Increased GOLM1 Expression Independently Predicts Unfavorable Overall Survival and Recurrence-Free Survival in Lung Adenocarcinoma

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Abstract

Golgi membrane protein 1 (GOLM1) is a transmembrane glycoprotein of the Golgi cisternae, which is implicated in carcinogenesis of multiple types of cancer. In this study, using data from the Gene Expression Omnibus and The Cancer Genome Atlas, we compared the expression of *GOLM1* in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) and studied its prognostic value in terms of overall survival (OS) and recurrence-free survival (RFS) in these 2 subtypes of non-small cell lung cancer (NSCLC). Results showed that *GOLM1* was significantly upregulated in both LUAD and LUSC tissues compared to the normal controls. However, *GOLM1* expression was higher in LUAD tissues than in LUSC tissues. More importantly, using over 10 years' survival data from 502 patients with LUAD and 494 patients with LUSC, we found that high *GOLM1* expression was associated with unfavorable OS and RFS in patients with LUAD, but not in patients with LUSC. The following univariate and multivariate analyses confirmed that increased *GOLM1* expression was an independent prognostic indicator of poor OS (hazard ratio [HR]: 1.30, 95% confidence interval [CI]: 1.11-1.54, $P = .002$) and RFS (HR: 1.37, 95% CI: 1.14-1.64, $P = .001$) in patients with LUAD. Of 511 cases with LUAD, 248 (48.5%) had heterozygous loss (−1), while 28 (5.5%) of 511 cases with LUAD had low-level copy gain (+1). In addition, we also found that the methylation status of 1 CpG site (chr9: 88,694,942-88,694,944) showed a weak negative correlation with *GOLM1* expression (Pearson $r = -0.25$). Based on these findings, we infer that *GOLM1* might serve as a valuable prognostic biomarker in LUAD, but not in LUSC. In addition, DNA copy number alterations and methylation might be 2 important mechanisms of dysregulated *GOLM1* in LUAD.

Keywords

GOLM1, lung adenocarcinoma, prognosis, copy number, methylation

Introduction

Golgi membrane protein 1 (GOLM1) is also known as Golgi phosphoprotein 2 or Golgi membrane protein GP73. It is a transmembrane glycoprotein of the Golgi cisternae, which is typically expressed in the epithelial cells of normal human tissues.[1] Since the Golgi apparatus has critical roles in modification and transportation of the proteins, the dysregulation of its associated proteins may result in significantly altered cellular processes and functions.[2]

A series of previous studies observed that *GOLM1* is upregulated in multiple cancers and modulates their malignant behaviors. In prostate cancer, *GOLM1* upregulation can promote cancer cell proliferation, migration, and invasion and inhibit apoptosis via activating the phosphoinositide

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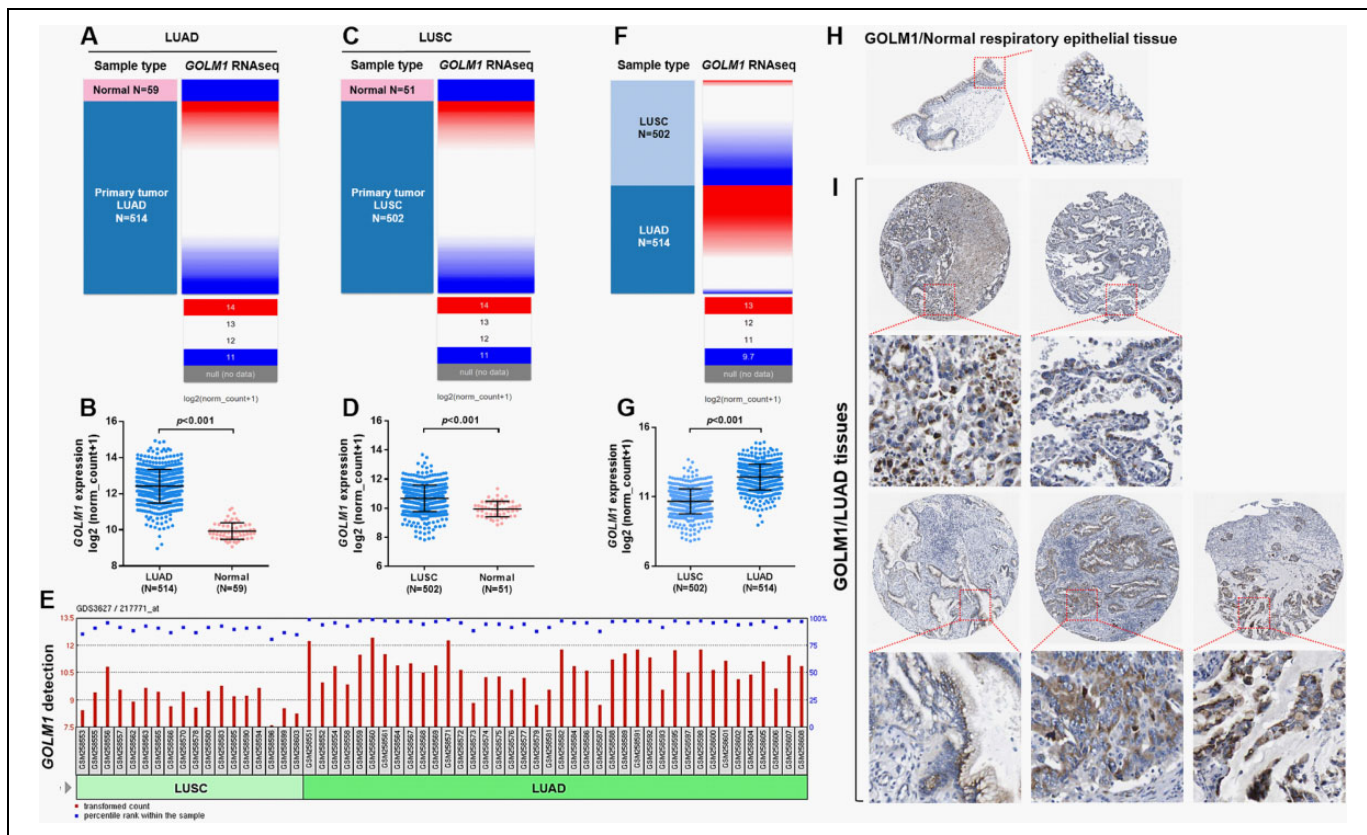Email: thoraciczt@163.com

