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Original Article

Identification of a glycolysis-associated lncRNA signature to predict survival of patients with colorectal cancer

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Abstract: Objective: Colorectal cancer (CRC) still has a poor prognosis and is one of the most common malignancies worldwide. Recently, a close correlation between glycolysis and the progression of CRC has been reported. Hence, explorations of the prognostic value of glycolysis-associated long noncoding RNAs in CRC patients are urgently needed. This study aimed to investigate the role of glycolysis-associated lncRNAs for predicting the prognosis and treatment response of CRC, thereby identifying more biomarkers for CRC. Methods: RNA sequencing (RNA-seq) data for CRC from The Cancer Genome Atlas database were used. A glycolysis-associated long noncoding RNA (lncRNA) signature was estimated by Cox regression analysis, and its predictive capacity was assessed by constructing a receiver operating characteristic (ROC) curve and performing a gene set enrichment analysis. Results: One of our constructed glycolysis-related clusters was strongly correlated with an immunosuppressive tumor environment. Moreover, a signature consisting of 14 glycolysis-associated lncRNAs was used as a prognostic model, and CRC patients were classified into a low-risk group and a high-risk group based on the average risk score of this signature. In addition, the low-risk group experienced longer overall survival (OS) than the high-risk group. The area under the ROC curve (AUC) validated the sensitivity and specificity of the signature. The signature was identified as an individual element and was closely related to the progression of CRC. Finally, two glycolysis-associated lncRNAs, namely, TNFRSF10A-AS1 and ZKSCAN2-DT, were further clinically verified to effectively predict the prognosis of CRC patients. Conclusion: Glycolysis-associated lncRNAs may be employed as prognostic and therapeutic biomarkers for CRC.

Keywords: Colorectal cancer, glycolysis, long noncoding RNA, prognosis, overall survival

Introduction

Colorectal cancer, one of the most common malignancies, is associated with high recurrence, mortality, and morbidity [1]. In recent years, the treatment of CRC has improved, but the 5-year survival of patients with CRC remains unsatisfactory [2]. The current treatments include endoscopic and local surgical excision, preoperative radiotherapy, local ablation of metastases, palliative chemotherapy, targeted therapy, and immunotherapy [3]. The 5-year relative survival rate varies from over 90% in patients with stage I disease to more than 10% in patients with stage IV disease. Screening has been shown to reduce the incidence and mortality of colorectal cancer. Hence, a better method for assessing the prognosis of CRC patients should be developed, and screening programs are urgently needed [4].

Molecular alterations in CRC have been reported in many studies, and their mechanisms could be investigated further for the diagnosis and treatment of CRC. Genes with common mutations, chromosomal changes and translocations, such as c-MYC, KRAS, BRAF, PIK3CA, PTEN, SMAD2 and SMAD4, can be used as predictive markers for determining the prognosis. In addition, alterations in ncRNAs, such as lncRNAs or miRNAs, play a role in prediction when used as biomarkers [5]. Nevertheless,

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these efforts have not substantially prolonged the survival of patients with CRC. Therefore, additional biomarkers associated with CRC carcinogenesis are needed.

Aerobic glycolysis (also known as the Warburg effect) is a key feature of cancer cells that tend to employ glycolysis [6, 7], even in the presence of sufficient oxygen. Increasing evidence has shown that, compared to normal tissues, tumors exhibit higher rates of glucose consumption and glycolysis [8].

Long noncoding RNAs that are more than 200 nucleotides (nt) long do not have the capacity to encode proteins [9]. At present, many studies have implicated lncRNAs in many types of human cancer and reported their involvement in many biologic processes of cancer, including growth, metastasis, metabolism, drug resistance and immune escape [10-13]. Moreover, lncRNAs play critical roles in various cellular processes, including glycolysis, DNA repair and cell differentiation [14]. Some studies have shown that lncRNAs substantially affect the growth and progression of CRC and may serve as biomarkers to predict survival [15-17].

The role of the glycolysis-related lncRNA signaling pathway in predicting the prognosis of CRC patients includes several aspects. First, by analyzing the expression patterns of glycolysis-related lncRNAs, molecules with prognostic value can be screened, and risk prediction models can be constructed. Second, these models can be used as an independent risk factor to evaluate patient outcome. Moreover, lncRNAs may influence the progression and prognosis of CRC by regulating specific signaling pathways. In addition, glycolysis-associated lncRNAs are associated with the infiltration of multiple immune cell types and immune function, and may regulate the progression of CRC by affecting immune cells in the tumor microenvironment. lncRNAs also influence tumor progression by participating in the regulation of metabolic reprogramming in tumor cells. Finally, lncRNAs may influence the prognosis of CRC patients by influencing drug resistance and the treatment response.

We first identified 816 glycolysis-related lncRNAs from The Cancer Genome Atlas (TCGA) database. Next, when three glycolysis-associated lncRNA clusters were constructed in CRC samples, the features of the immune microenvironment in different glycolysis-related lncRNA clusters were detected. Moreover, glycolysis-associated lncRNAs related to the prognosis of CRC were identified, and a new prognostic glycolysis-associated lncRNA signature for CRC was developed. These findings may relate to the pathogenesis and prognosis of CRC.

Materials and methods

Patients and database

TCGA database contains public RNA sequencing and clinical data from CRC patients. The genes were classified into lncRNA genes and protein-coding genes based on human genome annotations. In addition, 48 CRC patients were recruited for clinical verification. Participants were eligible for inclusion when they were enrolled if they: (1) had a pathologically confirmed diagnosis of colorectal adenocarcinoma, (2) were aged 18 years and older, (3) had undergone limited radical resection for colorectal cancer and had not undergone any preoperative treatment, such as radiation or chemotherapy, (4) had estimated life expectancy of ≥3 months, (5) were willing to participate in the study and signing of an informed consent form, (6) had no concurrent major comorbidities or conditions that could interfere with the study, (7) had complete clinical data for collection and analysis. Patients with the following conditions were excluded: (1) non-colorectal cancer cases, (2) histologic subtype was not adenocarcinoma, (3) concurrent presence of other malignant tumors (past or present), (4) presence of metastases outside the study scope, (5) patients who had received treatment that may interfere with the study such as undocumented special chemotherapy or targeted therapies, (6) received multiple surgeries or had unclear treatment timelines, (7) severe cardiovascular conditions such as myocardial infarction or heart failure, (8) had active infectious diseases such as hepatitis and HIV, (9) had active autoimmune diseases or current use of immunosuppressive drugs, (10) pregnant or breastfeeding women, (11) patients with mental or cognitive disorders that prevent study compliance, (12) patients unable to complete follow-up or data collection, (13) clinical or laboratory abnormalities indicating active systemic diseases such as severe liver or kidney dysfunction. CRC tissues and paired adjacent normal tissues were collected

by surgical resection. The Ethics Committee of Nantong Fourth People's Hospital approved this study, and all participants provided written informed consent.

