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Expression of *SUMO1P3* Compared with *SUMO1* is an Independent Predictor of Patient Outcome 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

ABCDEFG 1 Xiaolan Su
DE 2 Yang Wan
C 2 Linshen Xie
C 3 Xiufang Lin
B 2 Hongwen Zhao
C 4 Xiao Ju
ABEG 1,2 Aiping Fang

1 State Key Laboratory of Biotherapy and Cancer Center, West China Hospital and Healthy Food Evaluation Research Center, Sichuan University, Chengdu, Sichuan, P.R. China
2 West China School of Public Health and West China Fourth Hospital, Healthy Food Evaluation Research Center, Sichuan University, Chengdu, Sichuan, P.R. China
3 The Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, P.R. China
4 Sichuan Scientist Biotechnology Co., Ltd., Chengdu, Sichuan, P.R. China

Corresponding Author: Aiping Fang, e-mail: aipingfangcn@outlook.com
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Background: The small ubiquitin-like modifier 1 (*SUMO1*) and small ubiquitin-like modifier 1 pseudogene 3 (*SUMO1P3*) are long noncoding RNAs (lncRNAs). The prognostic significance of *SUMO1* and *SUMO1P3* expression in non-small cell lung cancer (NSCLC) remains unclear. This study aimed to use clinical, genetic, and survival data from the Cancer Genome Atlas (TCGA), to analyze the prognostic significance of *SUMO1* and *SUMO1P3* expression in the two main subtypes of NSCLC, lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC).

Material/Methods: Data were acquired from TCGA and *in silico* survival analysis was performed. *SUMO1* and *SUMO1P3* expression were compared between patients with LUAD and LUSC. Patient outcome was assessed as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Recurrence-free survival (RFS) was defined as the survival time from primary surgery to the time of locoregional or distant recurrence of lung cancer.

Results: *SUMO1P3* was significantly increased in LUSC and LUAD tissues compared with adjacent normal lung tissue and was significantly co-expressed with *SUMO1*. *SUMO1P3* expression was significantly increased in patients with LUAD but not LUSC with reduced RFS after primary or follow-up treatment. Although patients with LUAD who had high *SUMO1* or *SUMO1P3* expression had reduced RFS compared with low expression groups, univariate and multivariate analysis showed that only *SUMO1P3* expression was independently associated reduced RFS (HR, 1.418; 95% CI, 1.041–1.930; p=0.027).

Conclusions: *SUMO1P3* expression was an independent indicator of reduced RFS in patients with LUAD.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung • Prognosis • SUMO-1 Protein

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Background

Worldwide, lung cancer is a common malignancy that has a high annual mortality. In the US in 2018, it was estimated that there were 234,030 new cases of lung cancer and 154,050 deaths due to lung cancer [1]. About 85% of cases of lung cancer are non-small cell lung carcinoma (NSCLC) include the two main histological subtypes of lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD). These two subtypes of NSCLC vary significantly in their molecular biology and clinical features [2–4]. The high frequency of epidermal growth factor (EGFR) gene mutations and ALK-EML4 translocations have provided new targeted therapy for patients with LUAD, which are less effective for patients with LUSC [5]. In terms of survival, patients with LUAD have reduced overall survival (OS) compared with patients with LUSC [6]. The molecular differences between the two subtypes of NSCLC indicate that they may have different prognostic biomarkers.

Long noncoding RNAs (lncRNAs) contain more than 200 nucleotides and have no protein encoding capability. Small ubiquitin-like modifier 1 pseudogene 3 (*SUMO1P3*) is a lncRNA that is upregulated in several cancers and exerts its oncogenic effects via multiple pathways [7–11]. For example, *SUMO1P3* enhances the progression of breast cancer by negatively regulating the expression of miR-320a [10], and promotes abnormal growth and invasion of pancreatic cancer cells by facilitating the epithelial-mesenchymal (EMT) transition [11]. Also, *SUMO1P3* expression may have a role as a prognostic marker in cancer. In bladder cancer, the expression of *SUMO1P3* is associated with advanced TNM stage and increased histological grade [7]. The expression of *SUMO1P3* shows has been shown to have a prognostic role in predicting overall survival (OS) in patients with pancreatic cancer [11].

Pseudogenes can be functionally linked with protein-coding genes [12,13]. A recent study showed that the small ubiquitin-like modifier 1 (*SUMO1*) gene mediated a post-translational modification process called SUMOylation, which was also upregulated in NSCLC [14]. *SUMO1* dysregulation might be associated with chemosensitivity of NSCLC cells [15]. Also, *SUMO1* overexpression can promote changes in the cell cycle and the progression and invasion of NSCLC cells by enhancing NF-κB expression [14]. However, the expression profiles of *SUMO1P3* and the prognostic value of *SUMO1P3* and *SUMO1* in NSCLC remain to be characterized.

Therefore, this study aimed to use clinical, genetic, and survival data from the Cancer Genome Atlas (TCGA), to analyze the prognostic significance of *SUMO1* and *SUMO1P3* expression in the two main subtypes of NSCLC, LUAD and LUSC. Patient outcome was assessed as complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), overall survival (OS), and recurrence-free survival (RFS).

Material and Methods

Data acquisition and analysis

Three levels of data included clinical, genetic, and survival data were obtained from the Cancer Genome Atlas (TCGA) lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) databases and were obtained using the University of California Santa Cruz (UCSC) Xena Functional Genomics Explorer (*https://xenabrowser.net/*) [16]. The data from cases of primary lung cancer tissue and the adjacent normal lung tissue were extracted for analysis. Data from patients who received neoadjuvant chemotherapy for LUSC (N=9) and LUAD (N=3) were excluded. Cases without RNA-Seq data were also excluded for LUSC (N=3) and LUAD (N=6). After the screening, 494 cases of primary LUSC and 511 cases of primary LUAD were included for analysis.

