



Expression and prognostic analysis of Rho GTPase-activating protein 11A in lung adenocarcinoma

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Background: Rho GTPase-activating protein 11A (ARHGAP11A) is a member of the Rho GTPase-activating protein (RhoGAP) subfamily. However, its expression, prognostic significance and clinicopathologic factors correlation in lung adenocarcinoma is still unclear.

Methods: The original gene expression profile, survival data, and clinical information of patients with lung adenocarcinoma (LUAD) were downloaded from The Cancer Genome Atlas (TCGA) database. The expression difference of ARHGAP11A between LUAD tissues and adjacent normal tissues in the TCGA database was analyzed by using R software, and verified by the Oncomine database and immunohistochemical (IHC) assay of LUAD sections. Logistic regression was applied to analyze the relationship between the expression of ARHGAP11A and clinicopathological factors of LUAD. Kaplan-Meier (KM) survival curves and a Cox proportional-hazards model were selected to evaluate the prognostic significance of ARHGAP11A expression. Gene set enrichment analysis (GSEA) software was applied to screen the tumor signaling pathways associated with the low and high expression group of ARHGAP11A in LUAD.

Results: The TCGA database showed that the expression of ARHGAP11A was significantly higher in LUAD tissues than in normal tissues ($P < 0.001$). The up-regulation of ARHGAP11A in LUAD was verified by the Oncomine database ($P < 0.001$) and IHC assay ($P < 0.001$). Logistic regression analysis revealed the high expression of ARHGAP11A to be closely related to age, sex, advanced pathological stage, advanced T stage, and lymph node metastasis. The KM plots based on the TCGA and KM plotter databases indicated that patients with LUAD highly expressing ARHGAP11A had a poorer overall survival (OS) than patients with low expression of ARHGAP11A. Multivariate Cox regression analysis showed that the high expression of ARHGAP11A could be an important independent predictor of a poor prognosis of LUAD [hazards ratio (HR) = 1.385; $P < 0.001$]. GSEA indicated that 10 signal pathways were significantly enriched in LUAD samples with the ARHGAP11A expression phenotype.

Conclusions: ARHGAP11A may play a carcinogenic role in the malignant progression of LUAD, and it can be considered as a new independent prognostic factor and potential therapeutic target for LUAD.

Keywords: Lung adenocarcinoma (LUAD); Rho GTPase-activating protein 11A (ARHGAP11A); The Cancer Genome Atlas (TCGA); gene set enrichment analysis (GSEA); prognosis

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Introduction

Lung cancer is responsible for more mortality than any other malignancy in the world (1). Due to changes in lifestyle and increasing air pollution, lung cancer is rising in incidence every year (2). In recent years, lung adenocarcinoma (LUAD) has replaced lung squamous cell carcinoma as the most common histological type of lung cancer (3,4). With the rapid progress of medical imaging and early screening technology for lung cancer, as well as the continuous improvement of targeted lung cancer therapies, more and more lung cancer patients have benefited and significantly extended their survival. Nevertheless, at present, the 5-year survival rate of patients with non-small cell lung cancer is still less than 15% (5,6). Therefore, there is an urgent need to discover new diagnostic markers and therapeutic targets to improve the survival of patients with non-small cell lung cancer.

Rho GTPase-activating protein 11A (ARHGAP11A), also known as MP-GAP, is a member of the Rho GTPase-activating protein (RhoGAP) subfamily (7). RhoGAPs are down-regulated in tumors and are usually associated with malignant progression (8). Currently, the role of ARHGAP11A in cancer is still controversial. Recent studies have revealed that ARHGAP11A is highly expressed in colon cancer (9), basal-like breast cancer (10,11), and hepatocellular carcinoma (12). In human glioma cells, an ability of ARHGAP11A to physically bind to p53 and promote its function, to ultimately induce cell-cycle arrest and apoptosis, has been reported (13). Another study found that ARHGAP11A knockout results in G1-phase cell-cycle arrest in basal-like breast cancer cells (10). Interestingly, recent research showed that ARHGAP11A knockdown decreased cell proliferation, invasion, and migration in hepatocellular carcinoma (12,14). However, the expression and function of ARHGAP11A in LUAD has remained unclear.

Using The Cancer Genome Atlas (TCGA), Oncomine, and Kaplan-Meier (KM) plotter databases, and immunohistochemical (IHC) analysis, in this study, we apply novel and comprehensive bioinformatics methods to explore the differential expression of the ARHGAP11A gene and its correlations with clinicopathological characteristics and prognosis of LUAD, with the aim of revealing the role of ARHGAP11A in lung cancer progression and its significance as a potential prognostic biomarker. We present the following article in accordance with the REMARK reporting checklist (available at [\[dx.doi.org/10.21037/atm-21-2113\]\(http://dx.doi.org/10.21037/atm-21-2113\)\).](http://</p></div><div data-bbox=)

Methods

TCGA expression data and clinical information

The original messenger RNA (mRNA) expression profiles of 535 LUAD tissue samples and 59 normal tissue samples were downloaded from the TCGA database (<https://portal.gdc.cancer.gov/>). The original detailed clinical data of 522 patients with LUAD were also downloaded from the TCGA database. The clinical information obtained included survival time and survival status, age, sex, pathological stage, and the T, N, and M stages. The clinicopathological characteristics of the patients with LUAD are detailed in *Table 1*.

