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ORIGINAL RESEARCH

Identification of Fatty Acid Metabolism-Related Subtypes in Gastric Cancer Aided by Machine Learning

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Introduction: Gastric cancer, the fifth most common malignant tumor in the world, poses a serious threat to human health. However, the role of fatty acid metabolism (FAM) in gastric cancer remains incompletely understood. We aim to provide guidance for clinical decisions by utilizing public database of gastric adenocarcinoma to establish an FAM-related gene subtypes via machine learning algorithm.

Methods: The intersection of FMGs from KEGG, Hallmark, and Reactome bioinformatics databases and the DEGs of the TCGA-STAD cohort was used to decompose the gene matrix related to establish FAM-related gene subtypes by NMF. Comparison of immune infiltrating differences between subtypes using ESTIMATE and Cibersort algorithms. The multifactor Cox regression to identify independent risk genes for patient prognosis based on the subtypes. A prognostic model including independent risk genes was built using random survival forest and Cox regression. IHC validation in gastric cancer and adjacent tissues confirmed the above gene expression level.

Results: 71 DEGs related to FMGs of STAD were identified, which was used to established the FAM-related gene subtypes, C1 and C2. The immune infiltrating analysis showed that most immune features of C2 were significantly upregulated compared to C1. The independent risk genes were *CGβ8, UPK1B, and OR51G* based on the subtypes. A gastric cancer prognostic model consisting of independent risk genes was constructed and patients were classified into high-risk and low-risk groups with survival differential analysis. Finally, IHC showed that *CGβ8* and *UPK1B* expression were upregulated in gastric cancer, while *OR51G2* did not detect differences in expression.

Conclusion: The study developed a machine learning-based gastric cancer prognosis risk model using FMGs. This model effectively stratifies patients according to their risk levels and provides valuable insights for clinical decision-making, enabling accurate evaluation of patient prognosis.

Keywords: Gastric cancer, fatty acid metabolism-related genes, machine learning, genomics, signature

Introduction

Gastric cancer, being one of the most prevalent malignant tumors worldwide, exerts a profound impacts the overall well-being of humanity,[1,2] Diagnostic technologies such as gastrointestinal endoscopy and computed tomography (CT) enable some patients to identify and intervene in gastric cancer earlier, while D2 surgery is currently the primary treatment method for operable gastric cancer. Other treatments for gastric cancer, such as chemotherapy, targeted therapy, and immunotherapy, have significantly improved, However, the overall prognosis of gastric cancer remains poor with a surprisingly low 5-year survival

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rate that fails to exceed 30%.[3] There are several factors related to the prognosis of gastric cancer, including tumor differentiation degree, tissue type, TNM stage, and postoperative treatment mode, TNM stage is a reliable prognostic factor for cancer patients in clinical practice across various evaluation parameters.[4] However, gastric cancer is a tumor with high heterogeneity, and there are individual differences in the treatment effects of patients. Therefore, it is necessary to identify the heterogeneity of patients and develop an individualized treatment plan.

Metabolic reprogramming is a biological behavior that occurs in many different types of tumors to meet the needs of uncontrolled growth and progression of metastasis, and it has been rigorously identified as a marker of tumorigenesis and progression.[5] In addition to the Warburg effect,[6] abnormal fatty acid metabolism, which is one of the characteristics of tumor metabolic reprogramming, has gradually garnered more attention. Most tumor tissues are influenced by fatty acid (FA)-related signaling pathways, and the disruption of fatty acid metabolism caused by the de novo synthesis pathway affects the occurrence and development of malignant tumors.[7,8] Free fatty acids regulate the increase in vascular endothelial growth factor (VEGF) expression by binding to and activating the PPAR responsive elements (PPRE) in the promoter of VEGF through peroxisome proliferator activating receptor-γ (PPARγ).[9] The oxidation process of de novo synthesis of FA provides a carbon source for endothelial cell proliferation, plays a significant role in promoting the formation of blood vessels,[10] and affects the efficacy of drug therapy in patients with gastric cancer.[11]

The rapid development of high-throughput sequencing technology has led to the accumulation of tumor-related omics data at a fast pace, resulting in the establishment of biological information databases for different tumors, including genome, metabolome, and proteome, have been developed.[12,13] Many genes related to tumor development, treatment, and prognosis can be identified by mining these databases using machine learning algorithms, providing a new idea for clinical individualized treatment of cancer patients.[14,15] Currently, there are few studies on the analysis of the heterogeneity in gastric cancer based on fatty acid-related gene subtypes due to the fact that Stomach adenocarcinoma (STAD) accounts for over 90% of gastric cancer cases. Therefore, this study first screened out genes related to the differential expression of fatty acid metabolism in STAD. Then, it identified two subtypes through a non-negative matrix algorithm,[16] and analyzed the differences in survival prognosis, pathway functional enrichment, and immune infiltration degree between the subtypes. The prognostic risk model was constructed by combining random survival forest[17] with Cox regression. Risk stratification was performed on gastric cancer patients, and immunohistochemical staining experiments were used to validate the expression of the key genes in clinical samples, aiming to identify new targets that could be utilized in the treatment of gastric cancer and provide references for clinical decision-making guidance.