The following data were extracted from the included cases, including RNA-Seq data of gene expression, gender, age at diagnosis, history of tobacco smoking, tumor stage, grade, primary outcome following treatment, follow-up outcome, the presence of residual tumor, and canonical mutation in *KRAS/EGFR/ALK*, recurrence status, recurrence-free survival (RFS) in days, and overall survival (OS) in days. The longest follow-up was approximately 20 years. Primary treatment and follow-up outcome following treatment were defined as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). The CR, PR, and SD cases were all considered to be without disease progression. OS was defined as the survival time from the date of primary surgery to the time of death. Recurrence-free survival (RFS) was defined as the survival time from the date of primary surgery to the time of locoregional or distant recurrence of lung cancer. The differences in *SUMO1* and *SUMO1P3* expression between patients with controlled disease, CR, PR, and SD, and uncontrolled PD were compared.

Statistical analysis

Data integration and statistical analysis were performed using GraphPad Prism version 7.04 (GraphPad Software, La Jolla, CA, USA) and SPSS version 25.0 software (IBM, Chicago, IL, USA). One-way analysis of variance (ANOVA) with post hoc Tukey's multiple comparisons and Welch's unequal variance t-test were performed for multiple group comparison and comparison between two groups, respectively. Kaplan-Meier survival curves were used, and the Youden index compared *SUMO1* and *SUMO1P3* expression with receiver operating characteristic (ROC) analysis for prognostic significance for recurrence or mortality. The log-rank test was performed to compare the difference between the survival curves. The independent prognostic value of *SUMO1* and *SUMO1P3* expression was evaluated using results from univariate

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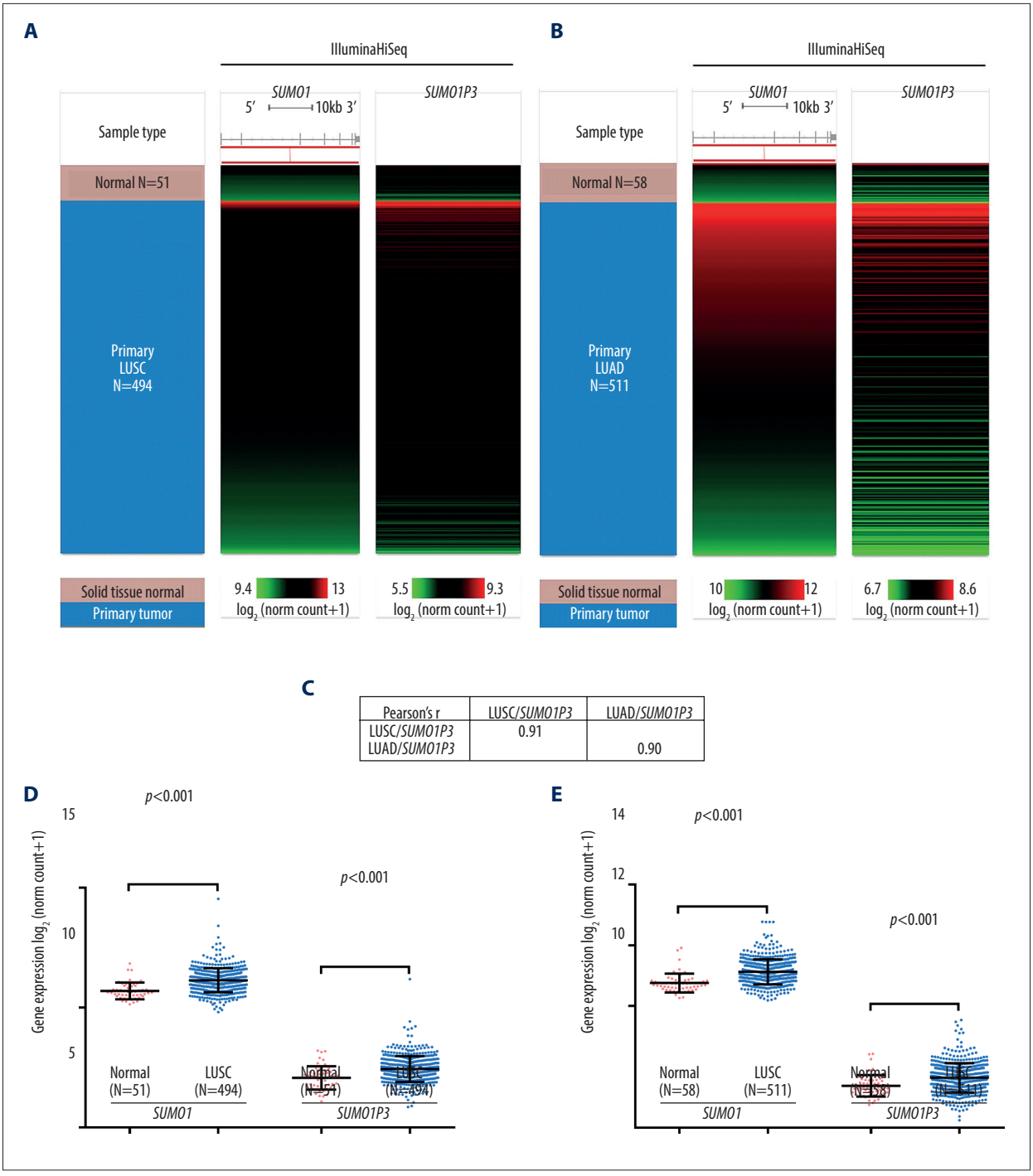

