Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220438

ALK, TIMP1, GALNT14, New Emergent Poor Prognosis Indicators for Patients in Early Stage or Grade of Lung Cancer

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Abstract. Lung cancer is presently the deadliest cancer worldwide, which causes large quantities of deaths, estimated more than 1.8 million, globally every year. Meanwhile, the diagnosis and prognosis for the early-stage lung cancer patients is always absent even until recent years, which has led to the result that the patients are mostly diagnosed with lung cancer in advanced stage. The present study searches for biomarkers related to early stage diagnosis so as to help deal with this factual problem. After analyzing plenty of samples on Kpalan-Meier plotter websites, this research discovers that ALK, GALNT14, TIMP1 are negatively related with OS of lung cancer patients. Further stratified analysis reveals that three proteins can indicate poor prognosis in the patients who got adenocarcinoma and were in early stage or grade. In addition, the present study also finds that the three proteins can respectively work as prognosis factor among three different groups of patients divided by gender, smoking history, and whether receiving chemotherapy or not. Conclusively, this research have discovered three biomarkers which can be applied in diagnosis, prognosis and treatment in the patients with early stage or grade of lung cancer.

Keywords: lung cancer, lung adenocarcinoma, prognostic factor, ALK, GALNT14, TIMP1, large sample analysis, P13K/AKT pathway.

1. Introduction

Lung cancer is the commonest diagnosed cancer around the world and leads to a large number of cancer deaths. It is estimated that roughly 1.8 million of new lung cancer cases are diagnosed every year [1]. In 2018, it was estimated that there were 2.1 million new cases of lung cancer diagnoses, occupying approximately 12% of cancer cases worldwide. And the incidence rate of female are generally lower than that of male [2,3]. In 2012, the number of deaths due to lung cancer was approximately 1.6 million, which may increase to 3 million in 2035 as estimated [1,4]. The prognosis of lung cancer in patients is relatively poor with 5-year survival rate ranging from only 4% to 17%, which hinges on the stage of disease at diagnosis [5].

Lung cancer is sorted to two primary categories: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NCLC). SCLC can be further divided into two subtypes, the pure SCLC and SCLC combined with NSCLC. In SCLC, there is a central tumor originated from airway submucosa as a peril-hilar mass. In histology studies, this type of cancer was discovered originating from

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DOI: 10.54254/2753-8818/3/20220438

neuroendocrine cells of the basal bronchial epithelium, which are small, spindle or round cells with granular chromatin, lack of cytoplasm and commonly observed with necrosis [5,6]. NSCLC is normally categorized into lung adenocarcinoma(LUAD), squamous cell carcinoma(SCC), and large-cell carcinoma. LUAD is the commonest type of NSCLC, occupying roughly 40% of lung cancer cases. LUAD originates from alveolar cells located in smaller airway epithelium. SCC accounts for 25% to 30% in all lung cancer cases. Large-cell carcinoma accounts for 5% to 10% in lung cancers [7]. NSCLC is normally staged through the TNM staging system, which was named and defined by American Joint Committee on Cancer (AJCC) [8]. The TNM systems determines stages of lung cancer from three directions, the size of primary tumor (T), the spread of tumor to lymph node (N), and the existence of metastasis (M). And TNM is eventually classified by combining tumor characteristics (T) from T1 to T4, the degree that lymph node involved (from N0 to N3), and the absence (M0) or presence of metastasis (M1). Generally, lung cancer can also be divided into 4 stages (Stage 1 to Stage 4) and 3 grades (Grade I, Grade II, Grade III). In histology classification, the tumor of stage 1 is limited, normally under 5 cm, without metastasis to lymph nodes. In stage 2, the tumor size is between 5 to 7 cm without metastasis to lymph nodes or with under 5 cm with only N1 lymph nodes metastasis. In stage 3, tumor have occurred accompanied with N1, N2, N3 lymph nodes metastasis without metastasis to distant organ (M0). Tumors in stage 4 have presented metastasis to distant organ/organs (M0), including bone, brain, liver and kidney. Grade is commonly used to describe the degree of atypia for tumor. Grade1 tumor is highly differentiated with low malignancy and physiologically close to heathly tissues. Grade 3 tumor is lowly differentiated with high malignancy and has great difference with normal tissue. The level of differentiation and malignancy of Grade 2 is between Grade 1 and Grade 3.

Lung cancer patients are commonly diagnosed in the advanced stage, which accounts for almost 75% of patients. Only 10% to 15% of new lung cancer cases are diagnosed in early stage [9]. The main cause is the lack of diagnosing and prognosing factors for early stage. Therefore, this research aims to search for biomarkers that are related to early-stage diagnosis so as to deal with this factual problem. The present study discovers that ALK, GALNT14, TIMP1 can be potential prognostic factors in early-stage lung cancer patients.

2. Materials and method

2.1. Data sources

The present research employed significant amount of merged lung cancer database data (including CAARRAY, GSE14814, GSE19188, GSE29013, GSE30219, GSE31210, GSE3141, GSE31908, GSE37745, GSE43580, GSE4573, GSE50081, GSE8894, TCGA overall n=1925, http://kmplot.com). Kaplan-Meier survival analysis and Log-Rank test were carried out on the prognosis of patients with different expression levels of ALK, GALNT14, TIMP1 in lung cancer [10].

