Original Article

Trophinin-associated protein expression is an independent prognostic biomarker in lung adenocarcinoma

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Contributions: (I) Conception and design: Z Chen, Z Chen; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Y Zhou, R Luo; (V) Data analysis and interpretation: Z Chen, K Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide, with lung adenocarcinoma (LAC) representing the most common subtype. Trophinin-associated protein (TROAP) is a cytoplasmic protein first identified to mediate the process of embryo transplantation, which has been recently found to be involved in microtubule regulation. However, limited information about the role of TROAP in LAC is available.

Methods: We evaluated the relationship of TROAP expression in LAC tissues with clinical pathologic parameters and the survival time in LAC patients based on a statistical analysis of The Cancer Genome Atlas (TCGA) lung cancer data (N=528). Differences in survival between high and low expression groups (median expression cutoff) from the Cox univariate/multivariate regression analysis were then compared.

Results: According to the Chi-square tests, we found high TROAP expression correlated with younger age (≤60) (P=0.047), male sex (P<0.005), an earlier T-stage (P=0.011), N-stage (P=0.017), M-stage (P=0.022), TNM (P=0.007), and a longer smoking history (>30 pack-year) (P<0.001). A Kaplan-Meier analysis demonstrated that high TROAP expression may correspond with poor overall survival of LAC patients in T3 stage (P=0.0013), N0 stage (P=0.014), and M0 stage (P=0.0023). Multivariate analysis confirmed that TROAP expression was related to overall survival in LAC patients independently [hazard ratio (HR): 1.784, 95% confidence interval (CI): 1.072–2.968, P=0.026].

Conclusions: Our results suggested that TROAP is an independent prognostic biomarker of poor survival in LAC.

Keywords: Trophinin-associated protein (TROAP); lung adenocarcinoma (LAC); biomarker; The Cancer Genome Atlas (TCGA)

Submitted Jan 04, 2019. Accepted for publication Apr 10, 2019.
doi: 10.21037/jtd.2019.04.86
View this article at: http://dx.doi.org/10.21037/jtd.2019.04.86

Introduction

According to the latest reports from *A Cancer Journal for Clinicians* (*CA*), lung cancer remains the leading cause of cancer incidence and cancer-related mortality worldwide (1), while adenocarcinoma represents the most common histological subtype (2). Despite recent advances in various treatment options during the last decade (including surgery, chemotherapy, targeted therapy, immunotherapy), the 5-year survival of LAC has not been improved to a satisfactory standard (3), and TNM staging remains the most important prognostic factor for predicting the recurrence rates and survival times of LAC patients (4). In addition to these classical clinical methods, novel prognostic tools based on individual tumor mutations and protein expression, such as WD repeat domain 62 (WDR62) (5),

lncRNA forebrain embryonic zinc finger protein 1 antisense RNA1 (FEZF1-AS1) (6), and transmembrane protease serine 4 (TMPRSS4) (7), have shown great potential in prognostic prediction. However, none of these genes have been generally acknowledged in clinical practice, which means a more stable, convenient and reliable prognostic biomarker is needed for LAC.

Trophinin-associated protein (TROAP), formally known as tastin, was first identified as a cytoplasmic protein that mediated the initial attachment of the trophoblast to the endometrial epithelium in early embryo implantation by forming a complex with trophinin and bystin (8-11). Previous studies showed that TROAP mRNA have higher expression levels in testis, bone marrow, and thymus (9,12). Additionally, the functions of the trophinin-tastin-bystin complex seemed to be only associated with embryo implantation. However, recent studies revealed that TROAP could regulate proper spindle assembly during mitosis as microtubule-associated proteins, while the loss of TROAP expression led to mitotic block and multipolar spindles (13).

In terms of malignant cancers, since TROAP was found highly expressed in human cancer cell lines (HeLa and Jurkat cells) (13,14), more and more studies have been conducted to investigate the relationships between TROAP and various cancers. Until now, high expression of TROAP was reported to be related to poorer outcomes in ovarian epithelial carcinoma (12,15), gastric cancer (16), colorectal cancer (17), and hepatocellular carcinoma (18). As a novel prognostic predictor, the relationship between TROAP expression and other types of cancers, including LAC, remains unclear. Given this situation, we evaluated the potential correlations between TROAP expression in LAC tissues and clinical pathologic information of these patients by analyzing the data from the TCGA lung cancer database and the UCSC Xena database. Furthermore, we assessed whether TROAP expression could be an independent prognostic biomarker for the overall survival of LAC patients.

