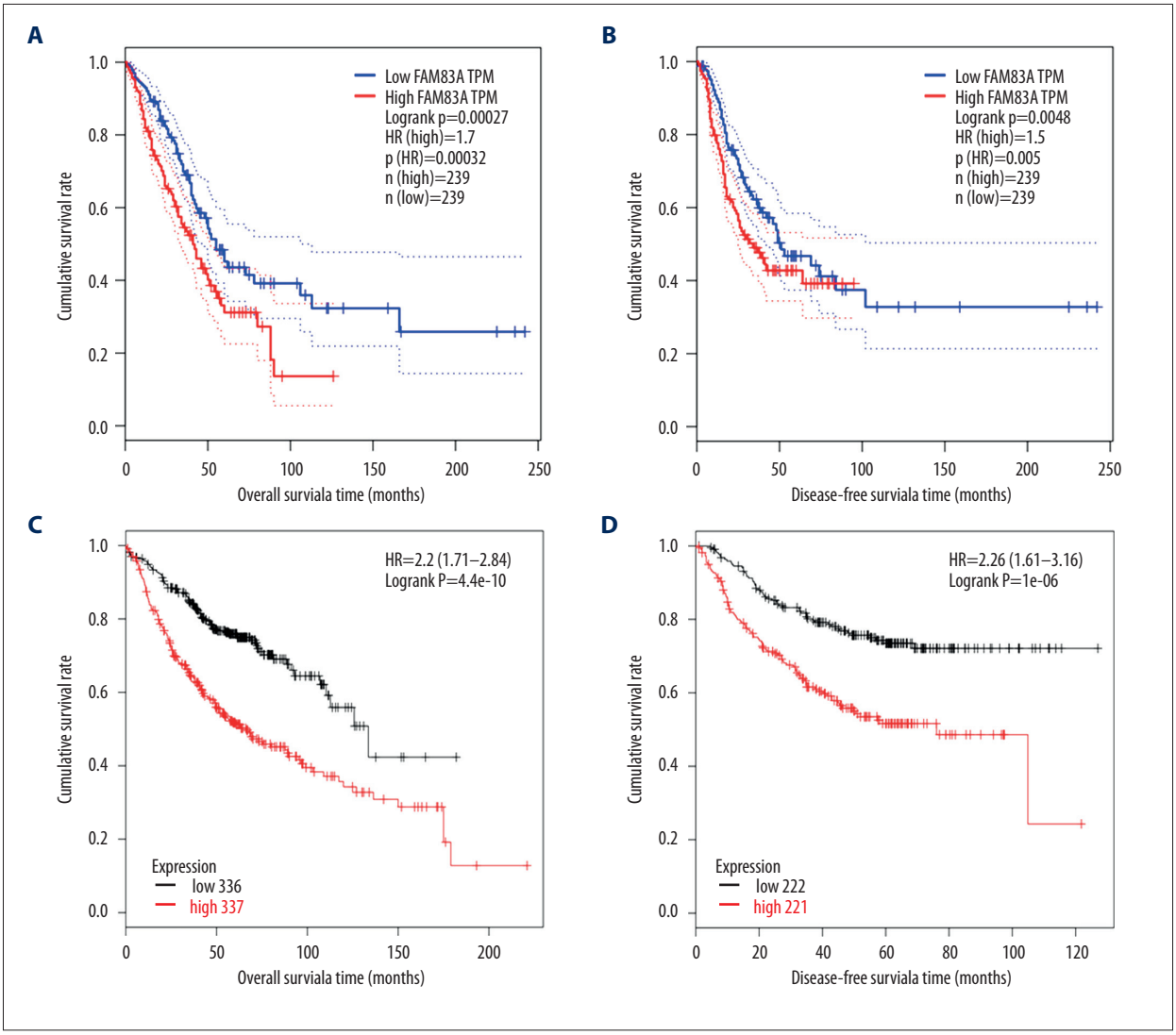

Figure 4. Overall survival (OS) and disease-free survival (DFS) curves of LUAD patients based on the differential expression levels FAM83A mRNA (low *vs.* high). (**A**) OS curve based on TCGA data; (**B**) DFS curve based on TCGA data; (**C**) OS curve based on GEO data (analyzed in Kaplan-Meier Plotter website); (**D**) DFS curve based on GEO data (analyzed in Kaplan-Meier Plotter website).

lung [8,10,19], breast [20–23], pancreatic [24], and ovarian cancer [25]. Researchers observed that the FAM83A gene might be a good candidate for early detection of these cancers, especially lung cancer [8,10]. Lee et al. [20] revealed that FAM83A conferred EGFR-TKI drug resistance in breast cancer cells and in mice, and the underlying mechanisms were that FAM83A could interact with and cause phosphorylation of c-RAF and PI3K p85, upstream of MAPK and downstream of EGFR. Boyer et al. [21] performed the quantitative proteomics with siRNA screening, showing that FAM83A and MAPK1 were both involved in the trastuzumab resistance in HER2-positive breast cancers, and similar findings were observed by Bartel et al. [22].

