

# A Pan-Cancer Analysis of the Tumorigenic Role of Yin-Yang1 (YY1) in Human Tumors

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## Research Article

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# Abstract

**Background:** Yin-yang1 (YY1) is a nuclear transcription factor possessing dual transcriptional activity, which has different expression in a variety of tumor tissues. However, it remains unclear that the role of YY1 in most tumors and its association with immune cell infiltration.

**Methods:** The expression of YY1 was analyzed in pan-cancer data which were downloaded from The Cancer Genome Atlas (TCGA) database. The clinical survival data downloading from TCGA was used to analyze the effect of YY1 on clinical prognosis. We had access to the R package “clusterProfiler” to make the enrichment analysis of YY1. The score of the immune cell infiltration of TCGA samples was downloaded from published articles and the correlation between YY1 expression and the immune cell infiltration was analyzed.

**Results:** YY1 had a high expression in 25 tumors and strongly associated with clinical stage. In most tumor types, the over-expression of YY1 was connected to the worse prognostic indicator, such as overall survival(OS), progression-free survival (PFS), disease-specific survival(DSS) and disease-free survival (DFS). Moreover, the expression of YY1 had a correlation with tumor mutation burden(TMB). Nearly all of immune-related genes had co-expression with YY1 and almost all genes had positive correlation with YY1 in all types of tumors. It's worth noting that the expression levels of B cells and T cells were lower in the group with high YY1 expression. In addition, 22 m6A methylation-related cells were co-expressed with YY1, such as METTL3, YTHDC1, FTO and so on.

**Conclusions:** Our study leads to a suggestion that YY1 may be a marker of bad prognosis and high expression of YY1 may lead to immune infiltration and be connected to m6A methylation.

## Introduction

YY1 is a member of the Zinc finger transcription factor family. It's a nuclear transcription factor which possesses double activity of transcription. It has extensive expression in a variety of human tissues, regulating the activity of transcription of a variety of genes and taking part in a variety of biological processes like embryonic formation, cell apoptosis, chromatin remodeling, etc[1]. Since YY1 was discovered, it has been proposed that how YY1 plays its biological role in the development and progression of tumor on account of the regulatory activity of YY1 on a variety of proteins relating to cancer and signaling pathways in the majority of cancers[2].

Currently, it is known that the function of YY1 can be realized mainly through the regulation of target genes in two main forms : 1) transcriptional activation. In metastatic renal cell carcinoma, it was found that the down-regulation of PTEN protein could promote the expression of YY1 through siRNA interference technology, thus promoting the proliferation of tumor cells [3]; 2) Transcriptional inhibition. YY1 inhibits proliferating cell nuclear antigen (PCNA) expression and phosphorylation of retinoblastoma suppressor protein (Rb) in breast cancer and glioma, thereby inhibiting the proliferation of tumor cells [4].

At present, although there is a large amount of experimental evidence based on cells or animals to support the association between YY1 and cancer [5-10], however, based on large clinical data, the widespread cancer evidence of the relationship between YY1 and a variety of tumor types is still lacking. Therefore, the cancer genome map from Atlas, TCGA and Gene Expression Omnibus (GEO) was used in this study. In addition, we also included several factors like survival status, immune infiltration, RNA methylation, genetic change and related cellular pathways to explore the feasible molecular mechanisms of YY1 in the pathogenic mechanism or clinical prognosis of diverse cancers.

## Results

### In Several Tumor Types YY1 was Highly Expressed and Associated With Clinical Stage

Firstly we evaluated analysis of the expression of YY1 in the pan-cancer data from TCGA, and the results showed that YY1 was highly expressed in 25 tumors which included Adrenocortical carcinoma(ACC), Breast invasive carcinoma(BRCA), Bladder Urothelial Carcinoma(BLCA), Cervical squamous cell carcinoma and endocervical adenocarcinoma(CSEC), Colon Adenocarcinoma(COAD), Cholangiocarcinoma(CHOL), Lymphoid Neoplasm Diffuse Large B-cell Lymphoma(DLBC), Esophageal carcinoma(ESCA), Glioblastoma multiforme(GBM), Head and Neck squamous cell carcinoma(HNSC), Kidney renal clear cell carcinoma(KIRC), Acute Myeloid Leukemia(LAML), Lower Grade Glioma(LGG), Liver hepatocellular carcinoma(LIHC), Lung adenocarcinoma(LUAD), Lung squamous cell carcinoma(LUSC), Ovarian serous cystadenocarcinoma(OV), Pancreatic adenocarcinoma(PAAD), Prostate adenocarcinoma(PRAD), Rectum adenocarcinoma(READ), Stomach adenocarcinoma(STAD), Thyroid carcinoma (THCA), Testicular Germ Cell Tumor(TGCT), Thymoma(THYM), Uterine Carcinosarcoma(UCS), Uterine Corpus Endometrial Carcinoma(UCEC) (Figure.1a). For tumors and normal tissues which were in pair, YY1 had an over-expression in PRAD, LUAD, LUSC, BLCA, KICH, KIRC, HNSC, STAD, COAD, READ, ESCA, LIHC, COAD and CHOL tumor tissues (Figure 1B-M). In addition, we found that YY1 expression was compactly associated with clinical stage. Then the correlation between YY1 expression and the pathological stages of cancers was analyzed by using the Pathological Stage Plot component of HEPIA2. It turned out that patients in relative high clinical stage of cancer got higher YY1 expression, including LIHC, KIRC, OV, SKCM(Figure. 2A-D, all  $P < 0.05$ ).

### YY1 Expression in Tumor Tissue Samples Differed from That in Normal Tissue Samples

The IHC outcomes furnished by HPA data was analyzed and the results of YY1 gene expression data from TCGA were made comparison in order to make assessment on the expression of YY1 at protein level (Figure 3A-L). Data analysis results of the two databases were consistent: moderate YY1 was found in normal kidney, prostate, liver and breast tissue IHC staining, and the tumor tissue was strongly stained.

### High Expression of YY1 was Associated with Poor Cancer Prognosis

The relationship between YY1 expression and some prognostic indicators like OS, PFS, DSS and DFS was analyzed via the TCGA cohort on the purpose of evaluating the value of YY1 in making predictions on the

patients' prognosis. Firstly, we studied the correlation between the expression of YY1 and OS. Cox proportional risk model analysis revealed that the expression level of YY1 was associated with LUAD(P =0.023), KIRP(P =0.023), UCES(P =0.007), LIHC(P =0.014), ACC(P =0.037), KIRC(P =0.006), THYM(P =0.035) (Figure.4A). It's revealed by Kaplan-Meier survival analysis that in LUAD, KIRP, UCES, LIHC and ACC, high expression of YY1 was prominently connected with worse OS, whereas high expression of YY1 was prominently connected with better OS in KIRC and THYM (Figure.4B–H).