Methods

Data collecting

The RNA-sequencing (RNA-Seq) expression data (level 3 data) was obtained from the TCGA lung cancer database (http://cancergenome.nih.gov/) with the RTCGAToolbox package in R (19), and the full clinical pathologic information of the corresponding patients was downloaded from the UCSC Xena database (https://xenabrowser.net/datapages/) according to their ID in TCGA. The expression value of TROAP mRNA was converted to normalized RNA-Seq by Expectation-Maximization (RSEM) values for further statistical analysis. The detailed pre-processing steps, including mapping and normalization, are described on the UCSC Xena website (http://xena.ucsc.edu/).

Statistical analysis

To evaluate the relationships between TROAP expression and clinical, pathologic parameters, high and low TROAP expression groups were defined by the median value of the TROAP expression. The correlation between TROAP expression and clinical, pathologic parameters was tested by the Chi-square tests using SPSS software version 19.0. Differences in overall survival between high and low expression groups were compared using Kaplan-Meier curves, and P values were calculated by a log-rank test. The survival package in R was used for the above tests. Univariate Cox regression analysis of the TROAP expression, along with other clinical, pathologic parameters, was used to estimate survival rates and screen the possible variables that may affect overall survival. Multivariate Cox analysis was performed to evaluate the effects of TROAP expression on overall survival, along with other clinical parameters which were correlated with overall survival in univariate analysis (T, N, and M stage, clinical stage, and radiation therapy history). This study was approved by the Medical Ethics Committee of the Sir Run Run Shaw Hospital affiliated to Zhejiang University School of Medicine (No. 20190319-18).

Results

Patient characteristics

From TCGA lung cancer database, the RNA-Seq expression data of 594 patients were collected, among which data from 66 patients were excluded due to patient TCGA ID being unable to be located on the UCSC Xena database. The final 528 samples with both TROAP expression information and full clinical characteristics were then submitted for statistical analysis. The demographic and clinical pathologic characteristics, including TNM stage, the location of the tumor, survival status, radiation therapy and smoking history, of the corresponding patients are described in *Table 1*.

Table 1 Clinical and pathologic information of TCGA lung adenocarcinoma database

Characteristics	Number (%)
TROAP	
High	263 (49.81)
Low	265 (50.19)
Age	
≤60	165 (31.25)
>60	344 (65.15)
NA	19 (3.60)
Gender	
Female	281 (53.22)
Male	247 (46.78)
Race	
Black or African American	52 (9.85)
White	403 (76.33)
NA	73 (13.83)
Location	
L-lower	81 (15.34)
L-upper	124 (23.48)
R-lower	96 (18.18)
R-upper	200 (37.88)
R-middle	23 (4.36)
M stage	
M0	360 (68.18)
M1	25 (4.73)
Mx	143 (27.08)
N stage	
N0	349 (66.10)
N1	98 (18.56)
N2	76 (14.39)
N3	5 (0.95)
T stage	
T1	175 (33.14)
T2	285 (53.98)
T3	49 (9.28)
T4	19 (3.60)
Clinical stage	
Stage I	289 (54.73)
Stage II	123 (23.30)
Stage III	83 (15.72)
Stage IV	26 (4.92)
Pack-years (smoking)	
≤30	158 (29.92)
>30	205 (38.83)
Radiation	
No	413 (78.22)
Yes	61 (11.55)
NA	54 (10.23)
Status	
Alive	336 (63.64)
Dead	192 (36.36)

TCGA, The Cancer Genome Atlas; TROAP, trophinin-associated protein.