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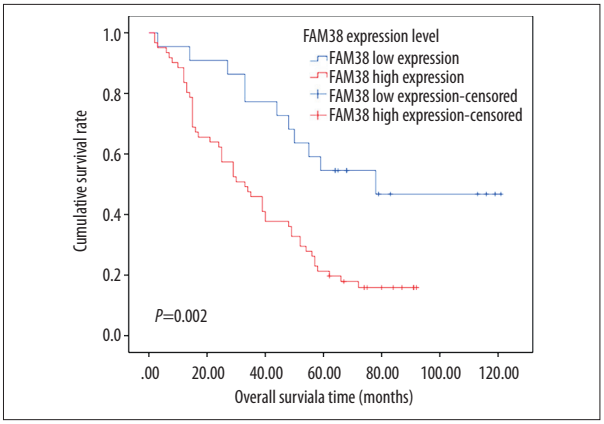

Figure 5. Overall survival (OS) curve of LUAD patients based on the immunohistochemical data under differential expression levels FAM83A protein (low *vs.* high).

Table 3. Kaplan-Meier univariate survival analysis of FAM83A and other clinicopathological parameters in LUAD patients.

Clinicopathological parameters	Mean survival time (months)	95% CI	*P* value
FAM83A levels			
Low	79.286	61.241–97.331	0.002
High	39.646	32.438–46.854	
Gender			
Male	49.569	37.470–61.668	0.499
Female	56.247	43.320–69.173	
Age (years)			
≤60	52.308	39.446–65.170	0.971
>60	53.146	40.891–65.400	
Histological differentiation			
Well/moderate	53.040	42.443–63.637	0.926
Poor	46.440	33.717–59.163	
Tumor size (cm)			
≤3	62.759	47.297–78.220	0.110
>3	42.342	34.249–50.436	
Tumor location			
Left lung	48.324	38.251–58.396	0.759
Right lung	52.478	40.361–64.594	
Lymph node metastasis			
No	72.237	57.350–87.125	0.000
Yes	35.560	28.624–42.497	
T stage			
T1	74.281	52.032–96.530	0.030
T2–T4	42.730	35.721–49.739	
TNM stage			
I	75.748	59.631–91.866	0.001
II+III+IV	37.119	30.318–43.920	
EGFR status			
Negative	56.976	46.684–67.268	0.046
Positive	32.357	21.979–42.735	

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Table 4. Cox multivariate analysis of FAM83A and other clinicopathological parameters in LUAD patients.

Covariates	HR	95% CI for HR	P value
FAM83A expression level (low *vs.* high)	3.194	1.576–6.471	0.001
Lymph node metastasis (no *vs.* yes)	1.294	0.585–2.864	0.524
T stage (T1 *vs.* T2–T4)	1.299	0.614–2.748	0.494
TNM stage (I *vs.* II+III+IV)	1.857	0.781–4.420	0.162
EGFR status (negative *vs.* positive)	1.904	0.942–3.846	0.073

Moreover, FAM83A overexpression was closely linked to the development, high disease stage, presence of distant metastasis, and poor prognosis in breast cancer [23]. Recently, Ning et al. [26] used the TCGA dataset to perform an integrated genomic analysis of lung squamous cell carcinoma, and found that 6 ceRNAs (PLAU, miR-31-5p, miR-455-3p, FAM83A-AS1, MIR31HG, and MIR99AHG) were significantly correlated patient survival. However, the expression levels of FAM83A in LUAD and its prognostic value have not been investigated in detail.

Therefore, in the present study, the bioinformatics mining method was used to examine the differential expression of FAM83A mRNA between LUAD and normal lung groups based on TCGA and GEO (from Oncomine database) data. Results from TCGA and Oncomine databases revealed that FAM83A mRNA expression levels were significantly higher in the LUAD group than in the normal lung group. Then, to confirm the predictive results, immunohistochemistry was used to investigate the expression levels of FAM83A protein in 83 cases of LUAD and matched normal lung tissues. Identical with the above predictive findings, the high positive rate of FAM83A protein in LUAD was 73.49%, but was only 22.89% in the normal group. Compared to the normal group, the expression levels of FAM83A protein were dramatically higher in the LUAD group. All these results suggest that FAM83A is an oncogene involved in promoting the occurrence and development of LUAD.

Subsequently, the relationship between FAM83A and clinicopathological factors of LUAD patients and its potential clinical prognostic value were investigated. Through mining the TCGA database and use of Kaplan-Meier Plotter, we observed that LUAD patients with high FAM83A mRNA levels had dramatically lower OS and DFS time than those with low FAM83A mRNA levels. Based on the immunohistochemical data, Kaplan-Meier univariate survival analysis showed that LUAD patients with high levels of FAM83A protein had remarkably decreased OS times than those with low levels of FAM83A protein. Moreover, Cox multivariate survival analysis demonstrated that FAM83A differential expression levels (low *vs.* high) were the only independent factors predicting the prognosis of LUAD patients. In summary, these findings suggest that FAM83A overexpression could serve as an independent factor to predict the poor prognosis of LUAD patients, and FAM83A might be an important target gene involved in the growth and metastasis of LUAD.

The present study has certain deficiencies. First, the number of retrospectively collected samples was relatively small, and this might have influenced the statistical analysis to some extent. Second, some cell functional experiments, including cell proliferation, migration, and invasion, were not performed. Third, the underlying mechanisms of FAM83A overexpression in LUAD were not explored in this study. These limitations will be addressed in our future studies.

Conclusions

Our study demonstrated that FAM83A was overexpressed in LUAD, and FAM83A overexpression could serve as an independent factor to predict the poor prognosis of LUAD patients. FAM83A may become a new potential therapeutic target for the treatment of LUAD.

Conflicts of interest

None.

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