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DATABASE ANALYSIS

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Junctional Adhesion Molecule-Like Protein (JAML) Is Correlated with Prognosis and Immune Infiltrates in Lung Adenocarcinoma

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Background: Junctional adhesion molecule-like protein (JAML) is a member of the junctional adhesion molecule family and mediates migration of immune cells, but its function in cancers remains unclear. This study aimed to evaluate the role of JAML in the prognosis and immune infiltrates of lung adenocarcinoma (LUAD).

Material/Methods: JAML expressions in LUAD tissues and normal tissues were compared using The Cancer Genome Atlas (TCGA) database and datasets from the Gene Expression Omnibus (GEO) database. The influence of JAML expression on prognosis was analyzed by Kaplan-Meier curve and Cox regression model. Interactive and functional analyses of JAML were performed by LinkedOmics and GeneMANIA databases. TIMER2.0, TISIDB, and GEPIA2 databases were used to investigate the correlation between JAML expression and immune infiltrates.

Results: JAML expression was decreased in LUAD ($P<0.001$), and lower JAML expression was associated with worse outcomes of LUAD patients. High JAML expression was the protective factor for overall survival (OS) (HR 0.706, 95% CI 0.500-0.997, $P=0.048$). Interactive and functional analyses suggested that co-expressed genes with JAML have an obvious link to immune-related pathways. In addition, JAML expression was positively associated with infiltrating levels of CD8+ T cells, CD4+ T cells, B cells, dendritic cells, macrophages, and neutrophils, and had significant correlations with diverse immune marker sets in LUAD.

Conclusions: JAML expression was significantly correlated with prognosis and immune infiltrates. These preliminary findings suggested JAML could be considered as a potential prognostic biomarker and therapeutic target for LUAD.

Keywords: Adenocarcinoma of Lung • JAML Protein, Human • Prognosis

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Background

Lung cancer is one of the most common malignant tumors and is the leading cause of cancer-related death worldwide [1,2]. Lung adenocarcinoma (LUAD) is the most frequent histological subtype [3]. More than half of cases have advanced or metastatic disease at the time of initial diagnosis and require systematic therapy [4]. Although chemotherapy remains an important component of systemic therapy, targeted therapy such as tyrosine kinase inhibitors (TKIs) has shown a better activity in oncogene-driven disease [5,6]. The recent development of immunotherapy has fundamentally shifted the treatment paradigm of patients without sensitive molecular mutations [7]. Immune checkpoint inhibitors (ICIs) have become the front-line treatment in patients with high PD-L1 expression [8]. However, immunotherapy remains ineffective for most patients, and secondary drug resistance is also a challenging problem [9].

Junctional adhesion molecule-like protein (JAML), also named AMICA1, is a junctional adhesion molecule (JAM) that belong to the immunoglobulin superfamily [10]. JAML can mediate the transendothelial migration (TEM) of immune cells and might be involved in modulating cellular responses during tissue immunity [11,12], suggesting that JAML influences the tumor immune microenvironment. In head and neck squamous cell carcinoma, JAML is one of the genes that play a potential role in tumor evolution mechanisms related to the tumor immune microenvironment [13]. However, the function of JAML in LUAD is poorly investigated. This study explored JAML expression in LUAD and its impact on prognosis based on bioinformatics analysis. The association between JAML expression

Table 1. Baseline characteristics of the LUAD patients.

Characteristics		N	(%)
Age	>65	261	50.6
	≤65	255	49.4
Gender	Male	249	46.5
	Female	286	53.5
Smoking history	Yes	446	85.6
	No	75	14.4
T stage	T1	175	32.9
	T2	289	54.3
	T3	49	9.2
	T4	19	3.6
N stage	N0	348	67.1
	N1	95	18.3
	N2	74	14.3
	N3	2	0.4
M stage	M0	361	93.5
	M1	25	6.5
Pathologic stage	Stage I	294	55.8
	Stage II	123	23.3
	Stage III	84	15.9
	Stage IV	26	4.9
JAML expression	High	268	50.1
	Low	267	49.9

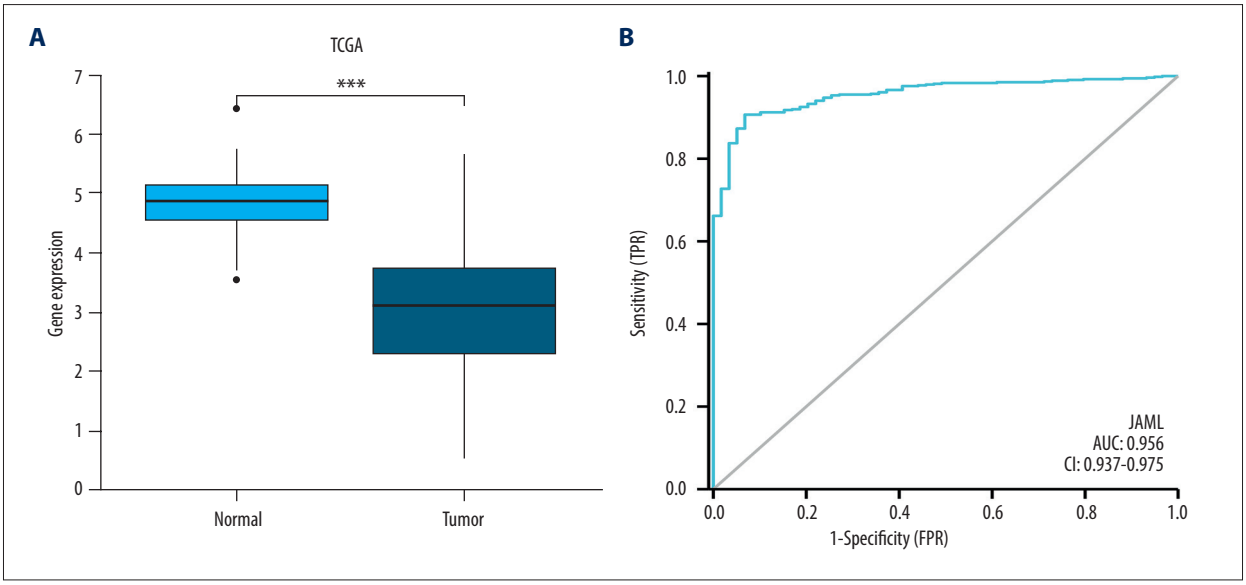

Figure 1. (**A**) JAML expression was lower in LUAD tissues than in normal tissues in TCGA database. (**B**) The ROC curve of JAML expression in LUAD. TPR – true positive rate; FPR – false positive rate. *** $P<0.001$. The figure was created using R statistical software (version 3.6.3).

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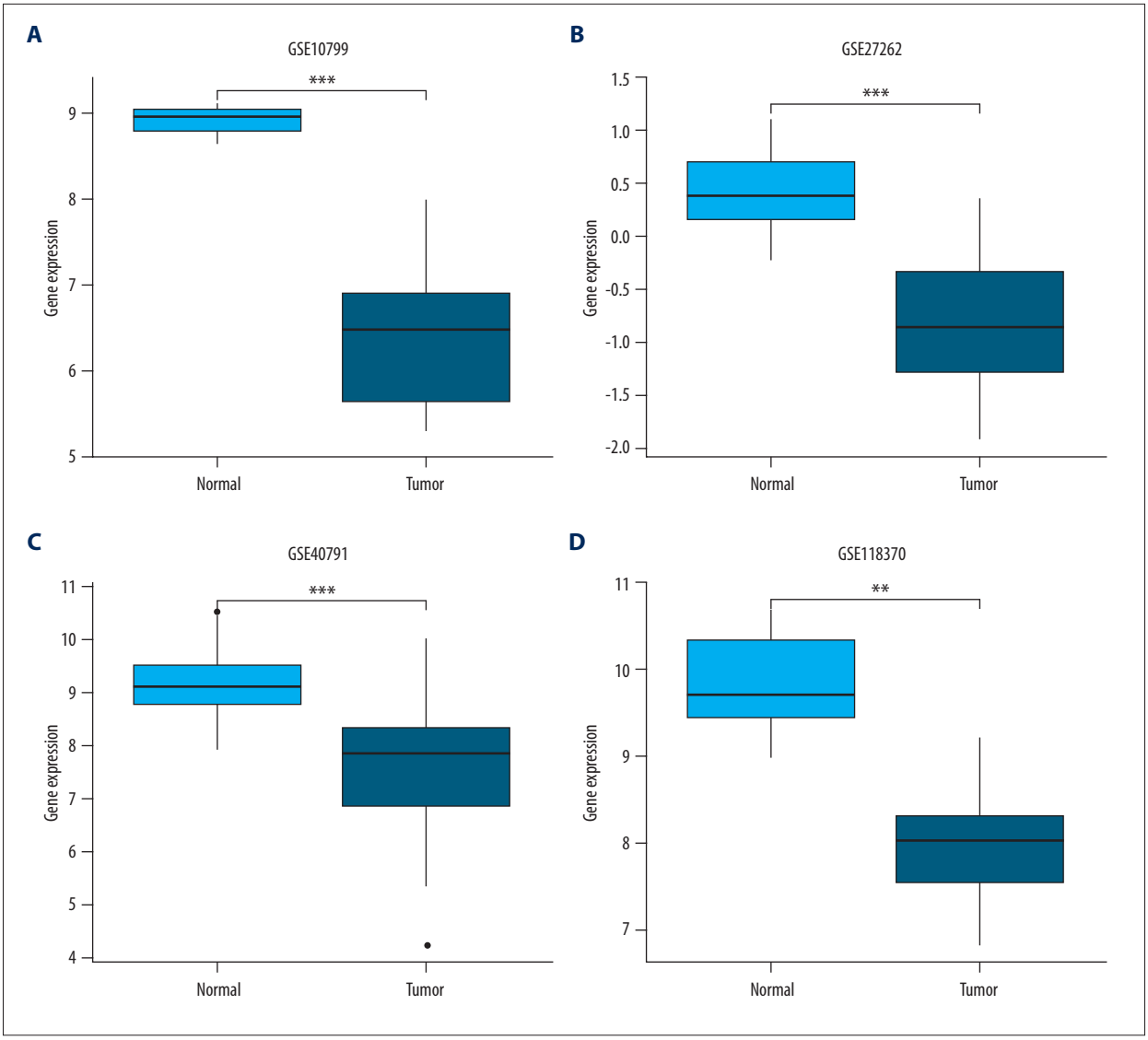