Moreover, we also studied the correlation between the expression of YY1 and DSS. Forest maps revealed that the expression of YY1 was correlated with DSS in ACC, PAAD and OV [Figure.5A,all  $p < 0.05$ ]. Meanwhile, Kaplan-meier Survival analysis manifested that in ACC(P =0.042) PAAD(P =0.039), higher YY1 expression was significantly correlated with decreased DSS (Figure.5B,C). However, in OV(P =0.01), higher YY1 expression was significantly correlated with increased DSS (Figure.5D).

Similarly, through data analysis of PFS, we found that in STAD, UCEC, THYM, LUAD, ACC, KIRP, LIHC and BLCA ,the expression of YY1 significant changed [Figure.6A,all  $p < 0.05$ ]. Among these types of tumors, in STAD ( $p = 0.039$ ), UCEC ( $p = 0.008$ ), LUAD ( $p = 0.01$ ), the ACC ( $p < 0.01$ ), KIRP(P =0.036), LIHC(P =0.049), BLCA(P =0.01),PFS decreased, while THYM(P =0.012) high YY1 expression group,PFS increased (Figure.6B–I).

Finally, through the Forest maps of the Cox proportional hazards models analysis, we found that the expression of YY1 in BLCA, ACC, UVM, LUAD KIRC, OV and THYM had a significant change [Figure.7A,all  $p < 0.05$ ]. To be specific, In BLCA(P =0.0029),ACC(P =0.017), UVM(P =0.048), LUAD(P =0.025), higher YY1 expression was notably correlated with decreased DSS , but in KIRC(P =0.0063), In OV(P =0.036) and THYM(P =0.026), higher YY1 expression was significantly correlated with increased DSS (Figure 7B–H).

### **Enrichment Analysis of YY1-related Cooperators**

In order to ulteriorly study the molecular mechanism in tumorigenesis of YY1 gene, we made attempts to screen out YY1 expression related genes of the binding protein targeting YY1 for a sequence of pathway enrichment analysis. Grounded on the STRING tool, to the amount of 50 YY1 binding proteins had been obtained supported by evidence of experiments. The interaction network of these proteins were displayed(Figure. 8A). Then the GEPIA2 tool combined with all expression data of tumors from TCGA was employed to obtain the first 100 gene maps associated with YY1 expression. Figure 6B,C is shown based on Metascape Online GO and KEGG analysis, bar chart. In addition, the hub genes in the YY1-binding and interacted genes were displayed by PPI network and MCODE, along with the connection and distribution of various functions of them(Figure.8D,E).

### **YY1 Expression Correlated With Tumor Mutation Burden and Tumor Microsatellite Instability**

Then, we studied if there is a correlation between the YY1 expression level and TMB and MSI. Results showed that in nine types of cancer, including ACC, PAAD, LUAD, LUSC, SKCM, ESCA, TIICA, DLBC, UVM, YY1 expression is associated with TMB ( $p < 0.05$ ). YY1 expression in ACC,PAAD,LUAD,LUSC and SKCM is

positively associated with TMB, while that in ESCA, TIICA, DLBC and UVM is negatively correlated with TMB (Figure. 9A). At the same time, Genetic variations of YY1 in TCGA tumors were detected using the cBioPortal database. The mutation features of YY1 on the basis of tumors from TCGA was displayed by employing the cBioPortal tool.(Figure. 9B). Then, we made observation on the genetic altered condition of YY1 in various tumor samples from the TCGA cohort. As displayed in Figure 9C, the highest change frequency of YY1 (> 3%) existed in patients with UCEC in which the “mutation” is the dominant type . The CNA “amplified” type was the predominant type of LUSC cases, with a change frequency of about 2.5% (Figure 8C). It is noteworthy that all cases of cholangiocarcinoma CHOL with genetic changes (~3% frequency) had YY1 copy number deletion (Figure. 9C). The connection between copy number of YY1 and expression of mRNA was shown in the dot plot and correlation plot(Figure. 9E) by cBioPortal. All  $p < 0.05$ . Finally, the relationship between YY1 and MSI in STAD (Figure. 9F) and PRAD (Figure. 9G) is illustrated by uESD Scatter.

### **YY1 Expression Levels Had a Correlation with Tumor Immune Cell Infiltration**

A co-expression analysis of gene was conducted to seek the relationship between the expression of YY1 and genes related to immunity in 33 kinds of tumors. Immune-activation genes and other genes encoded chemokine and chemokine receptor proteins. The heat map showed that nearly all of genes related to immunity had co-expression with YY1 (Figure. 10). It's worth noting that almost all genes had a positive correlation with YY1 in every tumor type that we analyzed ( $P < 0.05$ ).

Then, the impact of YY1 on the immune microenvironment of the tumor was ulteriorly analyzed. We examined the relationship between the expression level of YY1 and the infiltration level of immune cell , especially T cells and B cells. We screened out the top 12 tumors which had the highest correlation from the heat map of YY1 expression and immune cell infiltration level(Figure.11). It turned out that in most tumor types that we screened out, the expression levels of T cells and B cells were lower in the group with high YY1 expression. It was noted that in THCA, CESC, BRCA, LUSC, the difference of enrichment scores became more obvious ( $P < 0.001$ ), which meant the expression of YY1 had a negative correlation with the expression levels of T cells and B cells. In THYM, however, T cell expression increased in the group of high YY1 expression ( $P < 0.05$ ).

### **Correlation of YY1 Expression With RNA Methylation**

In addition, a co-expression analysis of YY1 and M6A methylation was conducted to explore the relationship between YY1 expression and RNA methylation. The outcomes showed that in PRAD, LUSC, KIRC, BLCA, LIHC and BRCA tumors, 22 m6A methylation-related cells were co-expressed with YY1 (Figure 12). It should be noted that in LIHC, all m6A methylation-related cells were significantly related to YY1( $p < 0.001$ ).

