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Peer Review of *World Journal of Gastrointestinal Oncology*, Jihwan Ko, MD, FRSPH, Director, Baekyang Jeil Internal Medicine Clinic, Busan 47181, South Korea. jihwanko65@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

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ORIGINAL ARTICLE

Retrospective Study

Using bioinformatics methods to elucidate fatty acid-binding protein 4 as a potential biomarker for colon adenocarcinoma

Yun Zhang, Wen-Li Zhu, Min Wu, Tian-Yuan Gao, Hui-Xian Hu, Zheng-Yuan Xu

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Abstract

BACKGROUND

Colon adenocarcinoma (COAD) ranks second in terms of cancer-related deaths. We found that fatty acid-binding protein 4 (*FABP4*), which is related to cell adhesion and immunity, affects the occurrence and development of COAD. This study focused on the possibility of using *FABP4* as a biomarker for COAD and constructed a nomogram for predicting the survival of COAD patients.

AIM

To verify the possibility of using *FABP4* as a biomarker for COAD.

METHODS

A total of 453 COAD tissue samples, along with 41 normal tissue samples, were obtained from The Cancer Genome Atlas database. The difference in *FABP4* expression between COAD tissues and normal tissues was analyzed, and the results were verified by immunohistochemistry. The WGCNA algorithm links *FABP4* expression with an enrichment analysis and with immune cell infiltration pathways. The biological functions of *FABP4* and its coexpressed genes were explored through enrichment analyses. The ESTIMATE, CIBERSORT and ssGSEA methods were used for the immune infiltration analysis. Finally, risk scores were

calculated by a Cox analysis. A nomogram was constructed by combining risk scores with routine clinicopathological factors. We assessed the accuracy of survival predictions based on the C-index. The C-index ranges from 0.5 to 1.0, and in general, a C-index value greater than 0.65 indicates a reasonable estimate. The results were validated using the Gene Expression Omnibus (GEO) database.

RESULTS

FABP4 was significantly differentially expressed in COAD. It is a promising auxiliary biomarker for screening and diagnosis. Enrichment analyses suggested that *FABP4* may influence the invasion and progression of COAD through cell adhesion. The immunological analysis revealed that *FABP4* expression in COAD was significantly positively correlated with immune cell infiltration. Moreover, a nomogram to predict the survival of COAD patients was successfully constructed by integrating the calculated risk scores of 15 candidate genes and routine clinicopathological factors. This nomogram could effectively predict 1-year, 3-year, and 5-year survival (C-index = 0.786) and was verified (C-index = 0.73).

CONCLUSION

This study established *FABP4* as an effective biomarker for screening, assisting in the diagnosis and determining the prognosis.

Key Words: *FABP4*; Colon adenocarcinoma; Biomarker; Cell adhesion; Immune pathways; Prognostic nomogram

Core Tip: Fatty acid-binding protein 4 (*FABP4*) can be used as a biomarker of colon adenocarcinoma (COAD). Based on this, a nomogram was constructed to effectively predict the survival of COAD patients. *FABP4* influences COAD invasion and progression through cell adhesion and immune-related pathways.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, accounting for approximately 10% of all cancers, and ranks second in mortality[1,2]. Metastasis occurs in 50%-60% of CRC patients[3] with a five-year overall survival (OS) rate of less than 20%[4,5]. Colon adenocarcinoma (COAD), the main type of CRC, develops from gene mutations in adenomatous lesions[6]. Previous studies have shown that a tumor immune microenvironment analysis has the potential to predict and guide immunotherapy[7,8]. Many studies have shown that fatty acid-binding protein 4 (*FABP4*) is inextricably related to tumor microenvironment (TME) disorders, and that the occurrence of colon cancer is inextricably related to TME disorders[9]. New sensitive and specific immunotherapy markers need further exploration due to tumor heterogeneity. Accordingly, novel and effective diagnostic and prognostic biomarkers for the early screening and personalized treatment of COAD patients are needed.

FABP4 is an important member of the fatty acid-binding protein (FABP) family, and is found in adipocytes, endothelial cells, and immune cells[10]; and acts as a link between tumor cells and components of the TME[11]. *FABP4* plays a crucial role in the pathogenesis of various metabolic pathologies and has been shown to be abnormally expressed in several cancer types[11,12]. *FABP4* has been identified as a biomarker and therapeutic target in tumors[11].

Recent studies have described the influence of *FABP4* on tumor malignancy, such as its ability to drive tumor resistance to apoptosis and promote recurrence[13]. *FABP4* enhances lipid transport and activates multiple signaling pathways involved in tumor transformation, proliferation, metastasis, and treatment resistance[14]. Several preliminary studies have shown a relationship between *FABP4* expression and the immune status of patients with CRC[15], but the screening, diagnostic and prognostic value of *FABP4* in COAD have not been extensively discussed.

Previous studies have shown an inextricable link between FABP4 and COAD, but no comprehensive bioinformatics studies have been conducted[9]. The aim of this study was to explore the combined value of *FABP4* as a potential biomarker for COAD. We analyzed the expression levels of FABP4 and clinicopathological factors of COAD and normal tissues using The Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus (GEO) databases, identified *FABP4* as an adverse prognostic factor, and performed a functional enrichment analysis and immune infiltration analysis. Our findings indicate that cell adhesion is the main biological process (BP) associated with *FABP4*, suggesting that it plays a role in promoting the occurrence and development of COAD through this process. A significant positive correlation between *FABP4* expression and tumor-infiltrating lymphocytes (TILs) was detected, indicating that *FABP4* promotes the occurrence and development of COAD through immune-related pathways. Finally, a risk score was calculated for *FABP4*

and its OS-related coexpressed gene set, and a nomogram was constructed by combining conventional clinicopathological factors. It is a good predictor of the 1-year, 3-year, and 5-year survival of COAD patients. This comprehensive analysis establishes *FABP4* as a biomarker for COAD and improves our understanding of the molecular function (MF) of *FABP4*, providing new insights into the onset and progression of COAD.

MATERIALS AND METHODS

Immunohistochemical staining

The study was approved by the Ethics Committee of Wannan Medical College [Wuhu, China; ethical approval number: (2023) 215], and written informed consent was obtained from COAD patients to perform immunohistochemical staining for *FABP4* (experiment date: December 2023). The inclusion criteria for patients were as follows: Had COAD (aged 30 to 90 years), male and female half. The exclusion criteria were pregnant women and nursing mothers. The paired COAD tissue and paracancerous tissue samples were obtained from the same subject. Ten patients with COAD diagnosed at the Second Affiliated Hospital of Wannan Medical College were randomly selected for immunohistochemical staining, and tumor tissue and adjacent tissue samples were collected from each patient. All the samples were completely deidentified before the start of the immunohistochemical staining experiment. Formalin-fixed, paraffin-embedded tissue blocks were used for the immunohistochemical analysis of *FABP4* expression according to the manufacturer's instructions. Briefly, after partial paraffin dewaxing and antigen retrieval with citrate buffer, 3% hydrogen peroxide was used to block endogenous peroxidase activity. After blocking with serum, the sections were incubated with a primary antibody (Affinity Biosciences, Cat. No. DF6035) at 4 °C overnight and then with a secondary antibody for two hours, followed by DAB color development and hematoxylin staining. Images were captured at × 100 and × 200 magnifications using a Leica upright microscope (Germany). The positive intensity of immunostaining was scored as 0 points (colorless), 1 point (light yellow), 2 points (brown yellow), or 3 points (dark brown). According to the mean percentage of positive tumor cells, the ratio of positive cells to tumor cells was < 10%, 10%-50%, 50%-75%, or > 75%. The scores ranged from 1 to 4 points. The percentage of positive tumor cells and staining intensity were multiplied to produce a weighted score: < 3 score (-), 3-5 score (+), 6-9 score (++), and > 9 score (+++). Scoring was performed in a double-blinded manner by two senior diagnostic physicians[16].

Samples and preprocessing

The study cohort comprised TCGA COAD database, which consists of 453 samples of COAD tumor tissue and 41 normal tissue samples. Raw RNA-seq data (counts) and processed RNA-seq data (FPKM), along with clinicopathological factor and survival status data, were obtained from the University of California, Santa Cruz Xena platform (https://xena.ucsc.edu).

The samples included patients with comprehensive clinical information, including age; sex; T, N, and M classification; tumor stage; and vital statistics. Data were analyzed and processed using R version 4.2.2 and the relevant R packages. The raw RNA-seq data were subjected to analysis of variance and the processed RNA-seq data (FPKM) were subjected to further analysis.

This study examined the categorization of *FABP4* mRNA expression levels in COAD samples and normal colon samples. The analysis involved ranking patients in the COAD database based on their mRNA expression level and determining the H-*FABP4* group and L-*FABP4* group based on the median value of *FABP4* expression.

WCGNA network construction

The R software package DESeq2 was used to compare expression profile data (counts) and identify differentially expressed genes (DEGs) between COAD samples and normal samples in TCGA database[17]. The threshold for determining DEGs was set at $|\log2 \text{ fold change}| > 1.5$, with a P value < 0.05 after adjustment.

The R package WGCNA was subsequently used to analyze the DEGs[18]. A power of two was selected to ensure that the constructed coexpression network approached a scale-free distribution. The DEGs were divided into ten different gene modules, with a minimum module size of 30. Correlations of the modules with the matrix score, immune score, estimated score, tumor purity, and *FABP4* expression were computed.