2.2. Statistical processing

The Kmplotter analysis tool (http://kmplot.com/analysis/) was used for the Kaplan-Meier survival analysis. The Kaplan-Meier analysis, matched with Log-rank test, was used to judge whether a certain factor was associated with prognosis among various of cancers. For each gene, the mean value of all probes was taken as the expression value of the gene. According to the expression value of the target gene, the patients were divided into high expression (above median) and low expression (below median) groups according to the median principle. P-values < 0.05 were considered to be statistically significant for all statistical treatments.

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3. Result

3.1. High expressions of ALK, GALNT14, TIMP1 are negatively associated with OS in LUAD (lung adenocarcinoma)

The analysis of lung cancer cases with Kaplain-Meier Plotter demonstrates that the high expressions of ALK, GALNT14, TIMP1 are related to poor prognosis in lung cancer. Further exploration reveals that high expressions of ALK, GALNT14, TIMP1 are associated with worse prognosis in LUAD patients compared with LUAD patients with low expressions of the three molecules. However, expression levels of the three molecules have no correlation with OS in SCC (squamous cell carcinoma). To be more specific, the median overall survivals of lung cancer patients with high expressions of ALK, GALNT14, TIMP1 are respectively 62, 57, 59 months, which are comparatively shorter than the median survivals of patients with low expression in the three molecules (Figure 1.A, median OS= 76,79,79.27 months). Combined with log-rank test, this result also demonstrates that high expressions of ALK, GALNT14, TIMP1 in lung cancer patients are negatively associated with OS of lung cancer patients (Figure 1.A, P=0.074, P=4.4e-05, P=0.00011). In LUAD patients, the median survivals of patients with high expressions of ALK, GALNT14, TIMP1 (Figure 1.B, median OS =69,75.43, 20 months) are significantly shorter than patients with low expressions of the three molecules (Fig 1.B, median OS=127, 112.67, 50.33 months). Combined with the log-rank test, it demonstrates that the high expressions of ALK, GALNT14, TIMP1 in LUAD patients are negatively associated with OS of LUAD patients (Figure 1. B, P=6.2e-07, P=0.00022, P=3.3e-10).However, in SCC patients, the high expressions of ALK, GALNT14, TIMP1 do not necessarily suggest a poor prognosis and have no relationship with OS of the patients. (Fig C, P=0.19, P=0.59, P=0.52).

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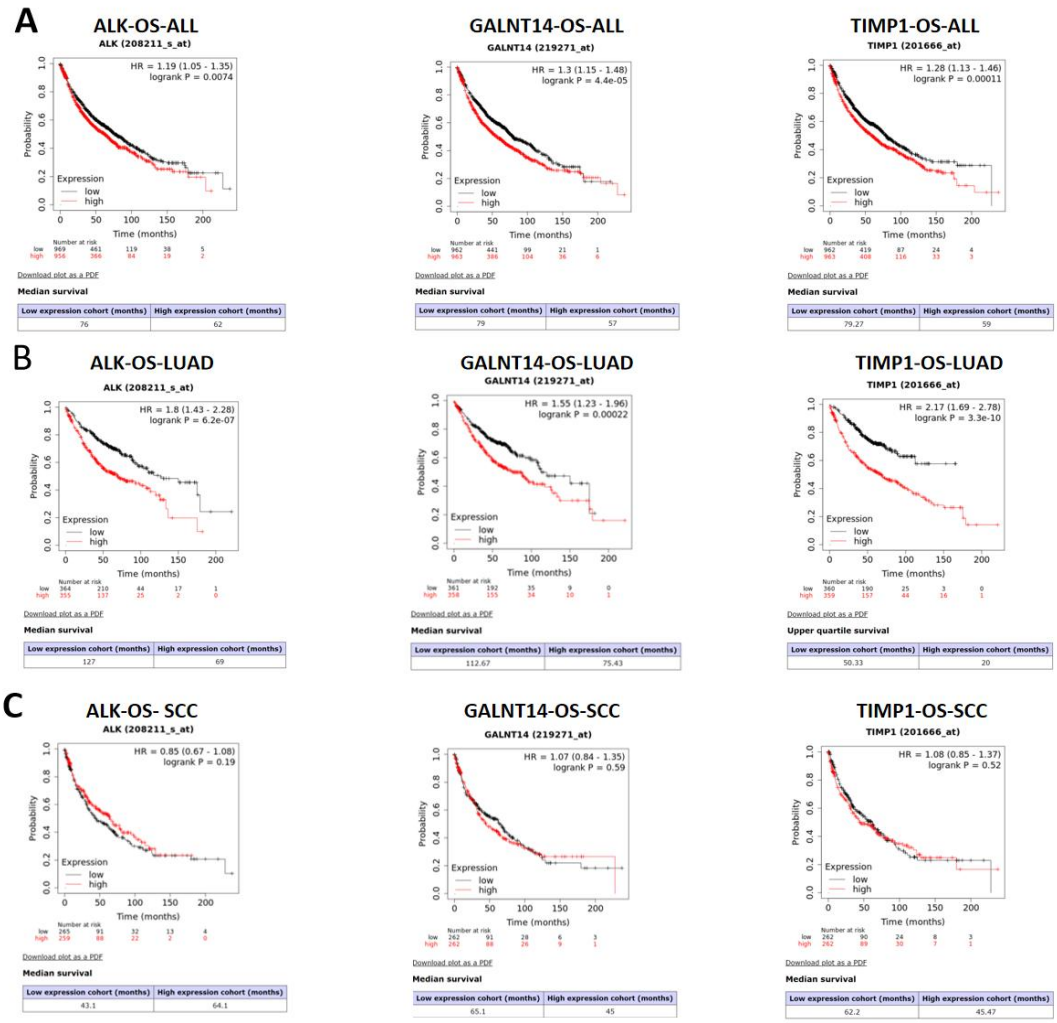