## **Discussion**

In recent years, studies have shown that YY1 has a high expression in various tumor tissues, including breast[15], prostate[16], ovarian[17], brain[18], osteosarcoma[19], colon[20], esophagus[21], pancreas[22,23], and melanoma[24], YY1 can promote the emergence and growth of tumors by regulating oncogene suppressor gene angiogenesis related factors and inhibiting tumor cell apoptosis, indicating that YY1 could play a significant part in judging the prognosis of tumor patients and tumor targeted therapy[25-28]. However, through literature search, we did not find any literature with generalized cancer analysis of YY1 at the level of overall tumor. Therefore, we made a comprehensive examination on YY1 genes in 33 various tumors grounded on TCGA and GEO database.

In our study, we used TCGA pan-cancer data to detect the expression level and prognostic function of YY1. On the basis of our results, it turned out that YY1 was highly expressed in 25 tumors compared to normal tissue, including ACC, BLCA, BRCA, CSEC, CHOL, COAD, DLBC, ESCA, GBM, HNSC, KIRC, LAML, LGG, LIHC, LUAD, LUSC, OV PAAD, PRAD, READ, STAD, TGCT, THCA, THYM, UCEC, UCS. Differences in expression levels of YY1 in diverse tumor types can extend to different potential capabilities and mechanisms. At the same time, YY1 expression levels are also related to different clinical stages of tumors. We further discovered that over-expression of YY1 usually predicts bad prognosis of tumors, such as LUAD, KIRP, UCES, In LIHC and ACC, high expression of YY1 was prominently connected with worse OS. These results implied that YY1 is likely to be a prognostic biomarker for cancer patients.

TMB is a pan-cancer predictive biomarker with great promise[29] and it can also assist in making prediction on prognosis in pan-cancer patients who already accepted immunotherapy[31]. Besides, MSI is a another significant biomarker in immune-checkpoint inhibitors (ICI)[30,32]. Our results showed that in nine types of cancer YY1 expression is associated with TMB and MSI is concerned with two types of cancer. In our study, although it seemed that there is no specific relevance between the expression of YY1 and TMB, which means the high expression of YY1 can lead to both increasing and decreasing TMB, this finding can still lead to a conclusion that YY1 expression level could influence the TMB and MSI of cancer, thus influencing the reaction of patients to suppression therapy of immune checkpoint which can provides a fresh reference for the immunotherapy prognosis.

The microenvironment of tumor, especially the immune microenvironment, is an important component of tumor biology and a growing body of evidence reveals its clinicopathological importance in making predictions on outcomes and therapeutic outcomes[33,34]. Our research shows that YY1 is connected with immune-related cell infiltration level, especially T cells and B cells. It was noted that the high expression of YY1 inhibited the presence of T cells and B cells in most tumor types, which means the high expression of YY1 has a certain inhibitory effect on the immune infiltration of immune cells. Next a gene co-expression analysis was conducted to observe the relationship between the expression of YY1 and genes related to immunity in 33 kinds of tumors. The heat map showed that nearly all of genes related to immunity had co-expression with YY1. This result further proves that YY1 may affect tumors by regulating immune-related genes and immune cells. Together, our findings indicate that YY1 could be a valuable prognostic biomarker and potential target for immunotherapy.

As is known to all, the morphological and functional diversity of RNA is based on the extensive modification of the four typical base groups of RNA. Since the 1960s, more than 150 chemical modifications of RNA have been discovered [35], among which m6A modification, namely the addition of methyl to the N-6 position of adenosine residue, is the most common in eukaryotes. Common posttranscriptional modifications. Therefore, in order to explore the correlation between the expression of YY1 and M6A methylation, we made a co-expression analysis of YY1 and M6A methylation. It is the first time to explore the correlation between methylation of YY1 promoter and cancer. We found that in PRAD, LUSC, KIRC, BLCA, LIHC and BRCA tumors, 22 m6A methylation-related cells were co-expressed with YY1, such as METTL3, YTHDC1, FTO, RBM15 and so on, which means YY1 expression was associated with RNA methylation. Therefore, YY1 methylation levels can be employed as a prognostic biomarker in cancer patients in years to come. However, the concrete correlation between YY1 and RNA methylation and the specific molecular mechanism of interaction between YY1 and RNA methylation need further experiments and research.

Taken together, our pan-cancer analysis of YY1 verified that YY1 highly expressed in a few tumor types and was associated with clinical stage. Then, on the basis of this conclusion, our study further revealed statistical correlation of YY1 expression with prognostic influence in clinical, immune cell infiltration, m6A methylation, tumor mutational burden and microsatellite instability, which can make a contribution to understanding what role YY1 are playing in tumorigenesis. Nevertheless, it is necessary that we need more basic and large clinical trails to validate these findings.

## Conclusion

Our study leads to a suggestion that YY1 may be a marker of bad prognosis and high expression of YY1 may lead to immune infiltration and be connected to m6A methylation.

## Materials And Methods

### Data acquisition and YY1 Expression Analysis

Profiles of YY1 expression and clinical pan-cancer data from TCGA (contains 11069 samples from 33 types of cancer) were downloaded by using the UCSC Xena (<https://xenabrowser.net/datapages/>) database, which can explore the expression of gene and phenotype information as an on-line tool. In order to avoid the analysis error caused by the small sample size, we selected not less than 5 normal samples of cancer species for follow-up analysis. On the purpose of standardization, quantile normalization was conducted on all data using the log<sub>2</sub>-scale transformation. The comparison of YY1 expression between normal samples and tumor samples were made by Wilcoxon test.

### Survival prognosis analysis

Kaplan-meier survival analysis was grounded on the best cut-off value pair, patients from TCGA were split into two groups with high YY1 expression and low YY1 expression, and overall survival (OS), progression-

free survival(PFS), disease-specific survival(DSS) and disease-free survival(DFS) were made comparison between the two groups. The optimal cut-off value was determined by using the surV-Cutpoint function in surVMINER R package. The survival curve between the two groups was made by Survival R package. Cox regression analysis took the expression of YY1 as a continuous variable to analyze the correlation between the expression of YY1 and the overall survival rate of the patients. Cases without prognostic follow-up were excluded from the survival analysis. Based on Cox proportional hazards model and Kaplan-Meier model, the risk ratio (HR) was calculated, with  $p \leq 0.05$  statistically significant differences.

### **Genetic variation analysis**

Firstly enter the cBioPortal website(<https://www.cbioportal.org/>)[11,12]. Then select “the TCGA pan-cancer map study” in the “rapid selection” section. Next, query the genetic change characteristics of YY1 by entering “YY1”. Lastly, in the “cancer type summary” module, the changing frequency of the mutation types along with CNA(copy number change) results of overall TCGA tumors can be found.

