Construction and Validation of a Metabolic Risk Model Predicting Prognosis of Colon Cancer

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Abstract

Background

Metabolic genes have played a significant role in tumor development and prognosis. In this study, we constructed a metabolic risk model to predict the prognosis of colon cancer based on The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO).

Methods

We downloaded gene expression profile from TCGA database and retrieved differentially expressed metabolic genes. Then we conducted univariate cox regression analysis and Least Absolute Shrinkage and Selection Operator (LASSO) Cox regression analysis to identify prognosis-related genes and construct the metabolic risk model. Then we validated the risk model in TCGA and GEO datasets by Kaplan-Meier analysis, time-dependent receiver operating characteristic (ROC), risk score, univariate and multivariate cox regression analysis. Finally, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and GO (Gene Ontology) enrichment analyses were conducted to reveal the biological processes and pathways of genes by Gene Set Enrichment Analysis (GSEA).

Results

We extracted 753 metabolic genes and identified 139 differentially expressed metabolic genes from TCGA database. Then 15 prognostic genes were dug out and 8 genes were filtered into LASSO cox regression analysis. An eight-gene prognostic model was constructed after 1000 resamples. The gene signature has been proved to have an excellent ability to predict prognosis by validation based on TCGA and GEO database. Finally, GSEA showed that multiplex metabolism pathways correlated with colon cancer.

Conclusion

We identified eight metabolic prognostic genes and developed a metabolic risk model based on TCGA and GEO database to predict overall survival rate of colon cancer.

1. Introduction

Colon cancer is a common malignant tumor which mainly occurs in the proximal colon. Colon cancer and rectal cancer are often grouped as "colorectal cancer"(CRC), which is the fourth most common cancer and the second leading cause of cancer-related death in America{#1}. There are estimated to be 147,950 newly diagnosed CRC individuals, including 104,610 colon cancer patients in America in 2020{#2}. In addition,

the colon cancer patients is rapidly shifting younger as a result of older individuals declining and younger individuals increasing{#3}. However, colon cancer is potentially preventable because most of the cases and deaths are attributable to a an unhealthy lifestyle, including high-fat and low-fiber diet, smoking and drinking, insufficient physical activity, and overweight{#4}. Although morbidity and mortality can be mitigated through appropriate screening, including imaging techniques and colonoscopy{#5}, approximately 80% of CRC patients show recurrence during the first 3 years. Thus, identifying reliable prognostic biomarkers to select high-risk colon cancer patients is important for improving the survival rate.

Recently, metabolic reprogramming has become a hot topic{#6}. Studies had been shown that tumor metabolism played a vital roles in tumor cells{#7}. Metabolism plays a vital role in the progression and prognosis of colon cancer{#8}. Energy metabolism is the basis of cell proliferation, and change of cell metabolism is the feature of tumor cells{#9}. Tumor cells change metabolic processes to satisfy the increased energy and nutritional demands, for growth and invasion{#10}. The pathogenesis, progression and prognosis of colon cancer is closely related to metabolic progress, including glucose metabolism, amino acid metabolism, and lipid metabolism{#11}. In this study, we constructed and validated a metabolic risk model of colon cancer based on the data downloaded from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) database, to explore the potential role of metabolic genes and accurately predict prognosis of colon cancer.

2. Materials And Methods

2.1. Data Collection

We retrieved and downloaded gene expression profile and clinical data (age, gender, tumor grade, TMN stage) from TCGA (https://portal.gdc.cancer.gov/) and GEO (http://www.ncbi.nlm.nih.gov/geo/). The data was extracted, annotated, and normalized by Strawberry Perl (version5.30.1.1). We downloaded the metabolic genes from Gene Set Enrichment Analysis (GSEA) platform (http://software.broadinstitute.org/gsea/downloads).

2.2. Differentially Expressed Metabolic Genes Identification

Metabolic genes were defined as genes enriched in metabolism pathways based on Kyoto Encyclopedia of Genes and Genomes (KEGG) database. We extracted and downloaded metabolic genes from TCGA and GEO database. Then, we adjusted different mRNA expression levels by ‘sva’ package and selected candidate metabolic genes by R software (version 3.6.1). Differentially expressed metabolic genes were screened through ‘limma’ package (version 3.44.1) on R, with the screening criteria false discovery rate (FDR) < 0.05 and |log2-fold change| > 1. Heatmap and volcano were constructed through ‘pheatmap’ package in R.

2.3. Construction of Metabolic Signature

We used the dataset from TCGA as the training cohort. Univariate cox regression analysis was performed to identify prognostic metabolic genes by “survival” and “survminer” package, with the screening criteria $P < 0.05$. We regarded overall survival (OS) as the primary outcome and genes with HR ≠ 1 were defined as better prognosis. The metabolic risk model was constructed after 1000 resamples by Least Absolute Shrinkage and Selection Operator (LASSO) Cox regression analysis through ‘glmnet’ and ‘survival’ package on R.