The module with the highest absolute significance was identified as the key module, as determined based on module membership degree (representing the Pearson correlation coefficient between genes and modules, |module membership (MM)| > 0.6) and gene significance (representing the Pearson correlation coefficient between genes and clinical parameters, |gene significance (GS)| > 0.5). Ultimately, a total of 146 hub genes were obtained.

Functional enrichment analysis

The DAVID tool (https://david-d.ncifcrf.gov/) was used to conduct Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of the key modules identified *via* WGCNA.

Furthermore, for the *FABP4* expression groups (H-*FABP4* and L-*FABP4*), a gene variation analysis was performed according to the criteria of a $|\log2 \text{ fold change}| > 1$ and a P value < 0.05 after adjustment. A total of 1358 genes were selected for the gene set enrichment analysis (GSEA) using the clusterProfiler package (version 4.6.0) in R to explore the biological functions of *FABP4* in COAD[19].

Simultaneously, gene set variation analysis (GSVA) was applied to examine the relationships between each patient and the biological functions. The biological functions of the genes identified *via* GSEA were obtained from the GSEA Molecular Signatures Database (https://www.gsea-msigdb.org/gsea/index.jsp), and their scores were calculated using

the R package GSVA (version 1.46.0). A heatmap of the enrichment results for COAD patients and the biological functions was generated using the pheatmap package in R.

The correlations between the expression of *FABP4* and cell adhesion molecules (CAMs) were analyzed using the Pearson algorithm (63 major CAMs were selected according to the four major groups of CAMs)[20-22], with $P < 0.05$ and an absolute value of the correlation coefficient $|R| > 0.4$.

Immune infiltration analysis

The TIMER online database (https://cistrome.shinyapps.io/timer/) can be utilized to conduct a comprehensive analysis of tumor-infiltrating immune cells[23]. This approach allows the calculation of *FABP4* subtype expression and the levels of six different types of tumor-infiltrating immune cells [B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells (DCs)] and their correlations with tumor purity.

In this study, the R package estimate was used to evaluate various aspects of the TME in COAD patients, including the stromal score, immune score, ESTIMATE score, and tumor purity[24]. CIBERSORT is a deconvolution algorithm that enables estimation of the proportions of 22 distinct immune cell types within each sample from COAD patients[25]. Single-sample GSEA (ssGSEA) is a quantitative method used to assess the levels of infiltration of 28 immune cell types based on their correlation with *FABP4* expression[26]. In this analysis, the R package GSVA was used to calculate correlations and determine the degree of infiltration for each immune cell type[27].

Nomogram construction and evaluation

Coexpressed genes with a correlation coefficient greater than 0.65 with *FABP4* were selected for the Cox analysis, and the gene sets significantly associated with OS were selected to calculate the risk score.

The formula was developed as follows: Risk score = $\sum$ [c (genes) × Exp (genes)] where coef represents the coefficient of each gene in the Cox regression analysis and Exp represents the expression level of each gene.

A nomogram was constructed *via* the rms package combined with the risk score and routine clinicopathological factors. The nomogram could effectively predict 1-year, 3-year, and 5-year survival. Calibration curves and the C-index were used to measure the accuracy of the nomogram. The calibration curves showed the consistency between the predicted OS and the actual OS. A C-index greater than 0.65 indicates a reasonable estimate[28].

Validation with the GEO database

For this study, we downloaded the expression matrix for RNA-seq data, clinicopathological factor data, and survival status data from the GSE39582 dataset from the National Center for Biotechnology Information GEO database (https://www.ncbi.nlm.nih.gov/geo). The GSE39582 cohort included 585 patients with stage I to IV COAD who underwent surgery between 1987 and 2007 at seven centers. The dataset consists of 566 COAD tissue samples (tumor) and 19 normal tissue samples (normal)[29]. We specifically included patients whose clinical information was complete in the analysis.

Statistical analysis

All clinical data, including age, sex, OS, tumor stage, T classification, N classification, and metastasis, along with the genetic expression matrix, were statistically analyzed using R version 4.2.2 and several R packages, such as tidyverse, DESeq2, ggplot2 and survminer. An unpaired *t* test was used to determine the significance of differences between two groups; one-way ANOVA was used to compare differences between three or more groups. Kaplan-Meier (K-M) curves were generated *via* the log-rank test to assess the significance of the difference in prognosis between the high *FABP4* expression group and the low *FABP4* expression group. Univariate and multifactorial analyses of OS were conducted with data from the TCGA to identify prognostic factors for COAD. The *P* value of the Pearson correlation analysis was corrected by the Bonferroni correction. For the immune infiltration analysis, *P* values are marked with asterisks. The notations used were "NS" for not statistically significant, $^{a}P < 0.05$, $^{b}P < 0.01$, and $^{c}P < 0.001$. A *P* value of less than 0.05 (with a 95%CI level) was considered to indicate statistical significance.

RESULTS

Diagnostic value of FABP4 expression in COAD

Compared with tissues in the normal control group, the tumor tissues in the experimental group presented significantly lower expression of the *FABP4* mRNA ($P < 0.001$; Figure 1A). A receiver operating characteristic curve was generated to validate its reliability as a valuable tool for distinguishing COAD. The area under the curve was calculated to be 92.52% (95%CI: 90.13%-94.91%), indicating that *FABP4* may serve as a highly effective tool to distinguish COAD (Figure 1B). Moreover, our immunohistochemical results revealed lower staining intensities in COAD tumor tissues than in adjacent noncancerous colon tissues, indicating lower protein expression in COAD (Figure 1C). Immunohistochemical scores are shown in Supplementary Table 1.

We assessed associations between *FABP4* expression and various clinical factors, including age, sex, tumor stage, T stage, N stage, and metastasis. The results are summarized in Supplementary Table 2. We observed a significant increase in *FABP4* expression in patients with an advanced tumor stage, advanced T classification, and advanced N classification.

Moreover, we conducted a subgroup analysis according to the tumor stage, T stage N stage, and metastasis. Interestingly, despite the low expression of *FABP4* in COAD tumors, its expression gradually increased with increasing tumor stage. A comparative analysis of samples from different groups in TCGA database revealed that *FABP4* was highly

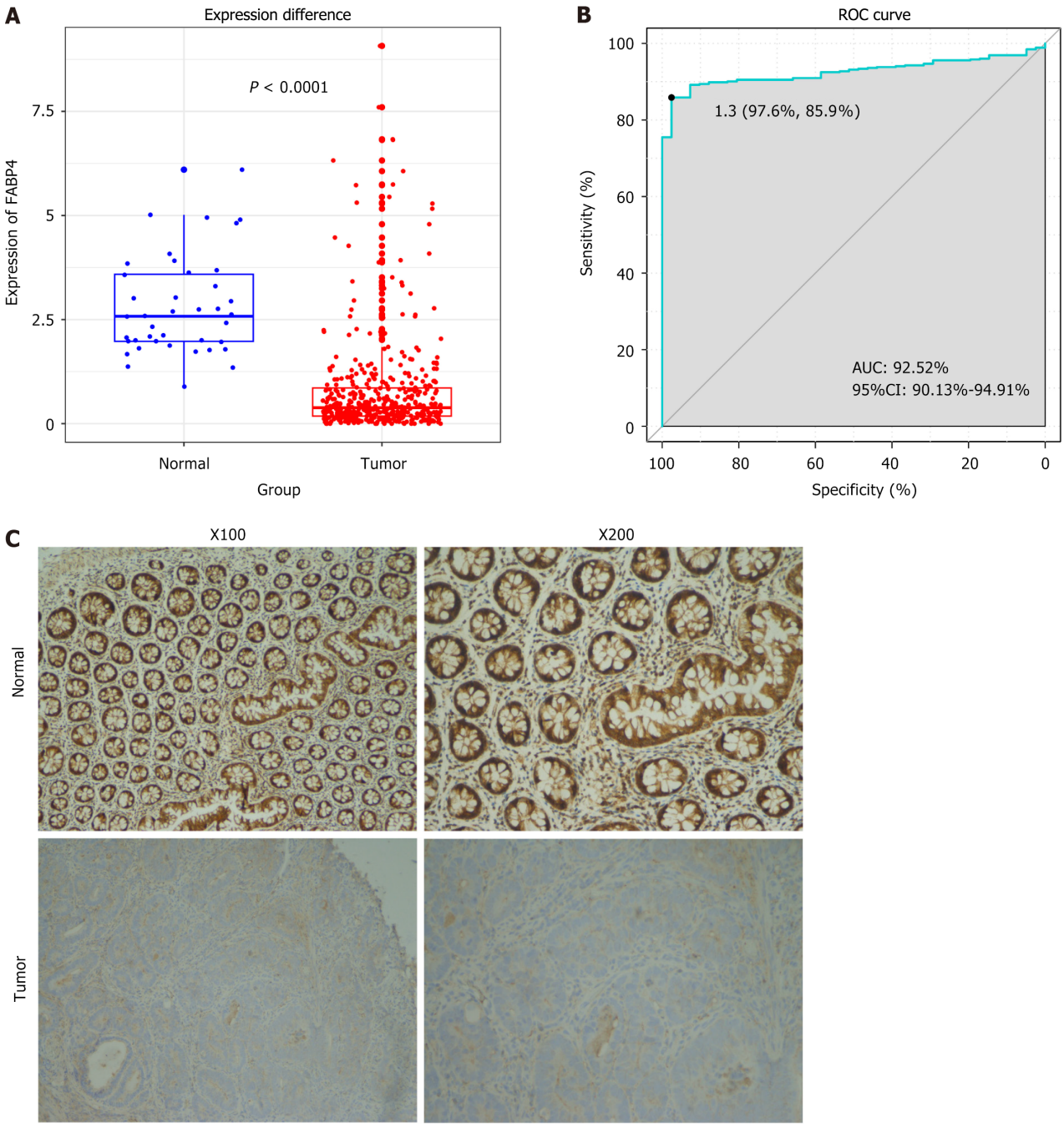


Figure 1 Diagnostic value of fatty acid-binding protein 4 expression in colon adenocarcinoma. A: Comparison of fatty acid-binding protein 4 (*FABP4*) mRNA expression levels in colon adenocarcinoma (COAD) tissues and normal tissues; B: Receiver operating characteristic curve for the diagnostic efficacy of *FABP4*; C: The FABP4 protein levels in COAD tissues and adjacent noncancerous colon tissues were determined *via* immunohistochemical staining at magnifications of × 100 and × 200. COAD: Colon adenocarcinoma; ROC: Receiver operating characteristic; AUC: Area under the curve.

enriched in high-grade tumor stages (Supplementary Figure 1A), T stages (Supplementary Figure 1B), and N stages (Supplementary Figure 1C). Additionally, *FABP4* was more highly expressed in metastatic COAD tumors. Although the trend in its expression was consistent across different stages, this difference was not statistically significant in TCGA dataset (Supplementary Figure 1D). These findings collectively suggest that *FABP4* enrichment in COAD tissues is associated with increased malignancy.

