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Expression of SWI/SNF chromatin remodeling complex-related genes is associated with immune infiltration and prognosis in lung cancer

YING ZHENG[1]
RONG ZHOU[2]
QIN-HUA YU[1]
DAN HU[1]
JIE WU[1,*]

[1] Department of Respiratory and Oncology, 72nd Group Army Hospital of PLA, Wuxing District, Huzhou, China

[2] Department of Orthopedics, 72nd Group Army Hospital of PLA, Wuxing District, Huzhou, China

***Correspondence:**
Jie Wu
E-mail address: drjiewu1690@outlook.com

Abbreviations

DSS	– disease-specific survival
DX	– diagnosis
LUAD	– lung adenocarcinoma
MSI	– microsatellite instability
NSCLC	– non-small cell lung cancer
OS	– overall survival
RNA-Seq	– RNA sequencing
SCRC	– switch/sucrose non-fermenting chromatin remodeling complex
SCRCRGs	– SCRC-related genes
SWI/SNF	– switch/sucrose non-fermenting
TMA	– tumor mutation burden

Keywords: lung adenocarcinoma; mating type switch/sucrose non-fermenting chromatin remodeling complex; immune infiltration; prognosis; bioinformatics

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Abstract

Background and purpose: *Lung adenocarcinoma (LUAD) is the most common type of lung cancer with poor prognosis. Mating type switch/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex (SCRC) is involved in the occurrence and progression of LUAD. This study aimed to investigate the relationship between SCRC-related genes (SCRCRGs) and prognosis of lung cancer.*

Materials and methods: *RNA sequencing data and corresponding clinical data of patients diagnosed with LUAD were obtained from The Cancer Genome Atlas database. Hierarchical analysis of the expression of 31 genes in 510 LUAD and 56 paracancerous tissue samples was conducted to distinguish patients according to expression profiles. The prognostic roles of the SCRCRGs were assessed. The identified prognostic factors were integrated to investigate the probability of overall survival (OS) in LUAD.*

Results: *No differences in OS, disease stable survival, disease free survival, and progression-free survival were noticed among the LUAD subgroups; however, the median survival period of Cluster_3 was longer than those of the other clusters. A total of 29 genes with significant differences between subgroups were identified. Significant differences in the expression of SCRCRGs, particularly SMARCA2, WDR77, and SMARCB1, were noticed between cancer and adjacent tissues. Following regression analysis using Lasso-Cox method, a model of five genes was obtained, which could predict the prognosis of LUAD.*

Conclusions: *In LUAD, the differences in expression profile of SCRCRGs were related to prognosis and immune infiltration. SMARCA2 can be exploited as a potential target for immunotherapy.*

INTRODUCTION

Lung cancer adversely affects the physical and mental health of individuals and is an important medical and health burden *(1)*. Approximately 2.208 million new cases of lung cancer have been recorded in 2020, and lung cancer is ranked second among all malignant tumors; additionally, it has caused approximately 1.796 million deaths, which is highest caused by any malignant tumor *(2)*. China has recorded 787,000 new cases of lung cancer and 631,000 deaths in 2015 *(3)*. Moreover, the mortality rate of lung cancer in China is steadily increasing *(4)*. Continuously optimized comprehensive treatment programs have successfully served a large number of patients, thereby improving the quality

of life of patients *(5–7)*. Lung cancer is divided into non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC accounts for approximately 80–85% of lung cancer, and more than 70% of patients with NSCLC are found to be in advanced stages at the time of diagnosis, often without surgical indications. Although the disease can be controlled by radiotherapy and chemotherapy, the outcomes are not promising. Moreover, even if it is diagnosed at an early stage, it eventually recurs and metastasizes even after treatment. Lung adenocarcinoma (LUAD) is the most common pathological type of lung cancer and accounts for most NSCLCs *(8)*. LUAD can be divided into subgroups according to mutation status of driving genes. Presently, mutations in *EGFR, KRAS, HER-2, BRAF,* and *PIK3CA* and rearrangements in *ALK, ROS-1,* and *RET* are utilized for diagnosing LUAD.

The mating type switch/sucrose non-fermenting (SWI/SNF) protein family is widely involved in cell differentiation and proliferation and DNA repair, and has been studied as tumor suppressor. Mutation in the SWI/SNF complex subunit and its abnormal expression have been observed in human cancer *(9–12)*. The mutation frequency of SWI/SNF complex in NSCLC is high, and that of different subunits is different; therefore, the effect of mutations in different subunits on the prognosis of NSCLC may vary *(13, 14)*. Therefore, in this study, we employed bioinformatics to analyze the relationship between SWI/SNF chromatin remodeling complex-related genes and the prognosis of lung cancer, including the expression of related genes in lung cancer, differences in survival and clinical data among different subtypes, and the relationship between different subtypes and immune cell infiltration and immune microenvironment.

MATERIAL AND METHODS

Samples and database

RNA sequencing (RNA-Seq) data and corresponding clinical data of patients diagnosed with LUAD were obtained from The Cancer Genome Atlas database (cbioportal.org) *(15)*. Pathologically diagnosed patients having detailed clinical records were enrolled in the current study. The samples were filtered depending upon whether the transcriptional information and clinical features were complete. Patients with LUAD were divided into four subgroups, including Cluster_1, Cluster_2, Cluster_3, and Cluster_4, depending on differential expression profiles of SCRCRGs. Clinical characteristics, including age, sex, grade of tumor, aneuploidy score, nonsynonymous tumor mutation burden (TMB), FAB, WBC, bone marrow blast percentage, and peripheral blood blast percentage, of individuals were assessed and compared between different subgroups. Finally, the data of 173 patients with LUAD were selected for this study.