### **Correlation of YY1 Expression With Tumor Mutation Burden(TMB) and Tumor Microsatellite Instability(MSI).**

Tumor Mutation Burden(TMB) is a quantifiable immune response biomarker which reflects the mutation numbers in tumor cells[13]. A Perl script was used to calculate the TMB score which was corrected then by the overall length of exon extras. The MSI rating of all samples was determined according to somatic mutation data which was downloaded from TCGA (<https://tcga.xenahubs.net>) and then we used Spearman rank correlation coefficient to analyze the relationship between YY1 expression and TMB and MSI.

### **Immune infiltration analysis**

Tumor Immune Estimation Resource (TIMER) is a comprehensive database (<https://cistrome.shinyapps.io/timer/>), which is employed to predict gene expression quantity relationship with the condition of each type of immune cell infiltration [14]. Next the correlation between YY1 expression and various tumor cells related to immune infiltration online was analyzed, including CD8+ T cells, CD4+ T cells, B cells, neutrophils, monocytes and dendritic cells.

### **YY1-related gene enrichment analysis**

To query protein name and species with STRING (YY1; Homosapiens), and then set the following parameters: the minimum interaction score required set to low reliability 0.150; The line color indicates the type of interactive evidence; Maximum number of interactive objects to display: no more than 50; Interaction source: At the end of the experiment, 50 experimentally verified proteins binding to YY1 were screened out and GEPIA2 was used for correlation analysis. Grounded on TCGA and GTEx data sets, the top 100 genes associated with YY1 were selected and YY1 was selected from them Log2TPM was used as the Pearson correlation analysis scatter plot for the pair of genes, and P value and correlation

coefficient R were given according to the correlated genes selected in the previous step. The correlation heat map between the selected genes and YY1 was made for further screening of the base. Next, the interactive Wayne figure (Venn diagram) viewer Jvarkit were used to make correlation of 100 gene and protein interactions of 50 intersection analysis. In addition, combine two sets of data in KEGG (kyotoencyclopediaofgenesanddrugs - names) road Analysis by gene list uploaded to DAVID (databaseforannotation, the visualization, andintegrateddiscovery), and select OFFICIAL\_GENE\_SYMBOL and Homosapiens as gene identifier and the species respectively, got the functional annotation data In the end, a kind of used for data analysis and visualization in flat platform (<http://www.bioinformatics.com.cn>) to draw bubble chart displays the pathway enrichment In addition, the GO(geneontology) rich set analysis for biologicalprocess (BP) cell compo-nent (CC) and partition work are also carried out (MolecularFunction,MF) data visualization.

## Statistical analysis

Univariate and multivariate Cox regression analyses were conducted via R package “survival”[32], and the hazard ratios (HRs) and 95% confidence intervals (CIs) in the same way. Additionally, the difference of diverse clinical factors was made comparison by means of the independent t test.  $P < 0.05$  manifested statistical significance.

## Abbreviations

YY1: Yin-yang1; TCGA: The Cancer Genome Atlas; OS: overall survival; PFS: progression-free survival; DSS: disease-specific survival; DFS: disease-free survival; TMB: tumor mutation burden

## Declarations

**Consent for publication:** All authors agree for publication.

**Availability of data and material:** Profiles of YY1 expression and clinical pan-cancer data from TCGA(contains 11069 samples from 33 types of cancer) were downloaded by using the UCSC Xena (<https://xenabrowser.net/datapages/>) database.

**Authors' contributions:** Ke-Hao Pan is the only first author. Nai-Peng Shi is the second author. Yi-Fan Liu, Ya-Li Wang and Ming Chen is the co-corresponding author. Yi-Fan Liu is the first corresponding author.

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**Informed consent:** This article does not contain any studies with human participants or animals performed by any of the authors.

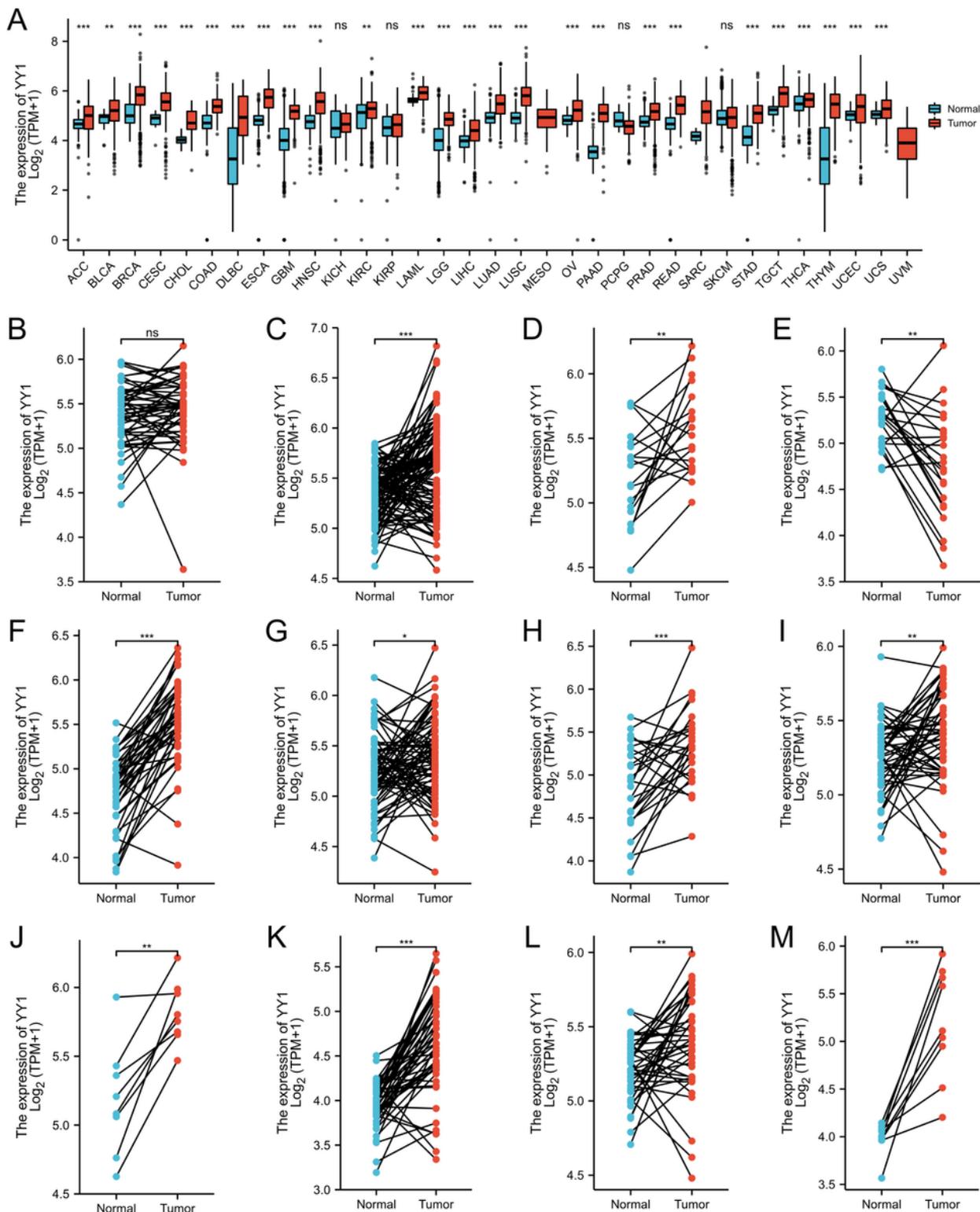
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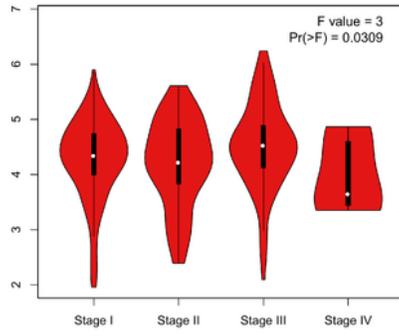
## Figures