2.4. Validation of Metabolic Risk Model

We applied the metabolic risk model to TCGA and GEO datasets to validate the predictive ability of the model. Patients were grouped into high- and low-risk groups according to the median risk score. Kaplan-Meier curves were generated by survival analysis through the “survival” package. Risk score curves were drawn using the ‘pheatmap’ package. Next, univariate and multivariate cox proportional hazards analysis were performed, and time-dependent receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) were used to evaluate the prognostic value of the model using the ‘survival ROC’ package. A nomogram was built to visualize the risk model and classic independent risk factors, including age, gender, tumor grade, and TMN stage, to calculate survival rate of cancer patients.

2.5. GSEA Analyses

GSEA software (version 4.0.3) for Windows was downloaded from website for functional analyses. KEGG and GO (Gene Ontology) enrichment analyses of the genes were performed to identify potential pathways and functions by GSEA.

3. Results

3.1. Data Extraction

We extracted 452 cases and 753 metabolic genes from TCGA database, including 361 up-regulated and 392 down-regulated genes. In addition, we downloaded 177 cases and obtained the gene expression profile from the GSE17536. Then we identified 139 differentially expressed metabolic genes from TCGA database, including 62 up-regulated and 77 down-regulated genes, which were shown in volcano plot (Fig. 1A) and heatmap (Fig. 1B).

3.2. Construction of Metabolic Signature

A total of 15 prognostic genes were dug out by univariate cox regression analysis. Among them, NAT2, ENOPH1, ACAA2, UGT2A3, PAFAH1B3, SUCLG2, CPT2, and ACOX1 were associated with better overall survival outcomes, while PKM, GPX3, LPCAT1, ADCY5, ADH1B, SPHK1, and PTGDS were associated with worse overall survival outcomes (Fig. 2). Then an eight-gene prognostic model was constructed after 1000 resamples by LASSO penalized Cox regression analysis. Risk score = 0.0005 × expression of PKM + 0.0092 × expression of GPX3 − 0.0039 × expression of ENOPH1 − 0.0010 × expression of ACAA2 − 0.0056 ×

expression of PAFAH1B3 − 0.0372 × expression of CPT2 − 0.0292 × expression of ACOX1 + 0.0025 × expression of PTGDS.

3.3. Validation of Metabolic Signature

Patients were grouped into high- and low-risk groups according to the median risk score. in the high-risk group, patients had a lower OS according to Kaplan–Meier curves (P 0.05, Fig. 3A, B) and risk score distribution than in the low-risk group (Fig. 4A, B). The differential expression of metabolic genes in high- and low-risk groups were shown in heatmaps (Fig. 4C, D). The AUC was 0.693 according to the ROC, which was higher than age, gender, ethnicity, tumor stage, or TMN stage (Fig. 5). Univariate Cox analysis showed that the risk of poor prognosis elevated with the risk score increasing (Fig. 6A). Multivariate Cox regression analysis demonstrated that the risk score could be an independent risk factor for OS (Fig. 6B). Nomogram was formed of age, gender, tumor stage, TNM stage and the risk score as well (Fig. 7A, B).

3.4. GSEA

The results of GSEA showed that patients in the low-risk group were more associated with metabolism-related pathways, and patients in the high-risk group were more associated with nonmetabolic pathways. KEGG analysis demonstrated that most of the enriched pathways focused on fatty acid metabolism, pyruvate metabolism, propanoate metabolism, and butanoate metabolism pathways (Fig. 8A). GO analysis showed that genes were mainly enriched in nucleoside bisphosphate metabolic process, and thioester metabolic process (Fig. 8B). In addition, there were several famous cancer-related pathways, such as cell adhesion molecules cams, cytokine-cytokine receptor interaction, peroxisome, peroxisomal transport, peroxisome organization.

4. Discussion

In this study, we established and verified an eight-gene metabolic risk model based on TCGA and GEO, to predict the prognosis of colon cancer. Firstly, we identified differentially expressed metabolic genes from TCGA and constructed a prognostic model by LASSO. Then, we verified the model by Kaplan–Meier curves, risk score, ROC curves, univariate and multivariate cox regression based on TCGA and GEO. Finally, we performed KEGG and GO analyses by GSEA.

Colon cancer is a malignant tumor with poor prognosis, so novel prognostic biomarkers is urgently needed. The prognostic models based on metabolic genes has been established in rectal cancer{#12}, lung adenocarcinoma{#13}, hepatocellular carcinoma{#14}, and acute myelogenous leukemia{#15}. However, it has not been applied on colon cancer. In this study, we identified differentially expressed metabolic genes and constructed a prognostic model firstly. In this model, the expression of ENOPH1, ACAA2, PAFAH1B3, CPT2, and ACOX1 predicted better prognosis, whereas the expression of PKM, GPX3 and PTGDS predicted worse prognosis. Most of the genes in our model have been proved to take part in pathogenesis, progression and prognosis of cancers.

