Original Article

Construction and validation of prognostic model for colorectal mucinous adenocarcinoma patients and identification of a new prognosis related gene *FAM174B*

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Background: Mucinous adenocarcinoma (MAC) is a peculiar histological subtype of colorectal cancer (CRC) with distinct medical, disease-related, and genetic characteristics. The prognosis of MAC is generally poorer less favorable compared to non-specific adenocarcinoma (AC), but the prognostic indicator of MAC is rare. Therefore, this study aims to identify potential biomarkers and construct a prognostic model to better predict patient outcomes in MAC.

Methods: We conducted differential genes expression investigation, weighted gene co-expression network analysis (WGCNA), and least absolute shrinkage and selection operator (LASSO)-Cox regression model using RNA sequencing (RNA-seq) data from The Cancer Genome Atlas (TCGA) to pinpoint hub genes. Then, the hub genes were used to construct a prognostic model for MAC. Kaplan-Meier survival, receiver operating characteristic (ROC), and Cox regression analysis were used to assess the prognostic utility of the model. The potential biological function of the hub gene was examined using gene set enrichment analysis (GSEA).

Results: Four hub genes, *FAM174B*, *CREB3L1*, *SPDEF*, and *RAP1GAP*, were identified between MAC and AC by differential genes expression analysis, WGCNA, and LASSO regression analysis. The prognostic signature model was constructed based on these four hub genes, which could divide MAC into low- and high-risk groups. The overall survival (OS) was notably lower in the high-risk group compared to the low-risk group (P=0.007). The area under the curves (AUCs) for 1-, 3-, and 5-year OS were 0.61 [95% confidence interval (CI): 0.73–0.49], 0.69 (95% CI: 0.76–0.63), and 0.77 (95% CI: 0.83–0.71), respectively. We also found that *FAM174B* expression was closely related to the OS of MAC (P=0.02). Further, the expression of *FAM174B* was positively correlated with MAC's Mucin type O-glycan biosynthesis. Finally, it was indicated that *FAM174B* was positively correlated with the critical molecules of mucus formation, *MUC5AC* (P=0.004, r=0.33), *MUC5B* (P<0.001, r=0.43), and *MUC2* (P<0.001, r=0.39).

Conclusions: We have developed and validated a four-gene prognostic model to predict the survival of MAC. Additionally, we found that *FAM174B* might correlate with mucin production in MAC.

Keywords: Mucinous adenocarcinoma (MAC); colorectal cancer (CRC); *FAM174B*; biomarker; prognosis

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Introduction

Colorectal cancer (CRC) ranks among the most prevalent malignancies and stands as the foremost cause of cancer-related mortality worldwide (1,2). CRC comprises several pathological subtypes, of which the most common is non-specific adenocarcinoma (AC). Mucinous adenocarcinoma (MAC) is a unique and rare histology subtype of CRC, accounting for 10–15% of all CRCs (3-5). The pathologic diagnostic criterion of MAC is that the extracellular mucus components account for at least 50% of the tumor volume (6,7). Numerous studies have demonstrated that the clinical characteristics, molecular characteristics, chemotherapy/radiotherapy response, and prognosis of MAC are distinct from those of AC. Compared with AC, MAC is more common in the proximal colon, has a higher tumor stage, poorer tumor differentiation, and is more likely to have lymph node metastasis (8-12). Regarding molecular characteristics, MAC exhibits higher *BRAF* mutation, microsatellite instability, and CpG island methylation phenotypes, but only a few molecules can be used for MAC identification (13,14).

Most studies have found that MAC is associated with poor prognosis (15-17); however, the prognostic indicator of MAC in CRC remains rare (16,18,19). Accurately predicting the prognosis of MAC patients can help clinicians provide more effective treatment strategies and follow-up management, potentially improving patients' prognoses. Abnormal expression of mucin-related molecules such as *MUC2*, *MUC5B*, and *MUC5AC* is a distinctive feature and key biomarker of MAC, but they have limited prognostic value in MAC patients (20,21). Thus, finding new biomarkers or models that can distinguish MAC and AC and predict prognosis has excellent clinical value in stratifying CRC patients and providing personalized treatment for MAC.

Therefore, in this study, we analyzed and screened out the differential genes related to the prognosis of CRC between MAC and AC, intended to explore potential prognostic indicators of MAC, as well as the biological functions of this critical biomarker. By doing so, we have constructed and validated a four-gene prognostic model to predict the survival of MAC and tentatively found that *FAM174B* might correlate with mucin production in MAC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-347/rc).

Highlight box

Key findings

- A four-gene prognostic model was constructed and validated to predict the survival of patients with mucinous adenocarcinoma (MAC).
- *FAM174B* was identified as potentially correlating with mucin production in MAC.

What is known and what is new?

- MAC is a subtype of colorectal cancer (CRC) characterized by high mucin production and generally poorer prognosis compared to non-specific adenocarcinoma (AC).
- This study identified *FAM174B*, along with *CREB3L1*, *SPDEF*, and *RAP1GAP*, as key genes in a prognostic model that can predict the survival of MAC patients. *FAM174B*'s correlation with mucin production was highlighted, suggesting its role in MAC pathology.

What is the implication, and what should change now?

- The prognostic model and the identification of *FAM174B* provide valuable tools for better predicting patient outcomes and understanding MAC pathology.
- Clinicians should consider incorporating this four-gene model into practice to improve prognosis accuracy and tailor treatment strategies for MAC patients. Further research should explore the biological functions of these genes, particularly *FAM174B*, in MAC.