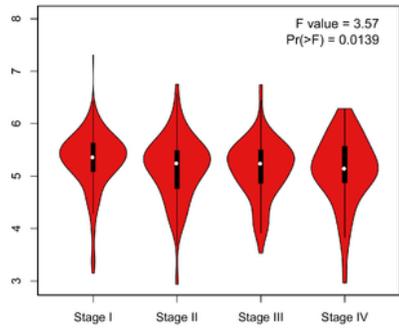
**Figure 1**

(A) Increased or decreased YY1 of different cancers compared with normal tissues in the TCGA and GTEx database. Differential expression levels of YY1 in PRAD (B), LUADLUSC (C), BLCA (D), KICH (E), KIRC (F), HNSC (G), STAD (H), COADREAD (I), ESCA (J), LIHC (K), COAD (L), CHOL (M). P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.

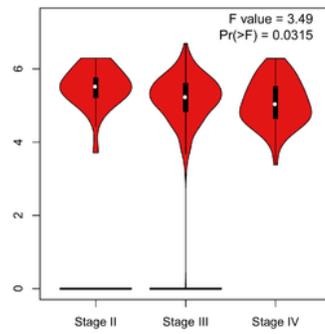
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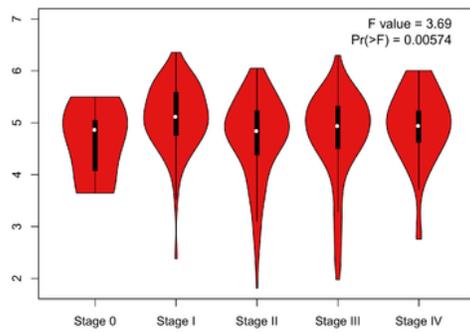
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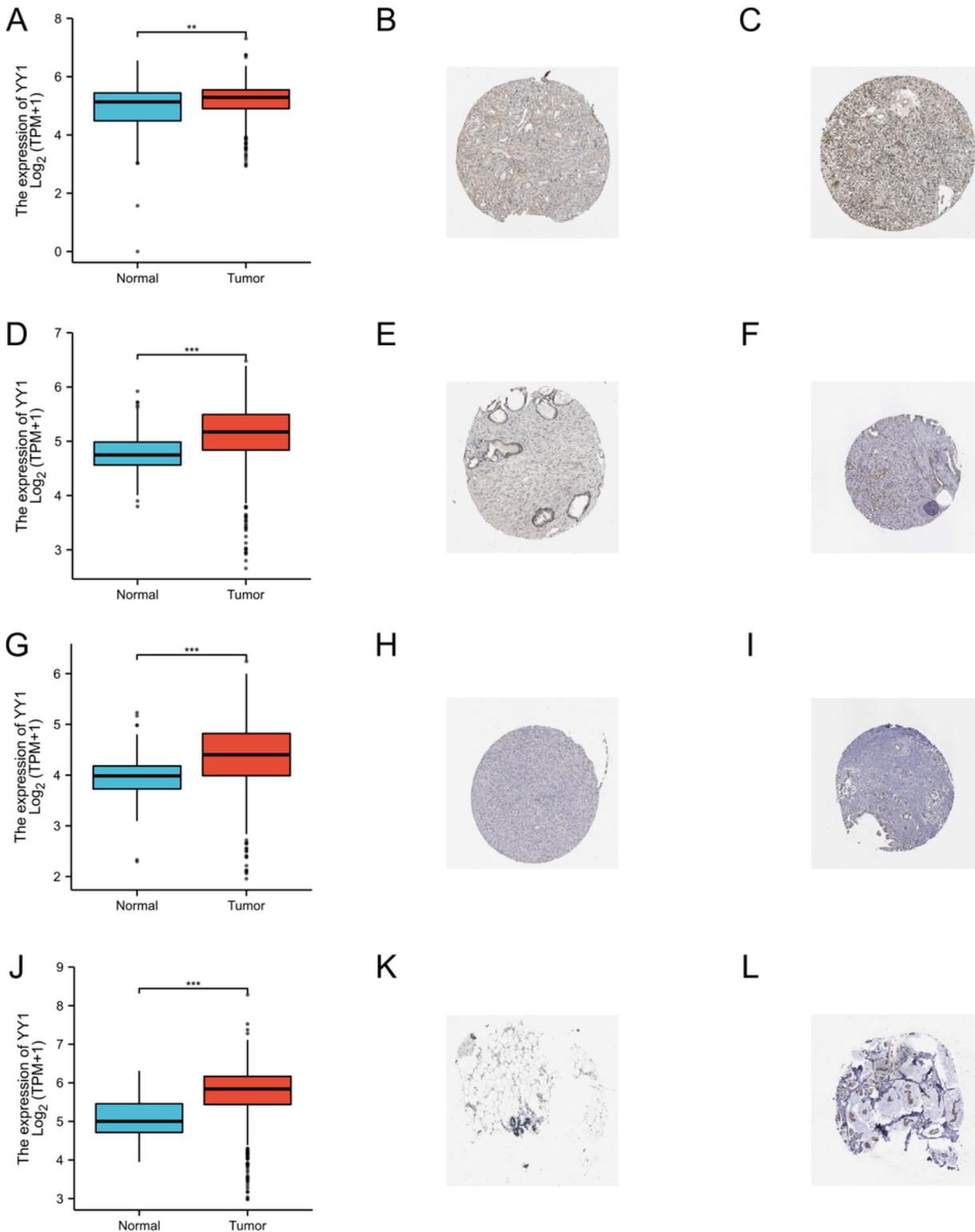


