Discover Oncology

Analysis

Effects of Coronin 2A on prognosis and immune microenvironment in tumor patients: a knowledge map of the novel biomarker via bioinformatics analysis

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Abstract

Background Recent studies have highlighted the vital role of CORO2A in tumor proliferation, migration, and metastasis. However, its immunological and prognostic significance across various cancers remains poorly understood.

Methods We conducted an analysis of CORO2A expression patterns, prognostic value, and immunological associations across multiple cancers using data from TCGA, Kaplan–Meier Plotter, PrognoScan, TISIDB databases, as well as GEPIA2, TIMER2, and Xiantao Academic Web. Additionally, CORO2A-associated gene enrichment analysis was performed using STRING, GEPIA2, GO, DAVID, and KEGG datasets.

Results Our findings revealed elevated CORO2A expression in most cancers compared to corresponding normal tissues. Lower CORO2A expression was associated with longer OS (overall survival), DFS (disease-free survival), RFS (recurrence-free survival), and DMFS (distant metastasis-free survival) in some cancer types, while the opposite trend was observed in others. CORO2A expression showed significant correlations with the abundance of tumor-infiltrating lymphocytes, immunomodulators, chemokines, as well as the infiltration levels of CAF (cancer-associated fibroblasts) and MDSC (myeloid-derived suppressor cells) across various cancers. We also found that the expression of CORO2A closely related to the markers of immune cell in LUAD and LUSC. Enrichment analysis revealed that CORO2A-related genes were primarily involved in actin filament organization, cell leading edge dynamics, actin binding, and pathways related to pathogenic Escherichia coli infection.

Conclusion Our pan-cancer study provided a relatively comprehensive understanding of the oncogenic roles of CORO2A across different tumor types. We identified CORO2A as a prognostic biomarker and demonstrated its correlation with immune cell infiltration in pan-cancer contexts.

Keywords Prognostic biomarker · Immune · Oncology

Abbreviations

OS	Overall survival
DFS	Disease-free survival
DMFS	Distant metastasis-free survival
RFS	Recurrence-free survival

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CAF	Cancer-associated fibroblasts
MDSC	Myeloid-derived suppressor cells
CORO2A	Coronin 2A
ACC	Adrenocortical carcinoma
BLCA	Bladder Urothelial Carcinoma
BRCA	Breast invasive carcinoma
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL	Cholangio carcinoma
COAD	Colon adenocarcinoma
DLBC	Lymphoid neoplasm diffuse large B-cell lymphoma
ESCA	Esophageal carcinoma
GBM	Glioblastoma multiforme
HNSC	Head and Neck squamous cell carcinoma
KICH	Kidney Chromophobe
KIRC	Kidney renal clear cell carcinoma
KIRP	Kidney renal papillary cell carcinoma
LAML	Acute Myeloid Leukemia
LGG	Brain Lower Grade Glioma
LIHC	Liver hepatocellular carcinoma
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
MESO	Mesothelioma
OV	Ovarian serous cystadenocarcinoma;PAADPancreatic adenocarcinoma
PCPG	Pheochromocytoma and Paraganglioma
PRAD	Prostate adenocarcinoma
READ	Rectum adenocarcinoma
SARC	Sarcoma
SKCM	Skin Cutaneous Melanoma
STAD	Stomach adenocarcinoma
TGCT	Testicular Germ Cell Tumors
THCA	Thyroid carcinoma
THYM	Thymoma
UCEC	Uterine Corpus Endometrial Carcinoma
UCS	Uterine Carcinosarcoma
UVM	Uveal Melanoma
OSCC	Oral squamous cell carcinoma

1 Introduction

The complexity of neoplastic pathogenesis and mechanisms results in considerable heterogeneity across various types of tumors. This heterogeneity involves genetic mutations, tumor microenvironment, immune cell composition, and treatment responses. Recognizing and addressing this heterogeneity is vital for developing tailored diagnostic and therapeutic strategies for each tumor type. Furthermore, acknowledging this heterogeneity underscores the importance of conducting comprehensive analyses, such as the one you have undertaken, to elucidate the unique roles and implications of specific genes or biomarkers across diverse cancer types. However, databases such as TCGA [1], PrognoScan [2], TIMER2 [3], GEPIA2 [4], Kaplan–Meier plotter [5], and TISIDB [6], offer extensive datasets on patients with various tumors. These resources allow us to analyze the role and pathogenesis of a gene across multiple cancer types, enabling pan-cancer studies.

Coronins constitute an evolutionarily conserved family of WD-repeat actin-binding proteins known to promote cell motility and modulate other actin-dependent processes [7–9]. Studies have highlighted their vital role in various cellular processes, including tumor cell migration and invasion [10]. CORA2A (Coronin 2A), also identified as WDR2, IR10, CLIPINB, and CRN5, belongs to the coronin family. It encodes a protein with five WD repeats, exhibiting structural similarities to

actin-binding proteins [7]. Furthermore, previous research has identified CORO2A as a novel component of the N-CoR (nuclear receptor co-repressor) complex, where it regulates the inactivation of inflammatory response genes through phosphorylation and nuclear receptor signaling pathways [11–13]. Recent studies have revealed that elevated expression of CORO2A is related to bad survival and malignant progression in colon cancer. Furthermore, CORO2A is a cornerstone in cancer-related cellular functions involving the actin cytoskeleton, as well as modulating the MAPK14 and PRMT5 signaling pathways [14]. In breast cancer, knockdown of CORO2A reduced the viability of cell proliferation and migration. Moreover, breast cancer patients with high CORO2A expression exhibited poorer survival prognosis [15]. A previous investigation in endometrioid carcinoma and clear cell carcinoma histocytes of epithelial ovarian cancer suggested that increased CORO2A expression was associated with shorter PFS time. However, the opposite trend was observed in patients with high-grade serous carcinomas [16]. High expression of CORO2A in OSCC (Oral squamous cell carcinoma) clinical tissues was highly predictive of poor prognosis in OSCC patients. Knockdown experiments showed that the expression of CORO2A promoted malignant transformation of cancer cells, such as cell proliferation, migration and invasion[17]. The above research results suggested that CORO2A might play a vital role in the carcinogenesis and tumor development. Nonetheless, the association between CORO2A and various tumor types has not been demonstrated for pan-cancer, despite extensive clinical data.

In the present research, we implemented a comprehensive study covering various factors including the condition of gene expression and survival prognosis, immunoinfiltration and enrichment analysis. Our primary aim was to explore the immunological and prognostic role of CORO2A in pan-cancer. To achieve this, we utilized data from multiple datasets including TCGA, GEPIA2, TIMER2, PrognoScan, Kaplan–Meier plotter, and TISIDB. By employing these diverse datasets, we aimed to further elucidate the potential molecular mechanism of CORO2A in the pathogenesis or clinical prognosis of different tumors.

2 Methods and materials

2.1 Expression analysis

We employed the TIMER2 (http://timer.cistrome.org/) and Xiantao Academic Web (https://www.xiantao.love/) to investigate the differential expression of the CORO2A gene in various tumors. Additionally, we explored the relationship between CORO2A expression and clinical pathology stage in pan-cancer using the GEPIA2 (http://gepia2.cancer-pku.cn/#index) Web tool.

2.2 Prognosis analysis

Initially, we utilized the GEPIA2 (http://gepia2.cancer-pku.cn/#index) Web tool to assess the impact of CORO2A expression on OS (Overall Survival) and DFS (Disease-free Survival) in pan-cancer. Subsequently, data from the Kaplan–Meier plotter (https://kmplot.com/analysis/) and PrognoScan databases (http://dna00.bio.kyutech.ac.jp/PrognoScan/index.html) were utilized to confirm the effects of CORO2A expression on survival prognosis.

2.3 Immune infiltrating analysis and prognosis analysis

We comprehensively investigated the correlation between CORO2A expression and the infiltration levels of immune cells using the TIMER2 and Xiantao Academic Web tools. Additionally, we employed TIMER2 Website to explore the impact of both CORO2A expression levels and immune cell infiltration on prognosis.

2.4 TISIDB dataset analysis

The TISIDB dataset (http://cis.hku.hk/TISIDB) serves as a comprehensive platform for the interactions between cancer and immune system, integrating a variety of heterogeneous data types. The TISIDB dataset was employed to conduct the correlation between CORO2A gene expression and various factors such as tumor-infiltrating lymphocytes (TILs), immune modulators, and chemokines. This approach provided a comprehensive understanding of CORO2A's involvement in the tumor microenvironment and immune responses.

2.5 Enrichment analysis

In our study, we initially identified the top 50 CORO2A-binding proteins employing the STRING Web tool (https://string-db.org/). CORO2A-protein interactions were obtained by BioGRID (https://thebiogrid.org). Subsequently, we obtained the top 100 CORO2A-associated genes through the utilization of the GEPIA2 tool. Additionally, the TIMER2 Web platform was employed to generate heatmap data pertaining to the selected genes. We then conducted a cross analysis and compared the CORO2A-connecting and crossed genes using the Bioinformatics & Evolutionary Genomics Web. Finally, we integrated the two sets of data to perform GO analysis and KEGG pathway analysis, aiming to gain insights into the potential biological functions and pathways associated with CORO2A and its interacting proteins and genes.

2.6 Statistical analysis

Survival diagrams were obtained via utilizing Kaplan–Meier Plotter, PrognoScan databases, TIMER2 Web, and GEPIA2 Web. These maps included Hazard Ratios (HR), P values, or P values from log-rank tests. Additionally, Spearman's and Pearson's relation analyses were employed to measure the relevancy between special variables, with a significance level set at $P < 0.05$ unless otherwise specified. This rigorous statistical approach ensured that our findings were supported by robust and statistically significant evidence.