Enolase-phosphatase 1 (ENOPH1), a bifunctional enolase-dephosphorylase enzyme{#16}, is required for polyamine biosynthesis {#17}. Previous studies showed that the overexpression of ENOPH1 remarkably promoted cell migration and invasiveness, whereas the downregulation of ENOPH1 significantly impaired cell migration and invasiveness{#18}. Acetyl-Coenzyme A acyltransferase 2 (ACAA2) exerts an effect on β-oxidation of fatty acid, which then provide energy{#19}. Previous showed that ACAA2 could abolished the apoptosis in human hepatocellular carcinoma{#20}, and played a vital role in the the metabolism processes in gliomas{#21}. The higher expression of ACAA2 was associated with better prognosis of colorectal cancer{#22}. Platelet activating factor acetyl hydrolase 1B3 (PAFAH1B3) is reported to play an important role in tumorigenesis and aggressiveness in many different cancerss{#23}. Blockers of PAFAH1B3 could heightened levels of tumor-suppressing lipids, then impairs pathogenicity of different cancers, including breast, ovarian, melanoma, and prostate cancer{#24}. Carnitine palmitoyl transferase 2 (CPT2), a rate-limiting enzyme for mitochondrial fatty acid transportation, had been proved to be a protective prognostic gene for colorectal cancer{#25}, which is in accordance with our results. Peroxisomal Acyl-Coa Oxidase 1 (ACOX1) is the rate-limiting enzyme in fatty acid β-oxidation. The inhibitor of ACOX1 is SIRT1, which has been proved to prevent oxidative damage and is downregulated in liver cancerr{#26}, suppresses colorectal cancer metastasis by transcriptional repression of miR-15b-5p{#27}.

Pyruvate kinase M (PKM), a metabolic regulator, participated in both glycolytic and non-glycolytic pathways. PKM also acts as protein kinase, which shifts the glucose metabolism from the respiratory chain to anaerobic glycolysis in tumor cells{#28}. PKM2 is upregulated in most cancer types, and contributes to tumorigenesis{#29}, which suggested that it could act as a remarkable therapeutic target{#30}. The glutathione peroxidases-3 (GPX3), a selenocysteine-containing redox enzyme, took part in reactive oxygen species signaling and immunomodulatory{#31}. Previous studies suggested that GPX3 prevented the colitis-associated carcinoma by immunomodulation{#32}. But the correlation between GPX and prognosis of colon cancer is not clear. The tumor suppressive effect of prostaglandin D2 (PGD2) on testicular cancer and gastric cancer has been confirmed{#33}. However, the correlation between PGD2 and colon cancer is unclear.

The results of GSEA revealed many metabolic pathways related to prognosis of colon cancer. In one hand, the results validated the close association between metabolic systems and colon cancer. Most significantly enriched pathways focused on metabolism, including butanoate metabolism, fatty acid metabolism, propanoate metabolism and pyruvate metabolism pathways. In the other hand, most of the metabolic pathways were enriched in the low-risk patients, while the non-metabolic pathways were enriched in the high-risk patients. These results uncovered the underlying molecular mechanisms and potential therapy target. In the future, colon cancer patients might benefit from metabolic-related therapy and management.

However, there were some limitations in this study. Firstly, there was no functional experiment in the real world. Moreover, it is relatively weak to take only metabolic genes into prognostic model because much

more complicated mechanisms together contributed to the development and progression of colon cancer.

5. Conclusions

We constructed and validated a metabolic risk model to predict the prognosis of colon cancer based on TCGA and GEO database. Metabolic-related therapied and managements could be considered for colon cancer patients. However, validation and functional experiments of the metabolic risk model are indispensable.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

All the authors listed have approved the submission and publication.

Availability of data and materials

The datasets and analyses during the current study are available in TCGA and GEO database.