Figure 1. Golgi membrane protein 1 (*GOLM1*) was significantly upregulated in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) compared to normal lung tissues. A-D, Heatmap (A and C) and plot chart (B and D) of *GOLM1* expression in LUAD (A and B) and LUSC (C and D) tissues compared to their respective normal controls. E, The GOLM1 detection call in 40 cases with LUAD and 18 cases with LUSC. Comparison was performed using data from GSE10245,[15] with GEO2R. F and G, Heatmap (F) and plot chart (G) comparing *GOLM1* expression between LUAD (N = 514) and LUSC (N = 502) cases in The Cancer Genome Atlas (TCGA). H and I, Immunohistochemistry (IHC) staining of *GOLM1* expression in normal respiratory epithelial tissue (H) and in 5 cases of normal LUAD tissues. Images were obtained from http://www.proteinatlas.org/ENSG00000135052-GOLM1/pathology/tissue/lung+cancer#ihc.

3 kinase-Akt-mammalian target of rapamycin (PI3K-AKT-mTOR) signaling[3] and has been considered as a biomarker for detecting prostate cancer and aggressiveness of the disease.[4,5] In hepatocellular carcinoma (HCC), aberrant *GOLM1* expression enhances proliferation and migration of HCC cell lines and growth of xenograft tumors in mice via its regulation of membrane protein trafficking.[6] In addition, it also has certain prognostic value in terms of overall survival (OS) and recurrence-free survival (RFS) in HCC.[7,8]

Recent studies found that *GOLM1* was upregulated in non-small cell lung cancer (NSCLC), and its upregulation was associated with unfavorable clinicopathological features and can promote the proliferation and invasion of NSCLC cells.[9,10] Actually, NSCLC constitutes of 3 subtypes, including lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large cell carcinoma, among which LUAD and LUSC are the dominant subtypes.[11] These 2 subtypes have distinct molecular features and also have different prognostic markers.[12-14] Patients with LUAD had significantly higher serum GOLM1 compared to healthy individuals.[10] Therefore, it is meaningful to explore the prognostic value of *GOLM1*

expression and the mechanisms of its dysregulation in each subtype of NSCLC.

In this study, by using data from The Cancer Genome Atlas (TCGA), we compared the expression of *GOLM1* in LUAD and LUSC and studied its prognostic value in terms of OS and RFS in these 2 subtypes of NSCLC.

Materials and Methods

Data Mining in Gene Expression Omnibus

The microarray data that compared gene expression profiles between LUAD and LUSC were retrieved in Gene Expression Omnibus (GEO) data sets. The expression of *GOLM1* in one previous array (GSE10245),[15] which examined gene expression in 40 LUAD cases and 18 LUSC cases, was examined using GEO2R.

Retrospective Data Mining in TCGA

The level 3 data in TCGA-LUAD and in TCGA-LUSC were downloaded using the UCSC Xena browser (https://xenabrow

ser.net/). These cohorts included over 500 cases of primary LUAD or LUSC, respectively. In TCGA-LUAD, tumor tissues from 514 patients and normal tissues from 59 controls were subjected to RNA-seq. In TCGA-LUSC, tumor tissues from 502 patients and normal tissues from 51 controls were subjected to RNA-seq; 502 of the 514 patients with LUAD and 494 of the 502 patients with LUSC had OS data recorded. Their clinicopathological information, including age at initial pathologic diagnosis, gender, smoking history, nodal status, pathologic stage, residual tumors, the history of radiation therapy/targeted molecular therapy, recurrence status, RFS in days, OS status, and OS in days, was downloaded.

The gene-level thresholded GISTIC2-processed copy number alterations (CNAs) and the DNA methylation status (Illumina (San Diego, California) 450k infinium methylation beadchip) of *GOLM1* were also downloaded. In the methylation beadchip, the methylation status of 6 CpG islands in *GOLM1* DNA was measured; 453 patients with LUAD and 371 patients with LUSC had *GOLM1* DNA CNAs and *GOLM1* RNA expression quantified at the same time.

Immunohistochemistry Staining of GOLM1

Immunohistochemistry (IHC) staining of GOLM1 in normal respiratory epithelial tissues and in LUAD tissues were reviewed using images in the Human Protein Atlas (HPA) (http://www.proteinatlas.org/),[16,17] an online database aiming to map all the human proteins in cells, tissues, and organs.

Data Mining in the Kaplan-Meier Plotter

The association between *GOLM1* expression and OS or first progression-free survival (FPS) in patients with LUAD was also examined by data mining in the Kaplan-Meier plotter, an online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in NSCLC by integrating 1715 samples of 10 independent data sets.[18] The OS and FPS curves were generated by using the optimal cutoff of *GOLM1* expression. The hazard ratio (HR) with 95% confidence intervals (CI) and log-rank *P* value were calculated.