Figure 2. Validation of lower JAML expression in LUAD than that in normal tissues in (**A**) GSE10799, (**B**) GSE27262, (**C**) GSE40791, and (**D**) GSE118370 datasets. ** *P*<0.01; *** *P*<0.001. The figure was created using R statistical software (version 3.6.3).

and the tumor immune microenvironment was investigated using the TIMER2.0, TISIDB, and GEPIA2 databases. The results revealed the significant impact of JAML expression on prognosis and tumor immune microenvironment of LUAD.

Material and Methods

Data Acquisition

The data of mRNA expression and clinicopathologic characteristics of LUAD patients were obtained from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/). The database is publicly open-access and local ethics committee approval is not necessary. A total of 535 LUAD samples and 59 normal tissue samples from the TCGA database were included in the study. The differential expression of JAML between normal tissues and LUAD was verified by the gene expression profiling datasets GSE10799, GSE27262, GSE40791, and GSE118370, which were obtained from Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/gds). GSE10799 included 16 LUAD samples and 3 normal lung tissue samples. GSE27262 included tumor and adjacent normal tissue pairs from 25 stage I LUAD patients. GSE40791 included 100 non-neoplastic lung samples, and 69, 12, and 13 stage I, II, and III LUAD frozen tissues, respectively. GSE118370 included 6 pairs of invasive LUAD tissues and normal lung tissues. The expressions of JAML protein were compared between LUAD and normal tissues, and were further compared in the Human Protein Atlas (https://www.proteinatlas.org/),

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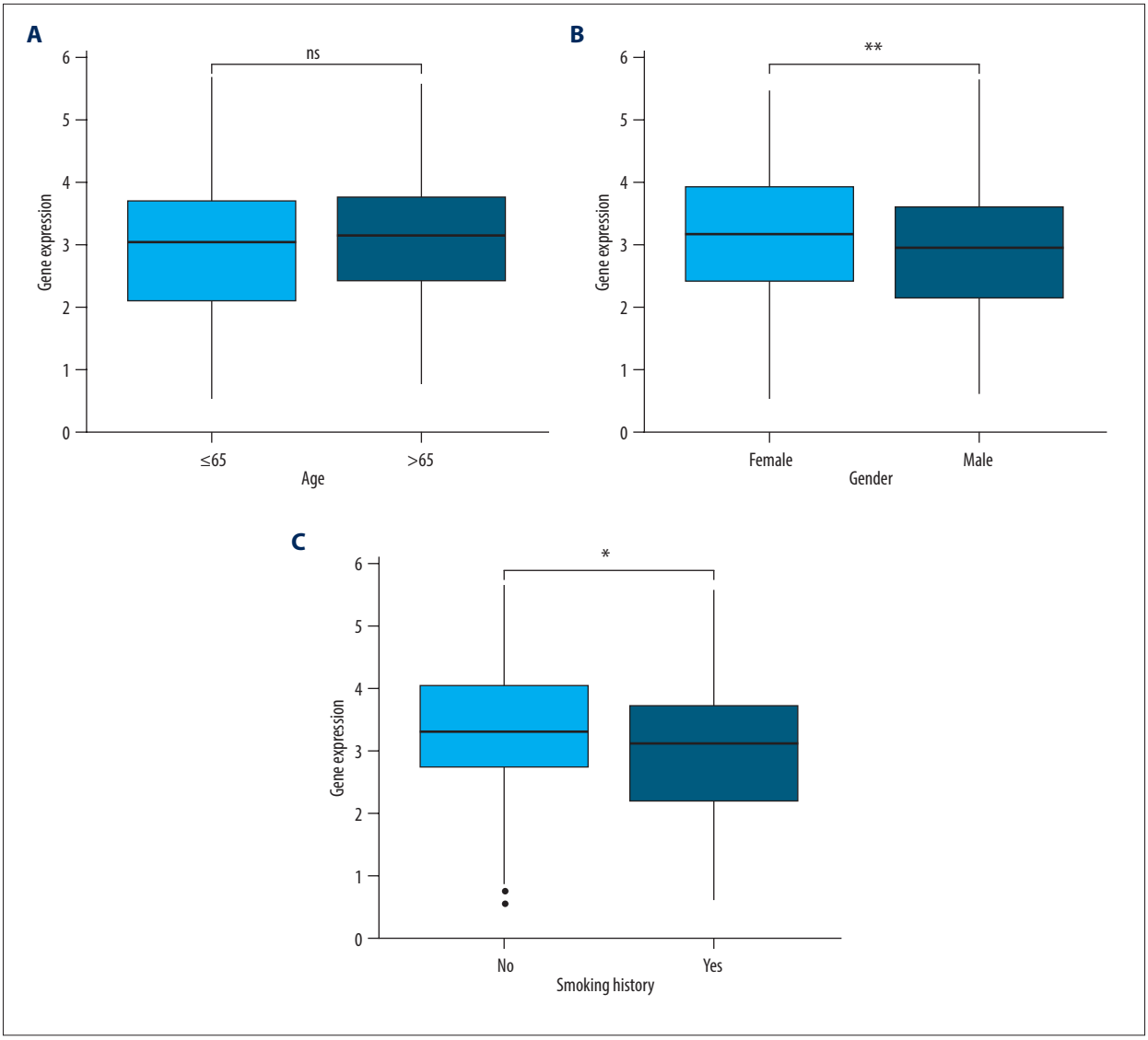

Figure 3. (**A**) There was no significant difference between JAML expression and age. (**B**) JAML expression was lower in males than in females. (**C**) JAML expression was lower in patients with smoking history than in those without smoking history. * $P<0.05$; ** $P<0.01$. The figure was created using R statistical software (version 3.6.3).

which provides protein immunohistochemistry in normal human tissues and tumor tissues.

LinkedOmics Database Analysis

The LinkedOmics database is a platform (http://www.linkedomics.org) to access, analyze, and compare cancer multi-omics data within and across tumor types [14]. The differentially expressed genes related to JAML were screened through the LinkFinder module in the database, and the correlation was tested using the Pearson correlation coefficient. The gene set enrichment analyses (GSEA) of Gene Ontology biological process (GO_BP) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were performed in the LinkInterpreter module.

GeneMANIA Database Analysis

GeneMANIA is a website (http://genemania.org) for generating hypotheses about gene function, analyzing gene lists, and prioritizing genes for functional assays [15]. Given a query gene list, GeneMANIA finds functionally similar genes using a wealth of genomics and proteomics data. We obtained the protein–protein interaction (PPI) network information of JAML using the online tool GeneMANIA.

TIMER2.0 Database Analysis

The Tumor Immune Estimation Resource (TIMER) is a public website (http://timer.cistrome.org/) providing comprehensive

