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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Clinical and Translational Research

Identification of survival-associated biomarkers based on three datasets by bioinformatics analysis in gastric cancer

Long-Kuan Yin, Hua-Yan Yuan, Jian-Jun Liu, Xiu-Lian Xu, Wei Wang, Xiang-Yu Bai, Pan Wang

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Gastric cancer (GC) is one of the most common malignant tumors with poor prognosis in terms of advanced stage. However, the survival-associated biomarkers for GC remains unclear.

AIM

To investigate the potential biomarkers of the prognosis of patients with GC, so as to provide new methods and strategies for the treatment of GC.

METHODS

RNA sequencing data from The Cancer Genome Atlas (TCGA) database of STAD tumors, and microarray data from Gene Expression Omnibus (GEO) database (GSE19826, GSE79973 and GSE29998) were obtained. The differentially expressed genes (DEGs) between GC patients and health people were picked out using R software (x64 4.1.3). The intersections were underwent between the above obtained co-expression of differential genes (co-DEGs) and the DEGs of GC from Gene Expression Profiling Interactive Analysis database, and Gene Ontology (GO) analysis, Kyoto Encyclopedia of Gene and Genome (KEGG) pathway analysis, Gene Set Enrichment Analysis (GSEA), Protein-protein Interaction (PPI) analysis and Kaplan-Meier Plotter survival analysis were performed on these DEGs. Using Immunohistochemistry (IHC) database of Human Protein Atlas (HPA), we verified the candidate Hub genes.

RESULTS

With DEGs analysis, there were 334 co-DEGs, including 133 up-regulated genes and 201 down-regulated genes. GO enrichment analysis showed that the co-DEGs

were involved in biological process, cell composition and molecular function pathways. KEGG enrichment analysis suggested the co-DEGs pathways were mainly enriched in ECM-receptor interaction, protein digestion and absorption pathways, *etc.* GSEA pathway analysis showed that co-DEGs mainly concentrated in cell cycle progression, mitotic cell cycle and cell cycle pathways, *etc.* PPI analysis showed 84 nodes and 654 edges for the co-DEGs. The survival analysis illustrated 11 Hub genes with notable significance for prognosis of patients were screened. Furtherly, using IHC database of HPA, we confirmed the above candidate Hub genes, and 10 Hub genes that associated with prognosis of GC were identified, namely BGN, CEP55, COL1A2, COL4A1, FZD2, MAOA, PDGFRB, SPARC, TIMP1 and VCAN.

CONCLUSION

The 10 Hub genes may be the potential biomarkers for predicting the prognosis of GC, which can provide new strategies and methods for the diagnosis and treatment of GC.

Key Words: Gastric cancer; Survival-associated biomarkers; Bioinformatics analysis; Hub genes

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Core Tip: Gastric cancer (GC) is one of the most common leading cause of death worldwide. The cases with advanced GC usually have poor prognosis. To date, the prognostic biomarkers of GC remain unclear. In this article, we investigated the co-expression of differential genes (co-DEGs) between GC tissues and normal tissues based on the data from Gene Expression Omnibus, Gene Expression Profiling Interactive Analysis and The Cancer Genome Atlas. By using bioinformatics analysis, the signal pathways of co-DEGs involvement in GC were identified, and 10 Hub biomarkers for the survival of GC were screened.

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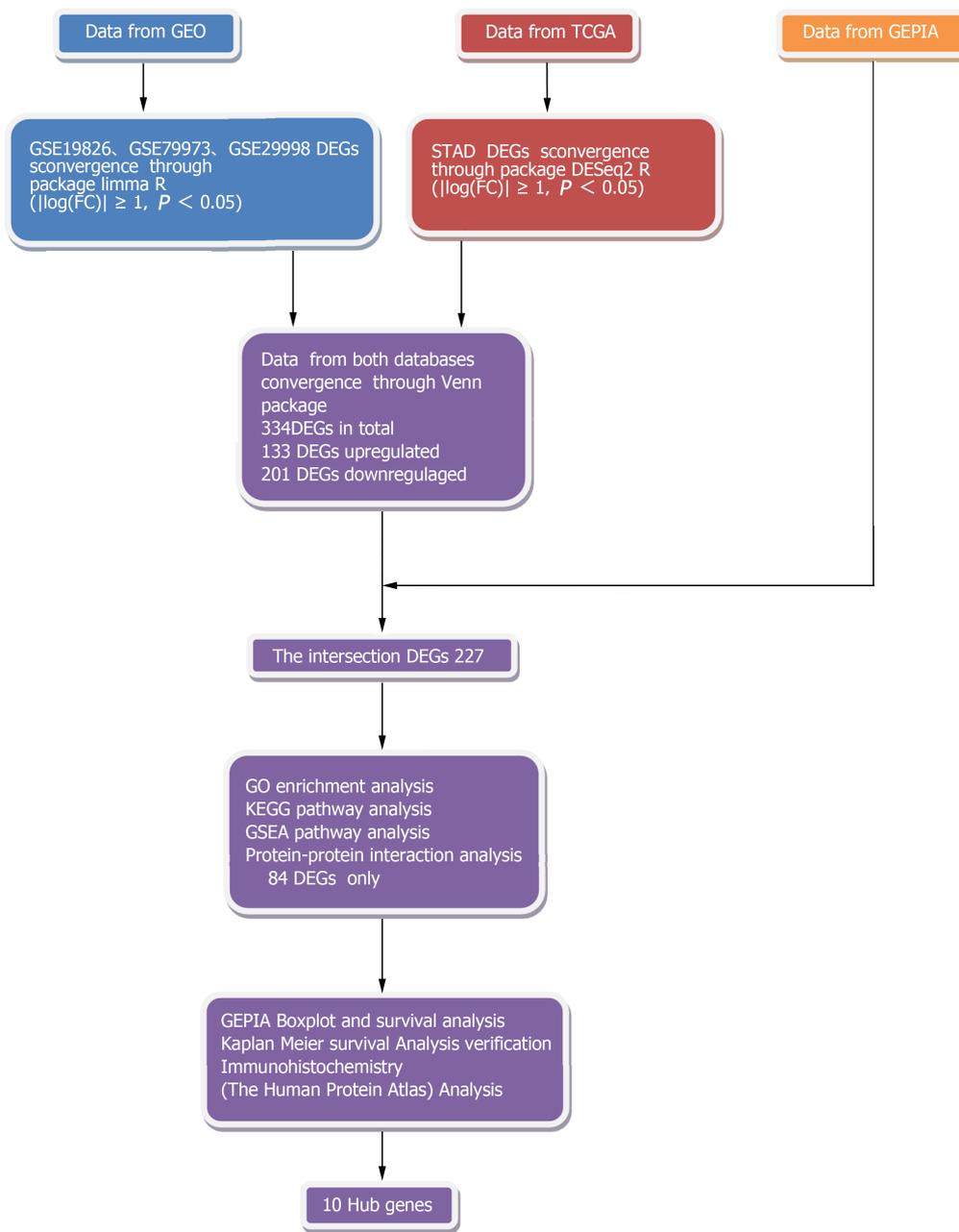
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INTRODUCTION

Gastric cancer (GC) is one of the most common malignant tumors with high morbidity and mortality[1-3]. It is known that the occurrence of GC is the result of multiple factors. The genetic factors, dietary habits and *Helicobacter pylori* infection play a very important role in the occurrence and development of GC[4-6]. The most common screening methods for GC are gastroscopy and pathological examination, which can effectively improve the detection rate of early GC[7,8]. However, those patients, who with advanced GC, have poor treatment effect and poor prognosis[9].

The development of GC is a complex pathological process involving changes of various genes and pathways[10]. Previous studies have shown that some changes were happened between the GC tissues and normal tissues, especially the expression of the genes[11]. The biomarkers measured in different stages of GC are helpful as indicators of early diagnosis, routine screening, postoperative monitoring or pharmacological response to a therapeutic intervention[12]. Therefore, exploring the survival related biomarkers of GC may provide more approaches for the treatment of GC, improving the overall survival time of the patients. To date, the survival related biomarkers for GC remains unclear. Currently, the development of high-throughput sequencing technology has generated a large number of functional genomic data[13], making it possible to reveal the survival related biomarkers of GC by analyzing the differential gene expression data between the GC tissues and the normal tissues. In recent years, bioinformatics is widely used to analyze the genomic and proteomic data of tumors, and to reveal the function of gene products at the molecular level for cancer [14].

In this study, bioinformatics strategy was used to obtain data from Gene Expression Omnibus (GEO), Gene Expression Profiling Interactive Analysis (GEPIA) and The Cancer Genome Atlas (TCGA). In briefly, the software of Gene Expression Profiling Interactive Analysis (GEPIA), R software (x64.1.3), STRING, Kaplan-Meier plotter and Human Protein Atlas (HPA), were performed to analyze and integrate the mRNA expression data of GC tissues and adjacent tissues or normal gastric tissues to explore the molecular functions (MF) of differential genes and signal pathways of GC. Finally, we successfully screened the genes of 10 key biomarkers for the survival of GC. The present study analyzed the high-throughput data of multi database and multi-chip datasets, which could more accurately reveal the potential prognosis biomarkers of GC. The detailed analysis workflow is as shown in [Figure 1](#).



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Figure 1 Flowchart for research into bioinformatics data from Gene Expression Omnibus, The Cancer Genome Atlas and Gene Expression Profiling Interactive Analysis. GEO: Gene Expression Omnibus; TCGA: The Cancer Genome Atlas; GEPIA: Gene Expression Profiling Interactive Analysis; DEGs: Differentially expressed genes; GO: Gene Ontology; KEEG: Kyoto Encyclopedia of Gene and Genome; GSEA: Gene Set Enrichment Analysis.

MATERIALS AND METHODS

Data sets download

GDC TCGA Stomach Cancer (STAD) related datasets were downloaded from UCSC Xena (<https://xenabrowser.net/>) database[15], including 373 GC tissue samples and 32 normal gastric tissue samples. R software (x64 4.1.3) was used to download and analyze datasets of gene expression profiles from GEO database (GSE19826, GSE79973 and GSE29998) with Tidyverse and query packages, including 72 GC tissue samples and 74 normal gastric tissue samples.

Differentially expressed genes screening

Based on TCGA data sets, the Tidyverse and DESeq2R packages of software (x64 4.1.3) were used for differential gene expression analysis. RNA sequencing data from normal and tumor tissue samples were extracted for analysis. Volcano map was drawn to show the folding changes and *P* values of differentially expressed genes (DEGs) ($|\text{LogFC}| \geq 1$, adjusted *P* value < 0.05). R software dealt with GEO data sets (GSE19826, GSE79973 and GSE29998, respectively), then the ID was converted, and the adjust *P* value < 0.05 and $|\text{LogFC}| \geq 1$ were set as the cut off criterion. Subsequently, a Venn

diagram method was used to screen out co-expression of differential genes (co-DEGs). Of these co-DEGs, only protein-coding genes were further analyzed.

Functional enrichment analysis of co-DEGs

GEPIA[16] is a newly developed interactive web server for analyzing the RNA sequencing expression data from the TCGA and the GTEx projects. The GEPIA data sets was analyzed using the stat packet of R software to predict the potential functions of the co-DEGs. The functional analyses of Gene Ontology (GO) analysis, Kyoto Encyclopedia of Gene and Genome (KEGG) pathway analysis and Gene Set Enrichment Analysis (GSEA) pathway analysis were performed on the co-DEGs by using R software. $P < 0.05$ was considered statistically significant.

Protein-protein interaction network analysis of co-DEGs

Protein-protein interaction (PPI) Analysis of the identified DEGs was constructed by STRING 11.5. The STRING Database [17] (<https://cn.string-db.org/>) is a database of known and predicted PPIs. Using STRING 11.5, the interaction network between the above co-DEGs and the related genes was presented by setting the maximum confidence at 0.9. Furthermore, and Cytoscape_v3.9.1 software was carried out for analyzing and mapping.

Survival analysis of co-DEGs

Using Boxplot functions of GEPIA database, we set $|\text{Log2FC}|$ cutoff ≥ 1 , P -value cutoff < 0.05 as the cut off criterion. The tumor-related data from STAD database were selected to match the normal gastric tissue data of TCGA and GTEx, the genes with significant differences were screened out, and box-plot was performed for the screened Hub genes.

Verifying the Hub genes again

Kaplan-Meier plotter[18] was able to assess the association between 30 K gene (mRNA, microRNA, protein) expression and survival in 25 K + samples from 21 tumor types, including breast cancer, ovarian cancer, lung cancer, GC, *etc.* We used Kaplan-Meier plotter online tool to perform visualization analysis of GC related database again, and verified the above results.

Immunohistochemical analysis to determine the final Hub genes

Due to the highly specific characteristics of antigen and antibody binding, immunohistochemistry (IHC) can reveal the relative distribution and abundance of proteins. Then, through HPA[19] (<https://www.proteinatlas.org>), currently the largest and most comprehensive Human tissue Protein spatial database, we can more intuitively observe the difference of Hub gene expression between normal stomach tissue and GC tissue. χ^2 test was used to compare the difference between the two groups, and $P < 0.05$ is statistically significant.

RESULTS

Identifying DEGs

The TCGA STAD counts dataset was processed by using Tidyverse and DESeq2 packages of R software (x64 4.1.3), and DEGs was screened ($|\text{Log2FC}|$ cutoff ≥ 1 , P -value cutoff < 0.05 as the cut off criterion). Our results showed that there were 2133 up-regulated genes and 2349 down-regulated genes. R software (x64 4.1.3) was used to process data sets (GSE19826, GSE79973 and GSE29998), and then ID conversion was performed. Limma package was used to process the above three data sets respectively, and the screening criteria were $|\log\text{FC}| \geq 1$ and P -value < 0.05 . There were 2202 up-regulated genes and 2700 down-regulated genes in GSE19826, 665 up-regulated genes and 1507 down-regulated genes in GSE79973, 4346 up-regulated genes and 3002 down-regulated genes in GSE29998, respectively. Heat maps were drawn by Pheatmap package of R software (x64 4.1.3) (Figures 2A, C and E), and volcano maps were drawn by ggplot2 package of R software (x64 4.1.3) (Figures 2B, D and F).

The TCGA STAD FPKM data set was processed by tidyverse and Pheatmap packages of R software (x64 4.1.3) combined with DEGs, and the heatmap was drawn (Figure 2G). Tidyverse, GGplot2 packages and DEGs were used to draw the volcano map (Figure 2H).

Venn Diagram package of R software (x64 4.1.3) was used to make Venn Diagram of DEGs in GEO and TCGA datasets. A total of 334 DEGs were obtained, including 133 up-regulated genes and 201 down-regulated genes (Figures 3A and B).

GO functional enrichment analysis of co-DEGs

GO functional enrichment analysis showed that the GO annotation of co-DEGs was divided into three parts: Biological process (BP), cell composition (CC) and MF, and a diagram of which was shown in Figures 4A-E and Table 1 (list of top 5 GO pathways). Arraying the ascending order of P value ($P < 0.05$), our results revealed that the GO pathways of DEGs were enriched as the follows: Collagen fibrillary tissue, cell division, extracellular matrix organization, skeletal system development and copper ion detoxification, *etc.*, were enriched in BP; extracellular space, extracellular matrix, extracellular region, collagen trimer and centromere, *etc.*, were enriched in CC; extracellular matrix structural components, extracellular matrix structural components that give tensile strength, platelet-derived growth factor binding, zinc ion binding, creatine kinase activity and so on, were enriched in MF (details in Supplementary Tables 1 and 2).

