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Screening Potential Prognostic Factors for Gastric Carcinoma and Indicators for Tumor Microenvironment Remodeling in Female and Male Patients Based on TCGA Data Mining

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Abstract

The tumor microenvironment (TME) participates largely in the genesis and development of gastric carcinoma (GC). Few studies have focused on the impact of gender on the dynamic modulation of the immune and stromal components in TME. In this paper, the authors used CIBERSORT and the ESTIMATE algorithm to analyze the ratio of tumor-infiltrating immune cells (TIC) and the number of immune and stromal components in 221 female and 348 male GC cases from the Cancer Genome Atlas (TCGA) database. The method of COX regression analysis and protein-protein interaction (PPI) network was used to analyze the differentially expressed genes (DEGs). Results showed that the Fc fragment of IgG receptor IIa (FCGR2A, also known as CD32) in females and GDNF family receptor alpha 1 (GFRA1) in males were analyzed as predictive factors by the intersection analysis of univariate COX and PPI. Moreover, FCGR2A was negatively correlated with the survival of female patients, while GFRA1 was positively related to the survival of male patients. Gene Set Enrichment Analysis (GSEA) demonstrated that genes in the FCGR2A high expression group were mainly enriched in the antigen processing and presentation pathway, while genes in the GFRA1 low expression group were mainly enriched in the cell cycle and DNA replication pathway. Furthermore, CIBERSORT analysis for the proportion of TIC revealed that macrophages M2 were positively correlated with FCGR2A expression. And B cells, T cells, monocytes, and macrophages were positively related to GFRA1 expression. The results indicated that the levels of FCGR2A and GFRA1 might be responsible for outlining the prognosis of female and male GC patients, respectively, which highlighted the impact of gender on the tumor progression and offered an extra insight for the therapeutics of GC patients.

Keywords

Gastric carcinoma
FCGR2A
GFRA1
Gender
Tumor microenvironment
Tumor-infiltrating immune cell

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1. Introduction

Gastric carcinoma (GC) is reported as the fifth most common cancer and the third leading cause of cancer mortality, with dismal clinical outcomes [1–2]. Its main pathogenesis includes H pylori and Epstein-Barr virus infection, familial inheritance, as well as environmental factors [3–4]. High intake of salts, nitrates, pickled foods, and smoking was associated with increased risk of GC [5–6]. Due to those various causes, GC is presented as a highly heterogeneous disease with diverse molecular signatures and histopathological appearances [7]. Although immunotherapy and neoadjuvant therapy have been widely used in clinics, the curative effect and 5-year survival rate of GC still need to be further improved. Affirmatively, tumor microenvironment (TME) formation or transition plays vital roles in GC progression and therapeutic response [8]. TME is mainly composed of two cell types: the stromal components, including fibroblasts, endothelial cells, mesenchymal stromal cells, etc., and the tumor-infiltrating immune cells (TICs) such as macrophages and T cells, whose reaction is regarded as a protective response against the tumor [9–10]. They not only secrete a lot of soluble molecules such as cytokines, chemokines, growth factors, antibodies, etc., but also contribute to the presence of hypoxia and acidity, which will determine the behavior of cancers like survival, growth, proliferation, and metastasis [11–12].

Previous studies have reported that the regulation of microRNA and the CXCL1-CXCR2 axis in TME had great clinicopathologic significance for GC [13–14]. However, few studies focused on the impact of gender on the TME composition and the prognosis effect. Therefore, the study screened transcriptome-sequencing results of GC in the TCGA database for further evaluation. The search conditions were as follows: cases (Primary sites: Stomach; Project: TCGA-STAD; Disease type: adenomas and adenocarcinomas; Gender: male or female); and files (Data Category: transcriptome profiling; workflow Type: HTSeq-FPKM). 130 female cases and 218 male cases were selected for analysis. ESTIMATE and CIBERSORT algorithms were used to calculate the TIC proportion of stromal and immune components of GC samples. Protein-protein interaction (PPI) network and univariate COX regression method were performed to analyze differentially expressed genes (DGEs) shared by ImmuneScore and StromalScore. The intersection analysis of core nodes in the PPI network and the top significant factors from the COX regression was used to find the key genes. As a result, the authors find different predictive biomarkers for the alteration of TME status in female and male GC cases, which were Fc fragment of IgG receptor IIa (FCGR2A, also known as CD32) and GDNF family receptor alpha 1 (GFRA1), respectively. The subsequent analysis of FCGR2A and GFRA1 contains survival and clinicopathological characteristics correlation analysis, Gene Set Enrichment Analysis (GSEA), and correlation with TICs. The analysis method followed the study of Bi et al. [15].

2. Results

2.1. Correlation of scores with the survival rate

The correlation between the proportion of immune and stromal and survival rate was evaluated by ImmuneScore and StromalScore, the higher score of which indicated a larger amount of immune or stromal components in TME. ESTIMATEScore denoted the comprehensive proportion of immune and stromal cells. The results showed that in female samples, StromalScore and ESTIMATEScore had evident positive correlation with the survival rate, while the ImmuneScore was the opposite (**Figure 1A–C**). Meanwhile, all three scores had a remarkably positive relationship with the survival rate in male samples (**Figure 1D–F**). The results indicated that both the immune and stromal components are important for the prognosis of GC patients.

2.2. Correlation of scores with clinicopathological staging characteristics

In order to understand the influence of the immune and stromal components on the clinicopathological staging characteristics, the authors evaluated the correlation of ImmuneScore, StromalScore, and ESTIMATEScore with tumor stage, grade, T classification, M classification, and N classification. In female samples, ImmuneScore, StromalScore, and ESTIMATEScore had significant positive correlation with tumor grade, especially between grade II and grade III (**Figure 2**). In contrast, other clinicopathological staging characteristics showed no evident relationship (**Figure 2**). In male samples, ImmuneScore, StromalScore, and ESTIMATEScore