Expression difference and survival analysis of ARHGAP11A

The Perl Programming Language (version 5.32.1) was used to classify and merge the original ARHGAP11A expression data. Then, the R package limma was applied for standardization and analysis of the ARHGAP11A expression data. The limma and beeswarm packages were applied to draw scatter diagrams. Perl was applied to delete cases with incomplete survival information from the clinical data, and it was then used to combine the complete survival data and ARHGAP11A expression data. Finally, the clinical data of 494 patients with LUAD who consistent with the criterion were obtained. The LUAD cohort was divided into a high-expression group and a low-expression group on the basis of the median expression of ARHGAP11A. The R packages survival and survminer were used to perform the survival analysis and to plot KM survival curves. The survival analysis of the TCGA data was verified using the KM plotter (<http://kmplot.com/>) database (15), with the search condition set as: (I) cancer: lung cancer; (II) affy id/gene symbol; ARHGAP11A 204492_at; (III) split patients by: auto select best cutoff; (IV) probe set options use: only JetSet best probe set; (V) survival: overall survival (OS); (VI) follow-up threshold: all; (VII) histology: adenocarcinoma.

Verification of ARHGAP11A expression by IHC

In this study, Paraffin-embedded specimens of 54 patients with LUAD and 21 patients with normal lung tissue was collected from the Fourth Affiliated Hospital of China

Table 1 Clinicopathological characteristics of patients with LUAD

Clinicopathological factors	Classification	Patients (n=522)	Proportion (%)
Age (years)	≤65	241	46.17
	>65	262	50.19
	Unknown	19	3.64
Sex	Male	242	46.36
	Female	280	53.64
Pathological stage	I	279	53.45
	II	124	23.75
	III	85	16.28
	IV	26	4.98
	Unknown	8	1.53
T stage	T1	172	32.95
	T2	281	53.83
	T3	47	9.00
	T4	19	3.64
	TX	3	0.57
N stage	N0	335	64.18
	N1	98	18.77
	N2	75	14.37
	N3	2	0.38
	NX	11	2.11
M stage	Unknown	1	0.19
	M0	353	67.62
	M1	25	4.79
	MX	140	26.82
Survival status	Unknown	4	0.77
	Alive	355	68.01
	Dead	167	31.99

LUAD, lung adenocarcinoma.

Medical University, and approved by the Ethics Committee of the Fourth Affiliated Hospital of China Medical University. Informed consent was taken from all the patients. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The immunostaining assay was carried out (16) and evaluated (17) as described previously. The SP immunohistochemical kit was used in adherence with the manufacturer's instructions. The LUAD

tissue sections were incubated with the primary antibody against ARHGAP11A (1:200; NBP1-93657, Novus Biologicals) overnight at 4 °C.

Verification of ARHGAP11A expression by the Oncomine Database

The Oncomine database (<http://www.oncomine.org>) is an online data-mining platform that provides standardized

cancer transcriptome data (18). We set the search conditions as follows: (I) gene: ARHGAP11A; (II) cancer type: LUAD; (III) analysis type: cancer *vs.* normal analysis; (IV) data type: mRNA; (V) data set selection threshold: P value <0.001, gene rank = ALL, fold change =1.5.

Univariate and multivariate Cox regression analysis

Perl was used to extract and merge the ARHGAP11A expression value, survival information, and clinicopathological data. Considering that the proportion of missing information for M stage exceeded 10%, the M stage was eliminated. Finally, ARHGAP11A expression, age, sex, pathological stage, T stage, and N stage were used in univariate Cox regression analysis. Factors with $P < 0.05$ in the univariate regression analysis were subjected to multivariate Cox regression analysis. According to the median expression of ARHGAP11A as the cutoff value, the LUAD cohort was divided into the ARHGAP11A high-expression group and the ARHGAP11A low-expression group. The survival and survminer packages of R language were used to draw forest plots of the multivariate Cox regression analysis.

Gene set enrichment analysis (GSEA)

Perl was used to obtain ARHGAP11A expression value and phenotype profiles data from TCGA database. According to the median value of ARHGAP11A in the TCGA database, the LUAD cohort was divided into the ARHGAP11A high-expression group and the ARHGAP11A low-expression group. GSEA software (version 4.1.0) was used to study the potential molecular mechanism and signal transduction pathways of ARHGAP11A in LUAD (19). C2 (c2.cp.kegg.v6.2.symbols.GMT) was selected as the reference gene set for running GSEA. In GSEA, 1,000 genomic cycles are performed to identify significant pathways (20). $P < 0.05$ and a false discovery rate (FDR) q-value served as statistical indicators.