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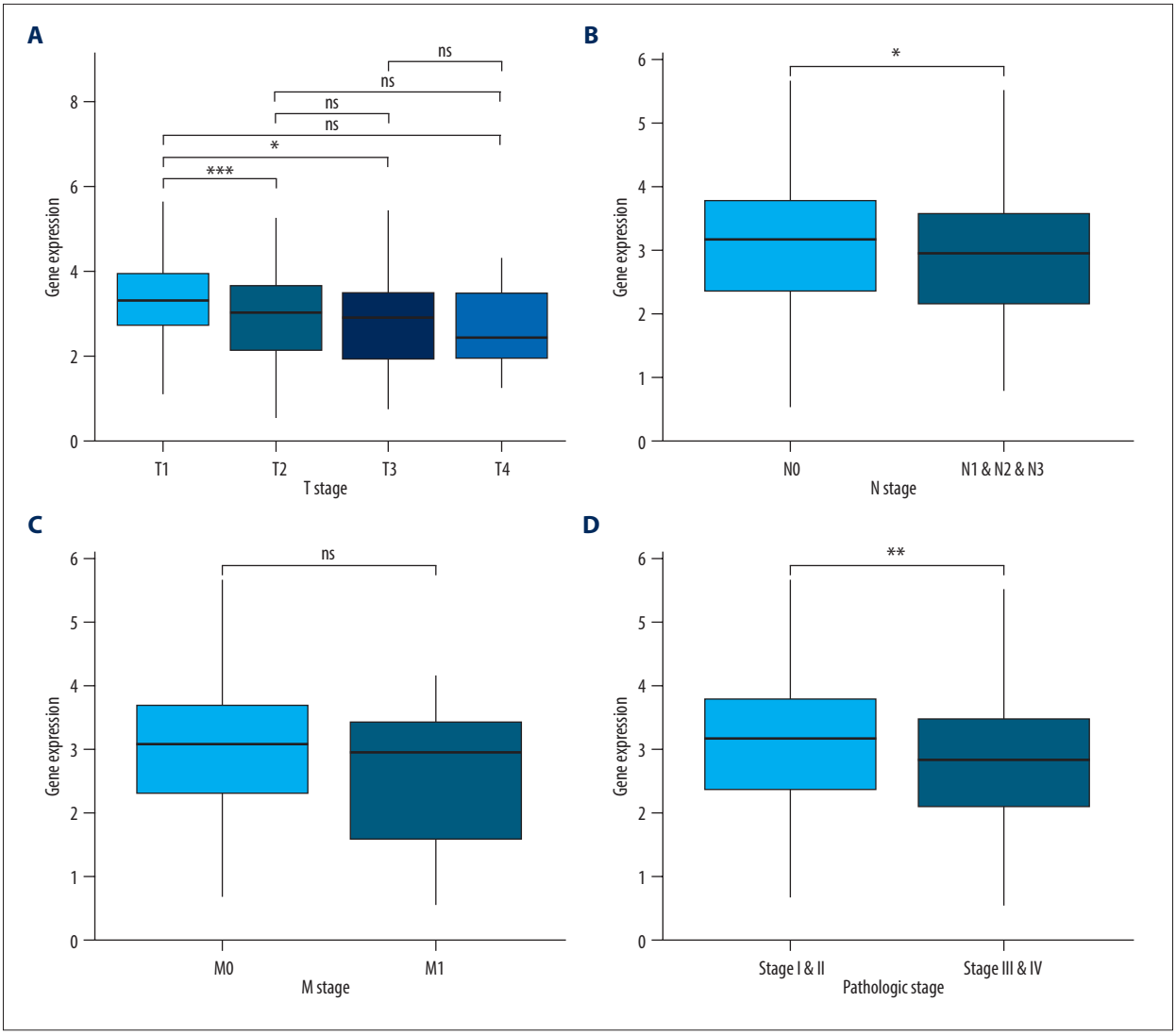

Figure 4. (**A**) JAML expression was lower in T2 and T3 stage than in T1 stage, but the difference was not observed in T4 stage. (**B**) Low JAML expression was associated with positive N stage. (**C**) There was no significant difference between JAML expression and M stage. (**D**) Low JAML expression was associated with advanced pathologic stage. ns, $P \geq 0.05$; * $P<0.05$; ** $P<0.01$; *** $P<0.001$. The figure was created using R statistical software (version 3.6.3).

analysis and visualization functions of tumor-infiltrating immune cells [16]. The correlations of JAML expression with the abundance of 6 types of infiltrating immune cells (CD8+ T cells, CD4+ T cells, B cells, dendritic cells, macrophages, and neutrophils) in LUAD were evaluated in the TIMER2.0 database.

TISIDB Analysis

The Tumor-Immune System Interaction Database (TISIDB) is a user-friendly web portal (http://cis.hku.hk/TISIDB/index.php) which provides comprehensive investigation of tumor-immune interactions [17]. The association between JAML expression and immune features was analyzed in TISIDB to verify the results from TIMER2.0 database analysis.

GEPIA2 Database Analysis

The Gene Expression Profiling Interactive Analysis (GEPIA) is an online database which provides key interactive and customizable functions, including differential expression analysis, correlation analysis, survival analysis, similar gene detection, and dimensionality reduction analysis [18]. The associations of JAML expression with multiple markers for immune cells were investigated in the GEPIA2 database.

Statistical Analysis

The *t* test was used to analyze the measurement data if the observed variables were normally distributed. Otherwise, the

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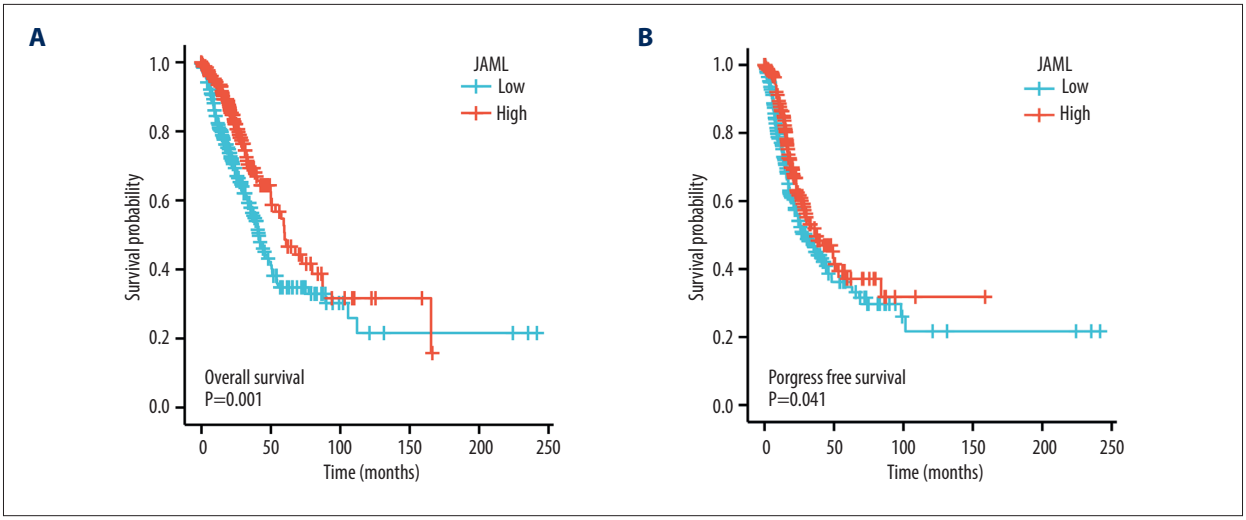

Figure 5. Kaplan-Meier survival curves for (**A**) overall survival (OS) and (**B**) progression-free survival (PFS) of the LUAD patients with high and low JAML expression level. The figure was created using R statistical software (version 3.6.3).

Table 2. Cox regression analysis of JAML and clinicopathologic characteristics with survival outcomes in LUAD.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Overall survival						
Age (>65 vs ≤65)	1.223	0.916-1.635	0.172			
Gender (Male vs Female)	1.070	0.803-1.426	0.642			
Smoking history (Yes vs No)	0.894	0.592-1.348	0.591			
T stage (T2 & T3 & T4 vs T1)	1.728	1.229-2.431	0.002	1.642	1.050-2.568	0.030
N stage (N1 & N2 & N3 vs N0)	2.601	1.944-3.480	<0.001	1.837	1.029-3.280	0.040
M stage (M1 vs M0)	2.136	1.248-3.653	0.006	1.413	0.765-2.610	0.270
Pathologic stage (Stage II & Stage III & Stage IV vs Stage I)	2.933	2.173-3.958	<0.001	1.435	0.769-2.677	0.257
JAML (High vs Low)	0.618	0.460-0.831	0.001	0.706	0.500-0.997	0.048
Progress free survival						
Age (>65 vs ≤65)	1.023	0.784-1.335	0.867			
Gender (Male vs Female)	1.172	0.901-1.526	0.236			
Smoking history (Yes vs No)	0.968	0.658-1.426	0.870			
T stage (T2 & T3 & T4 vs T1)	1.882	1.379-2.570	<0.001	1.509	1.090-2.090	0.013
N stage (N1 & N2 & N3 vs N0)	1.512	1.152-1.984	0.003	0.851	0.562-1.288	0.445
M stage (M1 vs M0)	1.513	0.855-2.676	0.155			
Pathologic stage (Stage II & Stage III & Stage IV vs Stage I)	1.960	1.502-2.557	<0.001	1.851	1.221-2.806	0.004
JAML (High vs Low)	0.758	0.581-0.989	0.041	0.846	0.644-1.111	0.229

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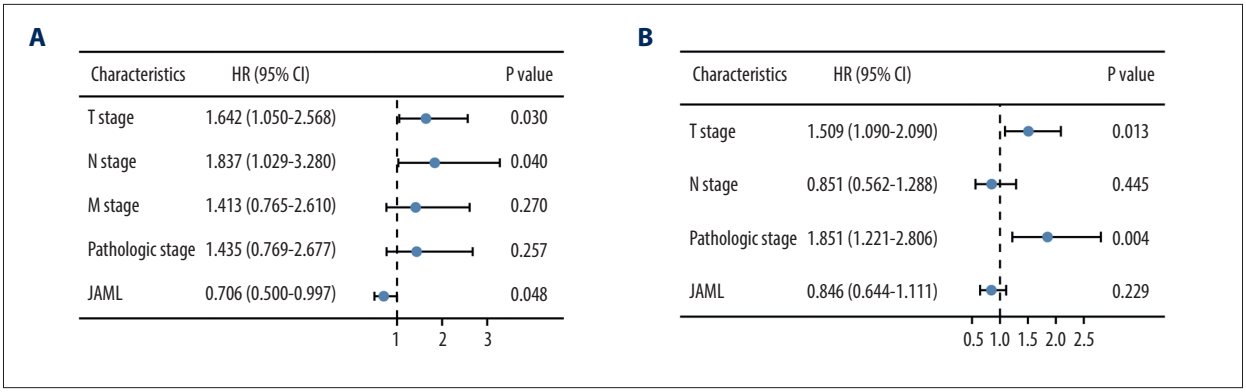

Figure 6. Multivariate Cox regression analysis of JAML expression and clinicopathologic characteristics with (**A**) overall survival (OS) and (**B**) progression-free survival (PFS) in LUAD. The figure was created using R statistical software (version 3.6.3).

