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# Reactive Oxygen Species Modulator 1 as a Novel Predictive Biomarker for Unfavorable Clinical Outcome in EGFR-Mutant Lung Adenocarcinoma Treated with Surgical Resection

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# Introduction

- Reactive oxygen species modulator 1 (Romo1) is a novel protein that regulates the production of intracellular reactive oxygen species.
- Romo1 has been shown to be associated with poor survival in various clinical settings for the treatment of lung cancer.
- These data suggest that Romo1 is a promising biomarker for malignancies.
- However, the clinical usefulness of this protein has never been explored in patients with cancer harboring driver genetic alterations.

Lung Cancer. 2015 Jan;87(1):45-52., Front Oncol. 2021;11:770230., Onco Targets Ther. 2019;12:8263-73

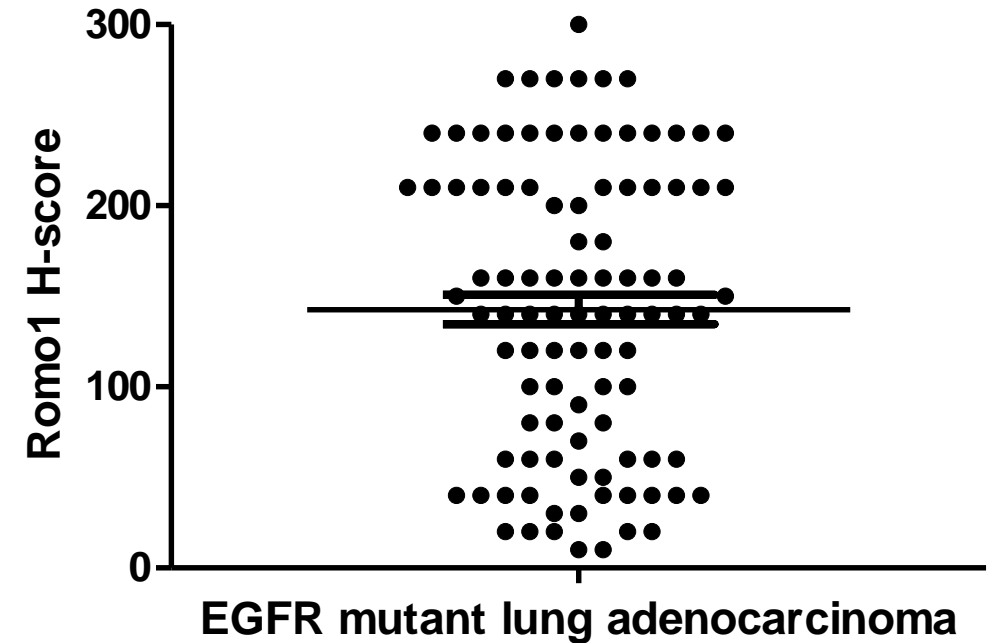
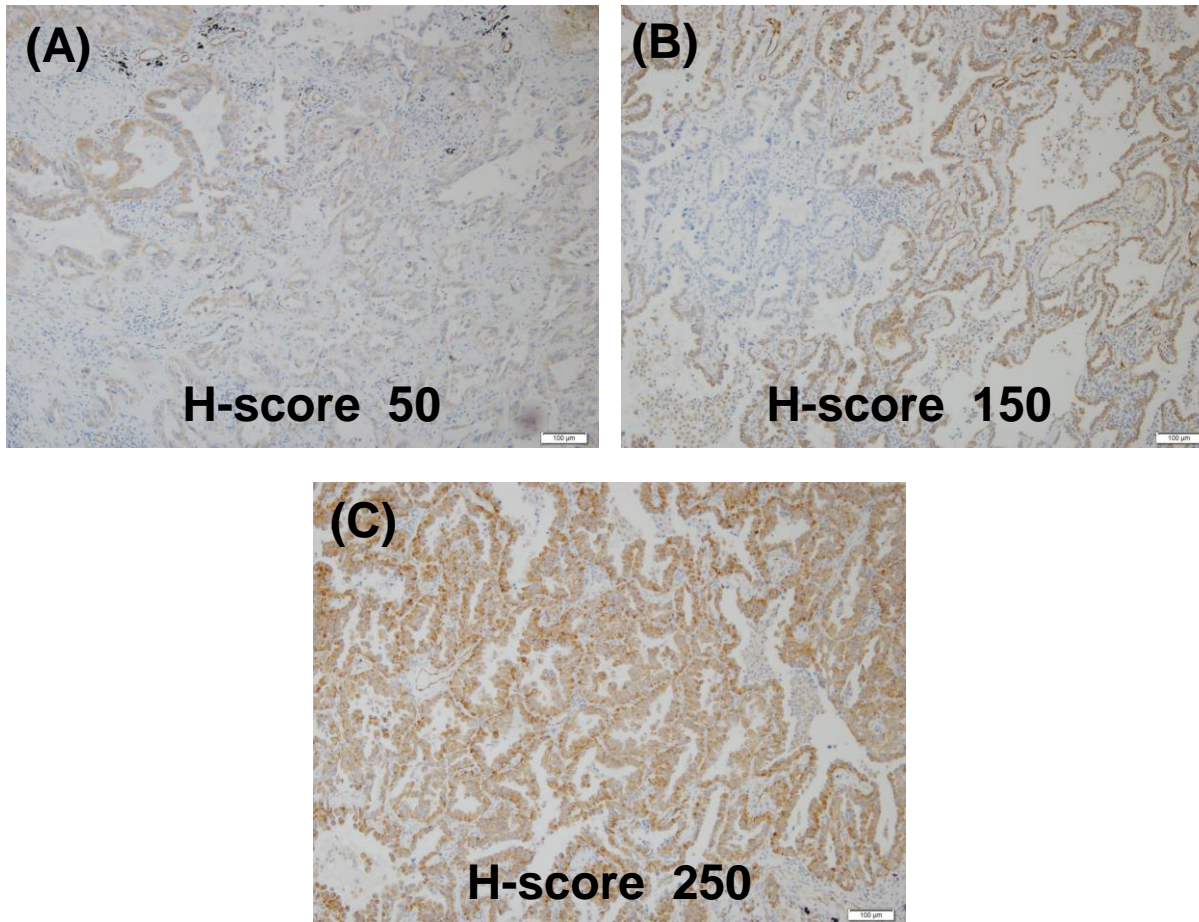
# Objectives