Statistical analysis

IHC score data are expressed as mean \pm standard deviation (S.D). Student's *t* test was applied to analyze the expression difference of ARHGAP11A in LUAD tissues and adjacent normal tissues. Statistical analysis were performed with R software (version 4.0.3) and GraphPad Prism (version 8.0.2). $P < 0.05$ was considered statistically significant, unless

indicated otherwise.

Results

The differential expression of ARHGAP11A in LUAD

The ARHGAP11A mRNA expression data of 535 LUAD tissues and 59 adjacent normal tissues were obtained from the TCGA database. Box plots showing the difference in ARHGAP11A mRNA expression between LUAD and normal tissues can be seen in *Figure 1A,B,C,D,E,F*. The expression of ARHGAP11A in LUAD tissues was significantly up-regulated compared with that in normal tissues ($P < 0.001$) (*Figure 1A*). Notably, the expression of ARHGAP11A in LUAD tissues was found to be closely related to sex ($P < 0.001$, *Figure 1B*), pathological stage ($P < 0.001$, *Figure 1C*), and advanced T stage ($P < 0.001$, *Figure 1D*), N stage ($P < 0.01$, *Figure 1E*), and M stage ($P < 0.05$, *Figure 1F*). These results showed that the difference in ARHGAP11A expression was closely related to the malignant progression of LUAD.

Verification of ARHGAP11A up-regulation in LUAD by Oncomine and IHC

Next, we used the Oncomine database to verify the mRNA expression difference of ARHGAP11A between normal tissues and LUAD tissues, and we obtained the same result as for TCGA. As shown in *Figure 2A*, the mRNA expression of ARHGAP11A in LUAD tissue was significantly up-regulated in the Okatama Lung dataset ($P = 7.56E-4$). At the same time, the protein expression difference of ARHGAP11A between normal tissues and LUAD tissues was evaluated through IHC analysis. Immunostaining of ARHGAP11A was detected in the cytoplasm. Compared with that in normal tissues, the protein expression level of ARHGAP11A in LUAD was significantly up-regulated (mean score: 7.717 *vs.* 2.714, $P < 0.0001$, *Figure 2B*). The immunostaining of ARHGAP11A in bronchial epithelium and bronchial epithelium was generally weak (*Figure 3A,B*). Weak immunostaining was detected in few LUAD tissues (score <4, *Figure 3C*), while strong diffuse immunostaining was detected in most LUAD tissues (score ≥ 4 , *Figure 3D*).