Prognostic analysis of FABP4 expression in COAD

Patients with varying levels of *FABP4* expression presented distinct clinical and pathological features. As *FABP4* expression increased, the tumor stage, T stage, and N stage exhibited nonuniform distributions. Additionally, the survival rate of patients exhibited a similar nonuniform distribution as the *FABP4* expression level increased (Figure 2A).

A K-M survival analysis was conducted using TCGA database to investigate the prognostic value of *FABP4* expression in COAD patients. The analysis revealed that the group with high *FABP4* expression (H-*FABP4*) experienced significantly shorter OS than did the group with low *FABP4* expression (L-*FABP4*) ($P = 0.009$; Figure 2B).

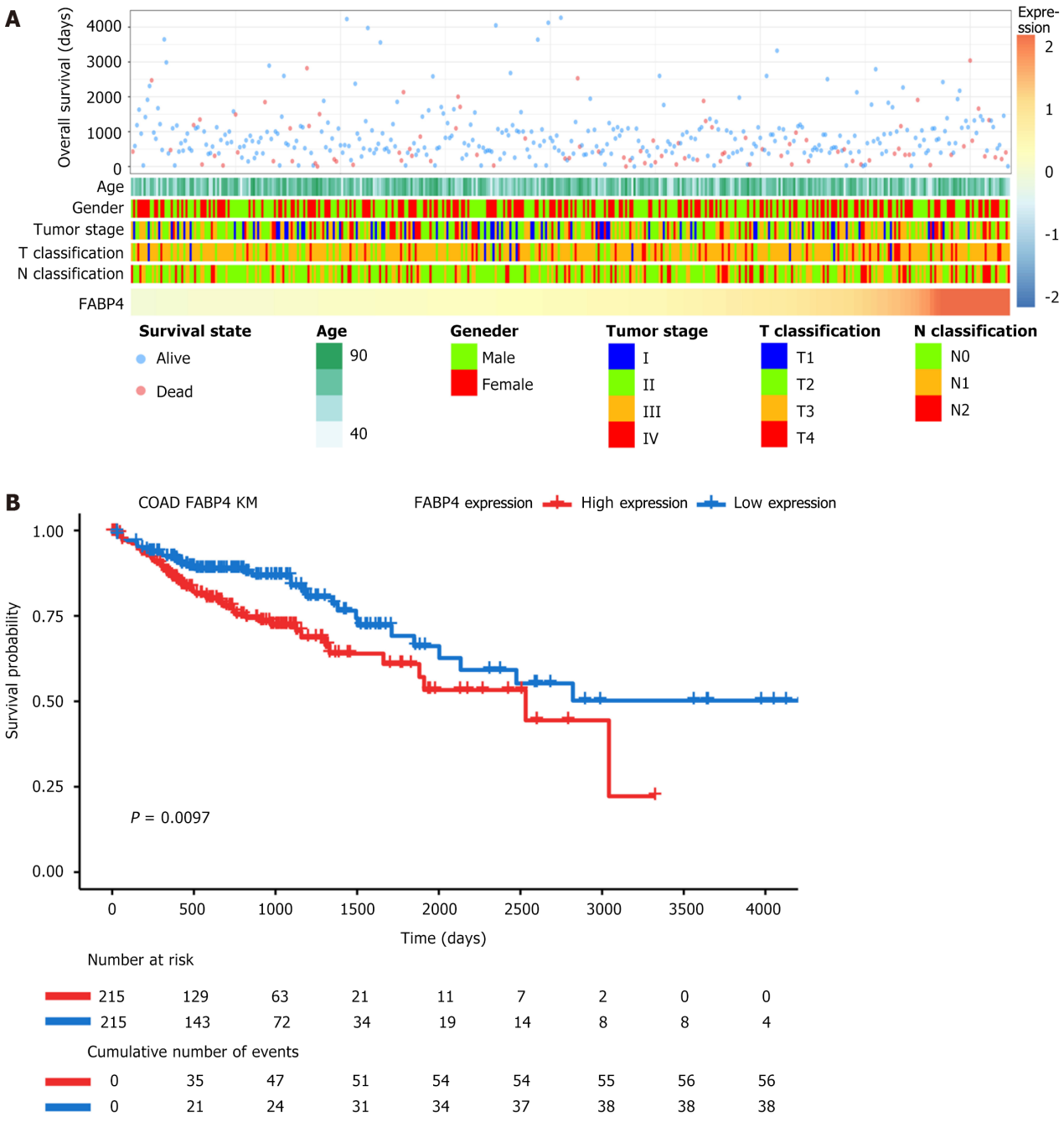


Figure 2 Relationships between fatty acid-binding protein 4 expression and clinical factors in patients with colon adenocarcinoma and Kaplan-Meier survival analysis of patients stratified according to fatty acid-binding protein 4 expression. A: The relationships between fatty acid-binding protein 4 (*FABP4*) expression and various clinical factors are ranked in ascending order of *FABP4* expression; B: Kaplan-Meier survival curves of the *FABP4* high-expression group and low-expression group. The cutoff for each group was the median expression of *FABP4*. COAD: Colon adenocarcinoma.

The univariate regression analysis and Cox regression analysis of TCGA data incorporating various established prognostic factors, such as the age at diagnosis, T stage, N stage, and disease type, showed that *FABP4* was an independent prognostic factor (Table 1), with OS as the primary endpoint. The multivariate analysis revealed that *FABP4* remained significant after adjusting for confounders. A hazard ratio (HR) of less than 1 was considered a good prognostic factor for COAD, whereas an HR greater than 1 was considered a poor prognostic factor for COAD.

Screening of FABP4-related genes and modules

A total of 3231 genes that were differentially expressed between COAD tissues and normal tissues were screened from TCGA to identify genes and modules associated with *FABP4*. A volcano plot and a heatmap (containing clustering relationships between genes) were generated to visually represent the DEGs (Figure 3A and B).

Subsequently, WGCNA was performed. The WGCNA parameters were adjusted, and the DEGs were organized into ten modules *via* the average linkage hierarchical clustering method (Figure 3C-E). Among these modules, the turquoise module comprised 1216 genes and presented the strongest correlation with *FABP4* expression (Pearson's correlation coefficient = 0.62, $P < 0.001$; Figure 3F).

Table 1 Univariate and multivariate analyses of prognostic factors for overall survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
FABP4 expression	1.175 (1.052-1.314)	0.004[a]	1.140 (1.015-1.280)	0.03[a]
Age	1.022 (1.004-1.040)	0.01[a]	1.028 (1.011-1.045)	0.001[a]
T classification	2.897 (1.934-4.339)	< 0.001[b]	2.224 (1.463-3.380)	< 0.001[b]
N classification	1.982 (1.572-2.499)	< 0.001[b]	1.862 (1.478-2.346)	< 0.001[b]
Disease type	1.149 (0.774-1.707)	0.04[a]	1.393 (0.938-2.068)	0.10

[a]$P < 0.05$.
[b]$P < 0.001$.
HR: Hazard ratio; *FABP4*: Fatty acid-binding protein 4.

A total of 146 genes were identified as hub genes in the turquoise module. These genes met the criteria of having an absolute module membership (MM) greater than 0.6 and an absolute gene significance (GS) greater than 0.5 (Figure 3G).

Functional enrichment analysis of FABP4

An analysis of the 146 hub genes in the blue module revealed that the cell adhesion pathway was the most prevalent. Specifically, the GO analysis of the BP, cellular component, and MF terms revealed "cell adhesion", "extracellular region", and "heparin binding", respectively, as the most significant terms (Figure 4A-C). Notably, "axon guidance" was identified as the most significant pathway in the KEGG analysis (Figure 4D).

Further investigation *via* GSEA was conducted to explore the mechanisms and functions of the 146 hub genes with the strongest correlation with *FABP4* expression. The analysis revealed enrichment in several entries, including "cell-cell adhesion *via* plasma membrane adhesion molecules" and "cell adhesion" (Figure 4E).

The impact of *FABP4* expression on BP terms and GSEA was evaluated in TCGA database to validate the results of the functional enrichment analyses. GSVA was utilized to determine functional enrichment scores based on their correlation with *FABP4* expression. The results confirmed a significant positive correlation between *FABP4* expression and cell adhesion (Figure 4F).