Statistical Analysis

Statistical analysis was conducted using GraphPad Prism 6.0 (GraphPad Inc., La Jolla, California) or SPSS 19.0 software package (SPSS Inc, Chicago, Illinois). Group comparison was performed using Welch unequal variances *t* test. Receiver operating characteristic (ROC) curve analysis for death and recurrence detection was applied to identify the best cutoff (Youden index) for *GOLM1* expression in Kaplan-Meier curves of OS and RFS. Therefore, if no significant difference was observed in OS/RFS under this model, there is no other cutoff that will generate significant results. In brief, the optimal cutoff threshold values were determined at the point on the ROC curve at which Youden index (sensitivity + [100% − specificity]) was maximal. Log-rank test was conducted to examine the
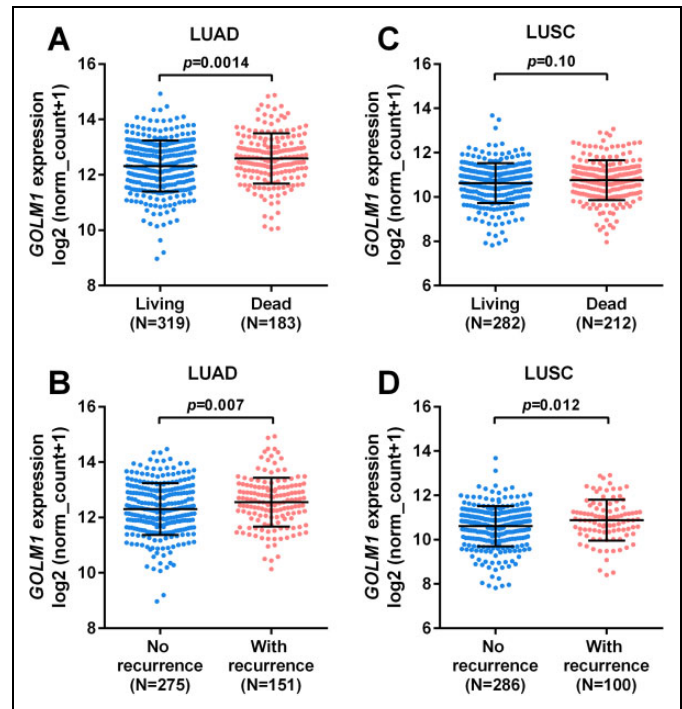

Figure 2. Comparison of Golgi membrane protein 1 (*GOLM1*) expression between the groups with different survival outcomes. A-D, Comparison of *GOLM1* expression between the deceased and the living groups (A and C) and between the groups with or without recurrence (B and D) in patients with lung adenocarcinoma (LUAD; A-B) and in patients with lung squamous cell carcinoma (LUSC; C-D). Survival data were obtained from The Cancer Genome Atlas (TCGA).

significance of the difference between the survival curves. Chi-square tests were used to assess the association between *GOLM1* expression and the clinicopathological parameters. Univariate and multivariate Cox regression analysis was performed to examine the independent prognostic value of *GOLM1* expression in terms of OS and RFS. The *GOLM1* expression was first treated as a continuous variable in univariate and multivariate analysis to avoid the loss of statistical power.[19] Univariate and multivariate analyses were also performed by setting its expression as category variables. Linear regression analysis was performed to assess the correlation between *GOLM1* expression and the methylation status of the CpG islands. *P* < .05 was considered statistically significant.

Results

Golgi Membrane Protein 1 Was Significantly Upregulated in LUAD and LUSC Compared to Normal Lung Tissues

