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Bioinformatics Analysis of the Expression and Clinical Significance of MMPs in Lung Adenocarcinoma

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Abstract: This study uses bioinformatics methods to analyze the expression and clinical significance of human MMP gene family (MMPs) in lung adenocarcinoma (LUAD). The GSE115002 dataset from the GEO database is downloaded to analyze the expression of MMPs. The chromosomal localization of differentially expressed MMPs is determined. Kaplan-Meier Plotter is used to analyze the relationship between MMPs' expression and the overall survival (OS) and disease-free survival (DFS) of LUAD patients. As a result, we found that the expression levels of MMP1, MMP3, MMP7, MMP9, MMP10, MMP11, MMP12 and MMP13 show marked elevation in tumor tissues. MMP-11 is located in the q36.3 segment of human chromosome 7, while MMP-9 is situated in the q13.12 segment of human chromosome 20. Other MMPs are primarily localized in the q22.2 region of human chromosome 11. Elevated expression of MMP1, MMP3, MMP7, MMP10, MMP11 and MMP12 is significantly associated with poor prognosis in LUAD patients. To conclude, the expression levels of MMP1, MMP3, MMP7, MMP10, MMP11 and MMP12 are significantly upregulated in LUAD. They are expected to become biomarkers for LUAD prognosis.

1. Introduction

New cases and deaths for lung cancer rank first in all cancers[1]. Lung adenocarcinoma (LUAD) is a main subtype of lung cancer[2]. Its occupation ratio has been increasing. In recent years, many single gene prognostic markers for LUAD have been discovered [3-5]. Single gene testing is relatively simple and cost-effective. However, its accuracy is easily affected by other factors.

Matrix metalloproteinases (MMPs) are a large family. They are capable of breaking down the extracellular matrix, thereby undermining the histological barrier that resists tumor cell infiltration. MMPs are associated with various diseases. Beata Gajewska et al. discovered that MMP-2 and MMP-9 are associated with diabetes[6]. Aaron Hilliard et al. discovered that MMP-9 is related with cataract's development[7]. MMP-7 was found to be associated with pancreatic cancer[8]. MMP-14 has been verified to be linked with the invasive and metastatic processes of cancer[9]. The aim of this study is to provide reliable prognostic markers for LUAD patients by analyzing MMPs.

2. Materials and Methods

2.1. Digging into MMPs significantly correlated with LUAD

The GEOquery package is used to download the GSE115002 dataset from the GEO database. After data cleaning and standardization correction, the limma package is loaded for analysis of differential expression genes (DEGs). The ggplot2 package is used to draw volcano maps. Based on the criteria of | Log2FC |>2 and adjust P-value<0.05, MMPs significantly correlated with human LUAD are selected and visualized by a heatmap.

2.2. Chromosome location analysis of MMPs

The chromosomal positions of the selected MMPs are analyzed according to the GRCh38/hg38 genome version in the UCSC database.