Figure 1. The Kaplan-Meier survival curves that demonstrate the relationships between ALK, GALNT14 , TIMP1 expression levels and OS in non-small cell lung cancer A : High expressions of ALK, GALNT14 and TIMP1 are negatively related with OS in overall LUAD (lung adenocarcinoma) and SCC (squamous cell carcinoma) (P=0.0074, P=4.4e-05 and P=0.00011). B: High expressions of ALK, GALNT14 and TIMP1 are negatively related to OS in LUAD (P=6.2e-07, P=0.00022, P=3.3e-10<0.05). C: Expression levels of ALK, GALNT14 and TIMP1 have no significant relationship with OS in SCC (P=0.19, P=0.59, P=0.52).

3.2. The prognostic significance of ALK, GALNT14, TIMP1 for lung cancer is limited in stage 1 and grade 2

The present study then investigates the prognostic significance of ALK, GALNT14, TIMP1 in different developing stages and grades of lung cancer. Further exploration shows that high expressions of ALK, GALNT14, TIMP1 are only related to poor prognosis in patients in Stage1 of lung cancer and high expressions of ALK, GALNT14 are only related to poor prognosis in patients in Grade 2 of lung cancer. To be more specific, the median overall survivals of lung cancer patients in stage 1 with high expressions of ALK, GALNT14, TIMP1 are respectively 77.77, 77.77, 72 months, which are significantly shorter than the median overall survivals of patients in stage 1 with low expression of ALK, GALNT14, TIMP1 (Figure 2.A, median OS=179.63, 112.67, 112.67). Combined with the result of the log-rank test, this result suggests that the high expressions of ALK, GALNT14, TIMP1 in Stage1 lung cancer patients are negatively associated with OS. (Figure 2. A, P=2.4e-05, P=7.1e-05 and

DOI: 10.54254/2753-8818/3/20220438

P=5.3e-08) However, the median survivals of lung cancer patients in Stage 2 or 3 with high expressions of ALK, GALNT14, TIMP1 have no significant difference with those in Stage 2 or Stage 3 with low expressions of ALK, GALNT14, TIMP1, which, combined with the log-rank test, indicating that the expression levels of ALK, GALNT14, TIMP1 have no significant correlation with OS of the lung cancer patients in Stage 2 or Stage 3. (Figure 2.B, P=0.28, P=0.76, P=0.058; Figure 2.C, P=0.52, P=0.28, P=0.49) What's more, the median survivals of the lung cancer patients in Grade 2 with high expressions of ALK, GALNT14 are respectively 62.3, 62.1 months, which are significantly shorter than the median overall survivals of lung cancer patients in Grade 2 with low expression of the two molecules (Figure 3.B, 85.65, 96 months). Combined with the log-rank test, this result demonstrates that high expressions of ALK, GALNT14 in lung cancer patients in Grade 2 are negatively associated with OS in these patients (Figure 3.B, P=0.01, P=0.019). However, according to the result of the log-rank test, the expression levels of ALK, GALNT14 do not have significant relationship with OS in lung cancer patients in Grade 1 or Grade 3 (Figure 3.A, P=0.53, P= 0.12; Figure 3.C, P=0.32, P=0.6); and the high expression of TIMP1 has no association with OS in lung cancer patients in Grade 1, Grade 2 or Grade 3 (Figure 3.A, P=0.46; Figure 3.B, P=0.35; Figure 3.C, P=0.75).