Bioinformatic analysis

SWI/SNF chromatin remodeling complex-related genes analyzed in the current study were collected from the Reactome database [Participating Molecules (R-HSA-4839726)] *(16)*. A total of 31 genes coding SWI/SNF chromatin remodeling complex-associated proteins were arrayed, and information on their expression (RNA-Seq V2 RSEM) was obtained from the transcriptome of LUAD. RNA-Seq data were obtained from the Cancer Genome Atlas database. The RNA-Seq values were transformed into Z-scores, and a hierarchical analysis of expression of 31 genes in the 510 LUAD samples and 56 paracancerous tissue samples was performed to distinguish patients according to the expression profiles. Subjects with similar gene expression patterns were incorporated into the same subgroups. The transcription levels were expressed as mRNA z-scores and clustered using hierarchical clustering algorithm *(17)*. A cluster heat map and a pattern were generated using Java TreeView according to the tumor stage *(18)*.

Assessment of immune infiltration

Immune infiltration was assessed using ImSig. ImSig is a set of gene signatures, which can be used to estimate the relative abundance of immune cells in tissue transcriptomic data, specifically in cancer datasets (https://github.com/ajitjohnson/imsig).

Analysis of prognostic association

The prognostic roles of SWI/SNF chromatin remodeling complex-related genes were assessed by comparing survival values between groups with different expressions. Overall survival (OS), progression-free survival, disease-free survival, and disease-specific survival (DSS) of each group were represented by survival curves. Differences in prognosis were detected between the clusters to determine the relevance of gene expression profiles to prognosis. Additionally, we compared the survival curves between cohorts regarding low and high expression of individual genes using GraphPad Prism v.8 (GraphPad Software, Inc., CA, USA).

Building and validating a predictive nomogram

Nomogram is widely used to predict cancer prognosis *(19)*. We integrated previously identified prognostic factors to investigate the probability of 1-, 3-, and 5-OS of LUAD from a nomogram. We validated the nomogram through discrimination and calibration. To assess discrimination of the nomogram, we calculated the concordance index by a bootstrap method with 1000 resamples. A calibration curve was generated to observe prediction probabilities of the nomogram against the observed rates. Moreover, the nomogram including all the prognostic factors were compared using the time-ROC curve, con-