Figure 1. Both *SUMO1* and *SUMO1P3* were significantly upregulated in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) tissue compared with adjacent normal lung tissue. (**A, B**) Heatmap showing the expression profile of *SUMO1* and *SUMO1P3* in tissues from patients with lung squamous cell carcinoma (LUSC) (n=494) and lung adenocarcinoma (LUAD) (n=511) compared with adjacent normal tissues (n=51 and n=58, respectively). (**C**) Pearson's r-value showing the correlation between *SUMO1* and *SUMO1P3* in LUSC (n=494) and LUAD (n=511) tissues. (**D, E**) Plot chart comparing the expression of *SUMO1* and *SUMO1P3* in LUSC (n=494) and LUAD (n=511) tissues compared with their respective adjacent normal tissues (n=51 and n=58, respectively).

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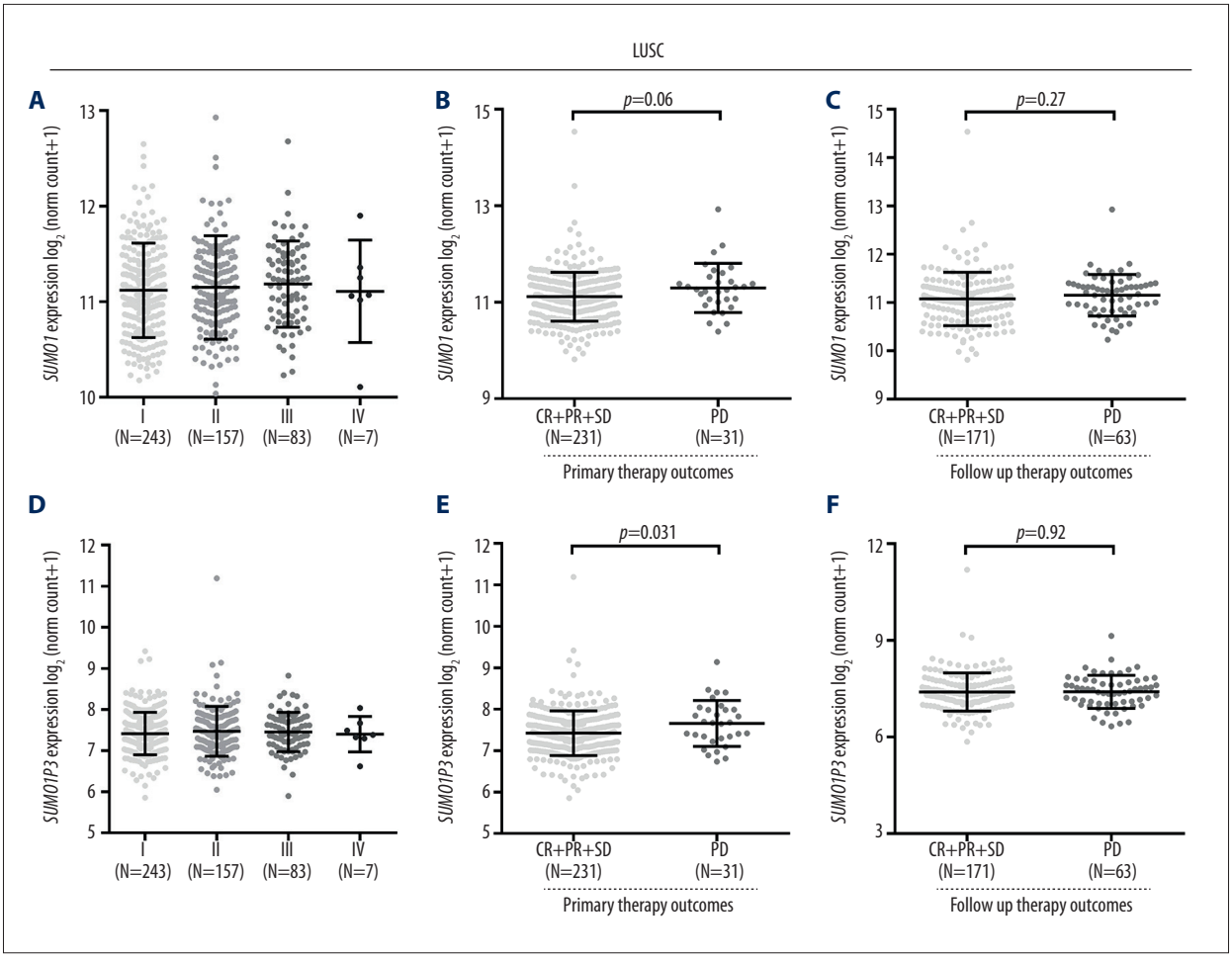

Figure 2. *SUMO1* and *SUMO1P3* expression in patients with lung squamous cell carcinoma (LUSC) in different stages or with different therapeutic responses. (**A, D**) *SUMO1* (**A**) and *SUMO1P3* (**D**) expression in patients with LUSC at different stages (**B, C, E, F**) *SUMO1* (**B, C**) and *SUMO1P3* (**E, F**) expression in patients with LUSC with different therapeutic responses after primary therapy (**B, E**) or after follow-up therapy (**C, F**).

and multivariate Cox regression models. *SUMO1* and *SUMO1P3* expression were treated as continuous variables in the model. A P-value <0.05 was considered to be statistically significant.

