ORIGINAL ARTICLE

A 6-lncRNA Signature to Improve Prognostic Prediction of Colon Cancer

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ABSTRACT

Background and Objective: Colorectal cancer is one of the most common malignant tumors in the world. The prognosis of colorectal cancer is thus variable despite the rapid development of treatment methods in recent years, the prognosis of colorectal cancer is still not satisfactory. Therefore, it is important to understand pathogenesis and development for more accurate prognostic methods. The present study aimed to identify a long non-coding (lnc) RNAs-based signature for prognosis in colon cancer patients.

Methods: Datasets from the GEO and TCGA databases were used, differential expression of lncRNA was analyzed, and a 6-lncRNA signature was identified. KEGG and GO was used to enrich the signal pathway to determine the biological effects of these 6-lncRNA.

Results: This study has established a prognosis model containing "LINC01494", "TRPM2-AS", "ATP1A1-AS1", "FRY-AS1", "LINC01360", and "RBFADN" based on data set of colorectal cancer patients available in the TCGA and GEO databases. The prognostic model of lncRNAs can predict the prognosis of patients with colorectal cancer.

Conclusion: The present study identified a 6-lncRNA signature that could predict the survival rate for colon cancer patients.

KEYWORDS: Bioinformatics, Long non-coding (lnc) RNA, Signature, Colon cancer.

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INTRODUCTION

Colorectal cancer is one of the most common malignant tumors in the world. Despite the rapid development of various treatments in recent years, the prognosis of patients with colorectal cancer is still not satisfactory. More than 70% of patients relapse within 24 months after surgery.[1-3] There is a significant heterogeneity in the quality of prognosis prediction in different prognostic methods for colorectal cancer.[4] Therefore, it is necessary to study the potential mechanism of colorectal cancer progression and to develop more accurate prognostic methods.

Cancer is a complex disease associated with a variety of genetic mutations, including epigenetic changes, chromosome translocation, deletion and

insertion.[5] Long non-coding RNA (lncRNA) is a non-coding RNA with a length of more than 200 nucleotides.[6] LncRNAs in combination with DNA and RNA, regulate local or global gene expression.[7] They are widely involved in a variety of physiological and pathological processes, including the regulation of cell death, growth, differentiation, chromatin modification, and epigenetic regulation.[8] LncRNAs regulate several cancer and tumor suppressor genes at transcriptional and post-transcriptional levels, affecting the proliferation, apoptosis, angiogenesis, invasion, migration and metastasis of tumor cells.[9,10] Some lncRNAs are differentially expressed in normal and tumor tissues.[11-15] They are also considered to be a more reliable prognostic biomarker of tumors.[16,17] It has been widely studied in many common cancers, such as breast cancer, colorectal cancer, head and neck cancer, and hepatocellular carcinoma.[18-22]

In recent years, high-throughput sequencing and gene chip technology have been widely used in the field of life sciences.[22-24] The use of bioinformatic methods, such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) database systems, to evaluate tumor-related molecules and their regulatory mechanisms, has greatly contributed to tumor research. Based on the data obtained from TCGA dataset, a 8-lncRNA model predicting tumor recurrence in patients with bladder cancer is established by WGCNA method.[25] A 10-lncRNA model classify breast cancer patients with high-risk and low risk disease recurrence.[26] Another model is 9-lncRNA prognostic nomogram, associated with the prognosis of patients with transparent cell renal cell carcinoma based on the TCGA database to predict the overall survival (OS) time of patients.[27] Runchen et al.[28] develop 8-lncRNA model, based on TCGA and GEO databases for predicting prognosis in elderly patients with non-small cell lung cancer. However, the study of lncRNA biomarkers, which can effectively predict the prognosis of patients with colorectal cancer, is far from enough. Therefore, this study aimed to develop a prognosis model of 6-lncRNA based on data sets of colorectal cancer patients in TCGA and GEO databases. The predictive ability of the model when tested may provide help for predicting the prognosis of patients with colorectal cancer.