Methods

Data collection

We retrieved RNA sequencing data from The Cancer

Table 1 Clinical characteristics of patients with colorectal adenocarcinoma in The Cancer Genome Atlas

Characteristics	Adenocarcinoma (N=543)	Mucinous adenocarcinoma (N=75)
Gender, n (%)		
Male	292 (47.2)	37 (6.0)
Female	251 (40.6)	38 (6.1)
Age (years), n (%)		
≥65	324 (52.4)	43 (7.0)
<65	219 (35.4)	32 (5.2)
Pathological stage, n (%)		
Stage I	95 (15.9)	10 (1.6)
Stage II	196 (32.7)	30 (4.9)
Stage III	152 (24.6)	26 (4.2)
Stage IV	81 (13.1)	8 (1.3)
Vital status, n (%)		
Alive	489 (79.1)	66 (10.7)
Dead	54 (8.7)	9 (1.5)

Genome Atlas (TCGA) database (which was downloaded on 25 December 2023, https://portal.gdc.cancer.gov/), encompassing 86 tissues of colorectal MAC and 612 tissues of non-specific AC, along with corresponding clinical information (*Table 1*). The eligibility criteria for samples included in the TCGA project were primarily based on the availability of tumor samples from patients diagnosed with CRC and samples were typically obtained from patients who had undergone surgical resection of their tumors as part of their clinical care. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Discovery of key differentially expressed genes (DEGs) in MAC tissues

The RNA sequencing data underwent differential expression analysis using the R package limma (version 3.40.6). Significantly differentially expressed genes between MAC and AC were identified based on a P value <0.05 and |log(fold change)| ≥1.2 criteria.

Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analysis

Enrichment analyses of KEGG were performed using the R software package clusterProfiler (version 3.14.3) to evaluate the outcomes (22). Statistical significance was defined as a false discovery rate (FDR) <0.01.

Weighted gene co-expression network analysis (WGCNA) and identification of hub genes

The gene expression profile from TCGA was utilized to eliminate genes with standard deviation of zero across samples. Employing the R software package (version R- 4.3.1) WGCNA, the function good samples. Genes were applied to eliminate outliers and samples (23). Subsequently, WGCNA was executed to construct a scale-free coexpression network. The significance of the gene was determined based on the mediating P value (gene significance = lgP) in the linear regression linking gene expression and clinical characteristics. Module eigengenes were defined as the primary principal component within each gene module, representing the overall gene expression within a specific module. Module membership was determined based on the association between module eigengene and a gene expression profile. Hub genes associated with MAC were identified by calculating module membership and gene significance values, using criteria of |module membership| >0.8 and |gene significance| >0.1 as the cut-off.

Construction of the prognostic model

The least absolute shrinkage and selection operator (LASSO) regression model is an innovative algorithm that addresses collinearity issues. Our investigation employed LASSO to Minimize redundancy in factors and pinpoint the most influential survival-relevant hub genes. the R software package glmnet was utilized to integrate gene expression data, overall survival (OS) status, and OS time, employing the LASSO-Cox method for regression analysis.

Evaluation of the robustness and validity of the prognostic model

The prognostic disparity between these groups was analyzed using the survfit function within the R software package (24). The risk score was determined using the following formula: risk score = (gene 1 expression level × coefficient) + (gene 2 expression level × coefficient) + ... + (gene n expression level × coefficient), and MAC patients are classified into high-risk and low-risk groups based on the magnitude of their risk scores. The high and low-risk groups were defined based on the median value of the risk scores calculated from our prognostic model. Kaplan-Meier survival curves and log-rank tests were employed to evaluate the statistical significance of the prognosis in both high- and low-risk groups.

Clinical significance of the hub genes

Patients were divided into high- (≥50%) and low-expression (<50%) groups based on hub gene expression levels. Kaplan-Meier survival curves and ROC analyses were then conducted. The relationship between hub gene expression and clinical characteristics was assessed using Wilcoxon and Kruskal-Wallis tests.

LinkedOmics analysis

Linkedomic (https://www.linkedomics.org/) was employed to conduct gene set enrichment analysis (GSEA) and evaluate the pathways and molecular mechanisms associated with *FAM174B* (24). The criteria for ranking included a FDR <0.05, and the analysis involved 500 simulations.

Statistical analysis

Initially, we identified the distinct genes between MAC and AC via differential analysis. Next, we utilized WGCNA to pinpoint 5 hub genes from the pool of differential genes. Subsequently, LASSO regression was applied to these 5 hub genes, culminating in a prognostic model comprising 4 genes. The prognostic model's performance was assessed through receiver operating characteristic (ROC) curves, from which the area under the curve (AUC), sensitivity, and specificity were derived. Other analysis was conducted using SPSS 26.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 8 (GraphPad, Inc., CA, USA). The distinction between the two groups was determined through either the paired two-tailed Student's *t*-test or the Mann-Whitney-Wilcoxon test. Statistical significance was established at P<0.05.

Results

Discovery of dysregulated genes in MAC

The analytical flowchart of this study is depicted in *Figure 1*. We obtained the transcriptomic data of MAC and AC samples from the TCGA-colon adenocarcinoma (COAD) and TCGA-rectal adenocarcinoma (READ) datasets and identified DEGs between MAC and AC. Results showed that 12,282 DEGs were upregulated and 3,357 DEGs were downregulated in MAC tissues compared with the AC tissues (|fold change| ≥1.2, P<0.05). According to the expression of DEGs, MAC tissues can be obviously distinguished from AC tissues. Furthermore, these DEGs were shown in the Volcano plot (*Figure 2A*), and the top 50 up- and down-regulated DEGs of MAC were displayed in the heatmap (*Figure 2B*). Subsequently, we performed a KEGG pathway enrichment analysis on the DEGs. The most enriched pathways that these differentially expressed genes were involved in were olfactory transduction, protein digestion and absorption, and cytokine-cytokine receptor interaction (*Figure 2C*).

