POC1A, a Novel Prognostic Biomarker that Correlated With Immunosuppressive Microenvironment in Pan-cancer

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Article

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Abstract

The effect of POC1 centriolar protein A (POC1A) in pan-cancer remains uncertain. In this study, POC1A expression in tumor tissues and normal tissues was analyzed using data from the Cancer Genome Atlas (TCGA) database and the Genotype-Tissue Expression (GTEx) project. Prognostic value and clinicopathological features of POC1A were assessed using the TCGA cohort. The correlation between POC1A and immune cell infiltration of TCGA samples download from ImmuCellAI and TIMER2 databases was explored. The association between POC1A and tumor mutation burden (TMB), microsatellite instability (MSI), and immune checkpoints genes was also assessed. In addition, gene set enrichment analysis (GSEA) was used to explore the potential molecular mechanism of POC1A in pan-cancer. We found that POC1A was highly expressed in almost all 33 tumors. High expression of POC1A was significantly associated with poor prognosis in most cases. Further, POC1A expression correlated with tumor immune infiltration and tumor microenvironment. In addition, POC1A expression was associated with immune checkpoint genes and TMB and MSI in pan-cancer. GSEA analysis revealed that POC1A is involved in the cell cycle-related and immune-related pathways.These results may elucidate the crucial roles played by POC1A in pan-cancer and identify POC1A as a potential novel prognosis biomarker and immunotherapy target in pan-cancer.

Introduction

Cancer is currently one of the leading causes of death worldwide(Siegel et al.,2021). Because most cancer patients are diagnosed in progressive stage, the cure rate is very low. Tumor immunotherapy has revolutionized the therapeutic effect of cancer, but only a small number of cancer patients can benefit from the treatment(Zhang et al.,2020). Current studies have shown that tumor microenvironmnt plays an important role in the occurrence and development of tumors(Schulz et al.,2019,Lin et al.,2020,Gill et al.,2021). Tumor microenvironment is mainly composed of tumor cells, fibroblasts, immune cells, various signal molecules and extracellular matrix, in which immune cells are an important part(Anderson et al.,2020). Tumor cells secrete immunosuppressive cytokines and reprogram immune cells in the tumor microenvironment, resulting in tumor immune microenvironment inhibition, so as to escape immune recognition and finally escape immune surveillance (Locy et al.,2018). Tumor immunosuppressive microenvironmnt will not only promote tumor progression, but also weaken the effect of immunotherapy(Taki et al.,2021). Therefore, it is urgent to find the novel biomarkers to identify tumor immunosuppressive microenvironment to improve the effectiveness of tumor immunotherapy.

As an important component of the centrosome, POC1A (POC1 centriolar protein homolog A), which is also called WDR51A, plays an important role in the formation and steady state of centrioles in biological processes(Keller et al.,2009). Numerous studies have confirmed that POC1A is related with facial dysmorphism and hypotrichosis (SOFT) syndrome, onychodysplasia, short stature, which is associated to abnormalities in cell mitosis(Koparir et al.,2015,Majore et al.,2021). All these studies reveal that POC1A may play a important role in cell proliferation. Therefore, POC1A is regarded as a factor that regulates the cell cycle(Venoux et al.,2013). At present, some studies have explored the role of POC1A in tumors.Wada et al. revealed that POC1A was a biomarker for predicting the recurrence of intrahepatic cholangiocarcinoma(Wada et al.,2021). Dastsooz et al. suggested that POC1A gene might be the new target for cancers therapies(Dastsooz et al.,2019).However, the role of POC1A in pan-cancer remains uncertain.

To the best of our knowledge, this is the first study to perform a pan-cancer analysis of POC1A using the TCGA database. To elucidate the potential molecular mechanism and clinical significance of POC1A in pan-cancer, the relation between POC1A expression and prognosis, tumor immunity microenvironment, immune checkpoint gene, tumor mutation burden (TMB), microsatellite instability (MSI), DNA methylation, and drug sensitivity was systematically explored.