Table 1 Gene ontology enrichment pathways of co-expression of differential genes (top 5)

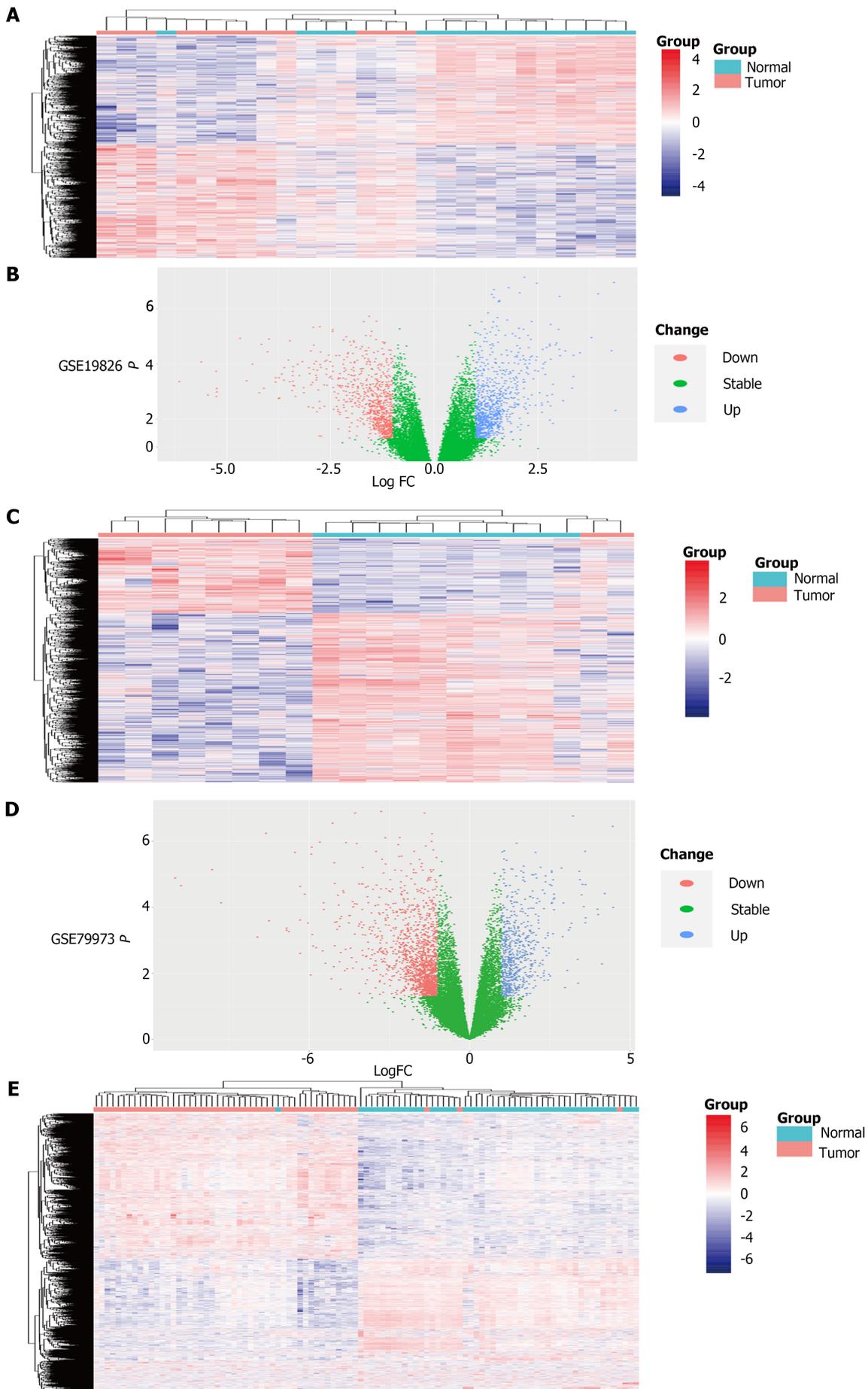
Category	Term	Count in gene set	P value	Genes
GOTERM_BP_DIRECT	GO:0030199: Collagen fibril organization	10	2.08E-08	COMP, COL3A1, ADAMTS2, FOXC1, COL1A2, COL5A1, COL12A1, COL5A2, SERPINH1, P3H4
	GO:0051301: Cell division	20	7.76E-08	CENPW, UBE2C, RCC2, CDCA7, KIF14, NCAPG, NDC80, CDC25B, CDC20, CCNB2, TPX2, CCNB1, PRCL, NUF2, CDK1, NEK2, KIF2C, BUB1, MAD2L1, SPC25
	GO:0030198: Extracellular matrix organization	13	2.67E-07	OLFML2B, MMP7, MMP1, TNFRSF11B, COL3A1, ADAMTS2, COL1A2, COL5A1, COL4A1, COL5A2, COL4A5, COL8A1, COL10A1
	GO:0001501: Skeletal system development	12	3.61E-07	TEAD4, COMP, COL3A1, VCAN, PKDCC, COL1A2, CDH11, COL5A2, COL10A1, TNFRSF11B, HOXA13, HOXC10
	GO:0010273: Detoxification of copper ion	6	7.19E-07	MT2A, MT1M, MT1G, MT1H, MT1X, MT1E
GOTERM_CC_DIRECT	GO:0005615: Extracellular space	61	6.57E-14	PIGR, SPARC, OLFML2B, CXCL8, COL12A1, CXCL17, COMP, VMO1, PLAUC2, FAM3B, COL10A1, SOSTDC1, CPXM1, TIMP1, CPA2, CHIA, MMP7, GPX3, GKN1, BGN, GKN2, PGC, PGF, SFRP4, ALDH3A1, VCAN, COL4A1, SCGB2A1, SFRP5, ANOS1, COL4A5, COL8A1, TFF2, TFF1, CELA3B, CPB1, TNFRSF11B, LRP8, SCUBE2, SELENBP1, CST2, CHAD, SPP1, SERPINH1, CKB, APOE, WNT2, CTHRC1, LINGO1, ANGPT2, CKM, SULF1, KLK11, ATP4A, COL3A1, COL1A2, COL5A1, FAP, COL5A2, ADA
	GO:0031012: Extracellular matrix	21	1.06E-11	LINGO1, OLFML2B, MMP7, MMP1, BGN, TNFRSF11B, COMP, COL3A1, ADAMTS2, VCAN, COL1A2, COL5A1, COL4A1, COL5A2, CHAD, ANOS1, COL4A5, COL8A1, COL10A1, TIMP1, APOE
	GO:0005576: Extracellular region	57	5.21E-10	SPARC, OLFML2B, CXCL8, PSCA, COL12A1, AQP4, COMP, LIPF, ADAMTS2, PLAUC2, FAM3B, COL10A1, OLR1, TIMP1, CPA2, CHIA, MMP7, GPX3, MMP1, GKN1, MAMDC2, BGN, PGF, SFRP4, VCAN, FNDC1, COL4A1, NRG4, ANOS1, COL4A5, COL8A1, TFF1, LY6E, PKDCC, TNFRSF11B, THY1, THBS2, PLA2G7, SCUBE2, PTPRZ1, SPP1, APOE, METTL7A, WNT2, GPIHBP1, CTHRC1, ANGPT2, B3GAT1, GUCA2B, COL3A1, AKR1B10, COL1A2, COL5A1, QPCT, COL5A2, APOC1, CNTN3
	GO:0005581: Collagen trimer	12	7.15E-09	COL3A1, COL1A2, COL5A1, COL4A1, MMP1, COL12A1, COL5A2, SERPINH1, COL10A1, COL4A5, TIMP1, CTHRC1
	GO:0000776: Kinetochore	11	4.23E-06	CENPW, NUF2, HJURP, KIF2C, CENPN, NEK2, CENPA, BUB1, NDC80, MAD2L1, SPC25
GOTERM_MF_DIRECT	GO:0005201: Extracellular matrix structural constituent	14	7.23E-09	SPARC, BGN, THBS2, COMP, COL3A1, COL1A2, COL5A1, COL4A1, COL5A2, ANOS1, COL4A5, COL8A1, COL10A1, CTHRC1
	GO:0030020: Extracellular matrix structural constituent conferring tensile strength	9	1.87E-08	COL3A1, COL1A2, COL5A1, COL4A1, COL12A1, COL5A2, COL10A1, COL4A5, COL8A1
	GO:0048407: Platelet-derived growth factor binding	5	5.29E-06	PDGFRB, COL3A1, COL1A2, COL5A1, COL4A1
	GO:0008270: Zinc ion binding	23	4.29E-04	CPA2, TRIM50, CPB1, MMP7, ADH1C, MMP1, MT1M, ESRRB, MT1X, ESRRG, MYRIP, ADH7, ADAMTS2, MT2A, CA2, QPCT, MT1G, ZNF385B, CPXM1, MT1H, TIMP1, ADA, MT1E
	GO:0004111: Creatine kinase activity	3	0.001918971	CKMT2, CKM, CKB

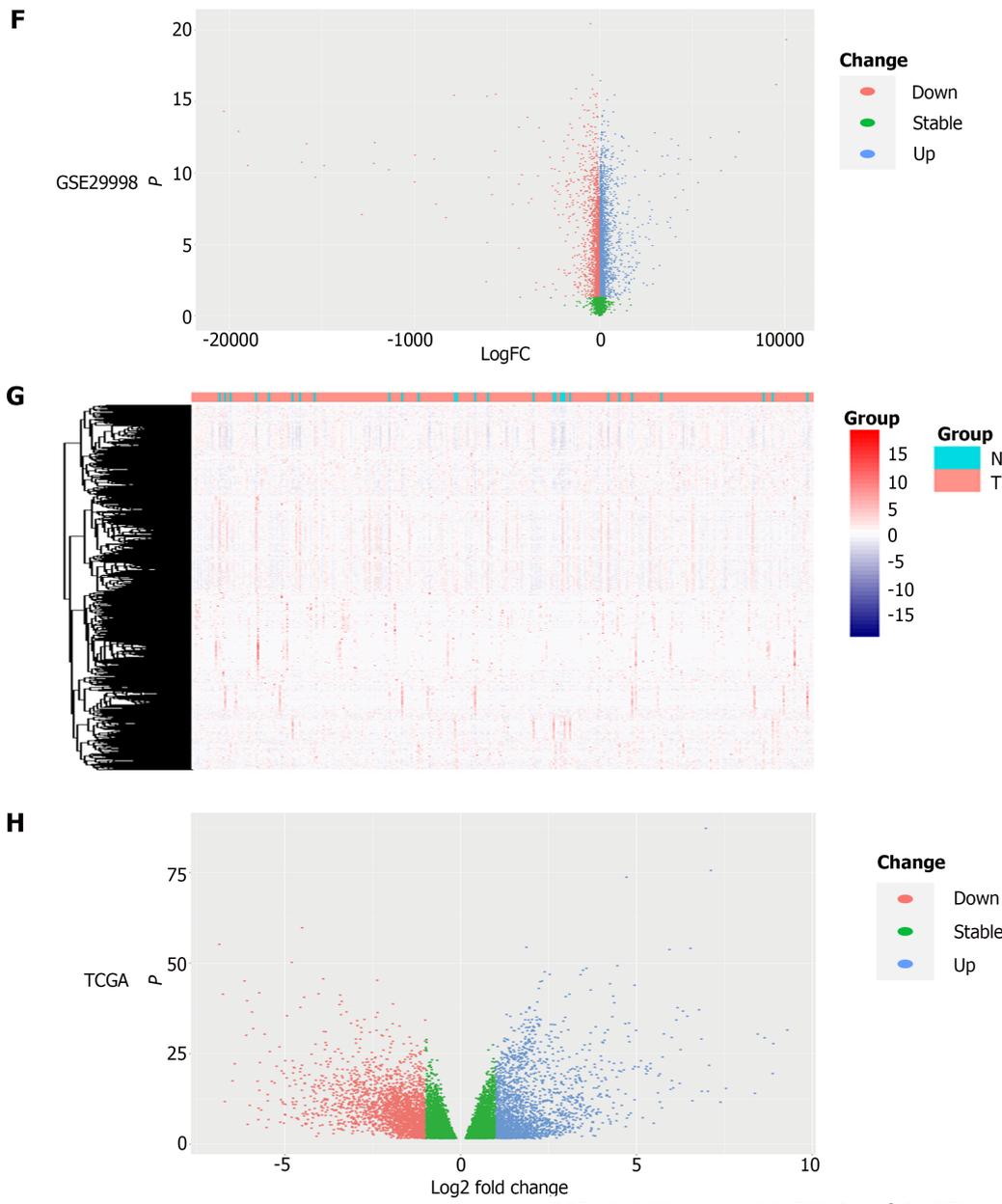
KEGG functional enrichment analysis of co-DEGs

Using KEGG functional enrichment analysis, the results of pathways were arranged in ascending order of P value, and the $P < 0.05$ is the cutoff value (as shown in Figures 4F-J). As shown in Table 2 (list of top 5 KEGG pathways), our findings suggested that co-DEGs pathways were mainly enriched in ECM-receptor interaction, protein digestion and absorption, gastric acid secretion, mineral absorption and cell cycle pathways, *etc.* (detailed in Supplementary Tables 1 and 2).

GSEA functional enrichment analysis of co-DEGs

The results of pathways were arranged in ascending order of P value (as shown in Figure 4k, $P < 0.05$). As shown in





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Figure 2 Identification of differentially expressed genes from The Cancer Genome Atlas and Gene Expression Omnibus Datasets. A: The heat map of GSE19826 data set, with 2202 up-regulated genes and 2700 down-regulated genes. The blue normal samples, and the red are tumor samples; B: The volcanic map of GSE19826 dataset; C: The heat map of GSE79973 dataset, with 665 up-regulated genes and 1507 down-regulated genes. The blue are normal samples, and the red are tumor samples; D: The volcanic map of GSE79973 dataset; E: The heat map of GSE29998 dataset, with 4346 up-regulated genes and 3002 down-regulated genes. The blue are normal samples, and the red are tumor samples; F: The volcanic map of GSE29998 data set; G: The heat map of The Cancer Genome Atlas (TCGA) data set, with 2133 up-regulated genes and 2349 down-regulated genes. The blue are normal samples, and the red are tumor samples; H: The volcanic map of TCGA dataset. In B, D, F and H, the red dots are down-regulated genes and the blue dots are up-regulated genes. TCGA: The Cancer Genome Atlas.

Table 3 (list of top 5 GSEA pathways), GSEA pathway analysis illustrated that co-DEGs mainly concentrated in cell cycle progression, mitotic cell cycle, cell cycle, organelle fission and mitosis pathways, *etc.* (detailed in **Supplementary Tables 1 and 2**).

PPI analysis of co-DEGs

STRING11.5 was conducted for PPI analysis on the above-mentioned differential expressed genes. The maximum confidence was set to 0.9, and the isolated genes without interaction were deleted (**Figure 5A**). Cytoscape_v3.9.1 software was used for further analyzing and mapping, showing 84 nodes and 654 edges (**Figure 5B**).