Glycolysis-related lncRNA extraction

Five glycolysis-associated gene sets extracted from the Gene Set Enrichment Analysis database included glycolysis-related genes. A Pearson correlation analysis was subsequently performed on the acquired lncRNAs and glycolysis-associated genes (filter: |R|>0.6 and P<0.001).

Consensus clustering analysis of glycolysis-related lncRNAs

Based on the expression of glycolysis-related lncRNAs, CRC patients were classified into three groups with optimal k-means clustering. The Consensus Cluster Plus R package was used to perform the clustering analysis.

Establishment and verification of the glycolysis-associated risk score model

A risk score model was constructed through a multivariate regression analysis of CRC survival-related lncRNAs, and the risk score for this model was formulated as follows:

$$\text{Risk score}=\sum_{Expi*\beta i}$$

(βi represents the coefficient of each lncRNA and Expi represents the expression of each lncRNA).

The average value of the risk score was used as a cutoff value to divide CRC patients into low-risk and high-risk groups. The patients whose risk scores were higher than the average value of the risk score were classified as a high-risk group, while those with lower than average risk score were the low-risk group. The overall survival of CRC patients in both groups was detected by analyzing Kaplan-Meier curves. The receiver operating characteristic curves were plotted with the "survival ROC" R package to evaluate the precision of the model.

Gene set enrichment analysis

The CRC samples database were classified into low-risk and high-risk groups based on the risk scores of the lncRNA signature. Gene set enrichment analysis (GSEA) was employed to detect signaling pathways and biological processes. A normal p value <0.05 and a false discovery rate <25% were considered significant.

Clinical sample collection

Tumor tissues and paired adjacent normal tissues were acquired from 48 patients with CRC by surgical resection. Histopathologicconfirmation of the diagnosis was performed, and no patients received preoperative treatment. Follow-up information was acquired at outpatient visits at 1-3-month intervals or by telephone calls and mail.

Quantitative real-time polymerase chain reaction (qRT-PCR)

TRIzol reagent was used to extract total RNA from the tissues. A NanoDrop 2000 spectrophotometer was used to measure the concentration and purity of the RNA. SYBR Green Mix and the Applied Biosystems 7500 PCR System were used for qRT-PCR assays. The expression levels of target genes were normalized to the expression of GAPDH, followed by calculation with the equation $2^{-\Delta\Delta Ct}$. The specific sequences of the primers used were as follows: TNFRSF10A-AS1 forward, 5'-TCTCAGATCACGTGACCTTGA-3', reverse, 5'-GTGGGCAGCTCTCATCCTAA-3'; ZKSCAN2-DT forward, 5'-TCCAGCTTGGTTGACAAAGTGAGAC-3', reverse, 5'-CCTCCTCGCCTTGCTCTTAATGC-3'; and GAPDH forward, 5'-CGCTCTCTGCTCCTCCTGTTC-3', reverse, 5'-ATCCGTTGACTCCGACCTTCAC-3'.

Statistical analysis

T test was used to observe the differences between two groups. The construction of survival curves was based on the Kaplan-Meier analysis, and the log-rank test was performed for comparisons. The data were analyzed using GraphPad Prism 8.0 software. R version 4.0.3 and the corresponding R packages were adopted to analyze all the data. P<0.05 was considered significant.

Results

Initial screen of glycolysis-related genes

If differences were detected between CRC samples and normal samples, five glycolysis-associated gene sets were investigated by the GSEA