- In this study, we evaluated the predictive value of Romo1 expression in patients with lung adenocarcinoma harboring epidermal growth factor receptor (EGFR) mutation which were treated with curative resection.
- In addition, we investigated which clinicopathological characteristics are associated with Romo1 expression in this patients group.

# Materials and Methods

- We retrospectively enrolled patients with stages I to IIIA EGFR-positive lung adenocarcinoma who received curative resection from January 2012 to December 2020 in our institute.
- Romo1 expression in tumor tissues was examined by IHC and evaluated by histologic scoring (H-score, range 0-300).
- Optimal cutoff H-score was determined at the point with the lowest p-value by the log-rank test for all possible H-scores.
- Univariate and multivariate analyses were performed to identify the clinicopathologic parameters, including Romo1 expression, which may be associated with disease-free survival (DFS).

# Representative examples of immunochemical staining & distribution of Romo1 expression (N=98)



- Median H-score: 140 (range 10-300)
- Optimal cutoff H-score: 200

# Distribution of patients according to different tissue Romo1 expression

	Romo1 expression		p-value
	Low (H-score <200)	High (H-score ≥200)	
<b>All</b>	73	25	
<b>Age</b>			0.9724
<70	47	16	
≥70	26	9	
<b>Sex</b>			0.9536
Male	20	7	
Female	53	18	
<b>Smoking history</b>			0.3535
Never	59	18	
Ever	14	7	
<b>Smoking intensity</b>			0.2673
<30 PY	67	21	
>30 PY	6	4	
<b>Stage</b>			<.0001
I, II	71	13	
IIIA	2	12	
<b>T stage</b>			0.0026
T1-2	73	22	
T3-4	0	3	