A high expression of ARHGAP11A in LUAD is related to a poor prognosis

We next analyzed the prognostic significance of

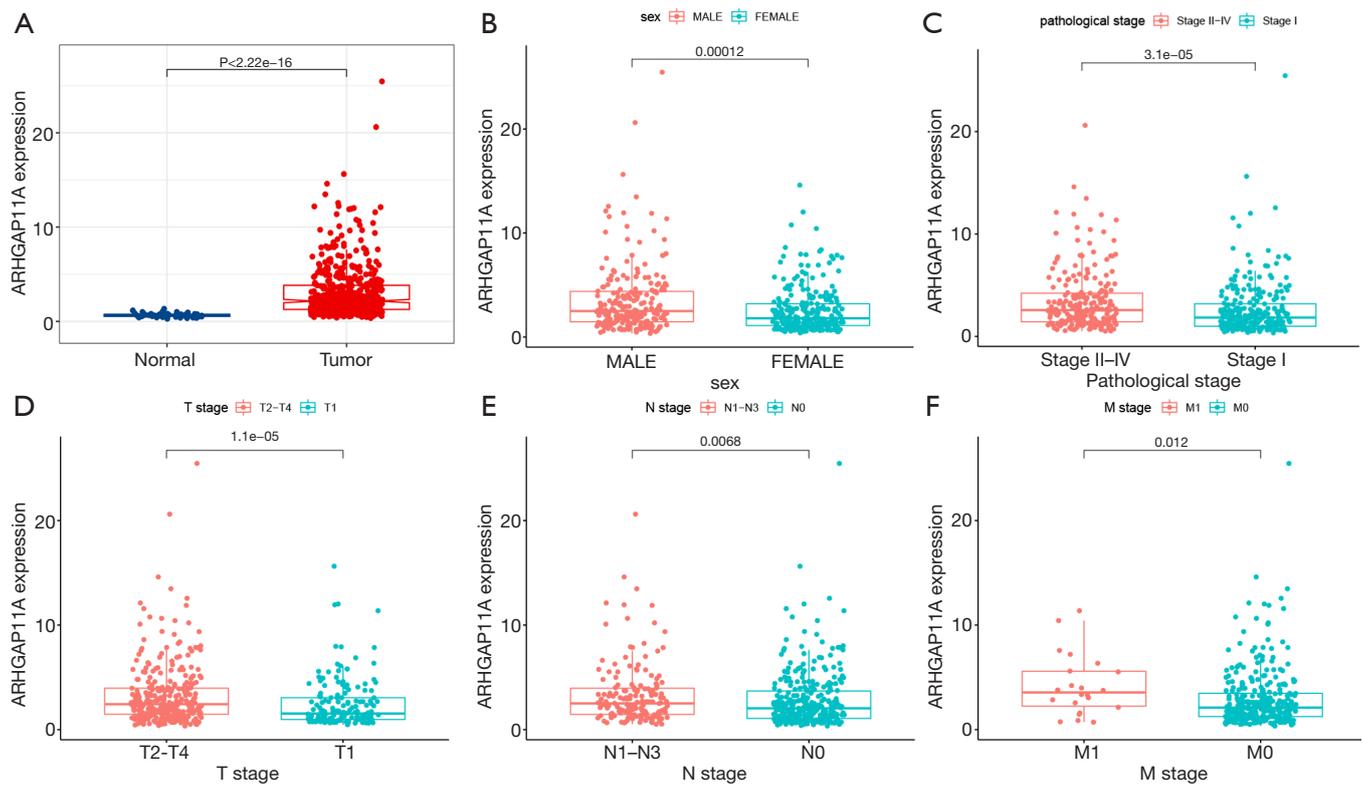


Figure 1 The expression of ARHGAP11A in LUAD tissues and its correlation with clinicopathological factors. The difference in ARHGAP11A expression between LUAD and normal tissues (A). The expression of ARHGAP11A was correlated with sex (B), pathological stage (C), T stage (D), N stage (E), and M stage (F). ARHGAP11A, Rho GTPase-activating protein 11A; LUAD, lung adenocarcinoma.

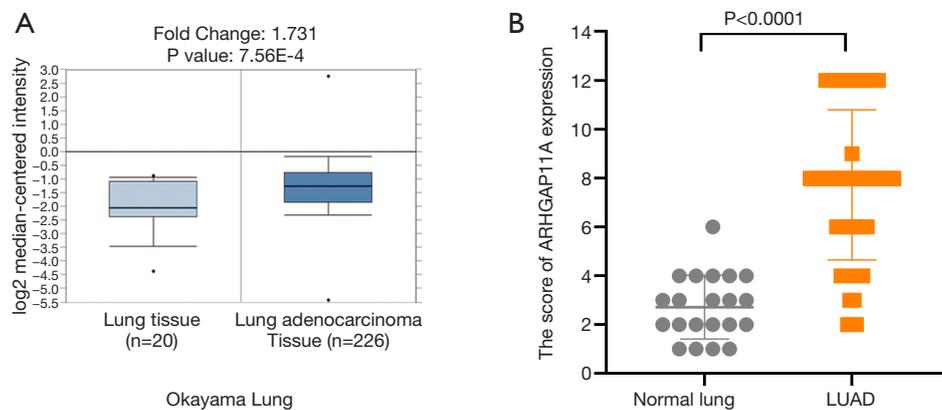


Figure 2 The expression of ARHGAP11A based on the Oncomine Okatama Lung dataset and IHC assay. ARHGAP11A mRNA expression in normal lung tissues and LUAD tissues in the Oncomine Okatama Lung dataset (A). ARHGAP11A protein expression in normal lung tissues and LUAD tissues by IHC assay (B). LUAD, lung adenocarcinoma; ARHGAP11A, Rho GTPase-activating protein 11A; IHC, immunohistochemical.