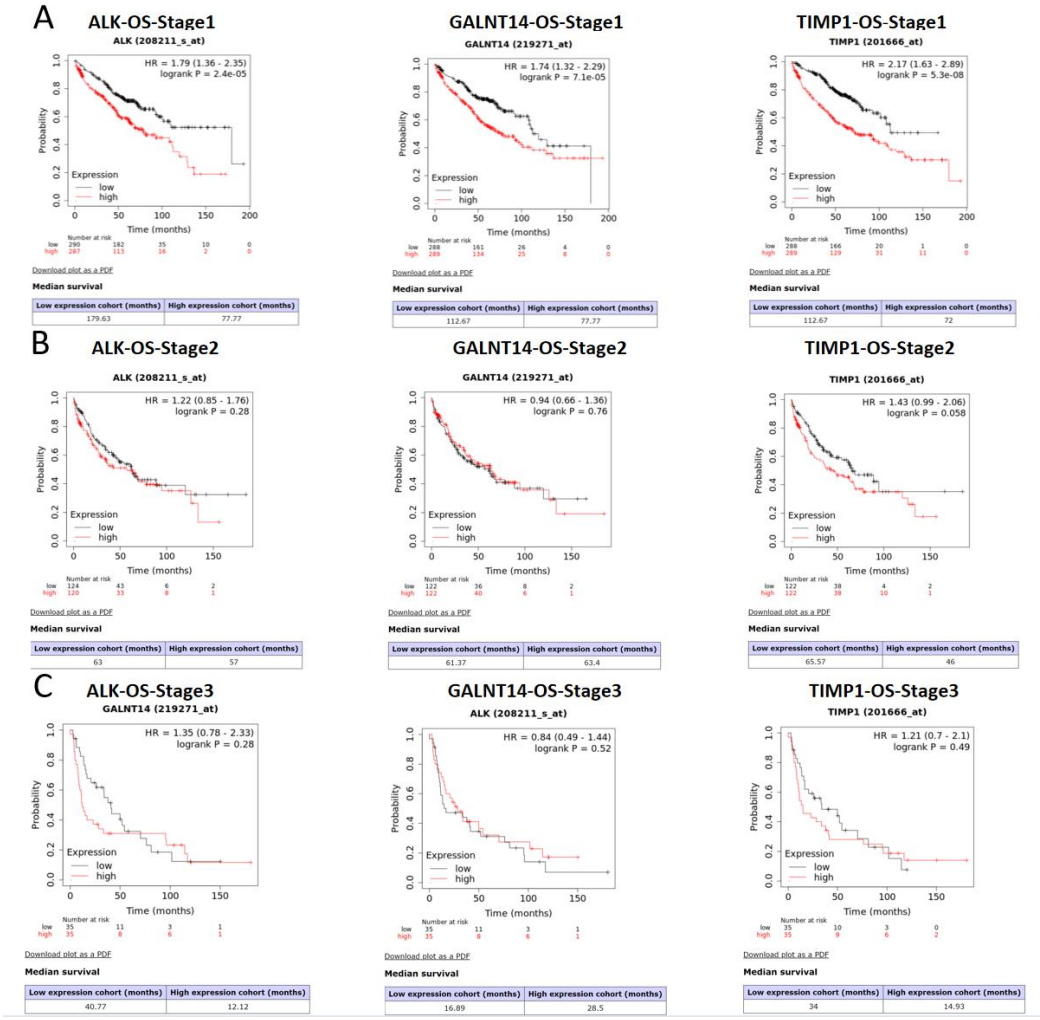


Figure 2. The Kaplan-Meier survival curves that demonstrate the relationships between ALK, GALNT14, TIMP1 expression levels and OS in different developing stages of non-small cell lung cancer A: High expressions of ALK, GALNT14 and TIMP1 are negatively related with OS in Stage 1 (P=2.4e-05, P=7.1e-05 and P=5.3e-08). B: Expression levels of ALK, GALNT14 and TIMP1 have no

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significant relationship with OS in Stage 2 (P=0.28, P=0.76, P=0.058). C: Expression levels of ALK, GALNT14 and TIMP1 have no significant relationship with OS in Stage 3 (P=0.52, P=0.28, P=0.49).