After the correlation coefficient was set, *FABP4* was significantly correlated with 15 CAMs, arranged in descending order of correlation coefficients in the correlation chord diagram (Supplementary Figure 2A). Among them, an analysis of the expression levels of the top five CAMs (*ITGA7*, *CDH19*, *CDH23*, *SELP*, and *PECAM1*, $P < 0.001$) with correlation coefficients revealed that their expression levels in tumors were significantly downregulated similar to those of *FABP4* (Supplementary Figure 2B-F).

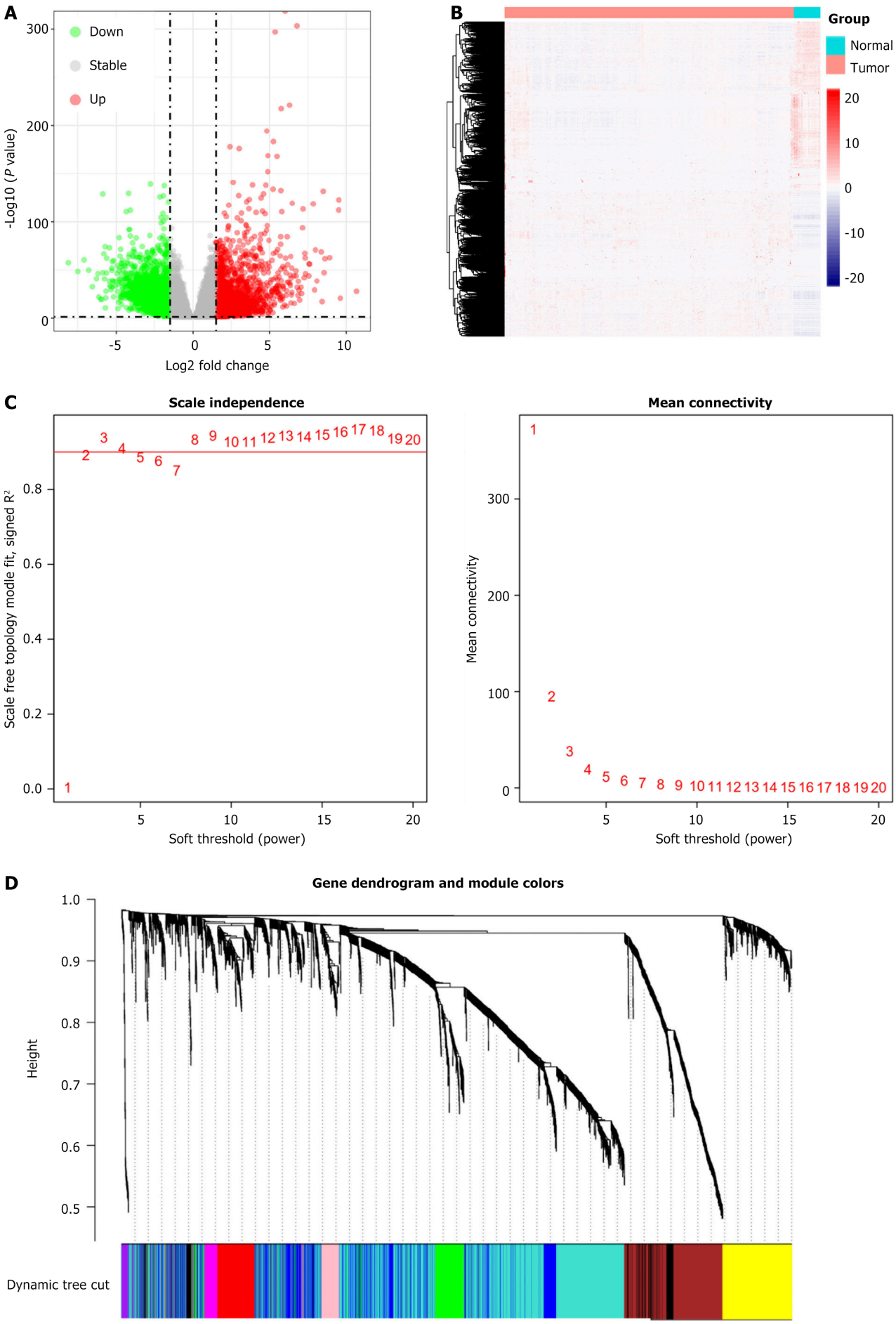
Immune infiltration analysis of FABP4

WGCNA revealed a potential correlation between *FABP4* expression and immune-related modules (Figure 3E), and an immune infiltration analysis of *FABP4* was conducted to explore this result further. According to the TIMER analysis, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and DCs were significantly positively correlated ($P < 0.001$) and tumor purity was significantly negatively correlated ($P < 0.001$) with *FABP4* expression (Figure 5A).

ESTIMATE, CIBERSORT, and ssGSEA were conducted to verify these findings in two groups stratified according to the expression level of *FABP4* in two groups: The high-expression group (H-*FABP4*) and the low-expression group (L-*FABP4*). The results of the ESTIMATE analysis revealed that the matrix score, immune score, and ESTIMATE score were higher in the H-*FABP4* group than in the L-*FABP4* group but that the tumor purity score was lower in the H-*FABP4* group (Figure 5B). Further analysis revealed that the H-*FABP4* group had greater proportions of macrophages and mast cells (Figure 5C). Moreover, ssGSEA revealed significant positive correlations between *FABP4* expression and 22 of the 28 TIL subtypes in COAD ($P < 0.05$; Figure 5D). According to the preliminary findings of the TIMER analysis, *FABP4* was associated with the immune cell infiltration in COAD. We further studied the relationship between *FABP4* and a variety of TILs to verify this finding, and the results further expanded the findings of the TIMER analysis.

A nomogram based on the prognostic value of FABP4

FABP4 and its coexpressed genes (correlation coefficient $|r| > 0.65$) were analyzed by Cox regression analysis. Fifteen genes that were significantly associated with OS were identified (*FABP4*, *PRG4*, *CYP11A1*, *CLDN11*, *PTH1R*, *PPP1R1A*, *TUSC5*, *ABCA9*, *PDE1B*, *CILP*, *CIDEA*, *GPX3*, *MRAP*, *TNNT3*, *PP1R1A*, and *PCOLCE2*). The risk score was calculated. When the survival analysis model was fitted with the risk score and clinicopathological factors from the TCGA, the risk score, T classification, age and tumor stage were used to construct a nomogram to predict the 1-year, 3-year, and 5-year survival of COAD patients (Figure 6A), with a C-index = 0.786. The nomogram and actual observations in the calibration curve showed satisfactory overlap in the TCGA training cohort (Figure 6B-D), indicating optimal predictive accuracy.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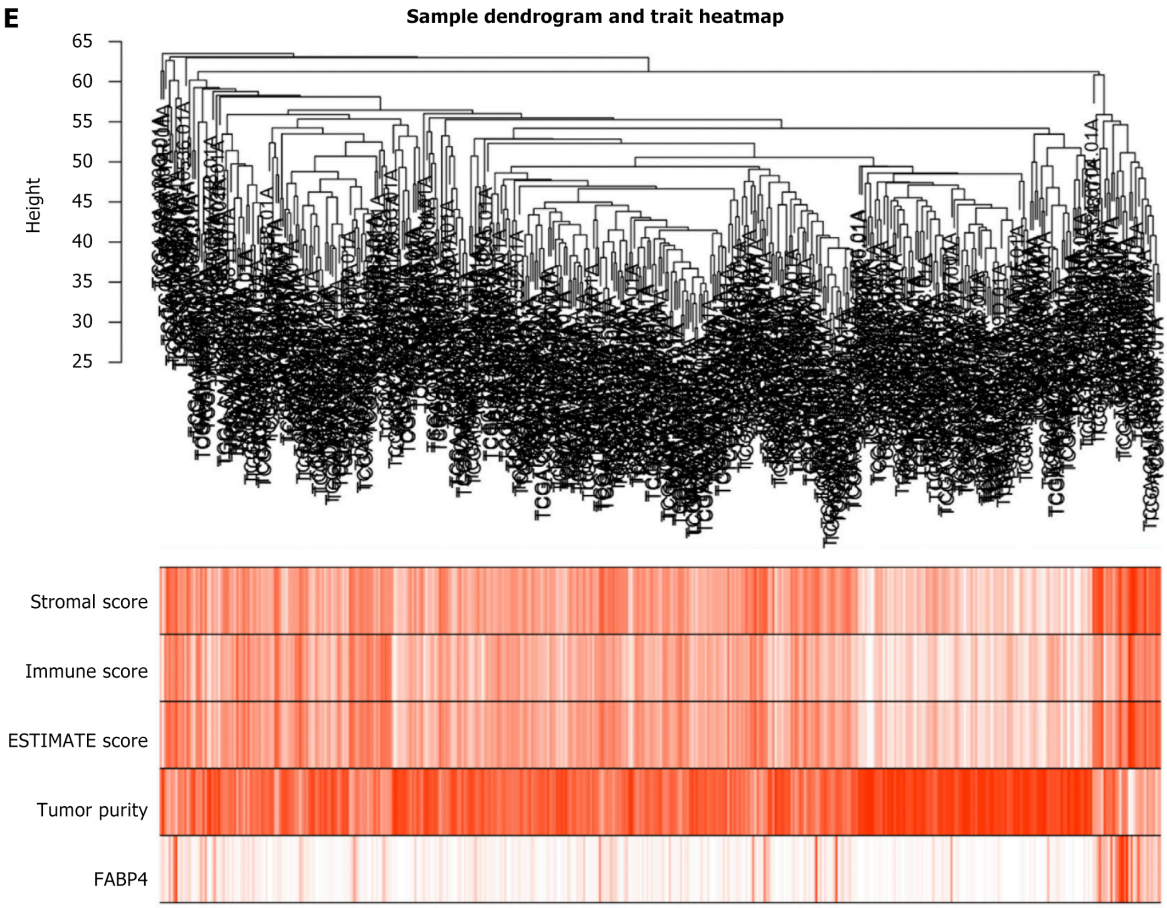
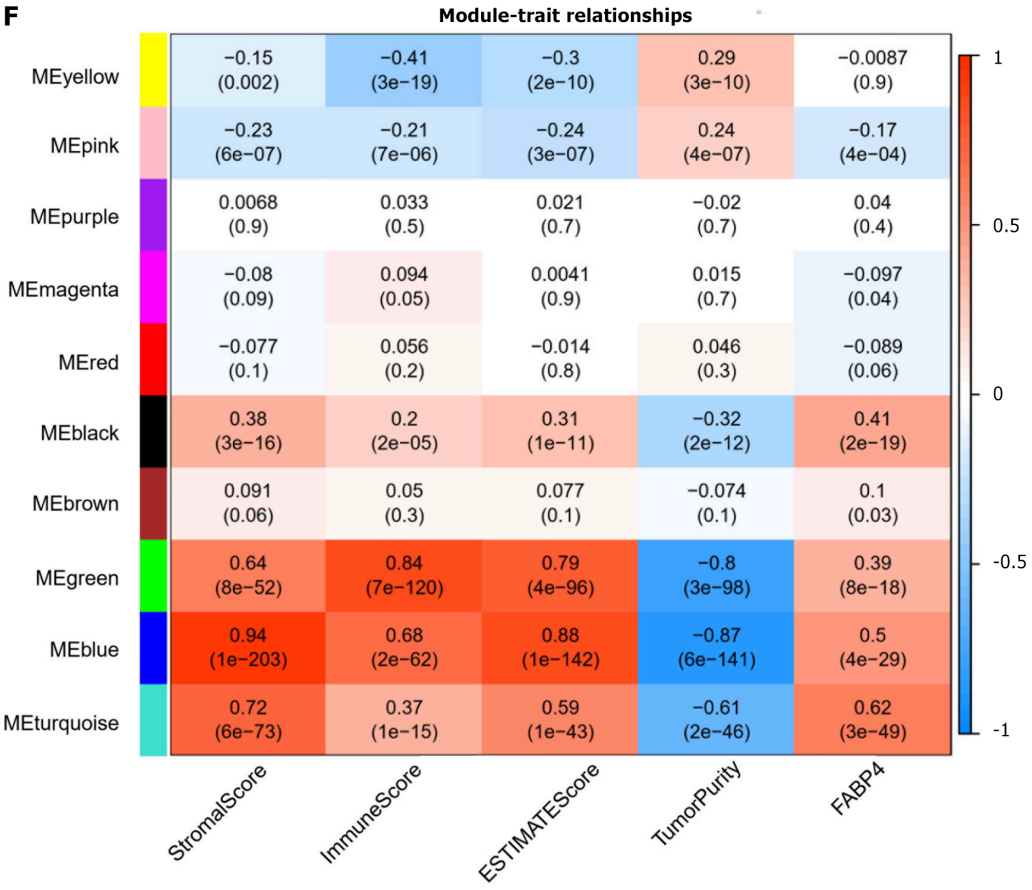
Gene dendrogram and module colors
Height
Dynamic tree cut