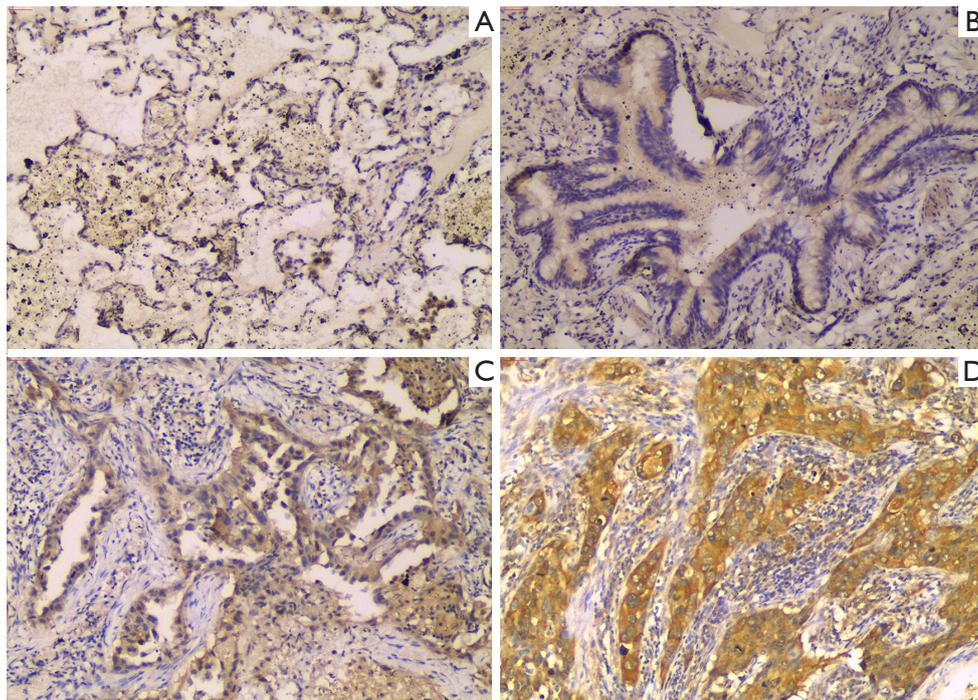


Figure 3 IHC assay of ARHGAP11A expression in 54 LUAD tissue samples and 21 normal tissue samples. ARHGAP11A expression in alveolar epithelium (A) and bronchial epithelium (B) was generally weak. Weak immunostaining of ARHGAP11A in LUAD (C), strong diffuse immunostaining of ARHGAP11A in LUAD (D). (Magnification, $\times 200$). IHC, immunohistochemical; ARHGAP11A, Rho GTPase-activating protein 11A; LUAD, lung adenocarcinoma.

ARHGAP11A expression in the TCGA LUAD cohort by performing KM survival analysis. The KM survival curves showed that, compared with the ARHGAP11A low-expression cohort, the ARHGAP11A high-expression cohort showed a significant correlation with poor OS ($P=0.002$, *Figure 4A*). The 5-year overall survival rate of patients with a high expression of ARHGAP11A (32.3%) was significantly lower than that of patients with a low expression of ARHGAP11A (38.8%). The median survival of the ARHGAP11A high-expression cohort was 2.9397 years, compared with 4.3836 years in the ARHGAP11A low-expression cohort. Using the KM plotter database, we further verified that the high expression of ARHGAP11A was closely related to a poor prognosis in patients with LUAD ($P=7.56E-4$, *Figure 4B*). The median survival of the ARHGAP11A low-expression group reached 117.33 months, compared with 61.3 months in the ARHGAP11A high-expression group. The above results suggest that the

high expression of ARHGAP11A is closely related to a poor prognosis of LUAD.

The relationship between ARHGAP11A expression and clinicopathological factors

To further investigate the correlation between ARHGAP11A expression and the clinicopathological features of LUAD, we obtained the clinical information of 522 patients with LUAD with complete data from the TCGA database. According to the median expression of ARHGAP11A in LUAD, the LUAD cohort was divided into a ARHGAP11A high-expression group and a ARHGAP11A low-expression group. Logistic regression analysis revealed that ARHGAP11A expression in LUAD was closely correlated with age [odds ratio (OR) =1.436, $P<0.05$], sex (OR =1.866, $P<0.001$), advanced pathological stage ($P<0.05$), advanced T stage ($P<0.05$), and lymph node

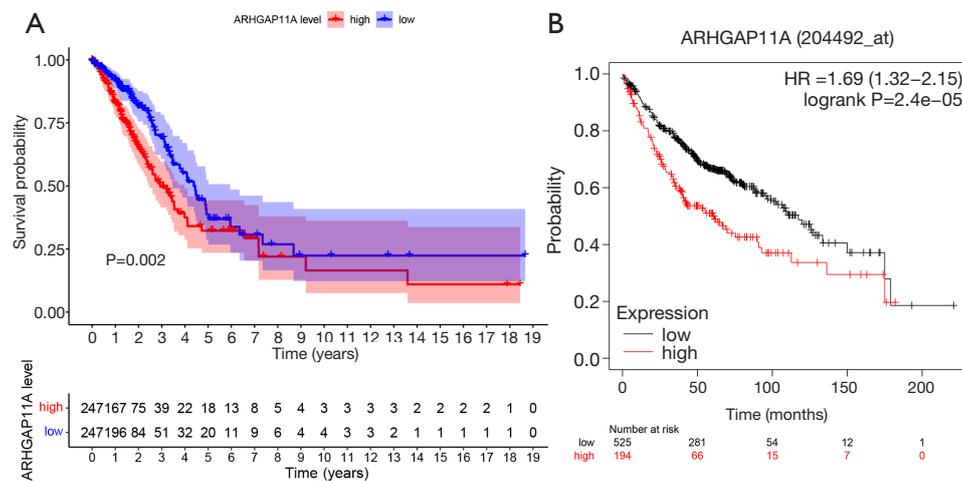


Figure 4 The prognostic significance of ARHGAP11A expression in LUAD. (A) Survival curves of patients with LUAD with high and low ARHGAP11A expression based on the TCGA database. (B) Survival curves of patients with LUAD with high and low ARHGAP11A expression based on the KM plotter database. ARHGAP11A, Rho GTPase-activating protein 11A; LUAD, lung adenocarcinoma; TCGA, The Cancer Genome Atlas.

metastasis (OR = 1.516, $P < 0.05$) (Table 2).