Results

Both *SUMO1* and *SUMO1P3* were significantly upregulated in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) tumor tissues compared with adjacent normal tissues

In this study, patient outcome was assessed as complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), and overall survival (OS). Recurrence-free survival (RFS) was defined as the survival time from the date of primary surgery to the time of locoregional or distant recurrence of lung cancer. Although the upregulation of *SUMO1* in lung cancer has previously been reported [14], the expression profile of its pseudogene *SUMO1P3* has not been characterized. Using RNA-Seq data from around 500 tumor samples, we compared the expression of *SUMO1P3* in both LUSC and LUAD. *SUMO1P3* showed a similar expression profile as *SUMO1* in both LUSC and LUAD (Figure 1A, 1B). *SUMO1P3* was strongly co-expressed with *SUMO1* in LUSC (Pearson's r=0.91) and LUAD (Pearson's r=0.90) tissues (Figure 1C). Similar to *SUMO1*, *SUMO1P3* expression was significantly increased in both LUSC and LUAD tissues compared with their adjacent normal tissues (p<0.001) (Figure 1D, 1E).

Patients with LUAD with PD after primary treatment or follow-up treatment showed significantly increased expression of *SUMO1P3*

In patients with LUSC, no significant differences in *SUMO1* or *SUMO1P3* expression were observed in tumors with different

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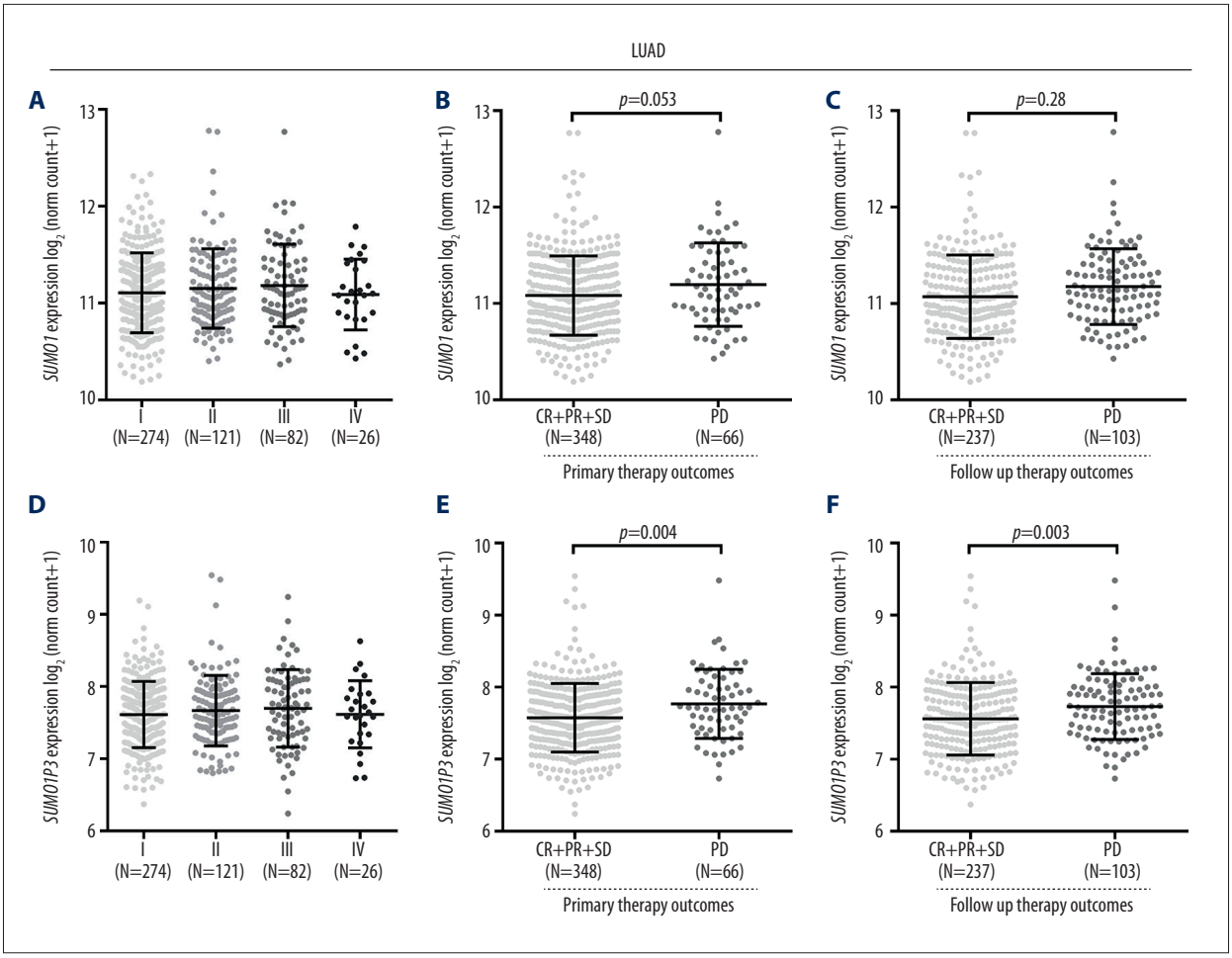