METHODS

Download of Transcript Group Data

In R Studio environment (R version 3.5.1), GEO query toolkit (Version: 2.58.0) was used to download colon cancer patients' lncRNA expression data from GEO, which were GSE29621 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE29621) and GSE38832 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi). GSE29621 and GSE38832, included 65 and 122 cancer patients'samples data. Their corresponding clinical data were also downloaded (https://www.ncbi.nlm.nih.gov/geo/download/?acc=GSE29621&format=file).Moreover, the RNAseq count file data of colon cancer patients were downloaded from the TCGA database and then were normalized by the TMM method in the edge R toolkit (Version:3.24.3). A total of n = 521 samples was obtained for the data set of TCGA_COAD. The pathological data of colon cancer in the TCGA database were downloaded from TCGA Clinical Data Resource (https://www.cell.com/cms/10.1016/j.cell.2018.02.052/attachment/f4eb6b31-8957-4817-a41f-e46fd2a1d9c3/mmc1.xls).

Data Pre-processing

Both GSE29621 and GSE38832 databases containing only DFS (disease-free survival, DFS) data, were included. It was known that patients in the stage III/IV used to have poor prognosis. Thereby patients having stage III/IV were selected to characterize the prognosis of patients. Among n = 63 patients, n = 24 were from GSE29621 and n = 39 from GSE38832. The two data sets came from different research teams, so the batch effect needed to be removed. At the same time, the patients with complete DFS information at the stage phase and the ones at stage III/IV were selected from the TCGA database, thus forming a group of n = 52 patients.

lncRNA Extraction from the GEO and the TCGA Databases

In the GEO database, the biomaRt toolkit (Version: 2.38.0) was applied to change the probe names of the chips to the symbols of lncRNAs. For situations in which multiple probes correspond to one symbol,

the average value was chosen so that each set of GEO would obtain 1314 lncRNA expression profiles.

For the TCGA data set, first of all, a collection was defined as lncRNAs containing "3prime_overlapping_ncRNA", "antisense_RNA", "bidirectional_promoter_lncRNA", "lincRNA", "macro_lncRNA", "non_coding", "processed_transcript", "sense_intronic" and "sense_overlapping". Based on the above collections, the genome annotation file (Homo_sapiens.GRCh38.90.chr.gtf) of hg38 was downloaded to clarify the gene biotype of each gene. According to the gene biotypes, the lncRNA data was screened out. Finally, a total of 14376 lncRNA data sets was obtained. Then the TMM value normalization was performed on the count file.

lncRNA Screening

Firstly, the GEO lncRNA expression profiles were combined, and the batch effect was removed followed by univariate Cox analysis to screen out the lncRNAs with $p < 0.01$, the "*glmnet*" function package (Version:4.1-1) to perform LASSO iterative analysis on the lncRNAs which were screened out through univariate Cox regression analysis. When the value of CVL (λ) reached its maximum, the corresponding "λ" was the optimal adjustment parameter, so as to get the key.

Construction of lncRNA Prognosis Model

Based on the selected lncRNA, a formula for risk scores was established. The formula is as follows:

$$RiskScore = \sum_{i=1}^{N} (\exp * \mathrm{coef})$$

Where "N" is the number of lncRNAs, "exp" was the expression value of lncRNA, and "coef" was the coefficient of lncRNA in the lasso Cox regression analysis.

Evaluation and Verification of the Model

In order to further evaluate the stability of the model, the TCGA data set was used to verify the model's robustness. The same formula was applied to calculate the survival curve. It was found that the differences can be distinguished easily.

KEGG/GO Enrichment Analysis

We used gene co-expression to predict the lncRNA-associated target genes in the TCGA training set. The Cluster Profiler R package (https://guangchuangyu.github.io/software/clusterProfiler/) was used to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of the lncRNA-related mRNAs.

RESULTS

1. Prognosis-related lncRNA Screening

Initially, univariate cox analysis was performed on lncRNAs of selected n = 63 patients, and a total of 22 lncRNAs with $P < 0.01$ were selected (S-Table1). Then the lasso cox survival model was used for these 22 lncRNAs and the R language toolkit glmnet was applied for analysis. The key lncRNAs were identified when "λ" was equal to 0.08177 (Fig.1). Lastly, six lncRNAs ("LINC01494", "TRPM2-AS", "ATP1A1-AS1", "FRY-AS1", "LINC01360", "RBFADN") were screened out as signature lncRNAs that could help to predict the overall survival rate of colon cancer.