Survival analysis of Hub genes

The Boxplot tool of GEPIA database was used for analyzing the above 84 selected gene nodes, and there was significant

Table 2 Kyoto Encyclopedia of Gene and Genome enrichment pathways of co-expression of differential genes (top 5)

Category	Term	Count in gene set	P value	Genes
KEGG_pathway	hsa04974: Protein digestion and absorption	13	2.23E-08	CPA2, CELA3B, CPB1, COL12A1, COL3A1, COL1A2, SLC7A8, COL5A1, COL4A1, COL5A2, COL4A5, COL8A1, COL10A1
	hsa04512: ECM-receptor interaction	8	2.57E-04	COMP, COL1A2, COL4A1, ITGA2, CHAD, SPP1, COL4A5, THBS2
	hsa04971: Gastric acid secretion	7	7.46E-04	ATP4B, ATP4A, KCNE2, CCKBR, CA2, KCNJ15, KCNJ16
	hsa04978: Mineral absorption	6	0.001635962	MT2A, MT1M, MT1G, MT1H, MT1X, MT1E
	hsa04110: Cell cycle	8	0.00218248	CDC20, CCNB2, CCNB1, ORC1, CDK1, BUB1, CDC25B, MAD2L1

KEEG: Kyoto Encyclopedia of Gene and Genome.

Table 3 Gene Set Enrichment Analysis enrichment pathways of co-expression of differential genes (top 5)

ID	Description	Set size	P value
GO	GO_CELL_CYCLE_PROCESS	41	1.00E-10
	GO_MITOTIC_CELL_CYCLE	37	1.40E-10
	GO_CELL_CYCLE	44	1.49E-10
	GO_ORGANELLE_FISSION	24	9.65E-08
	GO_MITOTIC_NUCLEAR_DIVISION	19	1.20E-07
	GO_CELL_CYCLE_PHASE_TRANSITION	21	1.82E-07

GO: Gene Ontology.

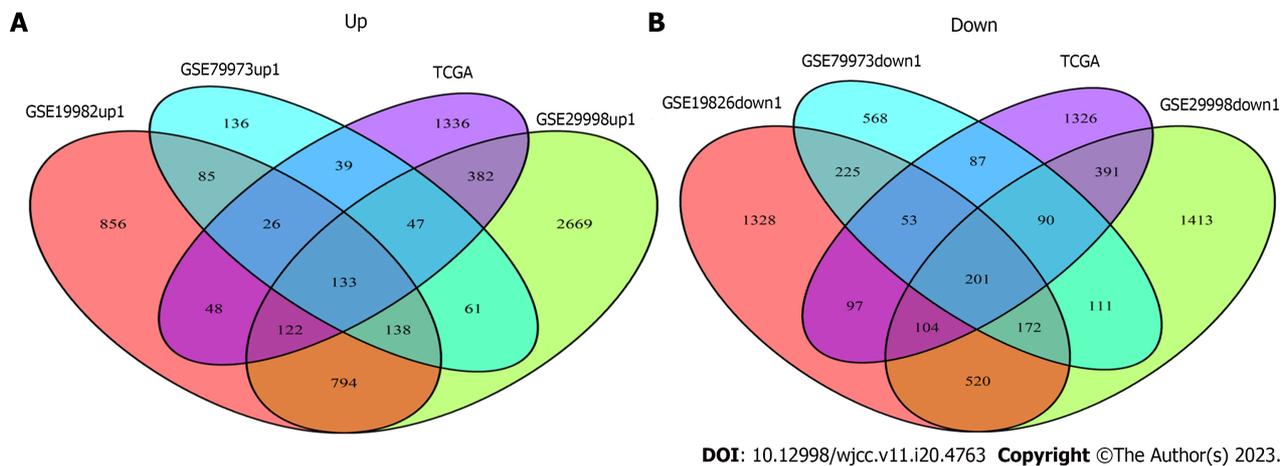
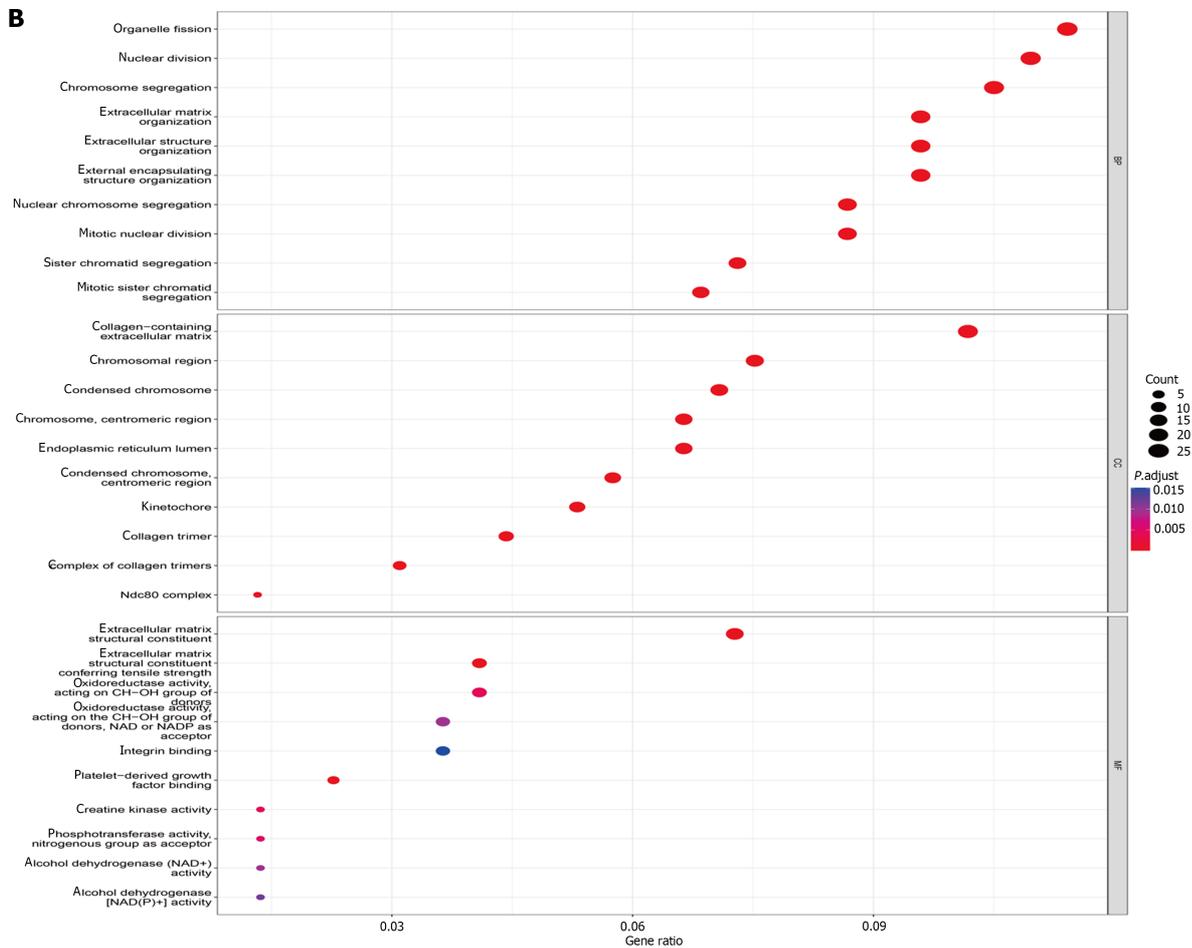
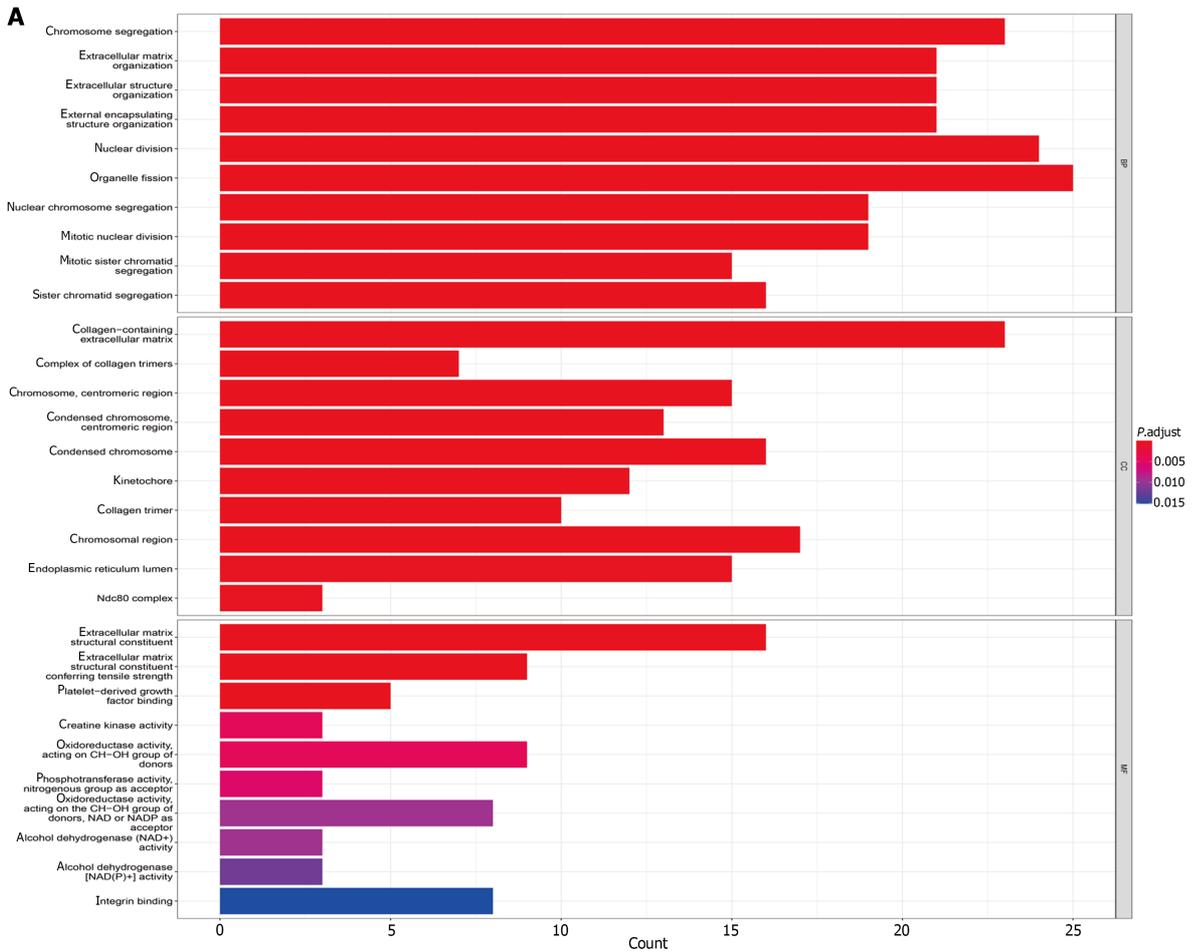
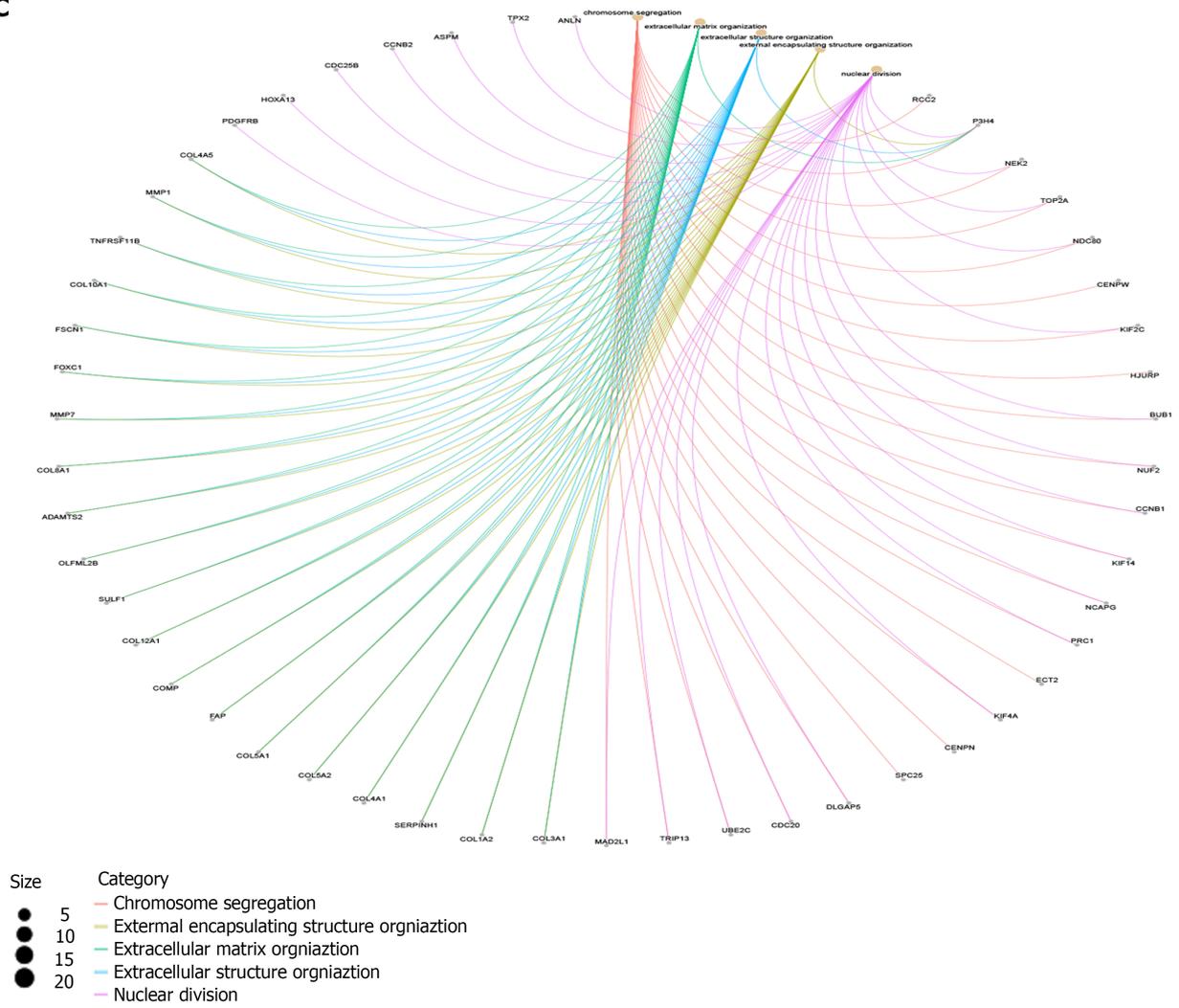


Figure 3 The Venn analysis of differentially expressed genes from Gene Expression Omnibus and The Cancer Genome Atlas datasets. A: The Venn diagram of GSE19826 (red) 2202 up-regulated genes, GSE79973 (blue) 665 up-regulated genes, GSE29998 (green) 4346 up-regulated genes, The Cancer Genome Atlas (TCGA)-STad (purple) 2133 up-regulated genes, among which 133 genes intersect; **B:** The Venn diagram of GSE19826 (red) 2700 down-regulated genes, GSE79973 (blue) 1507 down-regulated genes, GSE29998 (green) 3002 down-regulated genes, TCGA-STad (purple) 2349 down-regulated genes, among which 201 genes intersect. TCGA: The Cancer Genome Atlas.