Analysis of the effect of ARHGAP11A on patient survival in LUAD by Cox proportional-hazards model

To analyze the impact of ARHGAP11A expression and other clinicopathological factors on the survival of patients with LUAD, we then applied the Cox proportional-hazards model. As the missing data for M stage exceeded 10%, Cox regression analysis was performed on 475 patients with LUAD according to sex, age, pathological stage, T stage, N stage, and ARHGAP11A expression. Univariate analysis revealed that pathological stage [hazards ratio (HR) = 1.666; $P < 0.001$], T stage (HR = 1.526; $P < 0.001$), N stage (HR = 1.720; $P < 0.001$), and ARHGAP11A expression (HR = 1.516; $P < 0.001$) could all be important predictors of survival in patients with LUAD (Table 3). Variables with P value < 0.05 (ARHGAP11A expression, pathological stage, T stage, and N stage) were included in the multivariate Cox analysis. The high expression of ARHGAP11A was identified as being an independent prognostic factor for the malignant progression of LUAD (HR = 1.385; $P < 0.001$) (Figure 5 and Table 3).

Identification of ARHGAP11A-related signaling pathways in LUAD by GSEA

The expression and phenotype profiles of ARHGAP11A were obtained by further processing and sorting of TCGA

data sets. Then, the essential functions of ARHGAP11A and its related signal transduction pathways were studied using GSEA software. According to the difference in the normalized enrichment score, nominal P value, and FDR q value, 10 significantly enriched tumor-related signaling pathways were identified. As shown in Figure 6, 8 signaling pathways involved in the cell cycle, DNA replication, gap junction, non-small cell lung cancer, P53 signaling pathway, pathways in cancer, small cell lung cancer, and WNT signaling pathways were significantly enriched in the ARHGAP11A high-expression phenotype. Meanwhile, the arachidonic acid metabolism and PPAR signaling pathways were considerably enriched in the ARHGAP11A low-expression phenotype (Figure 6 and Table 4).

Discussion

The RhoGAP family is a well-known gene family that participates in the regulation of tumor progression (21,22). Many members of the RhoGAP family have been found to be down-regulated and to have the ability to activate Rho GTPases in various cancers. Consequently, the members of this family are considered to be tumor suppressors (23). For instance, Rich1 (24) and ARHGAP29 (25) have been reported to suppress the malignant progression of cancers. ARHGAP11A has been reported to physically bind to P53 and promote its function, eventually leading to cell

Table 2 Logistic regression analysis of the correlation of ARHGAP11A expression with clinicopathological features of patients with LUAD

Clinicopathological factors	Patients (N)	Odds ratio	P value
Age (years)			
≥65 vs. <65	494	1.436 (1.006–2.052)	0.047*
Sex			
Male vs. female	513	1.866 (1.315–2.657)	0.000*
Pathological stage			
Stage II vs. stage I	395	1.589 (1.033–2.455)	0.038*
Stage III vs. stage I	358	1.328 (1.037–1.709)	0.026*
Stage IV vs. stage I	300	1.343 (1.016–1.824)	0.045*
T stage			
Stage T2 vs. stage T1	444	2.009 (1.363–2.978)	0.000*
Stage T3 vs. stage T1	215	2.345 (1.208–4.699)	0.013*
Stage T4 vs. stage T1	187	3.154 (1.149–10.119)	0.035*
Lymph node metastasis			
Positive vs. negative	501	1.516 (1.047–2.204)	0.028*
Distant metastasis			
Yes vs. no	369	2.252 (0.974–5.648)	0.066

* indicate $P < 0.05$. LUAD, lung adenocarcinoma.

Table 3 Univariate and multivariate Cox regression analysis of ARHGAP11A expression and clinicopathological factors in patients with LUAD

Variable	Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.010	0.994–1.027	0.227			
Sex	1.049	0.765–1.437	0.768			
Pathological stage	1.666	1.437–1.930	0.000	1.386	1.122–1.712	0.002
T stage	1.526	1.250–1.862	0.000	1.162	0.943–1.434	0.160
N stage	1.720	1.440–2.055	0.000	1.226	0.967–1.554	0.092
ARHGAP11A expression	1.516	1.259–1.825	0.000	1.385	1.141–1.680	0.000

ARHGAP11A, Rho GTPase-activating protein 11A; LUAD, lung adenocarcinoma; HR, hazard ratio. CI, confidence interval.

cycle arrest in glioma (13). However, the latest cancer research has found that ARHGAP11A is up-regulated in colon cancer, in which it promotes cell motility and invasion (9). ARHGAP11A was found to promote breast cancer invasion by inhibiting RhoA (10,11). Two previous studies found that ARHGAP11A is closely related to the malignant progression of hepatocellular carcinoma (12,14). Therefore, the expression and function of ARHGAP11A in

tumors need to be clarified. Before now, the expression and mechanism of ARHGAP11A in lung cancer have remained unclear.