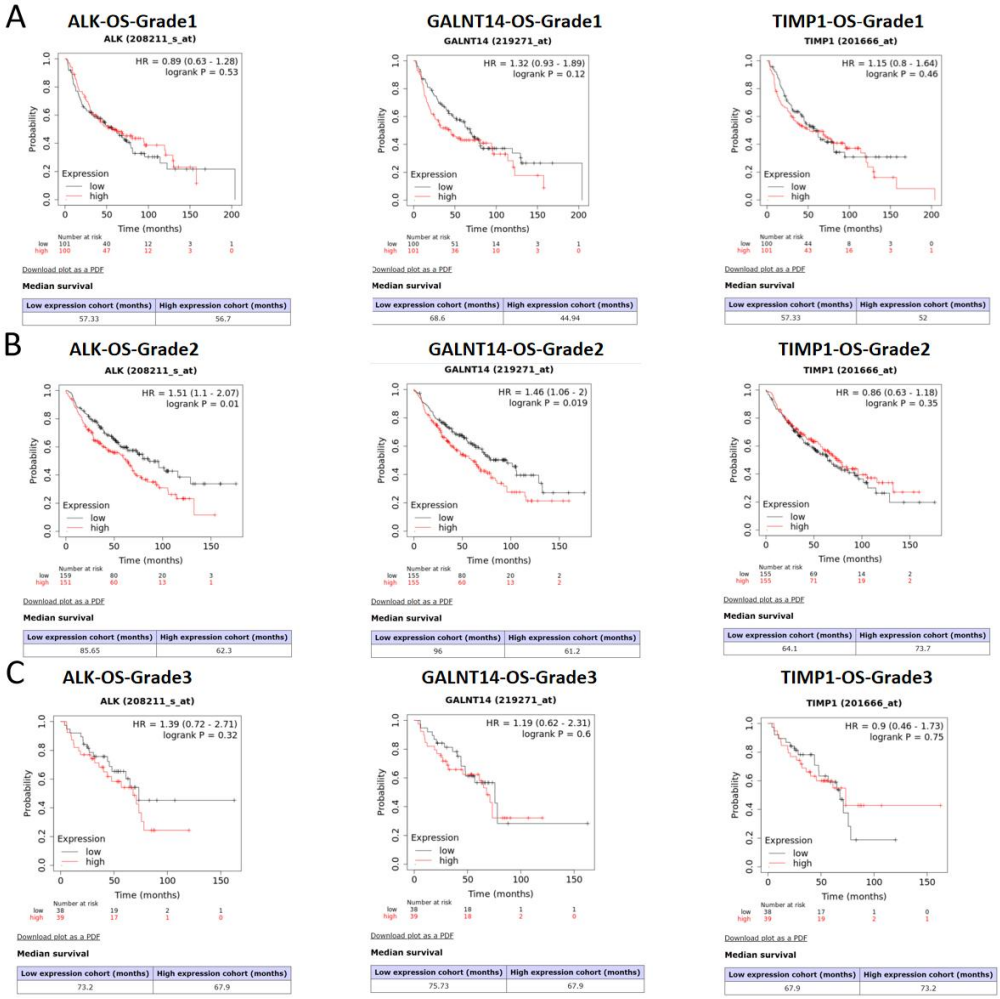


Figure 3. The Kaplan-Meier survival curves that demonstrate the relationships between ALK, GALNT14, TIMP1 expression levels and OS in different grades of non-small cell lung cancer A: Expression levels of ALK, GALNT14 and TIMP1 have no significant relationship with OS in Grade 1(P=0.53, P= 0.12, P=0.46). B: High expressions of ALK and GALNT14 are negatively related with OS in Grade 2 (P=0.01, P=0.019), while the expression level of TIMP1 has no significant relationship with OS in Grade 2(P=0.35). C: Expression levels of ALK, GALNT14 and TIMP1 have no significant relationship with OS in Grade 3 (P=0.32, P=0.6, P=0.75).

3.3. High expression of TIMP1 is negatively associated with OS in lung cancer patients who have never smoked

The analysis of lung cancer cases through Kalpan-Meier Plotter shows that ALK and GALNT14 are supposed to be the potential poor prognostic factors for lung cancer patients who have smoked or haven't smoked before while TIMP can only work as a poor prognostic factor in patients who have never smoked. According to the results of the log-rank test, high expressions of ALK and GALNT14 are negatively associated with OS in lung cancer patients who have smoked or never smoked (Fig 4.A, P=0.021, P=0.0076; Fig 4.B, P=9.3e-05, P=0.02); but high expressions of TIMP1 are only negatively associated with OS in lung cancer patients who have never smoked (Fig 4.B, P=0.00011). The expression level of TIMP1 has no relationship with OS in patients who have smoked (Fig 4.A, P=0.23).

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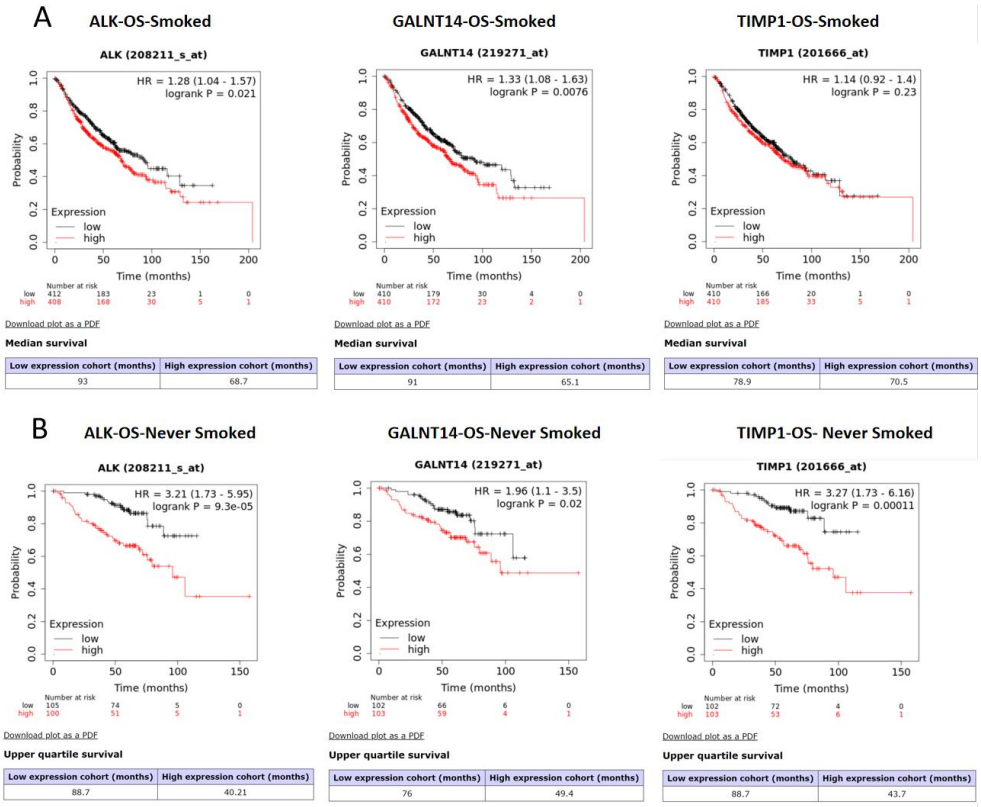


Figure 4. The Kaplan-Meier survival curves that demonstrate the relationships between ALK, GALNT14, TIMP1 expression levels and OS in the patients who have smoking history or never smoked A: High expressions of ALK and GALNT14 are negatively related to OS in patients who have smoking history (P=0.021, P= 0.0076), while the expression level of TIMP1 have no significant relationship with OS in patients who have smoking history (P=0.23). B: Expression levels of ALK, GALNT14 and TIMP1 are negatively related to OS in patients who have never smoked (P=9.3e-05, P=0.02, P=0.00011).