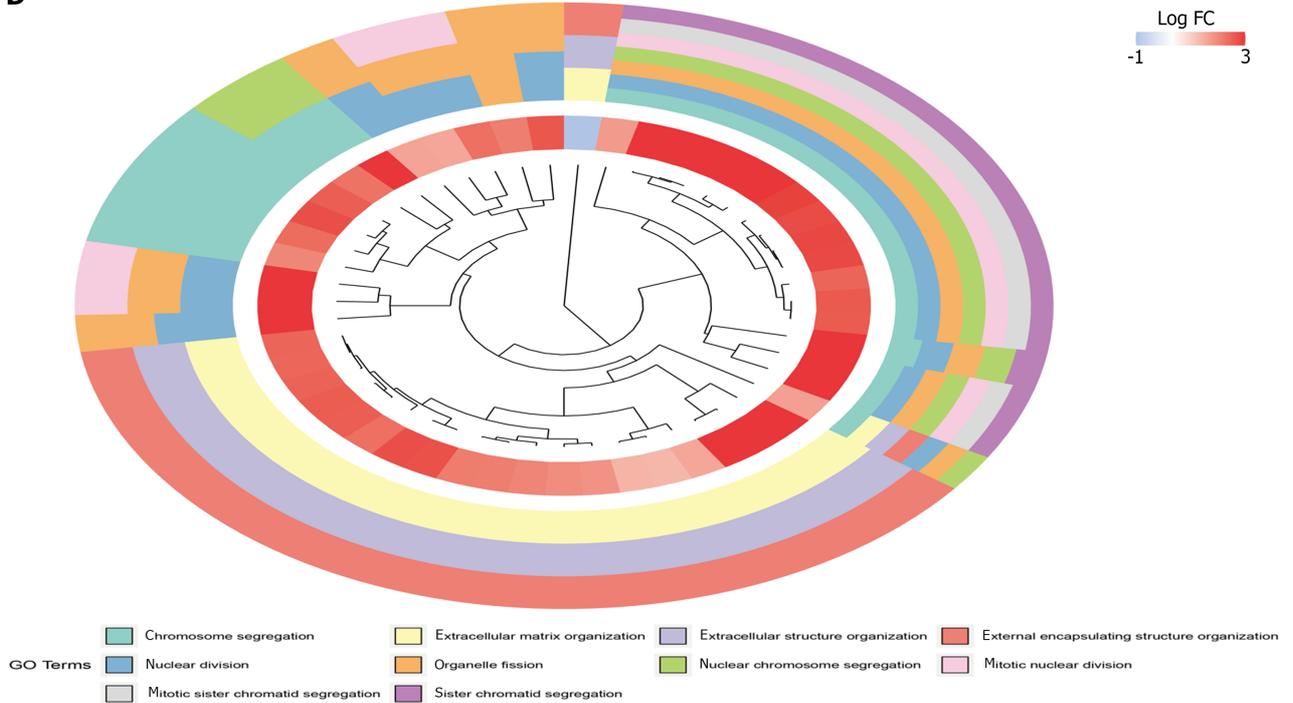
expression difference between the tumor tissues and normal tissues (Figure 6). Then, GEPIA’s survival tool was used for visual analysis of the selected genes [the cutoff value is Logrank $P < 0.05$ and hazard ratio (HR) < 0.05]. Our results suggested that 12 genes with notable significance for prognosis of patients were screened, including CEP55, COL1A2, COL3A1, gpihbp1, Vcan, TIMP1, SPARC, PDGFRb, MAOA, fzd2, COL4A1 and BGN. Visualized analysis of survival curve showed that CEP55 was the protective factor (Logrank $P < 0.05$, HR < 1). COL1A2, COL3A1, GPIHBP1, VCAN, TIMP1, SPARC, PDGFRB, MAOA, FZD2, COL4A1 and BGN were the risk factors (Logrank $P < 0.05$, HR > 1) (Figure 7).



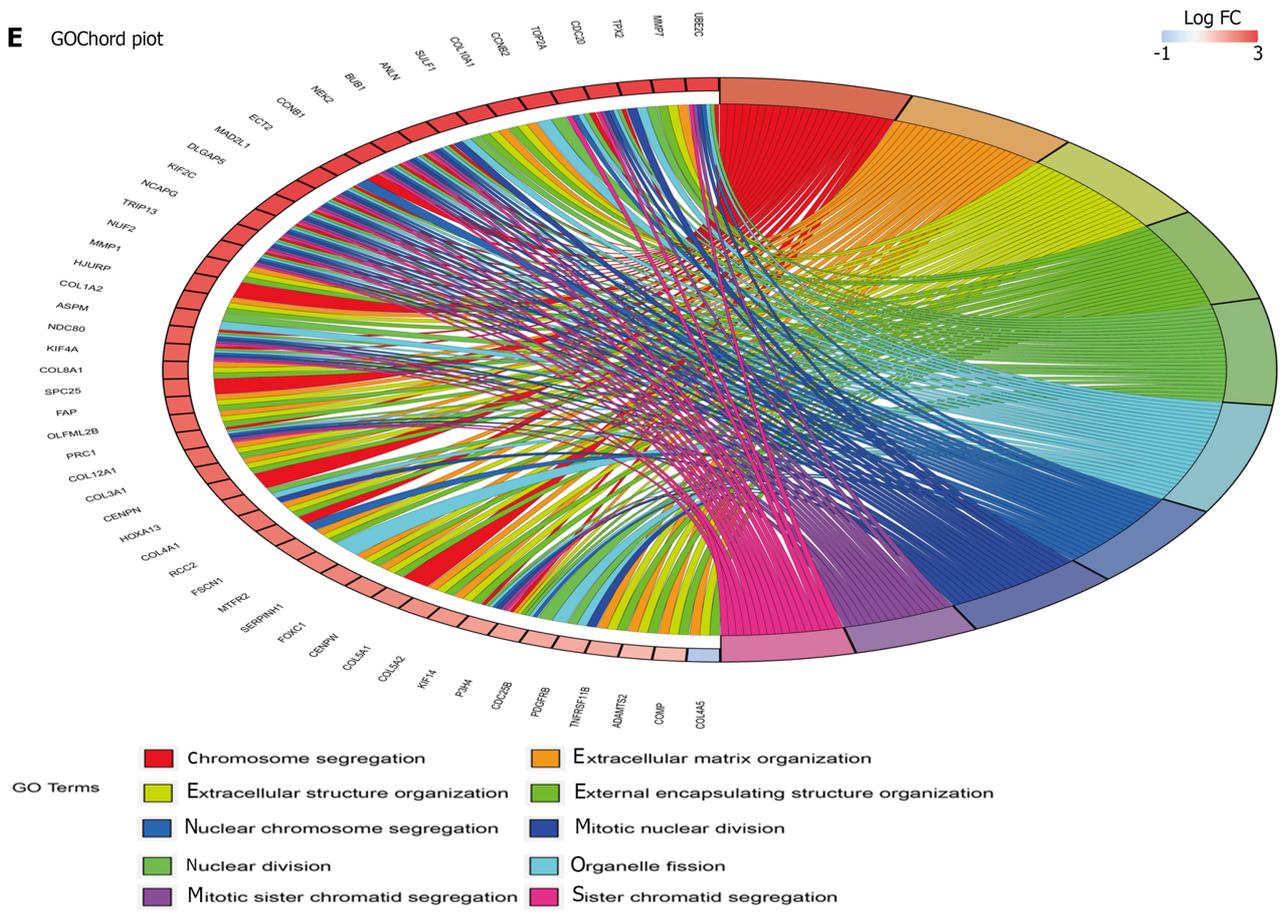
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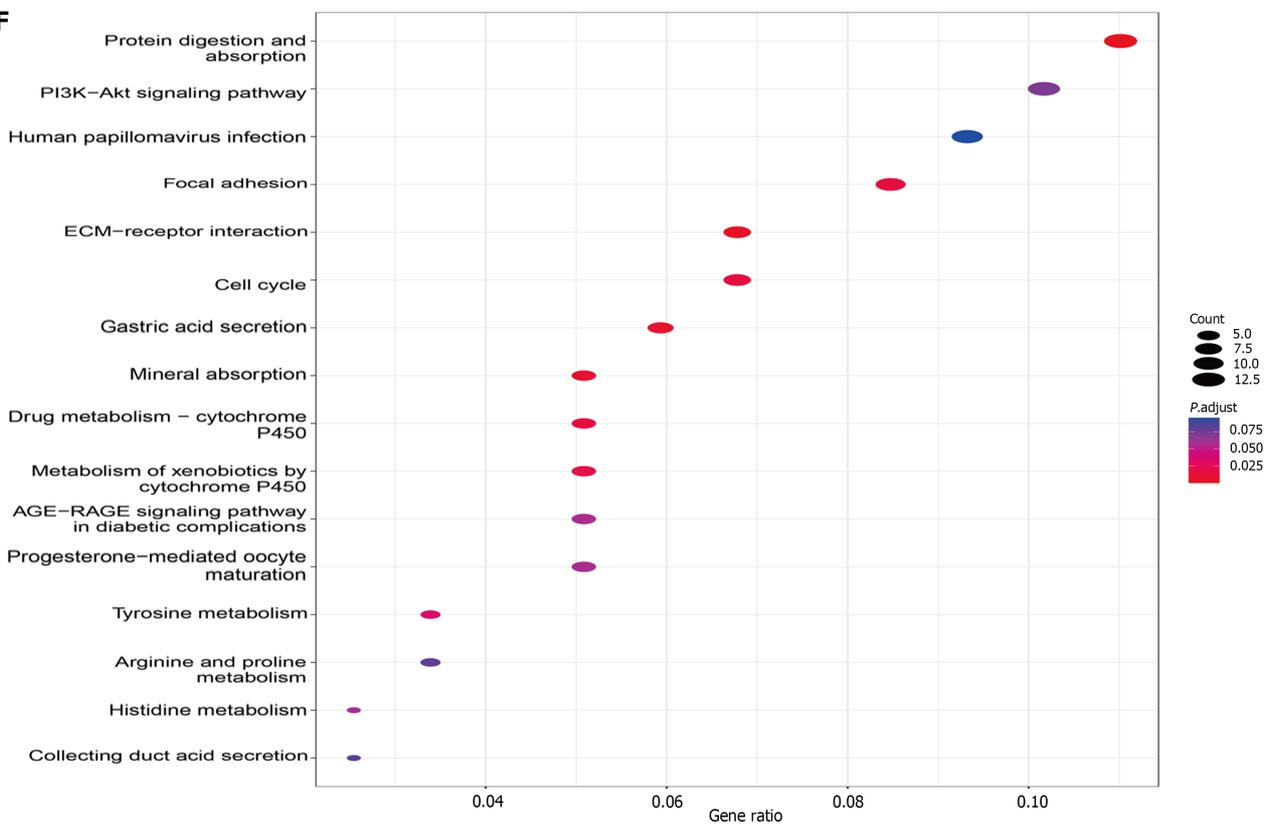
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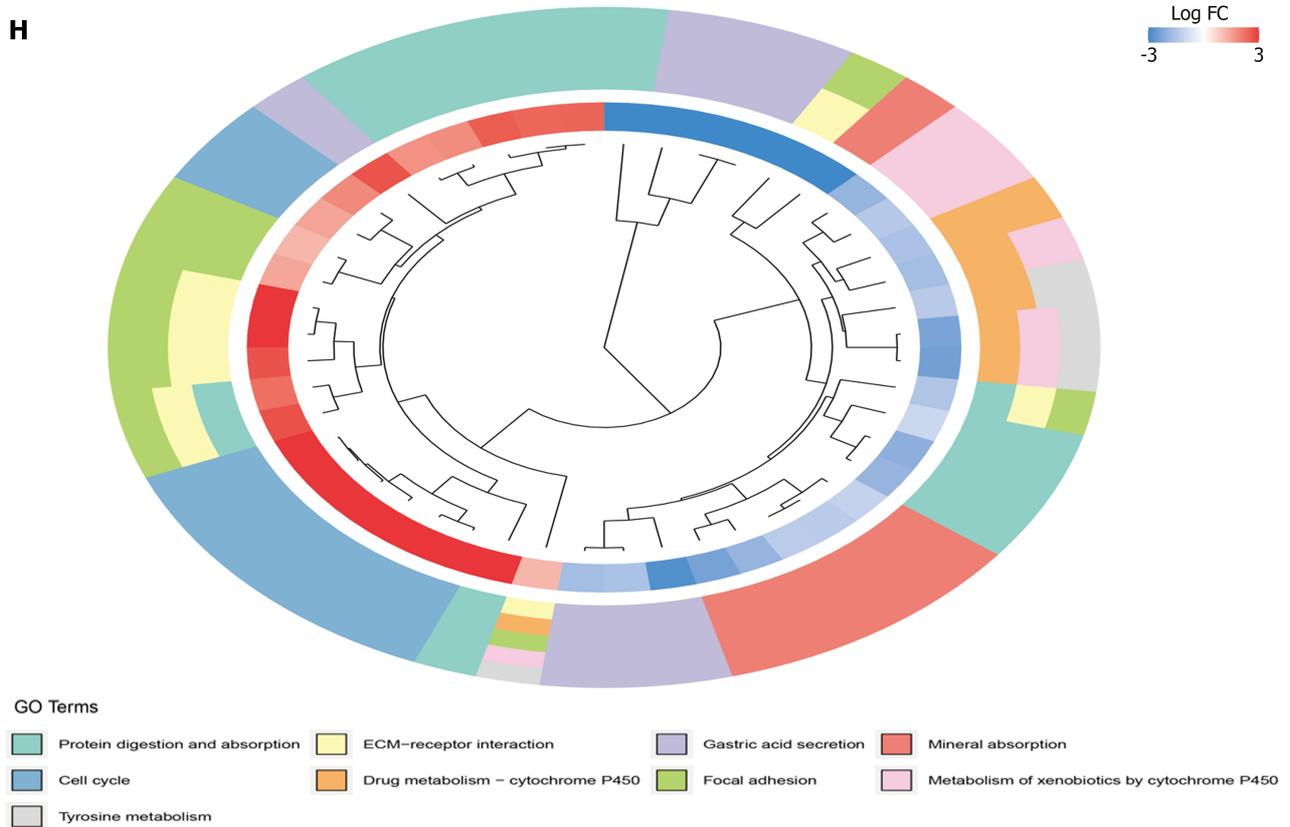
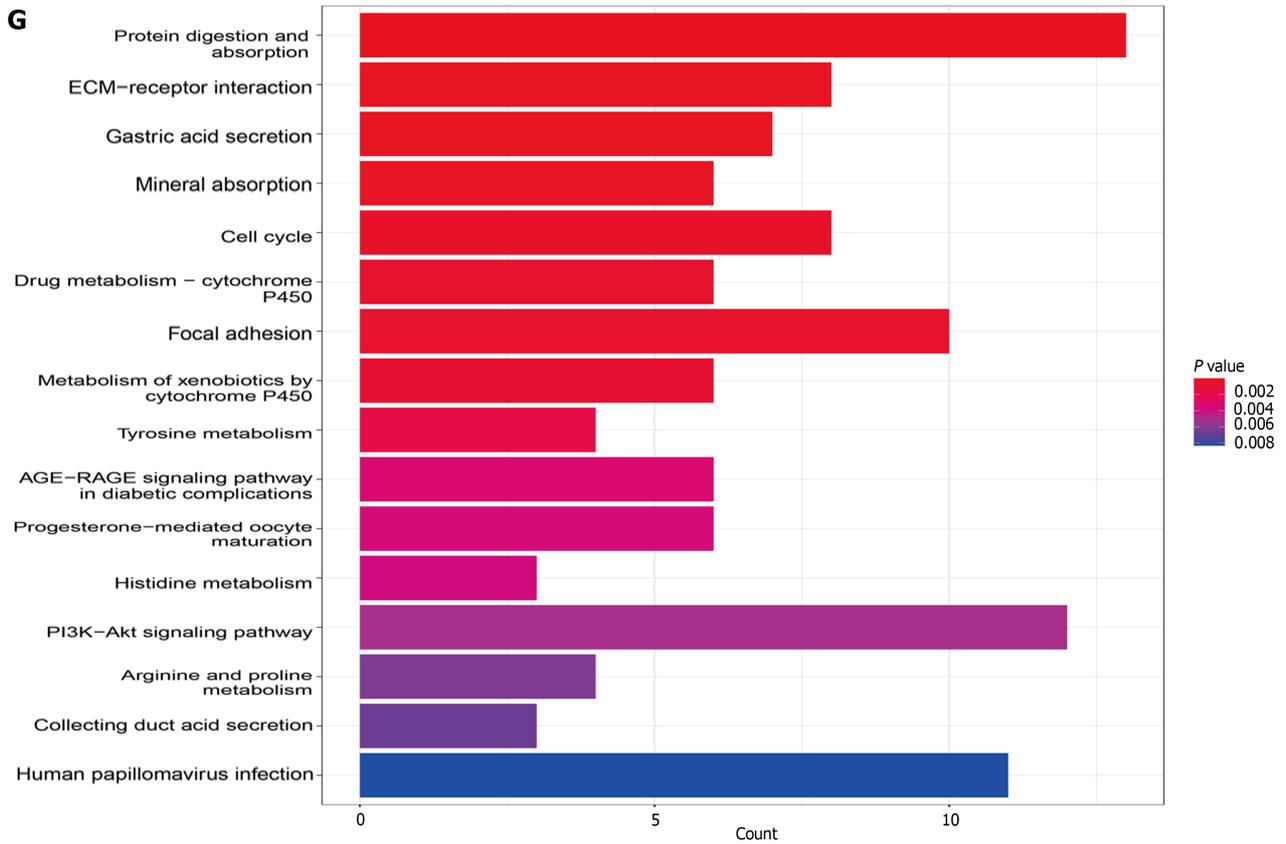