WGCNA and identification of crucial gene modules for MAC

After being initially screened, we then identified the critical gene modules related to MAC by performing WGCNA on the DEGs. Taking a soft-thresholding power of 3 (scale-free R^2 =0.95), we discovered 19 gene modules (*Figure 3A-3D*). Comparing the correlation heatmaps of module eigengenes with MAC (*Figure 3E*), the cyan module had the highest positive correlation with MAC (correlation coefficient =0.4, P<0.001). In addition, the cyan module scatter plot showed a significant positive correlation between its module membership and gene significance for MAC (correlation

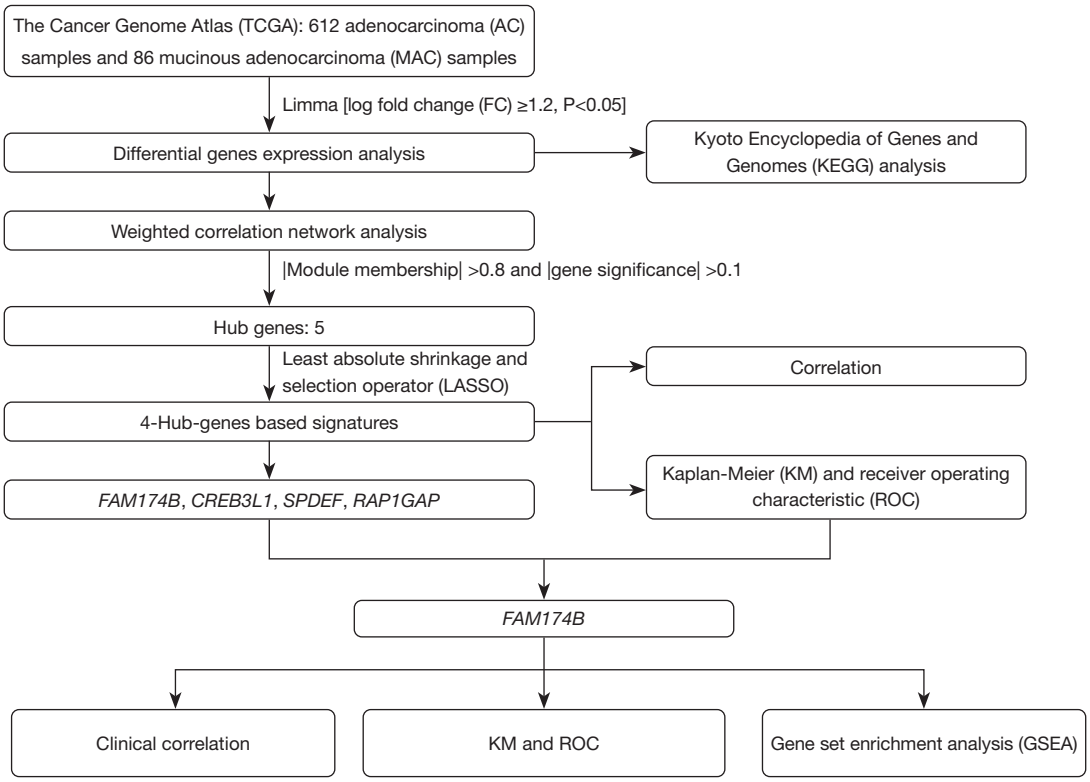

Figure 1 The flow chart of this study.

coefficient =0.77, P<0.001, *Figure 3F*). Hence, we extracted hub genes within the cyan module and ultimately identified five hub genes (*FAM174B*, *CREB3L1*, *SPDEF*, *RAP1GAP*, and *B3GNT6*) through screening.

Establishment and verification of a prognostic model for patients with MAC

Then, based on the initially identified hub genes, we used LASSO regression analysis to screen genes strongly associated with the OS time and constructed a risk assessment signature model in MAC patients. The results indicated that when the lambda coefficients were 0.2218, the prognostic signature of 4 hub genes was finally identified: *FAM174B*, *CREB3L1*, *SPDEF*, and *RAP1GAP* (*Figure 4A*,*4B*). Subsequently, we divided MAC patients into low-risk and high-risk groups based on the risk scores model from the four hub genes. The survival analysis further indicated that MAC patients' OS time significantly decreased after the risk score increased (*Figure 4C*). Subsequently, Kaplan-Meier survival analysis revealed that patients in the high-risk category exhibited significantly shorter OS compared to those in the low-risk category (P=0.007, *Figure 4D*). In addition, we assessed the performance of the four hub genes prognostic model. The AUCs for 1-, 3-, and 5-year OS were 0.61 [95% confidence interval (CI): 0.73–0.49], 0.69 (95% CI: 0.76–0.63), and 0.77 (95% CI: 0.83–0.71), respectively. Thus, the ROC curve analysis indicated that the four genes model had an excellent prognostic prediction capacity for MAC patients (*Figure 4E*). Moreover, these four hub genes exhibited close correlation in messenger RNA (mRNA) expression levels, suggesting potential functional interrelationships (*Figure 4F*).

Evaluation of the clinical relevance of the key genes

After the entire model assessment, the prognostic value of the four independent hub genes was also evaluated through Kaplan-Meier curves. Results showed that only *FAM174B* was closely associated with OS (*Figure 4D*, Figure S1). According to the expression level of *FAM174B*, patients were divided into *FAM174B* low- (<50%) and high-expression groups (≥50%). The OS of the *FAM174B* high-expression group was better than that of the *FAM174B*