Figure 3. *SUMO1* and *SUMO1P3* expression in patients with lung adenocarcinoma (LUAD) in different stages or with different therapeutic responses. (**A, D**) *SUMO1* (**A**) and *SUMO1P3* (**D**) expression in patients with LUAD in different stages. (**B, C, E, F**) *SUMO1* (**B, C**) and *SUMO1P3* (**E, F**) expression in patients with LUAD with different therapeutic responses after primary therapy (**B, E**) or after follow-up therapy (**C, F**).

stage (Figure 2A, 2D). As *SUMO1* expression was previously reported to be associated with chemosensitivity of lung cancer, *SUMO1* and *SUMO1P3* expression were analyzed for patients with different outcome following treatment. In patients with LUSC, no significant differences were observed in *SUMO1* expression between the PD and CR, PR, and SD groups after either primary therapy or follow-up therapy (Figure 2B, 2C). *SUMO1P3* expression was significantly increased in patients with LUSC with PD after primary therapy, compared with patients with CR, PR, and SD (Figure 2E). However, this difference was not observed in follow-up therapy (Figure 2F).

Then, we analyzed the associations in patients with LUAD. No significant differences were found in *SUMO1* or *SUMO1P3* expression for patients in different stages of lung cancer (Figure 3A, 3D). *SUMO1* expression was significantly increased in patients with PD after follow-up therapy, compared with that in patients with CR, PR, and SD (Figure 3C). This difference was not observed after primary therapy (Figure 3B). *SUMO1P3* expression was significantly increased in patients with PD after primary therapy or follow-up therapy, compared with that in patients with CR, PR, and SD (Figure 3E, 3F).

Patients with LUAD with poor survival outcomes had significantly increased *SUMO1P3* expression

Since we found that *SUMO1* and *SUMO1P3* upregulation was associated with PD in both patients with LUSC and LUAD, we further examined patients with different survival indicators. In patients with LUAD, the patients with the poor survival indicators or death or tumor recurrence had significantly increased *SUMO1* and *SUMO1P3* expression, compared with the patients with favorable survival indicators, who were alive or without recurrence (Figure 4A, 4B). These trends were not observed in patients with LUSC (Figure 4C, 4D).

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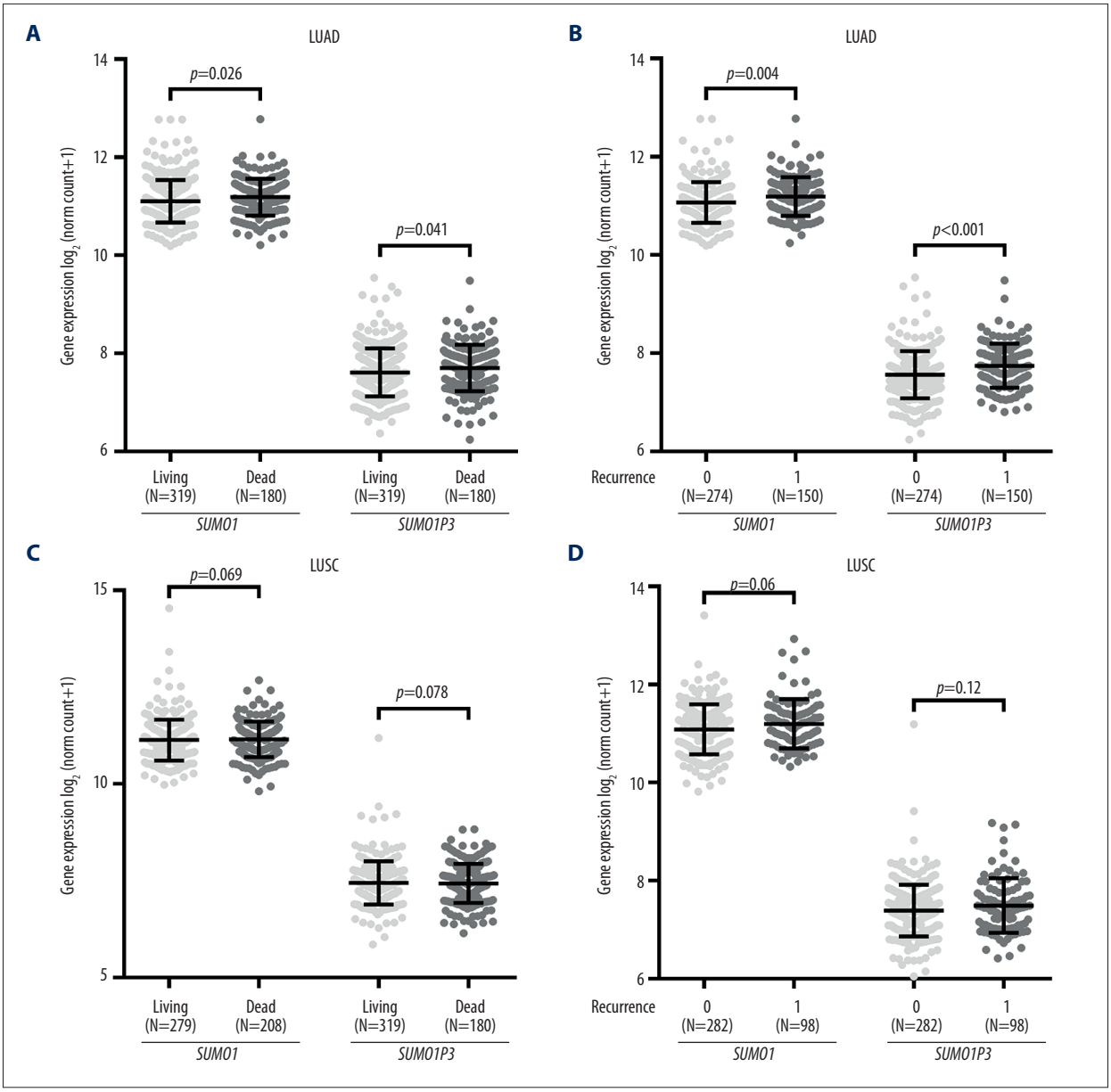

Figure 4. *SUMO1* and *SUMO1P3* expression in patients with different survival indicators. (**A–D**) Comparison of *SUMO1* and *SUMO1P3* expression in patients with lung adenocarcinoma (LUAD) (**A, B**) and lung squamous cell carcinoma (LUSC) (**C, D**) with different survival indicators. Recurrence, 0: no recurrence; 1: with recurrence.