3.4. High expression of ALK is negatively associated with OS in female lung cancer patients

The analysis of lung cancer cases on Kaplan-Meier plotter website demonstrates that high expressions of GALNT14, TIMP1 can indicate poor prognosis in no matter male or female lung cancer patients, while the high expression of ALK only indicates poor prognosis in male lung cancer patients. To be more specific, for female patients, the median of OS in the patients with high expressions of ALK, GALNT14, TIMP1 (Figure 5.A, 96.1, 87.7, 95.5 months) are comparatively shorter than the patients with low expressions of the three molecules (Fig. A, 108.97, 110.27, 105 months). Combined with the log-rank test result, it demonstrates that high expressions of ALK, GALNT14, TIMP1 are negatively associated with OS in the patients (Figure 5.A, P=0.021, P= 0.016, P=0.042). For male lung cancer patients, the median overall survivals of the patients with high expressions of GALNT14, TIMP1 (Figure 5.B, 48, 45.8 months) are comparatively shorter than the patients with low expressions of the two molecules (Fig. B, 68.1, 70 months). Combined with the log-rank test result, it demonstrates that the high expressions of GALNT14, TIMP1 are negatively associated with OS of the patients (Figure 5.B, P=0.018, P=0.00062). Nevertheless, the expression level of ALK has no relationship with OS in male lung cancer patients (Figure 5.B, P=0.097).

DOI: 10.54254/2753-8818/3/20220438

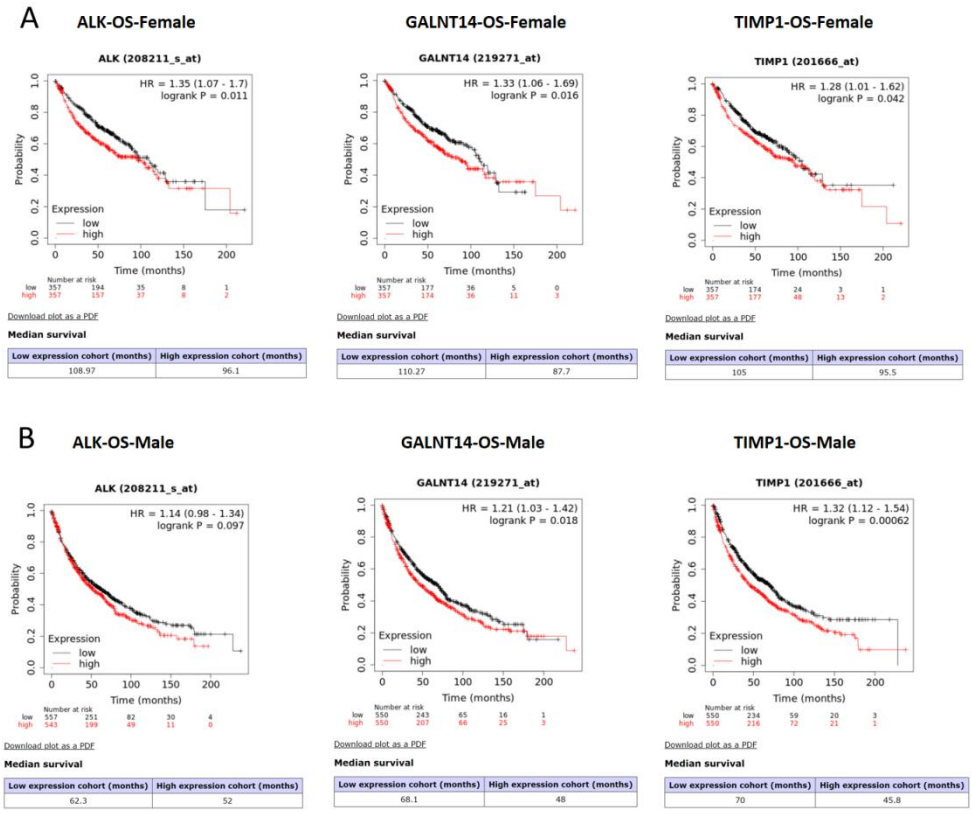


Figure 5. The Kaplan-Meier survival curves that demonstrate the relationships between ALK, GALNT14, TIMP1 expression levels and OS in different genders A: High expressions of ALK, GALNT14 and TIMP are negatively related to OS in female patients (P=0.011, P= 0.016, P=0.042). B: High expressions of TIMP1 and GALNT14 are negatively related to OS in male patients (P=0.00062, P=0.018) while the expression level of ALK has no significant relationship with OS in male patients (P=0.097).