Using RNA-seq data in TCGA, we compared *GOLM1* expression between cancerous and normal lung tissues. Results showed that both LUAD and LUSC tissues (N = 514 and 502, respectively) had significantly elevated *GOLM1* expression compared to their respective normal controls (N = 59 and 51 respectively; Figure 1A–D). Using data from 1 previous
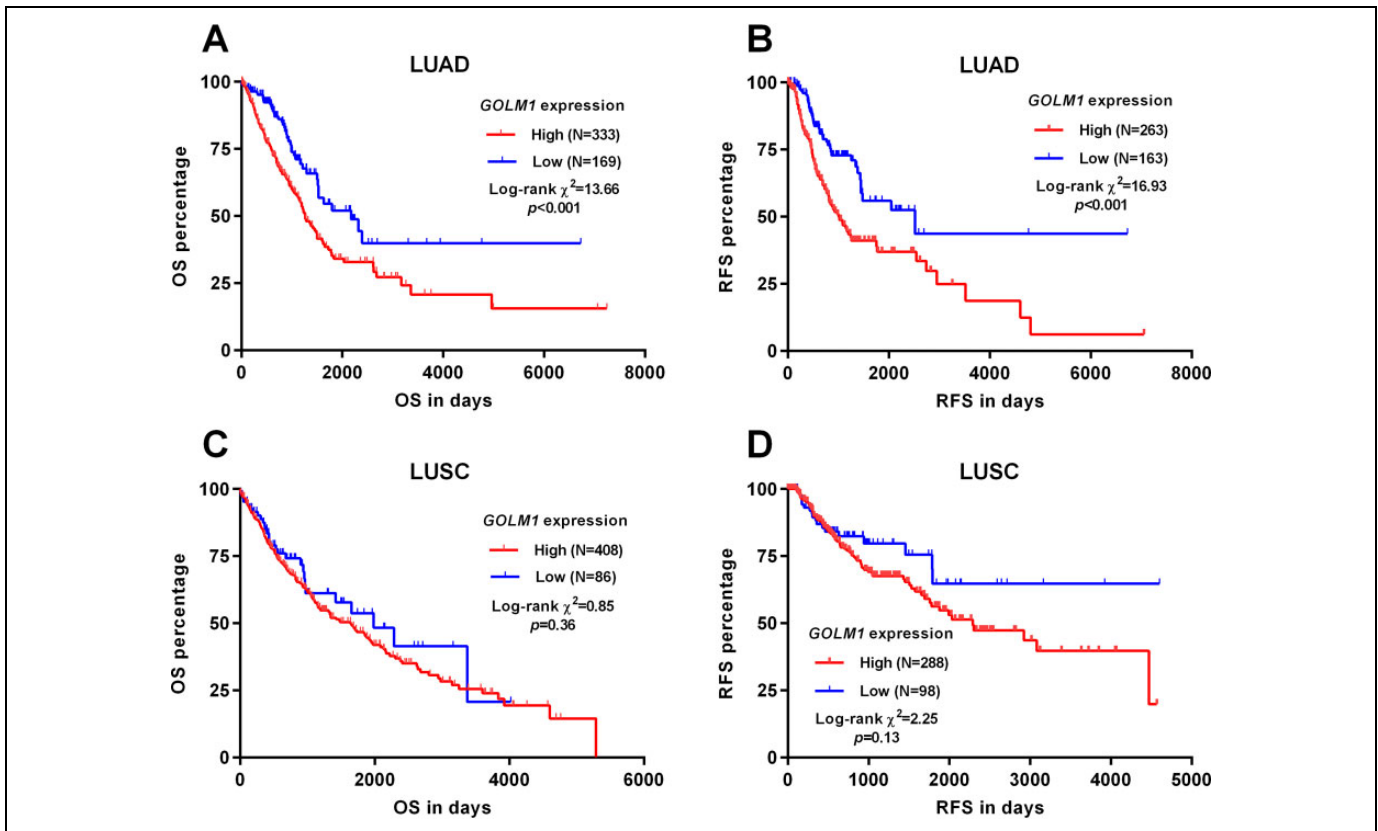
Figure 3. High Golgi membrane protein 1 (*GOLM1*) expression was associated with poor overall survival (OS) and recurrence-free survival (RFS) in patients with lung adenocarcinoma (LUAD), but not in patients with lung squamous cell carcinoma (LUSC). A-D, Kaplan-Meier curves of OS (A and C) and RFS (B and D) in patients with LUAD (A-B) and LUSC (C-D), respectively. Both patients with LUAD and LUSC were divided into high/low *GOLM1* expression group using the best cutoff model. Survival data were obtained from The Cancer Genome Atlas (TCGA).

array (GSE10245) that compared gene expression profiles between 40 cases with LUAD and 18 cases with LUSC, we found that *GOLM1* expression was significantly higher in LUAD tissues compared to LUSC tissues (Figure 1E). Group comparison using RNA-seq data from TCGA also confirmed substantially increased *GOLM1* expression in LUAD compared to LUSC tissues (Figure 1F-G). The IHC staining images in the HPA showed that normal respiratory epithelial tissues had moderate GOLM1 staining in cytoplasm and membrane (Figure 1H). In comparison, in 5 cases of LUAD tissues, nearly all cancer cells had moderate to high GOLM1 staining (Figure 1I).

Comparison of GOLM1 Expression Between the Groups With Different Survival Outcomes

Using OS and RFS as survival indicators, we compared the expression of *GOLM1* in patients with LUAD/LUSC with different survival outcomes. Results showed that in patients with LUAD, *GOLM1* expression was significantly higher in the deceased and recurrence groups compared to their respective control groups ($P = .0014$ and $.007$, respectively; Figure 2A and B). In comparison, no significant difference was observed between the living and dead patients with LUSC (Figure 2C). But the patients with LUSC with disease recurrence had a

significantly higher expression of *GOLM1* compared to the group without recurrence ($P = .012$; Figure 2D).

High GOLM1 Expression Was Associated With Poor OS and RFS in Patients With LUAD, but not in Patients With LUSC

By generating Kaplan-Meier survival curves, we analyzed the association between *GOLM1* expression and OS/RFS in patients with LUAD and LUSC, respectively. Both patients with LUAD and LUSC were divided into high/low *GOLM1* expression group by using the best cutoff model. Results showed that the high *GOLM1* expression group had significantly worse OS ($P < .001$) and RFS ($P < .001$) compared to the low *GOLM1* expression group (Figure 3A and B). In comparison, there was no significant association between *GOLM1* expression and OS or RFS in patients with LUSC ($P = .36$ and .13, respectively; Figure 3C and D).

The association between *GOLM1* expression and the clinicopathological features in patients with LUAD is summarized in Table 1. Chi-square analysis showed that the high *GOLM1* expression group was associated with a significantly higher rate of recurrence (112/275 vs 39/151, $P = .002$) and death (140/333 vs 43/169, $P < .001$), compared to the low *GOLM1*

Table 1. Comparison of the Clinicopathological Parameters Between High and Low *GOLM1* Expression Groups in Patients With LUAD.[a]

Parameters		GOLM1 Expression		χ^2	P Value
		High, N = 333	Low, N = 169		
Age, mean $\pm$ SD		64.77 $\pm$ 9.82	66.42 $\pm$ 10.15		.082
Gender	Female	178	93	0.11	.74
	Male	155	76		
Smoking history	2/3/4/5	282	134	1.80	.18
	1	43	29		
	No data	8	6		
Pathologic stage	III/IV	76	30	1.58	1.26
	I/II	253	135		
	Discrepancy/no data	4	4		
Nodal invasion	N0	208	116	3.40	.07
	N1/2/3	121	46		
	NX/no data	4	7		
Residual tumors	R0	228	108	0.20	.65
	R1/R2	10	6		
	RX/no data	95	55		
Radiation therapy	No	255	133	0.021	.89
	Yes	40	20		
	No data	38	16		
Targeted molecular therapy	No	193	103	0.35	.56
	Yes	102	48		
	No data	38	18		
Recurrence status	No	163	112	9.46	.0021
	Yes	112	39		
	No data	58	18		
Living status	Living	193	126	13.33	<.001
	Dead	140	43		