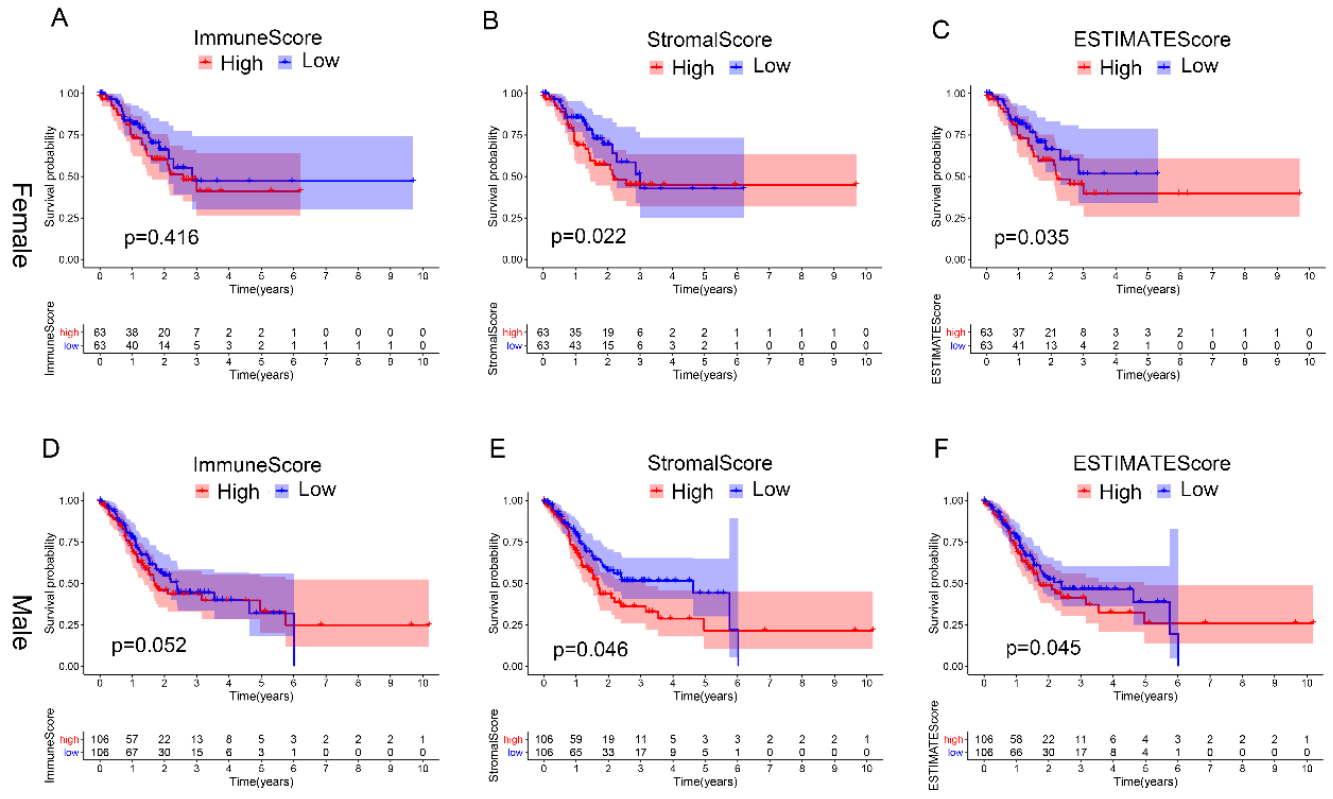

Figure 1. Correlation of scores with the survival of female and male GC patients. (A) Kaplan-Meier survival analysis for female GC patients grouped into high or low scores in ImmuneScore (A), StromalScore (B), and ESTIMATEScore (C), determined by the comparison with the median; Kaplan-Meier survival analysis for male GC patients grouped into high or low scores in ImmuneScore (D), StromalScore (E), and ESTIMATEScore (F), determined by the comparison with the median

had significant correlation with tumor grade as well as T classification (**Figure 3**). Besides, ESTIMATEScore had an evident relationship with tumor stage. The results implied that the immune and stromal components were related to GC development.

2.3. DEGs Shared by ImmuneScore and StromalScore Were Predominantly presented as the enrichment of immune-related genes

DGEs were identified by comparison analysis between high- and low- ImmuneScore/StomalScore samples and used for further GO and KEGG analysis. In female samples, a total of 811 DEGs were obtained, among which 741 were upregulated and 70 were downregulated (**Figure 4A–D**). In male samples, a total of 513 DEGs were obtained, among which 439 were upregulated and 74 were downregulated (**Figure 5A–D**). These DEGs were potential determinate factors for TME status.

Gene ontology (GO) enrichment analysis displayed that the main function of DEGs in the female sample was cell-cell adhesion and T cell activation (**Figure 4E**). The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis also showed the enrichment of the cell adhesion pathway and chemokine signaling pathway (**Figure 4F**). Meanwhile, GO results suggested that DGEs in the male sample were in charge of immune cell proliferation and migration (**Figure 5E**), KEGG analysis showed the enrichment of chemokine signaling pathway and chemokine-chemokine receptor interaction pathway. Therefore, the main functions of DEGs in females and males seemed to be mapped on immune and chemokine-related activities.

2.4. Intersection analysis of PPI network and univariate COX regression

STRING database and Cytoscape software were applied to construct PPI network of 811 DEGs in female samples as well as 513 DEGs in male samples (**Figure 6A, E**), and

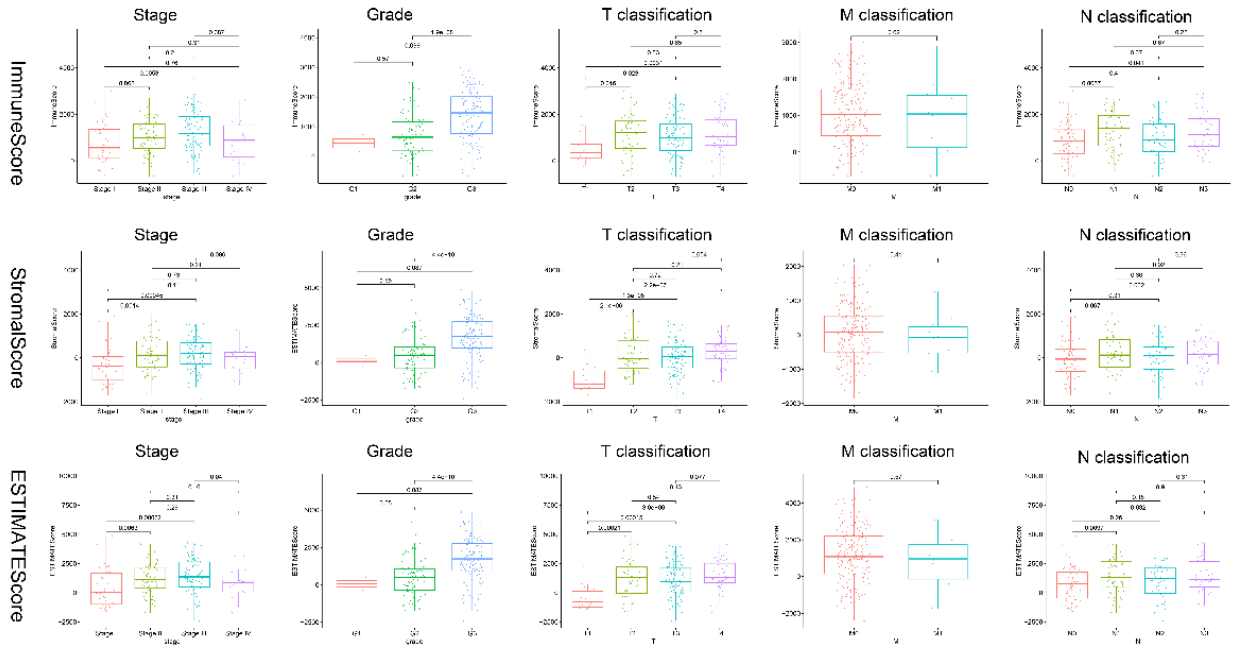

Figure 2. Correlation of ImmuneScore, StromalScore, and ESTIMATEScore with clinicopathological staging characteristics in female GC patients. (A) ImmuneScore of stage, grade, T classification, M classification, and N classification. (B) StromalScore of stage, grade, T classification, M classification, and N classification. (C) ESTIMATEScore of stage, grade, T classification, M classification, and N classification. The statistical method is the Kruskal-Wallis rank sum test