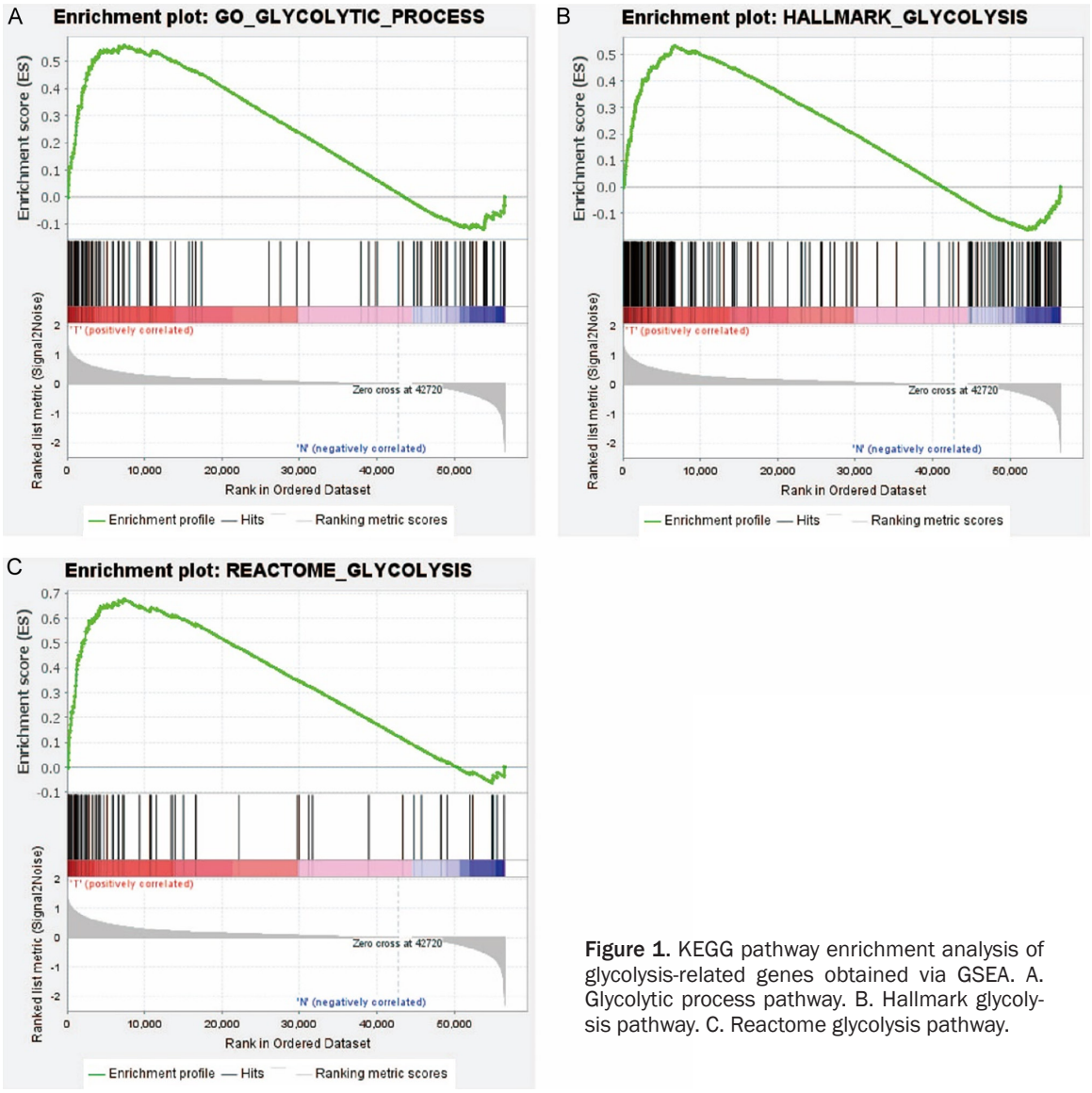


Figure 1. KEGG pathway enrichment analysis of glycolysis-related genes obtained via GSEA. A. Glycolytic process pathway. B. Hallmark glycolysis pathway. C. Reactome glycolysis pathway.

method. Three gene sets were enriched in CRC samples (**Figure 1A-C**).

Construction of glycolysis-related lncRNA clusters

Glycolysis-related lncRNAs were mapped to the expression profile of CRC samples for clustering analysis with the Consensus Cluster Plus tool to divide CRC samples into tumor clusters with various glycolysis phenotypes based on the expression of glycolysis-related lncRNAs. The number of clusters ranged from 1 to 9 (**Figure 2A**), and according to the CCP analysis, the most stable outcome was shown when the clusters were separated into three tumor clusters (Cluster 1, Cluster 2 and Cluster 3) (**Figure 2B**, **2C**). The Kaplan-Meier approach was adopted to calculate the OS of patients in various clusters, and the survival of patients in the three clusters was significantly different (**Figure 2D**). We further investigated whether glycolysis-related lncRNA clusters were related to the characteristics of CRC by investigating the associations between glycolysis-related lncRNA clusters and clinical features and found that, compared to Cluster 1 and Cluster 3, Cluster 2 had the highest tumor-node-metastasis (TNM) stage (**Figure 3**).

Identification of the prognostic value of glycolysis-associated lncRNAs

The above lncRNAs and clinical data were annotated, and the effect of every lncRNA on the prognosis was determined by univariate

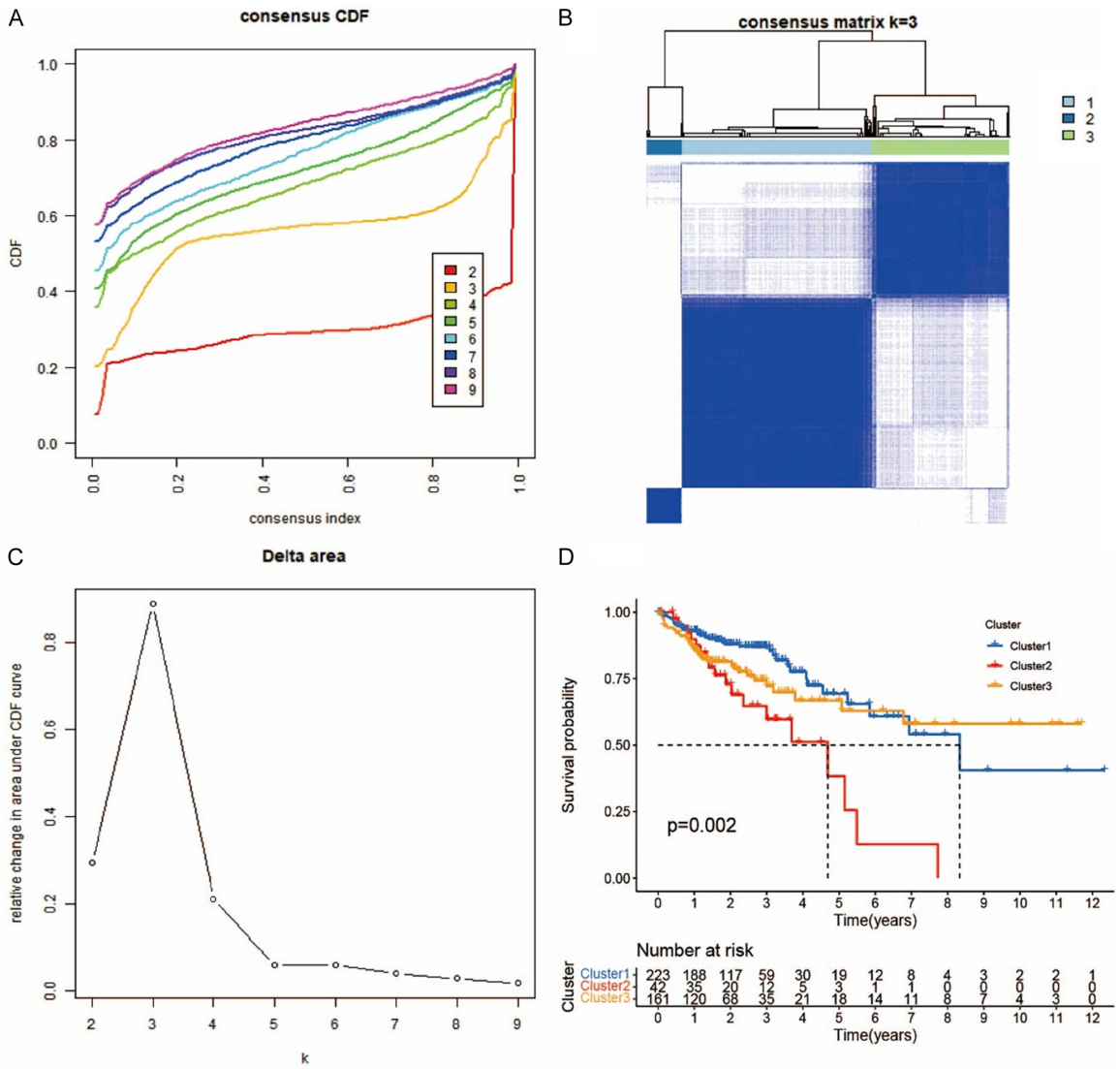


Figure 2. Unsupervised clustering analysis of CRC using glycolysis-related lncRNA expression data. A. Consensus cumulative distribution function (CDF) curve of the unsupervised clustering analysis. B. Delta area under the CDF curve of the clustering analysis. C. Cumulative distribution function graph of the consistency matrix at K=3. The white and blue heatmaps present the sample consensus. D. Survival curves of the three clusters.