Materials and Methods

Data Preparation and Processing

A total of 407 STAD data were downloaded from The Cancer Genome Atlas Program (TCGA) database, including RNA-seq data and clinical data of 375 gastric adenocarcinoma tissue samples and 32 paracancer tissue samples, which included patient survival time, survival state, and other data. Patients whose survival time, survival status, and clinicopathological characteristics were unknown within 30 days were excluded. As a result, 379 STAD patients were eligible for analysis. Differentially Expressed Genes (DEGs) in the TCGA-STAD cohort were detected using the "DEseq2" package in R language. The definition of DEGs should meet the requirements of $|\log2FC| > 1$ and $P < 0.05$ for statistical significance. KEGG, Hallmark, and Reactome bioinformatics databases were utilized used to search for gene sets related to Fatty acid metabolism pathway. After removing overlapping genes between different databases, a total of 309 Fatty acid metabolism-related genes (FMGs) were retrieved.

Identification of Subtypes Related to FMGs in Gastric Cancer

The intersection of FMGs and the DEGs of the TCGA-STAD cohort was used to decompose the gene matrix related to fatty acid metabolism using the non-negative matrix factorization (NMF) algorithm, with a rank ranging from 2 to 10. The optimal rank order and stable subtype are determined based on either the inflection point of the cophenetic curve showing the largest decline range in the NMF rank metric graph or the output result of the joint consensus matrix.

Survival Analysis of Subtypes Related to FMGs

Survival analysis of FMGs-related subtypes was performed using the "survival" package and the "survminer" package, and the K-M method (Log Rank test) was employed. The outcome events were classified as disease-specific survival (DSS), overall survival (OS), and progression-free interval (PFI). A significance level of $P < 0.05$ was considered.

Differences in the Biological Function of Subtypes Related to FMGs

The present study aims to elucidate the impact of differential expression of FMGs on the malignant biological characteristics of gastric cancer, as well as the potential regulatory mechanisms involved. Gene set variation analysis (GSVA) revealed differences in metabolic pathways between subtypes. And the thresholds was 0.05 in GSVA.

Differences in Immune Infiltration Among FMGs Related Subtypes

To further investigate potential differences in immune microenvironment infiltration among different subtypes of gastric cancer patients, the ESTIMATE algorithm was utilized to estimate the extent of non-tumor cell infiltration, and the Cibersort algorithm was employed to compare the variation in abundance infiltration of different subtypes across 22 types of immune cells.

Construction of a Signature

Firstly, the "edgeR" package was used to identify DEGs between FMG subtypes. The truncation criteria were set as $|\log2FC| > 1$ and $P < 0.05$. After that, dimension reduction analysis was performed using a random survival forest to screen independent risk genes associated with the prognosis of STAD patients. Subsequently, a prognosis model was constructed based on the coefficients from the Cox regression model and the expression levels of risk genes. Based on the median risk score derived from this model, patients were categorized into two distinct groups: high-risk and low-risk cohorts. The Kaplan-Meier method (Log Rank test) was employed to analyze differences in survival between these groups. The outcome events were DSS, OS, and PFI. A significance level of $P < 0.05$ was applied for statistical analysis. The flow chart was shown in Supplementary Figure 1.

Tissue Sample Collection

The experimental samples were all obtained from patients diagnosed pathologically with gastric adenocarcinoma in the Department of Gastrointestinal Surgery of Jining First People's Hospital. Cancer and adjacent tissues were collected from four patients between July and August 2023, which were authorized by the Ethical Board of Jining First People's Hospital with an ethics number of 2023 LSY No. (050). All participants provided written informed consent prior to enrolment in the study, and the study was complied with the Declaration of Helsinki.

Immunohistochemical Staining

The tissue specimen underwent fixation using polyformaldehyde. The paraffin-embedded tissue sections were dewaxed, hydrated, and rinsed with PBS. This was followed by antigen repair and blocking, incubation with primary and secondary antibodies, hematoxylin restaining, cleaning, dehydration, sealing, microscopic examination and filming. CGβ8 antibody was purchased from European Proteintech Company; UPK1B antibody was purchased from Beijing Boao Biotechnology Co., LTD; OR51G2 autoantibody was purchased from Jiangsu Affinity Biological Research Center Co., LTD. These instructions were applied for Western blot or immunocytochemical experiments. This study aimed to apply this antibody to IHC. UPK1B antibodies were purchased from Beijing Boao Biotechnology Co., LTD. All primary antibodies used in this study were rabbit anti-human antibodies while the secondary antibodies were goat anti-rabbit antibodies.

Statistical Analysis

Graph Pad Prism 8.0 software was used for statistical analysis. A comparison between the two groups was performed using an independent sample *t*-test. Quantitative data were presented as mean ± SEM (standard error of the mean), and statistical significance was determined at $P < 0.05$.

Results

Baseline Characteristics of Gastric Cancer Patients in the TCGA Database

According to the exclusion criteria, a total of 379 gastric adenocarcinoma samples were included. The detailed clinical case characteristics of the patients included their age, sex, tumor grade, T stage, N stage, M stage, survival time, and survival status at diagnosis as shown in Table 1.