3.5. High expression of GALNT14 is negatively associated with OS in patients who have not received chemotherapy

The analysis of lung cancer cases on Kaplan-Meier plotter website indicates that GANLT14 is supposed to be a potential poor prognostic factor for patients who have never received chemotherapy, and that expression levels of ALK, GALNT14, TIMP1 have no relationship with patients who have received chemotherapy (Figure 6.B, P=0.59, P= 0.45, P=0.66). Similarly, expression levels of ALK and TIMP1 have no association with patients who have not received chemotherapy (Figure 6.A, P=0.37, P= 0.39). However, high expression of GALNT14 is negatively associated with OS of patients who have not received chemotherapy (Figure 6, P=0.00016). Meanwhile, the median survival of patients who have not received chemotherapy with high expression of GALNT14 is 47.9 months, which is significantly shorter than those with low expression of GALNT14 (Figure 6.A, 128.8 months).

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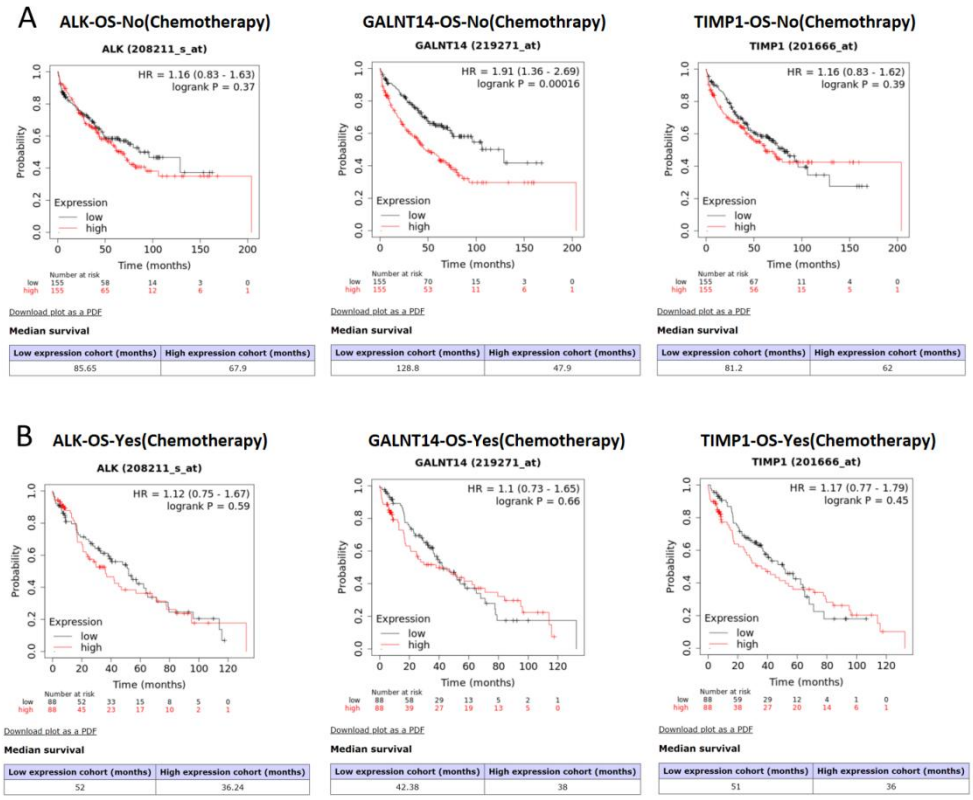


Figure 6. The Kaplan-Meier survival curves that demonstrate the relationship between ALK, GALNT14, TIMP1 expression levels and OS in patients who have received chemotherapy and not received chemotherapy A: High expressions of GALNT14 are negatively related to OS in female patients (P=0.00016) while expression levels of ALK and TIMP1 have no significant relationship with OS in patients who have not received chemotherapy (P=0.37, P= 0.39). B: Expression levels of ALK, GALNT14 and TIMP1 have no significant relationship with OS in patients who have received chemotherapy. (P=0.59, P= 0.45, P=0.66).

4. Conclusion and discussion

The present study discovers that ALK, GALNT14, TIMP1 can work as the potential poor prognostic factors in LUAD and be used to make prognosis for patients who are in early stage and grade of lung cancer (Stage1, Grade2). Interestingly, while high expression of TIMP1 can indicate poor prognosis in lung cancer patients who have never smoked, it cannot function as an prognostic factor in patient who have smoking history; while ALK can indicate poor prognosis of female lung cancer patients, it isn't able to suggest any prognosis in male lung cancer patients since high expression of ALK is negatively correlated with OS in female lung cancer patients but has no relationship with OS in male cancer patients; GANT14 can provide poor indicator of prognosis in lung cancer patients who have never received any chemotherapy.

ALK (anaplastic lymphoma kinase) gene encodes a transmembrane tyrosine kinase receptor which belongs to insulin receptor superfamily and plays a vital role in the development of brains. ALK normally expresses in the nerve system of embryo during the embryogenesis, but the expression of ALK decreases greatly after birth and only rarely occurs in nerve and endothelia cells of healthy human adults [11,12]. In oncogenesis, the rearrangement of chromosome is the commonest source of gene alternations in ALK, which normally results in fusions of multiple genes. Since the first discovery of the role that ALK-NMP1 fusion plays in oncogenesis, there have been over 19 different ALK fusion partners found, including EML4, KIF5B, KCL1, TFG, KIF5B, and TP. [12-14]. What's more, the high expression of ALK fusion proteins has also been proved to be associated with various

DOI: 10.54254/2753-8818/3/20220438

major oncogenic pathway, such as Ras/ERK, PI3K/Akt, and JAK/STAT. For example, the activation of NMP1-ALK fusion protein can induce the higher expression of STAT3 protein and transcription of STAT3 gene in ALK+TCL cells. Through the mediation of STATS, NMP/ALK can indirectly induce the expression of Interleukin 10 (IL-10), which plays a key role in immune escape in malignant cells by suppression of immune response against malignant cells [12]. Similarly, expression of EML4-ALK fusion protein can also induce significant activation of ERK and STAT3 and suppression of ERK or STAT3 pathway will significantly decrease the proliferation of lung cancer cell that express EML4-ALK, demonstrating that these pathways play a role in downstream of EML4-ALK in lung cancer cells [13].