3 Results

3.1 The different expression of CORO2A between pan-cancer and corresponding normal tissues

In Fig. 1A, the distinction of CORO2A expression between pan-cancer and normal tissues was analyzed by employing TIMER2 Web. The results exhibited that CORO2A expression was significantly elevated in BRCA (Breast invasive carcinoma), CESC (Cervical squamous cell carcinoma and endocervical adenocarcinoma), HNSC (Head and Neck squamous cell carcinoma), ESCA (Head and Neck squamous cell carcinoma), LIHC (Liver hepatocellular carcinoma), PAAD (Pancreatic adenocarcinoma), KIRC (Kidney renal clear cell carcinoma), PRAD (Prostate adenocarcinoma), PCPG (Pheochromocytoma and Paraganglioma), LUAD (Lung adenocarcinoma), LUSC (Lung squamous cell carcinoma), STAD (Stomach adenocarcinoma), UCEC (Uterine Corpus Endometrial Carcinoma), and THCA (Thyroid carcinoma), in comparison with the relevant normal tissues. However, in GBM (Glioblastoma multiforme), COAD (Colon adenocarcinoma), and KICH (Colon adenocarcinoma), CORO2A expression was markedly decreased compared to normal tissue. Because the data from TIMER2 Web did not match the normal tissue profiles of ACC (Adrenocortical carcinoma), LAML (Acute Myeloid Leukemia), DLBC (Lymphoid Neoplasm Diffuse Large B-cell Lymphoma), LGG (Brain Lower Grade Glioma), OV (Ovarian serous cystadenocarcinoma), TGCT (Testicular Germ Cell Tumors), THYM (Thymoma), and UCS (Uterine Carcinosarcoma), we employed the Xiantao Academic Web to match the normal tissues of TCGA and GTEx datasets for these cancers, thus further verifying CORO2A' expression in pan-tumor. The results were in accord with data analysis of TIMER2 Web (Fig. 1B). In addition, Fig. 1B further illustrated the consistency of lower expression of CORO2A in LAML, LGG, THYM, and UCS compared to their corresponding tissues, while CORO2A's expression in ACC and OV was increased, in comparsion with normal tissues. As shown in Fig. 1C, we employed the GEPIA2 tool to analyze the relationship between CORO2A expression and the clinicopathological staging of cancer patients, finding that marked results were shown in BRCA, KICH, LIHC, PAAD, TGCT, and THCA.

3.2 Prognosis analysis of CORO2A expression in pan-cancer via GEPIA2 Web

In this section, we utilized the GEPIA2 tool to investigate the prognostic differences between high and low CORO2A expression groups. As depicted in Fig. 2A, the impact of CORO2A expression on OS (Overall Survival) in pan-cancer was visualized using a heatmap, with significant results presented via Kaplan–Meier plots. We observed that the OS of the high CORO2A expression group in ACC and LUAD was notably longer than that of the low expression group. Conversely, in BRCA and GBM, the OS of the high CORO2A expression group was significantly shortened compared to the low expression group. Additionally, we assessed the effects of CORO2A expression on DFS (Disease-Free Survival) in pan-cancer (Fig. 2B). It was noted that the DFS of the low CORO2A expression group in ACC, LUAD, and PCPG was markedly shorter

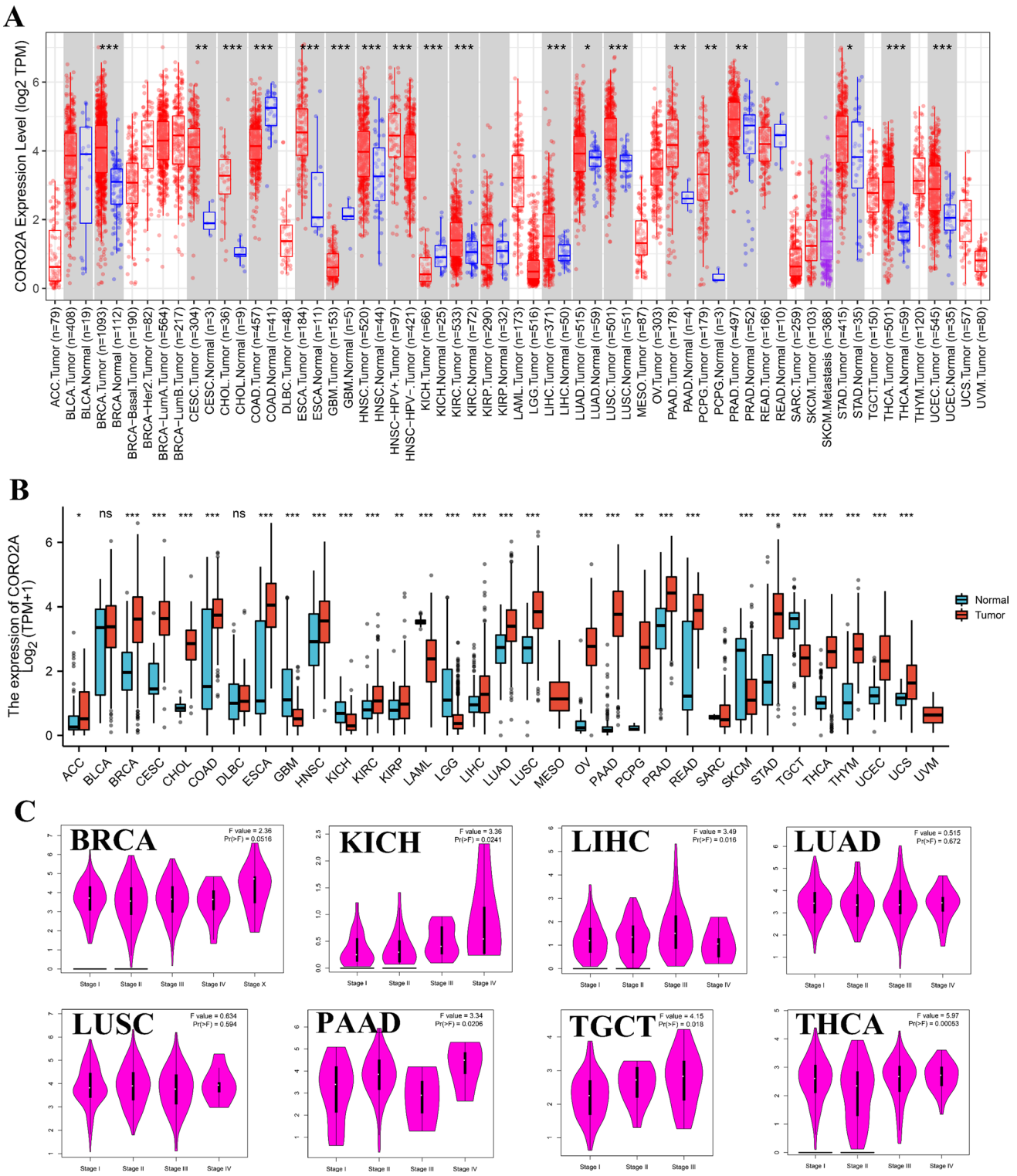


Fig. 1 The distinction of CORO2A expression between pan-tumor and regular tissues. CORO2A expression of pan-cancer and normal controls were analyzed by TIMER2.0 Web (**A**) and Xiantao Academic Web (**B**)**.** Correlation analyses between CORO2A expression and pathological stage of cancer patients were exhibited by GEPIA2 Web (**C**). Not significant (ns, $p \geq 0.05$), * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$

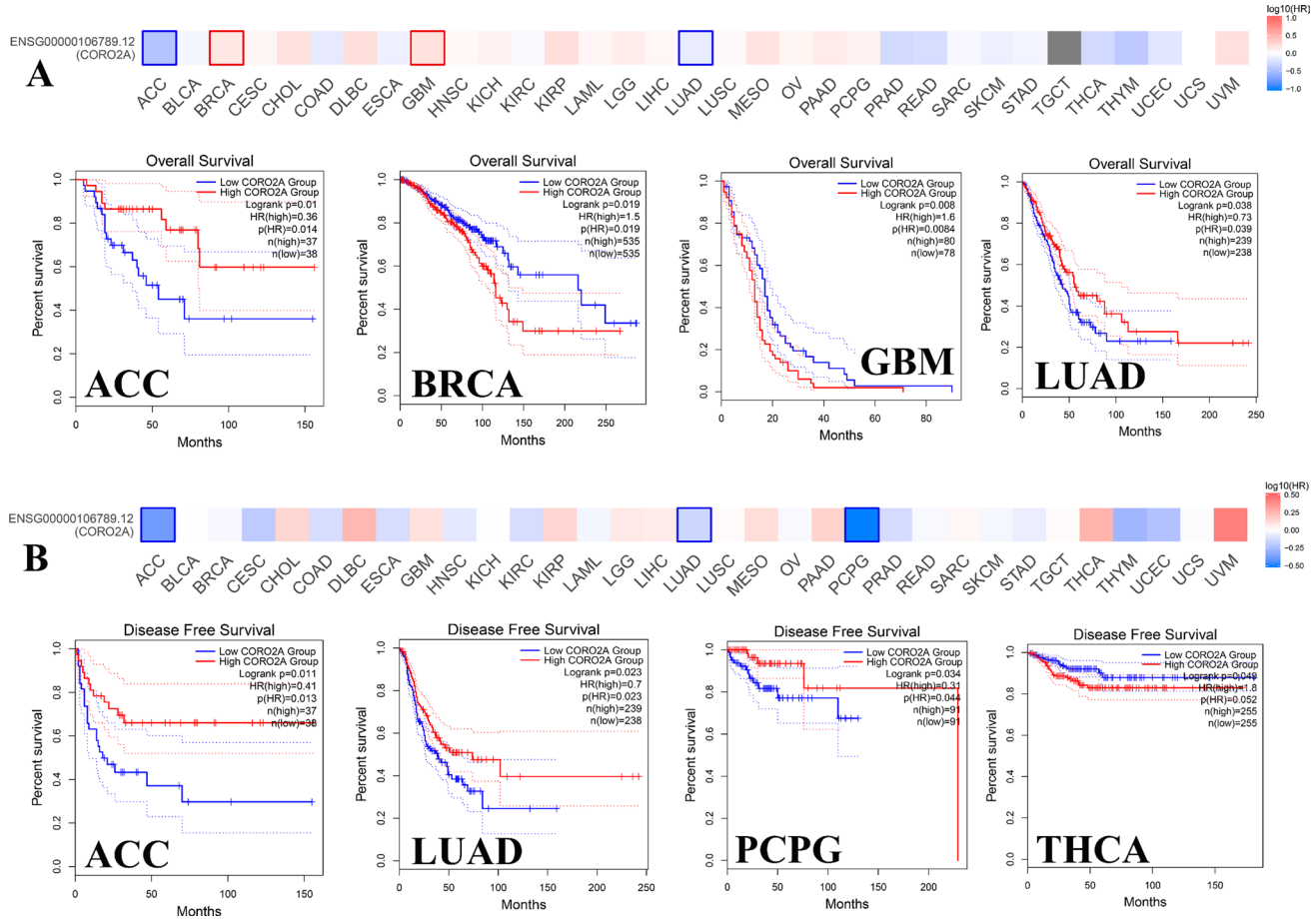


Fig. 2 Impacts of CORO2A expression on OS and DFS in pan-cancer via GEPIA2 Web. We used the GEPIA2 tool to explore prognostic difference in different cancer patients between high and low CORO2A group, including OS (**A**) and DFS (**B**)

than that of the high expression group. However, in THCA, DFS was notably longer in the low expression group compared to the high expression group.