Cox regression analysis to identify glycolysis-associated lncRNAs related to prognosis. Our results showed that 60 glycolysis-associated lncRNAs had significant prognostic value (**Figure 4A**). A multivariate regression model was subsequently established for these lncRNAs, and a model based on a fourteen-lncRNA signature was developed. The formula used to calculate the risk score of every CRC patient was as follows: risk score = AC016394.3*0.17+AC114730.3*0.88+AC008760.1*0.45+AC245041.1*0.50+AC073957.3*(-0.24)+LINC02593*0.46+AL161729.4*0.34+AC016737.1*(-0.69)+AC125807.2*0.05+TNFRSF10A-AS1*(-0.20)+ZKSCAN2-DT*0.46+AC138207.5*0.30+AC008764.8*(-1.74)+ATP2B1-AS1*1.17 (Supplementary Table 1). Moreover, all CRC patients from TCGA database were categorized into a low-risk group and a high-risk group according to the average risk score. According to the results of the Kaplan-Meier curve, low-risk CRC patients experienced markedly longer overall survival than high-risk CRC patients (**Figure 4B**). A heatmap was generated to depict the expression patterns of these 14 glycolysis-related lncRNAs, and a

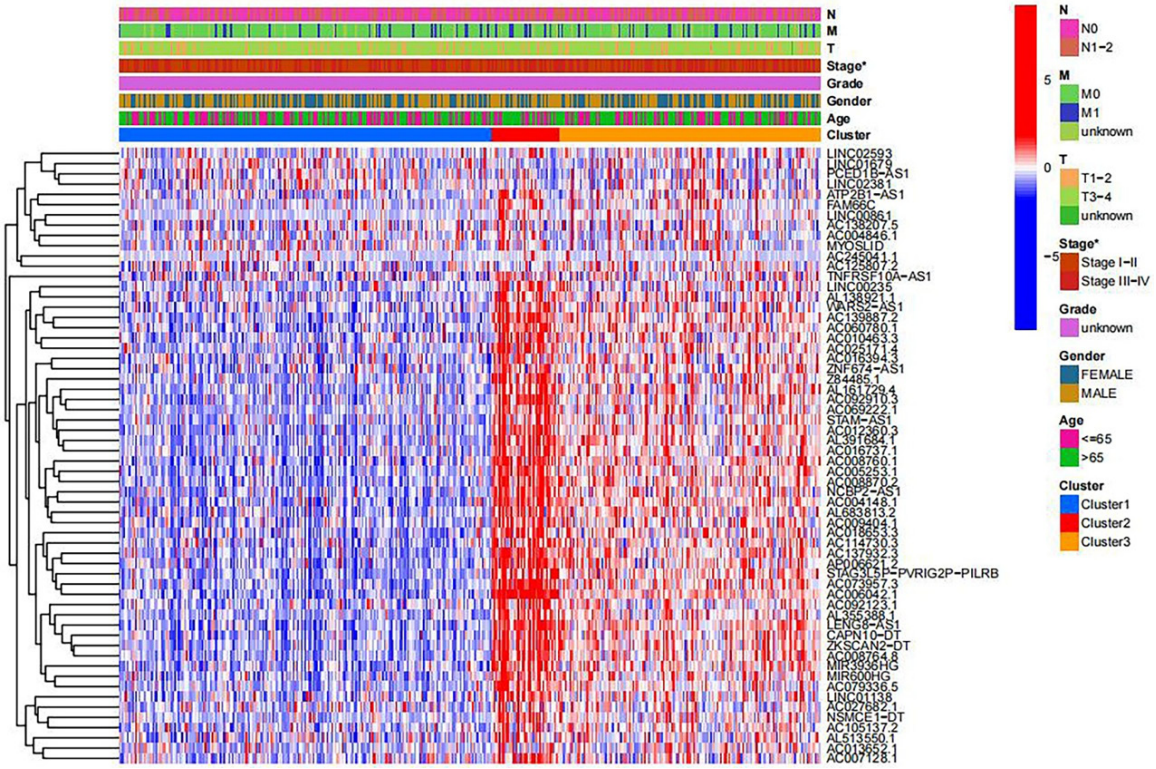


Figure 3. Heatmap of the correlations between glycolysis-related lncRNAs and clinical characteristics of patients in TCGA database.

scatterplot was created to visualize the risk and survival status of each CRC patient (**Figure 4C-E**).

Evaluation of the glycolysis-associated lncRNA signature as an independent prognostic factor for CRC patients

Univariate and multivariate Cox regression analyses were conducted to assess whether the constructed glycolysis-associated lncRNA signature could be individual prognostic factors for CRC patients, and the results revealed that the risk score could be considered an individual prognostic marker of CRC (**Figure 5A**, **5B**). Moreover, the sensitivity and specificity of this risk model for the prognosis of CRC patients were detected by constructing ROC curves. Our results revealed that the area under the ROC curve of this risk score was 0.715 (**Figure 5C**), which verified that this risk model had good predictive power. The time-dependent ROC curve of the risk model curve was as follows: 1 year - 0.715; 2 years - 0.753; and 3 years - 0.722 (**Figure 5D**). These results proved that our lncRNA signature had an excellent predictive value for the 1-year, 2-year and 3-year survival of CRC patients.

Gene set enrichment analysis

The hidden signaling pathways between the low-risk and high-risk groups were detected by gene set enrichment analysis. According to our results, several partial pathways were enriched in the high-risk group, and they are very important signaling pathways associated with tumorigenesis and CRC progression (**Figure 6**). Our research confirmed that the risk-associated model contributed to the progress of customized treatment for CRC patients.