TROAP expression was associated with clinical pathologic parameters of LAC

The necessary information of patients, including TROAP expression, age, gender, race, smoking history, TNM stage, and clinical stage, as well as the use of radiation therapy, and survival status are shown in *Table 1*. In order to evaluate the relationship between TROAP expression and clinical, pathologic parameters of LAC further, patients were divided into high and low TROAP expression groups according to the median value of TROAP expression. According to the Chi-square tests, we found high TROAP expression correlated with younger age (≤60) (P=0.047), male (P=0.005), earlier stage of T stage (P=0.011), N stage (P=0.017), M stage (P=0.022), and TNM (P=0.007), and longer smoking history (>30 pack-year) (P<0.001) (*Table 2*).

TROAP was an independent prognostic factor for poor overall survival in LAC

The further subgroup analysis on the Kaplan-Meier curves of overall survival and log-rank tests showed that

Table 2 Correlations of TROAP mRNA expression in lung adenocarcinoma tissue with clinical and pathologic parameters

Variable	Number	TROAP mRNA		P value
		High, n [%]	Low, n [%]	
Age				0.047
≤60	165	93 [56]	72 [44]	
>60	344	160 [47]	184 [53]	
Gender				<0.005
Female	281	118 [42]	163 [58]	
Male	247	145 [59]	102 [41]	
Race				0.067
Black or African American	52	34 [65]	18 [35]	
White	403	189 [47]	214 [53]	
Location				0.115
L-lower	81	31 [38]	50[62]	
L-upper	124	71 [57]	53 [43]	
R-lower	96	47 [49]	49 [51]	
R-upper	200	99 [49]	101 [51]	
R-middle	23	13 [57]	10 [43]	
M stage				0.022
M0	360	178 [49]	182 [51]	
M1	25	19 [76]	6 [24]	
Mx	143	66 [46]	77 [54]	
N stage				0.017
N0	349	162 [47]	187 [53]	
N1	98	55 [56]	43 [44]	
N2	76	45 [59]	31 [41]	
N3	5	4 [80]	1 [20]	
T stage				0.011
T1	175	70 [40]	105 [60]	
T2	285	159 [56]	126 [44]	
T3	49	25 [51]	24 [49]	
T4	19	9 [47]	10 [53]	
Stage				0.007
Stage I	289	127 [44]	162 [56]	
Stage II	123	67 [54]	56 [46]	
Stage III	83	47 [57]	36 [43]	
Stage IV	26	19 [73]	7 [27]	
Pack-years				<0.001
≤30	158	66 [42]	92 [58]	
>30	205	127 [62]	78 [38]	
Radiation				0.064
No	413	201 [49]	212 [51]	
Yes	61	38 [62]	23 [38]	
Status				0.012
Alive	336	153 [46]	183 [54]	
Dead	192	110 [57]	82 [43]	

TROAP, trophinin-associated protein.

high TROAP expression might be associated with poor overall survival of patients in the T3 stage (P=0.0013), N0 stage (P=0.014), and M0 stage (P=0.0023) (*Figure S1*). Furthermore, during univariate analysis, TROAP expression, T stage, N stage, clinical stage, and radiation therapy history were correlated with poor overall survival (*Table 3*). The following multivariate analysis confirmed that high TROAP expression was an independent prognostic factor for poor overall survival of LAC patients [hazard ratio (HR): 1.784, 95% confidence interval (CI): 1.072–2.968, P=0.026; *Table 4*].

Discussion

The present study demonstrated that high TROAP expression was correlated with younger age (≤60), male sex, earlier stage of T, N, M and TNM, and a longer smoking history (>30 pack-year). Patients with higher TROAP expressions in LAC tissues related to a poorer prognosis