3.3 Effects of CORO2A expression on survival prognosis in pan-cancer via using PrognoScan dataset

In this section, we delved deeper into the impact of CORO2A expression on prognosis across different cancer types. The results revealed significant differences in DFS and DMFS (Distant Metastasis-Free Survival) between the low and high expression groups in breast cancer, with the low expression group exhibiting notably prolonged DFS and DMFS compared to the high expression group (Fig. 3A, B). Similarly, in lung cancer, OS (Overall Survival) was extended in the high CORO2A expression group compared to the low expression group, consistent with previous findings from the GEPIA2 tool (Fig. 3C). Conversely, in colorectal cancer, the DFS of the high expression group surpassed that of the low expression group (Fig. 3D). Furthermore, our analysis indicated CORO2A as a potential poor prognostic biomarker for renal cancer (Fig. 3E), while it served as a favorable prognostic factor for ovarian cancer (Fig. 3F), AML (Acute Myeloid Leukemia) (Fig. 3G), and follicular lymphoma (Fig. 3H). These findings underscored the diverse prognostic implications of CORO2A expression across different cancer types.

3.4 Prognostic analysis of CORO2A in pan-cancer via employing Kaplan–Meier plotter dataset

In this segment, the RNA Sequencing data from the Kaplan–Meier plotter were utilized to further validate impacts of CORO2A expression on survival prognosis across various tumor types, as illustrated in Fig. 4. Notably, in bladder tumor, high expression level of the CORO2A gene was related to prolonged OS (Fig. 4A). Conversely, in breast cancer, low expression of CORO2A was linked to extended overall survival but detrimental to the recurrence-free survival (Fig. 4B, C). For

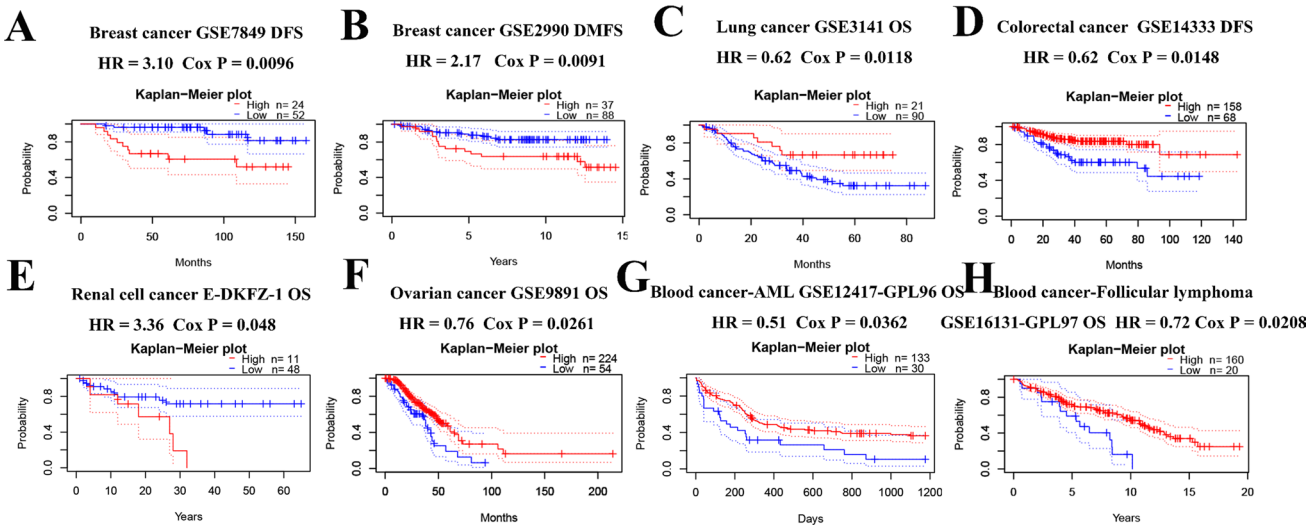


Fig. 3 Prognosis analysis of CORO2A expression in different tumors by using data from PrognoScan database. **A**, **B** CORO2A expression affected the DFS and DMFS in breast cancer patients. CORO2A expression played a vital role for OS in lung cancer (**C**), colorectal cancer (**D**), renal cancer (**E**), ovarian cancer (**F**), AML (**G**), and follicular lymphoma (**H**) tumor patients

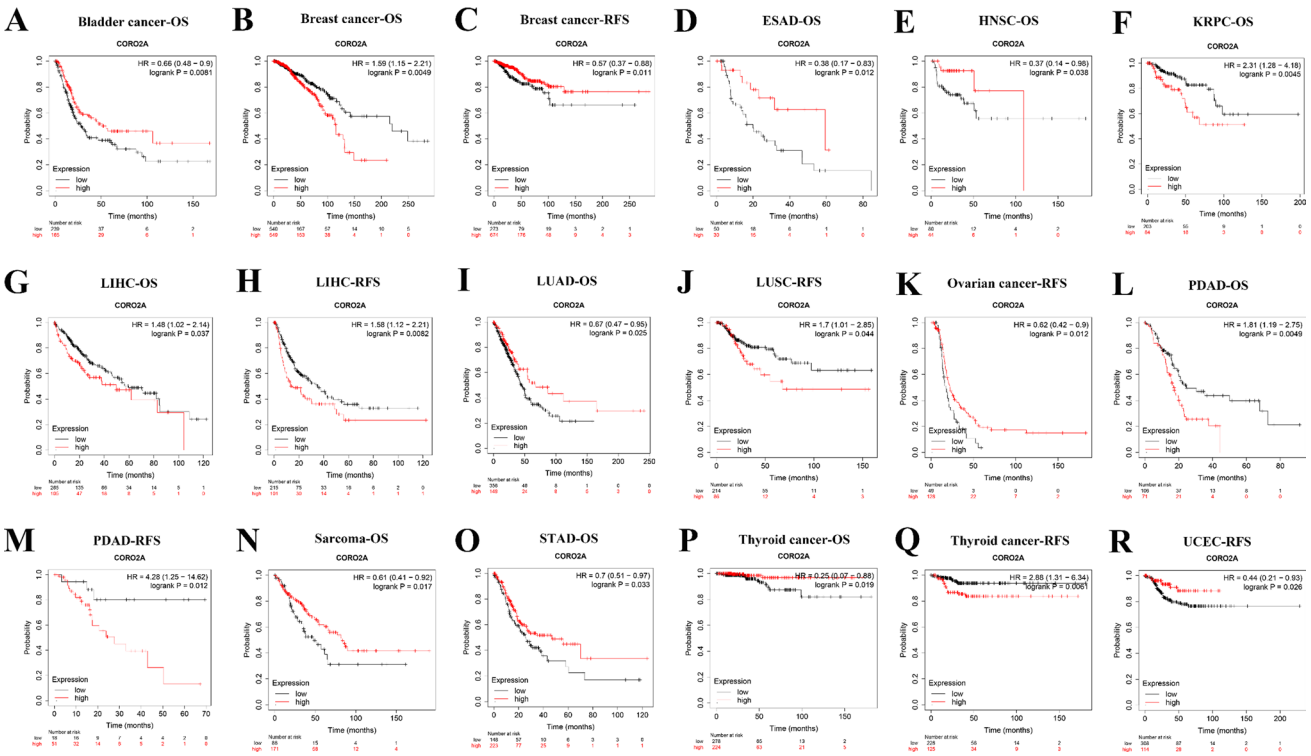


Fig. 4 Kaplan–Meier analysis of OS and RFS of pan-cancer by Kaplan–Meier plotter. Kaplan–Meier plotter was utilized to explore the impacts of CORO2A expression on prognosis in bladder cancer (**A**), breast cancer (**B**, **C**), ESAD (**D**), HNSC (**E**), KRPC (**F**), LIHC (**H**), LUAD (**I**), LUSC (J), ovarian cancer (**K**), PDAD (**L**, **M**), sarcoma (**N**), STAD (**O**), thyroid cancer (**P**, **Q**), UCEC (**R**)

ESAD and HNSC, the high CORO2A expression group exhibited longer overall survival compared to the low expression group (Fig. 4D, E), while the opposite trend was observed in KRPC (Kidney renal papillary cell carcinoma) and LIHC (Fig. 4F, G). Additionally, in LIHC, the disease-free survival of the high CORO2A expression group was markedly shortened, in comparison with the low expression group (Fig. 4H). In lung cancer, different pathological types had varying effects on overall survival, with the high expression group in LUAD and the low expression group in LUSC showing longer overall survival or recurrence-free survival, respectively (Fig. 4I, J). In ovarian cancer, higher CORO2A expression was associated

with lengthened recurrence-free survival (Fig. 4K). Conversely, in PADA, both overall survival and recurrence-free survival were reduced in the high CORO2A expression group (Fig. 4L, M). Furthermore, in sarcoma, STAD, and thyroid cancer, the high CORO2A expression group exhibited notably longer overall survival compared to the low expression group (Fig. 4N–P). Moreover, the effects of CORO2A expression on recurrence-free survival differed between thyroid cancer and UCEC (Fig. 4Q, R). These findings provide comprehensive insights into the prognostic implications of CORO2A expression across diverse cancer types.