Competing interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Funding

Not applicable

Authors' contributions

Analyzed the data and wrote the manuscript: Chao Li

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Figures

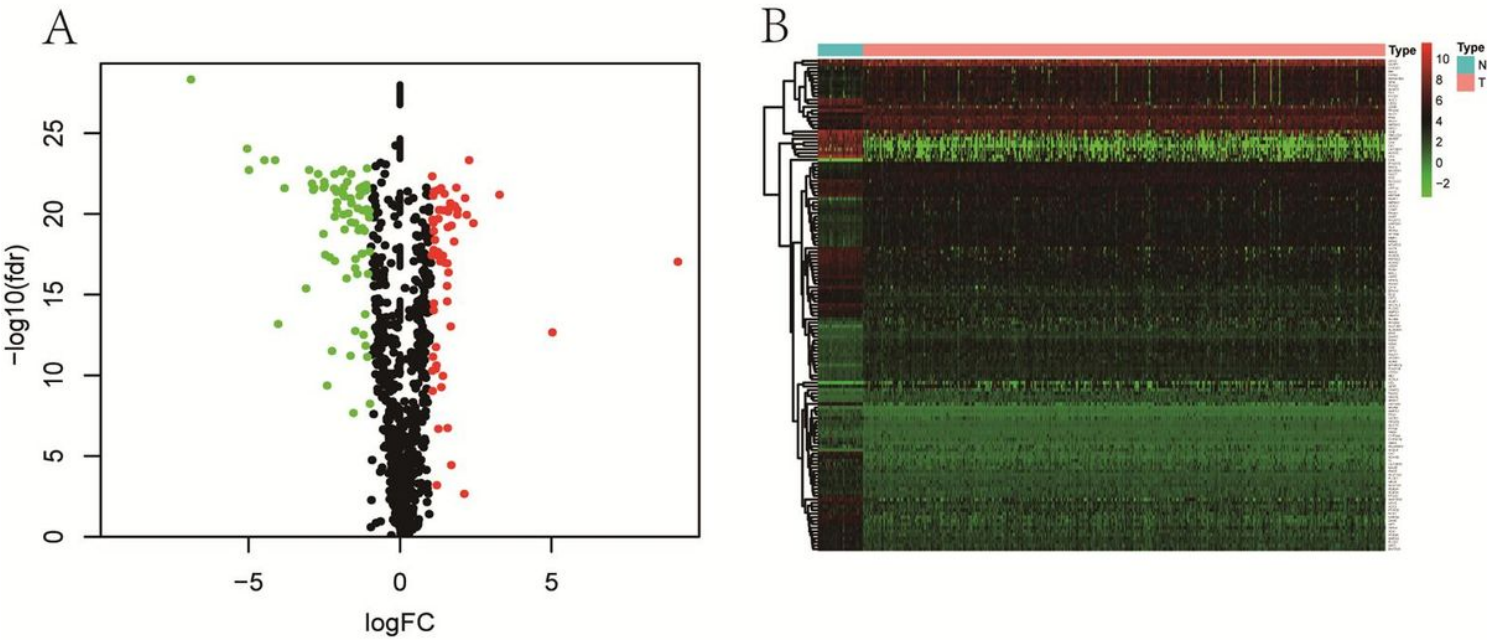

Figure 1

Volcano plot and Heatmap of differentially expressed metabolic genes. (A) Volcano plot of differentially expressed metabolic genes. The red points represent high expression genes, the green points represent low expression genes, the black points represent genes with no significant difference (FDR < 0.05, log FC > 1.0). (B) Heatmap of differentially expressed metabolic genes. Red indicates that the gene expression is relatively high, green indicates that the gene expression is relatively low, and black indicates no significant changes in gene expression (FDR < 0.05, absolute log FC > 1.0).