Table 3 Univariate analyses of overall survival in lung adenocarcinoma patients

Parameters	Univariate analysis		
	HR	95% CI	P value
TROAP			
Low	Reference		
High	1.779	1.247–2.538	0.001
Age			
≤60	Reference		
>60	0.914	0.634–1.317	0.628
Gender			
Female	Reference		
Male	1.117	0.789–1.579	0.533
Race			
American	Reference		
Asian	0.777	0.121–1.352	0.327
Black or African American	1.311	0.528–2.417	0.218
White	2.072	0.128–4.821	0.371
Location			
L-lower	Reference		
L-upper	1.023	0.569–1.841	0.939
R-lower	1.048	0.564–1.949	0.881
R-upper	0.972	0.557–1.697	0.920
R-middle	0.535	0.123–2.325	0.404
M stage			
M0	Reference		
M1	1.687	0.908–3.136	0.098
N stage			
N0	Reference		
N1	2.134	1.412–3.225	<0.001
N2	2.854	1.832–4.448	<0.001
T stage			
T1	Reference		
T2	1.803	1.134–2.868	0.013
T3	3.413	1.746–6.671	<0.001
T4	2.732	1.216–6.139	0.015
Clinical stage			
Stage I	Reference		
Stage II	1.994	1.281–3.103	0.002
Stage III	2.958	1.887–4.635	<0.001
Stage IV	2.522	1.306–4.870	0.006
Pack-years			
≤30	Reference		
>30	1.219	0.783–1.896	0.381
Radiation			
No	Reference		
Yes	0.527	0.326–0.825	<0.001

TROAP, trophinin-associated protein; HR, hazard ratio; CI, confidence interval.

generally, especially those in T3 stage, N0 stage and M0 stage. Moreover, TROAP expression could be a reliable independent prognostic biomarker for LAC patients in clinical practice.

Consistent with all previous studies (12,15-18), we observed higher TROAP expression levels in LAC tumor tissues with data mining from the TCGA lung cancer database. Conversely, Lian *et al.* reported decreased mRNA and protein expression of TROAP in Chinese hepatocellular carcinoma tissues, most of which were originated from hepatitis B virus -infected patients (20). This discrepancy was attributed to the different origins of the detection samples. An opposite result was presented by Yan *et al.* from a study based on the TCGA Liver Hepatocellular Carcinoma (TCGA-LHC) data. In Yan's study, all hepatocellular carcinoma samples caused by alcohol, hepatitis B virus, hepatitis C virus, and nonalcoholic steatohepatitis were included (18). This discrepancy reminded us that molecular pathogenesis could be different in the same type of cancer according to their etiology. Moreover, based on a better understanding of the mechanisms of tumorigenesis, we suggest new molecular classifications of various cancers, including lung cancer, should be identified despite existing clinical and pathologic classifications. These molecular classifications, with the potential to revolutionize present treatment principles,

Table 4 Multivariate analyses of overall survival in lung adenocarcinoma patients

Parameters	Multivariate analysis		
	HR	95% CI	P value
TROAP			
Low	Reference		
High	1.784	1.072–2.968	0.026
N stage			
N0	Reference		
N1	2.078		0.110
N2	1.725		0.403
T stage			
T1	Reference		
T2	1.810	0.924–3.549	0.084
T3	3.350	1.053–10.654	0.041
T4	5.907	0.983–15.522	0.053
Clinical stage			
Stage I	Reference		
Stage II	0.753	0.284–1.997	0.569
Stage III	0.769	0.192–3.078	0.712
Stage IV	0.830	0.253–2.721	0.758
Pack-years			
≤30	Reference		
>30	0.923	0.574–1.484	0.741
Radiation			
No	Reference		
Yes	0.435	0.225–0.619	0.012

TROAP, trophinin-associated protein; HR, hazard ratio; CI, confidence interval.

could be reliable and accurate prognostic factors for corresponding cancers.

The spindle assembly checkpoint, ensuring the fidelity of chromosome segregation to produce genetically identical daughter cells, is the major cell cycle control mechanism in mitosis and is essential to reducing genomic instability during cell cycle progression (21). Spindle assembly and function are intimately associated with microtubule dynamics spatially and temporally during the cell cycle (22). Along with other centrosomal and noncentrosomal proteins (23), TROAP helps to maintain the structural and dynamic features of centrosomes and contributes to normal spindle functioning as a microtubule-associated protein (24). During mitosis, two critical events, bipolar spindle assembly and centrosome integrity were controlled by TROAP, which was supposed to be essential for the microtubular cytoskeleton (8,14). A previous study showed that TROAP overexpression was associated with tumorigenesis and clinical pathologic characteristics of breast cancer, such as advanced stage, rapid speed of mitosis, and enhanced expression of several oncogenes (HER2, TOP2A and EGFR), while TROAP was hardly expressed in normal breast tissues (25). Li *et al.* found that the methylation of TROAP, one of the top 5 most significant phase-specific genes in HeLa and embryonic stem cells, would execute numerous functions to promote carcinogenesis in the G2 phase (26). In this study, we found that TROAP expression was strongly associated with T stage, N stage, M stage, and clinical stage in LAC. Thus we supposed that TROAP could promote cellular proliferation and tumor growth in LAC by propelling cell cycle progression.