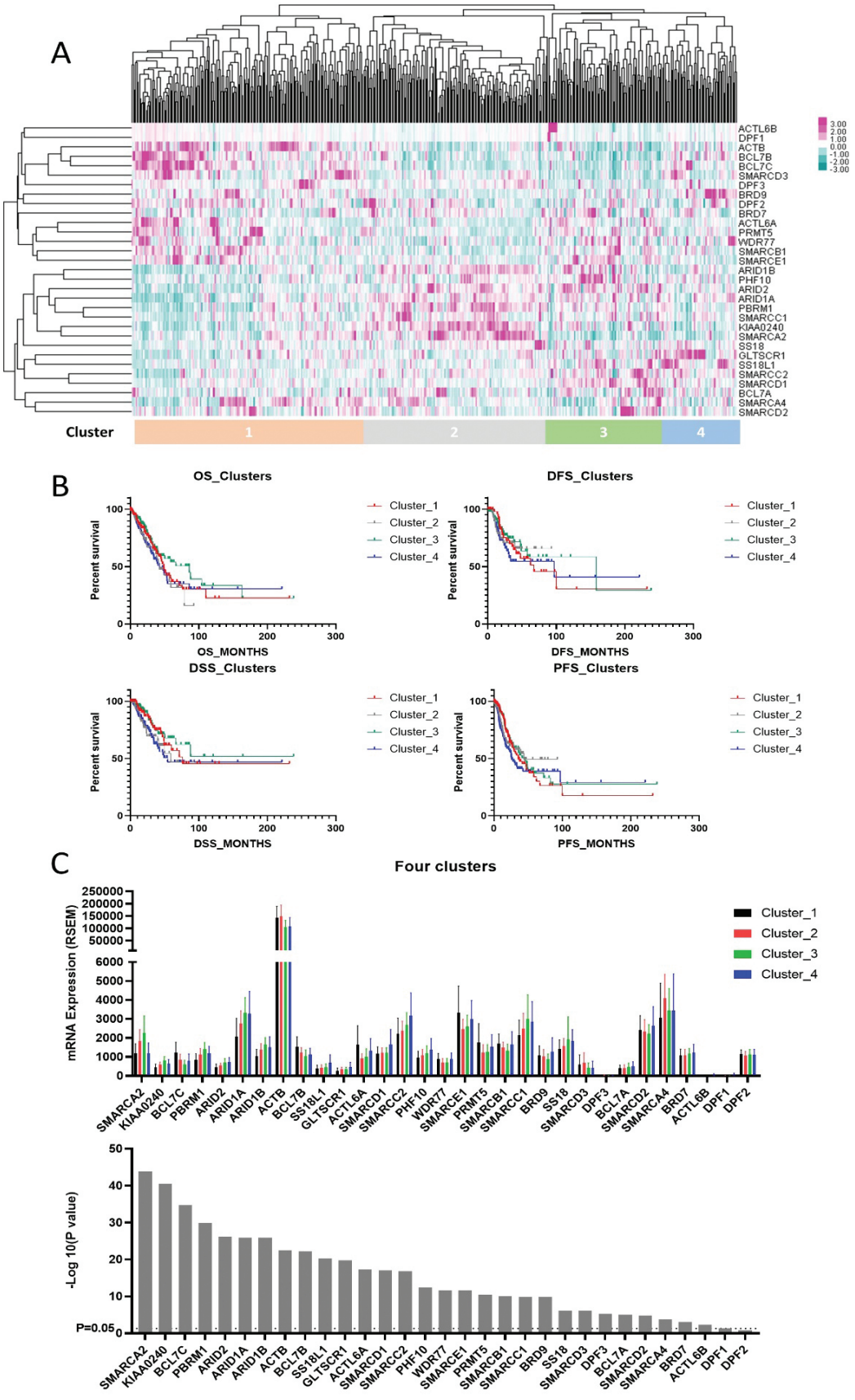

Figure 1. *The four subgroups of LUAD depending on differential expression profiles of SCRCRGs.*

Table 1. *Characteristics of patients divided by the expression spectrum of SCRCRGs.*

Characteristics	Cluster 1 (n=111)	Cluster 2 (n=84)	Cluster 3 (n=156)	Cluster 4 (n=159)	*P*-value
Age (n)	63.93±10.64	66.24±9.92	67.45±8.76	63.76±10.30	0.004
Male (n)	47	32	73	84	0.126
Tumor Type (n)					0.260
Lung Acinar Adenocarcinoma	1	2	7	8	
Lung Adenocarcinoma (NOS)	70	56	86	104	
Lung Adenocarcinoma, Mixed Subtype	30	15	33	29	
Lung Bronchioloalveolar Carcinoma, Mucinous	1	0	4	0	
Lung Bronchioloalveolar Carcinoma, Non-Mucinous	3	3	11	2	
Lung Clear Cell Adenocarcinoma	0	0	1	1	
Lung Micropapillary Adenocarcinoma	0	1	1	1	
Lung Mucinous Adenocarcinoma	0	0	2	0	
Lung Papillary Adenocarcinoma	4	4	7	7	
Lung Signet Ring Adenocarcinoma	0	0	1	0	
Lung Solid Pattern Predominant Adenocarcinoma	2	1	0	2	
Mucinous (Colloid) Carcinoma	0	2	3	5	
AJCC Stage (n)					0.232
1	53	45	91	86	
2	31	21	36	35	
3	20	18	18	27	
4	7	0	9	11	
New Tumor Event After Initial Treatment (n)					0.000
NA	26	4	15	20	
No	44	51	98	80	
Yes	41	29	43	59	
T Stage (n)					0.241
1	29	29	65	44	
2	66	47	69	93	
3	12	5	13	16	
4	4	3	7	5	
X	0	0	2	1	
N Stage (n)					0.219
NA	0	0	1	0	
0	63	49	111	105	
1	30	16	25	25	
2	16	16	15	26	
3	1	1	0	0	
X	1	2	4	3	
M Stage (n)					0.123
NA	0	0	3	1	
0	81	57	99	104	
1	7	0	7	11	
X	23	27	47	43	
Radiation Therapy (n)					0.000
NA	22	1	13	11	

No	69	73	131	129	
Yes	20	10	12	19	
Race (n)					0.570
NA	21	9	20	15	
American Indian or Alaska Native	0	0	1	0	
Asian	2	1	2	3	
Black or African American	12	6	14	20	
White	76	68	119	121	
Prior DX (n)					0.040
No	98	63	122	141	
Yes	12	18	30	17	
Yes, History of Synchronous and/or Bilateral Malignancy	1	3	4	1	
Person Neoplasm Cancer Status (n)					0.663
NA	21	13	31	28	
Tumor-free	63	52	99	92	
With Tumor	27	19	26	39	
Aneuploidy Score	15.41±7.88	14.36±7.53	12.24±8.20	17.66±6.53	0.000
MSI Score Mantis	0.31±0.03	0.32±0.03	0.31±0.02	0.32±0.02	0.026
MSI Sensor Score	0.26±0.77	0.11±0.49	0.06±0.15	0.16±0.41	0.010
TMB Nonsynonymous	10.82±10.66	8.26±8.15	8.31±9.47	12.41±12.40	0.002

cordance index, and the decision curve analysis. To evaluate the area under the curve, ROC analysis of the nomogram was performed using the R software package pROC v.1.17.0.1. Clinical net benefits of each model compared to all or none strategies were calculated using decision curve analysis.

Statistical analysis

We plotted survival curves corresponding to different groups and compared survivals using log-rank (Mantel-Cox) test in GraphPad Prism v.8. The quantitative variables were analyzed using one-way analysis of variance, and qualitative variables were assessed using Fisher's exact test and Spearman's correlation to determine differences in clinical characteristics between the identified subgroups in LUAD. Differences gene expression between clusters were analyzed by one-way analysis of variance. Regression analyses were performed to determine correlations between variables and to construct a prediction model. All tests were performed using SPSS v.24.0 (IBM, Inc., NY, USA). A *P*-value <0.05 was considered statistically significant.