2. Construction of lncRNA Prognosis Model

Finally, a risk model was established for the six screened-out lncRNAs: Risk score = (-0.36554* expression value of LINC01494) + (-0.33369*expression value of TRPM2-AS) + (-0.4779*expression value of ATP1A1-AS1) + (-0.17083*expression value of FRY-AS1) + (-0.02696*expression value of LINC01360) + (-0.03345*expression value of RBFADN)

According to the risk scores, the surv_cutpoint function in the survmier package was applied to determine the best cutoff value, and the patients were divided into two groups: the high-risk group (n = 159) and the low-risk group (n = 65). The survival analysis was carried out based on the risk scores and it was found that patients in both high and low risk groups could be easily separated. The survival curve is shown in (Fig.2) and more information about the patients in the training data

set is shown in (Fig.3).

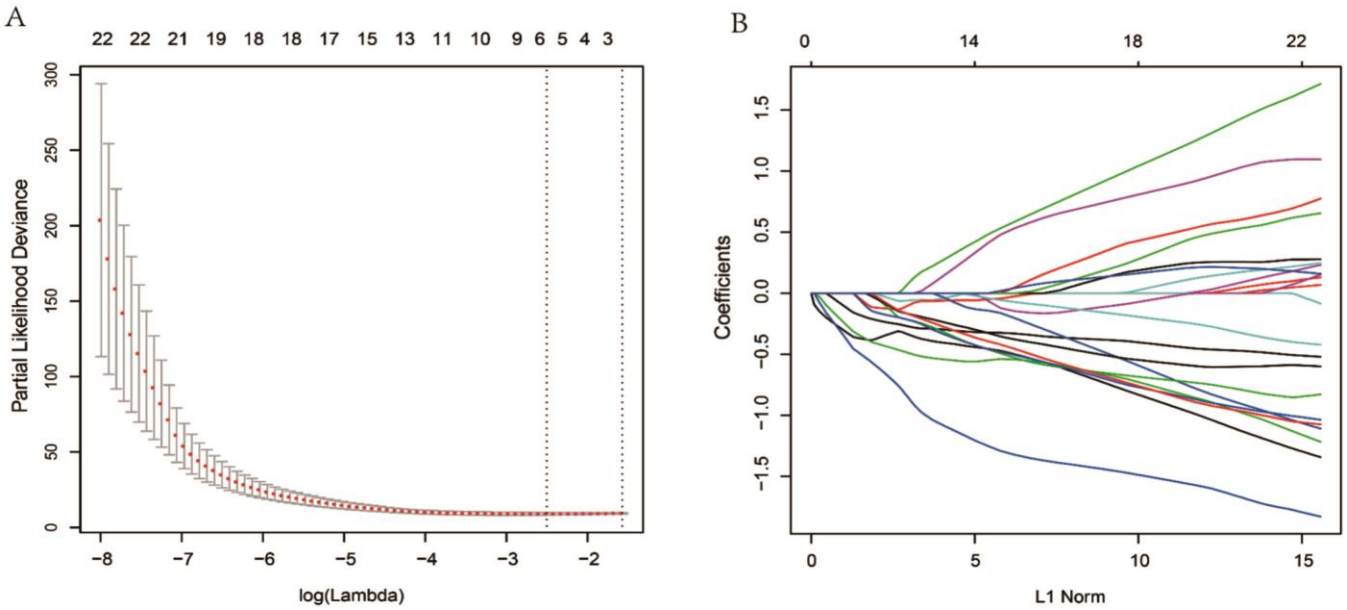

Fig.1 (A): Selection of optimal tuning parameter in the LASSO model. The dotted vertical lines are drawn at the optimal values by minimum criteria (left) and 1-SE criteria (right). The optimal = 0.08177 was determined by ten-time cross-validation via minimum criteria. Error bars represent standard error (SE). **(B)**: Construction of the six-lncRNA signature model. LASSO coefficient profiles of the 22 associated lncRNAs. A vertical line is drawn at the value determined by 10-fold cross validation.