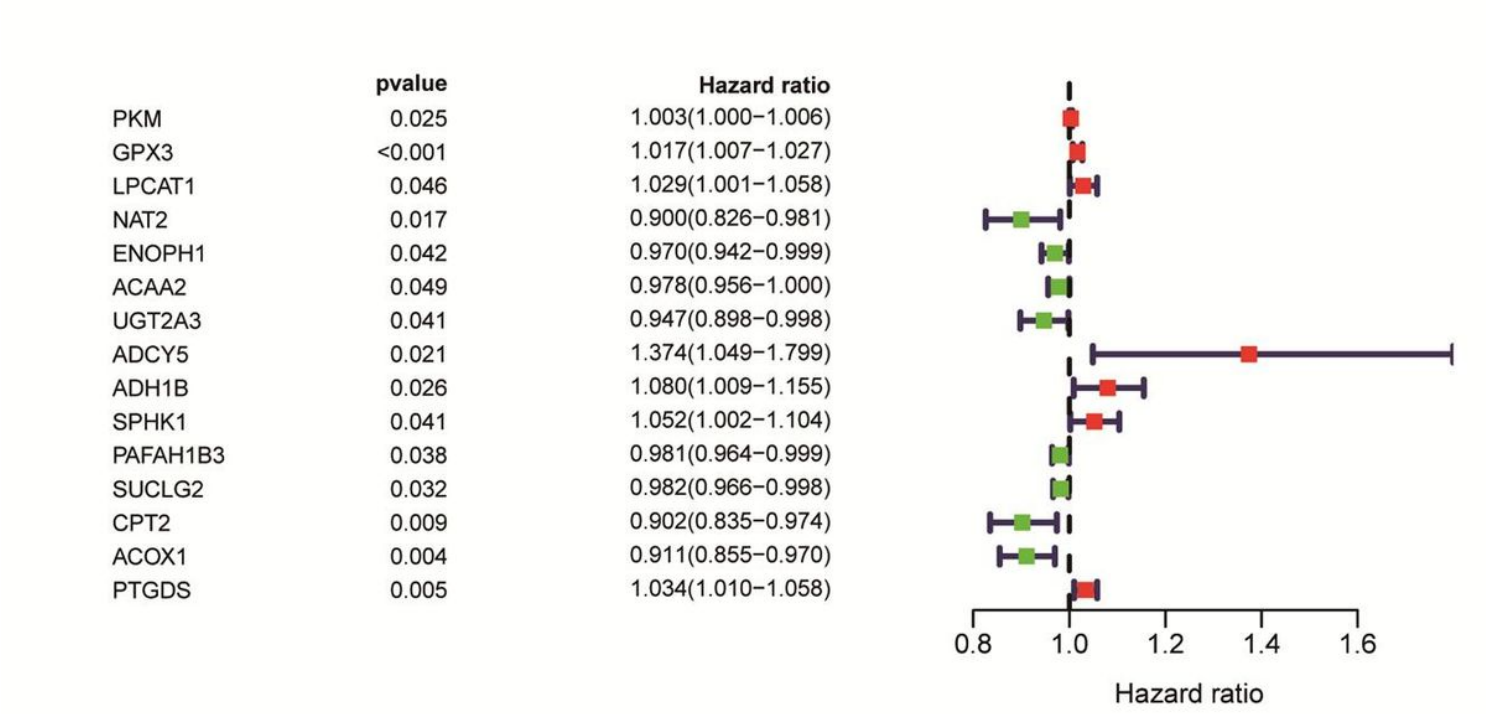

Figure 2

Forest plot of the univariate Cox regression analysis showing the prognostic metabolic genes. Genes with HR < 1 have better overall survival outcomes, while genes with HR>1 have worse overall survival outcomes.

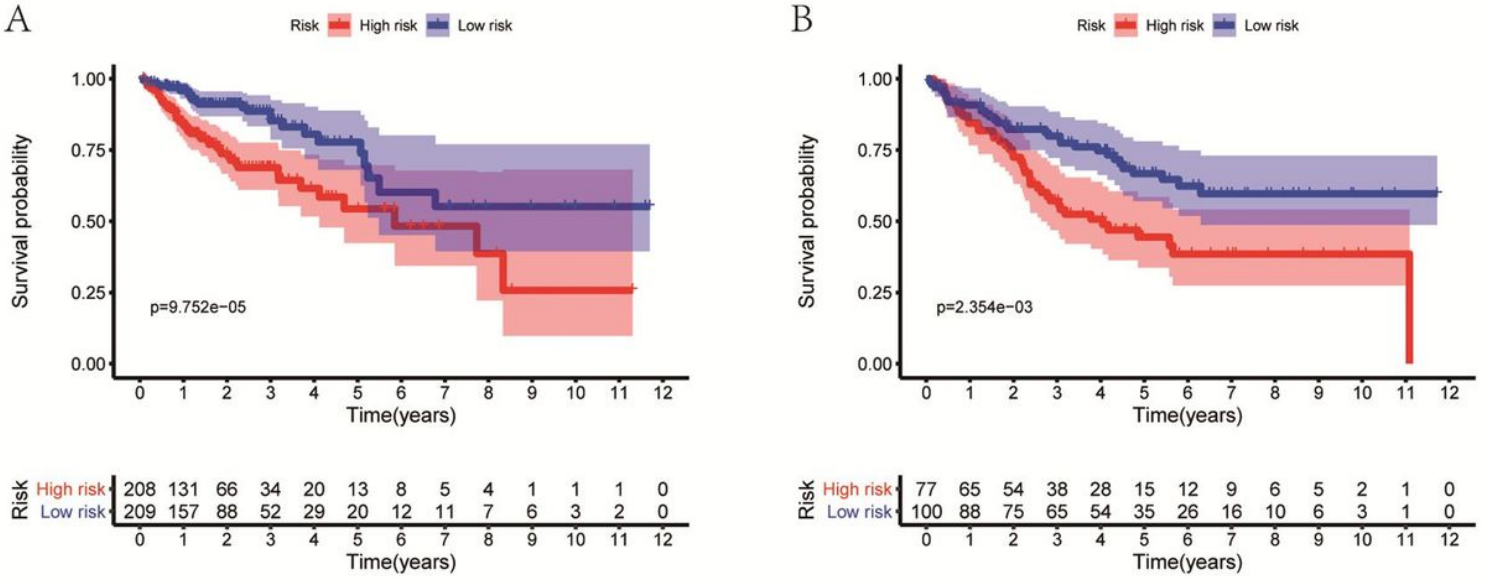

Figure 3

Validation of Metabolic Signature by Kaplan-Meier curves. (A) Kaplan-Meier curves of OS based on gene signature in TCGA. (B) Kaplan-Meier curves of OS based on gene signature in GEO.