To further explore the association between the upregulation of *SUMO1* and *SUMO1P3* and survival outcomes in patients with LUAD, Kaplan-Meier survival curves were generated and compared to determine the survival differences. The patient group with high *SUMO1* expression had a significantly reduced RFS (Figure 5B). No significant difference was observed in terms of OS (Figure 5A). In contrast, the patient group with high *SUMO1P3* expression had a significantly shorter OS (p=0.037) and RFS (p=0.007) compared with the group with low *SUMO1P3* expression (Figure 5C, 5D).

SUMO1P3 expression was an independent predictor of shorter RFS in patients with LUAD

The clinical parameters of patients with LUAD included in survival analysis are summarized in Table 1. To examine the prognostic significance of *SUMO1* and *SUMO1P3* expression in patients with LUAD, we further conducted univariate and multivariate analysis based on the Cox proportional hazard model. In univariate analysis, advanced T status, N status, and the presence of residual lung tumors were risk factors of unfavorable OS and RFS (Tables 2, Table 3). However, by treating

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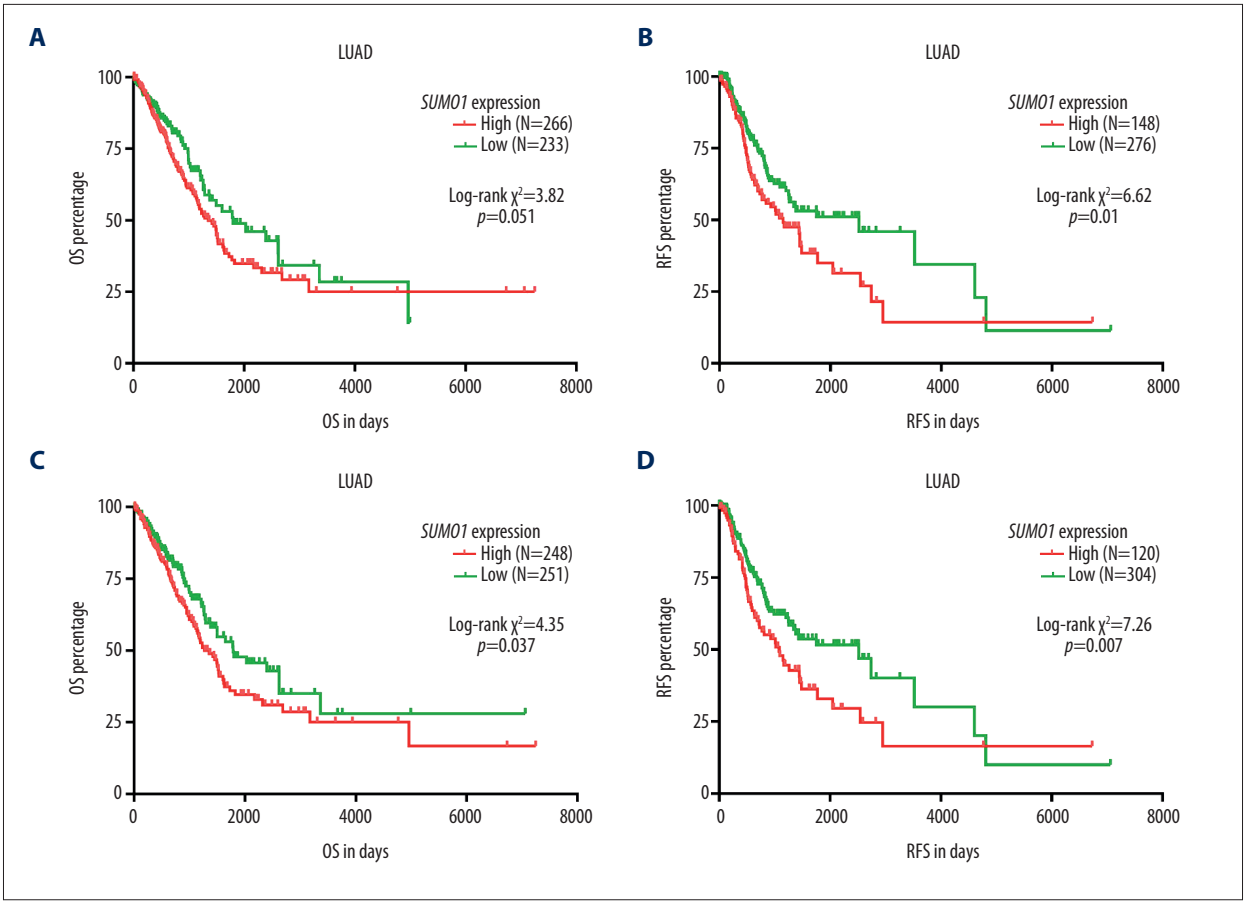

Figure 5. Kaplan-Meier curves of overall survival (OS) and recurrence-free survival (RFS) in patients with lung adenocarcinoma (LUAD). (**A–D**) Kaplan-Meier curves of overall survival (OS) (**A, C**) and recurrence-free survival (RFS) (**B, D**) in patients with lung adenocarcinoma (LUAD). Patients were separated into two groups according to the Youden Index of *SUMO1* (**A, B**) and *SUMO1P3* (**C, D**) expression in receiver operating characteristic (ROC) analysis for mortality (**A, C**) or recurrence (**B, D**).