3.5 Correlation analysis of CORO2A expression with abundance of TILs, immunomodulators and chemokines in TISIDB database

In this section, we delved into the association between CORO2A expression and TILs, immunomodulators, and chemokines across various cancer types to elucidate the immunological role of CORO2A in pan-cancer. The heatmap presented in Fig. 5A highlighted these relationships across different tumor types. Interestingly, we observed that CORO2A expression exhibited a predominantly positive correlation with all types of TILs in KIRP, whereas it displayed a negative correlation with TILs in PRAD. Furthermore, the heatmap depicted in Fig. 5B–D illustrated the correlation between CORO2A expression and immunomodulators, encompassing both immunoinhibitors, immunostimulatory factors, and MHC molecules. Notably, in LUSC and BRCA, CORO2A expression was predominantly negatively correlated with MHC molecules across pan-cancer. However, in certain contexts, CORO2A expression exhibited a positive relationship with MHC molecules. Similarly, Fig. 5E, F utilized heatmaps to elucidate relationship between CORO2A expression and chemokines (or receptors) among different cancer types. Interestingly, we observed diverse trends in the association between CORO2A expression and these chemokines or receptors in pan-tumor scenarios. These findings shed light on the complex interplay between CORO2A expression and various components of the immune system and chemokine signaling pathways

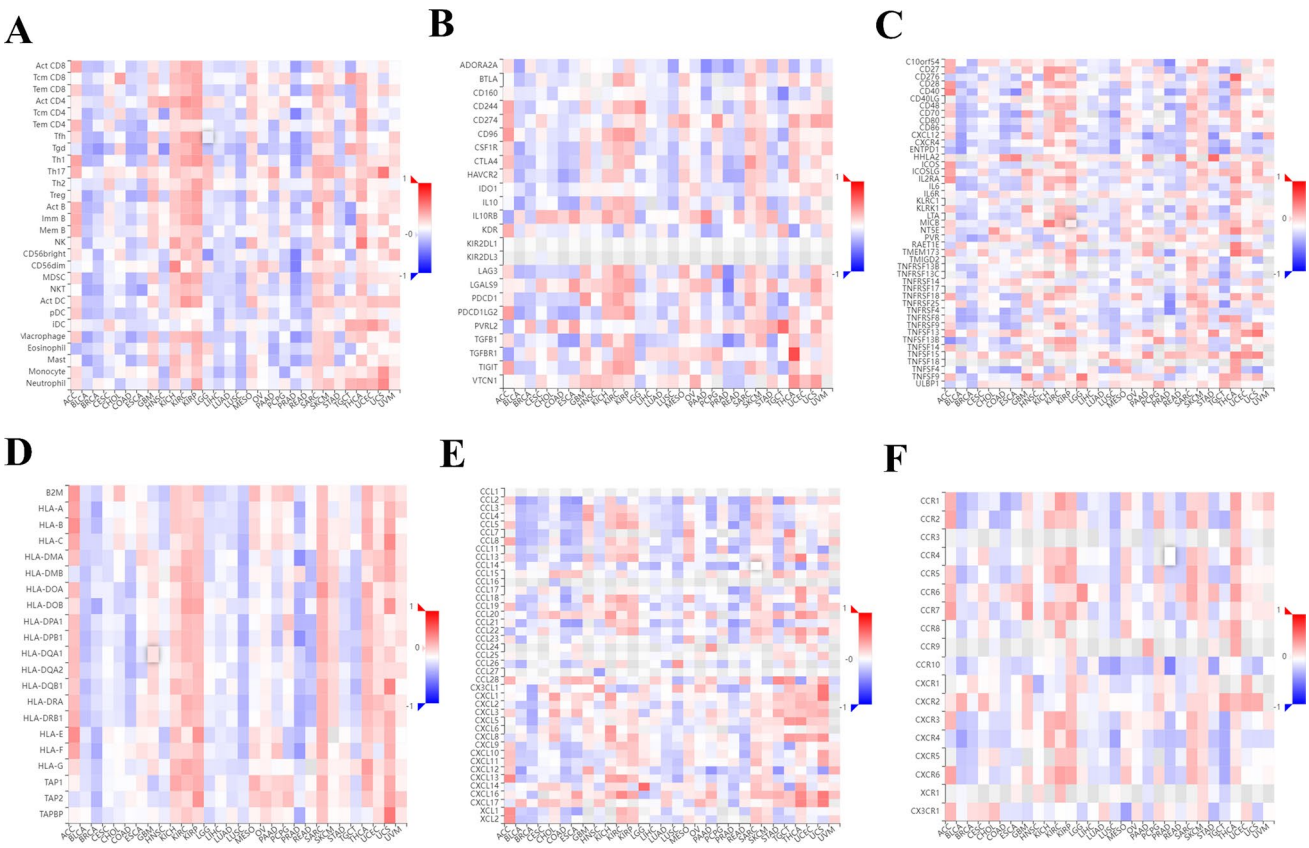


Fig. 5 Connections of CORO2A expression level of pan-cancer with TILs, immunomodulators and chemokines in TISIDB database. **A** Correlations between TILs and CORO2A. **B**–**D** Relationship between immunomodulators and CORO2A. **E**, **F** Relations between chemokines (or receptors) and CORO2A

across different cancer types, providing valuable insights into the immunological role of CORO2A in cancer progression and response to therapy.

3.6 CORO2A was related to the infiltration of CAF and MDSC in pan-cancer

Figure 6A depicted a heatmap illustrating the relationship between CORO2A expression and the presence of CAF (cancer-associated fibroblasts) and MDSC (myeloid-derived suppressor cells). In Fig. 6B–G, scatter plots demonstrate relationship

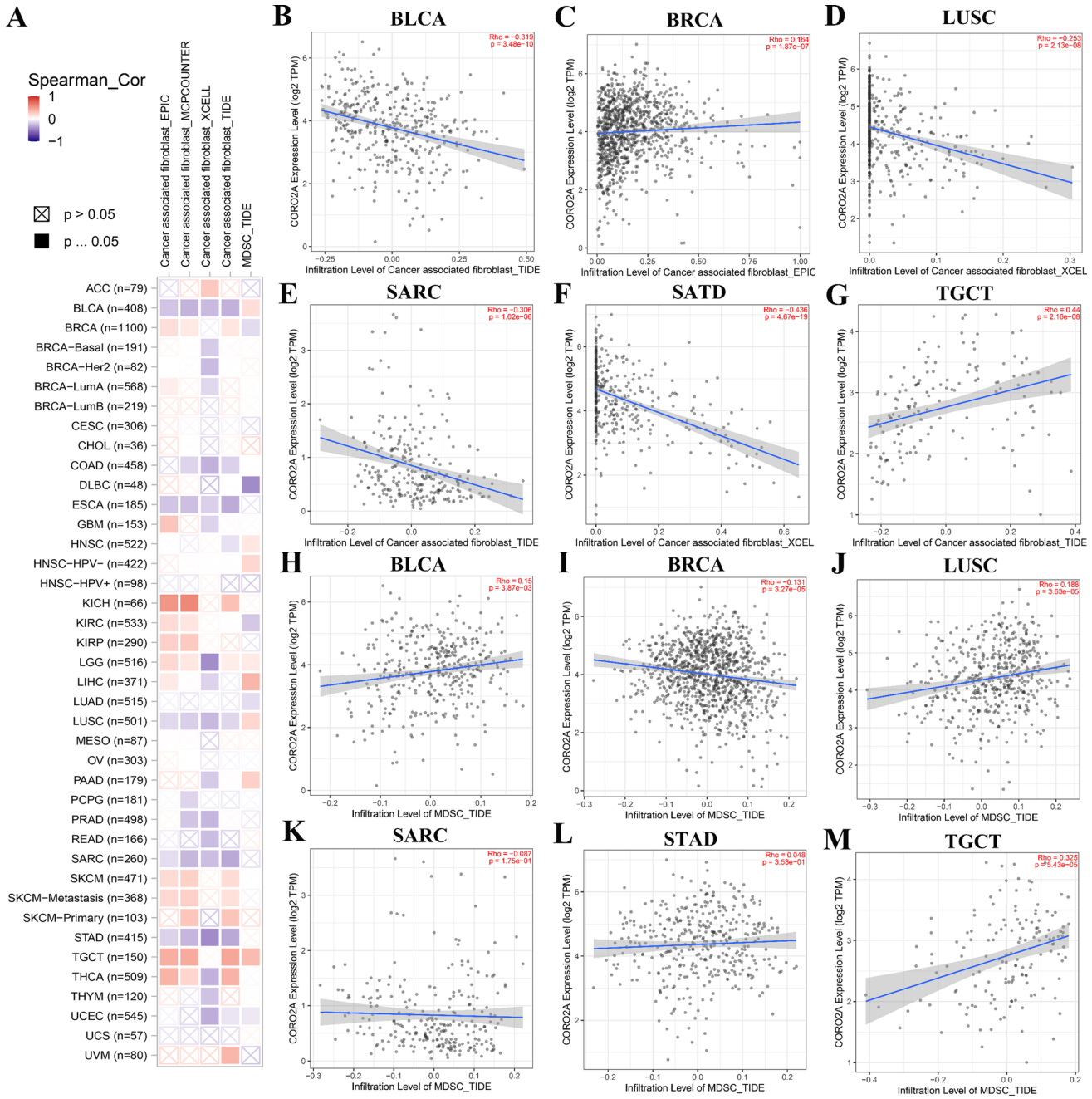


Fig. 6 The correlation between CORO2A and immunoinfiltration of CAF and MDSC cells was analyzed by TIMER2 tool website. **A** Heatmap of relationship of CORO2A expression with infiltration of CAF and MDSC in pan-cancer. We used the TEMER2 tool to exhibit Scatter diagram between CORO2A expression and CAF infiltration in BLCA (**B**), BRCA (**C**), LUSC (**D**), SARC (**E**), STAD (**F**), TGCT (**G**). Similarly, the association of CORO2A expression and MDSC infiltration in BLCA (**H**), BRCA (**I**), LUSC (**J**), SARC (**K**), STAD (**L**), TGCT (**M**) were showed by employing the TIMER2 tool

between CORO2A expression and the infiltration of CAF and MDSC in various tumor types, including BLCA, BRCA, LUSC, SARC, STAD, and TGCT, utilizing all four algorithms. Interestingly, it was observed that CORO2A expression showed a significant negative correlation with CAF infiltration in BLCA, LUSC, SARC, STAD, and TGCT, while it exhibited a positive association with CAF infiltration in BRCA. Conversely, regarding the relationship between CORO2A expression and MDSC infiltration, opposite patterns were observed in BLCA, BRCA, LUSC, SARC, and TGCT, except for SARC and STAD, compared to the correlation observed with CAF infiltration (Fig. 6H–M).

3.7 The effects of CORO2A expression and infiltration levels of CAF and MDSC on prognosis in pan-cancer through TIMER2 Web

In Fig. 7A, we presented the prognostic landscape of CORO2A expression and infiltration of CAF and MDSC across various cancers using heatmaps. Notably, in ACC (Fig. 7B), BLCA (Fig. 7C), HNSC-HPV$^+$ (Fig. 7G), KIRC (Fig. 7H), KIRP (Fig. 7I), and LGG (Fig. 7J), patients with high CORO2A expression and low CAF infiltration exhibited the longest overall survival (OS) compared to the other groups. Conversely, in BRCA-LumB (Fig. 7D), GBM (Fig. 7F), and STAD (Fig. 7K), patients with low CORO2A expression and low CAF infiltration experienced longer OS. Interestingly, for CESC (Fig. 7E), high CORO2A expression coupled with low CAF infiltration correlated with extended OS. Moving on to the impact of CORO2A expression and MDSC infiltration on patient prognosis (Fig. 7L–U), in ACC and BLCA, high CORO2A expression coupled with low MDSC infiltration was related to longer OS. Conversely, in CESC, KIRP, and MESO, longer OS was observed in the low CORO2A expression and low MDSC infiltration group. Moreover, in KIRC, KIRP, and SARC, patients with high CORO2A expression and low MDSC infiltration had significantly prolonged OS compared to those with high MDSC infiltration. Notably, in LGG and LIHC, longer OS was evident in the low CORO2A expression and low MDSC infiltration group compared to the low CORO2A expression and high MDSC infiltration group. Interestingly, in LUAD and MESO, regardless of CORO2A expression level, patients with low MDSC infiltration exhibited markedly longer OS compared to those with high MDSC infiltration. These findings underscored the intricate interplay between CORO2A expression, immune cell infiltration, and patient prognosis across diverse cancer types, providing valuable insights for future prognostic assessments and therapeutic strategies.