E GOChord plot



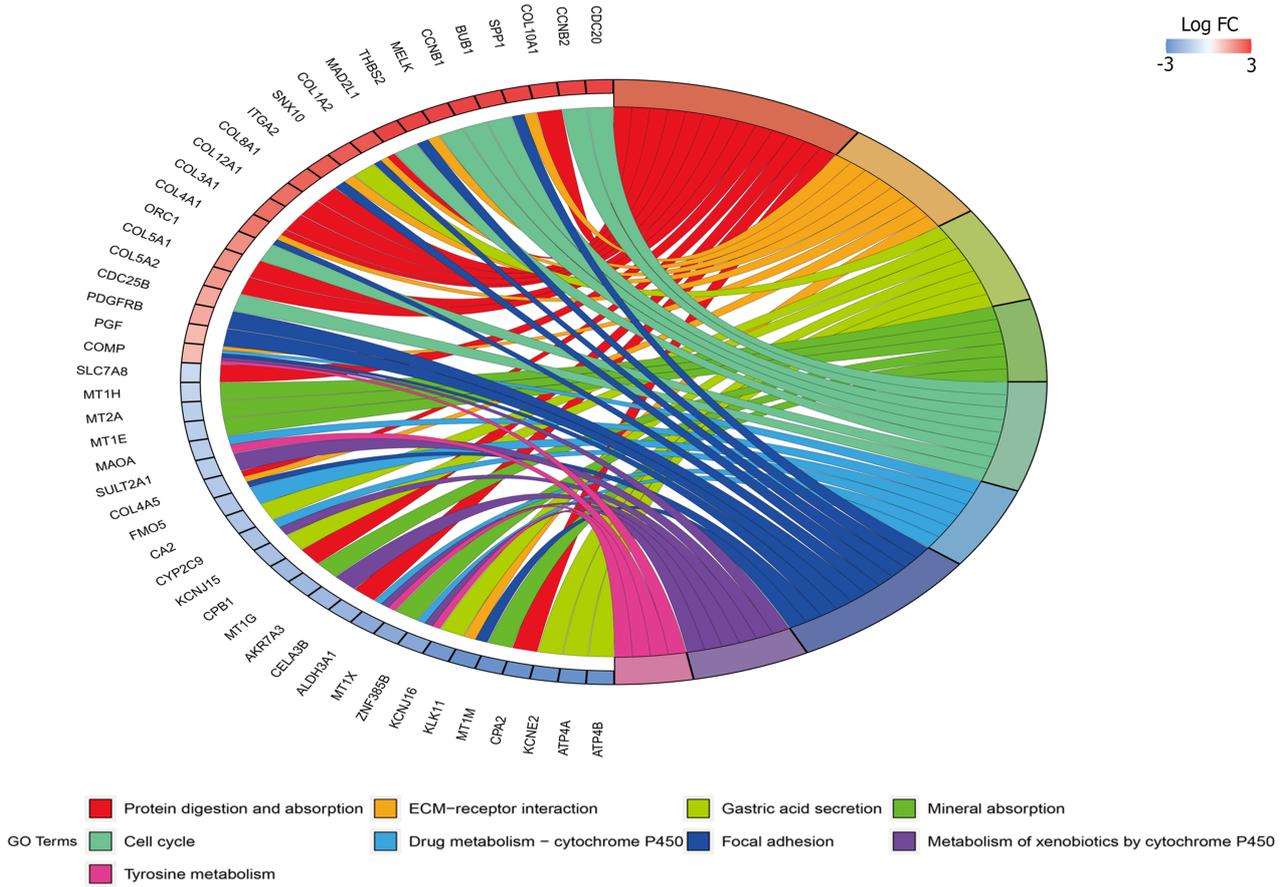
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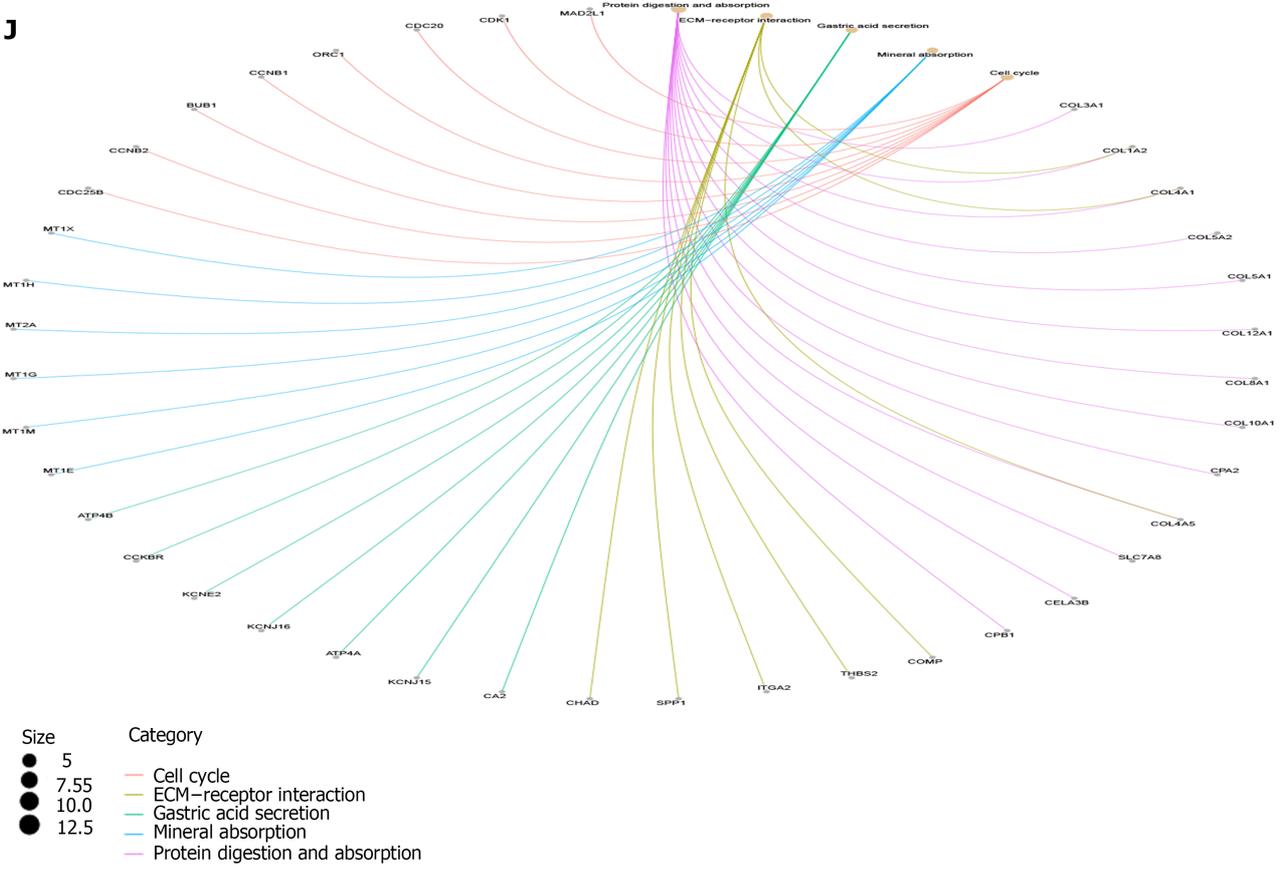


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GOChord plot



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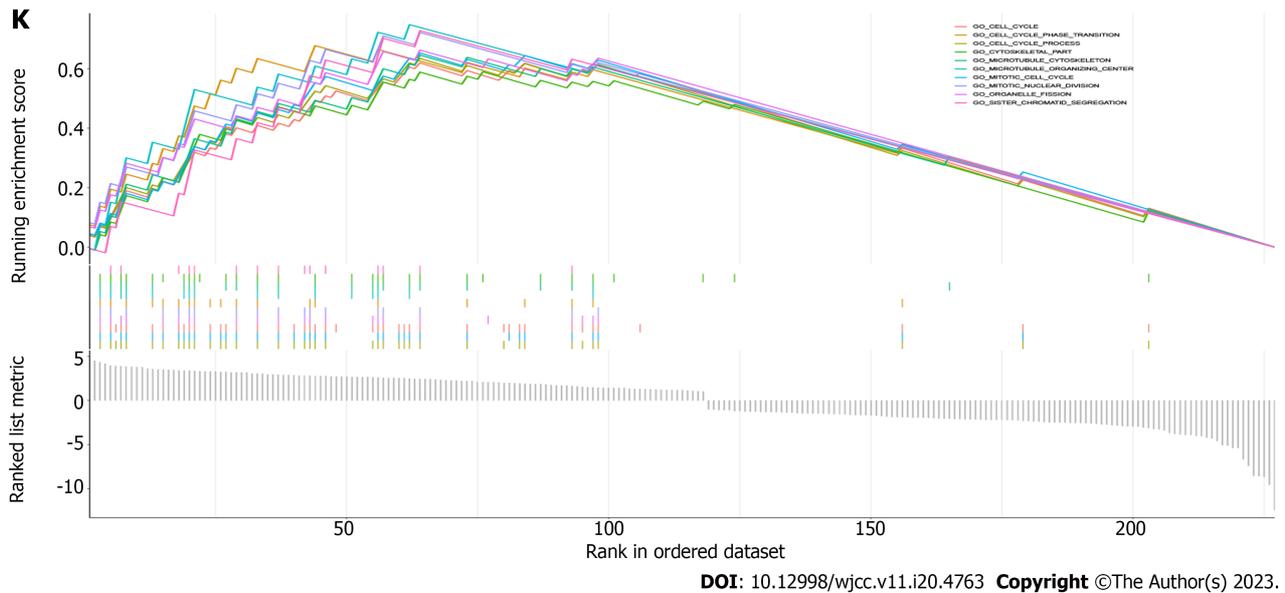


Figure 4 Gene Ontology, Kyoto Encyclopedia of Gene and Genome and Gene Set Enrichment Analysis enrichment analysis of co-expression of differential genes. A: The histogram of Gene Ontology (GO) analysis; B: The bubble diagram analyzed by GO; C: The network diagram analyzed by GO; D: The clustering diagram of GO analysis; E: The circle graph of GO analysis; F: Kyoto Encyclopedia of Gene and Genome (KEGG) analysis bubble diagram; G: KEGG analysis histogram; H: KEGG analysis cluster graph; I: KEGG analysis circle graph; J: KEGG analysis network diagram; K: Gene Set Enrichment Analysis diagram. GO: Gene Ontology.

Survival analysis validation of Hub gene

For the above results, Kaplan-Meier plotter online network was carried out for visual analysis and verification. Excluding COL3A1 (Logrank $P > 0.05$), 11 key genes, including CEP55, COL1A2, GPIHBP1, VCAN, TIMP1, SPARC, PDGFRB, MAOA, FZD2, COL4A1 and BGN, were obtained (Logrank $P < 0.05$). The results confirmed that CEP55 was a protective factor (Logrank $P < 0.05$, HR < 1); COL1A2, GPIHBP1, VCAN, TIMP1, SPARC, PDGFRB, MAOA, FZD2, COL4A1 and BGN were risk factors (Logrank $P < 0.05$, HR > 1) (Figure 8).