Extraction of Differentially Expressed FMGs in Gastric Cancer

The expression of DEGs in the TCGA-STAD cohort was analyzed firstly. Finally, 3741 DEGs were selected, including 2561 up-regulated genes and 1,180 down-regulated genes. The volcano map was drawn using the Limma package, as shown in Figure 1A. After removing overlapping genes, a total of 309 FMGs were obtained through retrieval of fatty acid metabolic pathway genes. The intersection between FMGs and DEGs indicated that there were 71 differentially expressed FMGs between gastric adenocarcinoma and adjacent tissues, as shown in Figure 1B. Among them, 11 up-regulated genes and 60 down-regulated genes were detected, and the top 20 were shown in Supplementary Table 1.

Table 1 Baseline Information Table of Enrolled Population

Characteristics	N	Percentage (%)
Age		
<65 years	165	43.5
≥65 years	214	56.4
Sex		
Male	252	66.5
Female	127	33.5
AJCC[1] stage		
I	50	13.2
II	127	33.5
III	165	43.5
IV	37	9.8
T stage		
T1	21	5.5
T2	80	21.1
T3	176	46.4
T4	102	27
N stage		
N0	117	30.9
N1	101	26.7
N2	76	20
N3	78	20.6
NX	7	1.8
M stage		
M0	341	90
M1	22	5.8
MX	16	4.2
OS[2] event		
Alive	240	63.3
Dead	139	36.7

Abbreviations: AJCC, The American Joint Committee on Cancer; OS, overall survival.

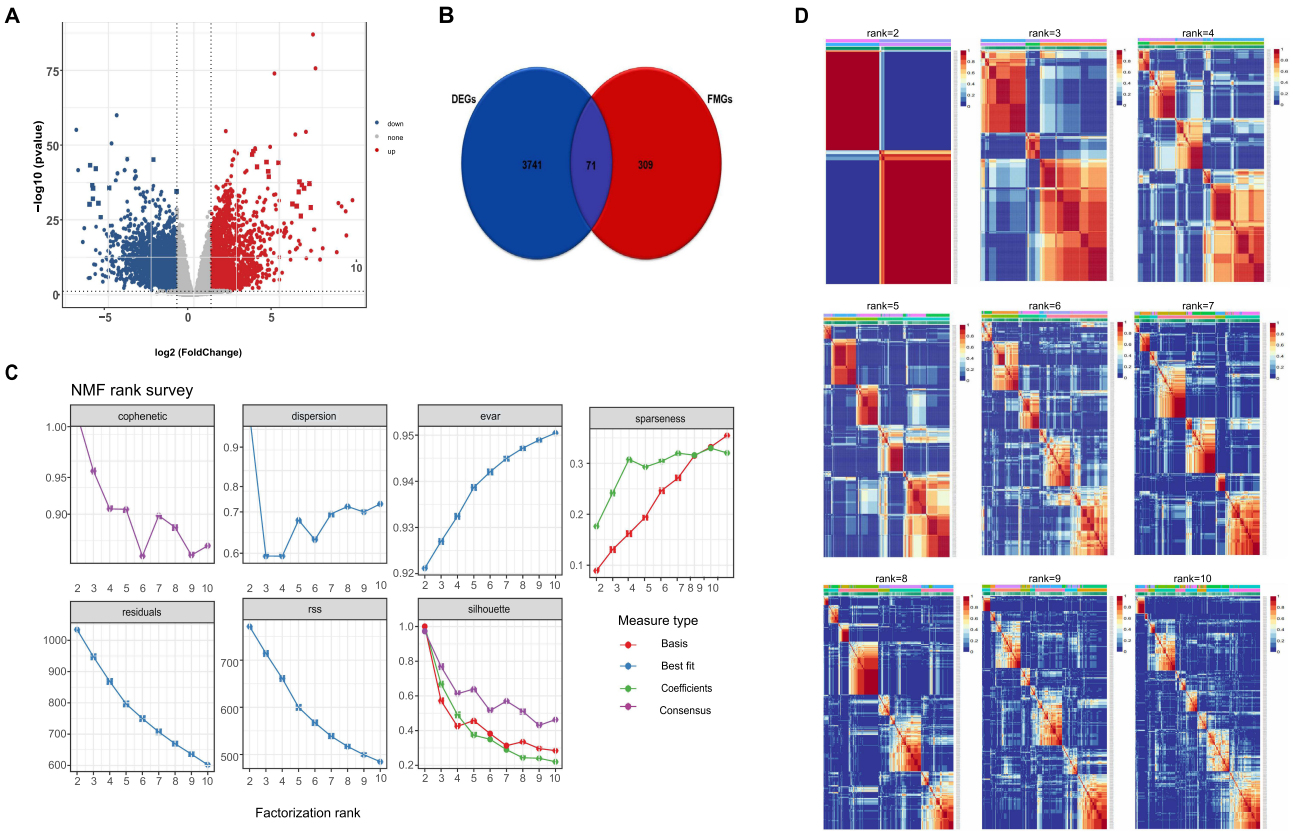

Figure 1 Identification of differentially expressed genes and identification of FMGs subtypes (**A**) Differential genes in TCGA-STAD; (**B**) Venn diagram of differentially expressed genes and genes related to fatty acid metabolism; (**C**) NMF rank metric chart; (**D**) Heat maps of subtypes with rank 2 to 10.
Abbreviations: FMGs, Fatty acid metabolism-related genes; NMF, the non-negative matrix factorization.