3.8 The correlation between CORO2A expression and infiltration of immune cells in LUAD and LUSC via Xian Tao Academic Web

In Fig. 8A, we employed lollipop plots to probe the association between CORO2A expression and infiltration of various immune cells in LUAD. Our analysis uncover an obviously positive association between CORO2A expression and Th17 cell infiltration ($r = 0.226$, $p < 0.001$), as depicted in Fig. 8B. Conversely, CORO2A expression exhibited negative associations with Tgd cell infiltration ($r = -0.143$, $p < 0.001$) and cytotoxic cell infiltration ($r = -0.138$, $p < 0.001$), as illustrated in Figs. 8C and D, respectively. For lung squamous cell carcinoma (LUSC), Fig. 8E presented lollipop plots demonstrating the relationship between CORO2A expression and immune cell infiltration. Notably, the top three significant associations were shown in scatter plots, indicating a negative relation between CORO2A expression and infiltration of Th1 cells ($r = -0.326$, $p < 0.001$) (Fig. 8F), CD8 + T cells ($r = -0.248$, $p < 0.001$) (Fig. 8G), and macrophages ($r = -0.232$, $p < 0.001$) (Fig. 8H). These findings provide insights into the complex interplay between CORO2A expression and immune cell infiltration in both LUAD and LUSC, shedding light on potential mechanisms underlying lung cancer progression and suggesting avenues for therapeutic intervention.

3.9 Connection analysis of CORO2A and immune cell markers in LUAD and LUSC

In our investigation of the immunological role of CORO2A, we delved into the connection between CORO2A expression and immune cell markers in both LUAD and LUSC. Figure 9A illustrated the correlation between CORO2A and markers of Th17 cells in LUAD. We observed significant positive associations with STAT3 ($r = 0.447$, $p < 0.0001$) and IL17RA ($r = 0.256$, $p < 0.0001$). For LUSC, Fig. 9B demonstrated a negative connection between CORO2A and markers of Th1 cells. Specifically, markers including IL12RB2 ($r = -0.209$, $p < 0.0001$), ILRA ($r = -0.191$, $p < 0.0001$), STAT4 ($r = -0.201$, $p < 0.0001$), and TBX21 ($r = -0.089$, $p = 0.0456$) exhibited this negative relationship with CORO2A expression. Regarding CD8$^+$ T cell markers in LUSC (Fig. 9C), we also observed negative correlations with CORO2A expression, notably for CD8A ($r = -0.107$, $p = 0.0151$) and CD8B ($r = -0.21$, $p < 0.0001$). Interestingly, our analysis revealed contrasting associations between CORO2A and markers of M1 and M2 macrophages. In Fig. 9D, CORO2A expression showed positive correlations with markers of M1

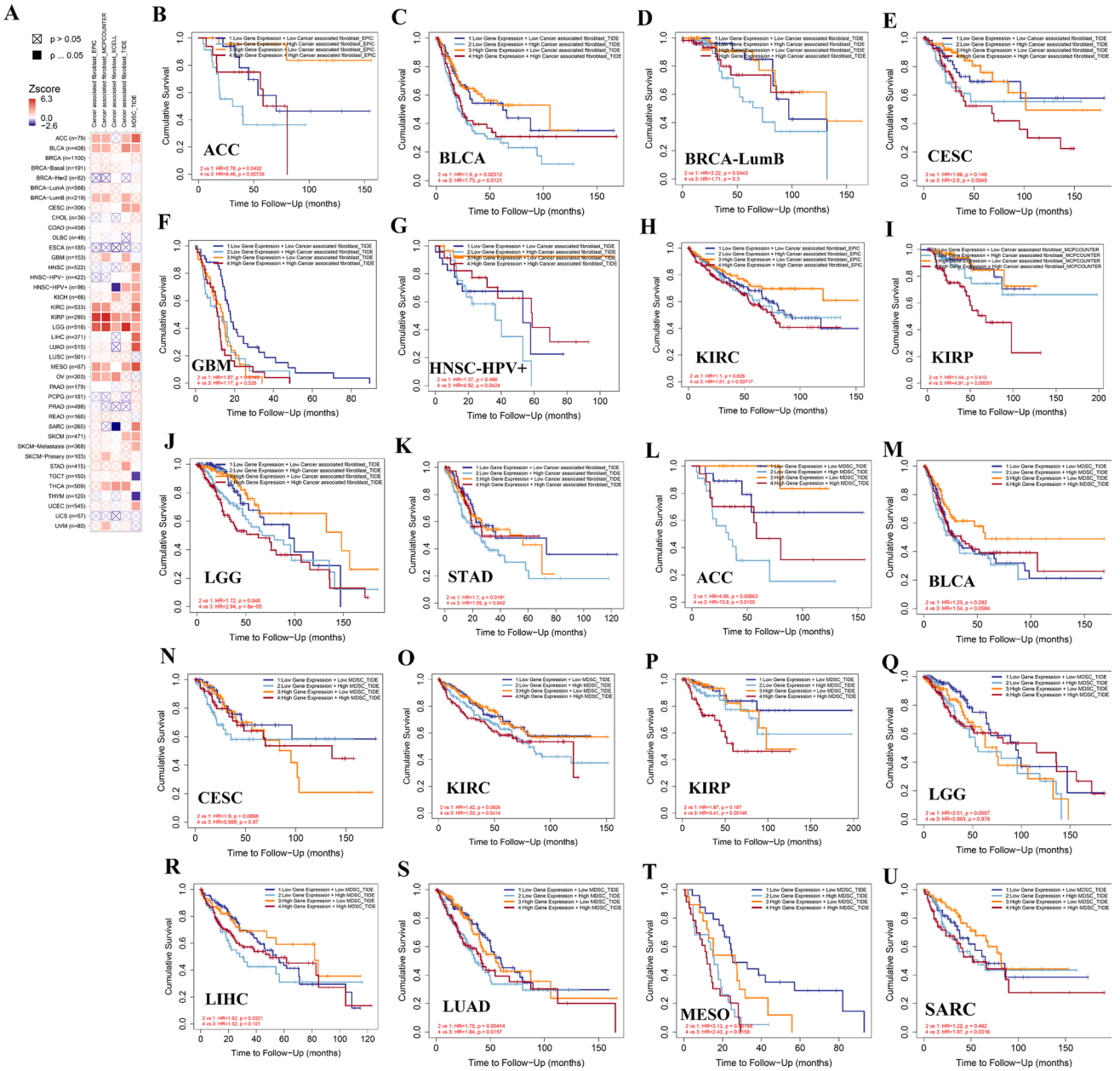


Fig. 7 The effects of CORO2A expression and infiltrating levels of CAF and MDSC on prognosis in pan-cancer through TIMER2 Web. **A** Prognostic heatmap of CORO2A expression combined with the infiltrating levels of CAF and MDSC in diverse cancers. **B**–**K** CORO2A expression combined CAF infiltration significantly affected the prognosis in ACC, BLCA, BRCA-LumB, CESC, GBM, HNSC-HPV^{+}, KIRC, KIRP, LGG, and STAD. **L**–**U** The obvious Kaplan–Meier analyses were showed by studying CORO2A expression combined MDSC infiltration in ACC, BLCA, CESC, KIRC, KIRP, LGG, LIHC, LUAD, MESO, and SARC

macrophages, such as IRF5 ($r = 0.237$, $p < 0.0001$) and NOS2 ($r = 0.117$, $p = 0.00859$). Conversely, in Fig. 9E, CORO2A expression exhibited negative correlations with markers of M2 macrophages, including MS4A4A ($r = -0.168$, $p = 0.000161$) and VSIG4 ($r = -0.191$, $p < 0.0001$). To validate our findings, we employed the GEPIA2 tool to further explore the relationship between CORO2A and immune cell markers in LUAD and LUSC (Table 1). Results indicated significant correlations between CORO2A expression and Th17 cell markers not only in LUAD and corresponding normal tissues but also in LUSC and corresponding normal tissues. Additionally, markers of Th1 cells and M2 macrophages were only correlated with