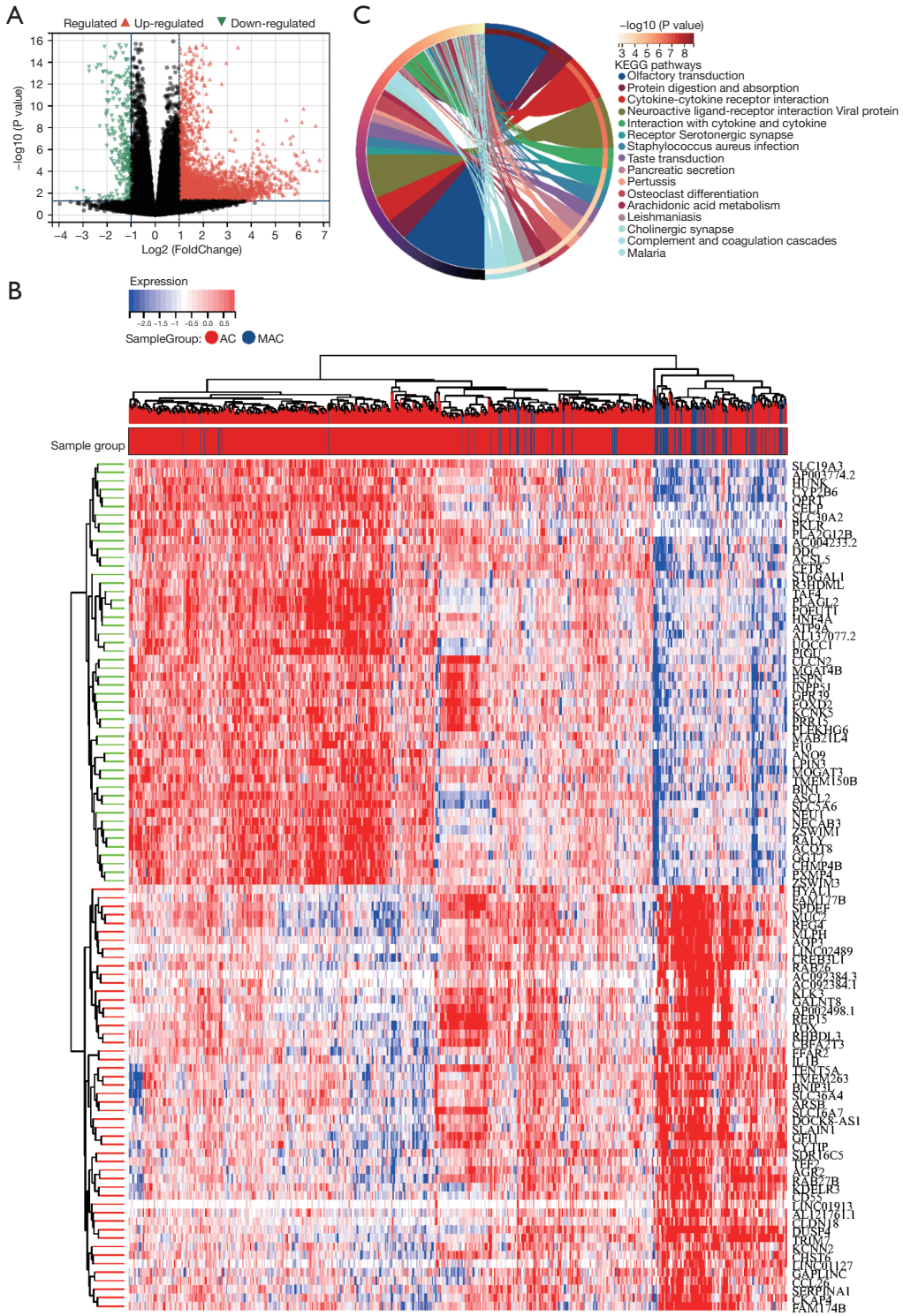

Figure 2 Detection of notably differentially expressed genes between MAC and non-specific AC samples. (A) Volcano plot illustrating the distribution of gene expression levels between MAC and AC samples. Black dots represent all differential genes with P value >0.05 and logFC <1.2. (B) Heatmap of the top 50 upregulated and downregulated genes in MAC, relative with AC tissues. (C) KEGG functional enrichment analysis of the DEGs (P<0.05). DEGs, differentially expressed genes; KEGG, Kyoto Encyclopedia of Genes and Genomes; MAC, mucinous adenocarcinoma; AC, adenocarcinoma; FC, fold change.