Determination of FMGs Subtypes of TCGA-STAD by NMF

The FMGs matrix underwent a decomposition process utilizing the "NMF" package available in the R programming language. The consensus matrix output results were jointly observed with the top points showing the largest decline range of the cophenetic curve to determine the optimal rank. It was found that the subtype classification had the best stability when rank=2, resulting in C1 and C2 subtypes. The NMF rank measurement chart and heat map of subtype classification are shown in Figure 1C and D.

The K-M method (Log Rank test) was used to analyze the survival difference between the C1 subtype and the C2 subtype. Survival analysis results showed that patients with the C1 subtype had a more significant advantages in 5-year DSS ($P = 0.011$) and PFI ($P = 0.046$) compared to those with the C2 subtype. There were significant differences in OS ($P = 0.0046$) between patients with these two subtypes, as shown in Figure 2A–C.

Enrichment Analysis of FMGs Subtype Pathways

Pathway enrichment analysis of C1 and C2 subtypes was performed using GSVA, and the top 50 significantly enriched KEGG pathways were listed. The GSVA results for the KEGG pathway are shown in Figure 2D. The heat map displays the enriched pathway in the C1 subtype, including lipid metabolism, drug metabolism, carbohydrate metabolism, retinol metabolism, ascorbic acid, and uronate metabolism, and the enriched pathways in the C2 subtype include vascular smooth muscle contraction, calcium ion signaling pathways, extracellular matrix receptors, genetic cardiac disease, and chondroitin sulfate.

Immunoinfiltration Relationship Among Patients with Different Subtypes of Gastric Cancer

The "ESTIMATE" package was used to assess the difference in immune infiltration between C1 and C2 subtypes, and the "vioplot" package was utilized for data visualization, as shown in the Figure 3, in order to observe the correlation

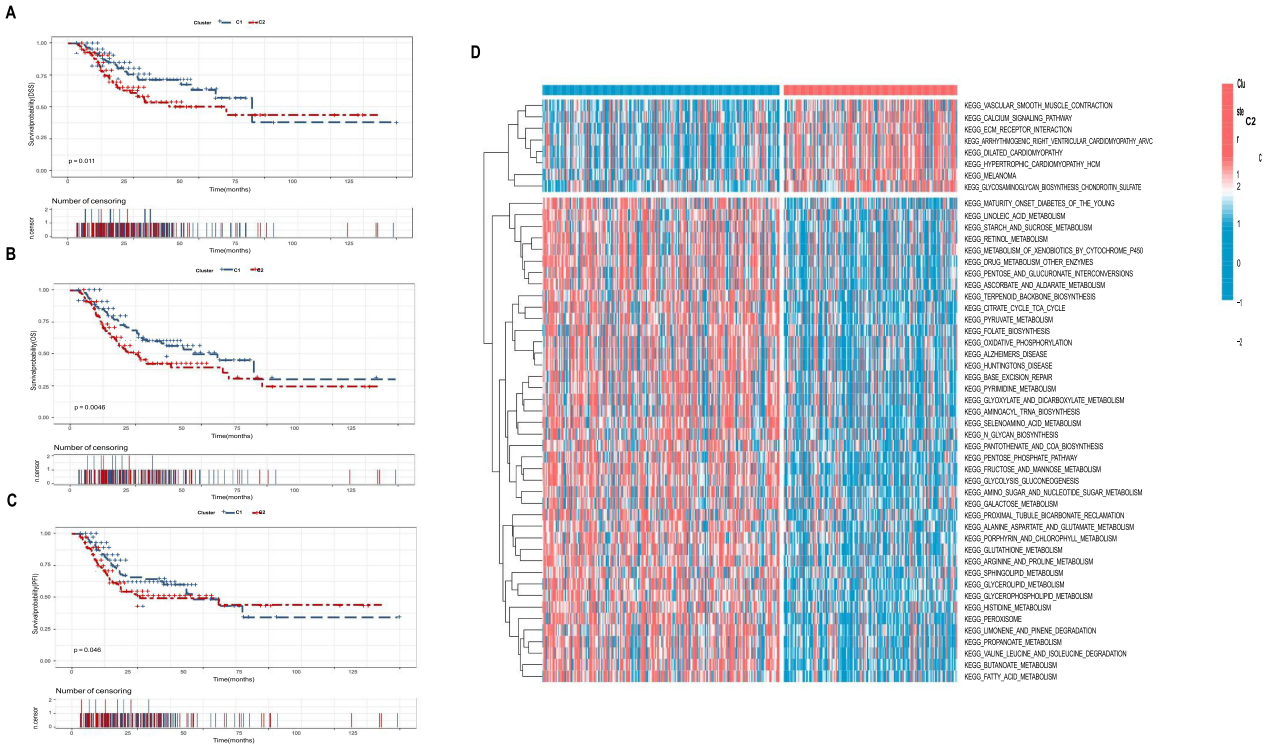

Figure 2 Survival difference and biological function difference of FMG sub-types in gastric cancer. (**A**)K-M curve of DSS (*P*= 0.011); (**B**) K-M curve of OS (*P*= 0.0046); (**C**) K-M curve of PFI (*P*= 0.046); (**D**)KEGG pathway enrichment analysis of FMGs.
Abbreviations: K-M, Kaplan-Meier; DSS, disease-specific survival; OS, overall survival; PFI, progression-free Interval.