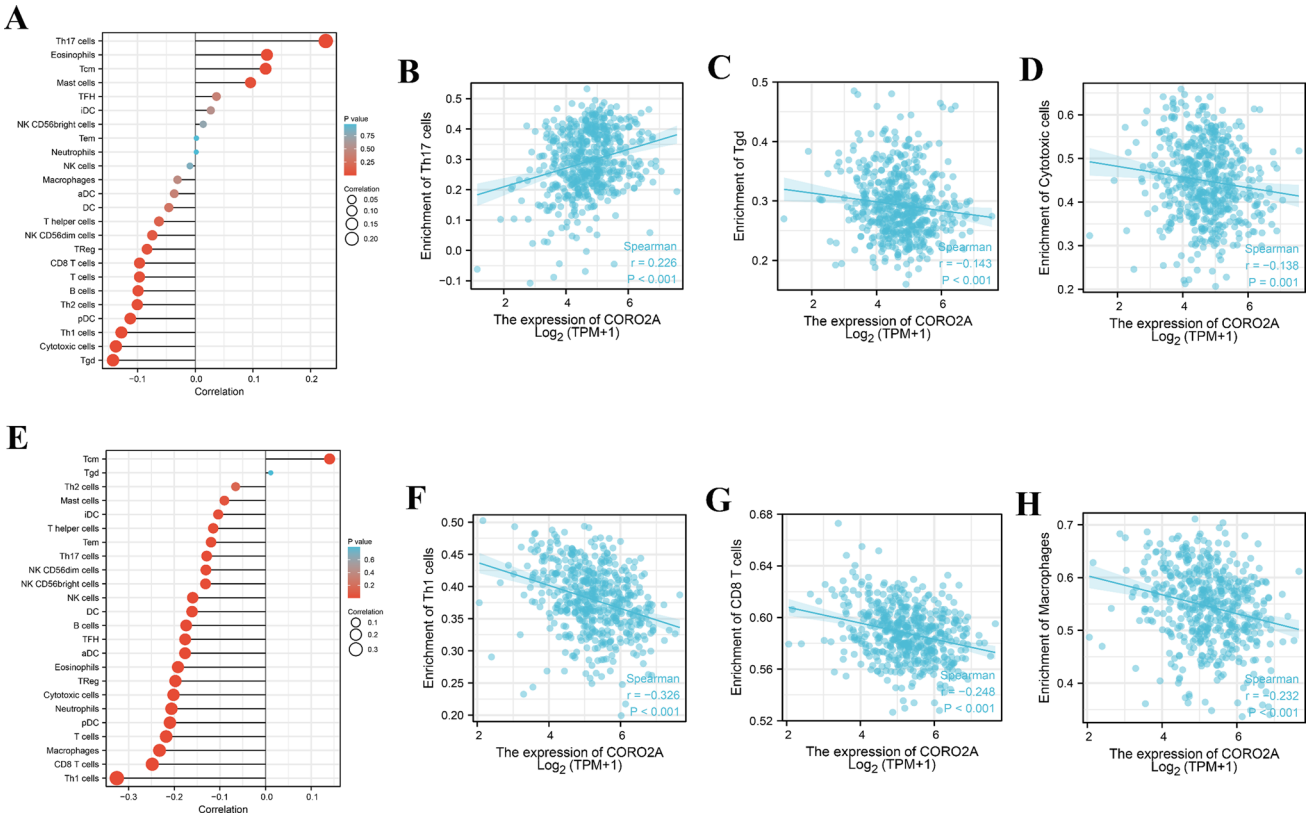


Fig. 8 The association between CORO2A and immune infiltrating cells in LUAD and LUSC via Xian Tao Academic Web. **A** Lollipop figure of CORO2A and immune infiltrating cells in LUAD. **B**–**D** Scatter diagram of CORO2A with infiltration of Th17, Tgd, and cytotoxic cells. **E** Lollipop figure of CORO2A and immune infiltrating cells in LUAD. **F–H** Scatter diagram of CORO2A with infiltration of Th1, CD8 T cells, and macrophages

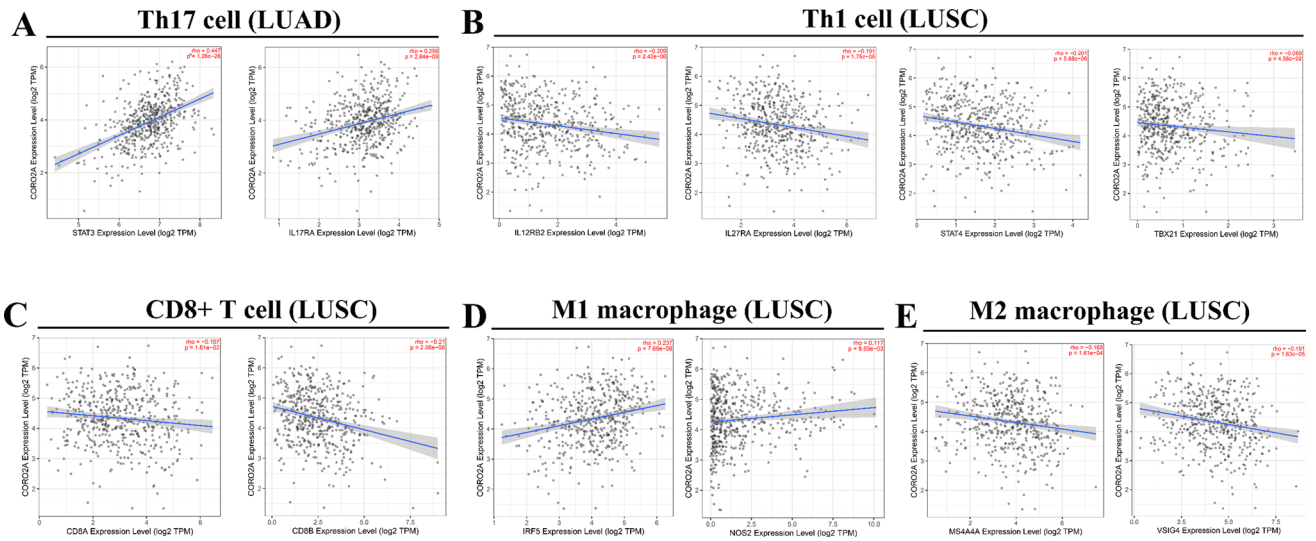


Fig. 9 Connection analysis of CORO2A and immune cell markers in LUAD and LUSC via TIMER2 Web. **A** CORO2A related to the markers of Th17 in LUAD. **B**–**E** CORO2A related to the markers of Th1, CD8 T cell, M1 macrophage, and M2 macrophage in LUSC

CORO2A expression in LUSC, not in LUAD or normal tissues. The expression of surface markers of T cell depletion was

Table 1 Correlation analysis between CORO2A and related genes and markers of Th17 cell, $CD8^+$ T cell, Th1 cell, macrophages, and T cell exhaustion in GEPIA2

Description	Gene markers	LUAD				Gene markers	LUSC			
		Cancer		Normal			Cancer		Normal	
		Cor	P	Cor	P		Cor	P	Cor	P
Th17 cell	STAT3	0.38	****	0.33	*	STAT3	0.2	****	0.35	*
	IL17RA	0.27	****	0.59	****	IL17RA	0.28	****	0.6	****
$CD8^+$ T cell	CD8A	−0.065	0.16	−0.092	0.49	CD8A	−0.078	0.085	−0.35	*
	CD8B	−0.13	**	−0.066	0.62	CD8B	−0.12	**	−0.4	**
Th1 cell	IL12RB2	0.043	0.35	0.03	0.82	IL12RB2	−0.18	****	−0.17	0.24
	IL27RA	0.02	0.66	0.34	****	IL27RA	−0.13	**	0.23	0.12
	STAT4	0.018	0.7	−0.02	0.88	STAT4	−0.19	****	−0.1	0.48
	TBX21	−0.066	0.15	−0.016	0.9	TBX21	−0.1	*	0.15	0.29
M1 Macrophage	NOS2	0.0067	0.88	0.14	0.27	NOS2	0.042	0.36	0.25	0.08
	IRF5	0.18	****	0.48	***	IRF5	0.21	****	0.33	*
M2 Macrophage	MS4A4A	−0.036	0.43	0.11	0.41	MS4A4A	−0.15	**	0.13	0.37
	VSIG4	−0.051	0.27	0.21	0.11	VSIG4	−0.16	***	0.42	0.21
T cell exhaustion	PD1 (PDCD1)	−0.09	*	0.054	0.69	PD1 (PDCD1)	−0.1	*	−0.1	0.49
	PD-L1 (CD274)	−0.041	0.37	0.16	−0.18	PD-L1 (CD274)	0.17	***	−0.034	0.81
	CTLA4	−0.12	**	0.028	0.83	CTLA4	−0.14	**	−0.084	0.56

Lung adenocarcinoma (LUAD); Lung squamous cell carcinoma (LUSC); tumor-associated macrophage (TAM); None, correlation without adjustment; Cor, R value of Spearman's correlation, *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001

significantly correlated with CORO2A only in LUAD and LUSC, but not in normal tissues. These comprehensive analyses deepen our understanding of the intricate interplay between CORO2A expression and immune cell markers in both LUAD and LUSC, providing valuable insights for further research and potential therapeutic strategies.

3.10 Prognostic analysis of CORO2A expression based on decreased or enriched levels of immune cell infiltrating in LUAD patients

In our previous findings, we established that the CORO2A gene held promise as a prognostic biomarker and was significantly correlated with immune cell infiltration across various cancer types. Here, we delved deeper into the prognostic analysis of CORO2A gene based on the levels of immune cell infiltration in patients with LUAD. As illustrated in Fig. 10A, we observed that LUAD patients with high CORO2A expression had markedly longer overall survival (OS), in comparison with those patients with low expression when the infiltration level of B cells was decreased. Conversely, when the B cell infiltration level was elevated, the high CORO2A expression group exhibited lower OS than the low expression group. Regarding other immune cell types, regardless of whether the levels of basophils or $CD4^+$ T cell infiltration were increased or decreased (Fig. 10B, C), the high CORO2A expression group consistently demonstrated longer OS than the low expression group. Similarly, when $CD8^+$ T cell infiltration was enriched, the high CORO2A expression group exhibited longer OS (Fig. 10D). Furthermore, regardless of the direction of eosinophils infiltration (increased or decreased), LUAD patients with high CORO2A expression had longer OS, in comparison with those patients with low expression (Fig. 10E). Similarly, when macrophage infiltration levels were enriched, the high CORO2A expression group showed markedly prolonged OS, in comparison with the low expression group (Fig. 10F). Additionally, our analysis revealed that in LUAD, longer OS in the high CORO2A expression group was evident only when the infiltration levels of NK cells, Treg cells, Th1 cells, and Th2 cells were decreased, in comparison with the low expression group (Fig. 10G–J).