RESULTS

Groups divided by SCRCRG expression

Lung adenocarcinoma was divided into four subgroups (Clusters 1–4) according to the differences in expression profiles of SCRCRGs (Figure 1A). OS, DSS, disease-free survival, and progression-free survival between the groups were not significantly different, but the median survival time of Cluster_3 was longer than those of the other clusters (Figure 1B). A total of 29 genes had significantly different expression between groups ($P<0.05$) (Figure 1C), suggesting that the expression of SCRCRGs in lung adenocarcinoma was heterogeneous. Significant differences in age, new tuner event after initial treatment, radiation therapy, prior diagnosis (DX), aneuploid score, microsatellite instability (MSI), and TMB between groups were noticed (Table 1).

Comparison of SCRCRG expression between cancer and paracancerous tissues

RNA-Seq analysis indicated significant differences in the expression profile of SCRCRGs between cancer and adjacent tissues (Figure 2A). Comparison of single genes between cancer and adjacent tissues suggested the expression patterns of *SMARCA2, WDR77,* and *SMARCB1* were significantly different (Figure 2B). Further comparison of individual genes in paired samples indicated that the expression of seven genes was highly altered (Figure 2C). *SMARCA2* expression was higher in paracancerous tissues than in cancer, whereas, other genes are highly expressed in cancerous tissues (Figure 2D), suggesting that *SMARCA2* may be associated with effective prognosis.

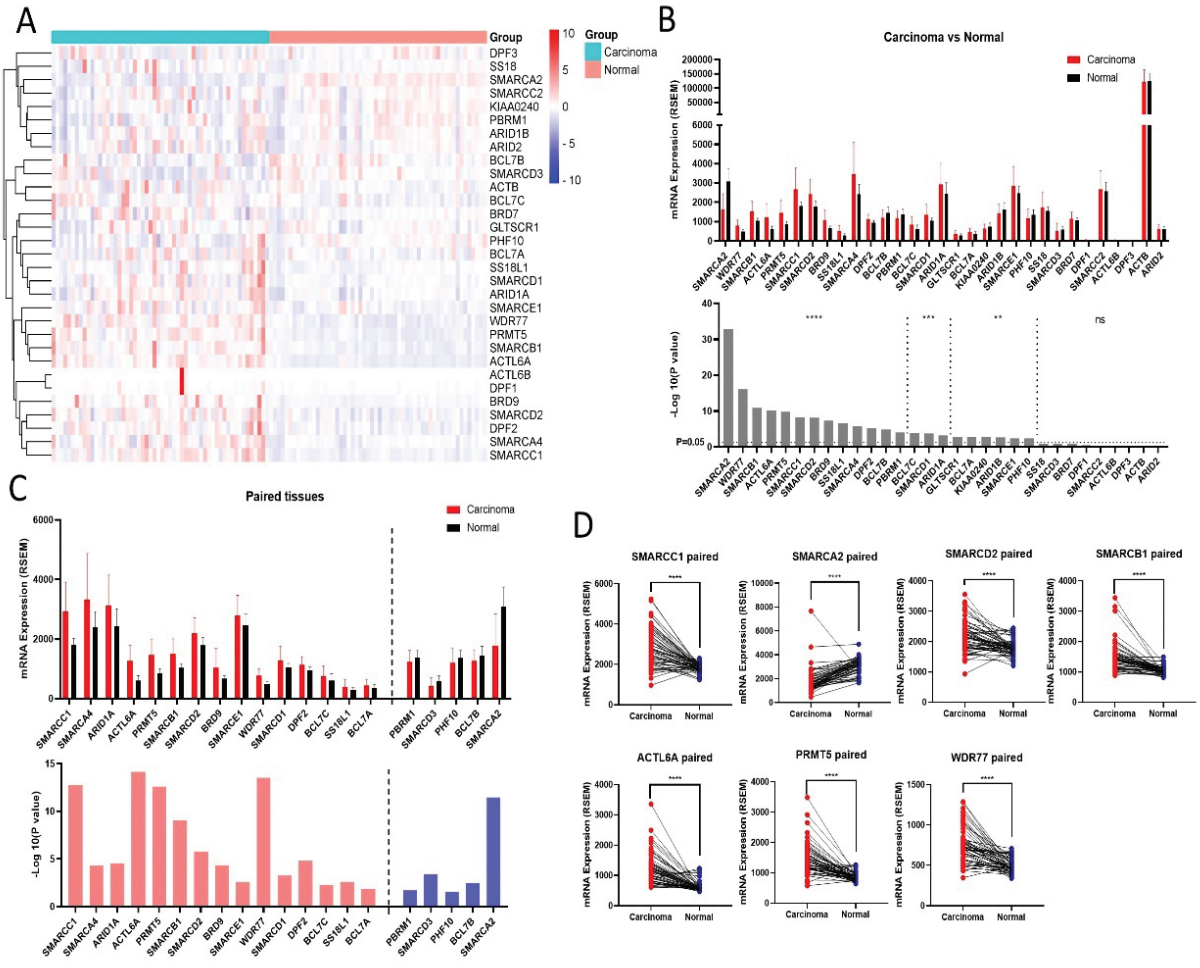

Figure 2. *Expression profiles of SCRCRGs between cancer and adjacent tissues.*

Relationship between SCRCRG expression and LUAD prognosis

Analysis of survival, integrating survival time, survival status and gene expression data using the Cox method indicated that *SS18L1* was a protective factor for prognosis; *ACTL6A* was a risk factor; and other genes had no significant correlation with prognosis (Figure 3A). To design a model for predicting prognosis, we used the Lasso-Cox method for regression analysis (R software package glmnet was used to integrate survival time, survival status, and gene expression data) and set up a 10-fold cross-validation to obtain the optimal model. The optimal value of Lambda was 0.00161533734716138. Finally, five gene models were obtained (Figure 3B) using the following formula:

Risk Score = 4.05337069858498e-06**ACTB* + 0.000233986443777923**ACTL6A* – 0.000520824159572521**SS18L1* – 0.000458454247642212**SMARCD3* + 0.00134359252674163**DPF1* (1) (Figure 3C).

The final model successfully predicted LUAD (OS, 37 months vs. 74 months, hazard ratio, 1.9), (Figure 3D).

The median survival time of Cluster_3 was relatively long in the early stage; therefore, its OS and DSS were better than those of the other groups (Figure 4A). Comparison of the baseline data of Cluster_3 and other clusters showed significant differences in age, new tuner event after initial treatment, radiation therapy, prior DX, aneuploid score, MSI, and TMB (Figure 4B); moreover, significant differences in the specific type of tumor (Figure 4C), recurrence after initial treatment (Figure 4D), and T stage (Figure 4E) were noticed. *SMARCA2* and *KIAA0240* were significantly overexpressed in Cluster_3 (Figure 4F). *SMARCA2* expression was significantly positively correlated with the expression of *KIAA0240, PBRM1*, and *ARID1B* and significantly negatively correlated with the expression of *BCL7C, PRMT5*, and *ACTL6A* (Figure 4G). Logistic regression analysis indicated that SMARCA2 expression was enough to distinguish between the patients of Cluster_3 and other clusters; area under the curve was 0.826; and the scatter plot clearly reflected differentiation potential (Figure 4H).