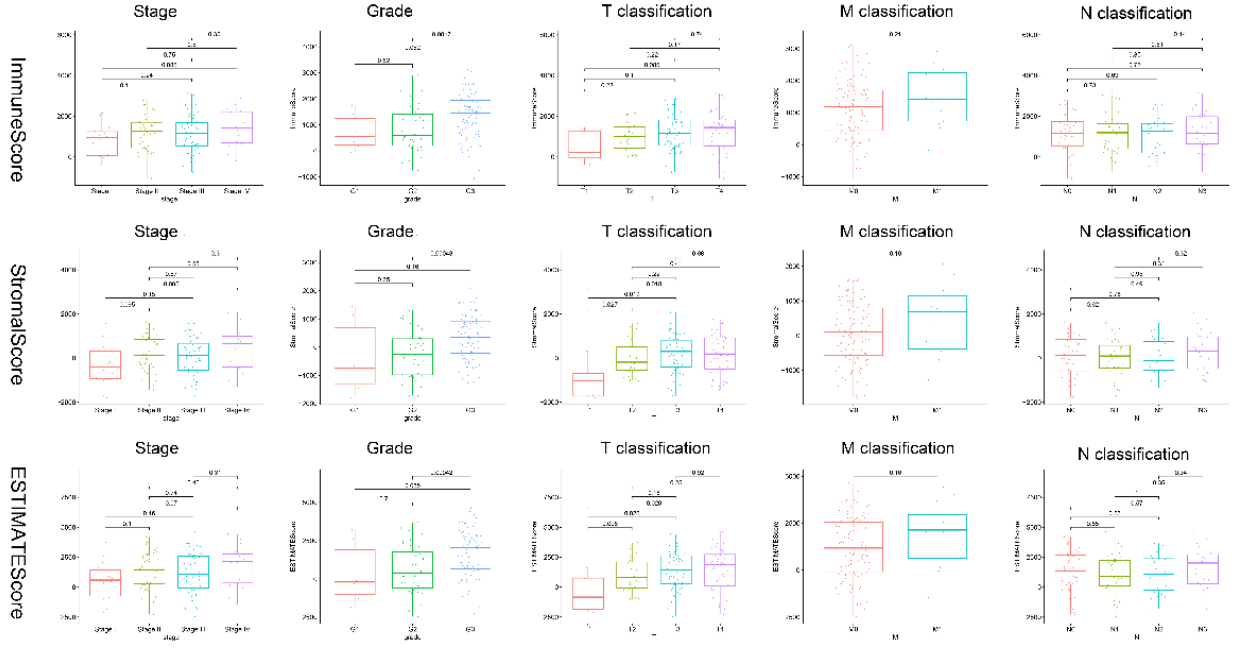

Figure 3. Correlation of ImmuneScore, StromalScore, and ESTIMATEScore with clinicopathological staging characteristics in male GC patients. (A) ImmuneScore, StromalScore (B), and ESTIMATEScore (C) of stage, grade, T classification, M classification, and N classification. The statistical method is the Kruskal-Wallis rank sum test

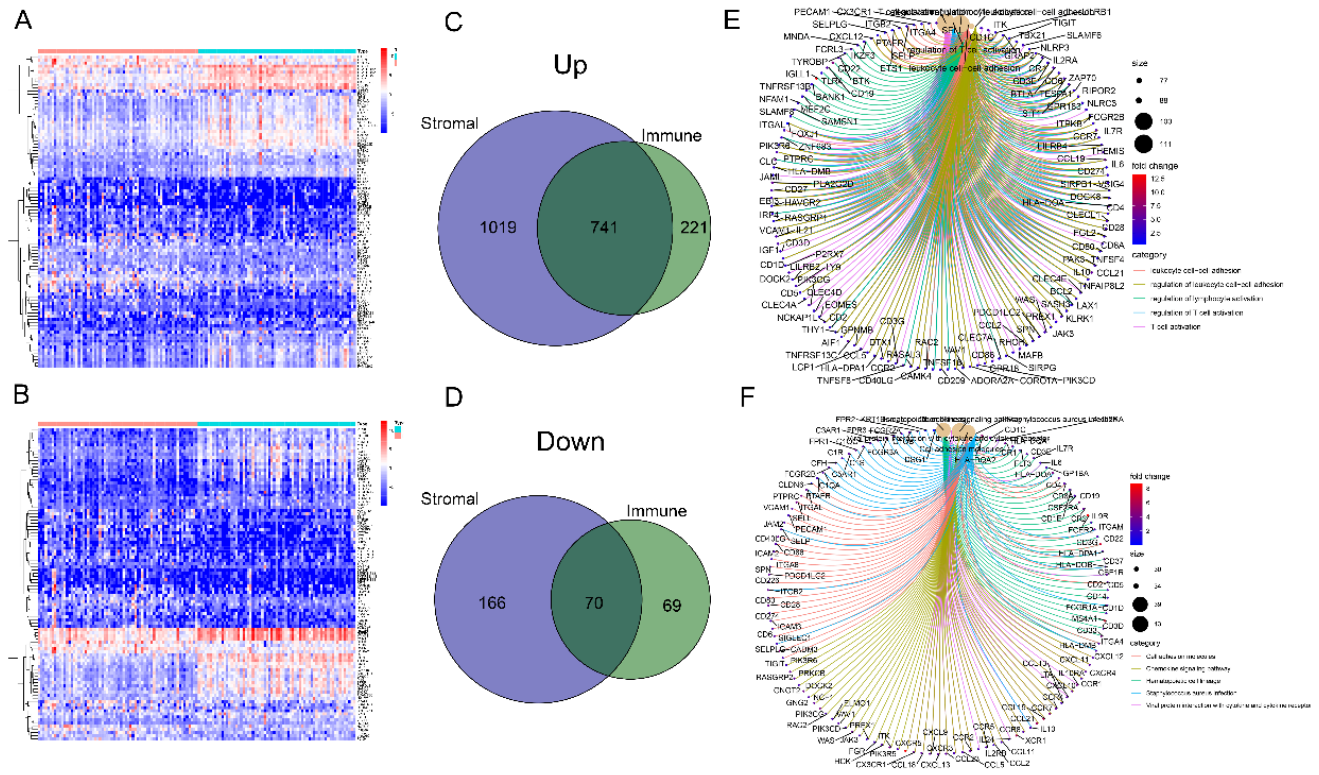

Figure 4. GO and KEGG analysis for DEGs in female GC patients. Heatmap for DEGs generated by comparison of the high scores and the low score group in ImmuneScore (A) and StromalScore (B). DEGs were determined by the Wilcoxon rank sum test with q<0.05 and fold-change >1 after log2 transformation as the significance threshold. Venn plots of up-regulated (C) and down-regulated (D) DEGs shared by ImmuneScore and StroamScore. GO (E) and KEGG (F) enrichment analysis for 811 DEGs. P<0.05 was determined as significantly enriched