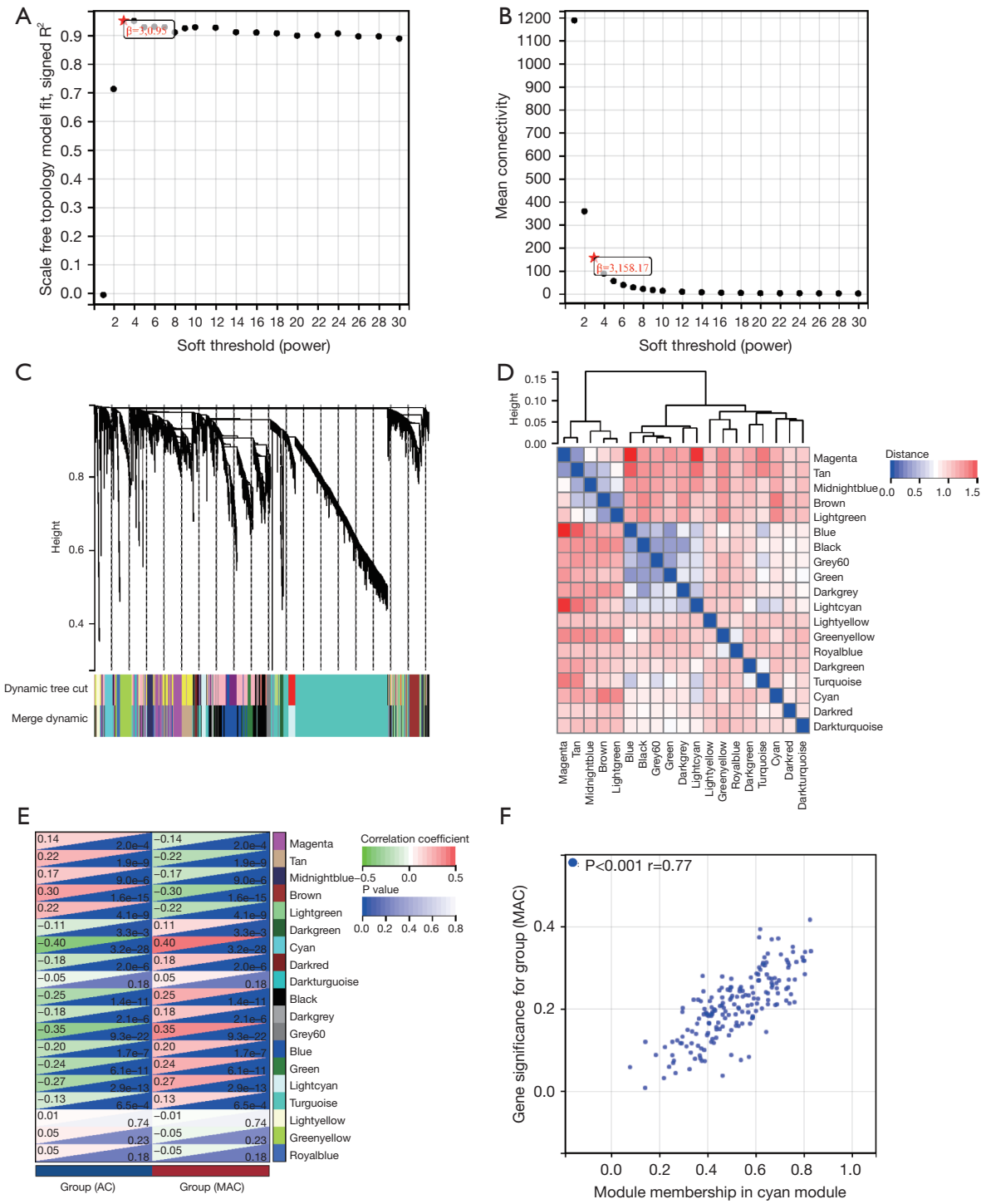

Figure 3 The investigation of pivotal modules associated with MAC using WGCNA. (A) Model fitting at different soft threshold forces. (B) Average connectivity analysis for different soft threshold forces. (C) Dendrogram illustrating modules of differentially expressed genes clustered based on dissimilarity. Colored bars indicate different gene modules identified through clustering analysis. (D) Clustering of module and heatmap. (E) Heatmap displaying correlation between module genes and MAC. (F) Scatter diagram in the cyan module for MAC. MAC, mucinous adenocarcinoma; WGCNA, weighted gene co-expression network analysis.

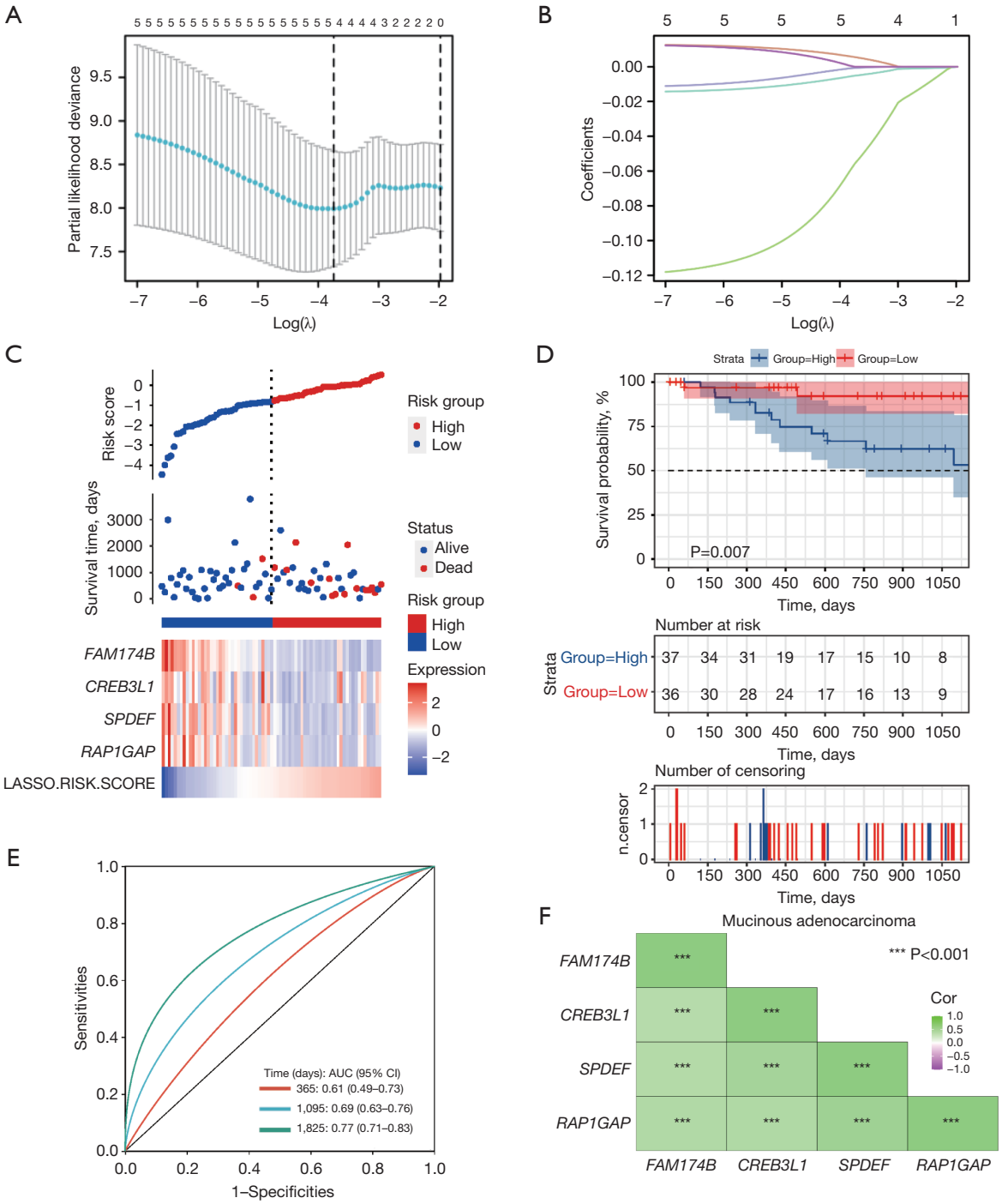

Figure 4 Development and validation of a four hub genes-based signature. (A,B) LASSO regression analysis was conducted to establish the prognostic model. (C) The risk score distribution among MAC patients (D) Kaplan-Meier plots for the low-risk and high-risk cohorts. (E) ROC for the four-genes model. (F) Correlation heatmap of the four hub genes. LASSO, least absolute shrinkage and selection operator; MAC, mucinous adenocarcinoma; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