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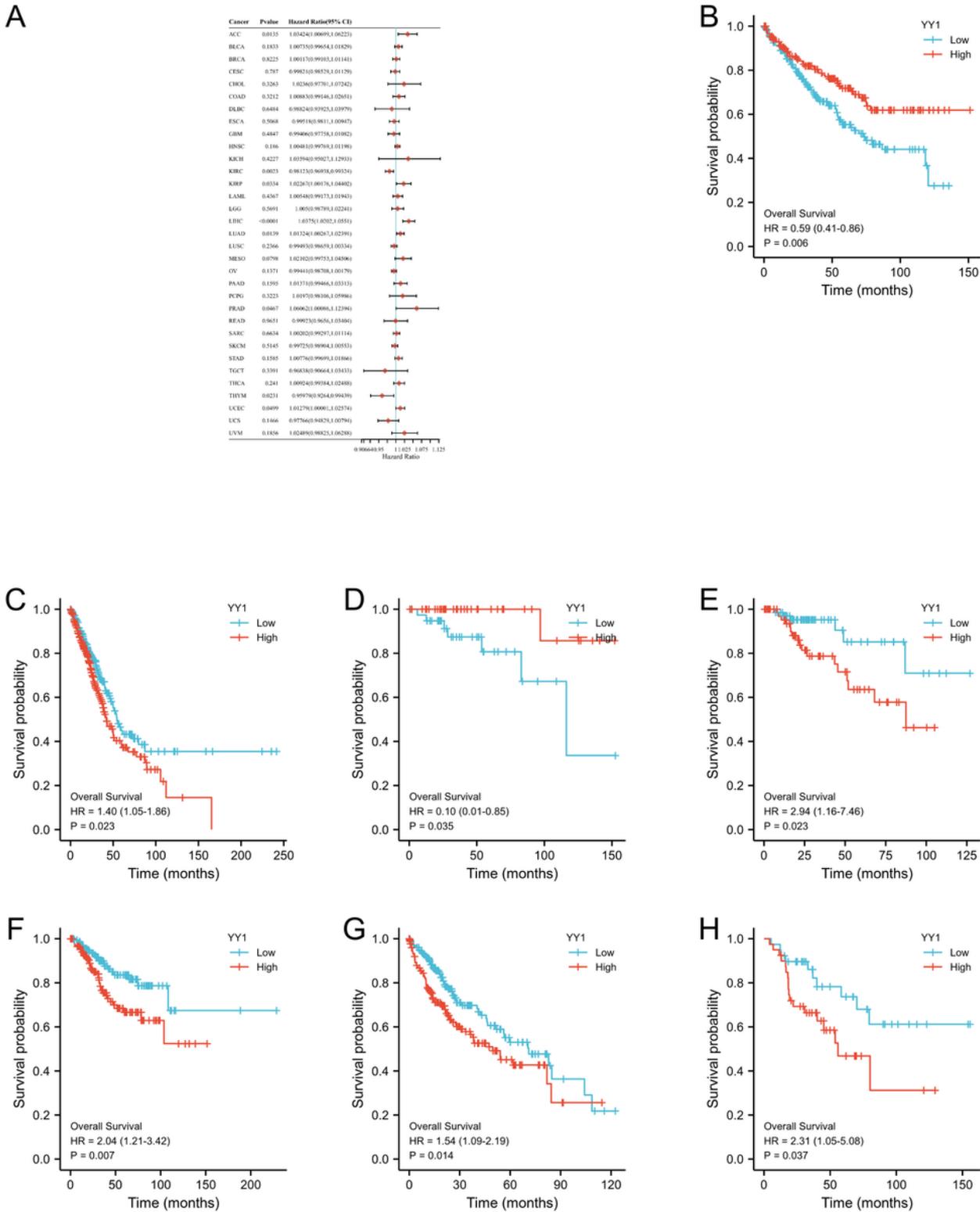
**Figure 2**

Association between YY1 expression and tumor stage in (A) LIHC, (B) KIRC, (C) OV, (D) SKCM.



**Figure 3**

Comparison of YY1 gene expression between normal and tumor tissues (left) and immunohistochemistry images in normal (middle) and tumor (right) tissues. YY1 protein expression was significantly higher in KIRC (A), PRAD (D), LIHC (G) and BRCA (J) tissues than normal tissues.  $P < 0.05$ ,  $**P < 0.01$ ,  $***P < 0.001$ .



**Figure 4**

Association between YY1 expression and overall survival time in months (OS). (A) Forest plot of OS associations in 33 types of tumor. (B-H) Kaplan-Meier analysis of the association between YY1 expression and OS. (B): KIRC, (C): LUAD, (D): THYM, (E): KIRP, (F): UCES, (G): LIHC, (H): ACC