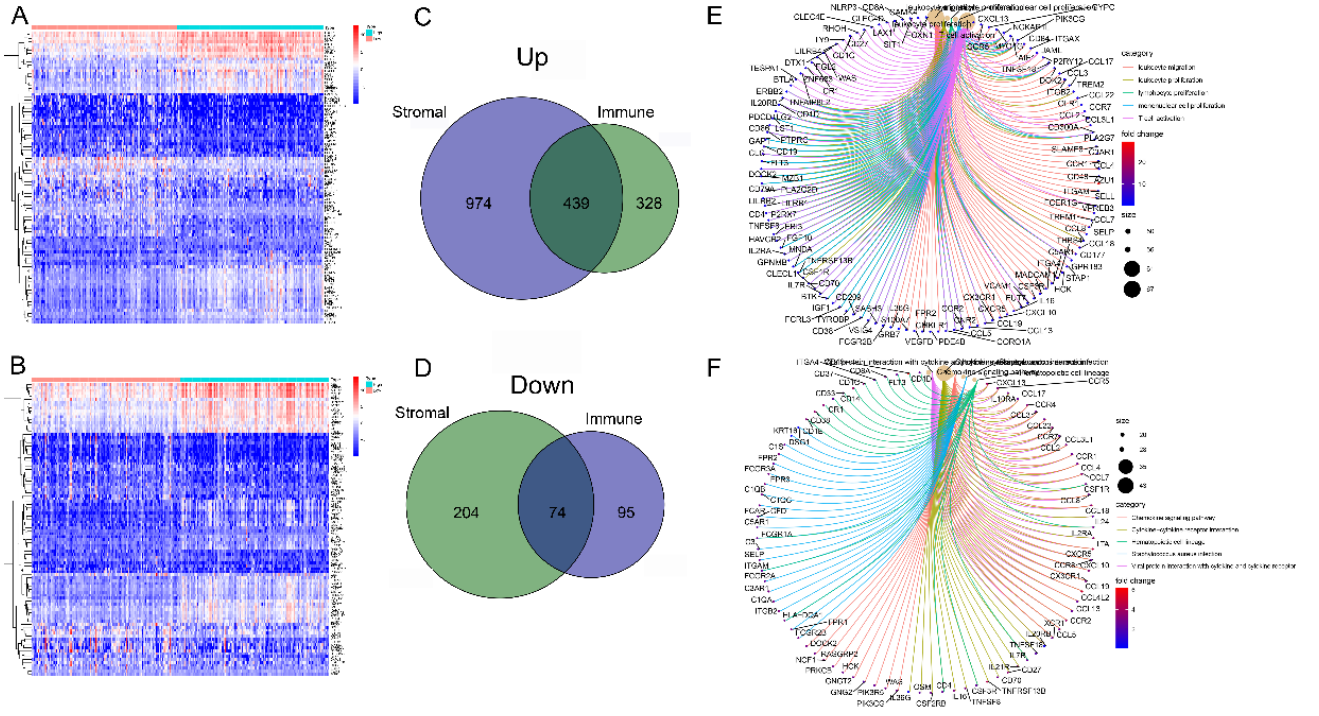

Figure 5. GO and KEGG analysis for DEGs in male GC patients. Heatmap for DEGs generated by comparison of the high scores and the low score group in ImmuneScore (A) and StromalScore (B). DEGs were determined by the Wilcoxon rank sum test with q<0.05 and fold-change >1 after log2 transformation as the significance threshold. Venn plots of up-regulated (C) and down-regulated (D) DEGs shared by ImmuneScore and StroamScore. GO (E) and KEGG (F) enrichment analysis for 513 DEGs. P<0.05 was determined as significantly enriched

the top 30 genes ordered by a number of adjacent nodes were shown in **Figure 6B** and **F**. Meanwhile, univariate COX regression analysis was carried out to evaluate the significant factors for the survival of GC patients in females and males, respectively (**Figure 6C** and **G**). Subsequently, the intersection analysis between the top leading genes of the PPI network and COX regression was performed to screen the key mediators for prognosis. The results showed that the overlapping genes from the above analyses were FCGR2A in female samples and GFRA1 in male samples (**Figure 6D** and **H**).

2.5. The correlation of FCGR2A and GFRA1 expression with the survival and clinicopathological staging characteristics in GC patients

All female samples were grouped into FCGR2A high- and low- low-expression groups compared with FCGR2A median expression; similarly, all male samples were grouped into GFRA1 high- and low- low-expression groups. FCGR2A was evidently highly expressed in female GC samples compared to normal samples (**Figure 7A**); the same result was obtained in pairing analysis between the GC samples and normal samples derived from the same patient (**Figure 7B**). GC female patients with high expression of FCGR2A had a significantly lower survival rate than those of the FCGR2A low expression group (**Figure 7C**). Also, FCGR2A was highly expressed in the G2 grade compared with the G3 grade (**Figure 7D**). For other clinicopathological staging characteristics, there were no significant changes (**Figure 7 E–H**). Whereas GFRA1 was significantly downregulated in male GC samples compared to normal samples (**Figure 7I**), the same result was obtained in pairing analysis between the GC samples and normal samples derived from the same patient (**Figure 7J**). GC male patients with low expression of GFRA1 had a significantly lower survival rate than that of the GFRA1 high expression group (**Figure 7K**). GFRA1 expression in stage II and stage III had significant changes compared to stage I. Also, GFRA1 expression in T3 and T4 had significant changes compared to the T1 phase (**Figure 7M–N**). For other clinicopathological staging characteristics, there were no significant changes (**Figure 7L, O–P**). The above results proved that the expression