Abbreviations: GOLM1, Golgi membrane protein; LUAD, lung adenocarcinoma; R0, No residual tumor; R1, Microscopic residual tumor; R2, Macroscopic residual tumor; RX, The presence of residual tumor cannot be assessed; SD, standard deviation.
[a]Smoking history: 1, lifelong nonsmoker; 2, current smoker; 3, current reformed smoker (for >15 years); 4, current reformed smoker (for $\leq$15 years); 5, current reformed smoker (duration not specified).

Table 2. Univariate and Multivariate Analysis of Overall Survival in Patients With LUAD.[a]

Parameters	Univariate Analysis				Multivariate Analysis			
	HR	95% CI		P	HR	95% CI		P
		Lower	Upper			Lower	Upper	
GOLM1 (continuous variable)								
Age (continuous)	1.01	0.99	1.02	.33				
Gender, female vs male	0.94	0.70	1.26	.67				
Smoking history, 2/3/4/5 vs 1	0.91	0.60	1.38	.66				
Pathologic stage III/IV vs I/II	2.65	1.94	3.61	<.001	1.74	1.20	2.52	.003
Nodal status, positive vs negative	2.57	1.91	3.45	<.001	1.87	1.32	2.65	<.001
Residual tumors, yes vs no	3.94	2.20	7.03	<.001	3.28	1.80	5.97	<.001
GOLM1	1.30	1.11	1.53	.001	1.30	1.11	1.54	.002
GOLM1 (category variables)								
Age (continuous)	1.01	0.99	1.02	.33				
Gender, female vs male	0.94	0.70	1.26	.67				
Smoking history, 2/3/4/5 vs 1	0.91	0.60	1.38	.66				
Pathologic stage III/IV vs I/II	2.65	1.94	3.61	<.001	1.75	1.21	2.53	.003
Nodal status, positive vs negative	2.57	1.91	3.45	<.001	1.85	1.30	2.61	.001
Residual tumors, yes vs no	3.94	2.20	7.03	<.001	3.28	1.81	5.94	<.001
GOLM1	1.90	1.35	2.67	<.001	1.87	1.32	2.66	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; GOLM1, Golgi membrane protein 1; LUAD, lung adenocarcinoma.
[a]Pathologic stage, nodal status, residual tumors, and GOLM1 expression were included in multivariable analysis.

Table 3. Univariate and Multivariate Analysis of Recurrence-Free Survival in Patients With LUAD.[a]

Parameters	Univariate Analysis				Multivariate Analysis			
		95% CI				95% CI		
	HR	Lower	Upper	P	HR	Lower	Upper	P
GOLM1 (continuous variable)								
Age (continuous)	1.01	0.99	1.03	.32				
Gender, female vs male	1.10	0.79	1.52	.57				
Smoking history, 2/3/4/5 vs. 1	1.21	0.75	1.94	.44				
Pathologic stage III/IV vs I/II	1.71	1.17	2.51	.006	1.34	0.84	2.15	.22
Nodal status, positive vs negative	1.63	1.18	2.26	.003	1.26	0.84	1.88	.26
Residual tumors, yes vs no	3.81	1.84	7.89	<.001	3.87	1.81	8.27	<.001
GOLM1	1.37	1.15	1.63	.001	1.37	1.14	1.64	.001
GOLM1 (category variables)								
Age (continuous)	1.01	0.99	1.03	.32				
Gender, female vs male	1.10	0.79	1.52	.57				
Smoking history, 2/3/4/5 vs 1	1.21	0.75	1.94	.44				
Pathologic stage III/IV vs I/II	1.71	1.17	2.51	.006	1.32	0.83	2.10	.25
Nodal status, positive vs negative	1.63	1.18	2.26	.003	1.26	0.84	1.89	.26
Residual tumors, yes vs no	3.81	1.84	7.89	<.001	3.99	1.87	8.48	<.001
GOLM1	2.08	1.46	2.97	<.001	2.09	1.45	3.01	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; GOLM1, Golgi membrane protein 1; LUAD, lung adenocarcinoma.
[a]Clinical stage, nodal status, residual tumors, and GOLM1 expression were included in multivariable analysis.

expression group (Table 1). No significant difference was observed in other clinicopathological features. Then, we conducted univariate and multivariate analyses to examine the independent prognostic value of *GOLM1* expression in terms of OS and RFS. Results showed that advanced pathologic stages (III/IV), nodal invasion, with residual tumors, and increased *GOLM1* expression were associated with unfavorable OS (Table 2) and RFS (Table 3) in patients with LUAD. Multivariate analysis showed that increased *GOLM1* expression was an independent prognostic indicator of poor OS (HR: 1.30, 95% CI: 1.11-1.54, $P = .002$, as a continuous variable; HR: 1.87, 95% CI: 1.32-2.66, $P < .001$, as category variables; Table 2) and RFS (HR: 1.37, 95% CI: 1.14-1.64, $P = .001$, as a continuous variable; HR: 2.09, 95% CI: 1.45-3.01, $P < .001$, as category variables; Table 3).