Verification of the prognostic value of two lncRNAs for clinical CRC patients

From **Figure 4E** and Supplementary Table 1, we chose two glycolysis-associated lncRNAs, namely, TNFRSF10A-AS1 and ZKSCAN2-DT, for further clinical verification. **Figure 7A** and **7B** show that the expression levels of TNFRSF10A-AS1 and ZKSCAN2-DT were higher in CRC tissues than in paired adjacent normal tissues

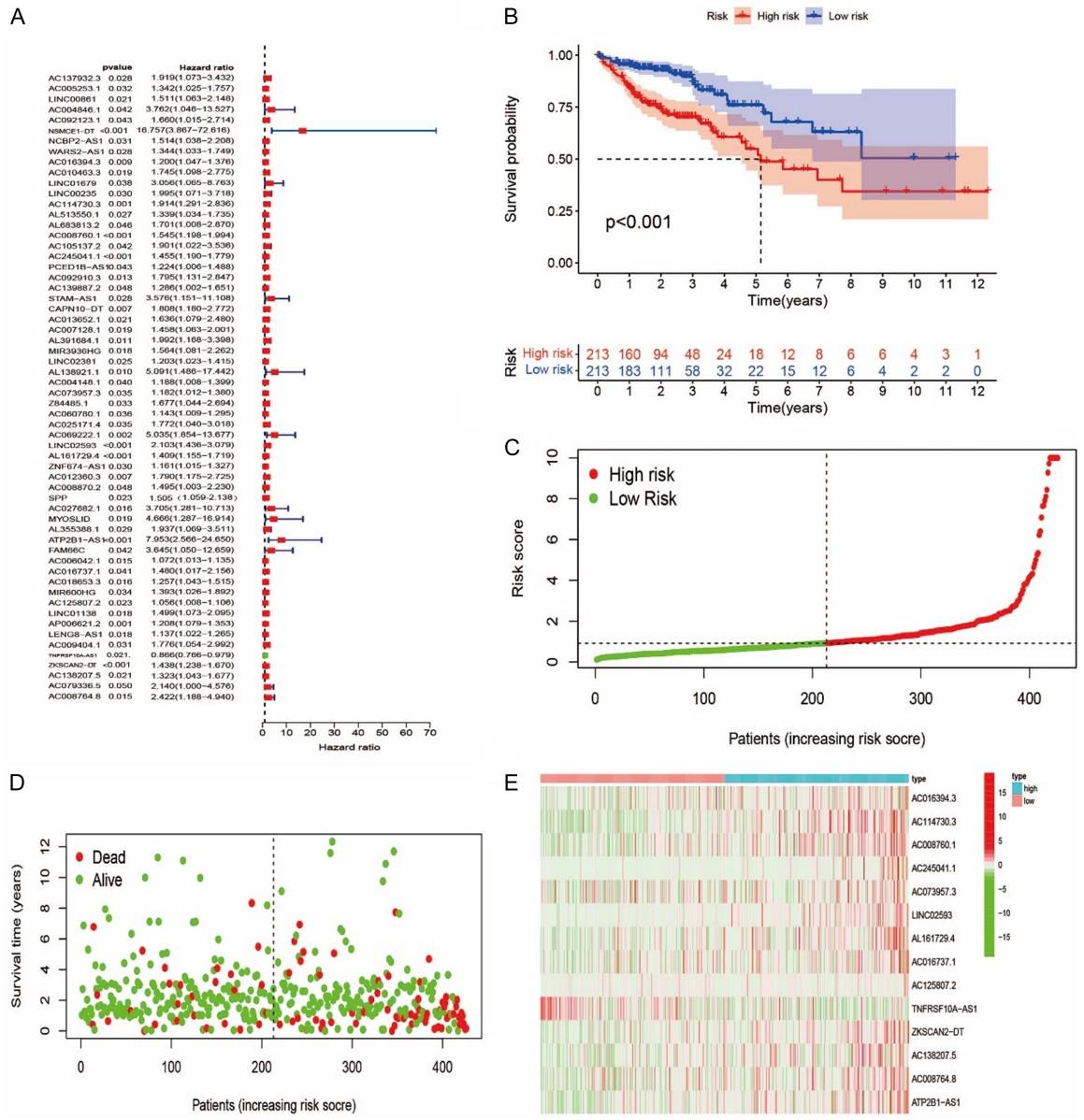


Figure 4. Construction of a prognostic glycolysis-related lncRNA signature for CRC. A. Univariate Cox regression analysis of the risk score and clinical features of CRC patients. B. Kaplan-Meier survival analysis of the low-risk and high-risk groups. C. Distribution of the risk score of each CRC patient. D. Survival status of each CRC patient. E. The heatmap shows the different expression levels of lncRNAs included in the signature in the low-risk and high-risk groups.

(both P<0.001). Moreover, according to Kaplan-Meier survival analysis, CRC patients with high TNFRSF10A-AS1 and ZKSCAN2-DT expression levels experienced shorter OS than those with low TNFRSF10A-AS1 and ZKSCAN2-DT expression levels (P=0.007 and 0.008, respectively) (**Figure 7C**, **7D**). These findings indicate that TNFRSF10A-AS1 and ZKSCAN2-DT1 were independent prognostic factors for CRC.

Discussion

Many studies have described the importance of lncRNAs, including tumor suppressors, carcinogenic functions and prognostic biomarkers, in CRC [18-20]. lncRNAs act as critical modulators of aerobic glycolysis [21, 22]. Hence, studies examining glycolysis-associated lncRNAs in CRC and their associations with immune cell infiltration are urgently needed.