low-expression group (P=0.02, *Figure 5A*). The AUC values for *FAM174B* predicting 1-, 3-, and 5-year OS were 0.73 (95% CI: 0.55–0.92), 0.82 (95% CI: 0.64–0.99), and 0.76 (95% CI: 0.56–0.96), respectively (*Figure 5B*). Subsequently, we explored the relationship between *FAM174B* expression levels and the clinical features of CRC patients. The findings indicated that *FAM174B* expression was significantly associated with MAC histology, but there was no noticeable difference in pT stages, Nodal stages, M stages, and pathological tumor, node, metastasis (pTNM) stages (*Figure 5C-5G*).

Assessment of the biological function of the FAM174B

To explore the role of *FAM174B* in MAC, we first performed GSEA to study the potential biological function of *FAM174B* in MAC. Based on the *FAM174B* expression level in 73 cases of MAC, cases were categorized and analyzed by *FAM174B* low and high expression groups. Differential analysis revealed 30 genes, each upregulated or downregulated in association with *FAM174B* (*Figure 6A,6B*). Analysis of differential gene enrichment showed that *FAM174B* expression was positively associated with mucin-type O-glycolipid biosynthesis and amino sugar and nucleotide sugar metabolism (*Figure 6C*).

The relationship of FAM174B and mucin production

The hallmark of MAC is abundant extracellular mucin in tumor tissue and mucin-type O-glycolipid biosynthesis is critical for mucin formation. Therefore, we speculate that *FAM174B* is important for mucin formation in MAC. Correlation analyses were performed between expression levels of *FAM174B* and MAC key mucin proteins to identify this hypothesis. Results showed that *FAM174B* expression was positively correlated with *MUC2* (P<0.001, Pearson r =0.39), *MUC5AC* (P=0.004, Pearson r =0.33) and *MUC5B* (P<0.001, Pearson r =0.43) (*Figure 7A-7C*). These results suggest that *FAM174B* may be a potential molecule associated with MAC mucin production.

Discussion

MAC is a pathologic type of CRC that differs from AC in many aspects, such as clinical characteristics, molecular characteristics, and chemotherapy/radiotherapy response. Multiple studies have shown that patients with MAC patients exhibit a poorer prognosis relative to individuals diagnosed with AC, but the poor prognosis of MAC remains controversial (16,25,26). Therefore, there is an urgent need to find biomarkers that are related to more prognostic features and can distinguish MAC and AC to help evaluate and predict the MAC patients. By screening the differential genes of MAC and AC, we can find reliable prerequisites for potential biomarkers to identify MAC and AC.

Based on the TCGA dataset, this study identified 15,639 differentially expressed genes in MAC samples compared with AC samples, including 12,282 upregulated genes and 3,357 down-regulated genes. MAC correlation analysis of DEGs by WGCNA identified cyan modules with the highest correlation with MAC. Then, LASSO regression analysis was employed to screen the four key genes, namely *FAM174B*, *CREB3L1*, *SPDEF*, and *RAP1GAP*. Currently, the biomarkers that discriminate between MAC and AC are predominantly mucins. The hub genes we screened by analyzing the differential genes of MAC and AC all have the potential to be biomarkers for discriminating between MAC and AC.

In addition, we established a risk score model based on these four hub genes. The ROC curve results showed that the model can accurately predict the prognosis of MAC patients, with AUCs of 3- and 5-year survival times of 0.69 and 0.77, respectively. The K-M plot results showed that only *FAM174B* was closely associated with OS, which indicates that *FAM174B* has a higher correlation with MAC prognosis than other hub genes and a closer relationship with MAC. The prognostic model we constructed is expected to provide clinical decisions and suggest predictive indicators of MAC survival. Still, due to the limited number of MAC patients, more patient data are needed for verification.

FAM174B is a hub pivotal gene that we screened for prognostic relevance and promises to be an essential gene in differentiating MAC from AC. In exploring the association between *FAM174B* and clinical characteristics, it was found that high expression of *FAM174B* in the T stage was more biased towards the early stage; in the N stage, it was more biased towards the absence of lymph node metastasis; in M stage, it was more biased towards the absence of distant metastasis. Likewise, pathological staging also favored early stages. This indicated that the hub gene *FAM174B* we screened may play a protective role in MAC. Subsequently, we conducted GSEA analysis in MAC and classified *FAM174B* into a high and low expression group. KEGG enrichment results showed that the high expression of *FAM174B* was significantly positively correlated with Mucin type O-glycan biosynthesis, which indicates that *FAM174B* may be involved