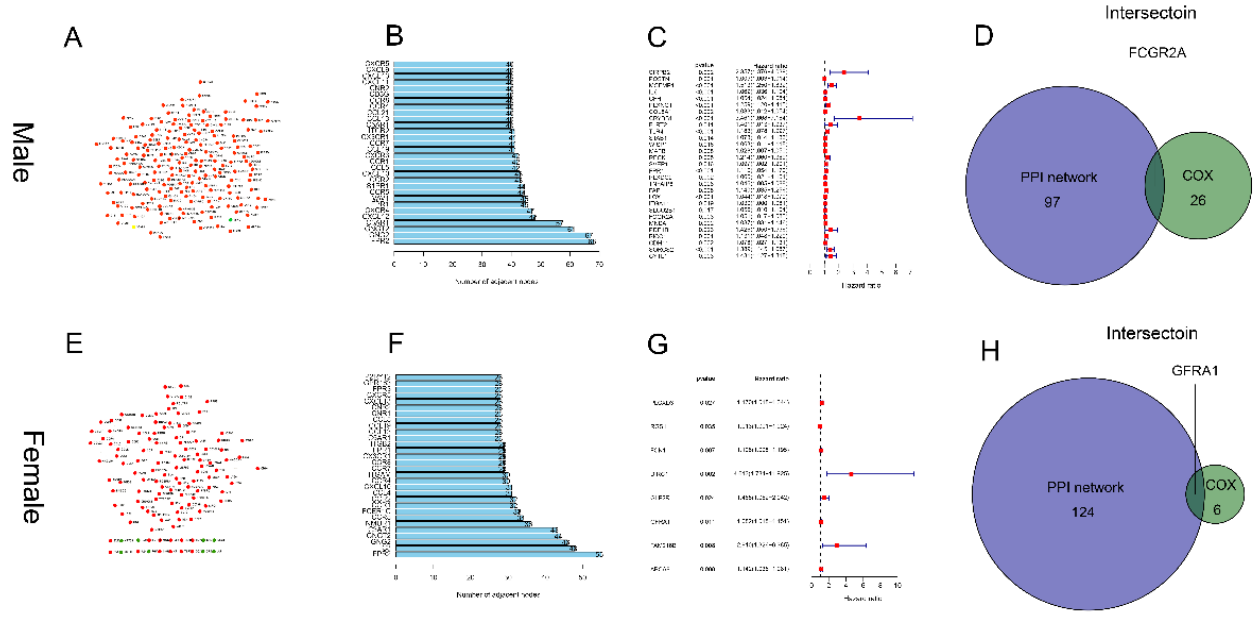

Figure 6. Protein-protein interaction network and univariate COX analysis in female and male GC patients. An interaction network constructed with the nodes with an interaction confidence value >0.9. in female (A) and male (E). The top 30 genes ordered by the number of nodes in female (B) and male (F). Univariate COX regression analysis with 811 DEGs in females (C) and 513 DEGs (G) in males, listing the top significant factors with $P < 0.005$. Venn plot showing the common factors shared by the leading 97 and 125 nodes in PPI and the top significant factors in univariate COX in female (D) and male (H), respectively

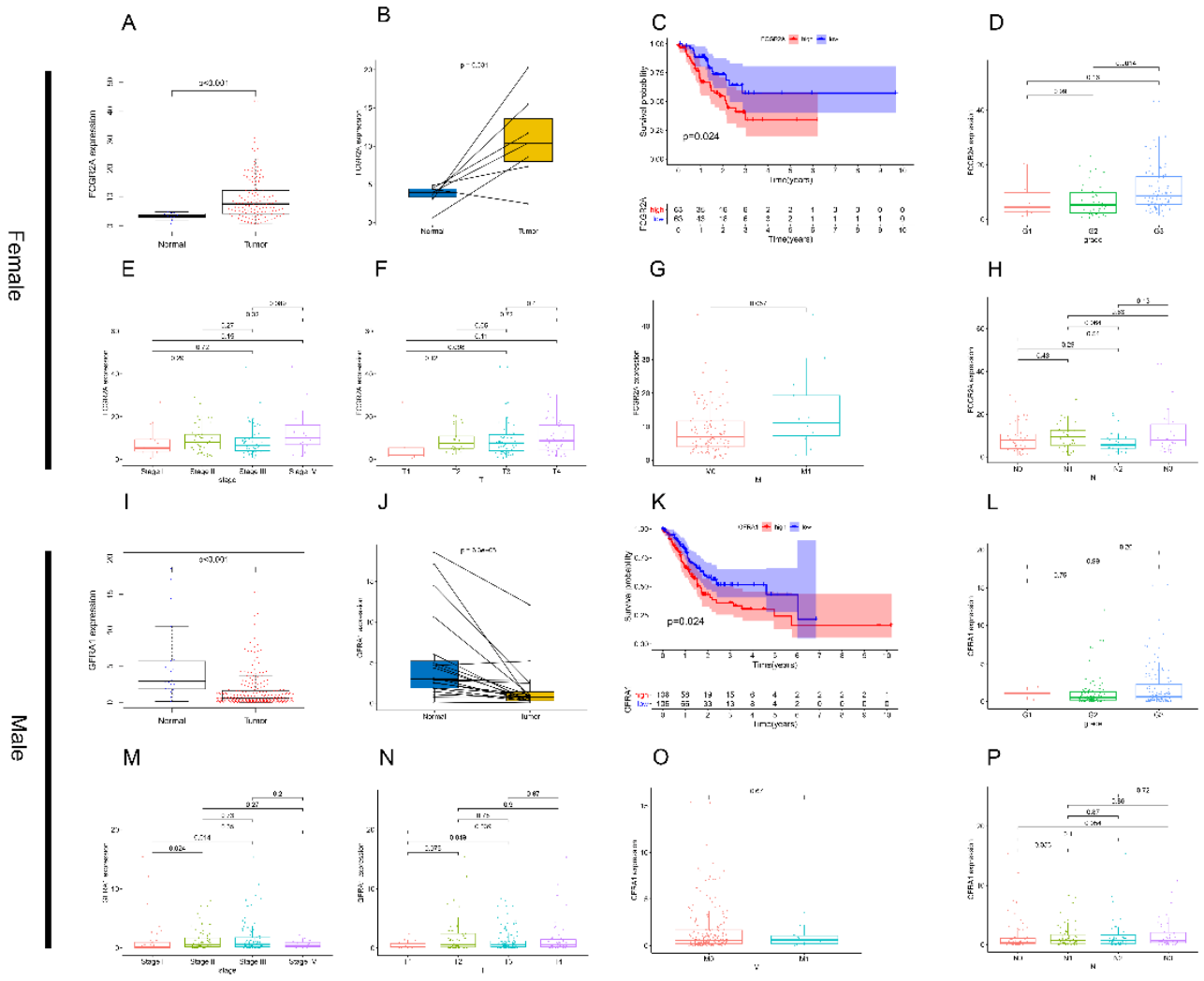

Figure 7. The differentiated expression of FCGR2A and GFRA1 in samples and correlation with survival and clinicopathological staging characteristics of female and male GC patients, respectively. Differentiated expression of FCGR2A (A) and GFRA1(I) in the normal and tumor samples. Paired differentiation analysis for expression of FCGR2A (B) and GFRA1(J) in the normal and tumor sample deriving from the same patient. Survival analysis for GC patients with different FCGR2A (C) and GFRA1 (K) expression. Patients were labeled with high expression or low expression depending on the comparison with the median expression level. The correlation of FCGR2A (D–H) and GFRA1 (L–P) expression with clinicopathological staging characteristics. The Wilcoxon rank sum or Kruskal-Wallis rank sum test served as the statistical significance test.

of FCGR2A in TME had a positive correlation with the prognosis of GC female patients, while the GFRA1 in TME had a negative correlation with the prognosis of GC male patients.