A

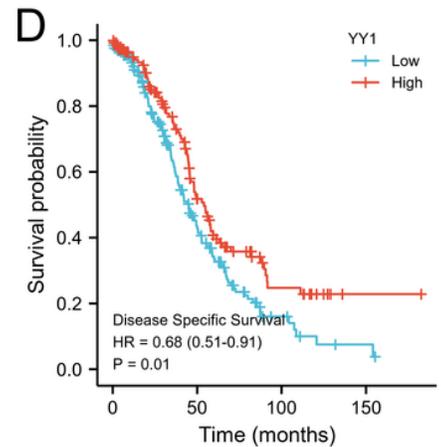
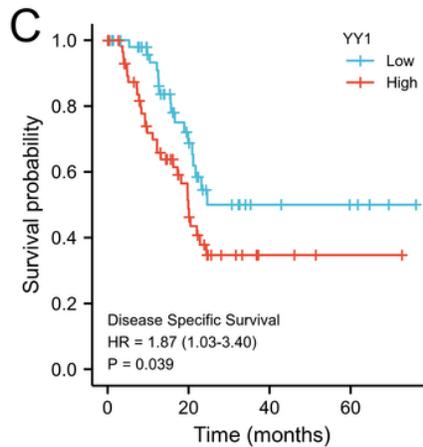
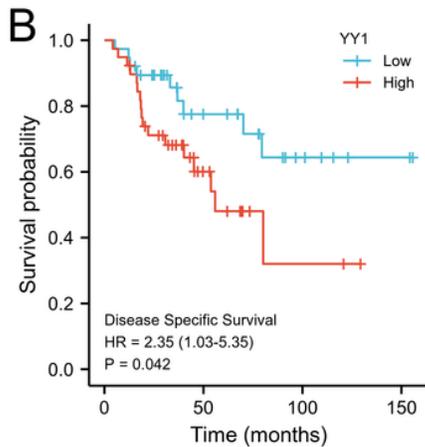
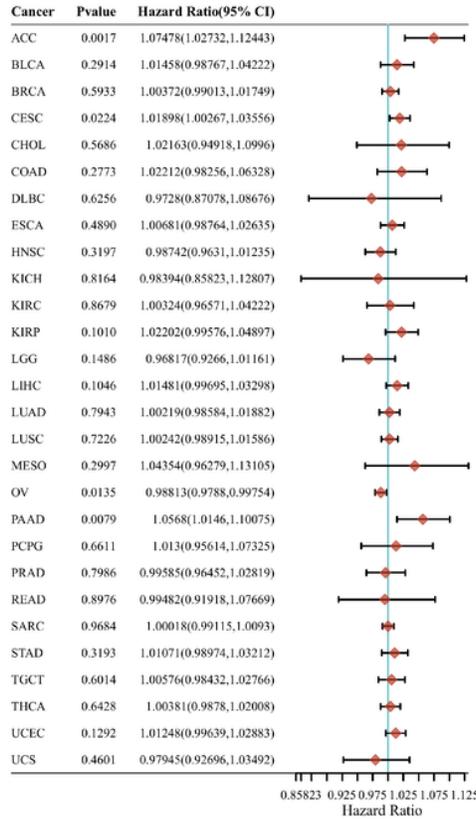


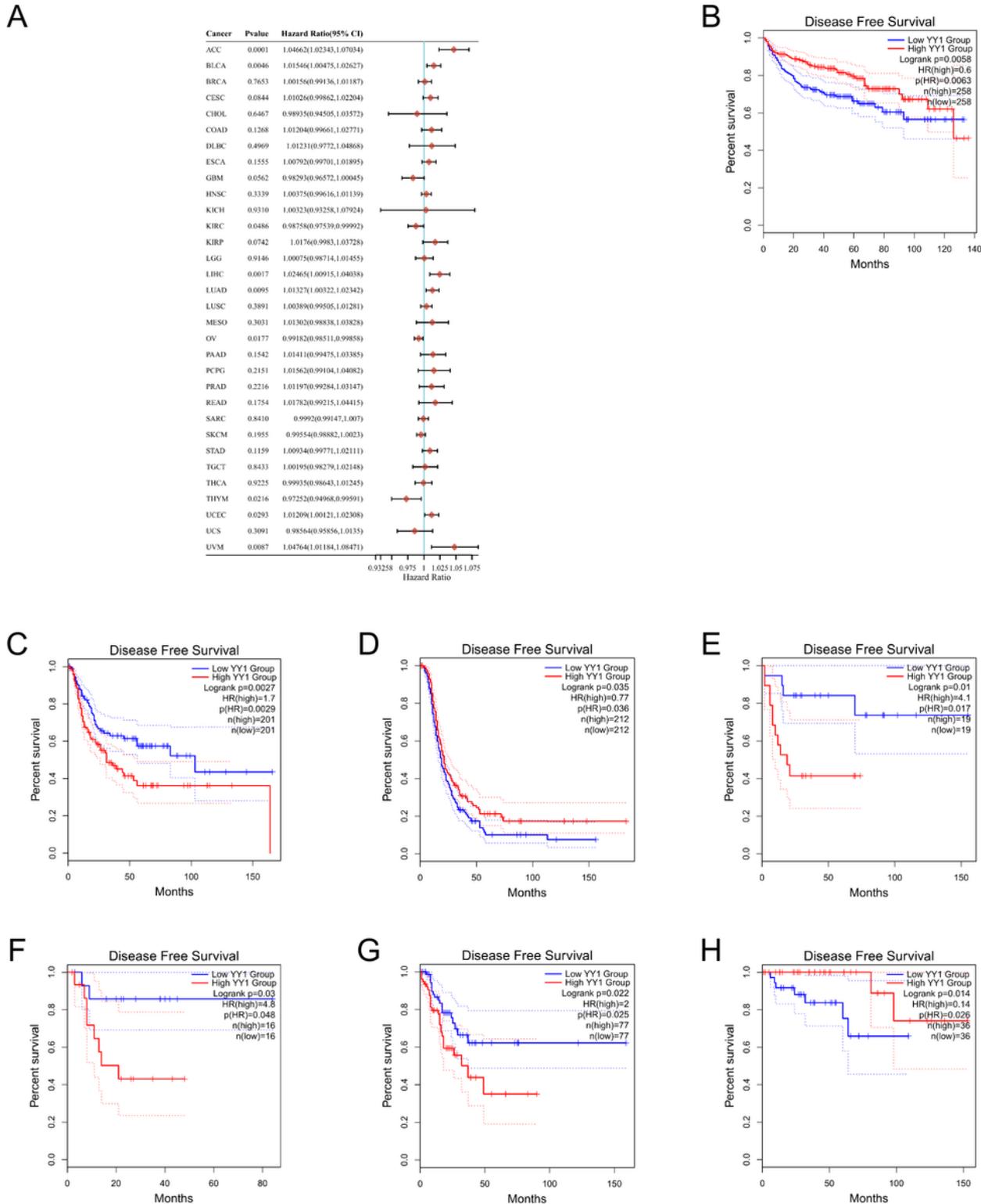
Figure 5

Association between YY1 expression levels and disease-specific survival (DSS). (A) Forest plot of association of YY1 expression and DSS in 33 types of tumor. (B-D) Kaplan-Meier analysis of the association between YY1 expression and DSS. (B): ACC, (C): PAAD, (D): OV.