Expression of GOLM1 Was Modulated by DNA CNAs and Methylation Status in LUAD

By examining CNAs in 511 cases of LUAD, we found 248 (48.5%) cases had heterozygous loss (−1), which was associated with significantly decreased *GOLM1* expression compared to the copy neutral cases (0, N = 232; Figure 4A and B). Besides, 28 (5.5%) cases had low-level copy gain (+1), which was associated with significantly increased *GOLM1* expression (Figure 4A and B). Then, we examined the methylation status of 6 CpG sites in *GOLM1* DNA in 453 patients with LUAD. Interestingly, we found that the methylation status of 1 CpG site (chr9: 88,694,942-88,694,944) showed a negative correlation with *GOLM1* expression (Figure 4C). By performing linear regression analysis, we confirmed a weak negative correlation (Pearson $r = -0.25$, $P < .001$; Figure 4D). Then, we examined the

association between *GOLM1* expression and its DNA CNAs/methylation in patients with LUSC with available data. Results showed that *GOLM1* DNA amplification (+1/+2) was more common in patients with LUSC (n = 94, 18.9%; Figure 5A). However, the DNA amplification was not necessarily associated with *GOLM1* upregulation, compared to the copy neutral cases (n = 175; Figure 5B, $P = .21$). Inconsistent with LUAD, DNA deletion was associated with decreased *GOLM1* expression in patients with LUSC (Figure 5A and B, $P = .0024$). Regarding *GOLM1* DNA methylation, we failed to identify apparent association between *GOLM1* expression and the methylation of the 6 CpG sites (Figure 5C). The CpG (chr9: 88,694,942-88,694,944) site negatively correlated with *GOLM1* expression in patients with LUAD and was not relevant to *GOLM1* expression in patients with LUSC (Pearson $r = 0.13$; Figure 5D).

Discussion

The Golgi apparatus is an organelle responsible for posttranslational modification and sorting of protein in mammalian cells. It is polarized in both structure and function, with cis- and trans-side executing different roles. Dysregulated functions of the Golgi apparatus are associated with malignant transformation and pathological development of cancers.[20-22] Golgi membrane protein 1 is a cis-Golgi-localized protein which is overexpressed in multiple types of cancer and is closely associated with cancer progression.[2,23,24]

Some previous studies found that *GOLM1* might be a potential diagnostic and prognostic biomarker in some cancers. Prostate tissue *GOLM1* RNA might outperform serum prostate-specific antigen in detecting prostate cancer.[4] In HCC, *GOLM1* expression might be a promising biomarker of
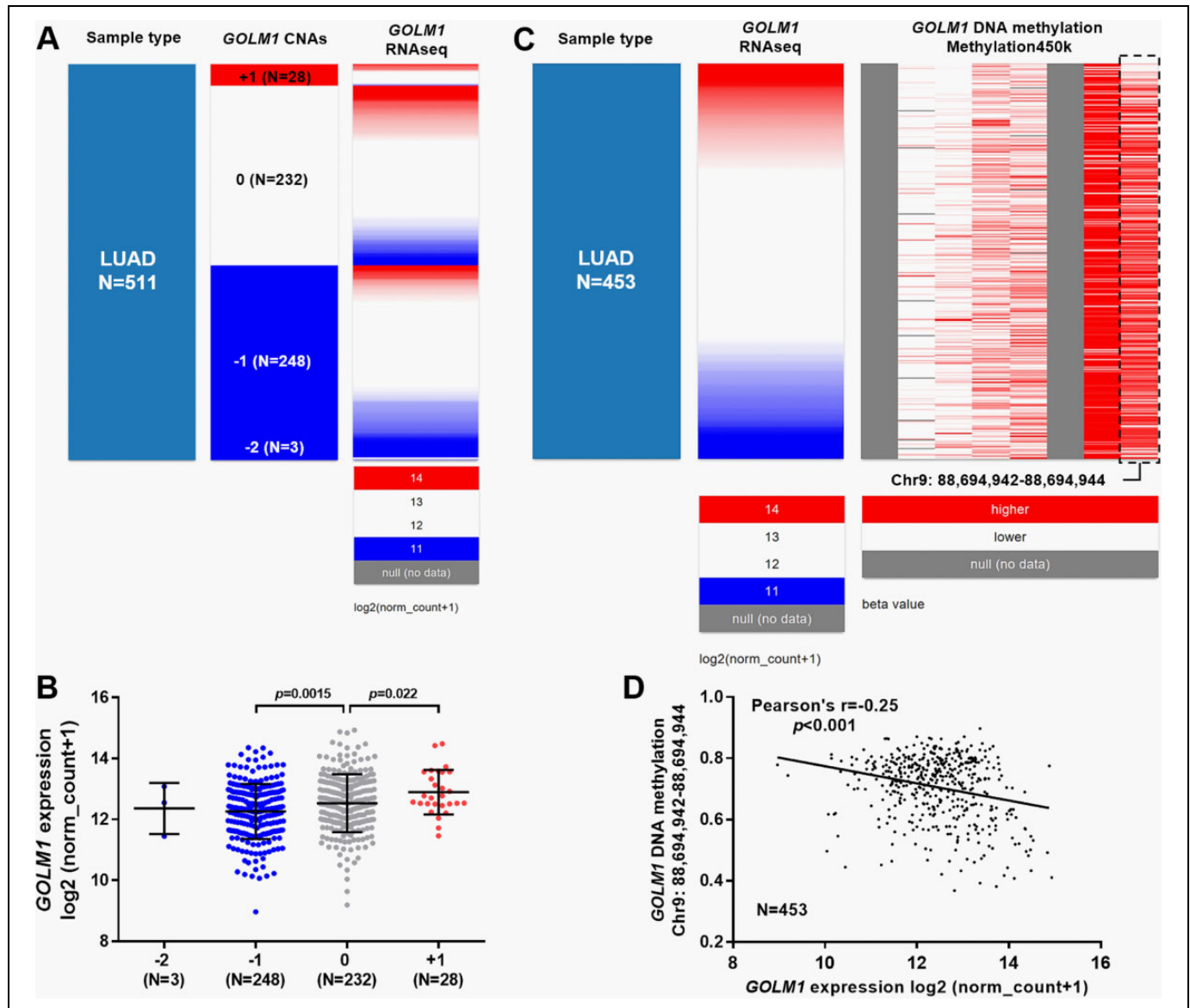
Figure 4. The correlation between Golgi membrane protein 1 (*GOLM1*) expression and its DNA copy number alterations (CNAs) or methylation in patients with lung adenocarcinoma (LUAD). A and B, Heatmap (A) and plot chart (B) of *GOLM1* expression in groups with different CNAs in patients with LUAD. Homozygous deletion (−2); heterozygous loss (−1), copy neutral (0), and low-level copy gain (+1) groups. C and D, Heatmap (C) and regression analysis (D) of the correlation between *GOLM1* expression and its DNA methylation in patients with LUAD.