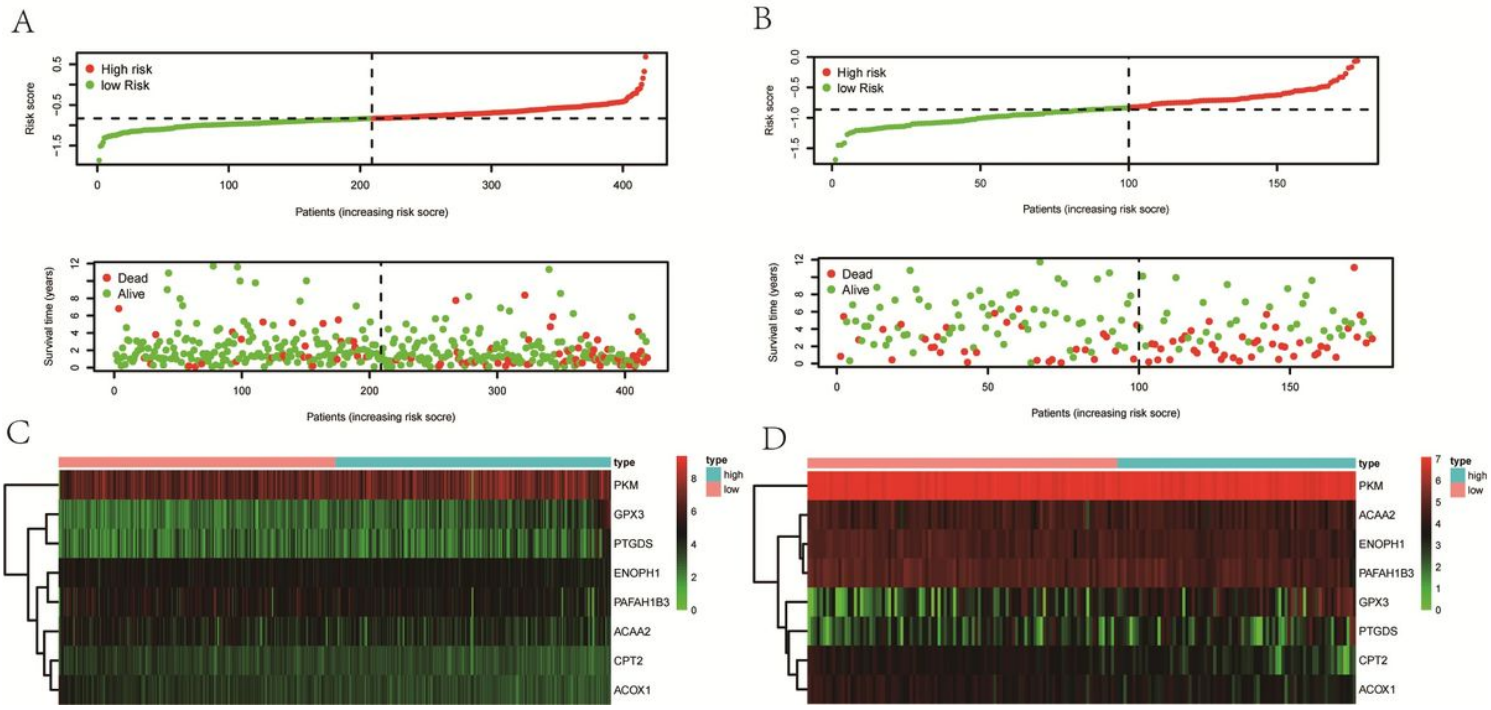

Figure 4

Validation of Metabolic Signature by risk score. (A) Risk score distribution of the eight-gene signatures in TCGA database. (B) Risk score distribution of the eight-gene signatures in GEO database. (C) Heatmaps of the differential expression of metabolic genes in high-risk and low-risk groups in the TCGA database. (D) Heatmaps of the differential expression of metabolic genes in high-risk and low-risk groups in the GEO database.