Figure 6

Association between YY1 expression and progression-free survival (PFS). (A) Forest plot of PFS association with YY1 expression in 33 tumor types. (B-l) Kaplan-Meier analysis of the association

between YY1 expression and PFS. (B): STAD, (C): THYM, (D) UCEC, (E): LUAD, (F): ACC, (G): KIRP, (H): LIHC, (I): BLCA.



**Figure 7**

Association between YY1 expression levels and disease-free survival (DFS). (A) Forest plot of association of YY1 expression and DFS in 33 types of tumor. (B-H) Kaplan-Meier analysis of the association between YY1 expression and DFS. (B): KIRC, (C): BLCA, (D): OV, (E): ACC, (F): UVM, (G): LUAD, (H): THYM.

## Figure 8

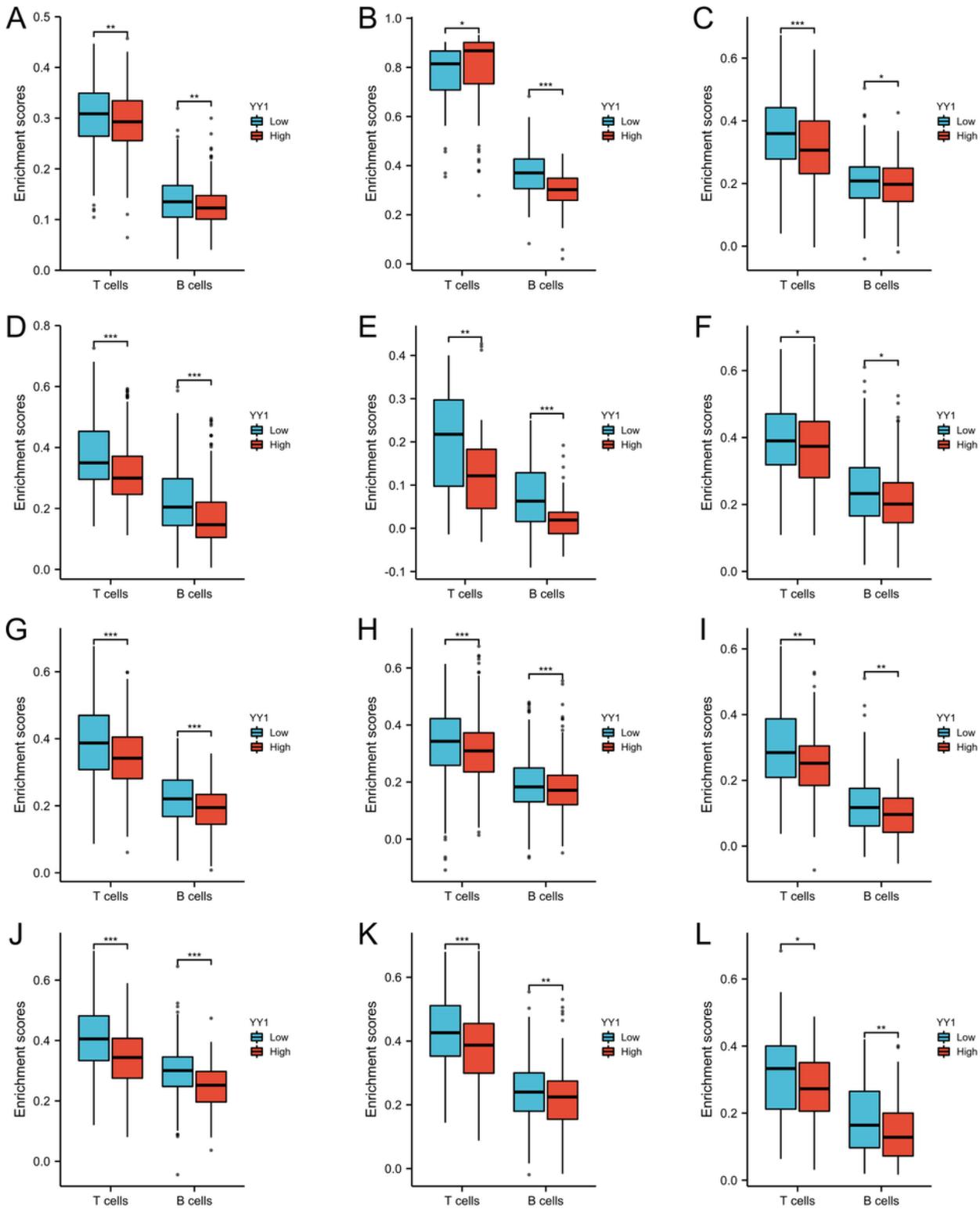
YY1-related gene enrichment analysis. (A) We first obtained the 50 available experimentally determined YY1-binding proteins using the STRING tool. (B-C) Using the GEPIA2 approach, we also obtained the top 100 YY1-correlated genes in TCGA projects and Graph showing the GO and KEGG analysis based on the Metascape Online, bar plot, and network showing the distribution and relationship of the different functions of YY1-binding and interacted genes. (D-E) PPI network and MCODE showing the hub genes in the YY1-binding and interacted genes.



expression are shown in the dot plot (D) and correlation plot (E) by cBioPortal. All  $P < 0.05$ . (F-G) Scatter diagram illustrating the relationship between YY1 and MSI in STAD (F) and PRAD (G).

## Figure 10

(A) Co-expression of YY1 and immune-related cells. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . (B) Co-expression of YY1 and immune-suppressive genes. (C) Co-expression of YY1 and immune-activation genes. (D) Co-expression of YY1 and chemokines. (E) Co-expression of YY1 and chemokines receptors.



**Figure 11**

Twelve tumors between YY1 expression and the tumor microenvironment including T cells and B cells. (A-L) Correlation between YY1 and T cells and B cells in KIRC (A), THYM (B), UCEC (C), THCA (D), BRCA (E), STAD (F), CESC (G), BRCA (H), SARC (I), LUSC (J), HNSC (K) and ESCA (L).

## Figure 12

M6A methylation coexpression heat map. Co-expression of YY1 and m6A methylation-related cells in (A) PRAD, (B) LUSC, (C) KIRC, (D) BLCA, (E) LIHC and (F) BRCA.