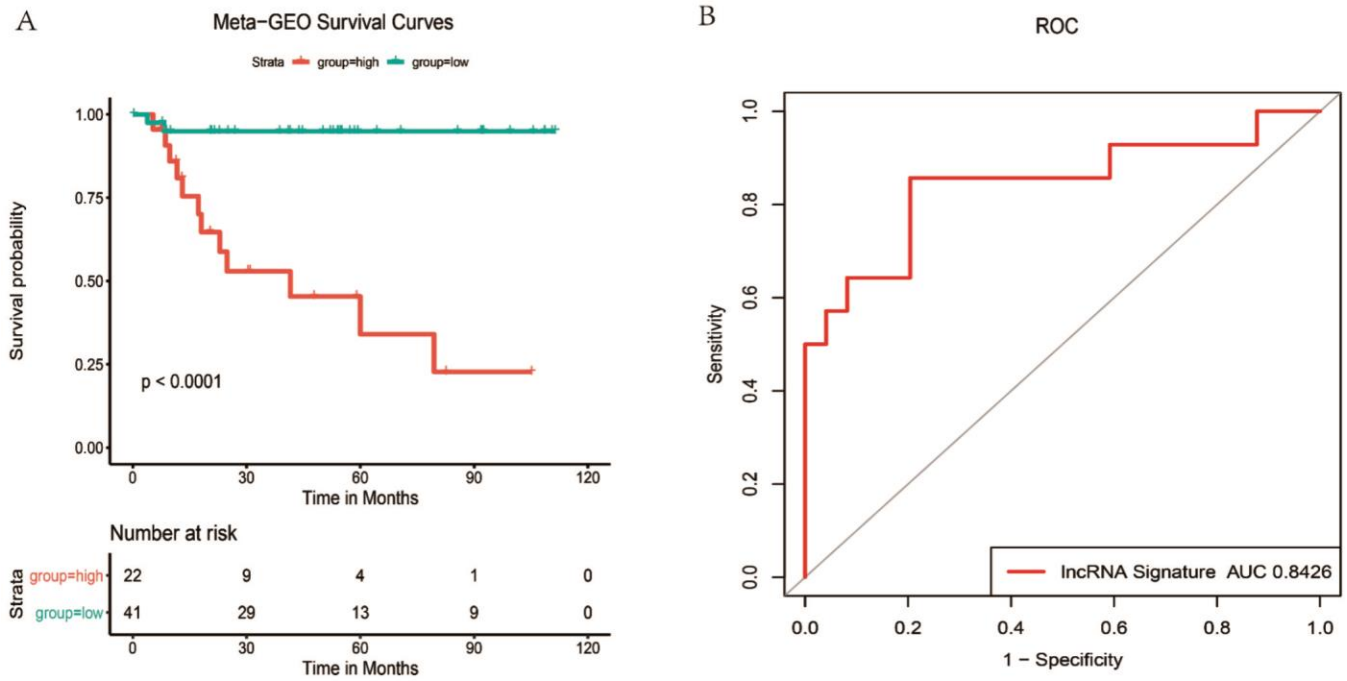

Fig.2 (A): Kaplan – Meier analysis of patients' disease – free survival in the high – risk (n = 22) and low – risk (n = 41) subgroups of the training set. **(B):** The time – independent ROC analysis of the risk score for prediction and DFS of the training set. The area under the curve was calculated for ROC curves.