3.11 Enrichment analysis of CORO2A expression in pan-cancer

In order to further investigate the role and mechanism of CORO2A expression in pan-cancer, we used the String tool to collect the top 50 CORO2A-binding proteins and utilized the GEPIA2 tool to obtain the top 100 CORO2A-associated genes. As shown in Fig. 11A, B, we used the data from the String and BioGRID databases (https://thebiogrid.org) to

Fig. 10 Prognostic analysis of CORO2A expression based on decreased or enriched levels of immune cell infiltrating in LUAD patients. Effect ▶ of CORO2A expression on OS of LUAD at different infiltrating levels of B cell (**A**), Basophils (**B**), $CD4^+$ T cell (**C**), $CD8^+$ T cell (**D**), Eosinophils (**E**), macrophages (**F**), NK-T cells (**G**), Treg cells (**H**), Th1 cells (**I**), and Th2 cells (**J**)

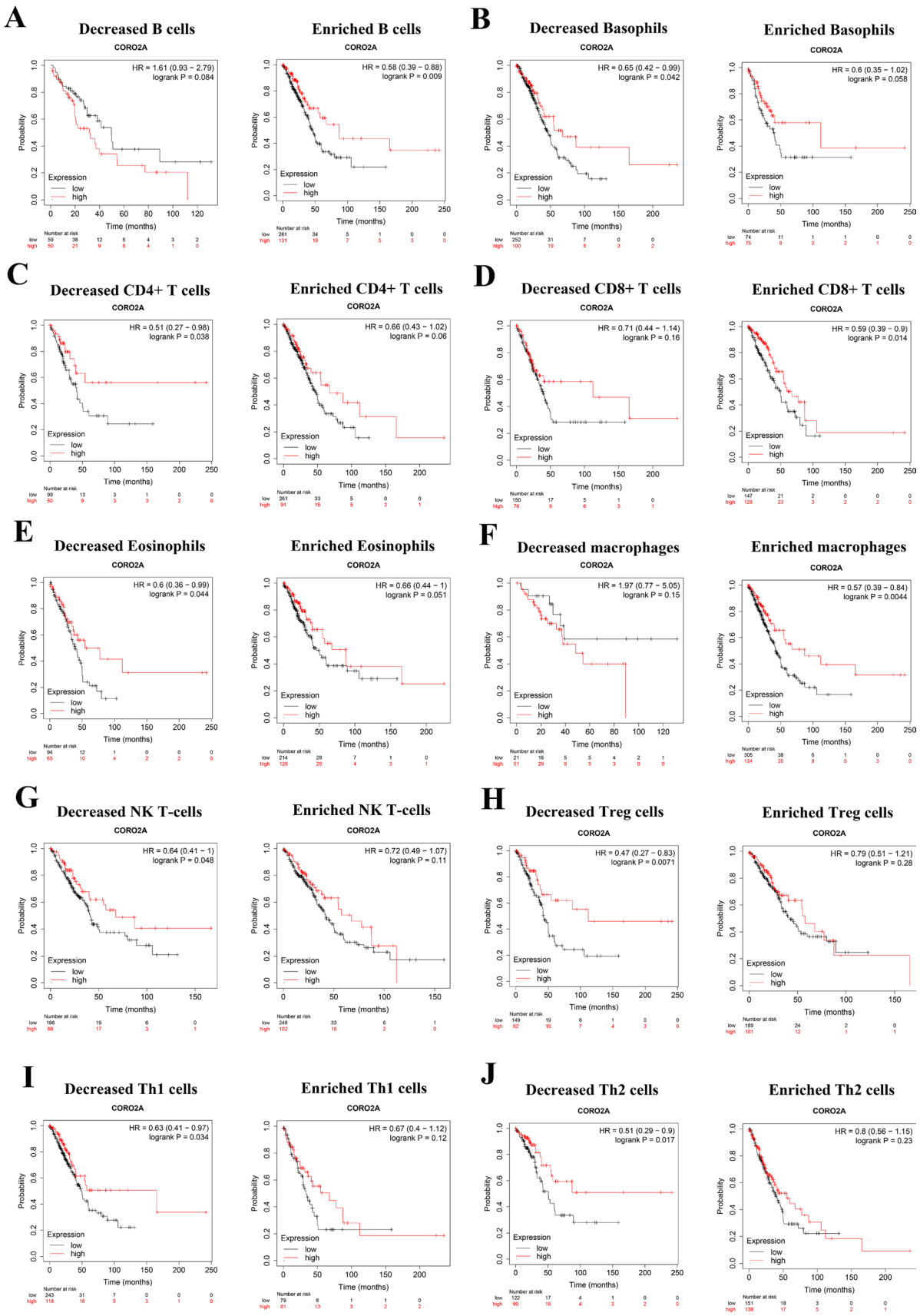
explore the relationship graph between CORO2A and its binding proteins. Subsequently, we employed the GEPIA2 tool to plot the top 6 genes associated with CORO2A expression in pan-cancer (Fig. 11C). From the scatter plot, we found that the expression of ATP8B1 (ATPase phospholipid transporting 8B1), CANT1 (calcium activated nucleotidase 1), FAM120A (family with sequence similarity 120A), GRHL2 (grainyhead like transcription factor 2), STYK1 (serine/threonine/tyrosine kinase 1), and TMEM87B (transmembrane protein 87B) were significantly correlated with CORO2A expression. Correlation analysis of these genes associated with CORO2A was analyzed by using the TIMER2 tool, and a related heatmap was given (Fig. 11D). The Venn diagram was used to make an interactive analysis of the proteins and genes obtained from the String and GEPIA databases, respectively, and we identified ACACA (acetyl-CoA carboxylase α) as a common gene (Fig. 11E). To further investigate the pathogenesis of the CORO2A gene in tumors, we combined KEGG and GO datasets for enrichment analysis. As depicted in Fig. 11F, GO analysis (including BP (Biological Process), MF (Molecular Function), CC (Cellular Component)) and KEGG pathway analysis were shown based on the CORO2A-binding and interacting genes, and the bubble diagram indicated that CORO2A-binding genes were mainly involved in actin filament organization, the cell leading edge, actin binding, and pathogenic Escherichia coli infection.

4 Discussion

The TCGA database offers comprehensive clinical information and multi-omics data for 33 types of cancer patients, greatly facilitating pan-cancer research [18–20]. Thanks to advancements in bioinformatics, coupled with the widespread use of computer technology and algorithms across various disciplines, we now have an actionable approach to study the impact of novel biomarkers on the survival and prognosis of patients with diverse tumors [21, 22]. In this study, we aim to investigate the role of CORO2A expression on prognosis and immune infiltration in pan-cancer through bioinformatic analysis.

It has been reported that coronin, a conserved F-actin-binding protein, is important for actin motility and dynamics. Thus far, all other members of the Coronin family have been discovered to regulate the actin cytoskeleton through their interaction with F-actin. CORO2A (Coronin 2A) is identified as an actin regulatory protein and it is also recognized as a component of the Oncor complex, whose function was previously unknown. CORO2A, an actin regulatory protein, is involved in mediating the Oncor switching mechanism of TLR-induced interaction with oligomeric nuclear actin [23]. To date, all other Coronin family members have been found to regulate the actin cytoskeleton through their interaction with F-actin. CORO2A localizes to stress fibers and some focal adhesions and is excluded from the leading edge. Previous studies have found that the high expression of CORO2A in some tumors was closely related to the malignant progression of tumor patients, and it could promote the proliferation, invasion, and migration of tumor cells. When the expression of CORO2A was inhibited or decreased, we found that the proliferation of cancer cells was limited, and the OS or DFS of tumor patients with low expression of CORO2A was significantly prolonged compared with patients with high expression of CORO2A [15, 17]. In this study, we found that the expression of CORO2A was significantly elevated in BRCA, CESC, ESCA, HNSC, KIRC, LIHC, LUAD, LUSC, PAAD, PCPG, PRAD, STAD, THCA, and UCEC, compared to corresponding normal tissues; however, in GBM, COAD, and KICH, CORO2A expression was markedly decreased compared to normal tissue. There was lower expression of CORO2A in LAML, LGG, THYM, and UCS than corresponding tissues, while the expression of CORO2A in ACC and OV was increased, compared to normal tissues. Thus, it can be seen that the expression level of CORO2A varied in diverse cancers. Therefore, we further explored whether its expression had a different impact on patients' prognosis in various tumors, and results in the present study showed that OS of the high CORO2A expression group in ACC, ESAD, HNSC, LUAD, STAD, ovarian cancer, bladder cancer, sarcoma, AML, follicular lymphoma, and thyroid cancer was dramatically longer than that of the low expression group; however, OS of the high CORO2A expression group was significantly shortened in BRCA, GBM, KPRC, LIHC, and PDAD, compared to the low expression group.

As everyone knows, in the tumor microenvironment, immune cells intertwine with tumor cells and play crucial roles in the occurrence, development, or metastasis of tumors across various tumor types [24]. Among all stromal cells present in the tumor microenvironment, cancer-associated fibroblasts (CAFs) are the most abundant. Numerous studies have demonstrated that CAFs play a positive role in promoting the malignant progression of cancer, and they are associated with poor prognosis, disease recurrence, and chemotherapy resistance [25, 26]. Additionally, myeloid-derived suppressor cells


A
Decreased B cells
CORO2A
HR = 1.61 (0.93 − 2.79)
logrank P = 0.084
Enriched B cells
CORO2A
HR = 0.58 (0.39 − 0.88)
logrank P = 0.009
B
Decreased Basophils
CORO2A
HR = 0.65 (0.42 − 0.99)
logrank P = 0.042
Enriched Basophils
CORO2A
HR = 0.6 (0.35 − 1.02)
logrank P = 0.058
C
Decreased CD4+ T cells
CORO2A
HR = 0.51 (0.27 − 0.98)
logrank P = 0.038
Enriched CD4+ T cells
CORO2A
HR = 0.66 (0.43 − 1.02)
logrank P = 0.06
D
Decreased CD8+ T cells
CORO2A
HR = 0.71 (0.44 − 1.14)
logrank P = 0.16
Enriched CD8+ T cells
CORO2A
HR = 0.59 (0.39 − 0.9)
logrank P = 0.014
E
Decreased Eosinophils
CORO2A
HR = 0.6 (0.36 − 0.99)
logrank P = 0.044
Enriched Eosinophils
CORO2A
HR = 0.66 (0.44 − 1)
logrank P = 0.051
F
Decreased macrophages
CORO2A
HR = 1.97 (0.77 − 5.05)
logrank P = 0.15
Enriched macrophages
CORO2A
HR = 0.57 (0.39 − 0.84)
logrank P = 0.0044
G
Decreased NK T-cells
CORO2A
HR = 0.64 (0.41 − 1)
logrank P = 0.048
Enriched NK T-cells
CORO2A
HR = 0.72 (0.49 − 1.07)
logrank P = 0.11
H
Decreased Treg cells
CORO2A
HR = 0.47 (0.27 − 0.83)
logrank P = 0.0071
Enriched Treg cells
CORO2A
HR = 0.79 (0.51 − 1.21)
logrank P = 0.28
I
Decreased Th1 cells
CORO2A
HR = 0.63 (0.41 − 0.97)
logrank P = 0.034
Enriched Th1 cells
CORO2A
HR = 0.67 (0.4 − 1.12)
logrank P = 0.12
J
Decreased Th2 cells
CORO2A
HR = 0.51 (0.29 − 0.9)
logrank P = 0.017
Enriched Th2 cells
CORO2A
HR = 0.8 (0.56 − 1.15)
logrank P = 0.23
Probability
Time (months)
Expression
low
high
Number at risk