Mann-Whitney U test was used. The receiver operating characteristic (ROC) curve was used to explore the diagnostic value of JAML expression for LUAD. The patients were divided into 2 groups according to the median expression of JAML. Kaplan-Meier method and the log-rank test were performed to analyze the impact of JAML expression on overall survival (OS) and progression-free survival (PFS). Cox regression analysis was performed to determine the degree of contribution of JAML expression on survival outcomes. All the above analyses were conducted using R statistical software (version 3.6.3) and SPSS software (version 24.0). Statistical significance was set at P value <0.05 (All P values presented were 2-sided).

Results

Decreased JAML Expression in LUAD

The baseline characteristics of the patients with LUAD are presented in **Table 1**. The JAML expression was significantly lower in LUAD samples in comparison to normal tissue samples in TCGA database (P<0.001, **Figure 1A**). The ROC curve showed the potential diagnostic value of JAML expression for LUAD (AUC 0.956, 95% CI 0.937-0.975) (**Figure 1B**). The analyses of datasets (GSE10799, GSE27262, GSE40791, and GSE118370) from the GEO database verified the decreased expression of JAML in LUAD compared to normal tissues (**Figure 2A-2D**). Correspondingly, the expression of JAML protein was downregulated in LUAD tissue in comparison to that in normal tissue in the Human Protein Atlas (**Supplementary Figure 1**).

Associations Between JAML Expression and Clinicopathologic Characteristics

The associations between JAML expression and clinicopathologic characteristics were analyzed to explore the role of JAML in LUAD progress. The results showed no significant association between JAML expression and age (**Figure 3A**), with lower expression of JAML in males and smokers (P=0.003 and 0.019, respectively, **Figure 3B, 3C**). T1 stage had higher expression of JAML than T2 and T3 stage (P=0.001 and 0.042, respectively), but the differential expression was not observed in T4 stage (**Figure 4A**). In addition, JAML expression decreased in positive N stage (N1, N2, and N3) and advanced pathologic stage (Stage III and IV) compared to N0 and early pathologic stage (Stage I and II) (P=0.021 and 0.006, respectively, **Figure 4B, 4D**), but JAML expression was not significantly associated with M stage (**Figure 4C**).

Low JAML Expression Showing Poor Survival Outcomes

Survival analyses by Kaplan-Meier method and the log-rank test showed that the patients with low JAML expression were correlated with inferior OS (P=0.001) and PFS (P=0.041) (**Figure 5A, 5B**). Univariate Cox regression analysis demonstrated that JAML expression was the significant factor for OS (HR 0.618, 95% CI 0.460-0.831) and PFS (HR 0.758, 95% CI 0.581-0.989) (**Table 2**). Multivariate Cox regression analysis proved that high JAML expression was the independent protective factor for OS (HR 0.706, 95% CI 0.500-0.997, P=0.048) (**Figure 6**).

Interaction Analysis of JAML in LUAD

The LinkFinder module in the LinkedOmics database was used to explore the co-expression pattern of JAML in LUAD. The number of observations in the search dataset was 515. A total of 10 820 genes (red dots) were positively correlated with JAML and 9168 genes (green dots) were negatively correlated (**Supplementary Figure 2**). The top 50 genes that were positively associated with JAML are presented in **Figure 7A** and the top 50 genes negatively associated with JAML are presented in **Figure 7B**. These genes are listed in **Supplementary Tables 1 and 2**, respectively.

In the LinkInterpreter module, GO term annotation showed that co-expressed genes of JAML were mainly involved in

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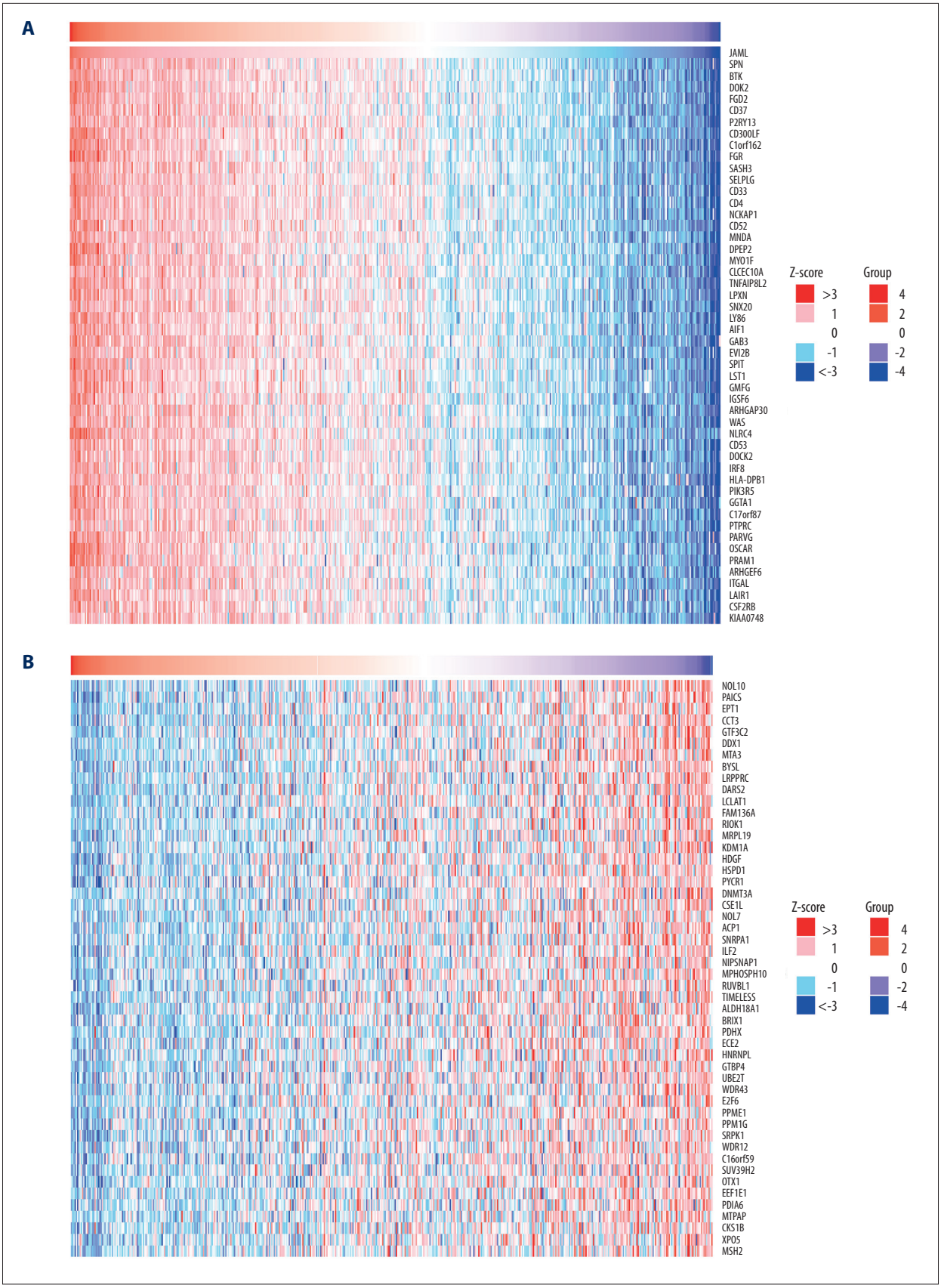

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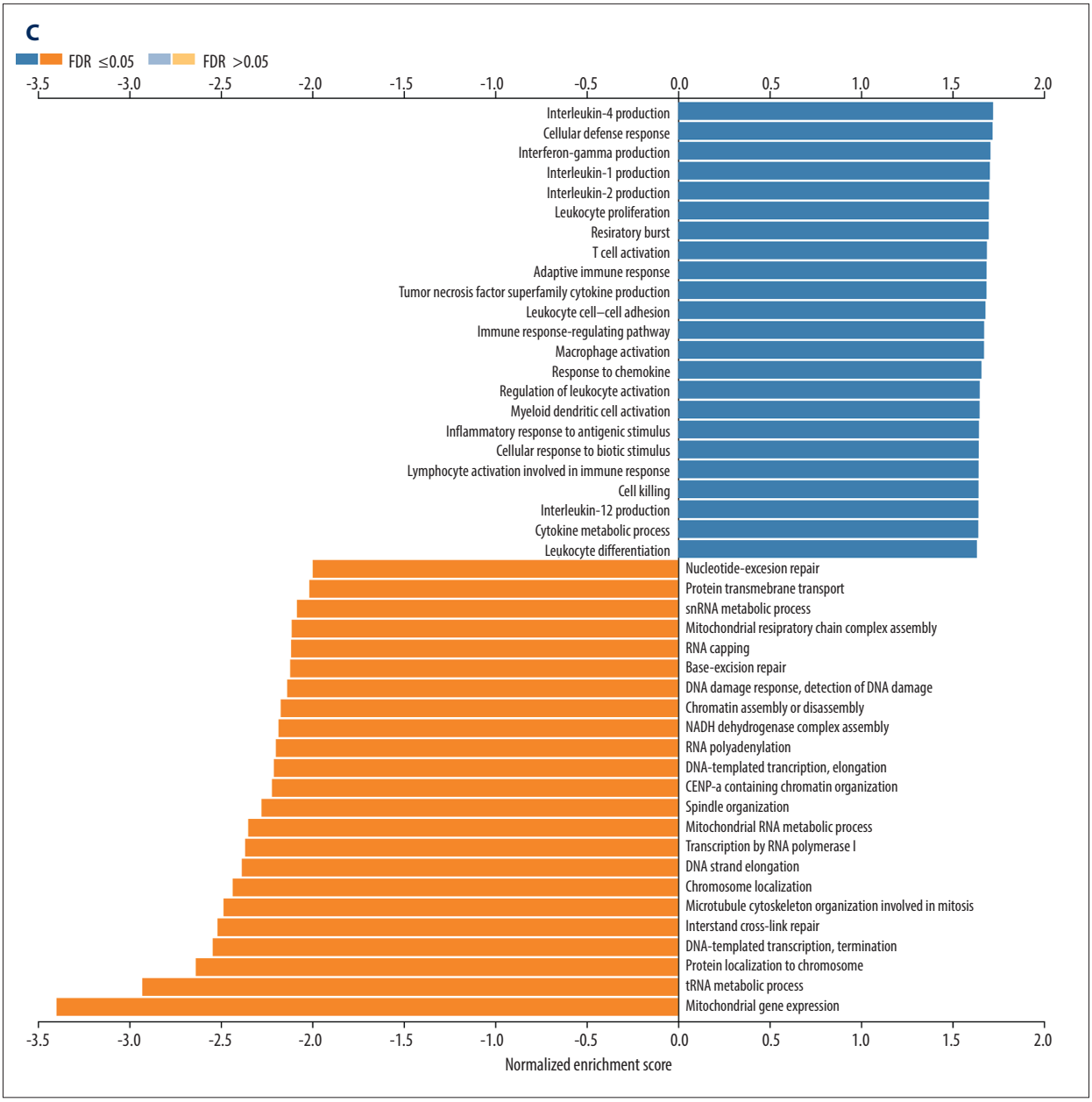