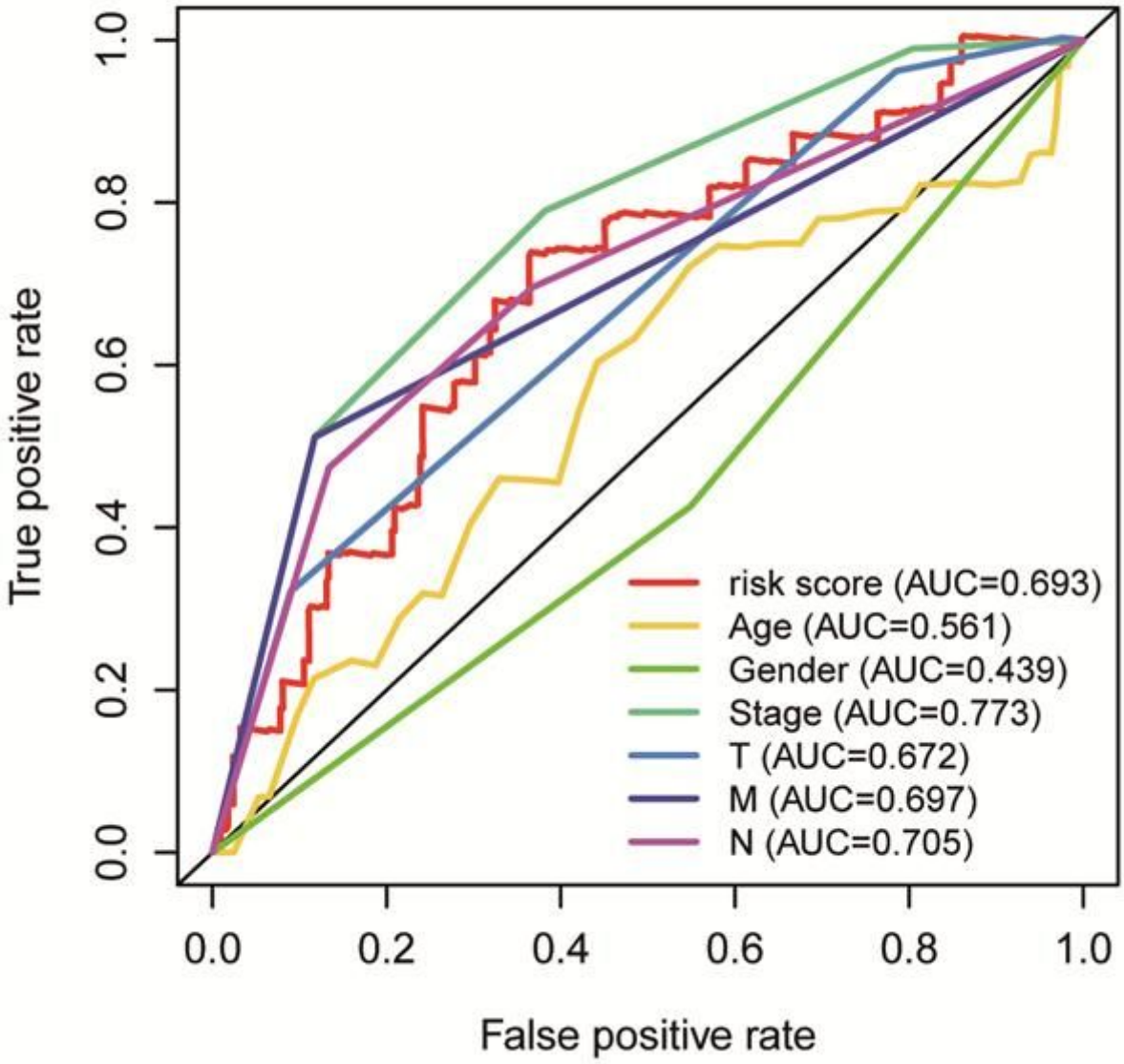

Figure 5

Validation of Metabolic Signature by Time-dependent ROC analysis in TCGA cohorts. ROC, receiver operating characteristic; AUC, area under the ROC curve.

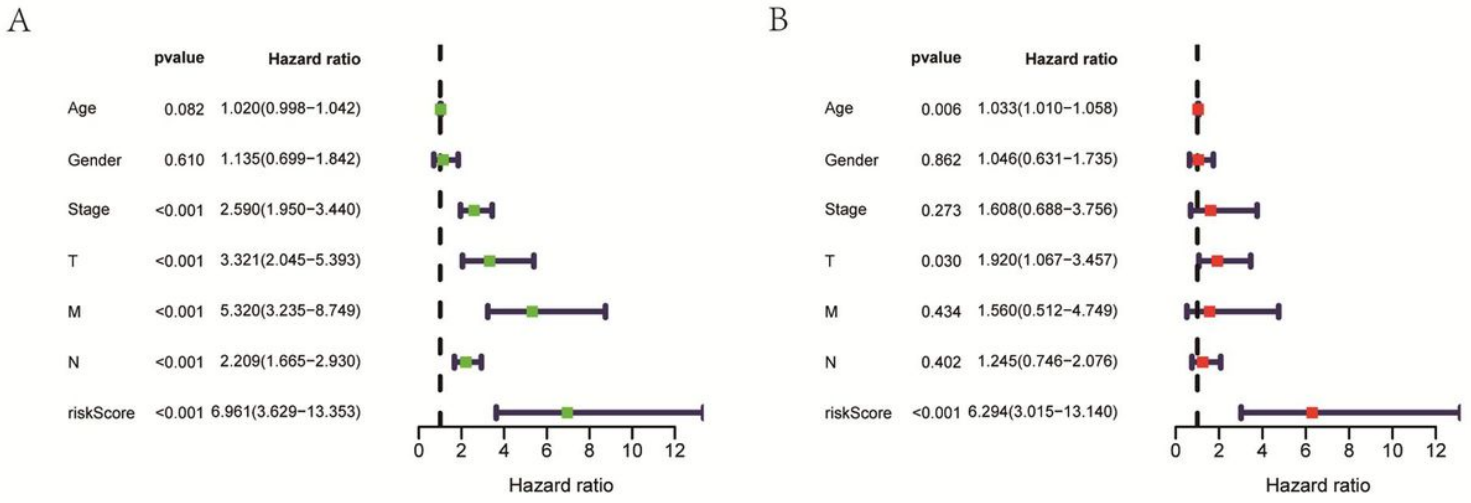

Figure 6

Univariate and Multivariate Cox analysis. (A) Prognostic value detection of the gene signature via univariate survival-related analysis in TCGA. (B) Prognostic value detection of the gene signature via multivariate survival-related analysis in TCGA.