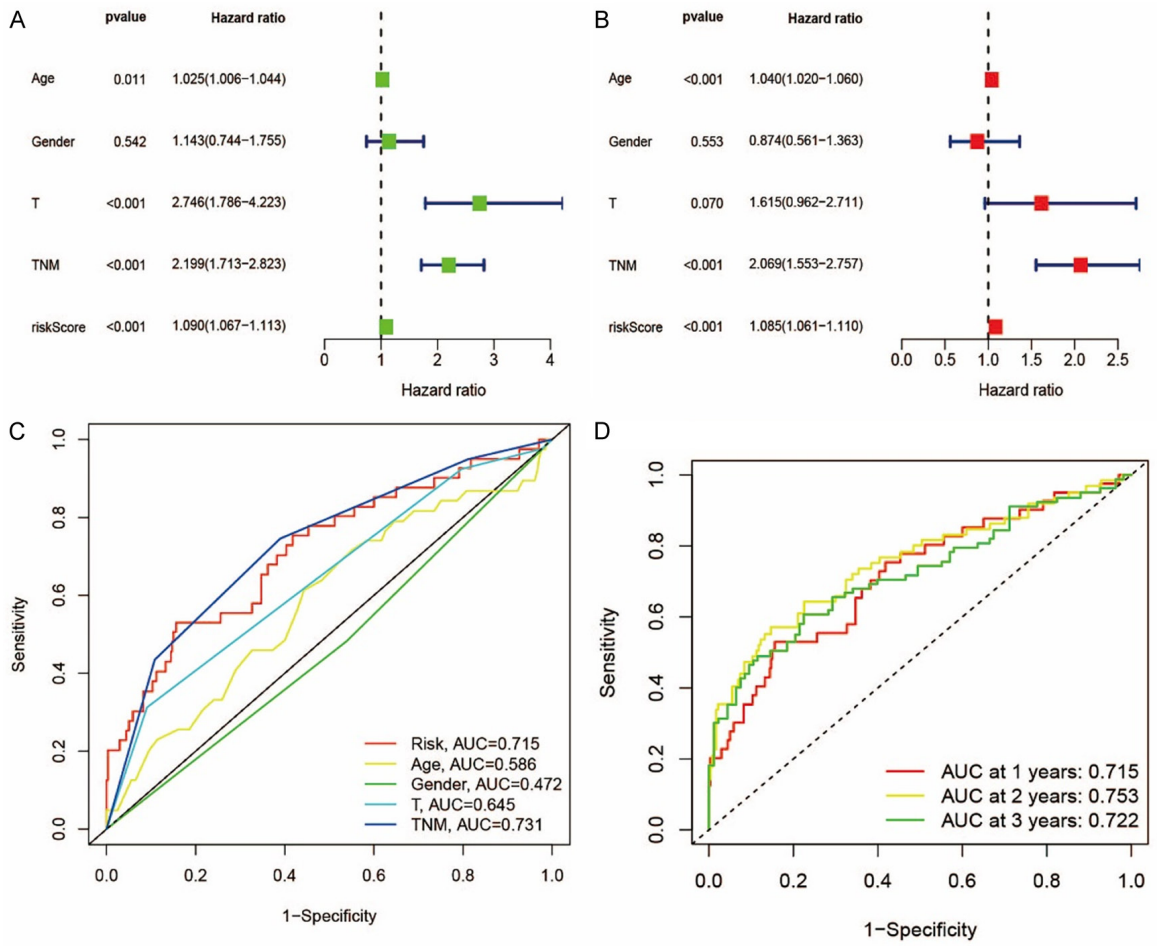
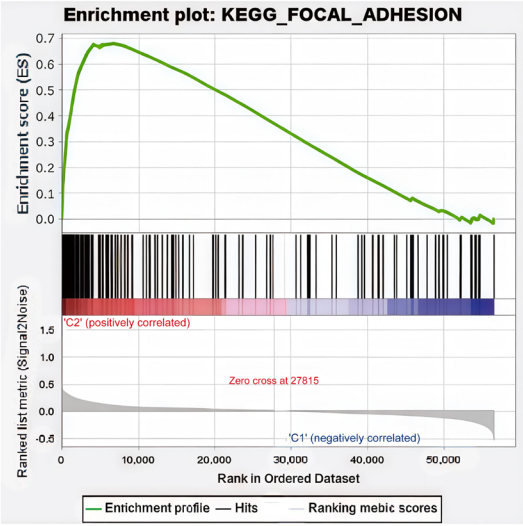


Figure 5. Independent prediction of the glycolysis-associated lncRNA risk signature. (A, B) Univariate (A) and multivariate (B) Cox regression analyses of the prognostic value of the risk signature and clinical factors. (C) AUCs for the risk signature and clinical factors according to the ROC curves. (D) Time-dependent ROC curve analysis of the risk signature for the prediction of 1-, 2-, and 3-year OS.

The tumor environment is composed of tumor cells, surrounding immune cells, fibroblasts, the extracellular matrix, chemokines and secreted cytokines. Infiltrating immune cells are components of the tumor environment that play critical roles in shaping the tumor environment. Previous studies have provided evidence that several lncRNAs, including those involved in antigen release and immune cell infiltration, have critical effects on the tumor immune response [22-24].

Recently, studies have proven that lncRNAs were biomarkers for the diagnosis and prognosis of cancers. For example, Bai et al. used 4 glycolysis-related lncRNAs to develop a risk model that can precisely judge the prognosis of hepatocellular carcinoma patients [23]. Jiang et al. recognized 36 prognostic glycolysis-associated lncRNAs and proposed a risk signature of 5 glycolysis-related lncRNAs that predicted survival in endometrial cancer [25]. In our study, we chose TNFRSF10A-AS1 and ZKSCAN2-DT from the 14 prognostic glycolysis-related lncRNAs in the signature for further clinical verification. As expected, TNFRSF10A-AS1 and ZKSCAN2-DT were clearly expressed at higher levels in CRC tissues than in paired adjacent normal tissues. Moreover, CRC patients with higher levels of TNFRSF10A-AS1 and ZKSCAN2-DT experienced shorter overall survival. Moreover, both TNFRSF10A-AS1 and ZKSCAN2-DT1 were independent prognostic factors for CRC, confirming the results of the bioinformatic analyses.

We examined the functions of lncRNAs in the 14 glycolysis-associated lncRNA signature in