In this study, we explored the functional role of ARHGAP11A expression in the malignant progression and prognosis of LUAD. To clarify the potential molecular regulatory mechanism of ARHGAP11A in LUAD progression, we also screened the ARHGAP11A-related

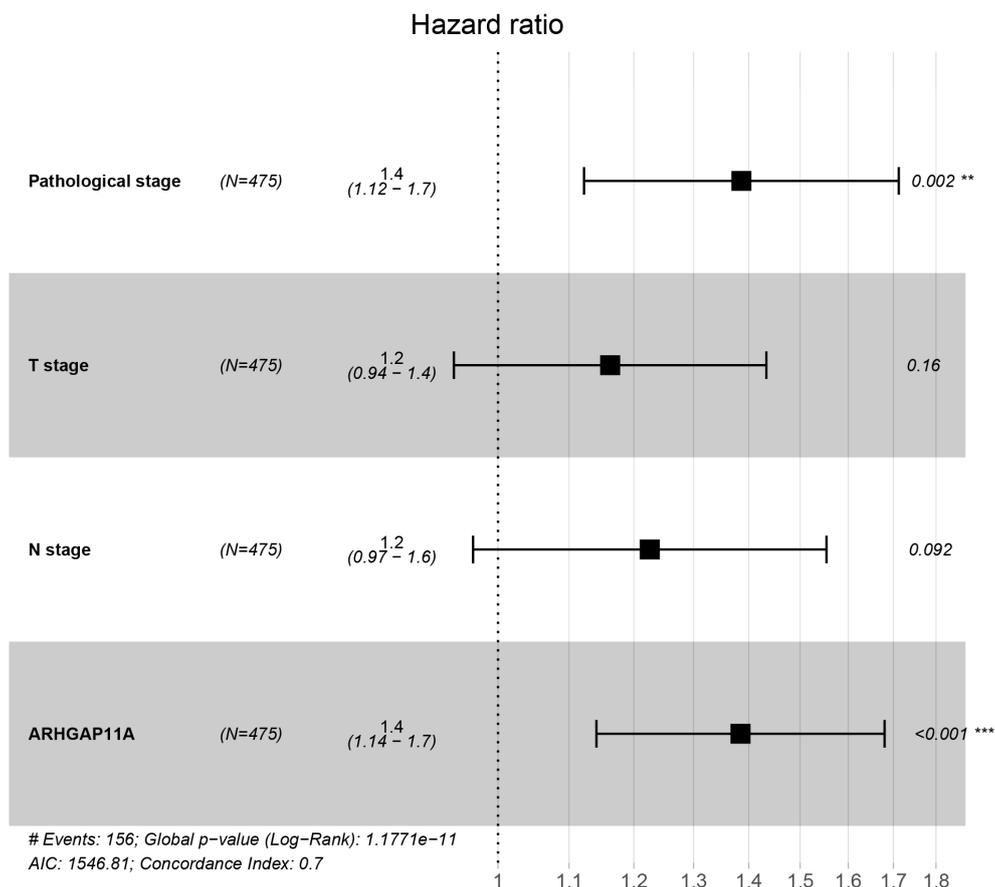


Figure 5 Forest plot for the multivariate Cox proportional-hazards model. ARHGAP11A expression could be an independent predictor of poor overall survival in LUAD (HR =1.385; P<0.001). ARHGAP11A, Rho GTPase-activating protein 11A; LUAD, lung adenocarcinoma; HR, hazard ratio. ** indicate P<0.01. *** indicate P<0.001.

tumor signaling pathways in LUAD.

First, we analyzed the expression differences of ARHGAP11A in the TCGA database. We found that ARHGAP11A mRNA expression was significantly higher in LUAD tissues than in adjacent normal tissues. Further, Oncomine analysis and IHC assay verified that the expression of ARHGAP11A is up-regulated in LUAD. These results are consistent with the predictions of previous studies (9). We also found that the expression of ARHGAP11A was closely related to sex, advanced pathological stage, advanced T stage, N stage, and M stage. This observation suggested that ARHGAP11A expression gradually increased with the malignant progression of LUAD. Logistic regression analysis further showed that the high expression of ARHGAP11A was significantly correlated with advanced pathological stage, advanced T stage and lymph node metastasis.

KM survival analysis showed that high ARHGAP11A expression was associated with poorer OS in patients with LUAD. The survival analysis of ARHGAP11A was consistent with previous studies of lung adenocarcinoma metastasis (26). The Cox proportional-hazards model was applied to analyze the effect of ARHGAP11A on LUAD survival. The univariate Cox regression analysis showed that pathological stage, T stage, and N stage were associated with the prognosis of patients with LUAD. Multivariate Cox analysis showed that ARHGAP11A may be an independent prognostic factor of LUAD.