SUMO1 and *SUMO1P3* expression as continuous variables, we found that they were not risk factors for reduced OS (Table 2). However, *SUMO1P3* expression was a risk factor for reduced RFS (Table 3). Multivariate analysis showed that *SUMO1P3* was an independent prognostic factor for RFS (HR, 1.418; 95% CI, 1.041–1.930; p=0.027) (Table 3). We further compared the expression of *SUMO1P3* between lung tumor tissue and adjacent normal tissue and the low *SUMO1P3* expression group in the RFS analysis. The results showed that there was no significant difference between these two groups (Figure 6).

Discussion

In this study, patient outcome was assessed as complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), and overall survival (OS). Recurrence-free survival (RFS) was defined as the survival time from the date of primary surgery to the time of locoregional or distant recurrence of lung cancer. The findings showed that *SUMO1P3* expression was significantly increased in both lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) tissues compared with adjacent normal tissues. In patients with LUAD, *SUMO1P3* expression was significantly increased in the PD group after primary therapy or follow-up therapy, compared with the CR, PR, and SD group. However, these trends were not confirmed in cases of LUSC. Also, although patients with LUAD with high *SUMO1* or *SUMO1P3* expression tended to have worse survival compared with the low expression group, the results of univariate and multivariate analysis indicated that only *SUMO1P3* expression had independent prognostic value in terms of RFS (HR, 1.418; 95% CI, 1.041–1.930; p=0.027). Further studies are required to determine whether *SUMO1P3* expression has the potential to be a specific prognostic biomarker in patients with LUAD.

Recent studies have shown the oncogenic properties of *SUMO1P3* in several human malignancies. *SUMO1P3* has been shown to act as a miR-320a sponge and participate in the regulation of cell proliferation, migration, and invasion of breast

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Table 1. Summary of the clinical parameters of LUAD patients included in survival analysis.

Parameters	LUAD patients included in survival analysis (N=499)
Age (y, mean ±SD)	65.33±9.92
Gender	
Male	228
Female	271
Pathologic T	
T1/T2	433
T3/T4	63
No data	3
Pathologic N	
N0	323
N1/N2/N3	165
No data	11
Pathologic stages	
I/II	387
III/IV	104
No data	8
Smoking history	
1	72
2/3/4/5	413
No data	14
Residual tumors	
No	334
Yes	16
No data	149
Mutation in KRAS/EGFR/ALK	
No	92
Yes	125
No data	282
OS data available	499
RFS data available	424

Smoking history: 1 – lifelong non-smoker; 2 – current smoker; 3 – current reformed smoker (for >15 yrs); 4 – current reformed smoker (for ≤15 yrs); 5 – current reformed smoker (duration not specified).

Table 2. Univariate analysis of OS in patients with LUAD.

Parameters	Univariate analysis			
	p	HR	95% CI (lower/upper)	
Age (continuous)	0.307	1.008	0.993	1.024
Gender				
Male (N=228)		1.000		
Female (N=271)	0.843	0.971	0.724	1.302
Smoking history				
1 (N=72)		1.000		
2/3/4/5 (N=413)	0.596	0.894	0.592	1.351
Pathological T stages				
T3/T4 (N=63)		1.000		
T1/T2 (N=433)	<0.001	0.423	0.289	0.620
Pathological N stages				
N1/N2/N3 (N=165)		1.000		
N0 (N=323)	<0.001	0.391	0.290	0.527
Pathological stages				
III/IV (N=104)		1.000		
I/II (N=387)	<0.001	0.385	0.281	0.527
Residual tumors				
Yes (N=16)		1.000		
No (N=334)	<0.001	0.248	0.139	0.443

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Table 2 continued. Univariate analysis of OS in patients with LUAD.

Parameters	Univariate analysis			
	p	HR	95% CI (lower/upper)	
Mutation in KRAS/EGFR/ALK				
Yes (N=92)		1.000		
No (N=125)	0.570	1.134	0.734	1.753
SUMO1 expression	0.273	1.204	0.864	1.676
SUMO1P3 expression	0.285	1.170	0.877	1.560

Smoking history: 1 – lifelong non-smoker; 2 – current smoker; 3 – current reformed smoker (for >15 yrs); 4 – Current reformed smoker (for ≤15 yrs); 5 – current reformed smoker (duration not specified); NX – regional lymph nodes cannot be assessed; RX – the presence of residual tumor cannot be assessed.

Table 3. Univariate and multivariate analysis of RFS in LUAD.