	Romo1 expression		p-value
	Low (H-score <200)	High (H score ≥200)	
<b>N stage</b>			<.0001
N0	70	10	
≥N1	3	15	
<b>Differentiation</b>			0.0107
Well/moderate	29	3	
Poor	44	22	
<b>EGFR mutation</b>			0.1370
19del	34	10	
L858R	36	11	
Others	3	4	
<b>Surgical technique</b>			0.2063
Lobectomy	52	21	
Segmentectomy	21	4	
<b>STAS*</b>			0.0701
Absent	66	19	
Present	7	6	

\*STAS, spread through air spaces

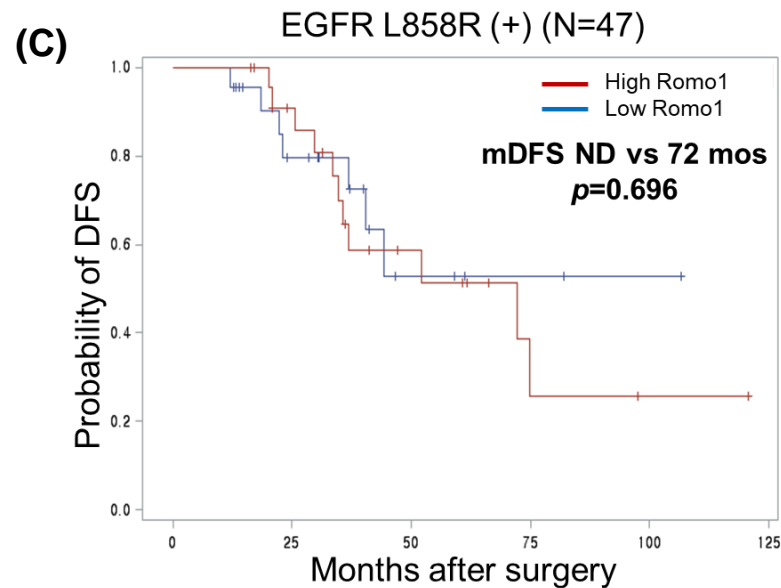
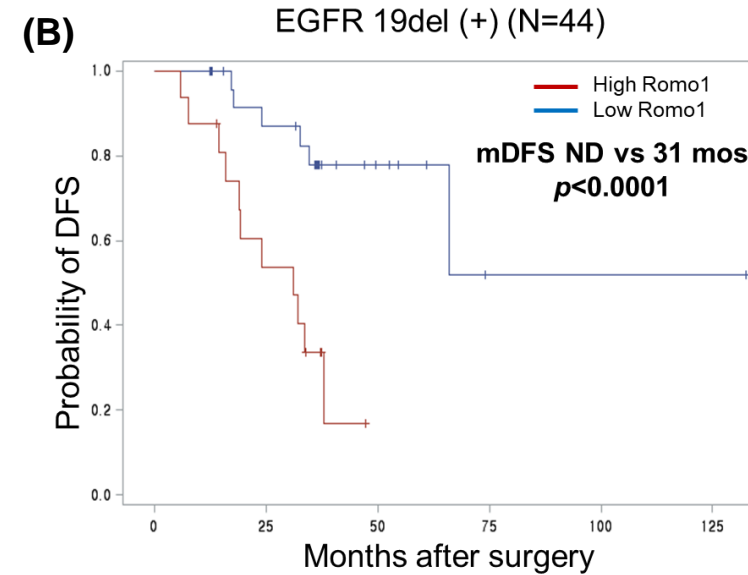
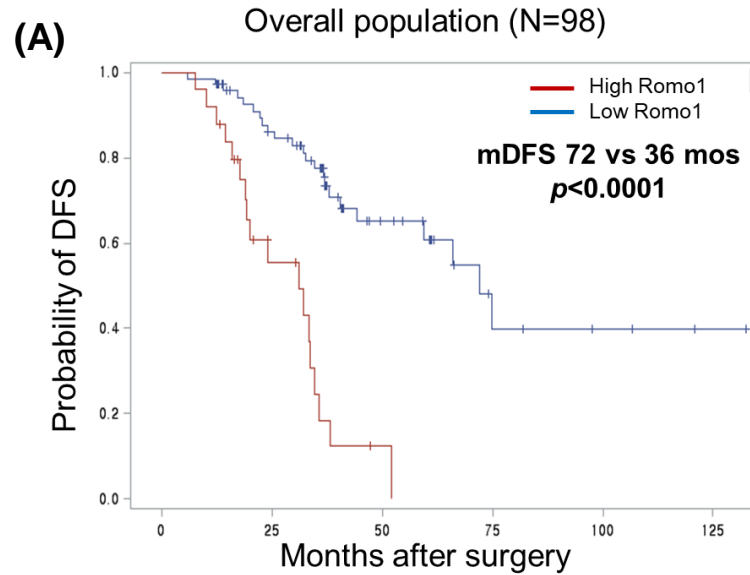
# DFS analysis results according to clinicopathological parameters of all study population