E
Sample dendrogram and trait heatmap
Height
65
60
55
50
45
40
35
30
25
Stromal score
Immune score
ESTIMATE score
Tumor purity
FABP4


F
Module-trait relationships
MEyellow
MEpink
MEpurple
MEmagenta
MEred
MEblack
MEbrown
MEgreen
MEblue
MEturquoise
−0.15 (0.002)
−0.41 (3e−19)
−0.3 (2e−10)
0.29 (3e−10)
−0.0087 (0.9)
−0.23 (6e−07)
−0.21 (7e−06)
−0.24 (3e−07)
0.24 (4e−07)
−0.17 (4e−04)
0.0068 (0.9)
0.033 (0.5)
0.021 (0.7)
−0.02 (0.7)
0.04 (0.4)
−0.08 (0.09)
0.094 (0.05)
0.0041 (0.9)
0.015 (0.7)
−0.097 (0.04)
−0.077 (0.1)
0.056 (0.2)
−0.014 (0.8)
0.046 (0.3)
−0.089 (0.06)
0.38 (3e−16)
0.2 (2e−05)
0.31 (1e−11)
−0.32 (2e−12)
0.41 (2e−19)
0.091 (0.06)
0.05 (0.3)
0.077 (0.1)
−0.074 (0.1)
0.1 (0.03)
0.64 (8e−52)
0.84 (7e−120)
0.79 (4e−96)
−0.8 (3e−98)
0.39 (8e−18)
0.94 (1e−203)
0.68 (2e−62)
0.88 (1e−142)
−0.87 (6e−141)
0.5 (4e−29)
0.72 (6e−73)
0.37 (1e−15)
0.59 (1e−43)
−0.61 (2e−46)
0.62 (3e−49)
StromalScore
ImmuneScore
ESTIMATEScore
TumorPurity
FABP4
1
0.5
0
-0.5
-1

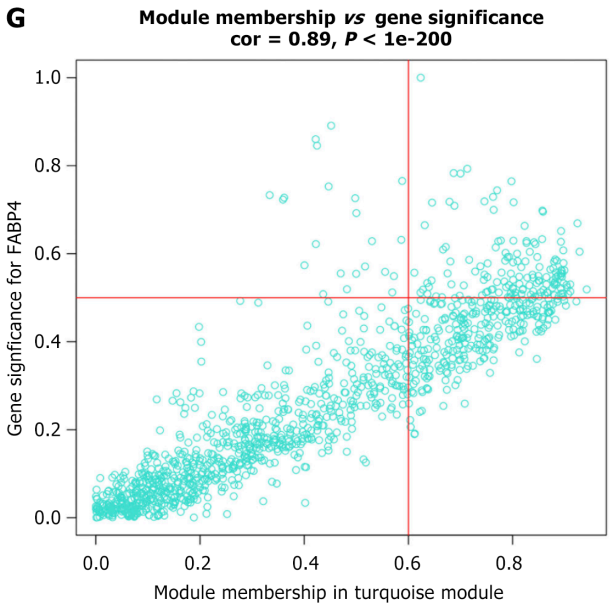


Figure 3 Screen for immune modules and genes related to fatty acid-binding protein 4 in colon adenocarcinoma tissues. A: Volcano plot of differentially expressed genes (DEGs) between colon adenocarcinoma (COAD) tissues and normal tissues in The Cancer Genome Atlas (TCGA) database; B: Heatmap of DEGs between COAD tissues and normal tissues in TCGA database; C: Calculation of the scale-free fit indices of various soft-thresholding powers (β) and analysis of the mean connectivity of various soft-thresholding powers (β); D: DEGs were clustered based on the dissimilarity measure (1-TOM) and divided into 10 modules; E: Clustering dendrogram of COAD patients; F: A correlation heatmap between module eigengenes and immune parameters (fatty acid-binding protein 4 was used as the main research object) in patients with COAD; G: Scatter plot of the turquoise module eigengenes. COAD: Colon adenocarcinoma; DEGs: Differentially expressed genes; TCGA: The Cancer Genome Atlas.