between C1 and C2 subtypes with the tumor microenvironment. Immunodetection point-related genes CD160, CD86, PDCD-1, and PDCD1LG2 were significantly increased in C2 subtype ($P < 0.05$). The ESTIMATE algorithm evaluated the stromal cell score, immune fine package score, and comprehensive estimate score among different subtypes. The results showed that the C2 subtype was significantly higher than the C1 subtype ($P < 0.05$). In activated B cells, activated $CD4^{+}$T cells, neutrophils, type 17 helper cells, CD56bright NK cells, CD56dim NK cells, eosinophils, naive B cells, naive dendritic cells, myeloid suppressor cells, mast cells, natural killer cells, natural killer T cells, plasmacytoid dendritic cells, regulatory T cells, follicular helper T cells, type I helper cells and type II helper cells had differences between groups ($P < 0.05$). There were significant differences in immune infiltration between the C1 and C2 subtypes, and most of the immune features of the C2 subtype showed significantly up-regulated compared to the C1 subtype.

The Signature of Gastric Cancer was Constructed Based on Machine Learning

Firstly, two subtypes of DEGs were extracted. Then, random survival forests were used for dimension reduction analysis to sort the importance of variables. A truncation value of 0.9 was set for gene importance. Finally, four model candidate genes (*UPK1B, CGβ8, SIX6*, and *OR51G2*) were screened with an error rate of approximately 37%, as shown in Figure 4A–F. These four genes were further included in multifactor Cox regression to identify independent risk genes for patient prognosis. The results indicated that *CGβ8, UPK1B*, and *OR51G2* served as independent prognostic factors for patients with gastric adenocarcinoma according to Table 2. The Cox regression coefficient and gene variables were utilized to construct the model and calculate risk scores for patients using the following formula: risks core = expression of *CGβ8* × 0.004321797 + expression of *UPK1B* × 0.000139908 + expression of *OR51G2* × 0.222133824.

Patients were divided into high-risk and low-risk groups based on their median risk score; those above the median score were classified as high-risk patients while those below it were considered low-risk patients. The survival analysis