GANLT14 belongs to polypeptide N-acetylgalactosaminyltransferase (GALNT) family, which is responsible for transferring N-acetyl-D-galactosamine (GalNAc) to hydroxyl groups on serines and threonines on in target peptide. GALNT14 has also been proved to transfer GalNAc to large proteins like mucins to initiate O-glycosylation. In oncogenesis, the alternation and dysregulated expression of GALNT14 has been proved to promote metastasis in various cancer, like Breast cancer, Overian cancer, NSCLC and Neuroblasoma, which is connected with some significant oncogenic pathways, such as Wnt/β-catenin, protein EGFR/mTOR, KRAS/PI3K, Ras/ERK, and P13K/AKT [14-18]. For instance, downregulation of GALNT14 significantly inhibits EGFR/Motor in ovarian cancer cell; and GALNT14 has also been proved to be involved in the glycosylation of EGFR. Since glycosylation has been reported to be related to the stability of protein, downregulation of GALNT14 possibly decreases the stability of EGFR through affecting O-glycosylation of EGFR, which has been proved by the fact that the downregulation of GALNT14 can significantly shortens the half-life of EGFR [16]. GALNT14 has also been proved to play a significant role in metastasis of LUAD through inducing the expression of HOXB9, which is achieved by increasing sensitivity of Wnt response and stability of β-catenin protein. What's more, in the lung metastatic breast cancer cells (BCCs), the overactivation of KRAS/P13K pathway increases the expression of GALNT14 in BCCs through mediation of c-JUN protein. GALNT14 then promote the lung metastasis of breast cancer through enhancing BCCs self-renewal and making BCCs grow successfully in lung parenchyma. Among this process, GALNT14 upregulates SOX4 expression to enhance BBCs self-renewal by inhibiting lung-derived BMPs (bone morphogenetic proteins), which functions on inhibiting self-renewal of cells. And then GALNT14 enables BCCs to receive FGF (Fiber Growth Factor) from Macrophages by activating O-GalNAcylation of FGFR1, which then enables BCCs to successfully grow in lung parenchyma [17]. O-GalNAcylation of FGFR1 may facilitate FGFR dimers, which activates downstream or related pathways like P13K/AKT and Ras/ERK through phosphorylation of FGFR kinase. GALNT14 may also induce the activation of P13K/AKT and Ras/ERK though promoting the O-GalNacylation of FGFR1 [18].

TIMP1 (tissue inhibitor of metalloproteases 1) gene belongs to TIMP gene family, which encodes proteins that are natural inhibitors of the Matrix Metalloproteins (MMPs). Since MPPs is involved in the degradation of the extracellular matrix and tumour cells require the proteolytic ability of MPPs to achieve the occurrence of the cells' growth, migration, invasion and metastasis, TIMPs, including TIMP1, are originally believed to be able to prevent the metastasis and invasion of tumor cells, which has been proved by amounts of early experiments. However, this conclusion is inconsistent with the results in following clinical experiments and TIMP1 has actually been proved to play a significant role in tumors' metastasis and procession through promoting proliferation, survival and growth of those tumor cells [19,20]. To be more specific, in B lymphocyte cell lines, human mammary epithelial cells, and hematopoietic cells, TIMP1 activates some survival-promoting cells, like P13K/AKT, to inhibit cell apoptosis and promote cell survival. TIMP1 has also been proved to activate P38, MAPK, and JNK to induce the proliferation and differentiation of UT-7 erythroid cells [20].

To sum up, the reason why ALK, GALNT14 and TIMP1 can work as the poor prognostic factors LUAD may be that the activation of the three molecules plays a significant role in activating P13K/AKT pathway, which is a common oncogenic pathway among LUAD. Since the overexpression of GALNT14 can increase the cellular proapoptotic receptors (Apo2L/TRAIL) sensitivity [21], the

DOI: 10.54254/2753-8818/3/20220438

chemotherapy which includes the use of proapoptotic receptor agonists dulanermin may have been received by those LUAD patients with high expression of GALNT14. And this deduction may explain why GALNT14 can indicate poor prognosis in patients who have not been treated with chemotherapy but fails to indicate poor prognosis in patients who have been treated with chemotherapy in this research. However, the specific underlying principle/principles behind this fact haven't been researched or found yet. In addition, the actual principles which may explain why ALK only indicates poor prognosis in female and TIMP1 specifically indicates poor prognosis in patients who do not have smoking history haven't been clear. Finally, the present study suggests that ALK, GALNT14 and TIMP1 may be used for the early stage or grade prognosis of LUAD patients.

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