2.6. GSEA analysis of FCGR2A and GFRA1

GSEA was carried out to analyze the high- and low-low-expression groups compared with the median level of FCGR2A and GFRA1 expression, respectively. The genes in the FCGR2A high expression group were mainly enriched in cell adhesion and chemokine signaling pathway (**Figure 8A**), while in the FCGR2A low expression group, the genes were mainly enriched in metabolic pathways (**Figure 8B**). The genes in the GFRA1 high-expression pathway were mainly enriched in the calcium signaling pathway and cell adhesion pathway (**Figure 8C**). As to the GFRA1 low-expression group, the genes were enriched in the cell cycle and DNA replication pathway (**Figure 8D**). These results indicated that FCGR2A and GFRA1 might be potential indicators for the status of TME in females and males, respectively.

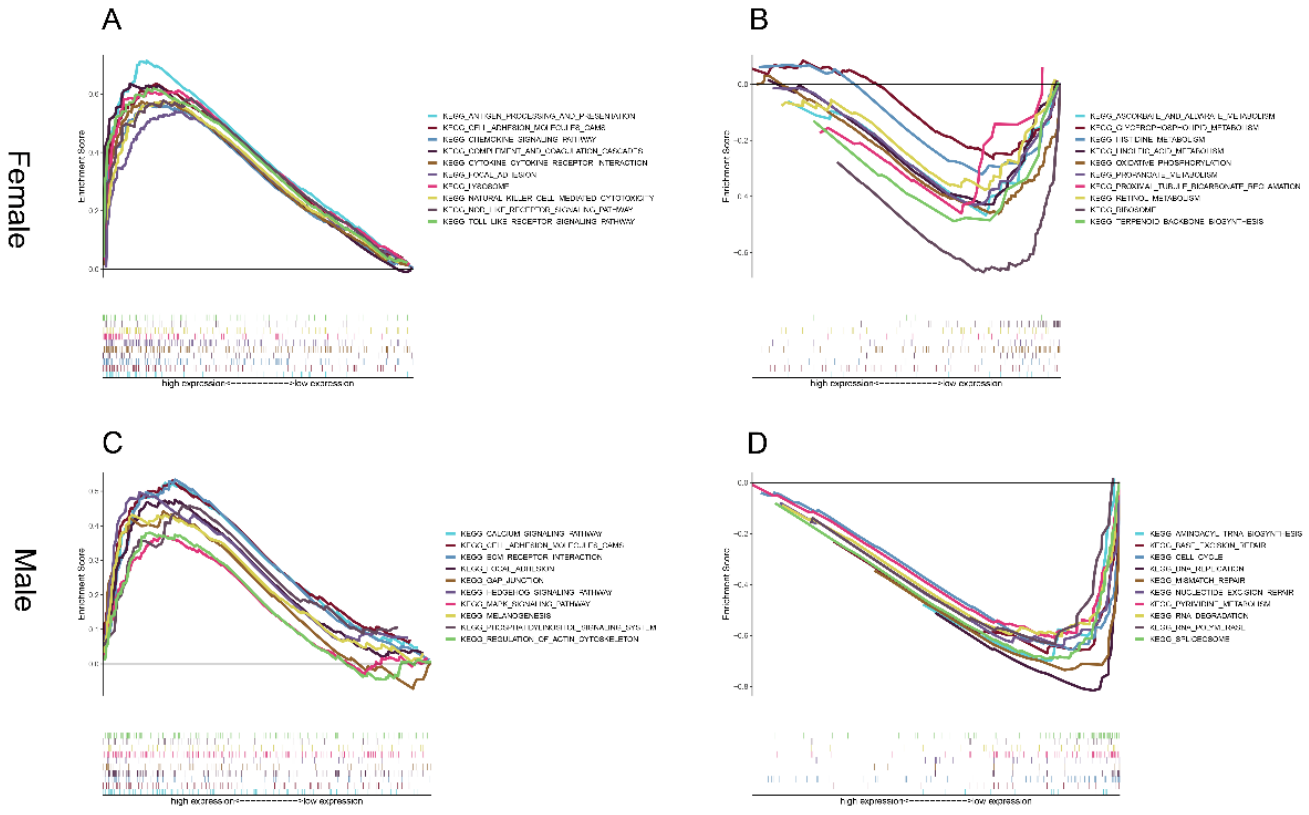

Figure 8. GSEA for samples with high expression and low expression of FCGR2A and GFRA1. The enriched gene sets in the HALLMARK collection by the high (A) and low (B) FCGR2A expression sample. The enriched gene sets in the HALLMARK collection by the high (C) and low (D) GFRA1 expression sample. Each line represents one particular gene set with a unique color, and up-regulated genes are located on the left, approaching the origin of the coordinates; by contrast, the down-regulated genes lie on the right of the x-axis. Only gene sets with NOM $P < 0.05$ and FDR $q < 0.06$ were considered significant. Only several leading gene sets were displayed in the plot

2.7. Correlation of FCGR2A and GFRA1 with the proportion of TICs

In order to further determine the correlation between FCGR2A expression and immune environment, the rate of tumor-infiltrating immune cell subsets was analyzed through the CIBERSORT algorithm. 22 kinds of immune cells in female samples and 21 kinds of immune cells in male samples were obtained (**Figure 9A** and **B**). The correlation between TICs in female and male samples was shown in **Figure 9C** and **D**. Then, the difference and correlation analysis were conducted, the results of which showed that four kinds of TICs were correlated with the expression of FGCR2A. Among them, memory B cells, T cell regulatory, and activated dendritic cells were negatively correlated with FCGR2A expression, whereas only macrophage M2 were positively correlated with FCGR2A expression (**Figure 10**). Meanwhile, 10 kinds of TICs were correlated with the expression of GFRA1 (**Figure 11**). Among them, naïve B cells, memory B cells, plasma cells, CD4 memory T cells, regulatory T cells (Tregs), monocytes, and mast cells were positively correlated with GFRA1 expression. Four kinds of TICs were negatively correlated with GFRA1 expression, including CD4 memory T cells, follicular helper T cells, macrophages M0, and macrophages M1. These results further proved that FCGR2A and GFRA1 affected the immune activity of female and male TME, respectively.