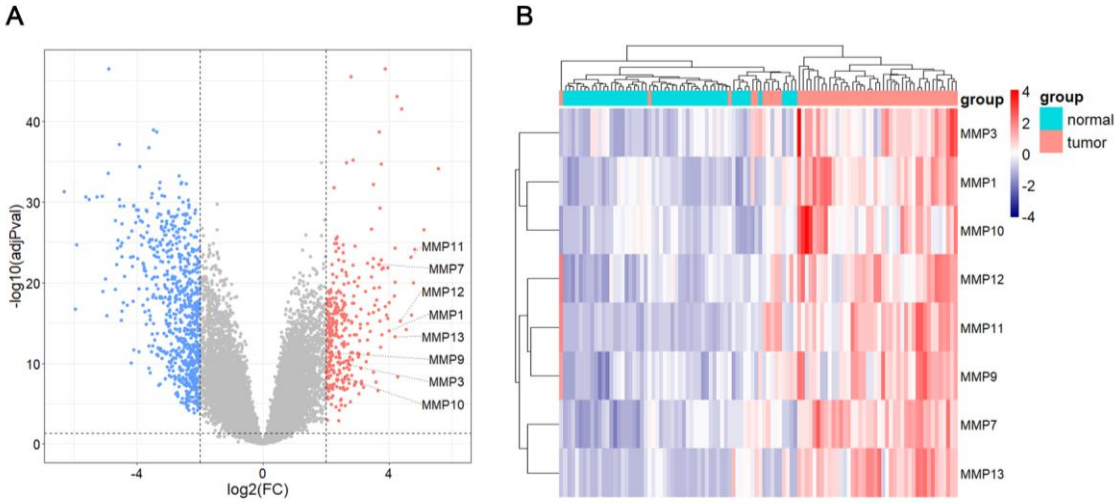
2.3. Prognostic analysis of MMPs

The Kaplan-Meier Plotter website is used to plot survival curves to explore the association between the expression level of MMPs and overall survival (OS) and disease-free survival (DFS) in LUAD patients.

3. Results

3.1. Identifying genes with altered expression in LUAD

After data cleaning, 21754 genes were obtained from the dataset, of which 1031 were differentially expressed genes, with 318 significantly up-regulated and 713 significantly down-regulated. The results were visualized using a volcano plot, where red represents upregulation and blue represents downregulation (see Figure 1A); 8 members of the MMP gene family were significantly upregulated in tumor tissue, including MMP1, MMP3, MMP7, MMP9, MMP10, MMP11, MMP12 and MMP13 (see Figure 1B).



A. for all DEGs; B. for MMPs with significant differences

Figure 1: Gene expression in LUAD

3.2. The position of MMPs on chromosomes

The query results of UCSC database show that MMP1, MMP3, MMP7, MMP10, MMP12 and MMP13 are all located in the q22.2 region of human chromosome 11, MMP11 resides in the q36.3 segment of human chromosome 7, and MMP9 resides in the q13.12 segment of human chromosome 20.

3.3. Prognostic analysis of MMPs in LUAD patients

We used the Kaplan Meier Plotter website to plot the survival curves of LUAD patients. OS data show that high expression of MMP1, MMP3, MMP7 and MMP10 is significantly correlated with poor prognosis in LUAD patients, P<0.05; There is no significant correlation between the expression of MMP9, MMP11, MMP12, MMP13 and the prognosis of LUAD patients (see Figure 2). DFS data show that high expression of MMP1, MMP3, MMP10, MMP11 and MMP12 is markedly linked with poor prognosis in LUAD patients, P<0.05; No significant relationship exists between the expression of MMP7, MMP9, MMP13 and the prognosis of LUAD patients (see Figure 3).