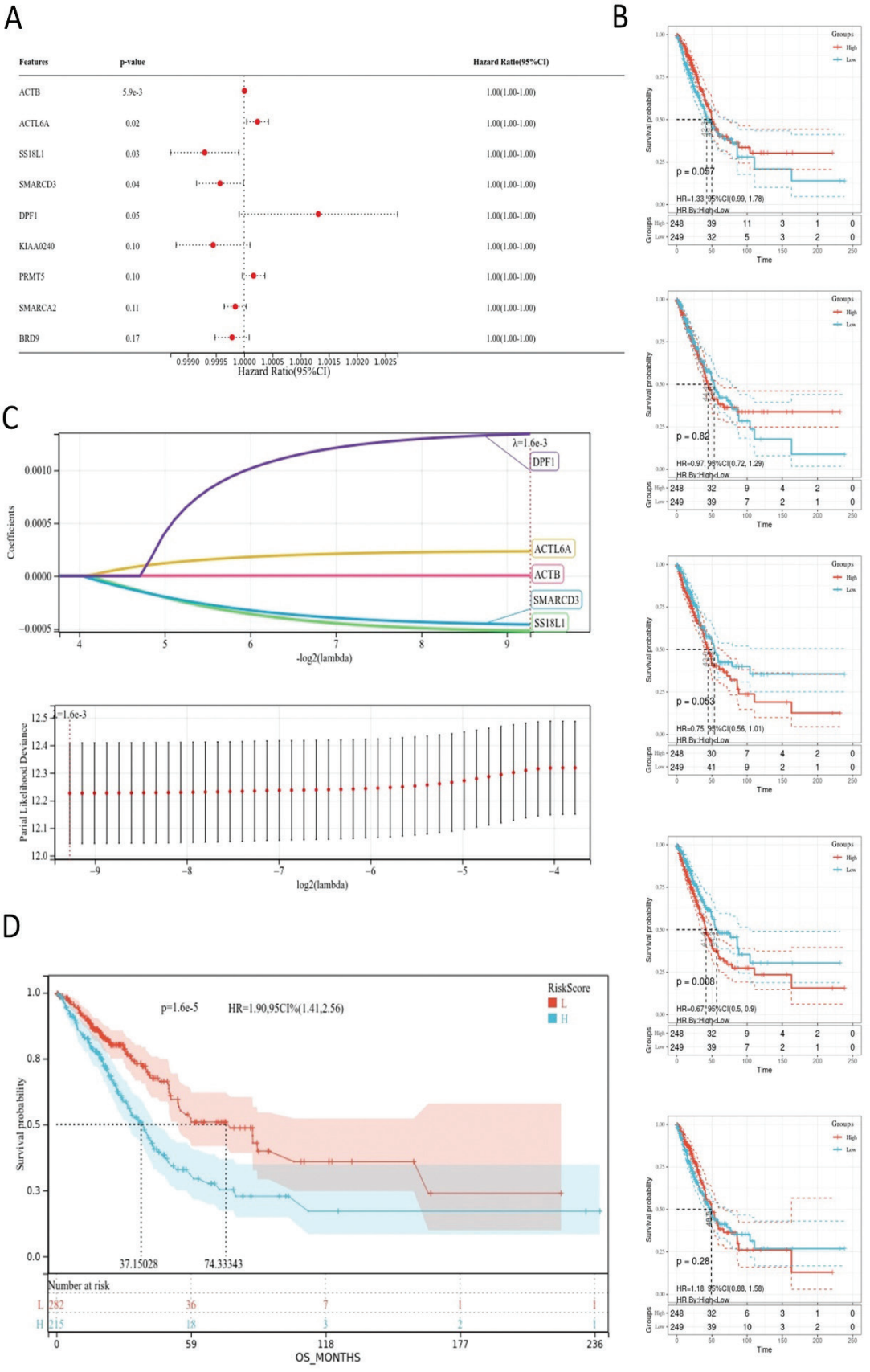

Figure 3. *Correlation between SCRCGs and prognosis of LUAD.*

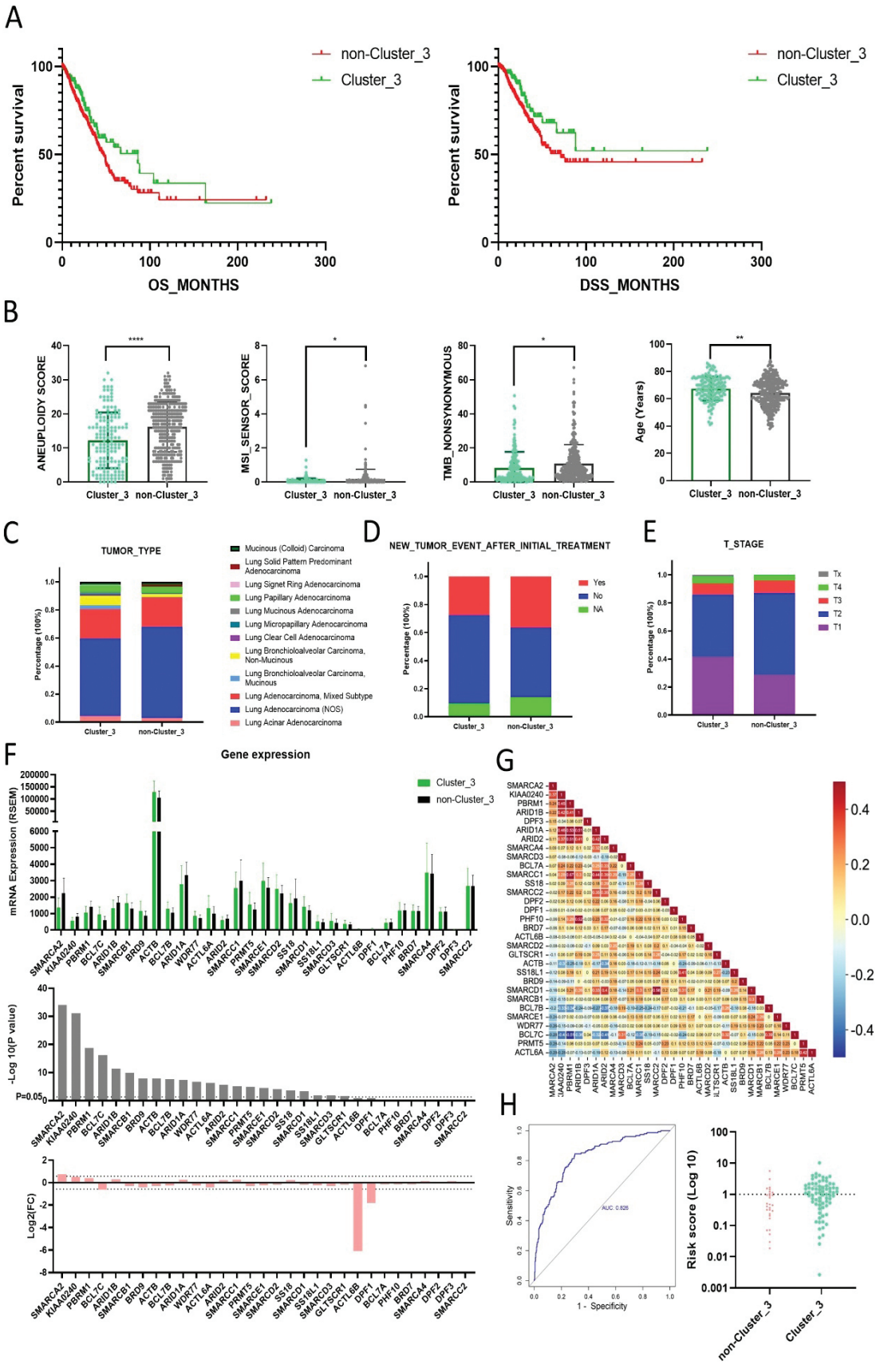

Figure 4. *Comparison of Cluster_3 with other clusters.*

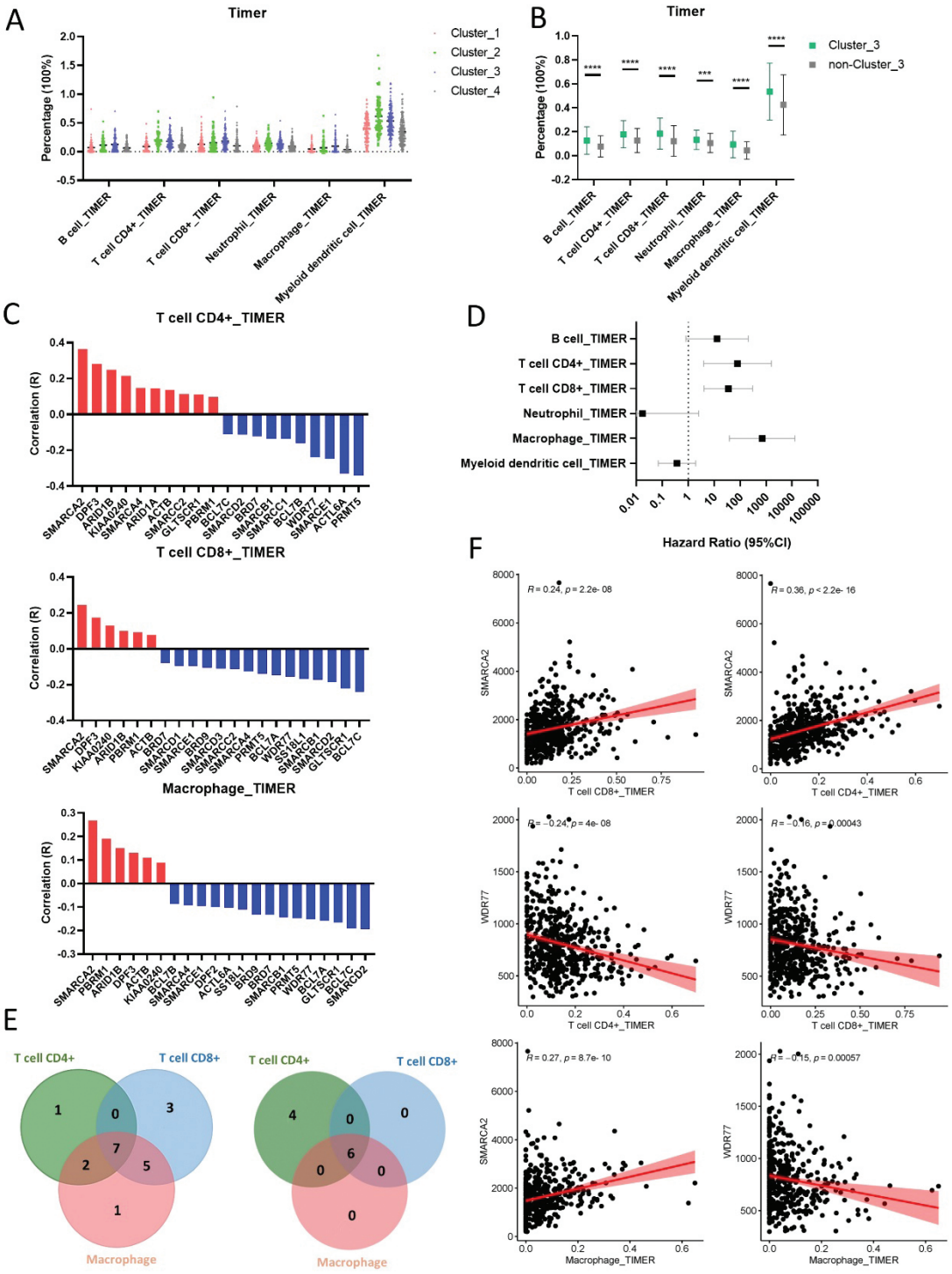

Figure 5. *Comparison of immune infiltration between clusters.*

Relationship between SCRCRG expression and the immune system in LUAD

Chromosomal instability affects recognition by the immune system, and differences in aneuploid score, MSI, and TMB may lead to the difference of immune infiltration. We noticed significant differences in immune infiltration among different groups (Figure 5A, Table 2). A significant difference in immune infiltration between Cluster_3 and other clusters was noticed (Figure 5B). Multivariate regression analysis showed that the differences in infiltration of CD4+ T cells, CD8+ T cells, and

Table 2. *Relationship between SCRCRG expression and immune system in LUAD.*

Tukey's multiple comparison test	B cell TIMER			T cell CD4+ TIMER		
	Mean Diff.	Summary	Adjusted P-Value	Mean Diff.	Summary	Adjusted P-Value
Cluster_1 vs. Cluster_2	-0.043	ns	0.097	-0.111	****	<0.0001
Cluster_1 vs. Cluster_3	-0.058	**	0.0022	-0.090	****	<0.0001
Cluster_1 vs. Cluster_4	0.004	ns	0.9959	-0.024	ns	0.4449