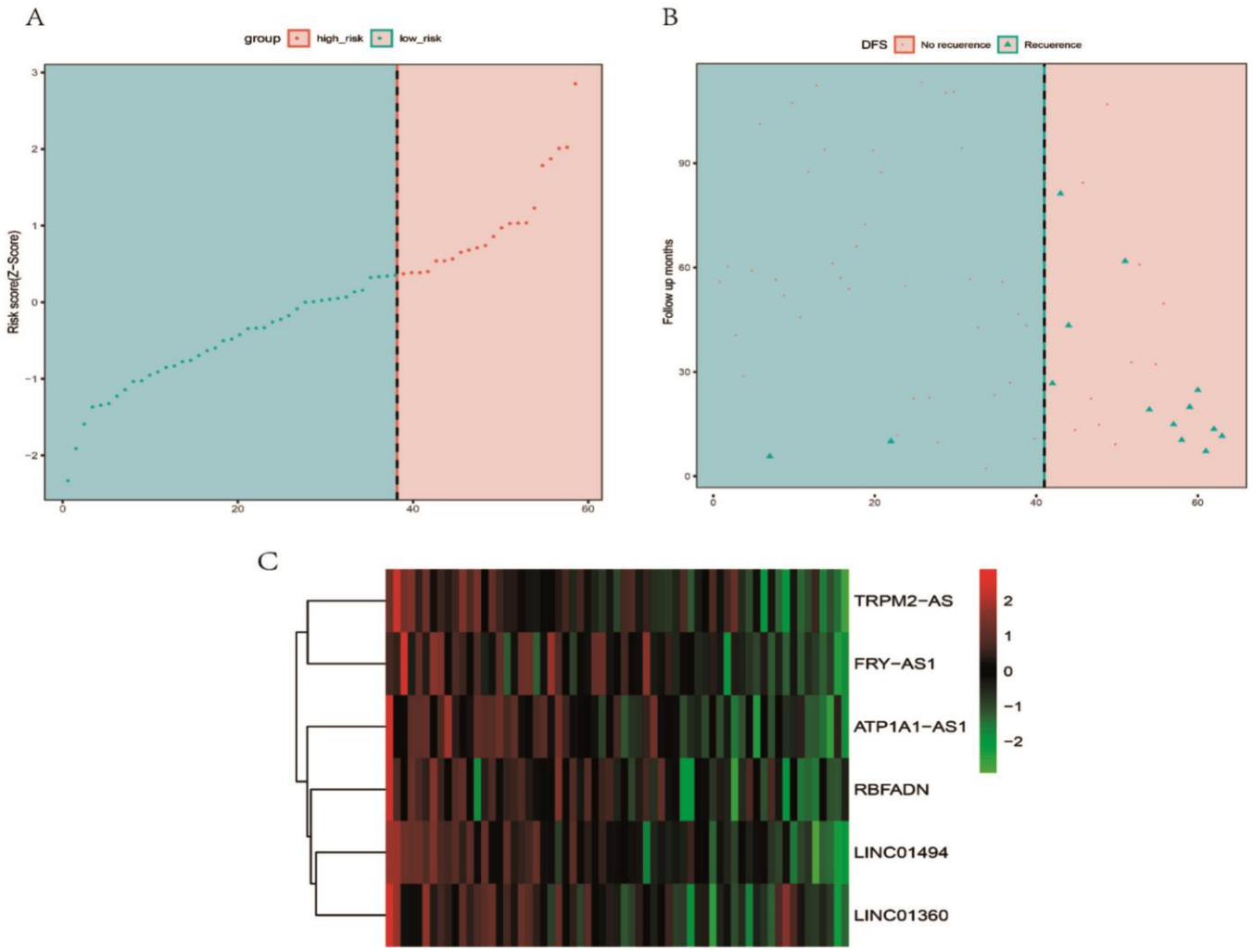

Fig.3 (A): The risk score in training dataset. **(B):** The disease-free survival information in training dataset. **(C):** The z-score transformed expression values are shown (top-down, TRPM2-AS, FRY-AS1, ATP1A1-AS1, RBFADN, LINC01494, LINC01360) in training dataset.

3. Validation of the 6-lncRNA Signature for Survival Prediction in the TCGA Dataset

In order to validate the predictive ability of the selected six lncRNAs, validation was performed in the TCGA data set. Firstly, the expression profile data of n = 52 patients at stage III/IV were obtained. The expression data of the six lncRNAs were then extracted from the TCGA database. With the same formula, it was found that they had similar results. The survival curve of the TCGA data set and the specific information of the patients are shown in (Fig.4).