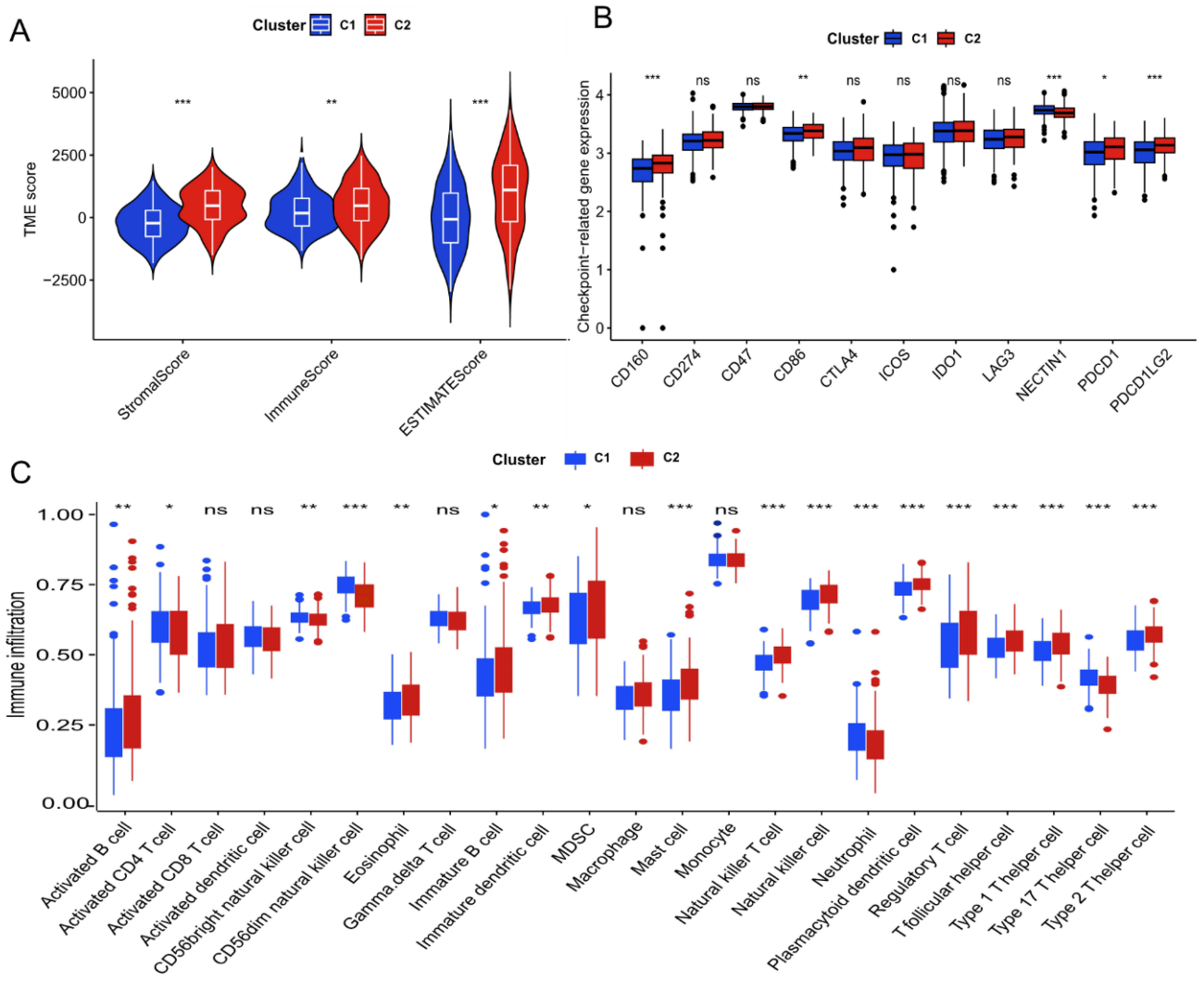

Figure 3 FMGs subtype immune microenvironment in TCGA-STAD data set. (**A**) Differences in stromal cell scores, immune cell scores, and composite estimates among subtypes; (**B**) Differences in immunodetection-related genes among subtypes; (**C**) Differences in immune cell scores among subtypes. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

results demonstrated patients with low risk had better clinical outcomes in terms of DSS, OS, or PFI compared to high-risk patients ($P < 0.0001$), as depicted in Figure 4G–I.

Experimental Verification of Core Gene Expression in the Prognostic Model for Gastric Cancer

In this study, IHC was used to verify the expression of core genes *CGβ8, UPK1B*, and *OR51G2* in clinical gastric cancer samples. DEGs expression analysis of model candidate genes in TCGA-STAD showed that log2FC of *CGβ8* was 5.207, log2FC of *UPK1B* was 3.896, log2F of *OR51G2C* was 1.499; all three were differentially up-regulated genes. The results of IHC staining showed varying degrees of expression for *CGβ8* and *UPK1B* in gastric cancer and paracancer tissue, with more deposition observed in cancer tissues as shown in Figure 5.

Discussion

Gastric cancer is a highly heterogeneous tumor with numerous prognostic factors. FA metabolism is significantly associated with the occurrence, development, and invasive potential of gastric cancer, which impacts the prognosis of patients. In this study, using the TCGA-STAD database as a starting point, we divided patients into the two subtypes (C1 and C2) based on the matrix of fatty acid-related genes using NMF algorithm. We then analyzed the differences in survival prognosis, pathway functional enrichment,

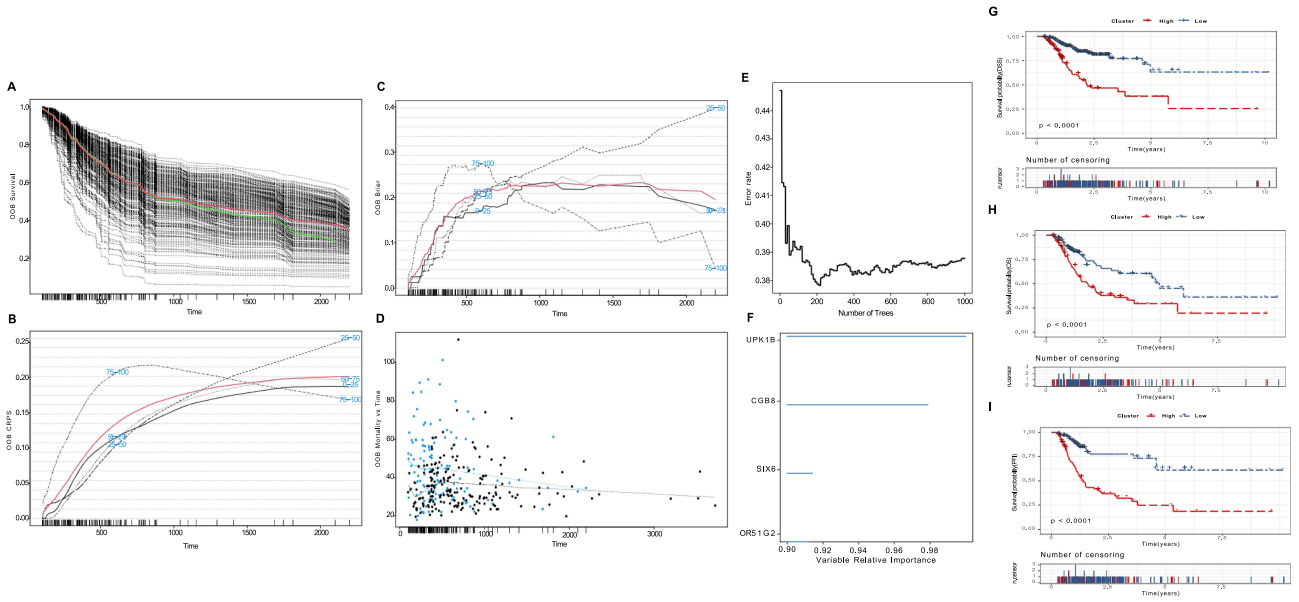

Figure 4 Output result of random survival forest and survival differ-ence between high-risk and low-risk patients. (**A–E**) The out-of-pocket error rate of the random survival forest model; (**F**) Ranking the importance of variables; (**G**) K-M curve of DSS ($P < 0.0001$); (**H**) K-M curve of OS ($P < 0.0001$); (**I**) K-M curve of PFI ($P < 0.0001$).

and degree of immune infiltration between these subtypes. Finally, we constructed a prognostic risk model (including CGβ8, UPK1B, and OR51G2), which can stratify patient risk and provide guidance for clinical decision-making.