chemotherapeutic resistance[25] and was associated with poor OS as well as disease-free survival.[26] One recent study reported that *GOLM1* might also be a valuable biomarker in NSCLC.[9] Its upregulation was associated with lymph node metastasis and advanced TNM Classification of Malignant Tumors (TNM) stage of NSCLC and might independently predict poor OS.[9] Both LUAD and LUSC are 2 major subtypes of NSCLC but actually are 2 molecularly heterogeneous diseases which have different prognostic markers. The differences in these subtypes are quite complex and far from being fully understood. Expression of PD-L1 is a significant poor prognostic factor in patients with LUAD, but not in those with LUSC.[27]

SOX2 gene amplification and protein overexpression are associated with better survival outcome in LUSC.[13] In comparison, *SOX2* upregulation is associated with increased cancer stem cell properties and unfavorable survival in LUAD[28,29] (just to name a few). Therefore, it is meaningful to examine the prognostic value of *GOLM1* in different subtypes of NSCLC.

In this study, using data from GEO data sets and TCGA-LUAD/LUSC, we found that *GOLM1* was significantly upregulated in both LUAD and LUSC tissues compared to the normal controls. However, *GOLM1* expression was higher in LUAD tissues than in LUSC tissues. More importantly, using over 10 years' survival data from 502 patients with LUAD and 494
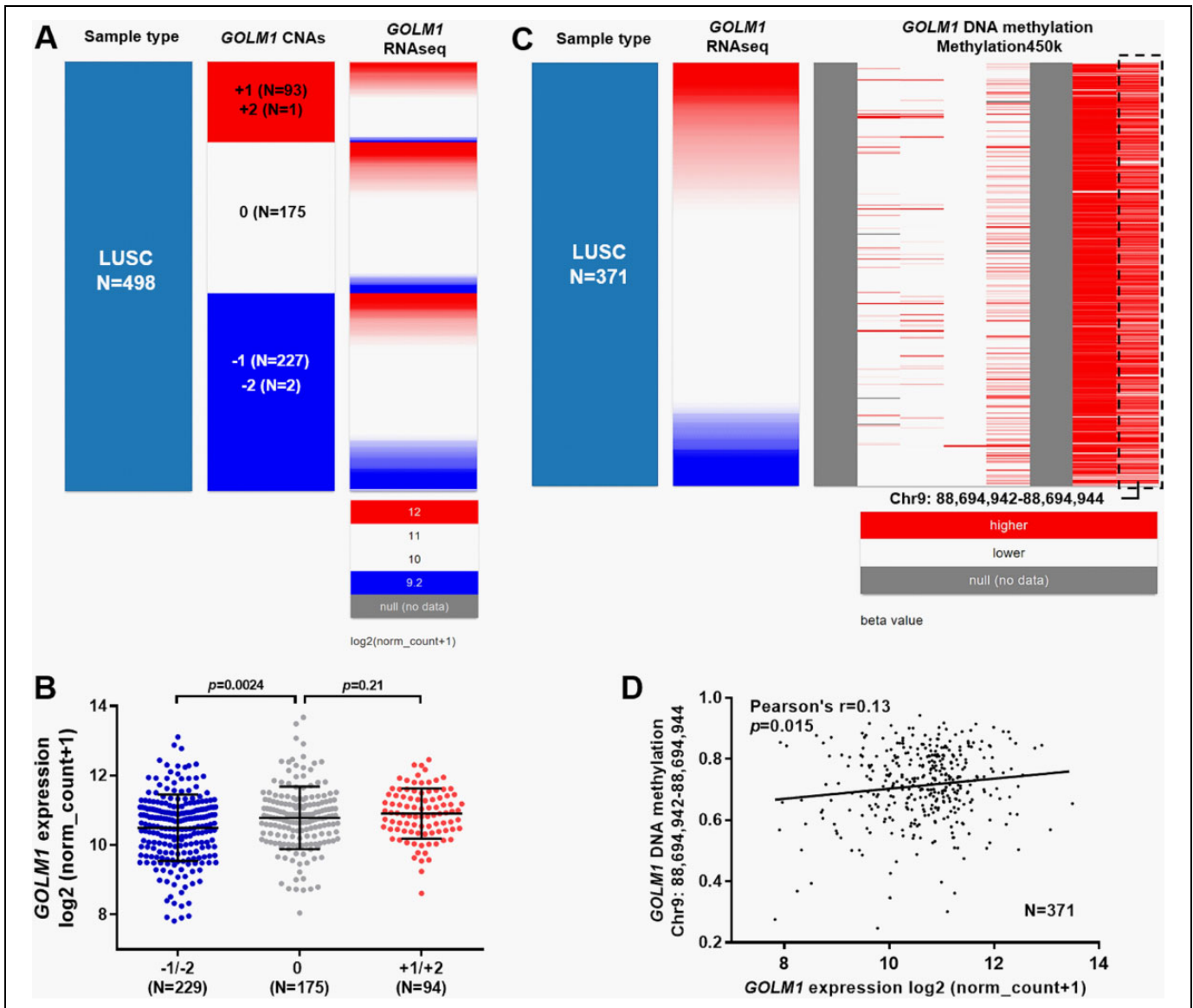
Figure 5. The correlation between Golgi membrane protein 1 (*GOLM1*) expression and its DNA CNAs or methylation in patients with lung squamous cell carcinoma (LUSC). A and B, Heatmap (A) and plot chart (B) of *GOLM1* expression in groups with different CNAs in patients with LUSC. Homozygous deletion (−2); heterozygous loss (−1), copy neutral (0), low-level copy gain (+1), and high-level amplification (+2) groups. C and D, Heatmap (C) and regression analysis (D) of the correlation between *GOLM1* expression and its DNA methylation in patients with LUSC.