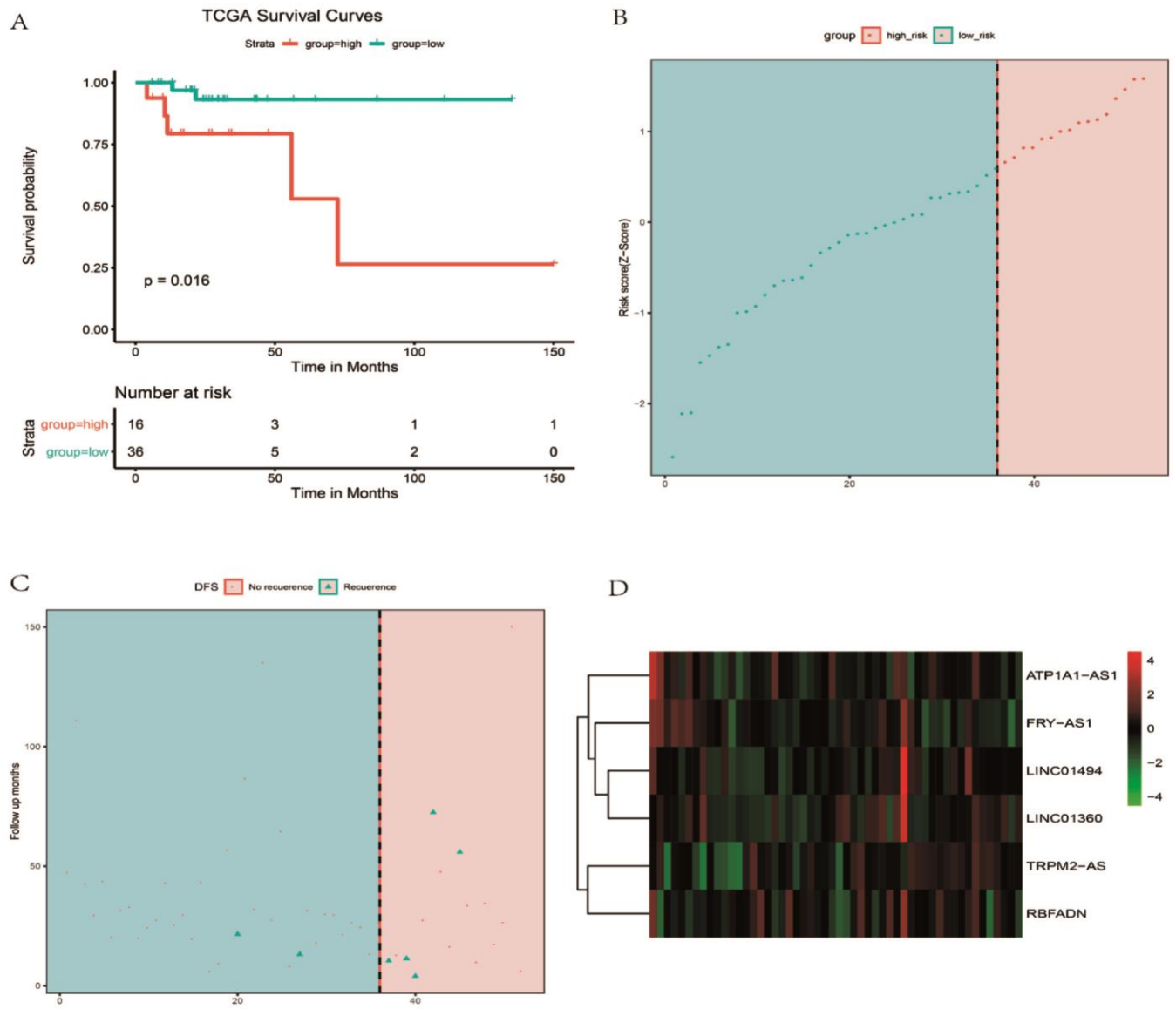

Fig.4 (**A-C)**: Kaplan – Meier analysis indicated that patients in the high – risk (n = 16) subgroup exhibited significantly poorer DFS than the low-risk subgroup (n = 36) in TCGA dataset. **(B-D)** The relationship between risk score, disease – free survival information, and z-score transformed expression values are shown (top-down, ATP1A1-AS1, FRY-AS1, LINC01494, LINC01360, TRPM2-AS, RBFADN).