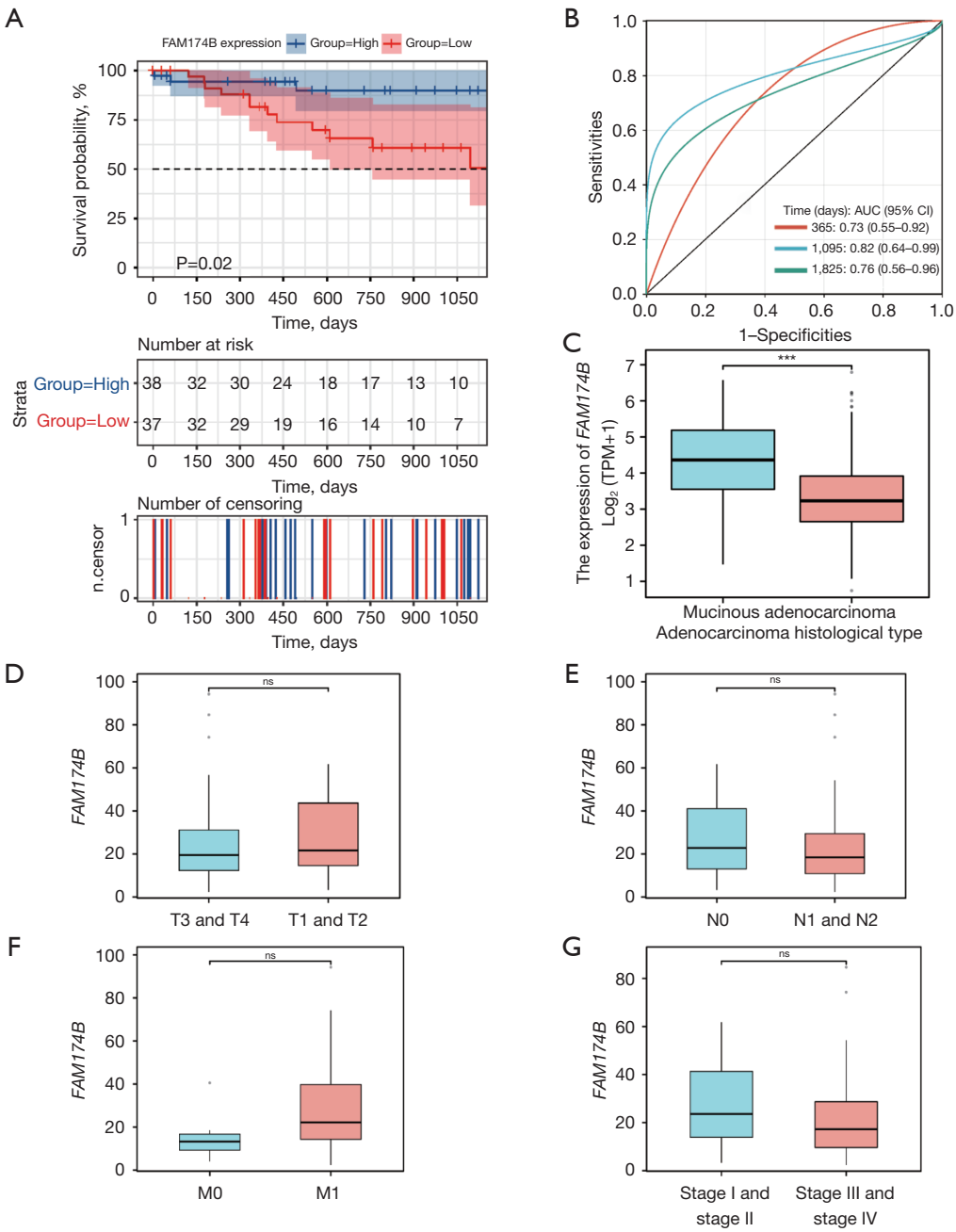

Figure 5 Correlation among *FAM174B* expression and clinical features. (A) Kaplan-Meier plots for high- and low-expression groups. (B) ROC curves for *FAM174B*. (C) Differential expression of *FAM174B* among AC and MAC samples. (D) Differences in *FAM174B* expression across various T stages. (E) Variation in *FAM174B* expression across different N stages. (F) Variation in *FAM174B* expression across different M stages. (G) Variation in *FAM174B* expression across different TNM grades. T, tumor; N, regional lymph node; M, metastasis. ns, no significance (P>0.05); ***, a highly significant result (P<0.001). ROC, receiver operating characteristic; MAC, mucinous adenocarcinoma; AC, adenocarcinoma; AUC, area under the curve; CI, confidence interval; TPM, transcript per million.