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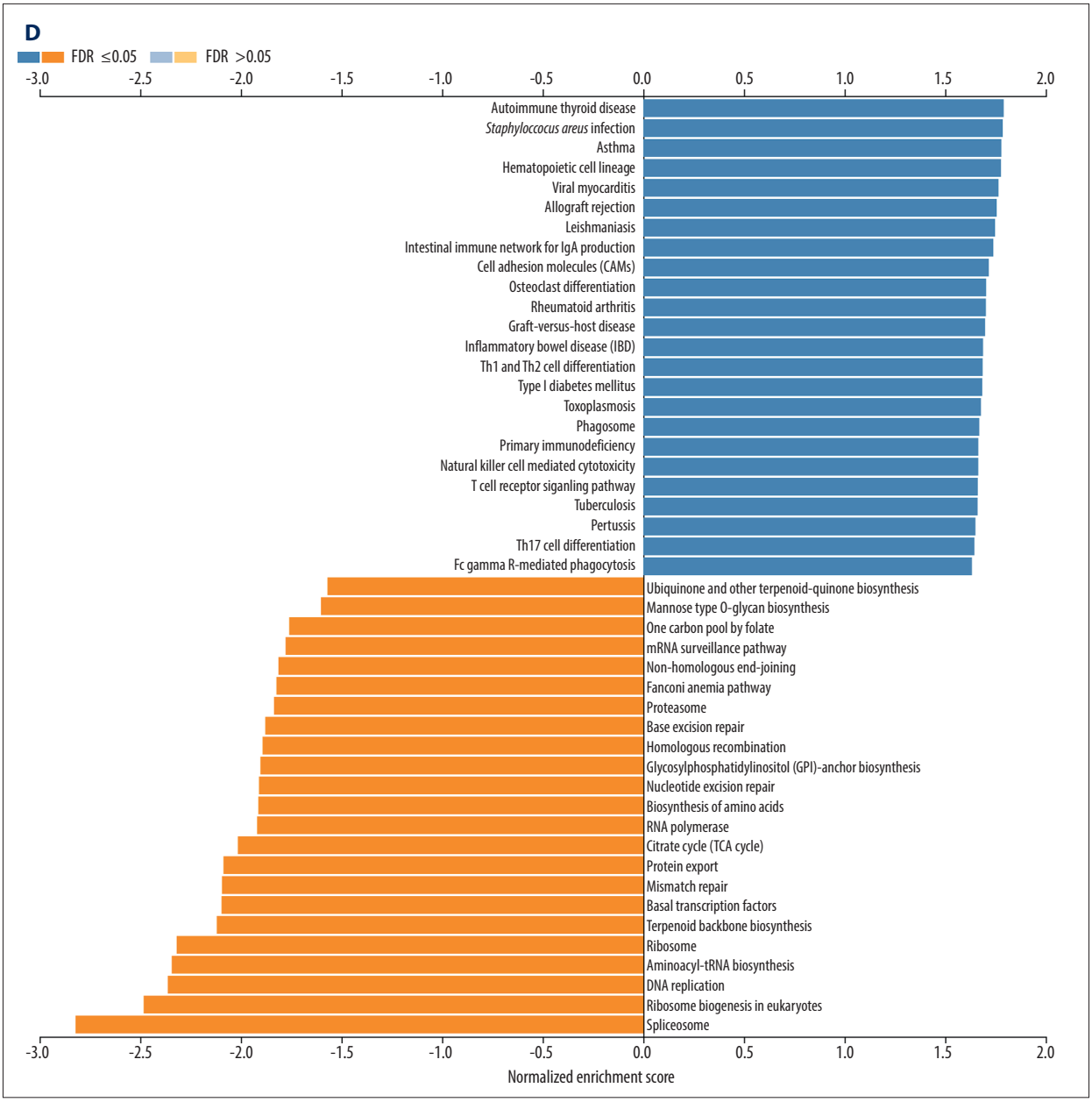

Figure 7. The co-expression genes with JAML in LUAD from the LinkedOmics database. (**A, B**) Heat maps of top 50 genes positively and negatively correlated with JAML in LUAD, respectively. (**C, D**) GO annotations and KEGG pathways of JAML in LUAD. The figure was created using the LinkedOmics database (http://www.linkedomics.org).

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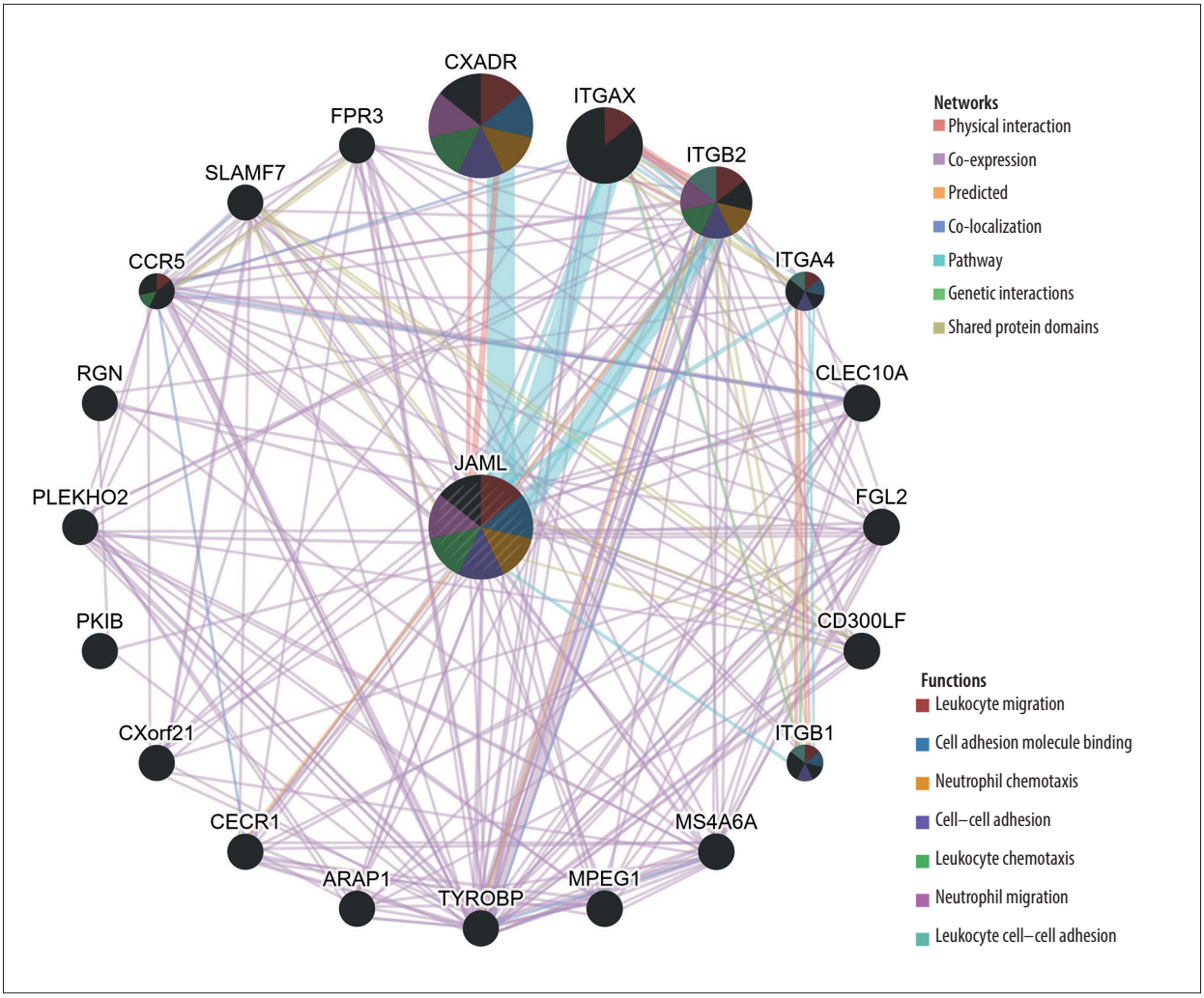

Figure 8. Protein–protein interaction network of JAML. The figure was created using the GeneMANIA database (http://genemania.org).

interleukin-4 production, cellular defense response, interferon-gamma production, interleukin-1 production, interleukin-2 production, leukocyte proliferation, T cell activation, adaptive immune response, leukocyte cell-cell adhesion, and immune response-regulation signaling pathway (**Figure 7C**). KEGG pathway analysis indicated enrichment in autoimmune thyroid disease, *Staphylococcus aureus* infection, asthma, hematopoietic cell lineage, viral myocarditis, allograft rejection, intestinal immune network for IgA production, cell adhesion molecules, and Th1 and Th2 cell differentiation (**Figure 7D**).