4. KEGG/GO Enrichment Analysis

In order to study the possible functions of the six lncRNAs, co-expression analysis was carried out for the six lncRNAs based on the TCGA database. We screened out mRNA positively correlated with at least one of the lncRNAs, and totally 2704 genes co-expressed with the mRNA. The Top14 KEGG pathways and GO terms were demonstrated and dot plots were drawn respectively, one of which is chosen for display (Fig.5), (S-Table-2; S-Table-3; S-Table-4).

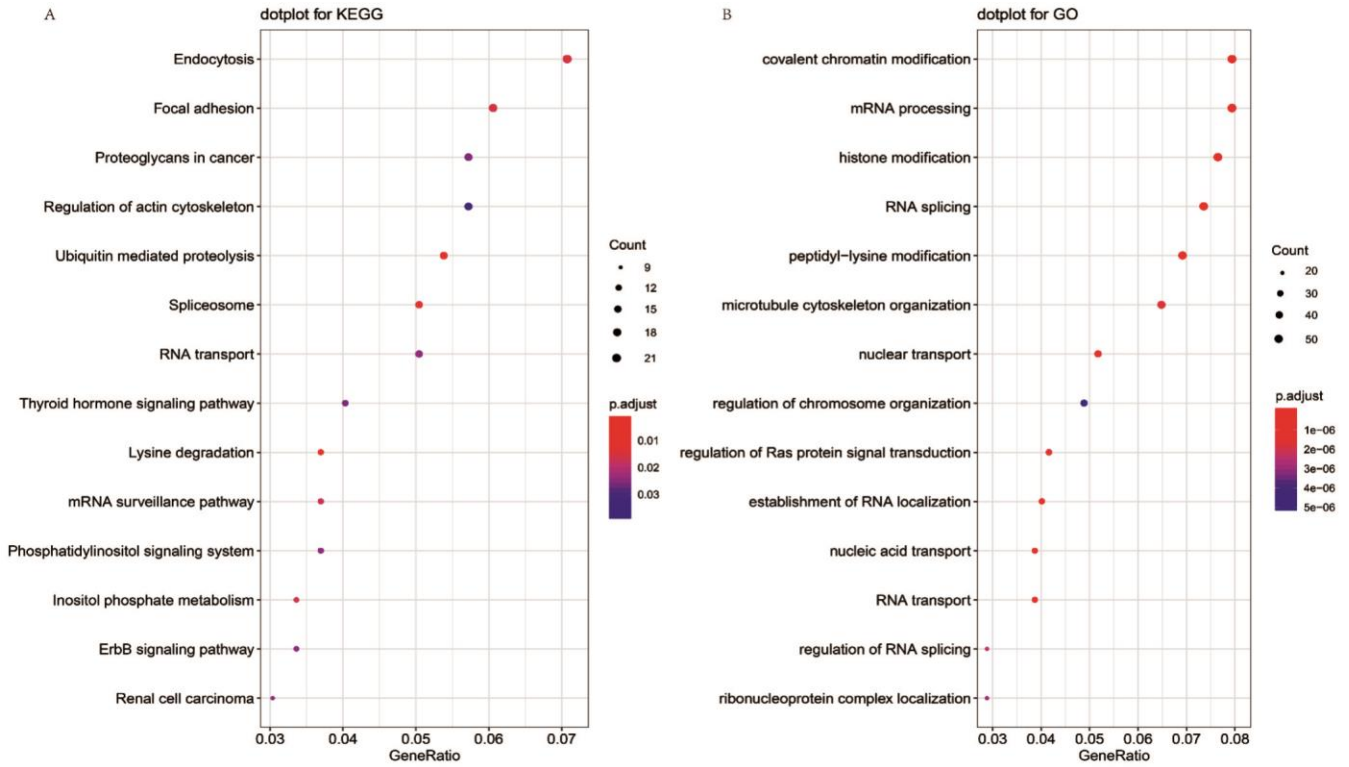

Fig.5 (A): Significantly enriched pathways of the 6-lncRNA correlated genes **(B):** The functional enrichment map of GO. Node size represents the number of gene in the pathways/GO term.