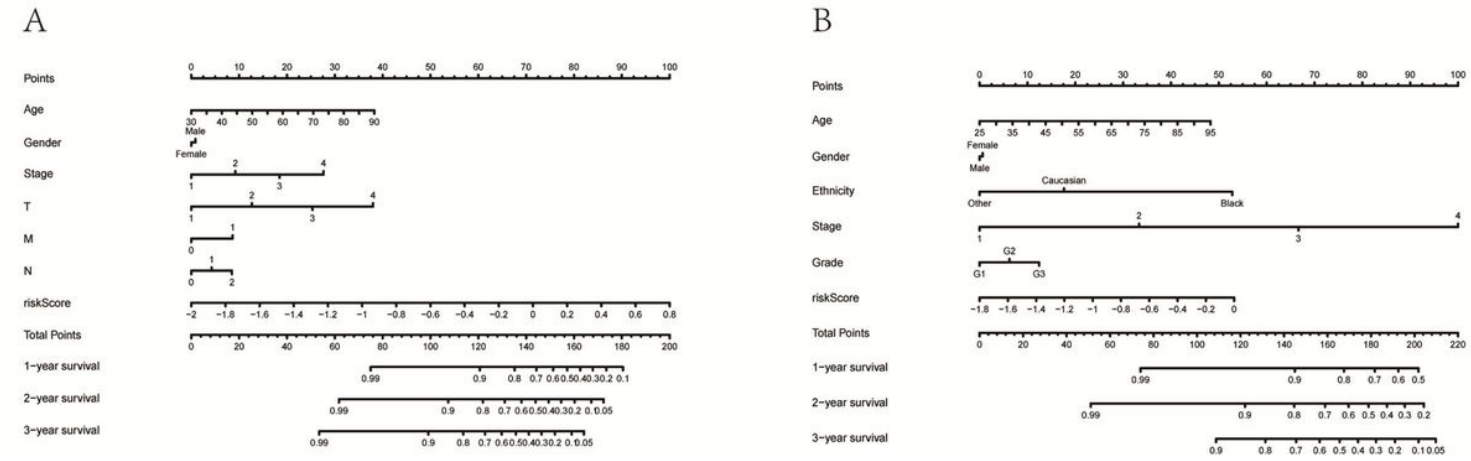

Figure 7

Nomogram was built to predict overall survival for colon cancer patients. (A) The nomogram plot was built based on TCGA cohort. (B) The nomogram plot was built based on the GEO cohort.

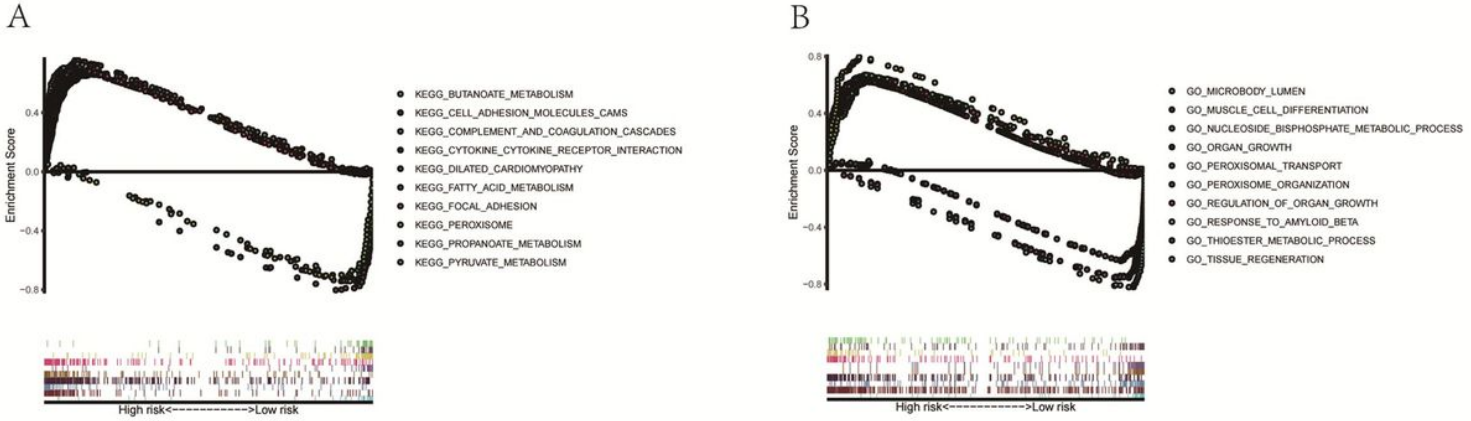

Figure 8

KEGG pathways and GO enrichment analyses by GSEA. (A) Top 10 representative KEGG pathways. (B) Top 10 representative GO terms.