Immunohistochemical analysis and final identification of Hub genes

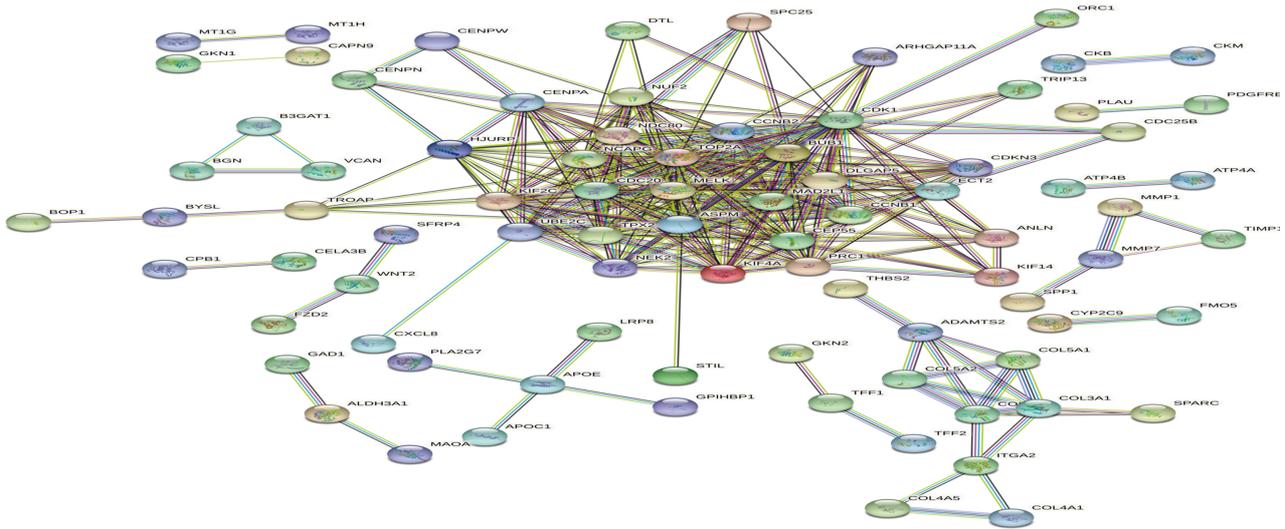
Compared with normal gastric tissues, the expressed proteins of 10 genes of BGN, CEP55, COL1A2, COL4A1, FZD2, MAOA, PDGFRB, SPARC, TIMP1 and VCAN were up-regulated in GC tissues by HPA IHC database ($P < 0.05$) (Figure 9). Therefore, in this study, 10 Hub genes related to the prognosis of GC were finally screened.

DISCUSSION

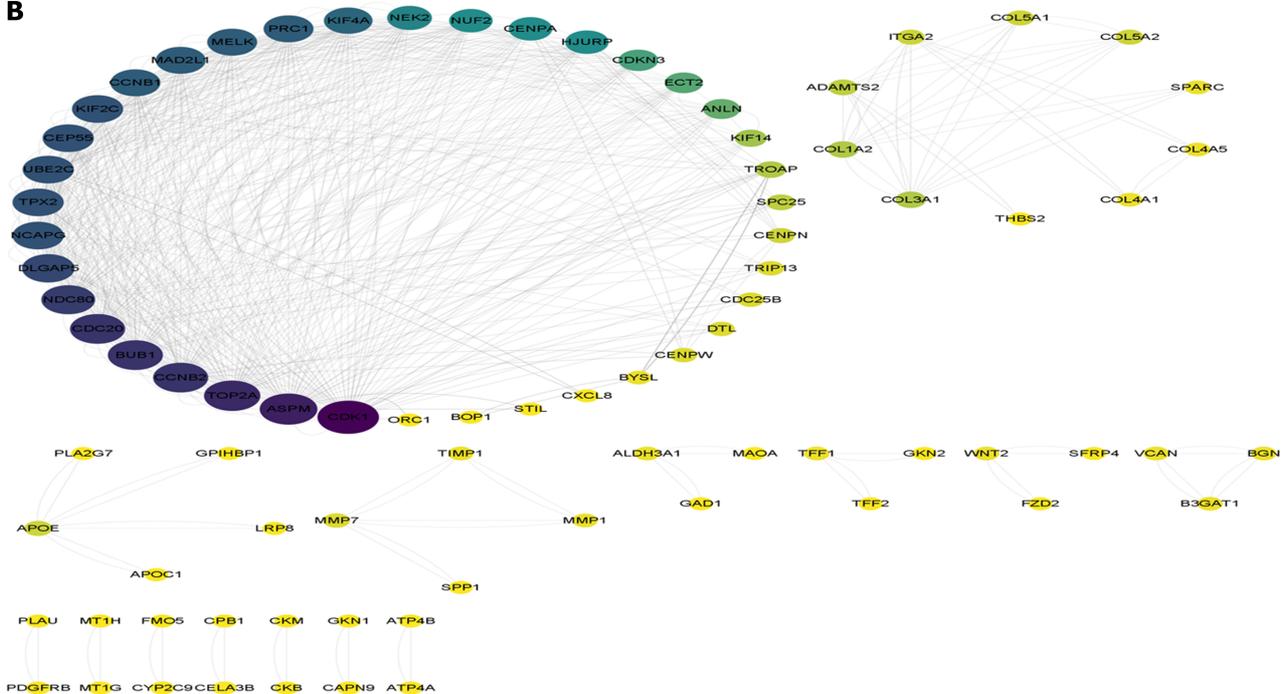
Based on GC gene expression data from GEO and TCGA databases, in this study, bioinformatics was conducted to screen differential expressed genes with relation to survival prognosis of GC. A total of 334 DEGs were analyzed by GO, KEGG and GSEA enrichment, respectively. By GO analysis (Figure 4), these DEGs were found to be enriched in BP, CC and MF. In KEGG analysis, ECM-receptor interaction, protein digestion and absorption, gastric acid secretion, mineral absorption, cell cycle and other signal pathways were enriched. GSEA pathway analysis showed that these DEGs were mainly concentrated in cell cycle progression, mitotic cell cycle, cell cycle, organelle fission, mitosis and other signaling pathways (Table 3). The GEPIA database was then used to verify the differences in expression of these key genes between tumors and normal tissues. The PPI network of these DEGs was analyzed and constructed by STRING11.5, and the credibility was set as the highest: 0.9. Eighty-four Hub genes were screened. GEPIA and Kaplan-Meier plotter identified 11 Hub genes (CEP55, COL1A2, GPIHBP1, VCAN, TIMP1, SPARC, PDGFRB, MAOA, FZD2, COL4A1, BGN) that were associated with GC prognosis. The combination of three databases (GEO, TCGA and GEPIA) makes our results more credible, which is a prominent feature of this study. Subsequently, 10 key genes involved in the prognosis of GC, including BGN, TIMP1, VCAN, COL1A2, COL4A1, FZD2, MAOA, PDGFRB, SPARC and CEP55, were screened by HPA immunohistochemical analysis.

The results of this study showed that BGN and VCAN genes, encoding multifunctional proteoglycans, which were highly expressed in GC tissues and associated with poor prognosis of patients. In this article, by GO, KEGG and GSEA analysis, we found that the two genes (BGN and VCAN) are mainly enriched in BP and MF such as extracellular matrix, extracellular matrix structural components, extracellular space and glycosaminoglycan binding (shown in Supplementary Tables 1 and 2). These BPs and MFs may be involved in the occurrence and development of GC, but the specific mechanism is still unclear, and further experimental research is needed. Previous studies have found that BGN may have important value in predicting the overall survival and tumor immune infiltration of GC[20]. BGN is not only a potential

A



B

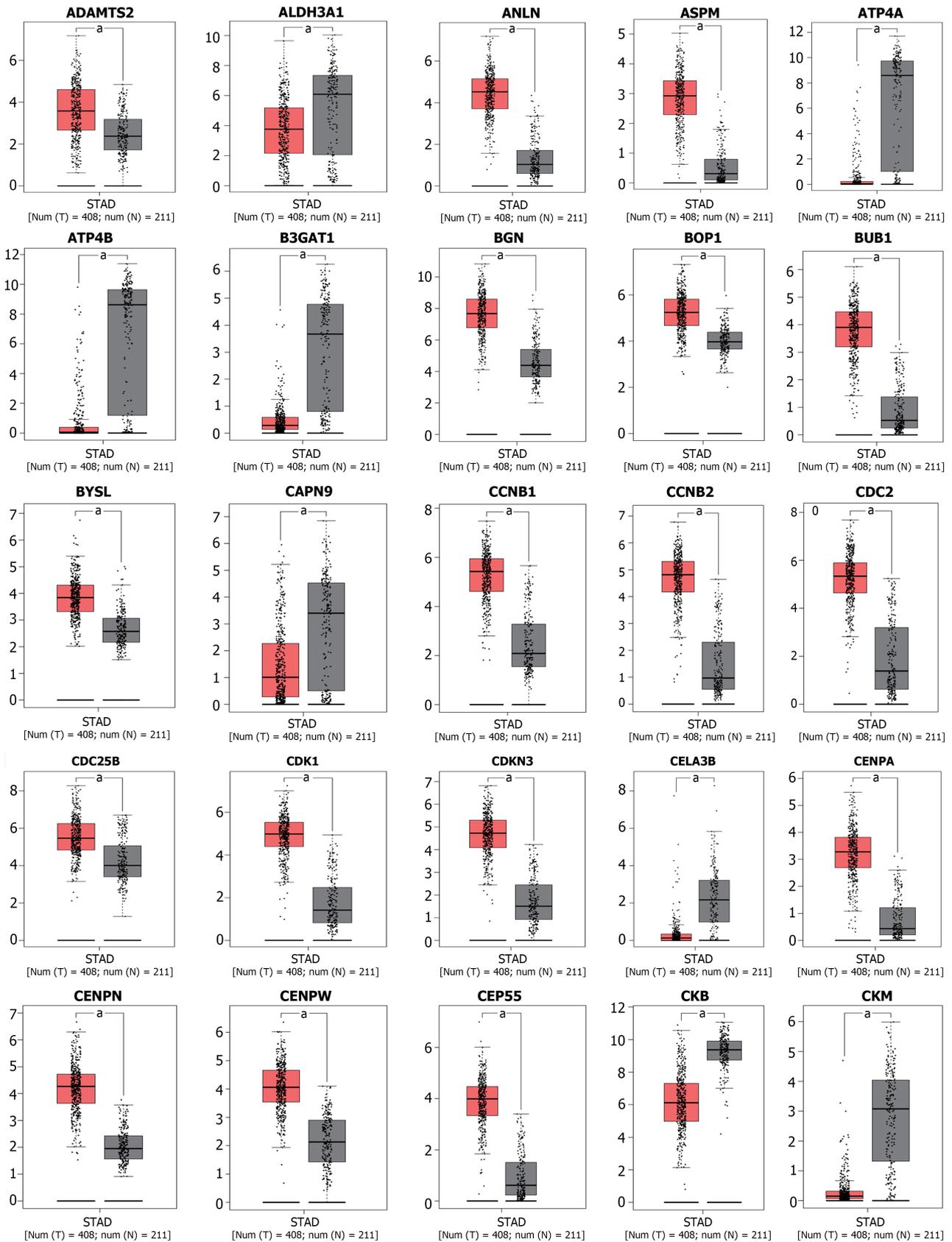


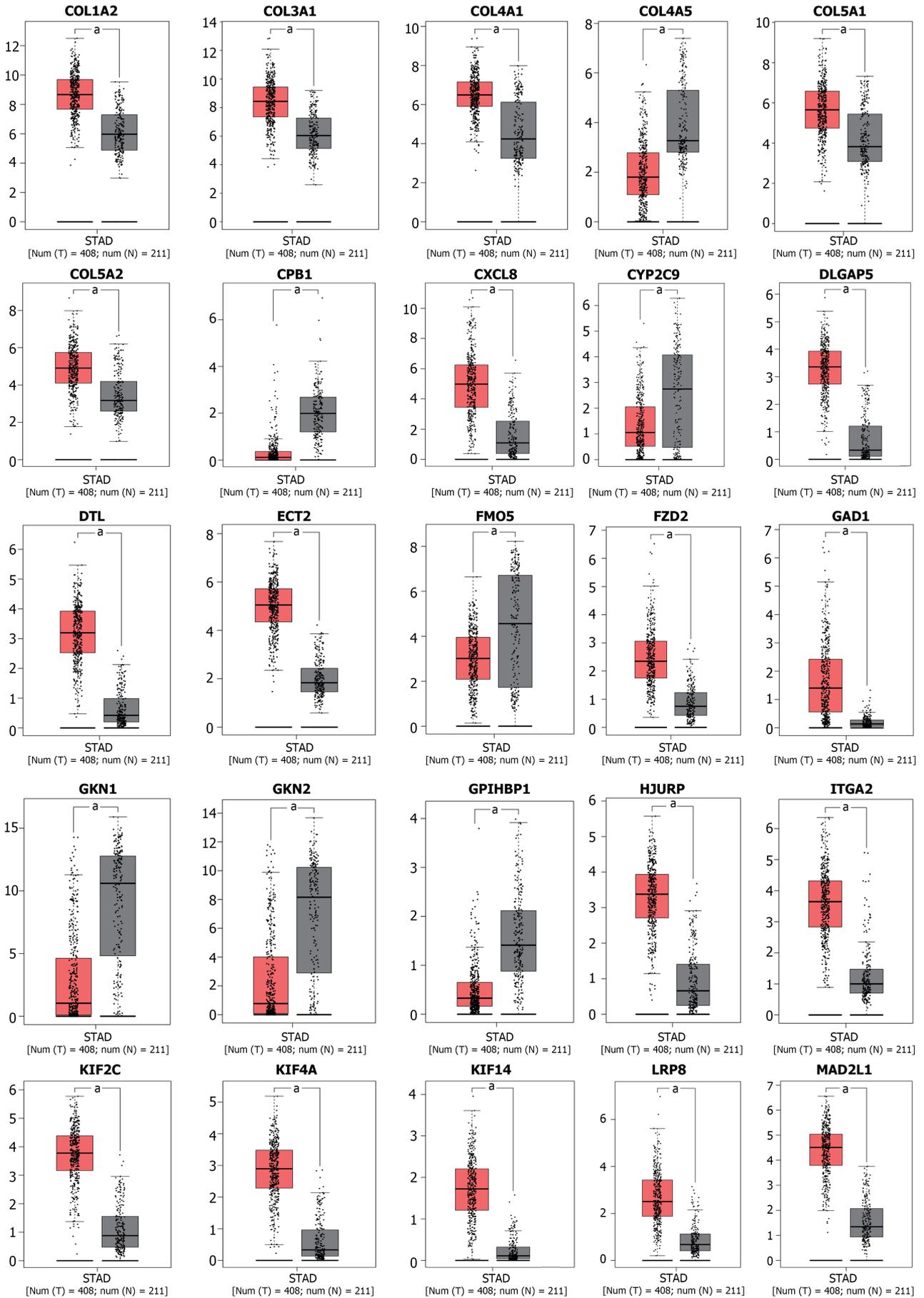
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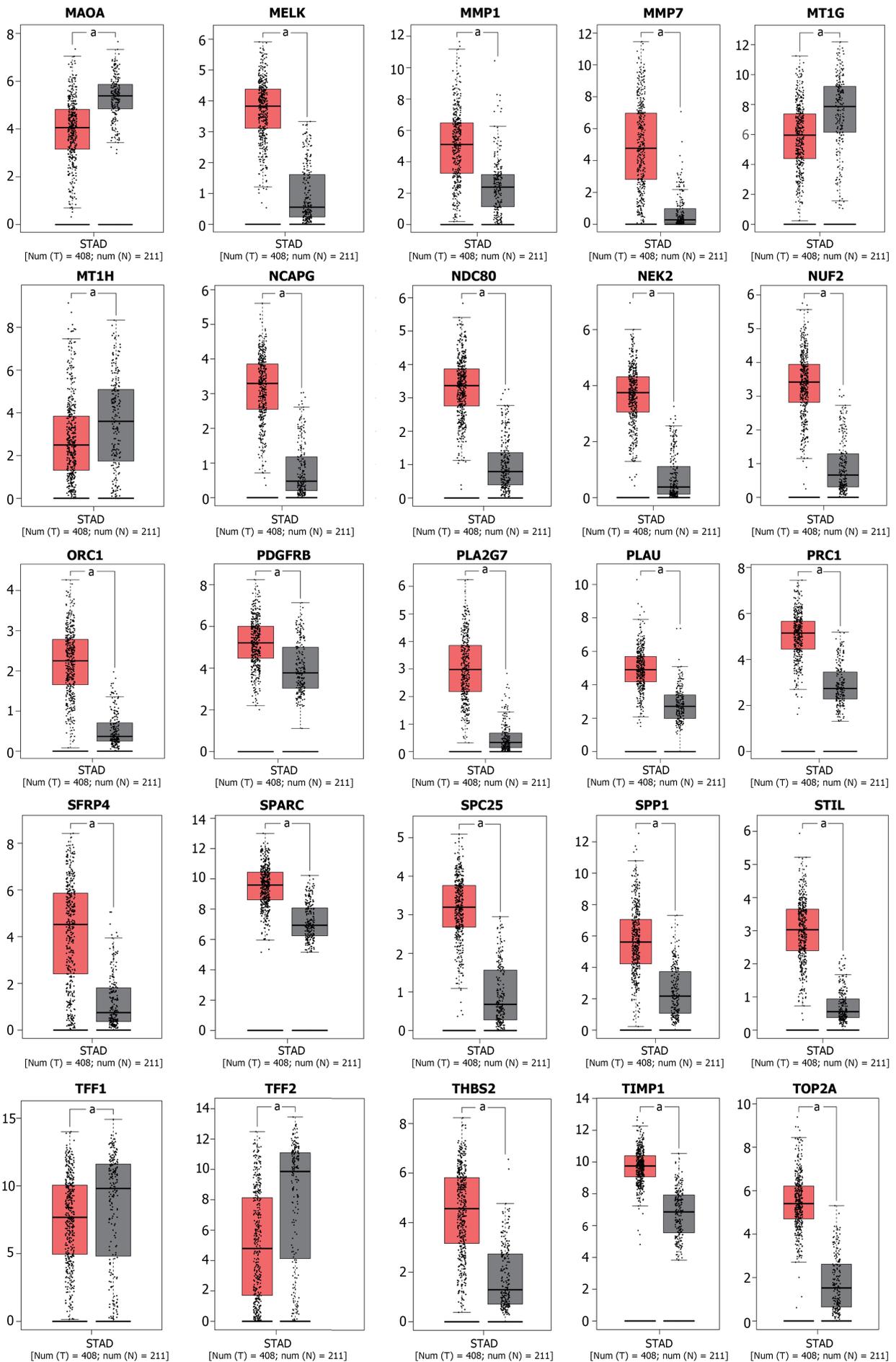
Figure 5 The protein-protein interaction analysis of co-expression of differential genes. A: The protein-protein interaction network diagram of co-expression of differential genes (co-DEGs) constructed by STRING11.5; B: 84 nodes and 654 edges of co-DEGs was revealed by Cytoscape software. ^a*P* < 0.05.