	Median DFS (months)	Univariate		Multivariate	
		HR (95% CI)	p-value	HR (95% CI)	p-value
<b>All</b>	52 (36.9-74.8)				
<b>Age</b>			0.7031	NA	
<70	52 (34.5-ND)	1.1 (0.61-2.2)			
≥70	66 (34.7-ND)	reference			
<b>Sex</b>			0.3004	NA	
Male	34 (25.6-ND)	1.4 (0.7-2.8)			
Female	66 (37.9-ND)	reference			
<b>Smoking history</b>			0.9850	NA	
Never	59 (36.9-ND)	reference			
Ever	52 (29.6-ND)	1 (0.5-2.1)			
<b>Smoking intensity</b>			0.7629	NA	
<30 PY	59 (36.9-74.8)	reference			
>30 PY	42 (22.4-ND)	1.2 (0.5-2.9)			
<b>Stage</b>			<.0001	0.0215	
I, II	66 (40.4-ND)	reference		reference	
IIIA	19 (12.5-31.2)	5.8 (2.8-12)		2.8 (1.2-6.9)	
<b>T stage</b>			0.3988	NA	
T1-2	59 (36.9-74.8)	reference			
T3-4	31 (ND-ND)	2.4 (0.3-17.8)			

	Median DFS (months)	Univariate		Multivariate	
		HR (95% CI)	p-value	HR (95% CI)	p-value
<b>Differentiation</b>			0.0019		0.0188
Well/moderate	ND (ND-ND)	reference		reference	
Poor	38 (32.2-59.4)	4.4 (1.7-11.2)		3.2 (1.2-8.4)	
<b>EGFR mutation</b>			0.4943	NA	
19del	66 (32.7-ND)	1.3 (0.6-2.5)			
L858R	72 (36.8-ND)	reference			
<b>Surgical technique</b>			0.4974	NA	
Lobectomy	52 (33.5-ND)	1.3 (0.6-2.9)			
Segmentectomy	66 (36.8-66)	reference			
<b>STAS*</b>			0.0594		0.9208
Absent	66 (37.9-ND)	reference		reference	
Present	34.53 (20-72.13)	2.0 (0.9-4.3)		1.0 (0.42-2.61)	
<b>Romo1 expression</b>			0.0118		0.0324
Low	72 (59.4-ND)	reference		reference	
High	36 (32.2-59.37)	2.9 (1.2-4.3)		2.2 (1.1-5.4)	

\*STAS, spread through air spaces

# Kaplan-Meier curves of DFS according to different expression levels of Romo1





# Summary

- Romo1 overexpression was significantly associated with more advanced stage, lymph node metastasis, and poorly-differentiated tumors, while it showed non-significant trend of association with STAS.
- Multivariate analysis showed that advanced stage (HR=2.8, p=0.0215), poor differentiation (HR=3.2, p=0.0188), and high Romo1 expression (HR=2.2, p=0.0324) were independently associated with shorter DFS.
- In the subgroup analysis, this association was also observed in patients with exon 19del.
- To the best of our knowledge, this is the first study to demonstrate the potential predictive value of Romo1 expression in surgically-resected lung cancer harboring driver genetic alterations.

# Conclusion

- In conclusion, Romo1 overexpression was significantly associated with early recurrence in EGFR-mutant lung adenocarcinoma treated with surgical resection.
- Our data suggest that Romo1 could be a promising predictive biomarker for this treatment setting.
- Further studies are needed using larger population and long-term survival data to validate our results and to elucidate whether Romo1 has both predictive and prognostic value.