Cluster_2 vs. Cluster_3	-0.014	ns	0.8574	0.021	ns	0.6448
Cluster_2 vs. Cluster_4	0.047	*	0.0374	0.087	****	<0.0001
Cluster_3 vs. Cluster_4	0.061	***	0.0002	0.066	****	<0.0001
Tukey's multiple comparison test	**T cell CD8+ TIMER**			**Neutrophil TIMER**		
	Mean Diff.	**Summary**	**Adjusted P-Value**	**Mean Diff.**	**Summary**	**Adjusted P-Value**
Cluster_1 vs. Cluster_2	-0.031	ns	0.358	-0.052	*	0.031
Cluster_1 vs. Cluster_3	-0.059	**	0.0015	-0.038	ns	0.089
Cluster_1 vs. Cluster_4	0.023	ns	0.5002	0.003	ns	0.9969
Cluster_2 vs. Cluster_3	-0.028	ns	0.3769	0.014	ns	0.8635
Cluster_2 vs. Cluster_4	0.053	*	0.0128	0.055	**	0.0096
Cluster_3 vs. Cluster_4	0.082	****	<0.0001	0.041	*	0.026
Tukey's multiple comparison test	**Macrophage TIMER**			**Myeloid dendritic cell TIMER**		
	Mean Diff.	**Summary**	**Adjusted P-Value**	**Mean Diff.**	**Summary**	**Adjusted P-Value**
Cluster_1 vs. Cluster_2	-0.023	ns	0.623	-0.216	****	<0.0001
Cluster_1 vs. Cluster_3	-0.049	*	0.0125	-0.137	****	<0.0001
Cluster_1 vs. Cluster_4	0.012	ns	0.8668	0.054	**	0.0048
Cluster_2 vs. Cluster_3	-0.027	ns	0.4335	0.079	****	<0.0001
Cluster_2 vs. Cluster_4	0.035	ns	0.1873	0.269	****	<0.0001
Cluster_3 vs. Cluster_4	0.062	***	0.0002	0.191	****	<0.0001