biomarker for survival and prognosis of GC, but also may be related to the enrichment of immune cells in GC[21]. In terms of the metastasis for GC, BGN mediates peritoneal metastasis of GC by regulating lncRNA SEMA3B-AS1/HMGB1/FBXW7 axis[22]. It has been reported that VCAN is involved in cell adhesion, proliferation, proliferation, migration and angiogenesis, and it plays a central role in tissue morphogenesis and maintenance. Some studies have found that the high expression of VCAN leads to poor prognosis of GC[23-25], which is consistent with our results of the present study. Therefore, BGN and VCAN genes promote the progression of GC through various BPs and molecular signaling pathways, which might also be potential prognosis biomarkers for GC.

As shown in **Supplementary Tables 1 and 2**, these findings also revealed that TIMP1 and MAOA genes, encoding enzyme proteins, predicted poor survival for patients; TIMP1 mainly participates in the degradation of extracellular matrix, promotes cell proliferation, and have anti-apoptosis function in tumors. Previous studies have found that TIMP1 is positively correlated with the pathological N stage of GC, which may inhibit the growth and metastasis of GC cells through mir-6745-TIMP1 axis[26,27], and Chemerin receptor antagonists down-regulate the expression of TIMP1 and TIMP2 through chemokine-like receptor-1 and G-protein coupled receptor 1 pathways, reducing the metastatic and invasive ability of GC cells[28]. Thus, TIMP1 could promote the progression of GC and shorten the survival period of







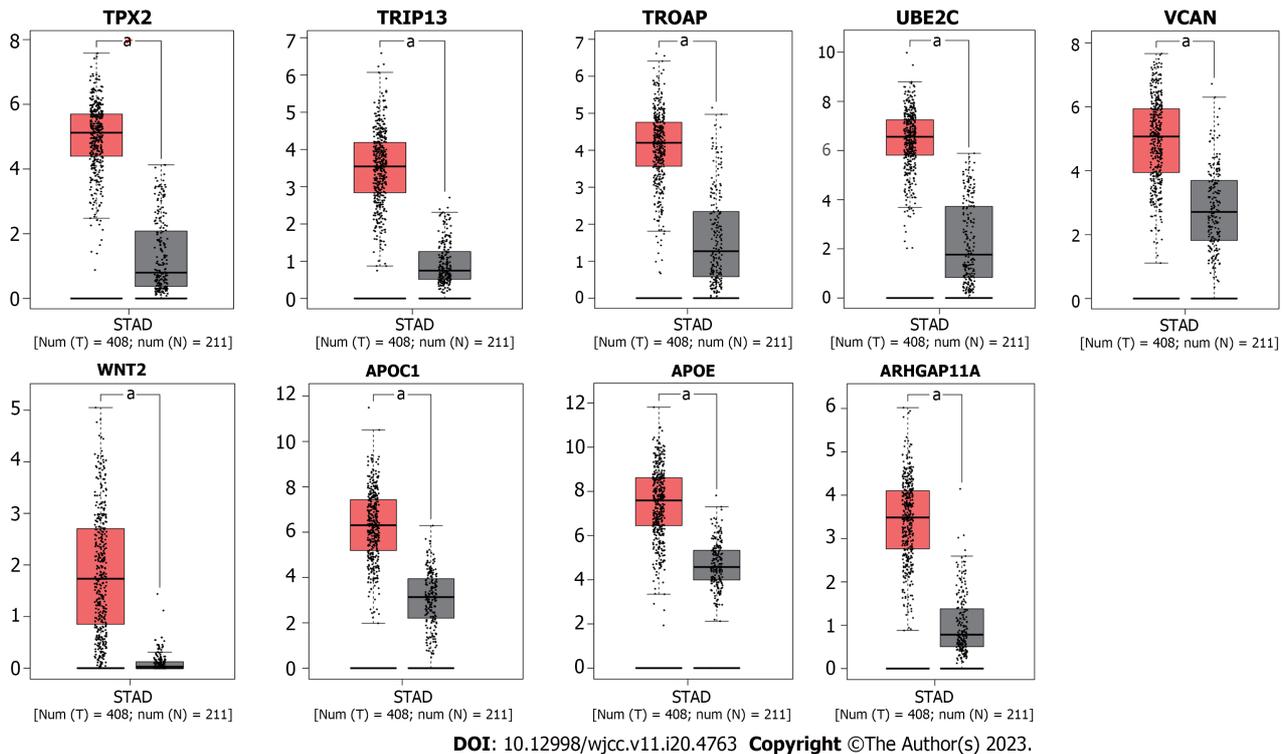


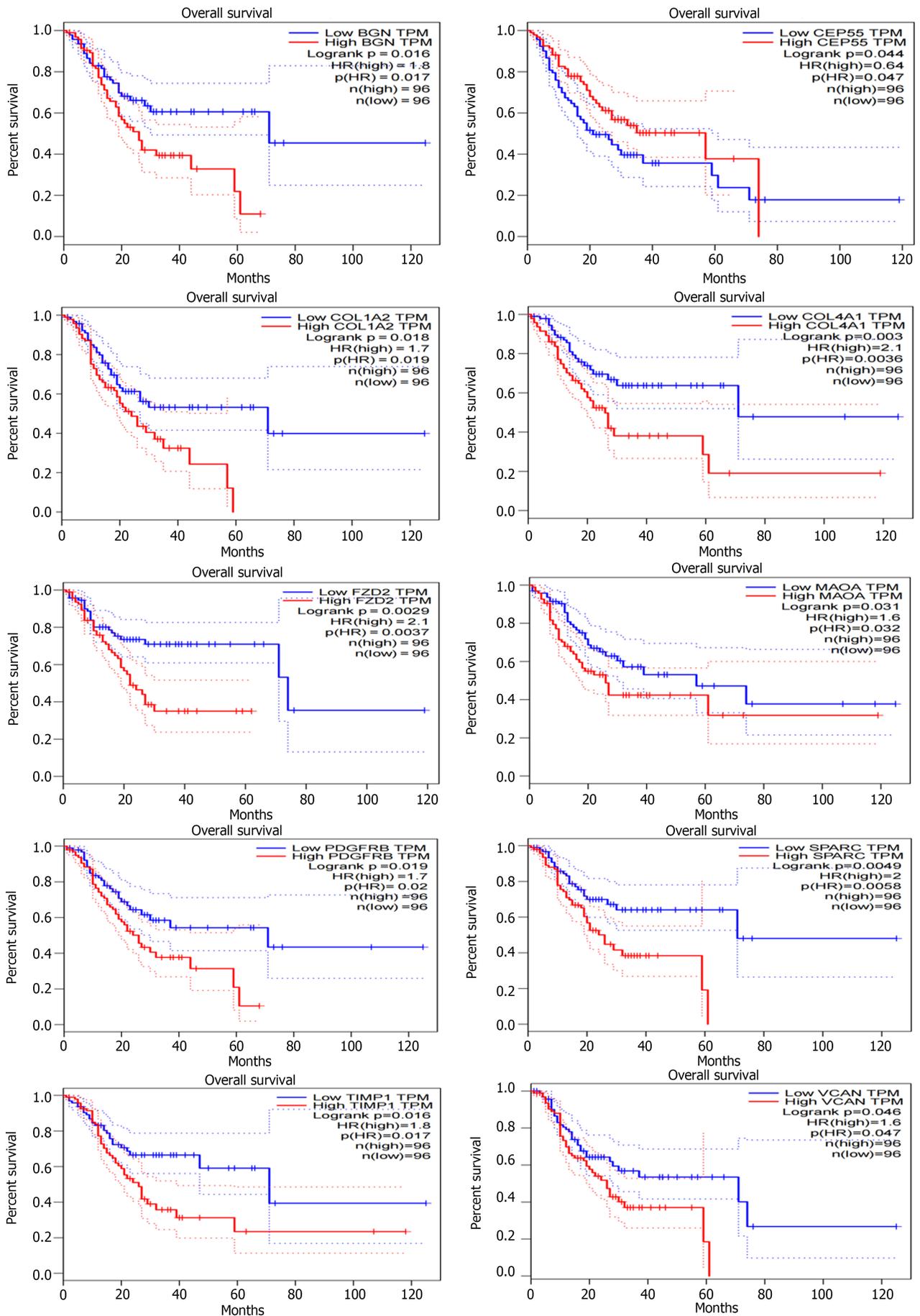
Figure 6 The Box diagram of 84 key genes visualized by Gene Expression Profiling Interactive Analysis, showing significant expression difference between the tumor tissues and normal tissues.

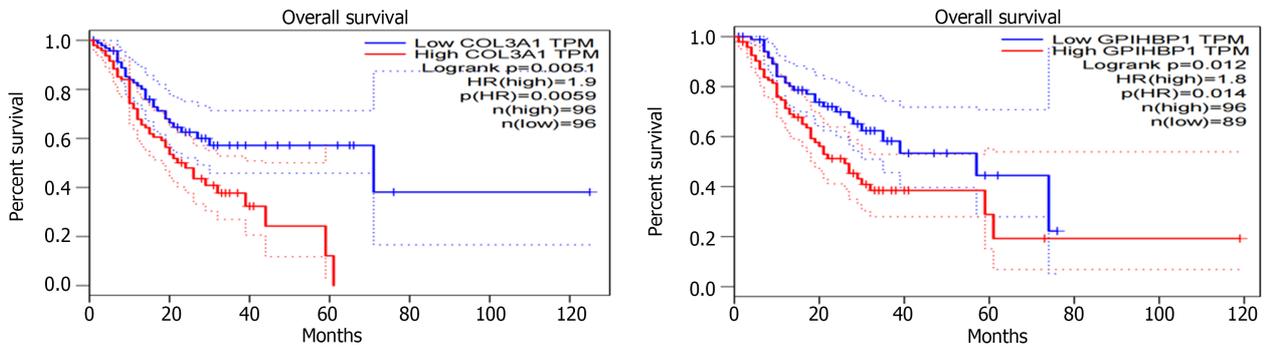
patients. MAOA, encoding a mitochondrial enzyme, catalyzes the oxidative deamination of amines. The loss or decrease of MAOA expression can be used as a marker to monitor the immunotherapeutic effect of GC[29]; MAOA can also facilitate the proliferation and metastatic ability of gastric tumor cells by regulating mitochondrial function and aerobic glycolysis[30]. In the present study, we found that MAOA may affect the molecular functions of cells, such as protein binding, flavin adenine dinucleotide binding, oxidoreductase and so on. Therefore, it might affect the survival and prognosis of patients with GC by regulating the metabolic function of cells.

In addition, the results of this article suggested that two high-expressed genes of FZD2 and PDGFRB, encoding receptor proteins, were related to the prognosis of patients. It has been reported that a protein encoded by FZD2 is involved in binding to β -catenin typical signaling pathways and participates in regulation β -catenin dependent pathways. At present, only few literatures indicate that FZD 2 may play a key role in the occurrence and development of GC[31]. Our results demonstrated that FZD2 may act on: Atypical Wnt signaling pathway, classical Wnt signaling pathway, Wnt protein binding and other BPs. Previous studies have reported that PDGFRB is related to immune cell infiltration in GC, and may serve as a potential prognosis biomarker for GC[32]. PDGFRB is significantly correlated with the malignant phenotype of tumors, and the high expression of PDGFRB significantly reduced the overall survival of patients with GC [33,34]. In this study, we found that PDGFRB might promote tumor angiogenesis, cell proliferation and cell migration, and inhibit the aging and apoptosis of tumor cells, increasing the possibility of GC metastasis (details in [Supplementary Tables 1 and 2](#)).

The other four genes (COL1A2, COL4A1, SPARC and CEP55) are related to the prognosis of GC, which mainly encode collagen, acidic matrix related protein and centrosome protein of GC cells. The previous studies have found that collagen-encoding genes COL1A1 and P4HA3 may be related to the prognosis of GC[35]. At the present study, we found that COL4A1 and COL1A2 may have some effects on extracellular matrix and its interaction with receptors, protein binding, protein digestion and absorption, and regulate PI3K Akt signaling pathway. For the CEP55, some researchers have reported that it participates in promoting the malignant biological behavior of GC cells[36]. The expression of CEP55 in GC tissues is elevated, and CEP55 can also be a potential therapeutic target for GC[37]. The high expression of SPARC is associated with poor prognosis and shorter overall survival in patients with GC[38-41]. Our results suggested that CEP55 and SPARC could affect cell mitosis, cytokinesis and extracellular matrix structure, but its mechanisms are still remaining unclear (details in [Supplementary Tables 1 and 2](#)).