patients with LUSC, we found that high *GOLM1* expression was associated with unfavorable OS and RFS in patients with LUAD, but not in patients with LUSC. The following univariate and multivariate analysis confirmed that increased *GOLM1* expression was an independent prognostic indicator of poor OS (HR: 1.30, 95% CI: 1.11-1.54, P = .002, as a continuous variable; HR: 1.87, 95% CI: 1.32-2.66, P < .001, as category variables) and RFS (HR: 1.37, 95% CI: 1.14-1.64, P = .001, as a continuous variable; HR: 2.09, 95% CI: 1.45-3.01, P < .001, as category variables) in patients with LUAD. Using data from the Kaplan-Meier plotter, we confirmed that *GOLM1* expression was irrelevant to survival outcomes in patients with LUSC (Supplementary Figure 1A and B). However, we also failed to validate the

association between *GOLM1* expression and the poor survival in patients with LUAD in this database (Supplementary Figure 1C and D). Actually, the Kaplan-Meier plotter used data from 1715 samples of 10 independent data sets,[18] among which the clinicopathological parameters (such as ethnicity, previous chemotherapy, and radiotherapy) of the patients varied significantly. The heterogeneity of the studies might contribute to the different results obtained from TCGA and the Kaplan-Meier plotter. In the future, prospective studies based on a large patient cohort could be performed to validate the findings.

Golgi membrane protein 1 can regulate several signaling pathways in different cancers. In prostate cancer, it activates the PI3K-AKT-mTOR signaling pathway, thereby promoting

cancer cell proliferation, migration, and invasion and inhibiting apoptosis.[3] Its expression is suppressed by miR-27b and miR-143/145 cluster in prostate cancer cells.[30,31] In HCC, *GOLM1* is a critical gene driving cancer cell metastasis. It can selectively interact with epidermal growth factor receptor (EGFR) and supports appropriate anchoring and recycling of EGFR/Receptor tyrosine kinase (RTK) between the trans-Golgi network and the plasma membrane, thereby resulting in prolonged activation of the downstream kinases.[23,32] As a crucial signaling transductor, EGFR plays a crucial role in regulating cell proliferation, differentiation, and apoptosis in both normal and cancer cells, via binding with its specific ligands, such as EGF and transforming growth factor (TGF) α.[33] In addition, it also promotes the epithelial–mesenchymal transition through the TGF-β1/Smad2 signaling pathway.[34] Actually, activating EGFR mutations are quite common in patients with LUAD (approximately 14%-19% of Western patients and 40%-48% of Asian patients) but are far less common in patients with LUSC (around 15% in Asian patients).[35,36] Therefore, as an important modulator of EGFR/RTK cell surface recycling, it is possible that *GOLM1* upregulation may exaggerate the malignant behaviors of LUAD. This also might help to explain the prognostic difference in *GOLM1* between LUAD and LUSC. However, it is necessary to explore the molecular regulative network of *GOLM1* in LUAD in future studies.

In this study, we also preliminarily examined the potential mechanisms of *GOLM1* dysregulation in NSCLC. By examining *GOLM1* DNA CNAs in 511 patients with LUAD and methylation in 453 patients with LUAD, we found that *GOLM1* expression was positively correlated with its copy numbers and negatively correlated with its DNA methylation. Therefore, we infer that CNAs and DNA methylation might be 2 important mechanisms of dysregulated *GOLM1* in LUAD. In comparison, although *GOLM1* expression was significantly decreased in *GOLM1* DNA deletion group in patients with LUSC, DNA amplification was not necessarily associated with increased *GOLM1* expression. In addition, DNA methylation of the CpG site (chr9: 88,694,942-88,694,944) was irrelevant to *GOLM1* expression in patients with LUSC. These findings suggest that *GOLM1* expression might be regulated by different mechanisms in the subtypes of NSCLC, which need to be explored by molecular studies in the future.

Conclusion

Golgi membrane protein 1 might serve as a valuable prognostic biomarker in LUAD, but not in LUSC. In addition, DNA CNAs and methylation might be 2 important mechanisms of dysregulated *GOLM1* in LUAD.

Authors' Note

Xi Liu and Lei Chen contributed equally to this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Supplemental Material

Supplementary material for this article is available online

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