The results from GeneMANIA database analysis revealed that the functions of JAML and their associated molecules were primarily related to leukocyte and neutrophil migration, cell adhesion molecule binding, neutrophil and leukocyte chemotaxis, and leukocyte cell-cell adhesion (**Figure 8**).

Correlations of JAML Expression with Immune Infiltrates

The correlation of JAML expression with immune cell infiltration was explored in the TIMER2.0 database. The result showed that JAML expression was significantly and positively associated with the infiltrating levels of CD8+ T cells, CD4+ T cells, B cells, dendritic cells, macrophages, and neutrophils (**Figure 9**). In TISIDB, JAML expression was also correlated with abundance of activated CD8+ T cells, activated CD4+ T cells, activated B cells, activated dendritic cells, macrophages, and neutrophils (**Figure 10**).

To further investigate the relationship between JAML and diverse immune infiltrating cells, the correlations between JAML and immune marker sets of immune cells in LUAD were analyzed in the GEPIA2 database. We found that the expression levels of most marker sets marking different T cells, B cell, regulatory T cell (Treg), tumor-associated macrophage (TAM), monocytes, neutrophils, and dendritic cell (DC) had significant

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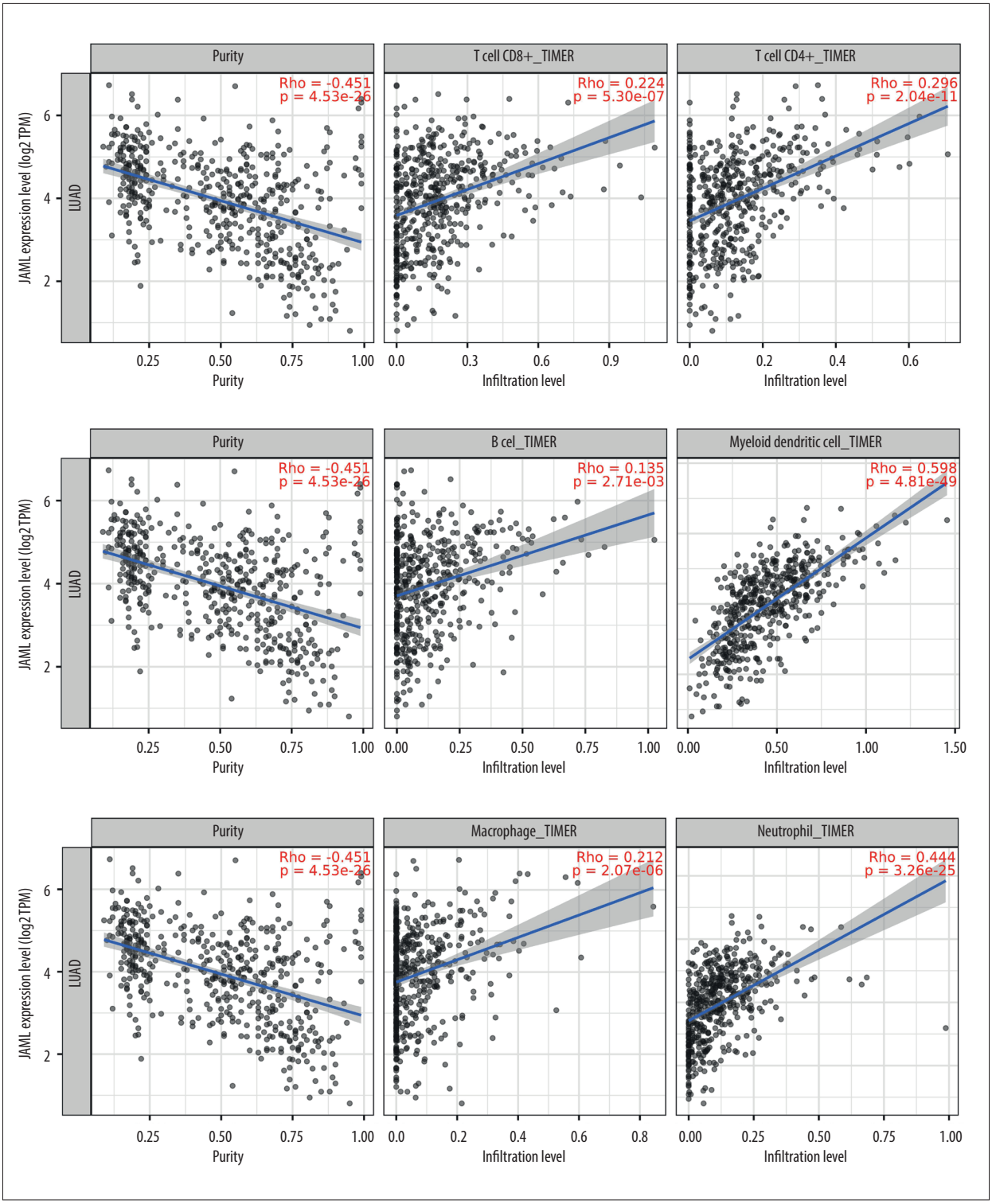

Figure 9. Correlation of JAML expression with immune infiltration in LUAD from the TIMER2.0 database. The figure was created using the TIMER2.0 database (http://timer.cistrome.org/).

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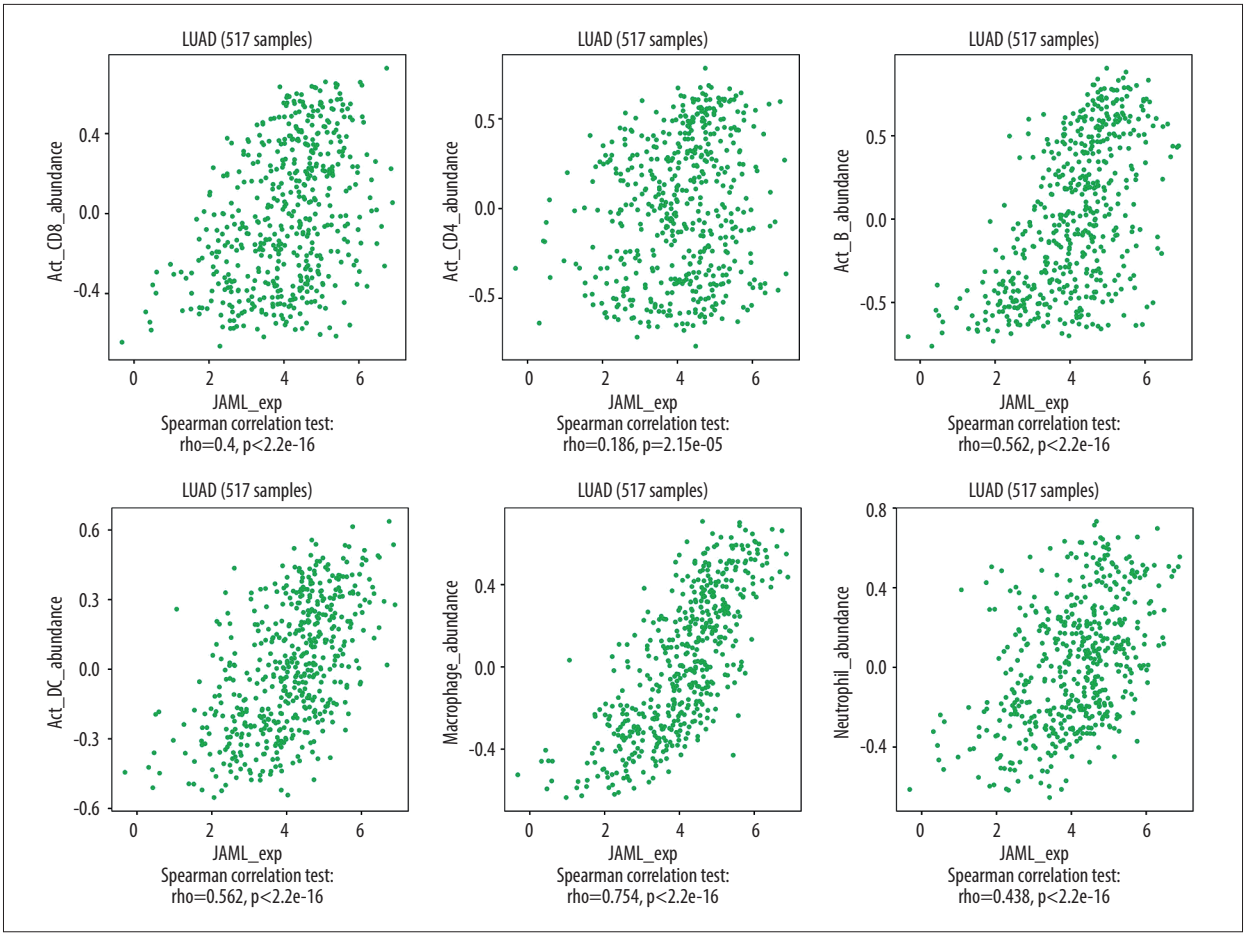

Figure 10. Correlation of JAML expression with immune infiltration in LUAD from the TISIDB. The figure was created using TISIDB (http://cis.hku.hk/TISIDB/index.php).

correlations with JAML expression in LUAD (**Table 3**). Marker genes of T cell exhaustion also had a positive correlation with JAML expression, especially TIM-3.