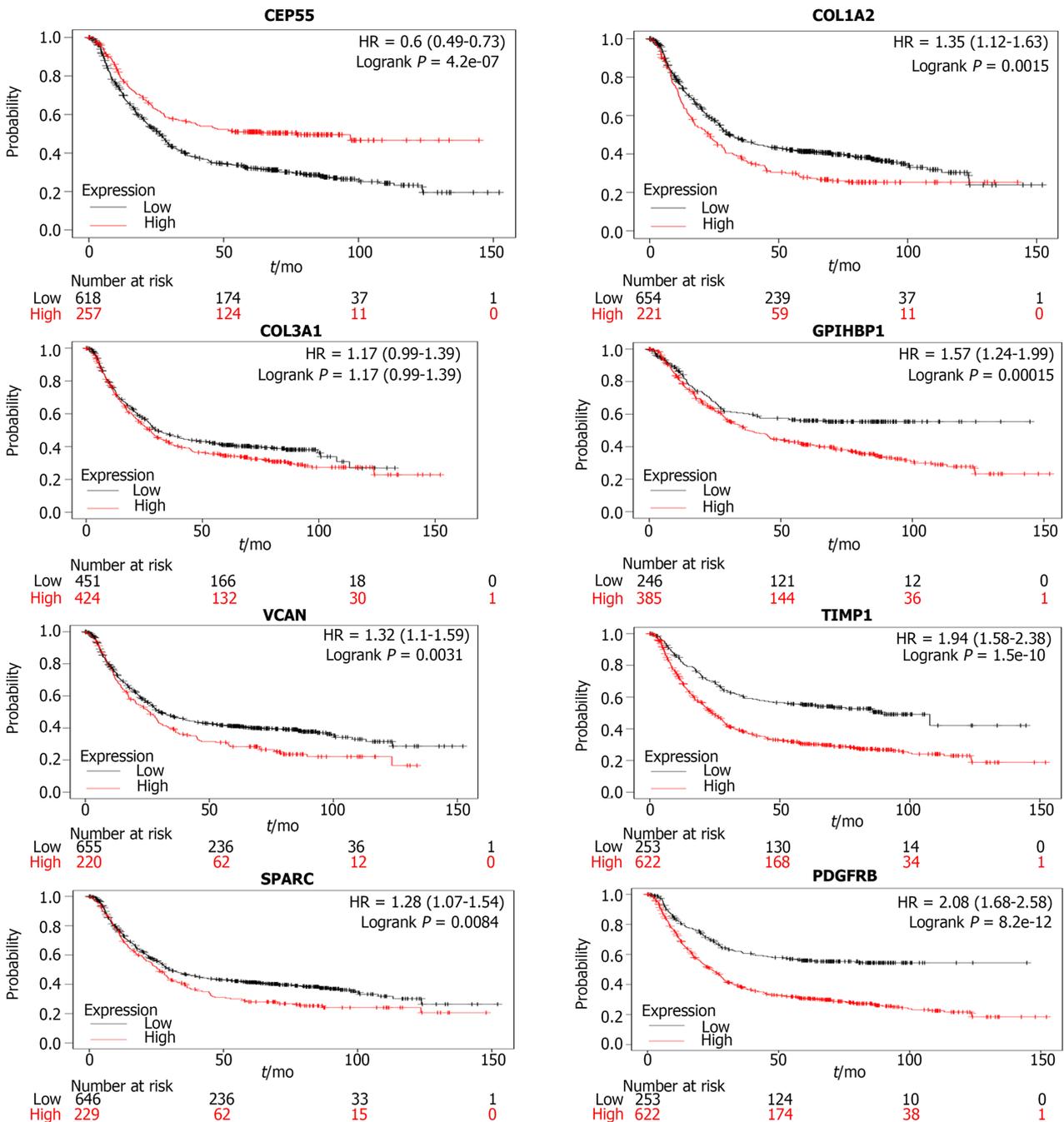
To sum up, this Bioinformatics present that BGN, CEP55, COL1A2, COL4A1, FZD2, MAOA, PDGFRB, SPARC, TIMP1 and VCAN, identified as the prognosis of GC, are involved in the occurrence and development of GC, and thus affect the survival and prognosis of patients by themselves or the encoded proteins. In this study, the 10 Hub genes obtained by comprehensive analysis of multiple databases and datasets may be used as survival biomarkers. Nevertheless, there are still many shortcomings in this study, for example, our data is currently limited to the online database, the selection of data may be biased or incomplete, and the relevant molecular mechanism needs further experimental research to verify.





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Figure 7 The prognosis of 12 key genes associated with gastric cancer screened by Gene Expression Profiling Interactive Analysis survival analysis tool, showing CEP55 was the protective factor (Logrank $P < 0.05$, hazard ratio < 1).



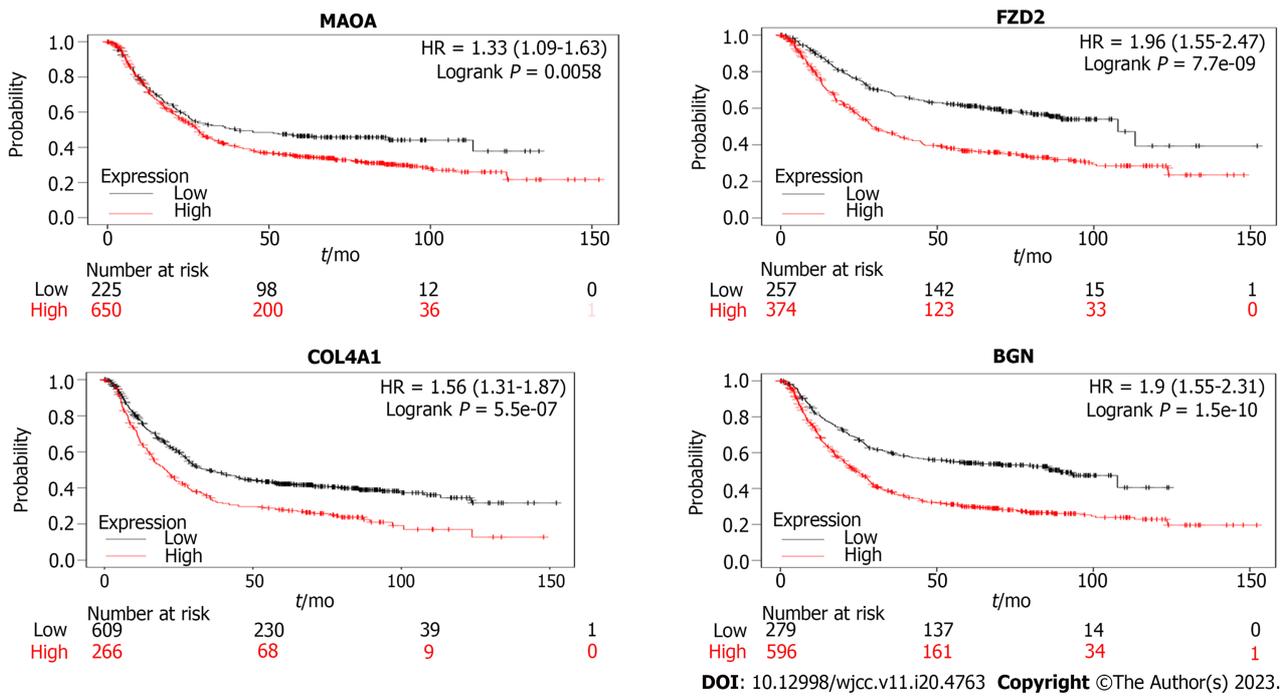
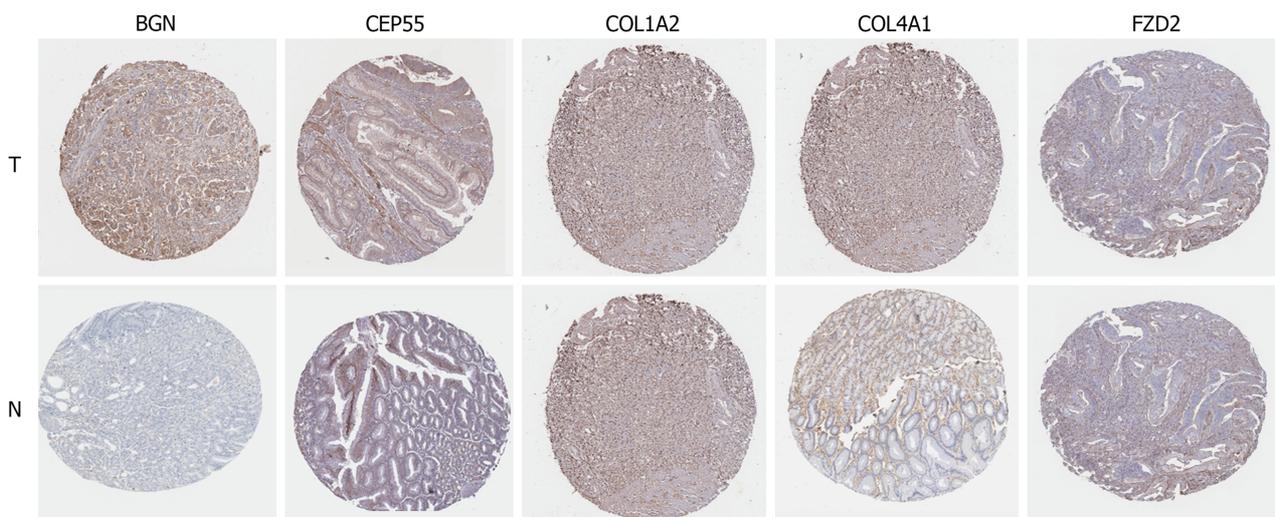
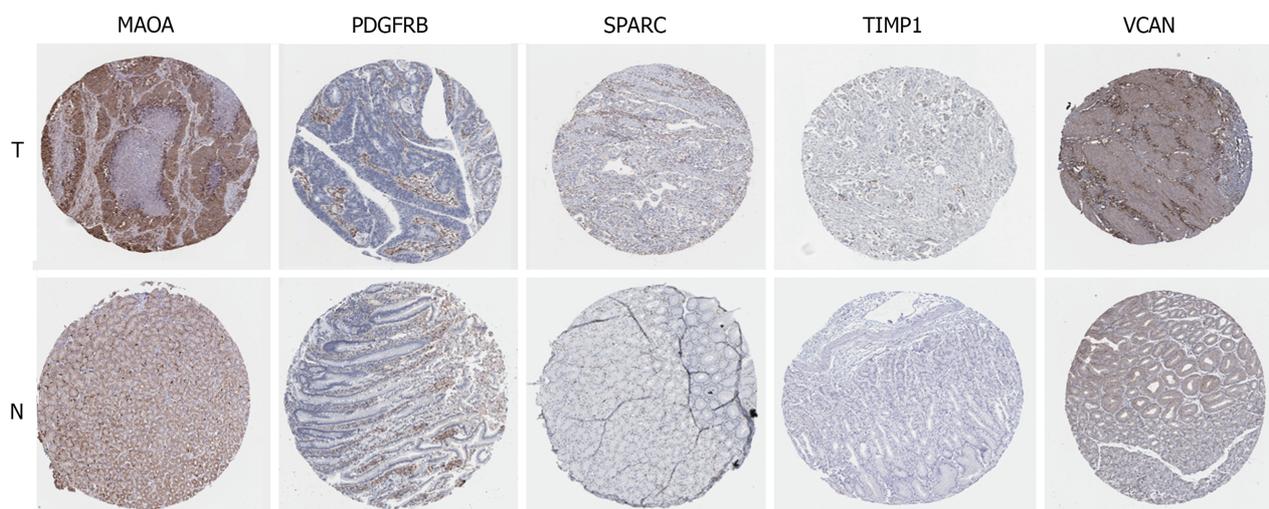


Figure 8 The prognosis of 12 genes screened out by Gene Expression Profiling Interactive Analysis survival analysis tool were analyzed and plotted by Kaplan Meier Plotter online network tool, confirming that CEP55 was a protective factor (Logrank $P < 0.05$, hazard ratio < 1).

CONCLUSION

In this study, we analyzed the gene expression profiles and sequencing data of GC tissues and adjacent or normal gastric tissues to explore the pathogenesis of GC using bioinformatics, investigated the signal pathways of co-DEGs involved in GC, and identified the 10 Hub genes correlated with the prognosis of patients with GC. The 10 key genes obtained through the analysis of multiple databases and datasets may be used as objective and reliable biomarkers for the survival analysis of patients. In addition, these genes or their encoded proteins can also be used as potential therapeutic targets for GC, improving the survival time of patients with GC. However, the mechanisms of 10 Hub genes in GC is still unclear, which needs further confirmation through molecular biology and clinical experiments.





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Figure 9 Elevated 10 protein expressions of BGN, CEP55, COL1A2, COL4A1, FZD2, MAOA, PDGFRB, SPARC, TIMP1 and VCAN were screened out from HPA immunohistochemistry database (hematoxylin and eosin \times 100). T: Tumor tissues; N: Normal tissues.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is one of the most common malignant tumors, and its pathogenesis and biomarkers are still unclear.

Research motivation

The present study for the first time investigated the 10 Hub genes as the potential biomarkers of the prognosis of patients using bioinformatics.

Research objectives

The aims of this study are to explore the potential biomarkers of the prognosis of patients with GC, so as to provide new strategies for the treatment of GC.

Research methods

In this study, bioinformatics strategy was used to obtain Datasets from The Cancer Genome Atlas, Gene Expression Omnibus and Gene Expression Profiling Interactive Analysis. The software of R software, STRING, Kaplan-Meier plotter and Human Protein Atlas, were performed to analyze and integrate the mRNA datasets, respectively.

Research results

The signal pathways of the involvement of the co-expression of differential genes in GC were screened out, and the 10 Hub genes, including BGN, CEP55, COL1A2, COL4A1, FZD2, MAOA, PDGFRB, SPARC, TIMP1 and VCAN, were associated with prognosis of GC and identified as the potential prognostic biomarkers of GC.

Research conclusions

The 10 key genes obtained through the analysis of multiple datasets may be used as objective and reliable biomarkers for the survival analysis of patients. In addition, these genes or their encoded proteins can also be as potential therapeutic targets for GC, improving the survival time of patients with GC.

Research perspectives

The mechanisms of 10 Hub genes in GC is still unclear, which needs further confirmation through molecular biology and clinical experiments.

FOOTNOTES

Author contributions: Yin LK and Yuan HY contributed equally to this work. Yin LK, Yuan HY, Liu JJ and Wang P contributed to data collection and manuscript drafting; Yin LK, Xu XL, Wang W, Bai XY and Wang P prepared for the figures and tables; and all authors have approved the final manuscript.

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ethical statement needed to be declared for this manuscript.

Clinical trial registration statement: All of the data of this paper are from the public database of TCGA, GEO and GEPIA, and no clinical trial registration needed for this manuscript.

Informed consent statement: All of the data of this paper are from the public database of TCGA, GEO and GEPIA, and no informed consent form documents are needed to be signed by any patients.

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

Data sharing statement: The data supporting the results of this study are available from GEO database (GSE19826, GSE79973 and GSE29998).

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