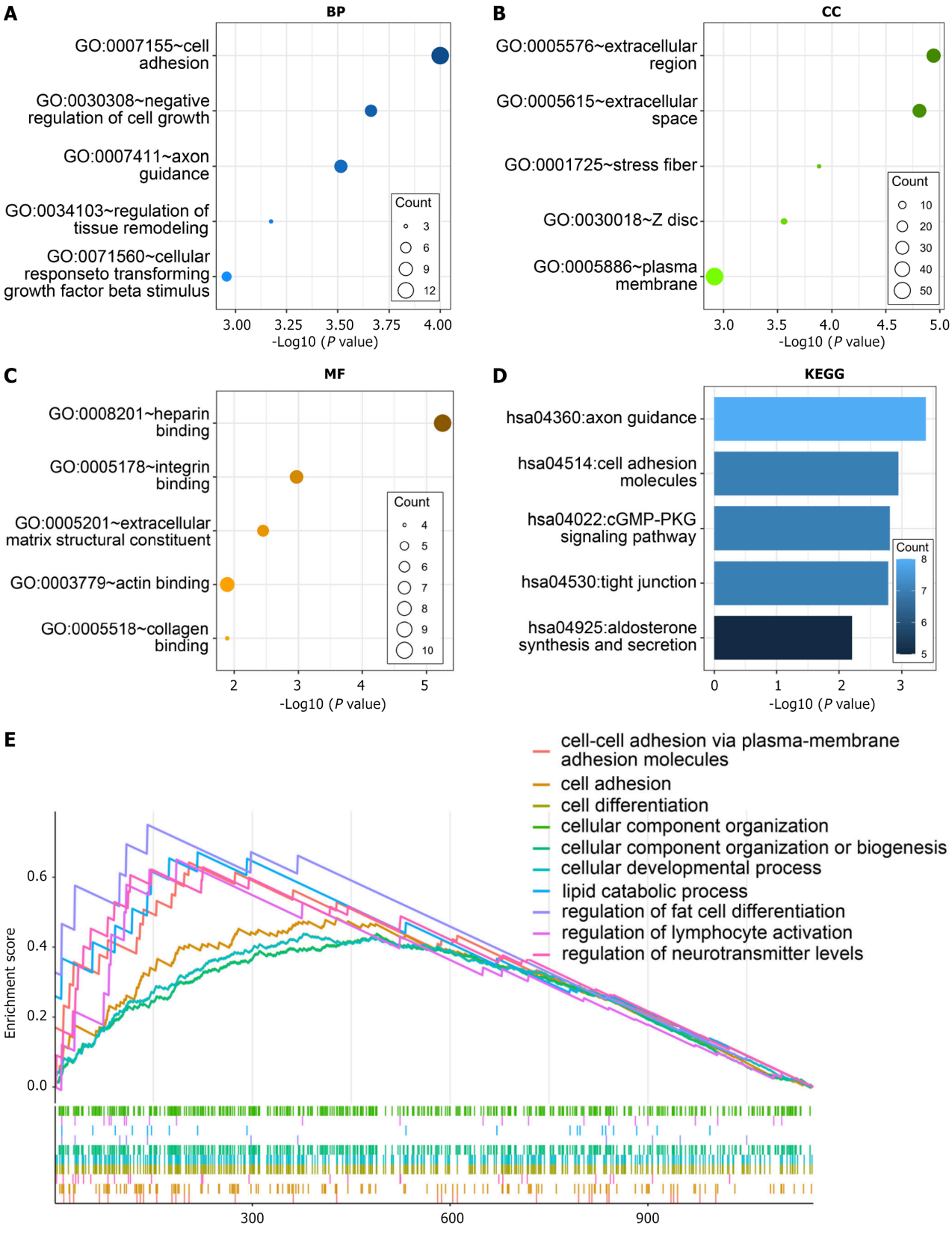
Validation based on the GEO database

Through our analysis of the GEO database, we determined that the expression level of *FABP4* can be used to effectively distinguish between tumor tissues and normal tissues (Supplementary Figure 3A and B). The K-M survival analysis revealed a significantly shorter survival time for patients in the H-*FABP4* group than for patients in the L-*FABP4* group (Supplementary Figure 3C). Moreover, the enrichment analysis revealed that *FABP4* is associated primarily with cell adhesion (Supplementary Figure 3D-G). The immune infiltration analysis revealed higher matrix, immune, and ESTIMATE scores for the H-*FABP4* group than for the L-*FABP4* group, although the tumor purity score was lower for the H-*FABP4* group (Supplementary Figure 4A). Additionally, the H-*FABP4* group presented greater proportions of macrophages and mast cells (Supplementary Figure 4B). *FABP4* expression was significantly positively correlated with 24 of the 28 TIL subtypes in COAD ($P < 0.05$; Supplementary Figure 4C). Moreover, the nomogram calibration curve also showed good agreement between the predicted value and the actual value (Figure 6E-G), with a C-index = 0.73. These findings are consistent with our results based on TCGA dataset.

DISCUSSION

The incidence and mortality rates of CRC, particularly metastatic CRC, remain high, with an overall five-year survival rate of less than 20%. In recent years, the discovery of specific biomarkers and combinations has improved the accuracy of CRC screening and facilitated the development of targeted drugs. Moreover, many studies of TCGA-based biomarkers, such as single genes for a single cancer[30], gene sets for a single cancer[31], single genes for multiple cancers[32], and gene sets for multiple cancers[33], have been conducted. However, relatively few studies have investigated COAD biomarkers and their associated functions. Our study revealed that *FABP4* affects the occurrence and development of COAD through cell adhesion and immune cell infiltration pathways, and is a potential biomarker for COAD. We found that *FABP4* can assist in the diagnosis of COAD, as it is expressed at significantly lower levels in COAD tissues than in normal tissues. We further confirmed the diagnostic efficacy of *FABP4 via* our own immunohistochemical staining and GEO validation data. Additionally, we found that high expression of *FABP4* is associated with an advanced tumor stage, T classification, and lymph node metastasis, suggesting that *FABP4* promotes metastasis and acts as an adverse prognostic factor. Regression and survival analyses confirmed a significant negative correlation between *FABP4* expression and the OS of COAD patients. Mouse experiments also support the hypothesis that inhibiting *FABP4* can hinder the interaction between tumor cells and adipose tissue, leading to decreased tumor cell proliferation and metastasis and blood vessel growth in tumors[34,35]. These findings indicate the protumor role of *FABP4* in COAD, and *FABP4* was shown to be a potential biomarker for COAD.

Previous studies have shown that COAD and CAMs are closely related[36]. Our systematic study of the role of *FABP4* in COAD revealed that *FABP4* is involved in cell adhesion and immune cell infiltration. Altered cell adhesion often


A
BP
GO:0007155~cell adhesion
GO:0030308~negative regulation of cell growth
GO:0007411~axon guidance
GO:0034103~regulation of tissue remodeling
GO:0071560~cellular responseto transforming growth factor beta stimulus
Count
3
6
9
12
3.00
3.25
3.50
3.75
4.00
-Log10 (P value)
B
CC
GO:0005576~extracellular region
GO:0005615~extracellular space
GO:0001725~stress fiber
GO:0030018~Z disc
GO:0005886~plasma membrane
Count
10
20
30
40
50
3.0
3.5
4.0
4.5
5.0
-Log10 (P value)
C
MF
GO:0008201~heparin binding
GO:0005178~integrin binding
GO:0005201~extracellular matrix structural constituent
GO:0003779~actin binding
GO:0005518~collagen binding
Count
4
5
6
7
8
9
10
2
3
4
5
-Log10 (P value)
D
KEGG
hsa04360:axon guidance
hsa04514:cell adhesion molecules
hsa04022:cGMP-PKG signaling pathway
hsa04530:tight junction
hsa04925:aldosterone synthesis and secretion
Count
8
7
6
5
0
1
2
3
-Log10 (P value)
E
cell-cell adhesion via plasma-membrane adhesion molecules
cell adhesion
cell differentiation
cellular component organization
cellular component organization or biogenesis
cellular developmental process
lipid catabolic process
regulation of fat cell differentiation
regulation of lymphocyte activation
regulation of neurotransmitter levels
Enrichment score
0.0
0.2
0.4
0.6
300
600
900

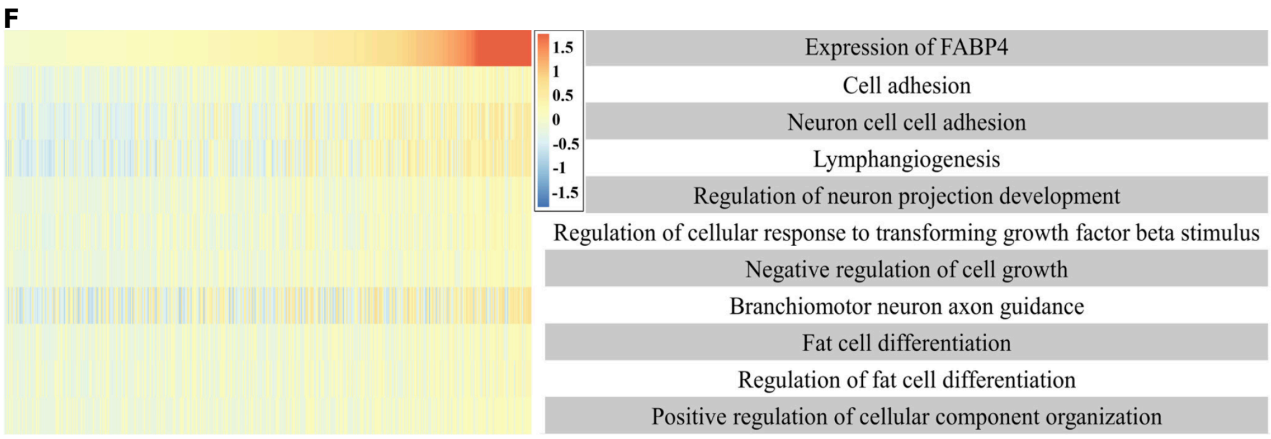


Figure 4 Results of the Gene Ontology and Kyoto Encyclopedia of Genes and Genomes functional enrichment analyses, gene set enrichment analysis and gene set variation analysis. A-C: Analysis of the biological process, cellular component and molecular function terms of genes strongly associated with fatty acid-binding protein 4 (*FABP4*); D: Kyoto Encyclopedia of Genes and Genomes analysis of genes strongly associated with *FABP4*; E: GSEA of genes highly correlated with *FABP4*; F: Correlation analysis between *FABP4* expression and functional enrichment scores. The heatmap shows the expression of *FABP4* and the enrichment scores of the functions of the genes in each patient in The Cancer Genome Atlas database. The samples were arranged in ascending order of *FABP4* expression. TCGA: The Cancer Genome Atlas; KEGG: Kyoto Encyclopedia of Genes and Genomes; *FABP4*: Fatty acid-binding protein 4; CC: Cellular component; BP: Biological process; MF: Molecular function.