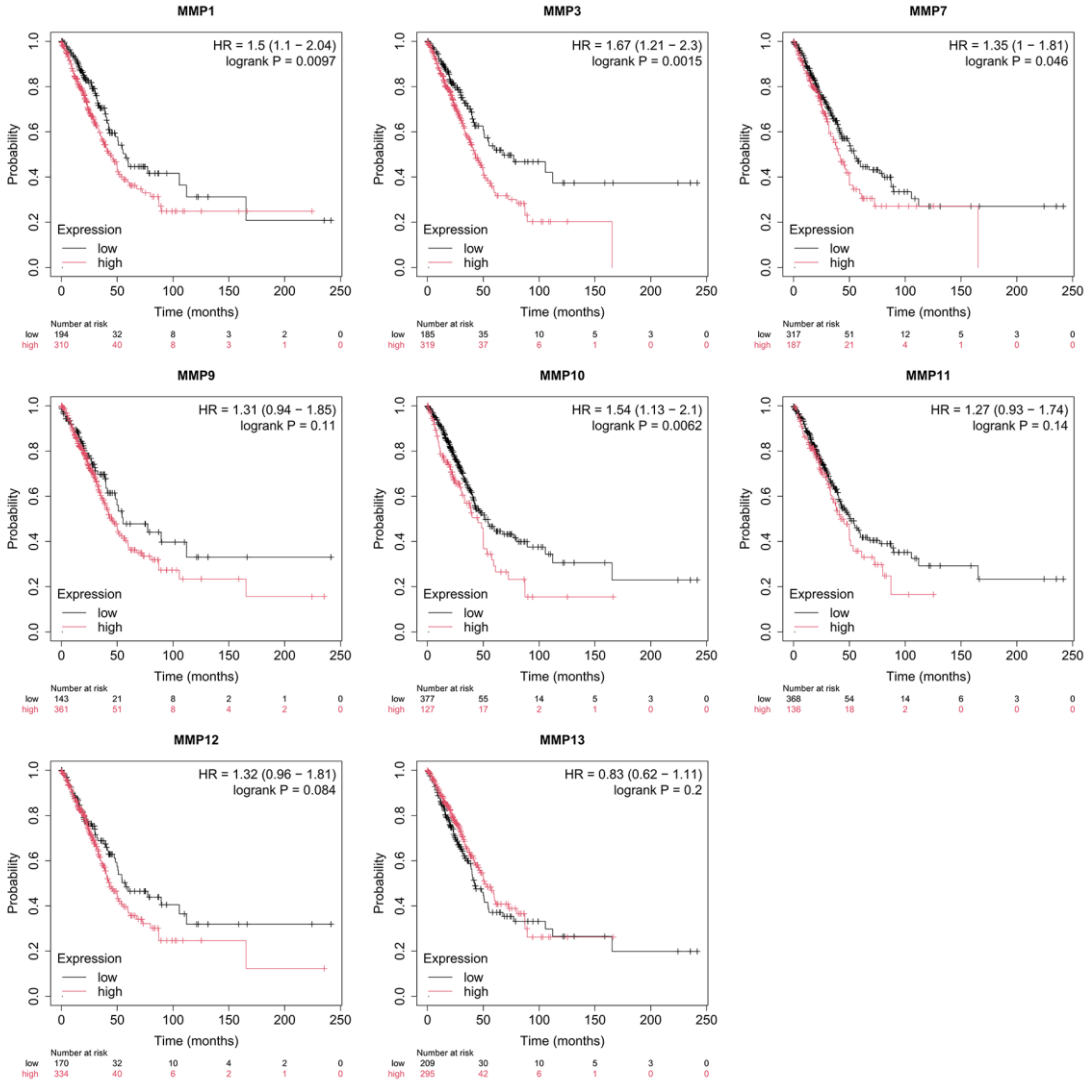


Figure 2: Relationship between MMPs and OS for LUAD patients

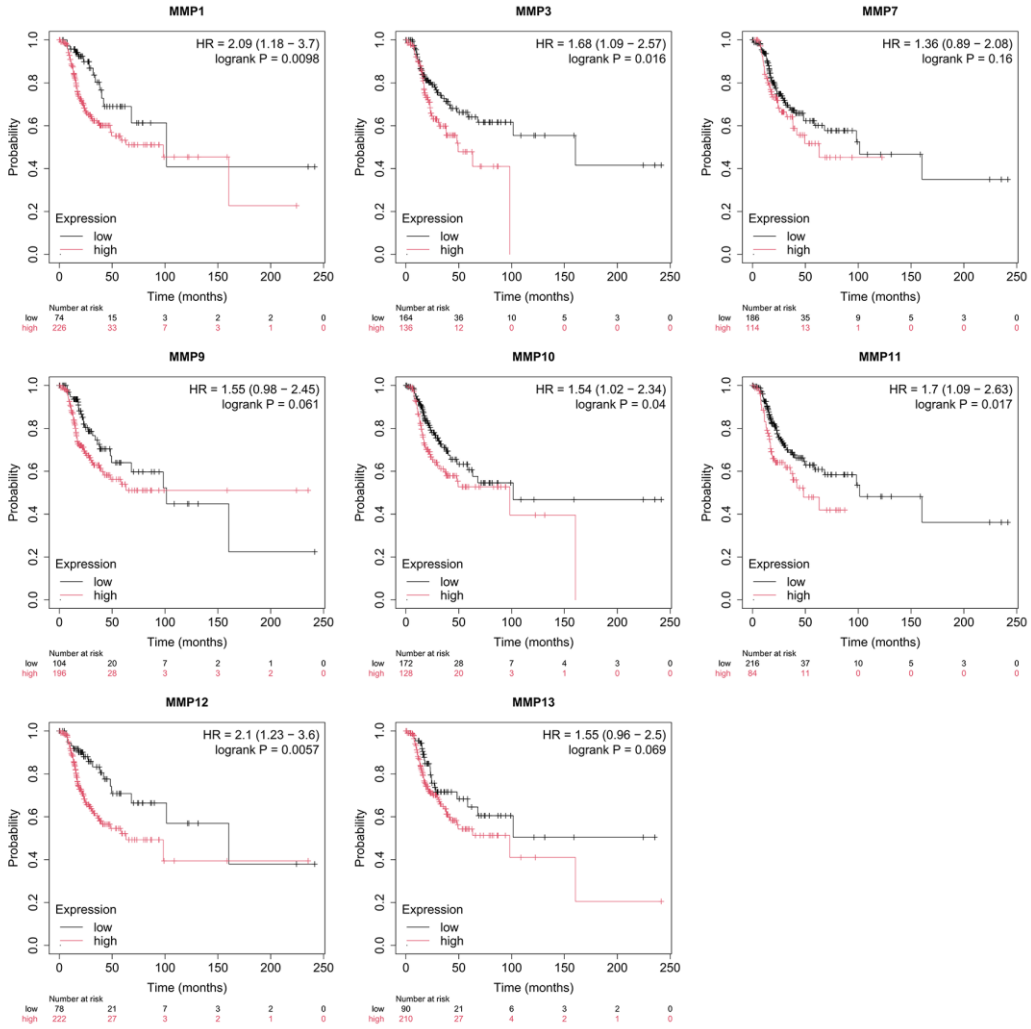


Figure 3: Relationship between MMPs and DFS for LUAD patients

4. Discussion

MMPs are highly expressed in many tumor tissues. MMP-1, MMP-2 and MMP-9 serve as biomarkers for early diagnosis of tumors[10]. MMPs can dissolve the extracellular matrix and help cancer cells migrate[11]. Therefore, their inhibitors are used to treat tumors. Inhibitors of MMP-2/MMP-9 can be used as anticancer drugs[12]. Inhibitors of MMP-8, MMP-10, MMP-13 have also been shown to be useful for tumor treatment[13,14].

In addition, MMPs can act as prognostic markers for tumors. MMP-2 and MMP-9 can indicate poor prognosis for glioma[15]. MMP-11 and MMP-15 can reflect the prognosis of liver cancer[16]. MMP-8 for colorectal cancer[17], MMP-7 for gastric cancer[18], and MMP-14 for non-small cell lung cancer[19] are all good prognostic markers.

This study found that, the expression of MMP-1, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-12 and MMP-13 in LUAD tumor tissues was markedly elevated compared to normal tissues. OS data shows that high expression of MMP-1, MMP-3, MMP-7 and MMP-10 is significantly correlated with poor prognosis in LUAD patients. DFS data show that high expression of MMP-1, MMP-3, MMP-10, MMP-11 and MMP-12 has a significant correlation with poor prognosis in LUAD patients. Thus, the high expression of MMP-1, MMP-3, MMP-7, MMP-10, MMP-11 and MMP-12 has a significant correlation with poor prognosis in LUAD patients.

5. Conclusions

Overall, this research examined the association between MMPs and the prognosis of LUAD. High expression of MMP-1, MMP-3, MMP-7, MMP-10, MMP-11 and MMP-12 was significantly correlated with poor prognosis in LUAD patients. They are expected to become biomarkers for evaluating the prognosis of LUAD. This provides direction for further research.

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