To explore the potential mechanism of ARHGAP11A in the malignant progression of LUAD, GSEA analysis was performed to screen ARHGAP11A-related signaling pathways. The results showed that the 10 significantly enriched signaling pathways were the arachidonic acid metabolism, cell cycle, DNA replication, gap junction, non-

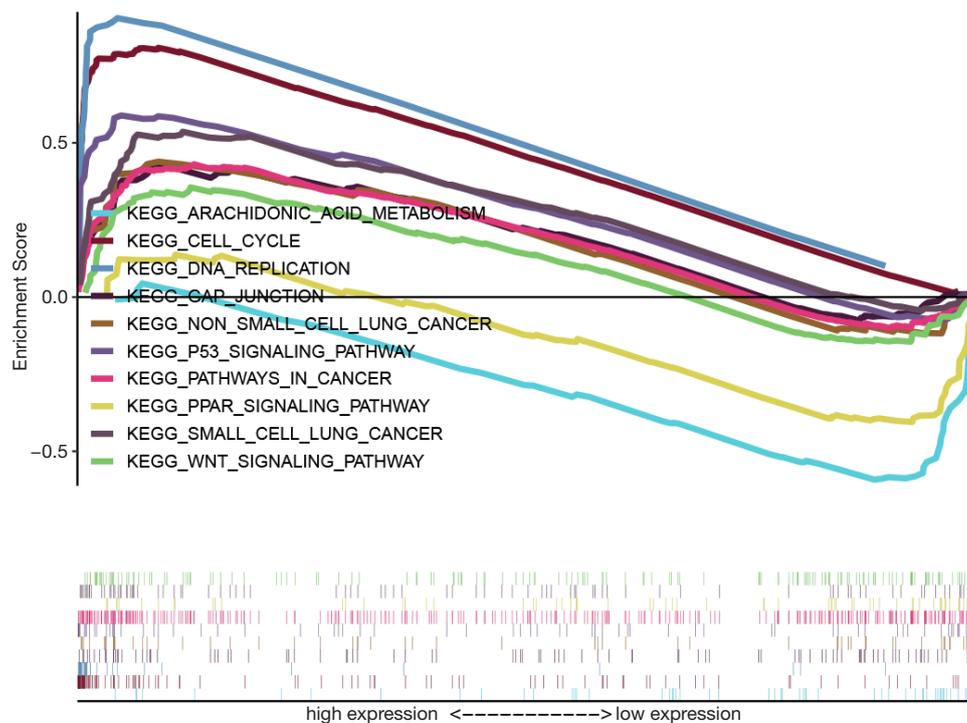


Figure 6 A multiple GSEA plot drawn with GSEA software. The 10 significant ARHGAP11A-related signaling pathways were the arachidonic acid metabolism, cell cycle, DNA replication, gap junction, non-small cell lung cancer, P53 signaling, pathways in cancer, PPAR signaling, small cell lung cancer, and WNT signaling pathways. GSEA, gene set enrichment analysis; ARHGAP11A, Rho GTPase-activating protein 11A.

Table 4 Significantly enriched gene sets with a high expression of ARHGAP11A

Significantly enriched gene set name	NES	NOM P value	FDR q value
KEGG_CELL_CYCLE	2.54	0.000	0.000
KEGG_P53_SIGNALING_PATHWAY	2.20	0.000	0.000
KEGG_DNA_REPLICATION	2.12	0.000	0.001
KEGG_PATHWAYS_IN_CANCER	1.84	0.004	0.026
KEGG_SMALL_CELL_LUNG_CANCER	1.96	0.000	0.009
KEGG_GAP_JUNCTION	1.66	0.026	0.076
KEGG_NON_SMALL_CELL_LUNG_CANCER	1.57	0.048	0.105
KEGG_WNT_SIGNALING_PATHWAY	1.49	0.041	0.147

ARHGAP11A, Rho GTPase-activating protein 11A; NES, normalized enrichment score; NOM P value, nominal P value; FDR, false discovery rate.

small cell lung cancer, P53 signaling, pathways in cancer, PPAR signaling, small cell lung cancer, and WNT signaling pathways.

In this study, we applied systematic bioinformatics

methods to analyze the expression of ARHGAP11A and its clinical correlations in LUAD. This analytical approach is scientific and precise; however, our study still has some limitations. Firstly, the TCGA database does not include

the specific treatment plans or surgical details of patients, which play an essential role in prognosis. However, despite this limitation, our study still supports the value of ARHGAP11A as a potential prognostic marker for LUAD. Furthermore, we will supplement the treatment information of clinical data in follow-up research and conduct an in-depth exploration of the clinical relevance of ARHGAP11A.

In conclusion, mainly through analysis of the TCGA database, our study found that ARHGAP11A is significantly up-regulated in LUAD. The expression of ARHGAP11A is closely related to clinicopathological characteristics such as sex and pathological stage. The results of our survival analysis and multivariate Cox analysis suggest that ARHGAP11A could be an independent prognostic factor in the malignant progression of LUAD. To sum up, ARHGAP11A may play a carcinogenic role in the malignant progression of LUAD, and it can be considered as a new prognostic factor and potential therapeutic target in LUAD.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of the Fourth Affiliated Hospital of China Medical University. Informed consent

was taken from all the patients. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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