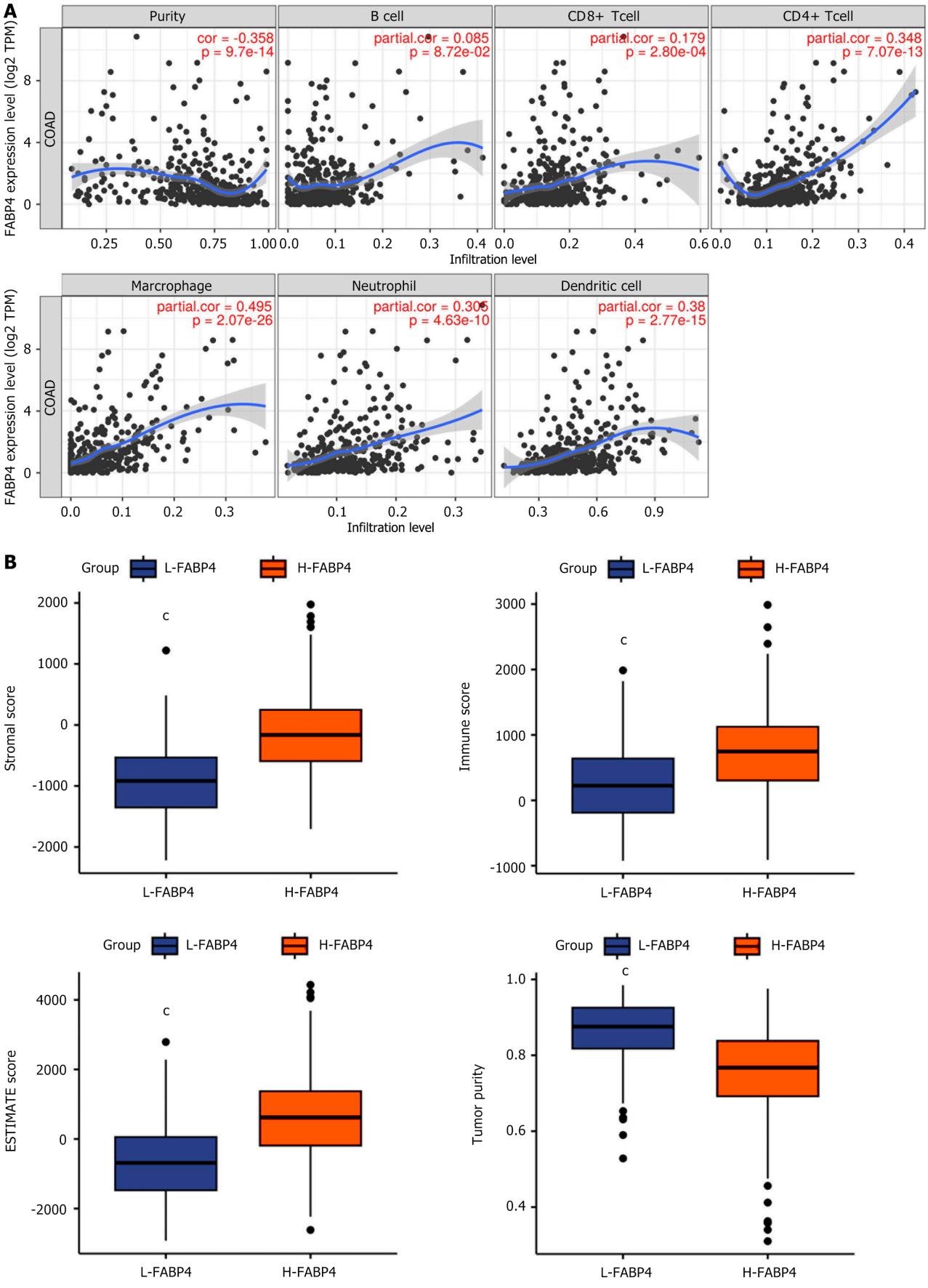
results in aggressive and migratory phenotypes in tumor cells[37], and *FABP4* may impact the prognosis and survival of COAD patient through its influence on cell adhesion[37]. Studies indicate that *FABP4* may produce energy through fatty acid oxidation in COAD, activating tumor cell metabolism and signaling pathways, which in turn enhance cell adhesion, migration, and invasion[35]. These results support our conclusion that *FABP4* is significantly correlated with cell adhesion, indicating its potential role in promoting COAD invasion and spread *via* cell adhesion. Moreover, in recent decades, advancements in genomic research and the development of precision-targeted therapies have significantly improved the prognosis of patients with advanced CRC, including those with COAD[38]. CRC drugs targeting *VEGF*, *EGFR*, *BRAFV600E*, *PDL1*, and others are currently being used in first-line treatment or are included in clinical studies for CRC. Pan *et al*[39] found through immunohistochemistry that patients with COAD and elevated *FABP4* expression had increased CD8 infiltration, suggesting that *FABP4* is closely related to immune response and metastasis, and may be a potential therapeutic target for COAD. Our results revealed a significantly elevated ratio of macrophages to mast cells in the H-*FABP4* group. *FABP4* is expressed mainly in adipocytes, macrophages and endothelial cells[40-42], and *FABP4* expression in macrophages can mediate the inflammatory response and cholesterol accumulation, which helps to provide a more favorable microenvironment for tumor growth. Cancer cells disrupt the integrity of the intestinal barrier by interacting with immune cells, stromal cells, and the extracellular matrix, which together form the TME[9]. The TME affects tumor progression, immunotherapy resistance, immune escape, and tumor invasion. High levels of M2 macrophage infiltration are associated with a poor prognosis, and mast cells are also involved in immune evasion in cancer[43,44]. These results suggest that *FABP4* may promote the occurrence and development of COAD by suppressing immune function.

The predictive accuracy of the nomogram constructed in our research was a C-index of 0.786 in TCGA database and 0.73 in the verification analysis using the GEO database. These findings indicate that it can predict the 1-year, 3-year, and 5-year survival of COAD patients well. The relevant literature has confirmed that *FABP4* plays an important role in the prognostic assessment and survival prediction of COAD patients. Among them, based on *FABP4*-associated immunomodulators, the Chongqing Medical University team constructed a 2-immunomodulator signature to predict the prognosis of patients with COAD. The C-index of the nomogram they constructed in TCGA training set was 0.584, with no verification set[15]. The Miao *et al*[45] screened 12 immune genes, including *FABP4*, and constructed a nomogram to predict the survival of patients with COAD. The C-index of the nomogram was 0.77 in TCGA training set and 0.72 in the GEO verification set[45]. These findings further support the feasibility and value of *FABP4* as a biomarker for COAD and indicate that the prediction model we constructed has better predictive accuracy.

However, our study has several limitations. First, this study lacked prospective clinical validation. The conclusions of the enrichment analysis and immune infiltration analysis should be verified in clinical trials. Previous studies used xenograft models of cancer. Our future studies that could validate these findings in patient-derived xenograft models or larger cohorts. Second, this study relied too heavily on retrospective datasets. Some clinicopathological factors in TCGA and GEO databases are incomplete, and thus the validation and application of the constructed nomogram for the prognostic value of *FABP4* need to be further explored.

CONCLUSION

This study revealed that elevated *FABP4* expression is strongly associated with COAD progression and a shortened


A
Purity
B cell
CD8+ Tcell
CD4+ Tcell
cor = -0.358
p = 9.7e-14
partial.cor = 0.085
p = 8.72e-02
partial.cor = 0.179
p = 2.80e-04
partial.cor = 0.348
p = 7.07e-13
FABP4 expression level (log2 TPM)
COAD
Infiltration level
Marcrophage
Neutrophil
Dendritic cell
partial.cor = 0.495
p = 2.07e-26
partial.cor = 0.305
p = 4.63e-10
partial.cor = 0.38
p = 2.77e-15
B
Group
L-FABP4
H-FABP4
Stromal score
Immune score
ESTIMATE score
Tumor purity
c