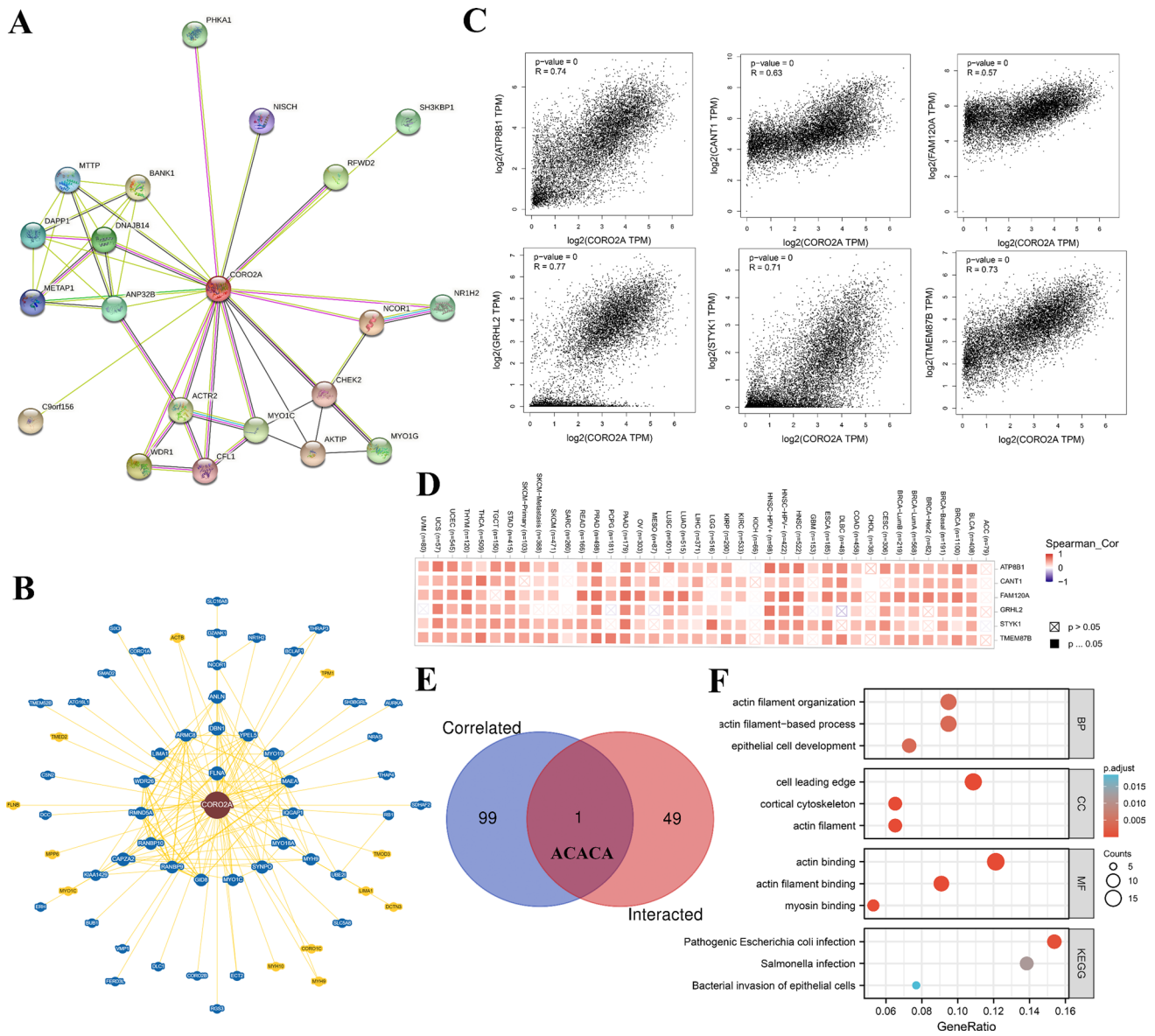


Fig. 11 Enrichment analysis of CORO2A expression in pan-cancer. **A** The useable experimentally determined CORO2A-connecting proteins were conducted utilizing STRING dataset. **B** CORO2A-protein interactions were obtained by BioGRID. **C** Scatter plot was employed to show the association of CORO2A and top 6 of CORO2A-correlated genes via using the GEPIA2 approach, including ATP8B1, CANT1, FAM120A, GRHL2, STYK1, and TMEM87B. **D** Heatmap was used to exhibit the relationship of CORO2A and top 6 of CORO2A-correlated genes in pan-cancer. **E** The CORO2A-binding genes and related genes were analyzed by intersection analysis. **F** GO analysis and KEGG pathway analysis were showed based on the CORO2A-binding and interacted genes

(MDSCs) are a major host component contributing to the immunosuppressive environment. They play a vital role in inhibiting tumor growth and progression mediated by antitumor immunity, as well as in increasing resistance to chemotherapy and immunotherapy [27]. Our results indicated that CORO2A expression was significantly and negatively correlated with the infiltration of cancer-associated fibroblasts (CAFs) in BLCA, LUSC, SARC, STAD, and TGCT, while it was positively associated with CAF infiltration in BRCA. Considering the impact of CORO2A expression on the overall survival of cancer patients, we observed that the infiltration level of CAF was increased in patients with poor prognosis when CORO2A expression was low. Conversely, the infiltration level of CAF was decreased in patients with poor prognosis when CORO2A expression was high. These findings suggested a negative correlation between CORO2A expression and CAF infiltration levels, which in turn affects patient prognosis. Furthermore, we investigated the effects of CORO2A expression and infiltration levels of both CAFs and MDSCs on prognosis across various cancer types using the TIMER2 Web tool. Our finding uncovered that patients with low infiltration levels of CAF or MDSCs had longer overall survival compared to those with high infiltration levels of CAF or

MDSCs. Interestingly, in LUAD and MESO, regardless of whether CORO2A expression was low or high, patients in the low MDSC infiltration group exhibited obviously longer overall survival than those in the high MDSC infiltration group. Moreover, we explored the effects of infiltrating levels of other immune cells on OS in LUAD patients. The results showed that only when the infiltration levels of $CD4^+$ T cells, Basophils, Eosinophils, NK cells, Treg cells, Th1 cells, and Th2 cells were decreased, did the OS of the high CORO2A expression group noticeably extend compared to the low expression group in LUAD. These findings highlighted the intricate interplay between CORO2A expression, immune cell infiltration, and patient prognosis in cancer, particularly in LUAD. Hence, we concluded that CORO2A expression was markedly related to the infiltration of immune cells and played a crucial role in survival prognosis in pan-cancer. In recent years, increasing evidence has shown that actin regulatory proteins are involved in malignancy [28]. Hence, we concluded that CORO2A expression was markedly related to the infiltration of immune cells and played a crucial role in survival prognosis in pan-cancer. In recent years, increasing evidence has shown that actin regulatory proteins are involved in malignancy. Our results show that CORO2A expression is closely related to surface markers of T cell depletion, such as PD-L1, PD-1 and CTLA4, which further suggest the close relationship between CORO2A and tumor immunotherapy. It may affect the therapeutic effect and clinical prognosis of tumor patients by interfering the expression of immune molecules.

In order to further investigate the role and mechanism of CORO2A expression in pan-cancer, we used the String tool to collect the top 50 CORO2A-binding proteins and utilized the GEPIA2 tool to obtain the top 100 CORO2A-associated genes. Furthermore, we used the Venn diagram to make an interactive analysis of the proteins and genes obtained from the String and GEPIA databases, respectively, and we identified ACACA (acetyl-CoA carboxylase α) as a common gene. The downregulation of ACACA inhibits the malignant progression of prostate cancer by inhibiting mitochondrial potential, and inhibition of ACACA can inhibit the occurrence of liver cancer [29, 30]. This indicates that the gene and protein interacting with CORO2A gene ACACA is closely related to the survival prognosis of cancer patients, and it can become a new biomarker for the prognosis of cancer patients together with CORO2A. Recently studies showed that We integrated the KEGG and GO databases for enrichment analysis in order to better understand the pathophysiology of the CORO2A gene in malignancies. The bubble diagram showed that CORO2A-binding genes were primarily involved in actin filament organization, the cell leading edge, actin binding, and pathogenic Escherichia coli infection. These enrichment items are closely related to the function of CORO2A itself, suggesting that this protein may also be an actin-binding protein that regulates cell movement, which is consistent with the annotation in the gene database of National library of medicine.

4.1 Limitation

In this study, we initially used multiple public databases to comprehensively analyze the function of CORO2A in general cancer prognosis and immunity. Our preliminary results showed that CORO2A expression exerts various functions, including its role in prognosis and immune response, across different tumor types. However, this work includes limitations that must be addressed, even though bioinformatics analysis is a useful tool for precise data analysis and the prediction of possible biomarkers. By using experimental techniques like real-time PCR and western blot, as well as in conjunction with knock-out or overexpression experiments to investigate the molecular pathways, we hope to validate our findings in future cell and animal investigations. Techniques such as flow cytometry, immunoprecipitation, and immune cell co-culture can be used to further evaluate the relationship between CORO2A and immune cells and infiltration. For example, immune cell subpopulations (such as T cells, B cells, and macrophages) in peripheral blood or lymphoid tissue were isolated by flow sorting technique. The expression level of CORO2A was detected by qPCR or Western blot, and the correlation between Coro2A and immune cell activation/inhibition markers (such as CD69, PD-1, and IL-2). Immune cell lines with CORO2A knockout/overexpression (such as Jurkat T cells or THP-1 macrophages) were constructed and their effects on immune response were evaluated, such as T cell activation, macrophage polarization, etc. Furthermore, it is essential to validate the findings of this paper in order to guarantee their dependability and generalizability in the cohort of pan-cancer species, particularly lung cancer. Additional prospective, multicenter investigations are necessary to corroborate the findings because this study was retrospective. We can improve the validity and relevance of our findings for the field of pan-cancer research by resolving these issues and integrating various research techniques.

5 Conclusion

Taken together, we suggest that CORO2A is a potential prognostic biomarker associated with immune cell infiltration in pan-carcinoma. This study is the first to comprehensively understand the carcinogenic role of CORO2A in pan-carcinoma.

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Author contributions Conceptualization, Minghe Lv; Data curation, Minghe Lv; Formal analysis, Minghe Lv; Investigation, Minghe Lv; Methodology, Minghe Lv; Project administration, Minghe Lv and Ruping Zhao; Software, Minghe Lv; Supervision, Minghe Lv, Ruping Zhao, and Jingping Yu; Validation, Minghe Lv and Hongwei Zeng; Visualization, Minghe Lv; Writing—original draft, Minghe Lv; Writing—review & editing, Minghe Lv and Ruping Zhao.

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Data availability The datasets generated and analyzed during the current study are available in TCGA, GTEx, GEPIA2, TIMER2, Xiantao Academic Web, PrognoScan, Kaplan–Meier Plotter, String, BioGRID databases and TISIDB datasets.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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