Fukuda and Sugihara reported that the cell adhesion molecules, including L-selectin and trophinin, play a pivotal role in human embryo implantation (11). Trophinin is a membrane protein which is supposed to have self-binding activity and thus mediates homophilic cell adhesion, while TROAP is a cytoplasmic protein required for trophinin to exhibit cell adhesion activity (9). In trophoblastic cells, once trophinin binds to TROAP in the cytoplasm, the extracellular domain of trophinin can function as a cell adhesion molecule (8). After the initial attachment of embryonic cells to the maternal epithelial cells, a stronger adhesion is induced, and significant morphological changes are observed in the embryo implantation site. Aggressive behaviors of trophoblasts during embryo implantation resemble those of malignant tumor cells, and it is not surprising if some mechanisms are shared by trophoblasts and cancer cells (10,27). Indeed, Chen *et al.* identified trophinin as an enhancer for cell invasion and a prognostic factor for early-stage lung cancer (28). Moreover, another previous study has confirmed that knockdown of TROAP, targeted by miR-519d-3p, significantly suppressed cell proliferation, migration and invasion, inducing cell cycle G0/G1 phase arrest and promoting cell apoptosis of colorectal cancer cells (17).

The present study showed that high TROAP expression was closely related to more lymph node metastasis, more distant metastasis, later clinical stages and shorter survival

times. Therefore, we assume that TROAP may contribute to cancer cell proliferation, migration and invasion by regulation of microtubule-associated proteins. However, further investigations are needed to verify our hypothesis and elucidate the underlying molecular mechanisms. Multivariate analysis of this study showed that radiotherapy history was another independent prognostic factor of poor survival in LAC patients. However as we all know, treated with radiation is a clinical decision according to patient's clinical and pathological situations, not a defining characteristic. That is to say: radiotherapy history cannot be a proper predictive factor. Inconsistent with previous studies, multivariate analysis showed that P values of T stage, N stage, M stage, and clinical stage (TNM staging) were greater than 0.05, although univariate analyses suggested that they were risk factors for survival in LAC patients. We attributed this discrepancy to a small sample size and more samples should be included to validate our results.

Although we have found an effective prognostic biomarker to predict the prognosis of LAC, the limitations of the present study should also be acknowledged. Firstly, the statistical analysis is based on the data from the TCGA database and should be validated in other cohorts and a larger number of samples in future studies. Secondly, further studies should be performed to reveal the mechanisms of TROAP involved in the cellular proliferation, migration and invasion of LAC. Finally, as some other genes and proteins reported to be related to prognosis of lung cancer patients, a proper predictive model should be generated by combining clinical, pathologic features and whole genome sequencing.

This study as far as we know is the first study to clarify the relationship between TROAP expression and clinical pathologic characteristics in LAC, and to report that TROAP may serve as an independent prognostic factor for poor survival in LAC. Such information is likely to be of great use in the management of LAC patients in the future.

Acknowledgments

Funding: This research was supported by Zhejiang Provincial Natural Science Foundation of China under Grant No. LQ19H280007.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Medical Ethics Committee of the Sir Run Run Shaw Hospital affiliated to Zhejiang University School of Medicine (No. 20190319-18).