Parameters	Univariate analysis				Multivariate analysis			
	p	HR	95% CI (lower/upper)		*p*	HR	95% CI (lower/upper)	
Age (Continuous)	0.356	1.008	0.991	1.025				
Gender								
Male (N=191)		1.000						
Female (N=233)	0.516	1.114	0.805	1.541				
Smoking history								
2/3/4/5 (N=345)		1.000						
1 (N=65)	0.454	1.199	0.746	1.926				
Pathological T stages								
T3/T4 (N=46)		1.000						
T1/T2 (N=375)	**0.002**	0.468	0.291	0.754	**0.018**	0.546	0.330	0.903
Pathological N stages								
N1/N2/N3 (N=133)		1.000						
N0 (N=279)	**0.005**	0.622	0.448	0.863	0.062	0.685	0.460	1.020
Pathological stages								
III/IV (N=80)		1.000						
I/II (N=337)	**0.009**	0.599	0.407	0.882	0.519	0.849	0.517	1.396
Residual tumors								
Yes (N=12)		1.000						
No (N=273)	0.000	0.262	0.126	0.543				
Mutation in KRAS/EGFR/ALK								
Yes (N=77)		1.000						
No (N=108)	0.787	1.063	0.684	1.653				
SUMO1 expression	0.095	1.342	0.950	1.898				
SUMO1P3 expression	0.016	1.451	1.073	1.962	**0.027**	1.418	1.041	1.930

Smoking history: 1 – lifelong non-smoker; 2 – current smoker; 3 – current reformed smoker (for >15 yrs); 4 – Current reformed smoker (for ≤15 yrs); 5 – Current reformed smoker (duration not specified); NX – regional lymph nodes cannot be assessed; RX – the presence of residual tumor cannot be assessed.

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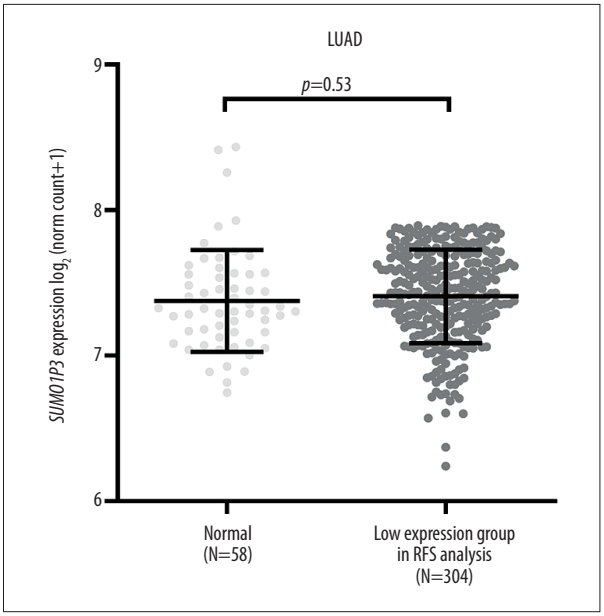

Figure 6. Comparison of *SUMO1P3* expression between adjacent normal tissue and the low expression group in recurrence-free survival (RFS) analysis.

cancer cells [10]. Knockdown of *SUMO1P3* has been shown to inhibit the expression of cyclin D1, vimentin, and VEGF-A, resulting in restored E-cadherin expression in xenograft colon tumor tissues [17]. These molecular mechanisms can partly explain the correlation between increased *SUMO1P3* expression and poor prognosis in malignancy.

In mammals, four SUMO encoding genes, *SUMO1-4* have been identified, among which only *SUMO1, SUMO2,* and *SUMO3* have been extensively studied. *SUMO2* and *SUMO3* share 99% similarity with identical amino acid sequences, while *SUMO1* only has around 50% similarity with *SUMO2* and *SUMO3* [18]. Based on their sequence similarity, their expression levels, and their response to stress, *SUMO1, SUMO2,* and *SUMO3* are categorized into subfamilies [19,20]. SUMOylation directly results in subsequent changes in substrate protein localization, stability, interactions or function to influence a series of cellular processes, including the regulation of the transcriptional process, recycling of proteins, and cellular apoptosis [18]. Previous studies have shown that dysregulated *SUMO1* expression is associated with chemoresistance of some tumors, including testicular germ cell tumors [21], osteosarcoma [22], and NSCLC [15]. The findings in the present study showed that patients with LUAD with PD after follow-up therapy had increased expression of *SUMO1*, which supported that *SUMO1* might have a role in modulating therapeutic responses.

Pseudogenes have previously been regarded as nonfunctional, but increasing studies have shown that although they have lost their protein-coding ability, pseudogenes exert a wide range of regulatory functions. For example, the PTEN pseudogene (*PTENP1*) is targeted by PTEN-targeting microRNAs to maintain the protein expression of PTEN [12]. The long noncoding RNA (lncRNA) pituitary tumor-transforming 3, pseudogene (*PTTG3P*) can promote hepatocellular carcinoma cell growth and metastasis by enhancing the expression of *PTTG1* and activating PI3K/AKT signaling [23]. lncRNA RAS suppressor protein 1 pseudogene 2 (*RSU1P2*) is involved in the tumorigenesis of cervical cancer by acting as a competing endogenous RNA (ceRNA) against let-7a [24]. These findings indicate that the pseudogene might exert regulatory effects on the expression of the corresponding gene. Correlation analysis has shown that *SUMO1P3* was strongly co-expressed with *SUMO1* in both LUAD and LUSC, suggesting that there might be interactions between these two molecules as potential therapeutic targets [25–27]. However, it is necessary to validate the prognostic value of *SUMO1P3* with independent studies and to study whether it could be detected using tumor byproducts in the blood, such as cell-free DNA or circulating tumor cells. These future studies might determine the future clinical potential of *SUMO1P3* as a diagnostic or prognostic cancer biomarker.

Conclusions

SUMO1P3 expression was an independent indicator of reduced recurrence-free survival (RFS) in patients with LUAD.

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