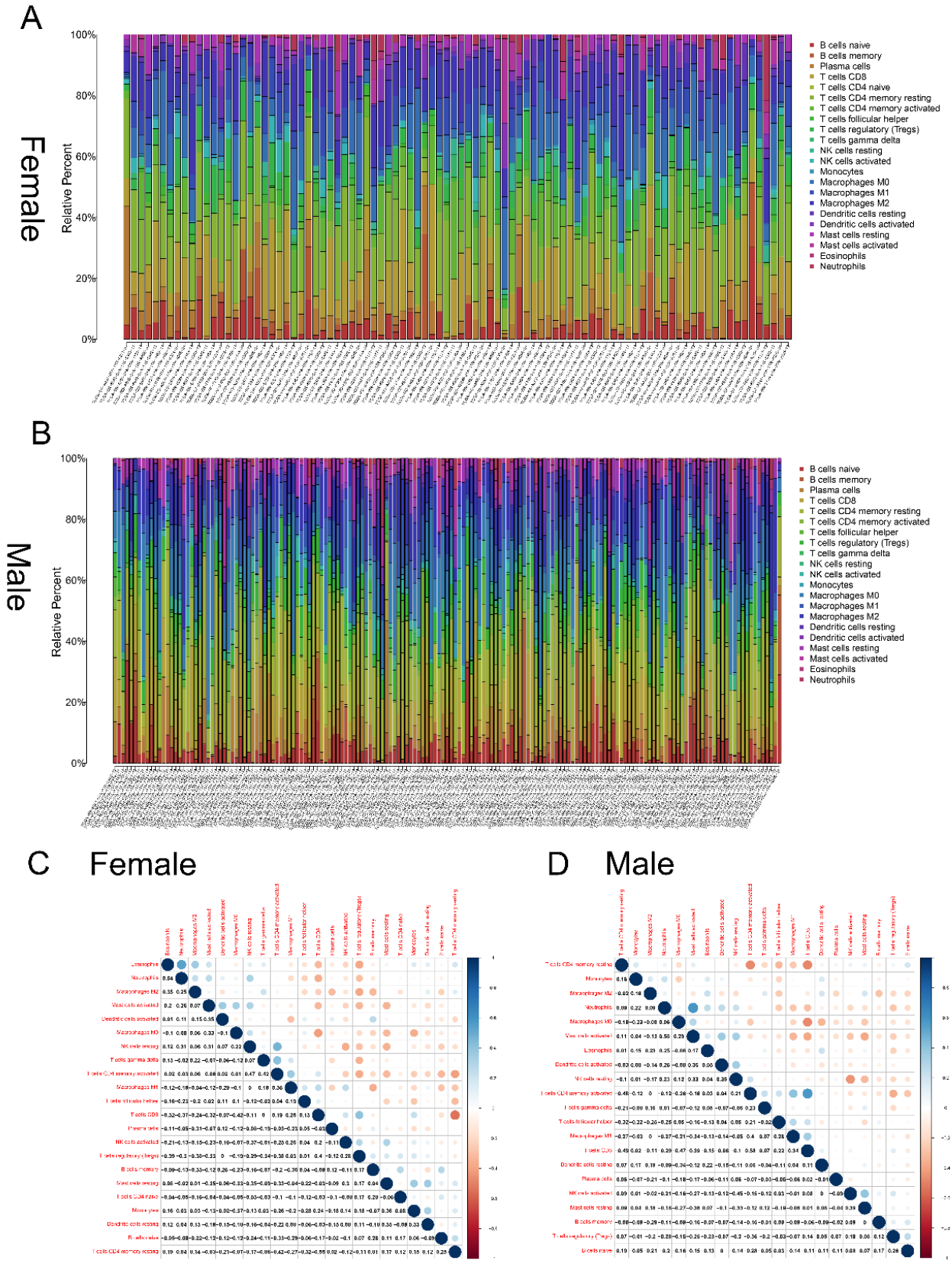

Figure 9. TIC profile in tumor samples and correlation analysis. Barplot showing the proportion of 22 kinds of TICs in female (A) and 21 kinds of TICs in male (B) GC samples. Column names of the plot were sample ID. Heatmap showing the correlation between TICs and numeric in each tiny box, indicating the *P* value of correlation between two kinds of cells in female (C) and male (D) GC patients. The shade of each tiny color box represented the corresponding correlation value between two cells, and the Pearson coefficient was used for the significance test

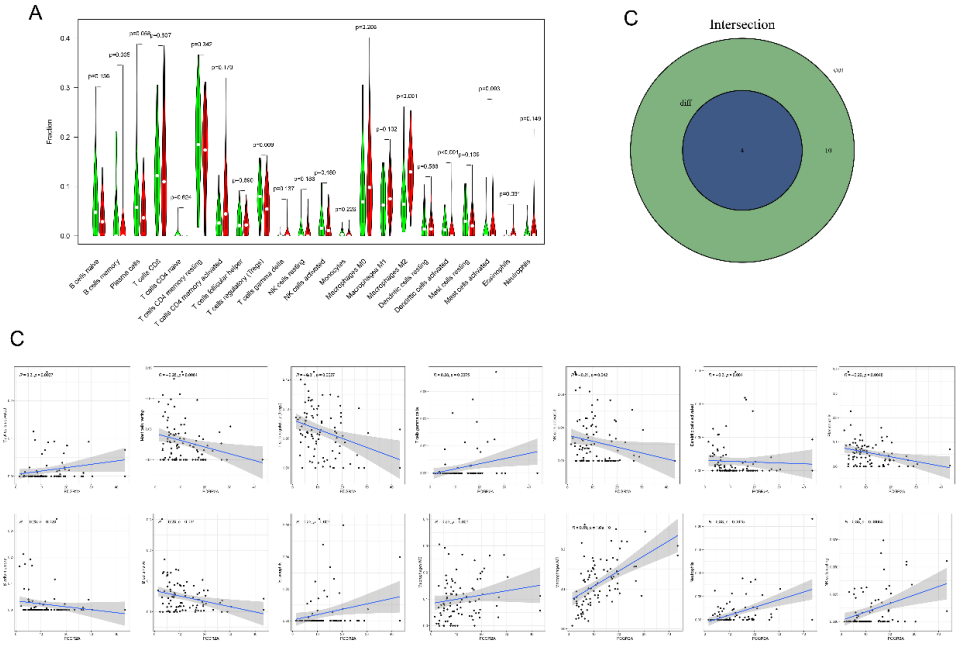

Figure 10. Correlation of TICs proportion with FCGR2A expression in female GC patients. (A) A violin plot showed the ratio differentiation of 22 kinds of immune cells between GC samples with low or high FCGR2A expression relative to the median of FCGR2A expression level, and the Wilcoxon rank sum was used for the significance test. (B) The scatter plot showed the correlation of 14 kinds of TICs proportion with the FCGR2A expression ($P < 0.05$). The blue line in each plot was a fitted linear model indicating the proportion tropism of the immune cell along with FCGR2A expression, and the Pearson coefficient was used for the correlation test. (C) Venn plot displayed four kinds of TICs correlated with FCGR2A expression, codetermined by difference and correlation tests displayed in violin and scatter plots, respectively