Discussion

Tumorigenesis involves a succession of complex genetic alterations, and avoiding immune destruction is one of the critical processes [19]. T cell infiltration is widely accepted as a key component of adaptive cancer immune and tumor-infiltrating lymphocytes within the tumor microenvironment and are considered prognostic markers in various cancers [20,21]. JAMs are intercellular adhesion molecules that importantly participate in the transmigration of monocytes, neutrophils, and some T cells through homophilic and heterophilic interactions [22]. Increasing evidence suggests that JAM family members could have potential clinical relevance in cancer development and function as tumor suppressors [23,24]. JAML has been reported as a new JAM family member, and its role in LUAD has not yet been fully elucidated.

This study explored the effect of JAML expression on the progress and prognosis of LUAD on the basis of various public databases. By analyzing the data from TCGA and GEO databases, we found that LUAD samples had lower JAML expression compared to normal tissue samples. Decreased JAML expression was observed in advanced T stage, N stage, and pathologic stage, while the differential expression was not significant in T4 stage and M stage. In addition, the survival analysis revealed that high expression of JAML in LUAD had favorable OS and PFS in comparison to low expression. Cox regression analysis further proved the protective role of high JAML expression in OS. These results suggested that JAML is closely correlated with LUAD tumorigenesis and progression and might act as a tumor suppressor. Two recent bioinformatics studies have also demonstrated that JAML is one of the favorable genes in LUAD, and low JAML expression could increase lung cancer risk [25,26]. However, its role in the tumor immune microenvironment was unknown.

Previous studies indicated that JAML plays an important role in γδ T cell activation and tissue homeostasis [27,28]. JAML

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Table 3. Correlation analysis between JAML and markers of immune cells in GEPIA.

Cell type	Gene marker	Normal		Tumor	
		R	P	R	P
B cell	CD19	0.051	0.7	0.26	5.1e-09
	CD79A	0.034	0.8	0.17	0.00019
CD8+ T cell	CD8A	0.0034	0.98	0.26	4.4e-09
	CD8B	0.046	0.73	0.14	0.0022
Tfh	BCL6	-7e-04	1	0.11	0.019
	IL21	-0.049	0.71	0.24	9.5e-08
Th1	TBX21	-0.096	0.47	0.095	0.036
	STAT4	-0.023	0.86	0.27	8.2e-10
	STAT1	-0.02	0.88	0.14	0.0016
	IFNG	-0.011	0.94	0.19	4.2e-05
	TNF	0.15	0.26	0.37	0
Th2	GATA3	-0.077	0.56	-0.0012	0.98
	IL13	-0.1	0.44	0.19	1.7e-05
	STAT6	0.11	0.41	0.31	3.8e-12
	STAT5A	0.5	5.5e-05	0.62	0
Th17	STAT3	-0.0029	0.98	0.078	0.085
	IL17A	0.079	0.55	0.12	0.0085
Treg	FOXP3	0.11	0.42	0.47	0
	STAT5B	-0.077	0.56	0.36	2.2e-16
	CCR8	0.14	0.3	0.48	0
	TGFB1	0.51	3.8e-05	0.35	3.1e-15
M1	NOS2	-0.24	0.065	-0.022	0.63
	IRF5	0.79	1e-13	0.42	0
	PTGS2	-0.086	0.52	-0.14	0.0029
M2	CD163	0.29	0.027	0.39	0
	VSIG4	0.68	4.3e-09	0.64	0
	MS4A4A	0.7	5.1e-10	0.6	0
TAM	CCL2	-0.039	0.77	0.2	7.4e-06
	CD68	0.66	1.2e-08	0.61	0
	IL10	-0.044	0.74	0.4	0
Monocyte	CD86	0.45	0.00037	0.64	0
	CD115	0.49	7.6e-05	0.64	0

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Table 3 continued. Correlation analysis between JAML and markers of immune cells in GEPIA.

Cell type	Gene marker	Normal		Tumor	
		R	P	R	P
Neutrophil	CD66b	0.057	0.67	0.27	1.5e-09
	CCR7	0.097	0.47	0.46	0
	CD11b	0.6	5e-07	0.72	0
Natural killer cell	XCL1	-0.18	0.17	-0.031	0.49
	CD7	0.031	0.81	0.1	0.028
	KIR3DL1	0.045	0.73	0.069	0.13
Dendritic cell	CD1C	-0.0066	0.96	0.53	0
	CD141	-0.11	0.4	0.18	4.9e-05
	CD11c	0.8	2.6e-14	0.65	0
T cell exhaustion	PDCD1	0.052	0.7	0.25	3.2e-08
	CTLA4	0.055	0.68	0.37	0
	LAG3	-0.097	0.47	0.11	0.013
	TIM-3	0.36	0.0047	0.62	0

Tfh – follicular helper T cell; Th – T helper cell; Treg – regulatory T cell; TAM – tumor-associated macrophage.

was also identified as a crucial component of DC migration and can promote response to DC-based cancer immunotherapy [29]. Similarly, our study demonstrated the significant association between JAML and the tumor immune microenvironment. LinkedOmics database analysis pointed out that most co-expressed genes with JAML had obvious links to immune-related pathways, which agrees with the result of GeneMANIA database analysis. Moreover, JAML expression had a significantly consistent correlation with the infiltration levels of CD8+ T cells, CD4+ T cells, B cells, dendritic cells, macrophages, and neutrophils. The correlation between JAML expression and the marker genes of immune cells also suggests the role of JAML in recruitment and regulation of immune infiltrating cells. First, JAML expression was associated with most markers of T helper cells, which suggested that JAML could potentially regulate T cell functions in LUAD. Second, significant correlations were also found between JAML expression and markers of monocytes. Intriguingly, JAML expression was positively correlated with the expression of Treg and T cell exhaustion markers, which contributed to the formation of an immunosuppressive microenvironment. A recent report demonstrated that high frequency of circulating Tregs was associated with a favorable response to ICIs therapy [30]. In addition, M2 macrophage markers such as VSIG4 and MS4A4A showed strong correlations with JAML expression, while M1 macrophage markers showed weak correlations. These results revealed the potential role of JAML in polarization of TAM. Taken together, our findings suggest that JAML is specifically correlated with immune infiltrating cells and plays a vital role in immune regulation in the LUAD microenvironment, but the interaction between JAML and the immune microenvironment is complicated, and does not just lead to a completely positive or negative effect.

There were several limitations in our study. First, all the data analyzed in our study were obtained from online databases, and data heterogeneity was difficult to avoid. Cox regression analysis showed M stage was not significantly associated with PFS. This discrepancy might be caused by data heterogeneity and limited samples. Second, the role of JAML in regulating immune microenvironment seemed to be complicated, and the details of mechanisms by which JAML regulates T cell functions remain unknown. Finally, our results need to be validated by further studies.

Conclusions

Our preliminary findings showed that JAML was downregulated in LUAD, and low JAML expression was associated with tumor progression and poor prognosis. High JAML expression was an independent protective factor for OS and could be considered as a prognostic biomarker. Because of the significant association between JAML expression and the infiltration of diverse immune cells, JAML might play important roles in regulation of the immune microenvironment in LUAD.