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Cite this article as: Chen Z, Zhou Y, Luo R, Liu K, Chen Z. Trophinin-associated protein expression is an independent prognostic biomarker in lung adenocarcinoma. J Thorac Dis 2019;11(5):2043-2050. doi: 10.21037/jtd.2019.04.86

Supplementary

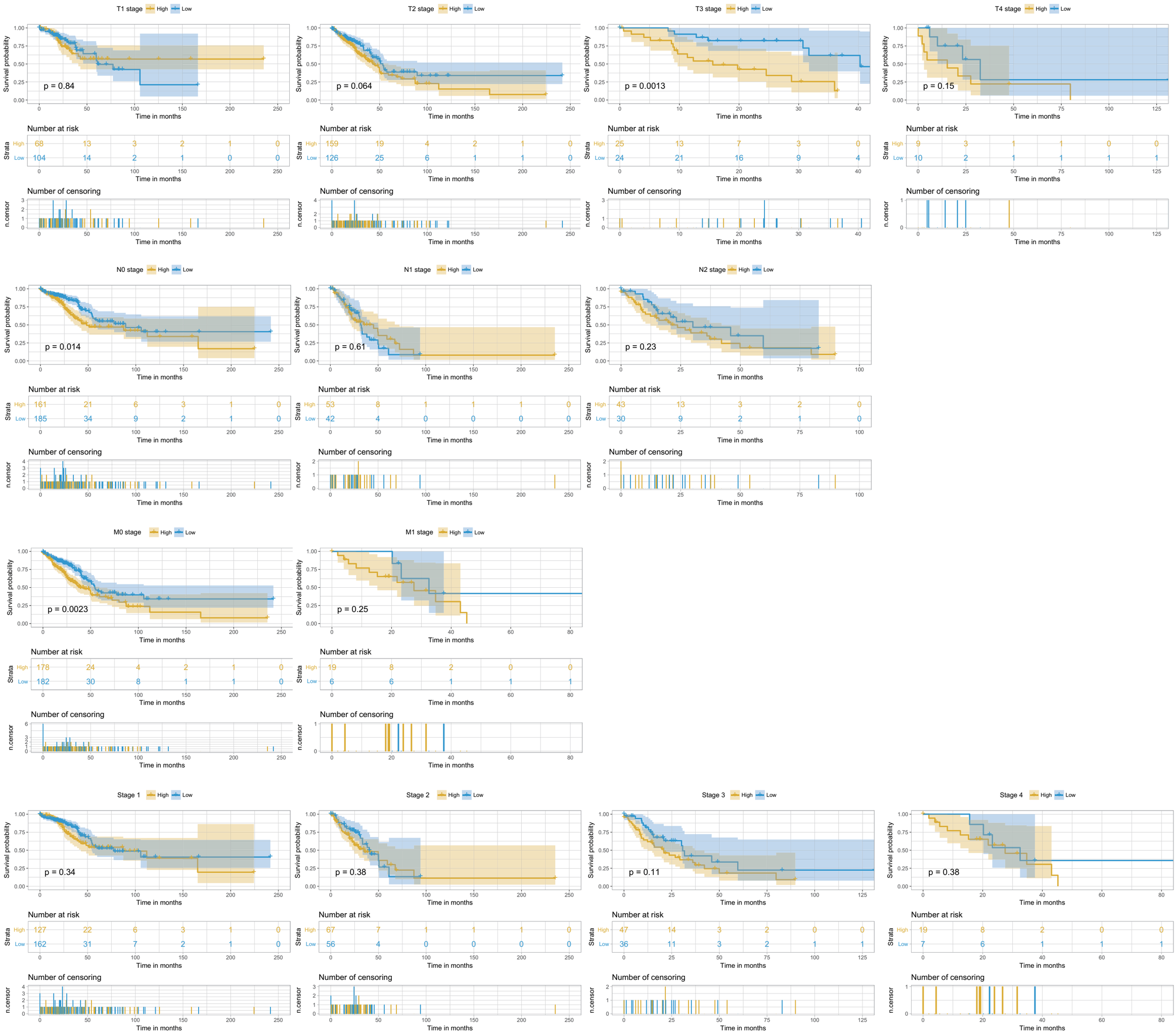

Figure S1 Kaplan-Meier curves for survival of overall survival for subgroup analysis according to TROAP expression in lung adenocarcinoma tissues. It is shown that high TROAP expression might be associated with poor overall survival of patients in the T3 stage (P=0.0013), N0 stage (P=0.014), and M0 stage (P=0.0023). TROAP, trophinin-associated protein.