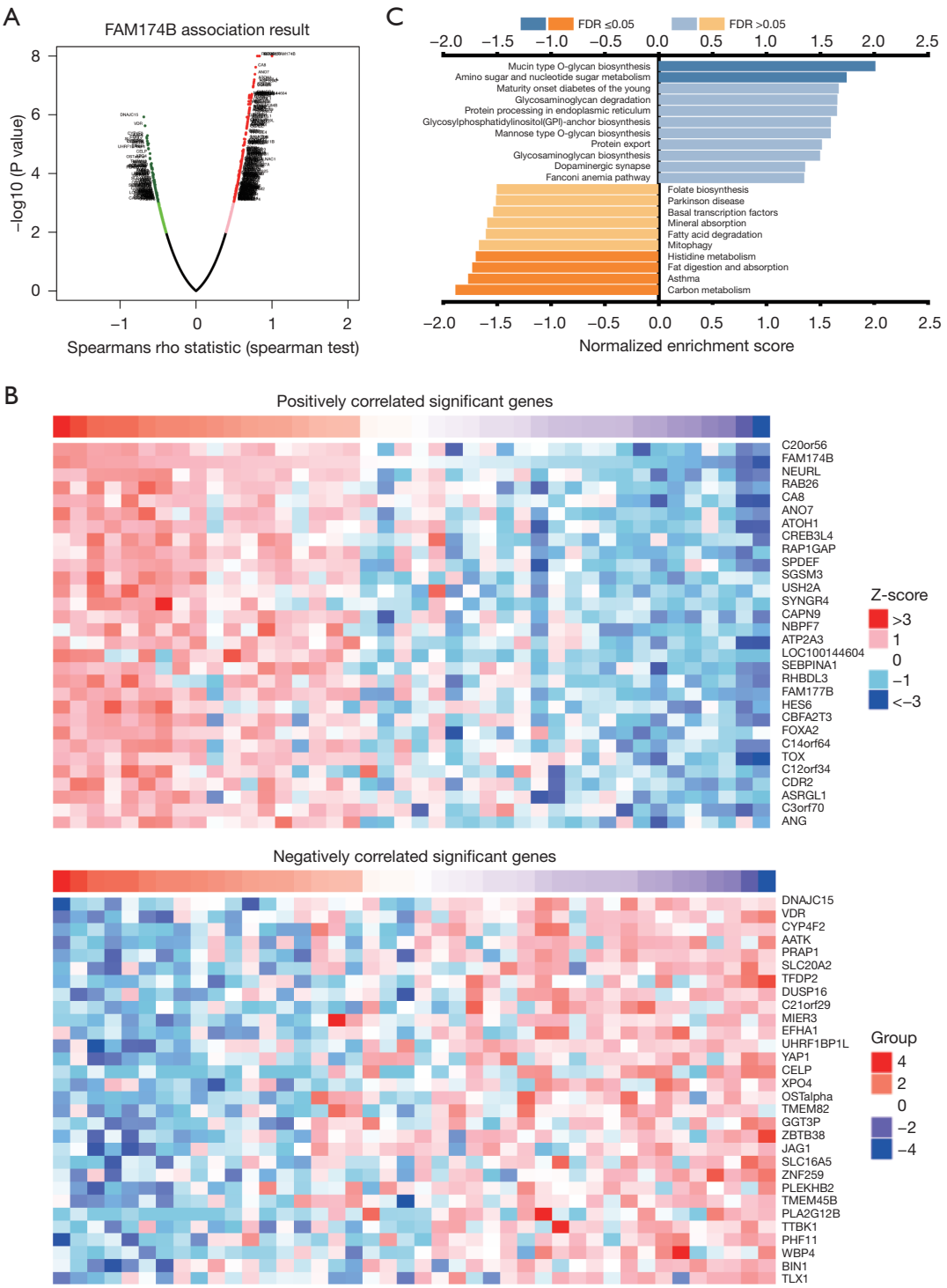

Figure 6 GSEA for *FAM174B*. (A) Correlations between differentially expressed genes. The black dots represent all differential genes with P value >0.05. The light green dots (negatively correlated) and pink dots (positively correlated) mean P value <0.01. The dark green dots (negatively correlated) and red dots (positively correlated) mean P value <0.001. (B) *FAM174B* in MAC based on Pearson correlation analysis. (C) GSEA for *FAM174B* in MAC. FDR, false discovery rate; GSEA, gene set enrichment analysis; MAC, mucinous adenocarcinoma.

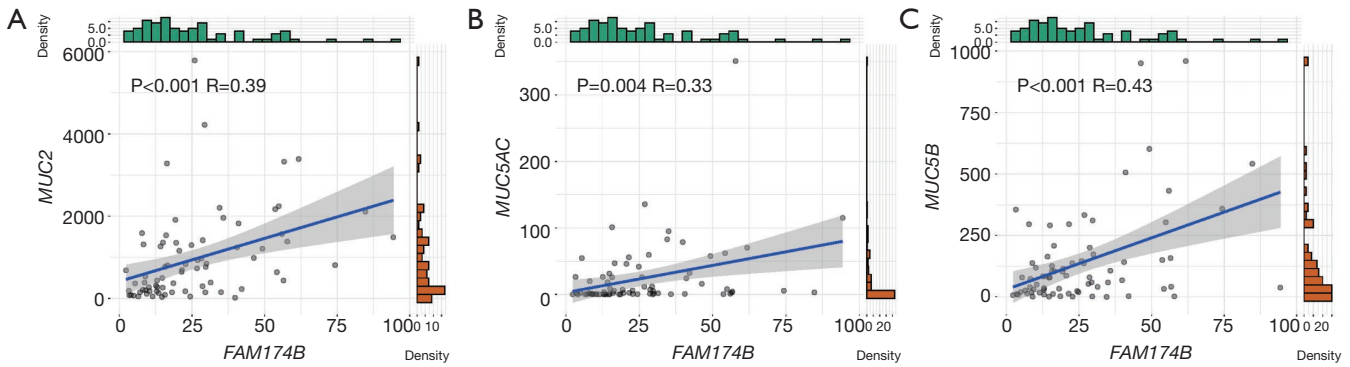

Figure 7 Relationship of *FAM174B* expression with mucin protein of MAC. (A-C) Scatter plots display the correlation between *FAM174B* and mucin protein (*MUC2*, *MUC5AC*, *MUC5B*). MAC, mucinous adenocarcinoma.

in the O-glycan biosynthesis. Abnormal expression of mucin is one of the most striking features of MAC.

Because O-glycan biosynthesis is related to mucin synthesis, we attempted to explore the correlation between *FAM174B* and mucin. *FAM174B* showed a positive correlation with the essential genes *MUC5AC*, *MUC5B*, and *MUC2* in mucin, further suggesting that *FAM174B* may be related to MAC mucus production. Under normal circumstances, mucin acts as a protective barrier for epithelial cells (20,27). In addition, aberrant expression of mucin has been associated with tumor growth, invasion, metastasis, apoptosis resistance, and chemotherapy resistance (28,29). Currently, the mucoid characteristics of MAC suggest that it originates from *MUC2*-expressing cells. Mutations in the *MUC2* gene are an essential cause of aberrant mucus production (30). Secondly, *MUC2* is also associated with the inactivation of tumor suppressor genes, such as *TP53* (31-33). In addition, abnormal activation of the Wnt/β-Catenin signaling pathway is a vital switch supporting *MUC2* expression (13,34,35). Therefore, the association between *FAM174B* and *MUC2* is a direction for further exploration in our research. However, there are some limitations in this study. First, the incidence of MAC is lower than that of AC, so not many data have been collected; second, in order to include a sufficient number of genes, 1.2 times the differential genes were selected, which affected the significance of the difference; third, this study was conducted only through data analysis and verification, we will choose IHC tissue for verification as the next step.

Conclusions

We have developed and validated a four-gene prognostic model to predict the survival of MAC. Additionally, we found that *FAM174B* might correlate with mucin production in MAC.

Acknowledgments

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-347/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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