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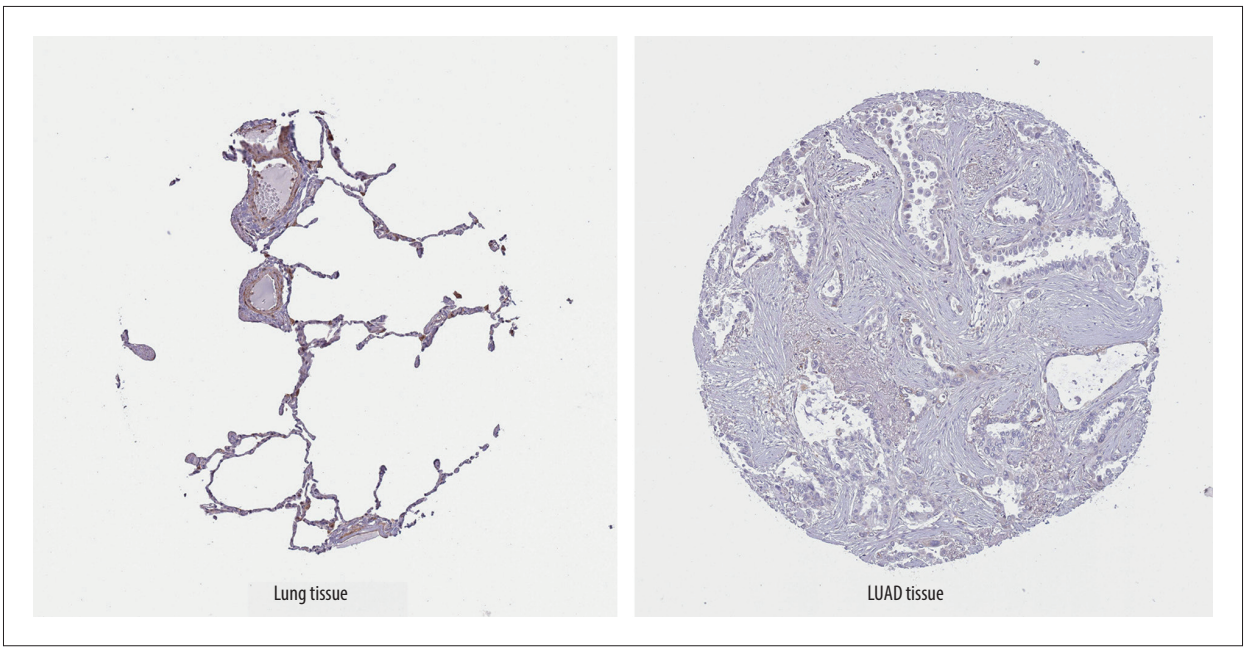
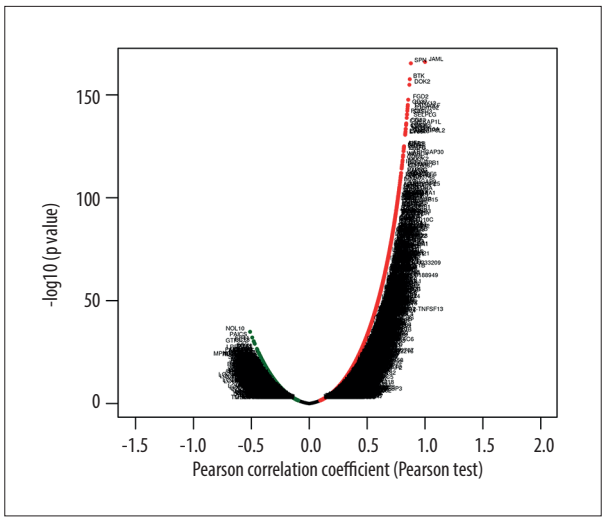
Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Supplementary Materials



Supplementary Figure 1. The level of JAML protein in LUAD tissue was lower than that in normal tissue in the Human Protein Atlas (Antibody HPA047919, 10X). The figure was download in Human Protein Atlas (https://www.proteinatlas.org/).



Supplementary Figure 2. All genes significantly associated with JAML as distinguished by Pearson test in LUAD from the LinkedOmics database. The figure was created using the LinkedOmics database (http://www.linkedomics.org).

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Supplementary Table 1. The top 50 genes that were positively associated with JAML.

Gene	Statistic	P value	FDR
SPN	0.87776	4.59E-166	4.59E-162
BTK	0.868331	2.42E-158	1.61E-154
DOK2	0.864833	1.25E-155	6.25E-152
FGD2	0.854968	2.28E-148	9.11E-145
CD37	0.851339	7.85E-146	2.61E-142
P2RY13	0.850216	4.64E-145	1.32E-141
CD300LF	0.848648	5.41E-144	1.35E-140
C1orf162	0.847151	5.49E-143	1.22E-139
FGR	0.844632	2.57E-141	5.14E-138
SASH3	0.844313	4.16E-141	7.56E-138
SELPLG	0.841924	1.49E-139	2.48E-136
CD33	0.837684	7.36E-137	1.13E-133
CD4	0.837089	1.73E-136	2.47E-133
NCKAP1L	0.836384	4.75E-136	6.33E-133
CD52	0.833422	3.14E-134	3.93E-131
MNDA	0.833371	3.37E-134	3.97E-131
DPEP2	0.833195	4.32E-134	4.79E-131
MYO1F	0.831197	6.93E-133	7.29E-130
CLEC10A	0.830327	2.30E-132	2.30E-129
TNFAIP8L2	0.82949	7.23E-132	6.88E-129
LPXN	0.829277	9.66E-132	8.78E-129
SNX20	0.828918	1.58E-131	1.37E-128
LY86	0.828598	2.43E-131	2.03E-128
AIF1	0.818807	9.59E-126	7.67E-123
GAB3	0.818328	1.76E-125	1.36E-122
EVI2B	0.818197	2.08E-125	1.54E-122
SPI1	0.817413	5.64E-125	4.02E-122
LST1	0.816492	1.80E-124	1.24E-121
GMFG	0.814586	1.95E-123	1.30E-120
IGSF6	0.814375	2.54E-123	1.64E-120
ARHGAP30	0.810786	2.08E-121	1.30E-118
WAS	0.809297	1.26E-120	7.64E-118
NLRC4	0.809137	1.53E-120	8.99E-118
CD53	0.806027	6.24E-119	3.56E-116
DOCK2	0.804383	4.31E-118	2.39E-115
IRF8	0.801908	7.66E-117	4.14E-114
HLA-DPB1	0.800373	4.46E-116	2.35E-113
PIK3R5	0.799322	1.48E-115	7.59E-113
GGTA1	0.798294	4.74E-115	2.37E-112
C17orf87	0.798012	6.52E-115	3.18E-112
PTPRC	0.793513	9.81E-113	4.57E-110
PARVG	0.793511	9.84E-113	4.57E-110
OSCAR	0.790969	1.58E-111	7.18E-109
PRAM1	0.790017	4.43E-111	1.97E-108
ARHGEF6	0.788939	1.41E-110	6.15E-108
ITGAL	0.788848	1.56E-110	6.63E-108
LAIR1	0.788761	1.71E-110	7.13E-108
CSF2RB	0.788263	2.92E-110	1.19E-107
KIAA0748	0.786265	2.44E-109	9.76E-107
SPN	0.87776	4.59E-166	4.59E-162

FDR – false discovery rate. FDR is calculated by Benjamini-Hochberg method.

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Supplementary Table 2. The top 50 genes that were negatively associated with JAML.

Gene	Statistic	P value	FDR
NOL10	-0.51092951	1.37E-35	3.83E-34
PAICS	-0.492426981	8.24E-33	2.10E-31
EPT1	-0.479806564	5.21E-31	1.23E-29
CCT3	-0.473560742	3.81E-30	8.72E-29
GTF3C2	-0.470759665	9.17E-30	2.07E-28
DDX1	-0.451984988	2.70E-27	5.51E-26
MTA3	-0.450196909	4.56E-27	9.22E-26
BYSL	-0.449148965	6.19E-27	1.24E-25
LRPPRC	-0.446968299	1.16E-26	2.30E-25
DARS2	-0.438029268	1.48E-25	2.73E-24
LCLAT1	-0.437012796	1.97E-25	3.62E-24
FAM136A	-0.435259685	3.21E-25	5.84E-24
RIOK1	-0.43496507	3.48E-25	6.32E-24
MRPL19	-0.434044684	4.49E-25	8.07E-24
KDM1A	-0.433790315	4.82E-25	8.62E-24
HDGF	-0.433363013	5.42E-25	9.66E-24
HSPD1	-0.432022959	7.84E-25	1.39E-23
PYCR1	-0.42743364	2.74E-24	4.74E-23
DNMT3A	-0.427429731	2.74E-24	4.74E-23
CSE1L	-0.42684456	3.22E-24	5.54E-23
NOL7	-0.426054068	3.98E-24	6.80E-23
ACP1	-0.424019031	6.87E-24	1.15E-22
SNRPA1	-0.423378865	8.15E-24	1.35E-22
ILF2	-0.422186973	1.12E-23	1.85E-22
NIPSNAP1	-0.421238332	1.44E-23	2.37E-22
MPHOSPH10	-0.419935807	2.03E-23	3.31E-22
RUVBL1	-0.418151527	3.25E-23	5.27E-22
TIMELESS	-0.418075487	3.32E-23	5.37E-22
ALDH18A1	-0.417346714	4.01E-23	6.48E-22
BRIX1	-0.416611963	4.86E-23	7.79E-22
PDHX	-0.415261828	6.91E-23	1.10E-21
ECE2	-0.412297009	1.49E-22	2.31E-21
HNRNPL	-0.411482989	1.83E-22	2.84E-21
GTPBP4	-0.410508562	2.35E-22	3.61E-21
UBE2T	-0.410446562	2.39E-22	3.66E-21
WDR43	-0.409903728	2.75E-22	4.18E-21
E2F6	-0.40926218	3.23E-22	4.89E-21
PPME1	-0.409126497	3.35E-22	5.06E-21
PPM1G	-0.408779249	3.66E-22	5.50E-21
SRPK1	-0.406311958	6.83E-22	1.01E-20
WDR12	-0.406101292	7.20E-22	1.06E-20
C16orf59	-0.405757077	7.85E-22	1.16E-20
SUV39H2	-0.404666375	1.03E-21	1.51E-20
OTX1	-0.403071134	1.54E-21	2.24E-20
EEF1E1	-0.402243284	1.89E-21	2.74E-20
PDIA6	-0.401305041	2.39E-21	3.43E-20
MTPAP	-0.401274609	2.40E-21	3.46E-20
CKS1B	-0.401157274	2.48E-21	3.55E-20
XPO5	-0.401034671	2.55E-21	3.66E-20
MSH2	-0.400699429	2.77E-21	3.96E-20

FDR – false discovery rate. FDR is calculated by Benjamini-Hochberg method.

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