To explore the potential regulatory pathway of FMGs in the malignant biological behavior of gastric cancer, GSVA results of the KEGG pathway showed that the main enrichment pathways of FMG subtypes include carbohydrates metabolism, lipid metabolism, calcium ion signaling pathway, etc. Studies have found that a ketogenic diet may enhance chemotherapy's effect and improve radiotherapy's anti-tumor effect. Therefore, adjusting the fat-to-carbohydrate ratio in C1 subtype gastric cancer patients' diet may affect the therapeutic effect of the disease.[18] The metabolism of ascorbic acid and uronate is an important pathway in carbohydrate metabolism, which possesses strong antioxidant properties that protect cells from oxidative damage. Vitamin C, also known as ascorbic acid, is effective in high-dose vitamin C supplementation. Therefore, when patients with subtype C2 gastric cancer undergo anti-tumor therapy combined with high-dose vitamin C, it may alter the iron metabolism in cells and induce the production of reactive oxygen species. This can cause specific DNA damage to tumor cells leading to cell death[19] and improve the therapeutic effect on patients.

Aberrant FA metabolism significantly contributes to the initiation and progression of diverse cancer types, both in vitro and in vivo, thereby influencing tumor invasiveness. Sung et al[20] observed a significant reduction in the abundance of *Roseburia*, a bacterium known for its production of short-chain fatty acids, in individuals with chronic atrophic gastritis. This bacterium has been found to exert a protective effect on the gastric mucosa. Moreover, butyrate can inhibit the proliferation of gastric cancer cells and induce apoptosis by downregulating BCL-2, an apoptotic regulator involved in mitochondrial-mediated pathways.[21] As a short-chain fatty acid HDAC inhibitor[22], valproic acid (VPA) can inhibit the activity of HDAC1/2, stimulate the expression of cell cycle regulatory genes p53 and p21, induce cell cycle arrest, reduce the expression of anti-apoptotic Bcl-2 protein, and induce autophagy in gastric cancer cells.[23] Currently, HDAC inhibitors are primarily approved for blood tumors such as non-Hodgkin

Table 2 Results of Multivariate Cox Regression

Gene	Coef	HR[1]	HR.95L	HR.95H	*p*-value
CGβ8	0.004321797	1.00433115	1.002413459	1.006252509	9.34E-06
UPK1B	0.000139908	1.000139918	1.000065389	1.000214453	0.000233542
OR51G2	0.222133824	1.248738478	1.130294801	1.379593878	1.25E-05

Abbreviation: HR, hazard ratio.