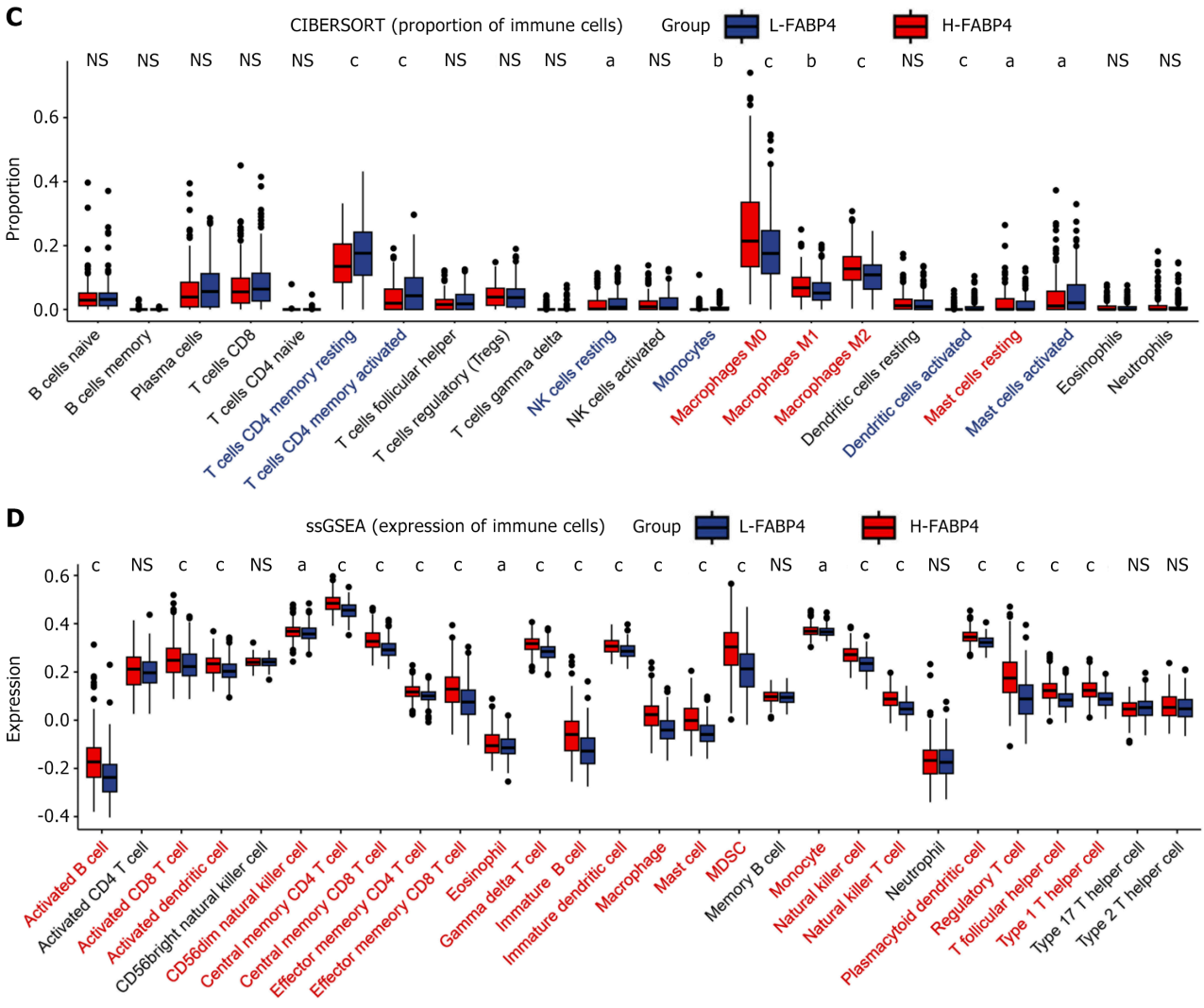
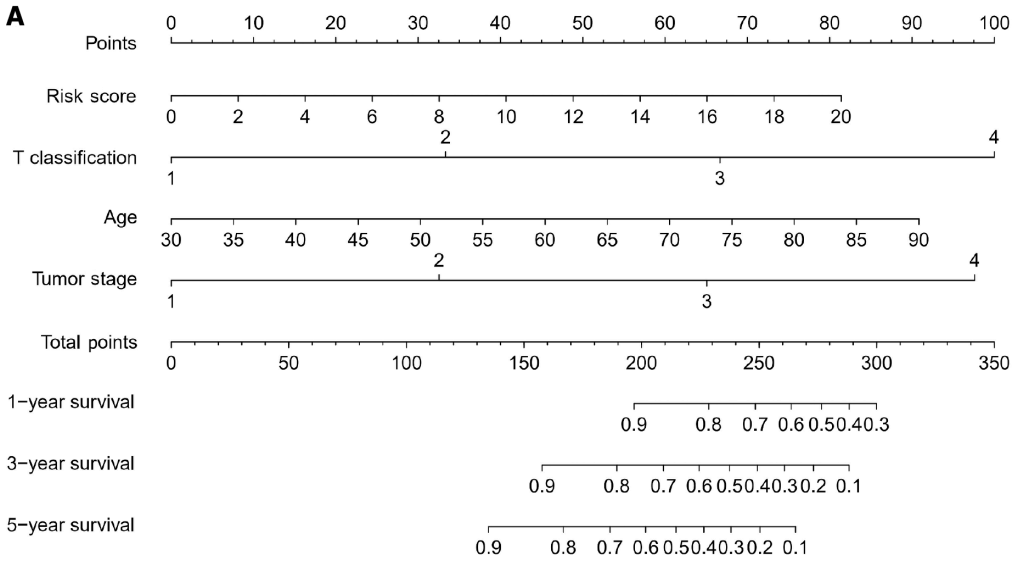


Figure 5 Comparison of immune characteristics associated with fatty acid-binding protein 4 expression. A: The expression level of fatty acid-binding protein 4 (*FABP4*) was significantly positively correlated with the infiltration level of immune cells in colon adenocarcinoma; B: Comparisons of the stromal score, immune score, ESTIMATE score, and tumor purity between the high *FABP4* expression group and the low *FABP4* expression group; C: Proportion of immune cells in the high *FABP4* expression group and low *FABP4* expression group; D: Comparison of immune cell infiltration between the high *FABP4* expression group and the low *FABP4* expression group. *P* values are labeled with asterisks. NS: Not significant; [a]*P* < 0.05; [b]*P* < 0.01; and [c]*P* < 0.001; COAD: Colon adenocarcinoma; ESTIMATE: Estimation of STromal and Immune cells in MAlignant Tumor tissues using Expression data; ssGSEA: Single-sample gene set enrichment analysis.



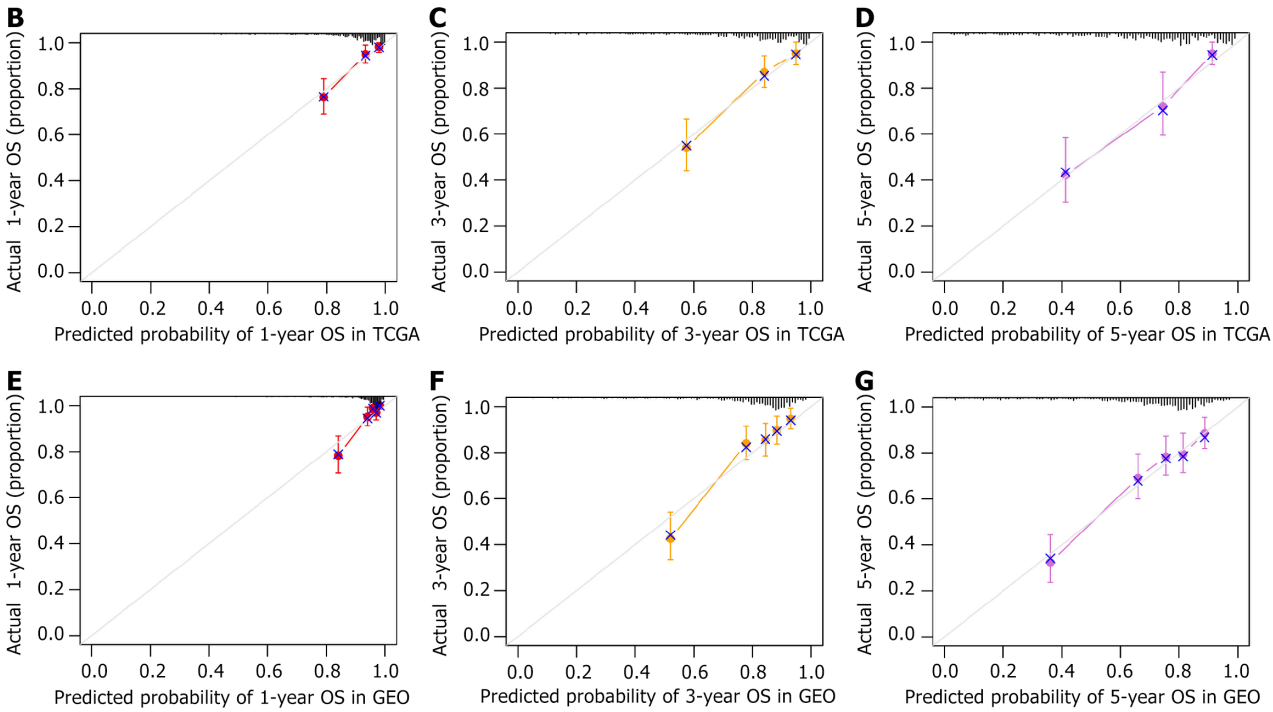


Figure 6 Prognostic value of the nomogram based on the fatty acid-binding protein 4 risk score in colon adenocarcinoma patients. A: A nomogram was constructed to predict the 1-year, 3-year, and 5-year overall survival (OS) rates by combining the risk score, T classification, age, and tumor stage; B-D: Calibration curves of the nomogram for predicting and observing 1-year, 3-year, and 5-year OS in The Cancer Genome Atlas training cohort. The dashed line at 45° indicates a perfect prediction; E-G: Calibration curves of the nomogram for predicting and observing 1-year, 3-year, and 5-year OS in the Gene Expression Omnibus validation cohort. COAD: Colon adenocarcinoma; TCGA: The Cancer Genome Atlas; OS: Overall survival; GEO: Gene Expression Omnibus.

survival time, indicating its potential as a biomarker for COAD. *FABP4* promotes the invasion and metastasis of COAD cells by altering their adhesion characteristics and ultimately affects the prognosis and survival of COAD patients. A nomogram was constructed using the calculated risk scores of *FABP4* and its coexpressed genes combined with clinicopathological factors to predict the survival of COAD patients. This study establishes the potential of *FABP4* as a biomarker for COAD, provides a basis for further studies of *FABP4*, and provides new insights into cancer mechanisms.

FOOTNOTES

Author contributions: Xu ZY and Hu HX designed the research study; Zhang Y and Zhu WL collected the data; Zhang Y and Zhu WL wrote the paper; Wu M and Gao TY performed the statistical analyses; Wu M and Gao TY revised the manuscript; and all the authors checked and approved the final manuscript. Zhang Y and Zhu WL contributed equally to this work as co-first authors. Xu ZY and Hu HX were appointed as corresponding authors for this paper. First, the two associate professors participated in the design of the research study, provided research ideas, made important revisions to the paper during the writing process, and ultimately finalized the manuscript. Second, these two associate professors played a significant role in project management and team collaboration. Finally, Associate Professor Xu ZY also obtained funding, and Associate Professor Hu HX participated in the submission and communicated with the journal. Therefore, both corresponding authors have made important contributions to the article, and these contributions are equal. For this reason, the article designates these two authors as co-corresponding authors.

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Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Data will be made available on reasonable request at xuzy@wnmc.edu.cn.

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