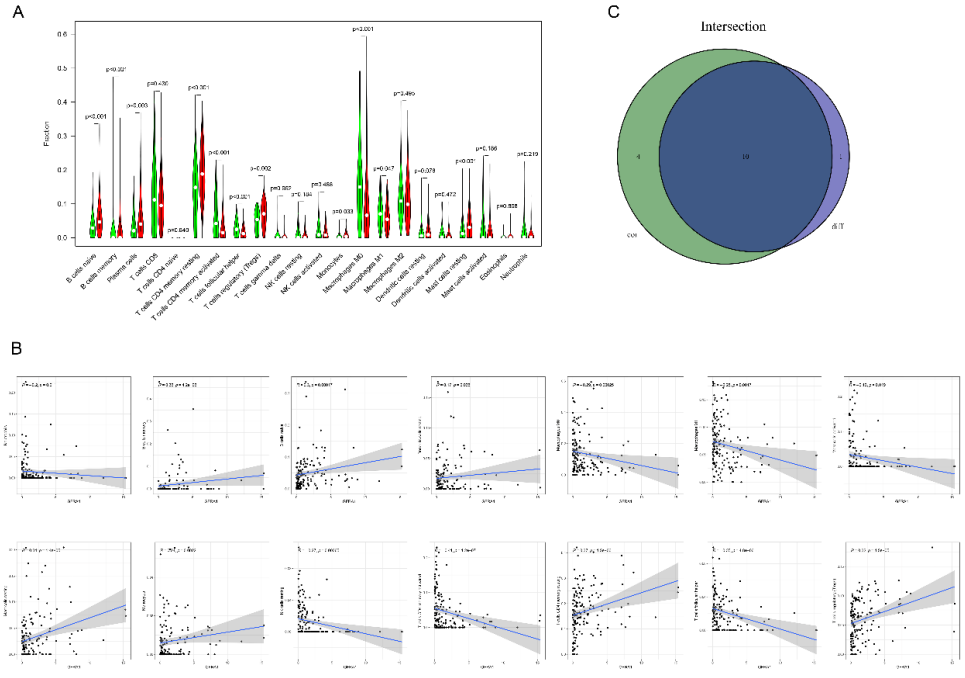

Figure 11. Correlation of TICs proportion with GFRA1 expression in male GC patients. (A) A violin plot showed the ratio differentiation of 21 kinds of immune cells between GC samples with low or high GFRA1 expression relative to the median of GFRA1 expression level, and the Wilcoxon rank sum was used for the significance test. (B) The scatter plot showed the correlation of 14 kinds of TICs proportion with the GFRA1 expression ($P < 0.05$). The blue line in each plot was a fitted linear model indicating the proportion tropism of the immune cell along with GFRA1 expression, and the Pearson coefficient was used for the correlation test. (C) A Venn plot displayed ten kinds of TICs correlated with GFRA1 expression, codetermined by difference and correlation tests displayed in violin and scatter plots, respectively

3. Discussion

In this data mining study, the authors aimed to determine TME-related genes that play critical roles in survival as well as clinicopathological staging characteristics in GC patients from the TCGA database. The important role of TME had long been studied. Chunwei Peng et al. gathered data of 494 GC patients for TME analysis, the results of which demonstrated that the tumor-stromal ratio could be easily implemented in routine pathology diagnostics [16]. Xiaolong Wu reported that GC patients with a high level of T cell inflammation were more likely to benefit from adjuvant chemotherapy [17]. In contrast, it was reported that stromal-relevant genes were identified as adverse prognostic factors in GC [18]. Interestingly, our study found that a high StromalScore was positively correlated with the survival rate of both female and male patients, while a high ImmuneScore was negatively correlated with the survival rate in female samples and positively correlated with male samples. Further analysis screened FCGR2A and GFRA1 as significant factors in immune activation in female and male GC patients, respectively. More importantly, they were identified as indicators for the status of TME through a series of bioinformatics analyses.

FCGR2A encodes one member of a family of immunoglobulin Fc receptor genes found on the surface of phagocytosis cells, including macrophages and neutrophils [19]. It had two polymorphic alleles at the amino acid position, which were associated with increased risk of GC patients [20]. Clinical studies reported that FCGR2A Polymorphisms were associated with clinical outcomes of tumors, including colorectal cancer and neuroblastoma, and Renal Cell Carcinoma [21–24]. In contrast, either FCGR2A or FCGR3A polymorphisms affect the clinical outcome of follicular lymphoma patients [25]. Besides, it was reported that FCGR2A variant rs1801274 was evidently correlated with gastric cancer risk [26]. Consistently, the analysis found that FCGR2A was highly expressed in GC female patients compared to normal people and was negatively associated with the survival rate. However, only one kind of TICs was positively correlated with the expression of FCGR2A, which is macrophages M2. As the main tumor-infiltrating leukocytes, macrophages play vital roles in cancer-related inflammation [27]. Depending on the polarization status, tumor-associated macrophages (TAMs) can either promote antitumor immune responses (M2) or contribute to tumor progression (M1) [28]. The ratio of M2/M1 phenotype is relevant in tumor initiation, progression, and dissemination [29]. FCGR2A phosphorylation is important for activation of macrophage phagocytosis function, as well as mediating production of proinflammatory cytokines [30–31]. Therefore, highly expressed FCGR2A in macrophages promotes M2-M1 switch by inducing proinflammatory cytokines production, which has a bad influence on survival rate.

As the receptor of glial cell-derived neurotrophic factor (GDNF), GFRA1 is involved in the regulation of proliferation, differentiation, and migration of neuronal cells [32]. Also, it is reported that GFRA1 is upregulated in many cancers and participates in cancer cell progression, metastasis, and autophagy by activating the classic RET-RAS-ERK, RET-RAS-PI3K-AKT, and SRC-AMPK signaling pathways [33–36]. In contrast to the previous studies, our analysis showed that the expression of GFRA1 was significantly decreased in male GC patients and positively correlated with the survival rate. The underlying mechanism still needs to be further explored. Based on TICs analysis, 10 kinds of cells were correlated with GFRA1 expression, mainly including B cells and T cells. The study also implied that low expression of GFRA1 facilitates the cell cycle and DNA replication pathway in male GC patients based on GSEA analysis.

The present study provided new insight into susceptibility factors of immunoregulatory gene variants in the carcinogenesis of GC in both genders. The authors determined TME-related genes in both female and male GC samples through the functional enrichment analysis in the TCGA database. FCGR2A might be a negative indicator for the survival of female patients, while GFRA1 serves as a positive indicator for the survival of male patients. Therefore, further investigation should be conducted to clarify the accurate function and potential role of FCGR2A and GFRA1 in GC patients.

Funding

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Disclosure statement

The authors declare no conflict of interest.

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