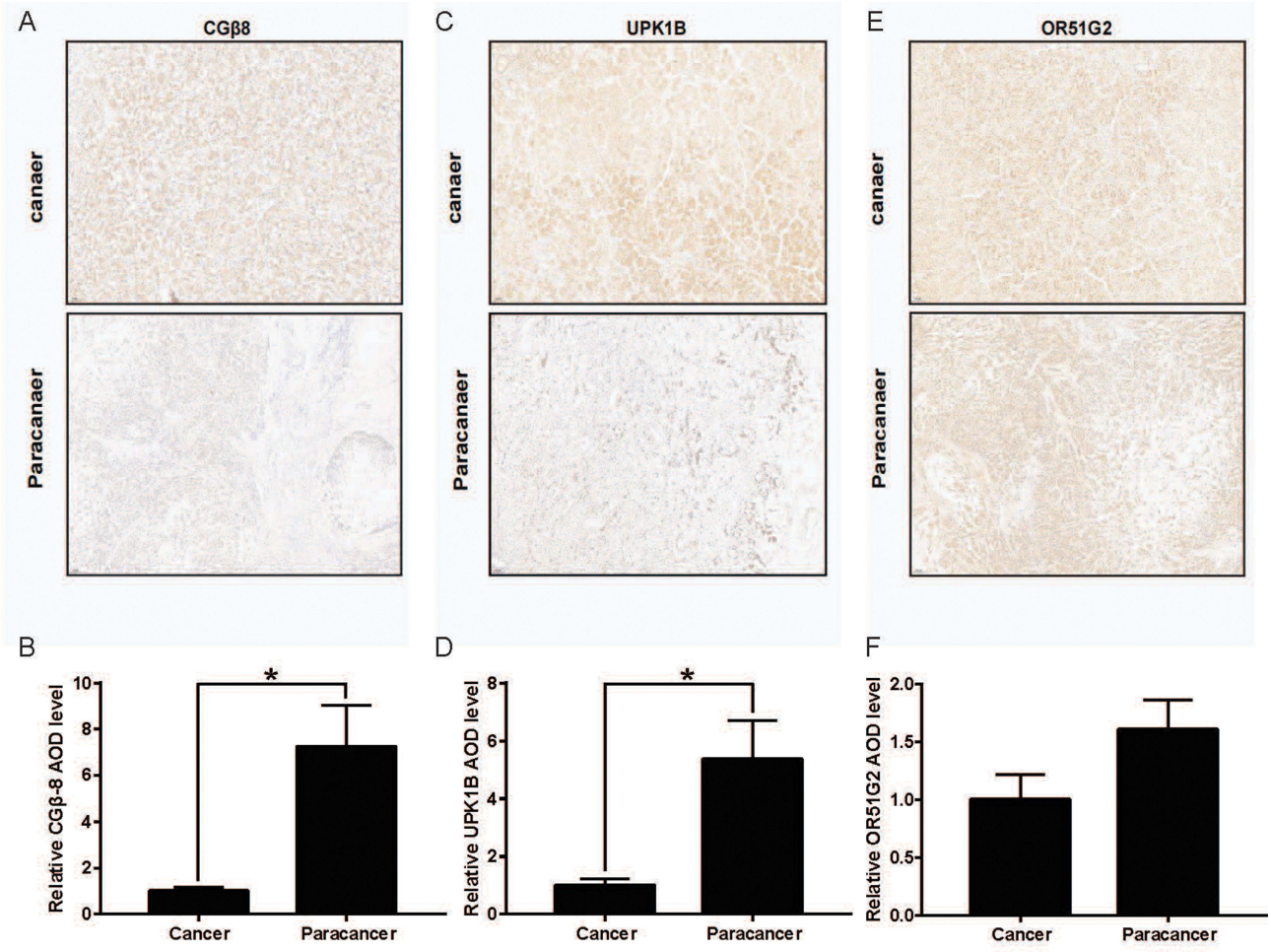

Figure 5 The expression of CGβ8 (**A** and **B**), UPK1B (**C** and **D**), and OR51G2 (**E** and **F**) proteins in gastric cancer/paracancer tissues was detected by IHC. IHC: Immunohistochemical staining. (n= 4 / group; *, $P < 0.05$).

lymphoma[24] and multiple myeloma.[25] VPA is not only used in anticonvulsant therapy[26], but it may also become a potential therapeutic drug for gastric cancer.

In this study, differences in immune infiltration among FMG subtypes were also discussed. The results showed that compared with the C1 subtype, tumors of the C2 subtype exhibited a higher level of immune infiltration, which was associated with increased mutation in numerous matrix and immune-related proteins. Additionally, the expression levels of immune checkpoints of PD-L1 and PD-L2 were also higher. In summary, the C2 subtype gastric cancer patients in this study may have a good response to conventional immune checkpoint inhibitors treatment. Among the two subtypes, the C1 subtype has a better overall survival prognosis, and it exhibits lower expression of immune checkpoints and immune cells compared to the C2 subtype. Therefore, the degree of immune system recognition and attack may be more severe for the C2 subtype.

Finally, based on the FMG subtype, this study constructed a prognostic risk model consisting of *CGβ8, UPK1B*, and *OR51G2*, all of which were identified as adverse prognostic factors for patients. Patients were then divided into high-risk and low-risk group according to their median risk score. The application of K-M survival analysis revealed significant and statistically notable differences in DSS, OS, and PFI between cohorts classified as high and low risk ($P < 0.001$). *CGβ8* is one of the alleles that encode the human chorionic gonadotropin (HCG)β subunit.[27] Zhao R[28] et al found that the expression of *HCG β8* encoded HCG and its receptor in gastric cancer tissues was significantly higher than that in adjacent tissues. It is possible to promote tumor cell proliferation by activating c-Met expression, which depends on the PKA signaling pathway. UPK1B is a structural protein of uroepithelial cells that can enhance tumor cell proliferation, invasion, and metastasis.[29] Combining the GEO database and TCGA database, some scholars have also discovered that

UPK1B is one of the genes associated with gastric cancer.[30] The human olfactory receptor (OR) gene family is an important member of G-protein-coupled receptors in sensory neurons, playing a crucial role not only in olfactory epithelial cells but also in tumor cell invasion.[31] The OR gene family is overexpressed in tumors and considered as a tumor biomarker.[32] The function of the OR family in gastric cancer and its potential molecular mechanism are still largely unknown. *OR51G2*, a pivotal gene in the prognostic model investigated in this study, was initially discovered to be significantly linked to the prognosis of patients suffering from gastric adenocarcinoma. IHC experiments showed that *OR51G2* was expressed in both gastric cancer tissues and adjacent tissues. Additional clinical samples may be required to validate the expression pattern of *OR51G2* and assess any potential differences between gastric cancer tissues and adjacent tissues. In summary, our findings indicate that *OR51G2* holds a novel position within the prognostic model of gastric cancer as a negative prognostic factor. In contrast, *CGβ8* and *UPK1B* have been extensively elucidated for their significant contributions in facilitating malignant biological behavior of gastric cancer, firmly establishing their association with poor prognosis among patients.

Based on the current research results, information can be collected from a large sample of gastric cancer patients can in the future. The robustness of the prognosis model can be further evaluated by analyzing the expression of key genes in the model and following up with patients to determine their survival time and state.

Conclusion

Utilizing machine learning algorithms, this study developed a gastric cancer prognosis risk model based on FMGs from the TCGA-STAD database. This model facilitates patient stratification according to their risk levels, evaluation of patient prognosis, and provides valuable insights for clinical decision-making. Additionally, we conducted basic experiments to examine the expression of model genes in both gastric cancer tissues and adjacent tissues. Based on these research findings, future collection of large-scale data from gastric cancer patients can be utilized to analyze the expression patterns of key genes in the prognostic model and validate its reliability through follow-up assessments of patients' survival time and status. Furthermore, GSVA analysis results can be employed to explore and confirm potential therapeutic opportunities by investigating the underlying mechanisms associated with enriched pathways in gastric cancer.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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