Enrichment plot: KEGG_FOCAL_ADHESION
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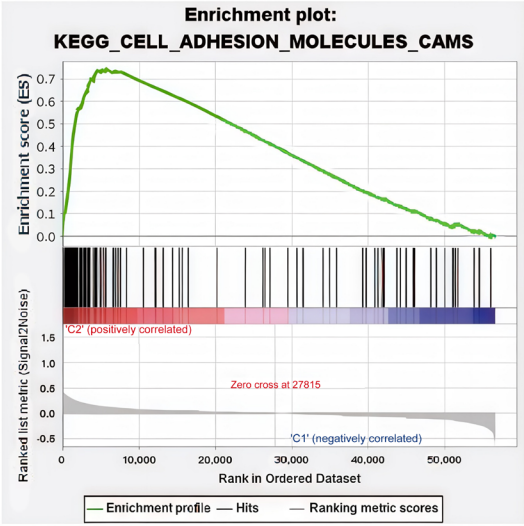
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KEGG_CELL_ADHESION_MOLECULES_CAMS
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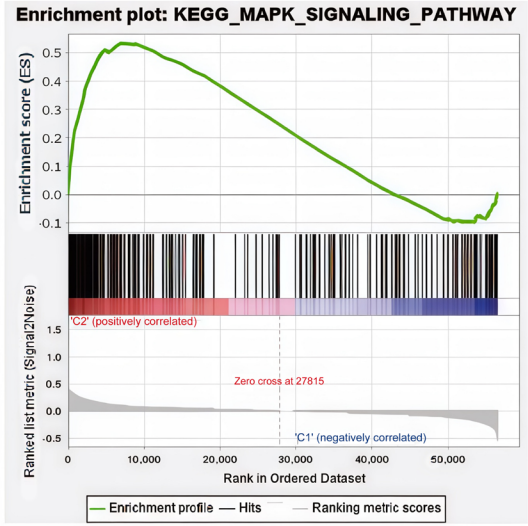
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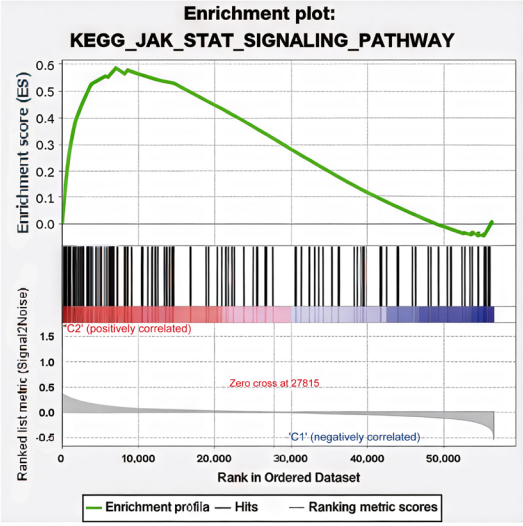
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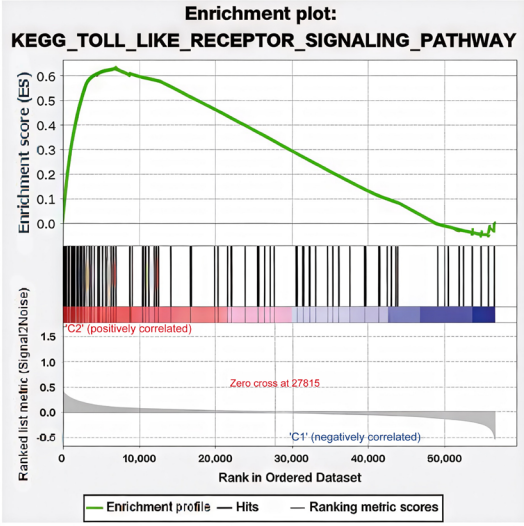
Enrichment plot:
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY
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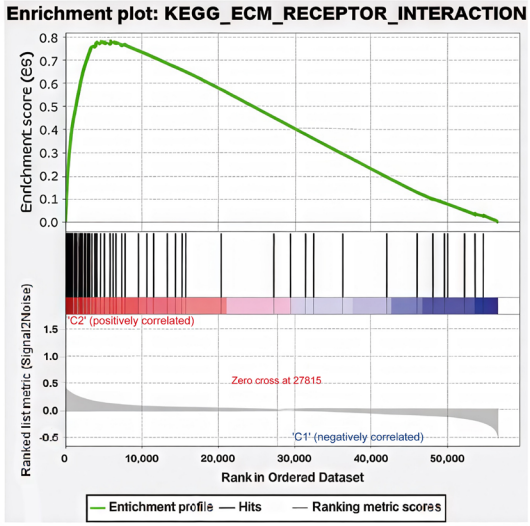
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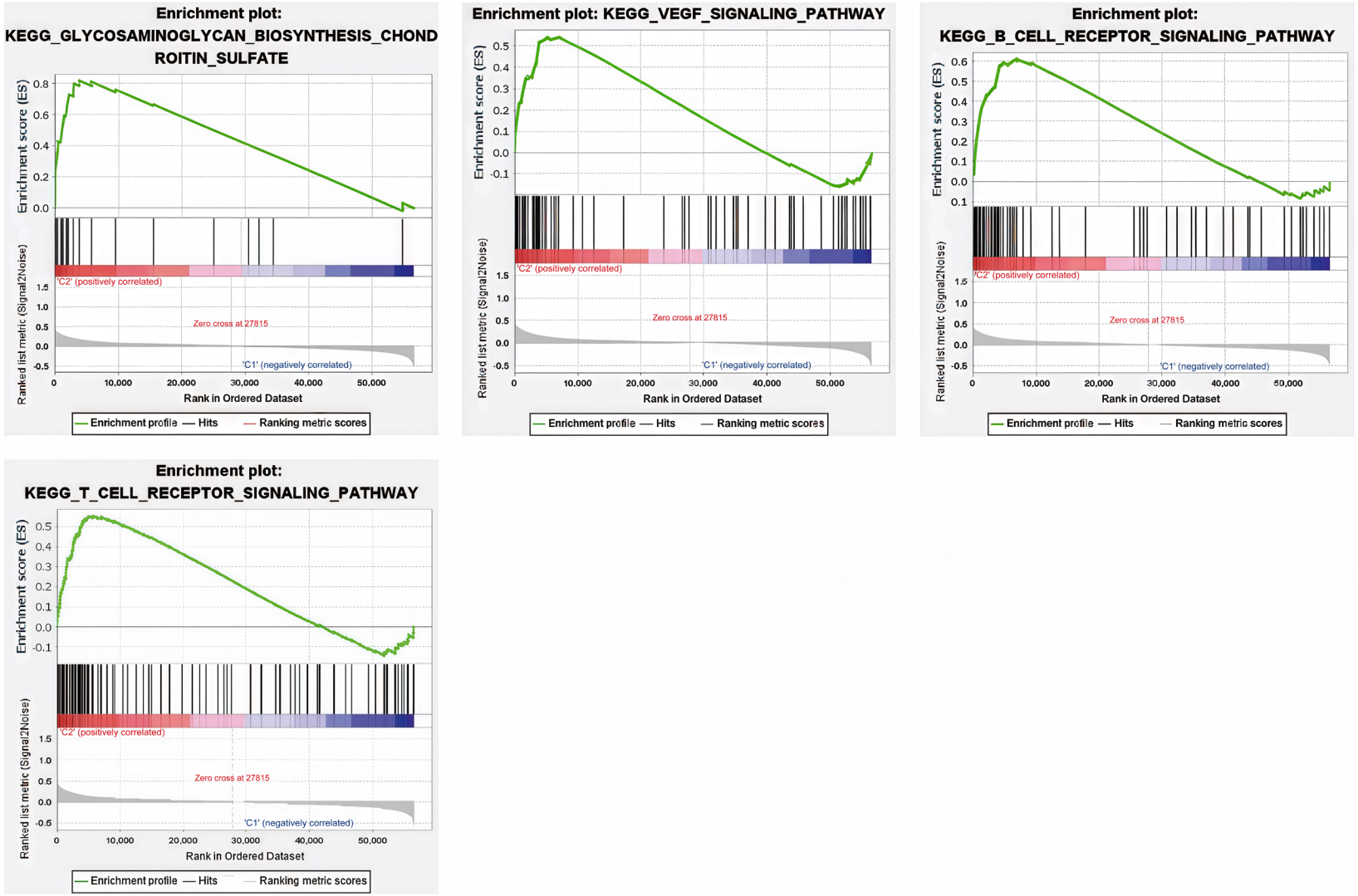

Figure 6. Some signaling pathways were enriched in the high-risk group, including cancer-related pathways.