DISCUSSION

Colorectal cancer is one of the most common malignant digestive tract tumors in the world with high morbidity and mortality.[29] The occurrence of colorectal cancer is considered to be a complex process involving multiple steps, stages and molecules combined with genetic and environmental factors. As for early diagnosis, the current screening examination has some problems, such as poor specificity, and patient compliance. A large number of patients have failed treatment due to the limitation of the prognostic factors.[30] Therefore, it is significant to find new molecular markers to help clinical evaluation of diagnosis and prognosis.

In this study, a 6-lncRNA model was established to predict the prognosis of patients with colorectal cancer. The data sets from GEO and TCGA databases were used. Six key lncRNAs were selected as signature lncRNAs to predict the overall survival rate of colorectal cancer. The 6-lncRNA model in this study could significantly separate patients with high and low risk of colorectal cancer. The good prediction ability of the model is further verified in TCGA dataset.

lncRNAs could regulate the expression of downstream genes during chromatin modification, transcription or after transcription, and then participate in a variety of biological processes such as cell proliferation, invasion and apoptosis, which is closely related to the occurrence and development of tumor.[9]lncRNAs has great potential as a new molecular biomarker for prognostic prediction of colorectal cancer.[31,32] Similarly, in current study, a model of six lncRNAs (LINC01494, TRPM2-AS, ATP1A1-AS1, FRY-AS1, LINC01360, and RBFADN) showed lncRNA as a stable and reproducible prognostic biomarker.

Among the six lncRNA, TRPM2-AS is the most studied lncRNA at present. TRPM2-AS promotes the progression of gastric cancer through the miR-195/HMGA1 signal axis, and may act as a new biomarker in patients with gastric cancer.[33] TRPM2-AS promote apoptosis in small cell lung cancer and prostate cancer.[34,35] In hepatocellular carcinoma, the inhibition of TRPM2-AS expression promotes the apoptosis of HCC cells in vitro.[36]

Another lncRNA ATP1A1-AS1 regulates the signaling pathways associated with Na/K-ATP enzyme-related enzymes in human renal cells.[37] The biological effects of the remaining four lncRNAs have not yet been clarified.

Because the function of 6 lncRNAs in colorectal cancer is not clear, KEGG and GO analysis are performed to explore the potential biological functions of 6 lncRNAs. Most of them are enriched in endocytosis, focal adhesion, spliceosome, covalent chromatin modification, mRNA processing, histone modification, RNA splicing, and microtubule cytoskeleton organization. Endocytosis has been verified to be closely related to the invasiveness of tumor cells.[38] Integrin receptors in focal adhesion interact with extracellular matrix and cytoskeleton – actins. This can provide adhesion to the matrix, and transmit the mechanical tension of the cell to the plasma membrane, and then to the external environment, which plays an important role in tumor invasion, migration and drug resistance.[39-42] Spliceosome is closely related to tumor survival, tumorigenicity, invasion and metastasis, which could also be used as a target for new antineoplastic drugs.[43-45] Other aspects of enrichment are also closely related to the occurrence and development of tumors.[46-49]

CONCLUSION

Six-lncRNA model established in this study has great potential in predicting the prognosis of colorectal cancer, which provides strong evidence for the development of effective prognostic biomarkers in colorectal cancer patients.

LIMITATIONS OF THE STUDY

The sample size involved in this study is still not large enough, and there is a lack of more clinical data verification, therefore this study has certain limitations, more research is needed to explore better prognostic prediction models.

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CONFLICTS OF INTEREST

None to declare.

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Author's Contribution

WY, CL: Concept and design of study, Acquisition, analysis of data and drafting of manuscript.

PL: Acquisition of data, and drafting of manuscript.

CY, HY: Intellectual input, critical review of the manuscript.

HW, SY, SM, SJ: Acquisition of data and critical revision of manuscript.

ALL AUTHORS: Approval of the final version of the manuscript to be published.