[1]ns, not significant; *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001

macrophages between groups were independent (Figure 5C). The genes related with these immune cells had linear correlation with the immune cells (Figure 5D). In addition, some common regulatory genes were noticed among the positively and negatively correlated genes (Figure 5E). Furthermore, a general correlation with *SMARCA2* and *WDR77* was noticed, and they were the most significant genes (Figure 5F). *SMARCA2* expression was high in Cluster_3, which suggested that anti-tumor immunity was activated in patients of Cluster_3.

DISCUSSION

The prognosis of LUAD is generally poor; however, some patients show long-term remission or even clinical cure after timely and active treatment. In clinical practice, predicting the prognosis of patients with LUAD is highly significant for formulating a reasonable management plan for the patients. The present study showed that the expression of SCRCRGs in LUAD was significantly heterogeneous, and no significant differences were noticed between the subgroups divided depending on the expression of SCRCRGs during age, new tumor event after initial treatment, radiation therapy, prior DX, aneuploid score, MSI, and TMB. Moreover, a significant difference was noticed in the expression profile of SCRCRGs between cancer and adjacent tissues, of which *SMARCA2*, *WDR77*, and *SMARCB1* were most significant. *SS18L1* was a protective factor for prognosis; *ACTL6A* was a risk factor, and other genes had no significant correlation with prognosis. We used Lasso-Cox method for regression analysis and finally obtained a model constructed by five genes, which could predict the prognosis of LUAD. *SMARCA2* expression was sufficient to distinguish Cluster_3 from other clusters. The analysis of immune microenvironment showed a general correlation between immune cell-related genes and *SMARCA2* and *WDR77*, while *SMARCA2* was highly expressed in Cluster_3, suggesting the activation of anti-tumor immunity in Cluster_3.

The role of SCRCRGs, including *SMARCA4, SMARCA2, ARID1A*, and *ARID2*, in the occurrence and progression of lung cancer have been extensively studied. In patients with NSCLC, the mutation rates of *ARID1A* and *SMARCA4* subunits are 28.1% and 27.4%, respectively, and the co-mutation rate of SWI/SNF complex subunit was 14.1% *(20)*. Additionally, patients with NSCLC having SWI/SNF complex subunit mutations have lower co-mutation rate of driver genes and shorter OS than those with SWI/SNF complex wild-type *(20)*. *SMARCA4* is lost in 5-10% of NSCLC cases, and most of these patients have poorly differentiated adenocarcinoma with short survival and poor prognosis *(21–23)*. Loss of *SMARCA4/2* leads to the inhibition of chemotherapy-induced cell apoptosis, and SMARCA2 activation by histone deacetylase inhibitor restores IP3R3 expression in *SMARCA4/2*-deficient cancer cells and enhances cellular response to cisplatin *(14)*. SMARCA2 inhibits cancer cell vitality and tumor progression *(24)*. We noticed a significant difference in *SMARCA2* expression between cancer and paracancer tissues, which is consistent with the results of previous studies. Therefore, *SMARCA2* may play an important role in the occurrence and development of LUAD and can be used as a drug target.

WDR77 is required for the proliferation of lung and prostate epithelial cells during early stages of development and is reactivated during prostate and lung tumorigenesis *(25, 26)*. We noticed that *WDR77* expression in paracancerous tissues was significantly lower than that in cancerous tissues. However, the role of WDR77 in the occurrence and development of LUAD is still unclear. SMARCB1 is the core component of SWI/SNF complex. Rickard et al. have detected the deletion of *SMARCB1* allele in a patient with small cell lung cancer *(27)*. We observed that *SMARCB1* expression in LUAD tissues was significantly higher than that in paracancerous tissue. Therefore, the role of *SMARCB1* may vary in different lung cancers.

This study has some limitations. First, this study is based on the existing database, and the patients have received surgical treatment. In reality, many patients with LUAD do not undergo surgery. Therefore, this study suffers from case selection bias. Second, the results of this study have not been verified in another group of cases or experimental approaches.

CONCLUSION

In LUAD, the differences of expression profiles of SWI/SNF chromatin remodeling complex-related genes are related to prognosis and immune infiltration. High expression of *SMARCA2* correlates with better prognosis. In addition, it may regulate the immune response and can be used as a potential target for immunotherapy.

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