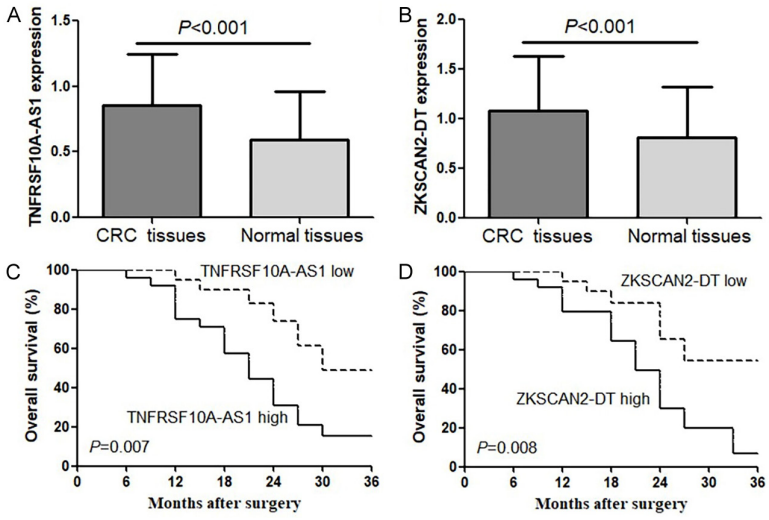

Figure 7. Verification of the prognostic value of two lncRNAs, TNFRSF10A-AS1 and ZKSCAN2-DT, in clinical CRC patients. (A, B) qRT-PCR analyses of the expression levels of TNFRSF10A-AS1 (A) and ZKSCAN2-DT (B) in 48 paired CRC tissues and adjacent normal tissues. (C, D) Relationships between TNFRSF10A-AS1 (C) or ZKSCAN2-DT (D) expression and the overall survival of CRC patients were estimated by Kaplan-Meier analysis.

CRC by performing a KEGG pathway analysis of the genes that were dysregulated between the low-risk group and high-risk group. According to the results of GSEA, these lncRNAs were involved in focal adhesion, cell adhesion molecule signaling, the MAPK signaling pathway, the JAK/STAT signaling pathway, the Toll-like receptor signaling pathway, ECM-receptor interactions, glycosaminoglycan biosynthesis, chondroitin sulfate, the VEGF signaling pathway, the B-cell receptor signaling pathway and the T-cell receptor signaling pathway.

Glycolysis is an important pathway for the energy metabolism of tumor cells, and its metabolites can affect the tumor microenvironment, especially by promoting the formation of an immunosuppressive environment, providing conditions for tumor progression and evasion of immune surveillance. This study demonstrated that specific glycolysis-associated lncRNAs could be biomarkers for the prognostic assessment of CRC patients. The expression patterns of these lncRNAs were closely correlated with OS, helping to distinguish between low-risk and high-risk patient groups. This prognostic model consisting of 14 glycolysis-associated lncRNAs was also able to stratify CRC patients based on risk scores, thus providing guidance for treatment decisions. ROC curves and AUC values are important tools for evaluating the diagnostic performance of prognostic models. High AUC values indicate that the model has good sensitivity and specificity, which is critical for determining the diagnosis treatment.

The expression patterns of glycolysis-associated lncRNAs are closely related to the biological progression of CRC, suggesting that they play a key role in metabolic reprogramming, proliferation, invasion, and metastasis of tumors. The identification and validation of specific glycolysis-associated lncRNAs may provide new strategies for individualized medicine for CRC patients, including prognostic assessment, treatment response monitoring, and the development of novel therapeutic targets.

Shortcomingsof this study are as follows. Although we confirmed the high expression of TNFRSF10A-AS1 and ZKSCAN2-DT in CRC patients, we have not further clarified the specific pathways by which TNFRSF10A-AS1 and ZKSCAN2-DT function in CRC. We will continue to improve our studies in the future to verify the specific mechanisms underlying the effects of TNFRSF10A-AS1 and ZKSCAN2-DT on the occurrence and development of CRC, including how they affect glycolysis and how they interact with the tumor immune microenvironment, which will help in the development of new therapeutic strategies.

In summary, we constructed three glycolysis-associated and prognostic lncRNA clusters with marked differences in the immune microenvironment. Moreover, 14 glycolysis-related lncRNAs that can predict the prognosis of CRC patients were identified. The bioinformatic analysis revealed that glycolysis-related lncRNAs may modulate CRC progression through a series of cancer-related pathways. Our work will aid in predicting the prognosis of CRC patients and might provide effective clinical applications for antitumor immunotherapy.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Fourteen prognosis-related and glycolysis-associated lncRNAs in CRC

ID	coef	HR	HR.95L	HR.95H	*P* value
AC016394.3	0.168796438	1.183879122	0.985343779	1.422417033	0.071495882
AC114730.3	0.879753364	2.410305164	1.467856821	3.957859446	0.000507566
AC008760.1	0.449756627	1.567930547	1.076404991	2.283904499	0.019097434
AC245041.1	0.504574885	1.65628126	1.279510591	2.143997581	0.000127266
AC073957.3	-0.239390694	0.787107304	0.624304531	0.992364908	0.042888918
LINC02593	0.458382192	1.58151333	0.938539567	2.664974925	0.08512107
AL161729.4	0.344466918	1.411237414	1.057632003	1.883066165	0.019246877
AC016737.1	-0.687497274	0.502832949	0.246659643	1.025060165	0.058510517
AC125807.2	0.052326261	1.053719474	1.001919271	1.108197799	0.041899564
TNFRSF10A-AS1	-0.197894458	0.820456441	0.713890666	0.942929784	0.005307128
ZKSCAN2-DT	0.463822627	1.590140898	1.280610885	1.974485854	2.68E-05
AC138207.5	0.304765411	1.35630679	1.035687482	1.776180694	0.026774372
AC008764.8	-1.735670695	0.176281929	0.042208151	0.736239757	0.017322155
ATP2B1-AS1	1.170082351	3.222257983	0.725546963	14.31050923	0.123999935