Materials And Methods

Gene expression analysis

The tumor immune estimation resource version 2 (TIMER2) database (http://timer.cistrome.org) was used to explore the expression differences between POC1A in different tumor tissues or tissue subtypes and adjacent normal tissues obtained from the TCGA project(Li et al.,2020). Distributions of gene expression levels were represented as box plots. Statistical significance of

differential expression evaluated using the Wilcoxon test. For tumors without normal control, such as CESC, DLBC, GBM, OV, PAAD, PCPG, SARC, UCS, THYM, LGG, etc., TCGA and Genotype-Tissue Expression (GTEx) databases were used to obtain POC1A expression profile data of tumor tissues and matched normal tissues. The R language was employed for analyses and graphics. Subsequently, the tumor stage information of the TCGA database was utilized to explore the expression of POC1A in different tumor stages. TCGA and GTEx expression profiles and clinical information were downloaded from UCSC Xena (https://xenabrowser.net/datapages/).

Gene alteration analysis

The mutation and copy number variation (CNV) data of POC1A were downloaded from the cBioPortal database (https://www.cbioportal.org/)(Cerami et al.,2012) .

Survival prognosis analysis

Kaplan-Meier and Univariate Cox regression (UniCox) analyses were used to explore the effect of POC1A expression on prognosis in pan-cancer. The best cutoff value was used to distinguish the high and low expression groups of POC1A. Overall survival (OS), disease-specific survival (DSS), disease-free interval (DFI), and progression-free interval (PFI) were evaluated. Data were analyzed using the R package “survminer” and “survival”.

Immune infiltration analysis

The immunosuppressive microenvironment is one of the reasons for the poor prognosis of tumor patients; therefore, the correlation between POC1A and the immune microenvironment was further explored. The immune cell infiltration data of TCGA were downloaded from the ImmuCellAI database (http://bioinfo.life.hust.edu.cn/ImmuCellAI#!/)(Miao et al.,2020) and TIMER2 database (http://timer.comp-genomics.org/) (Li et al.,2020). The correlation between POC1A and immune cell infiltration was calculated. StromalScore, ImmuneScore, and ESTIMATEScore (Sum of StromalScore and ImmuneScore) were calculated using the R language “estimate” package. The correlation between POC1A expression and these scores was evaluated.

Immune checkpoints genes analysis

Immune checkpoint-related genes are closely related to tumor immune regulation. The relationship between POC1A expression and the expression of immune checkpoint genes was analyzed. In addition, the correlation between POC1A and immune regulatory genes was explored.

TMB and MSI analysis

Tumor mutation burden (TMB) is associated with the efficacy of immunotherapy in various cancers. The TMB of each tumor sample was calculated and the relationship between POC1A expression and TMB was analyzed using Spearman’s rank correlation coefficient. The correlation between POC1A expression and MSI was also analyzed.

Gene set enrichment analysis (GSEA) of POC1A in pan-Cancer

The GSEA was used to evaluate the expression profile of POC1A in pan-cancer based on the Reactome database. The analysis was implemented in the R package “clusterprofiler”. The top 20 results of each tumor identified by GSEA analysis were displayed.

Correlation between POC1A expression and drug sensitivity analysis in pan-cancer

The half-maximal inhibitory concentration (IC_{50}) values of 192 drugs and gene expression profiles for 809 cell lines were downloaded from the Genomics of Drug Sensitivity in Cancer database (GDSC: https://www.cancerrxgene.org/). The correlation between POC1A expression and IC_{50} values of 192 drugs was analyzed.

Results

POC1A is highly expressed in pan-cancer

The TIMER2 webserver was used to explore POC1A expression in pan-cancer. As shown in **Figure 1A**, the expression levels of POC1A were significantly higher in the tumor tissues of BLCA, BRCA, CHOL, COAD, ESCA, HNSC, HNSC-HPV, LIHC, LUAD, LUSC, PRAD, STAD, THCA, UCEC ($P<0.001$), READ ($P<0.01$), and KIRP ($P<0.05$) compared to the adjacent normal tissues. The expression of P0C1A was assessed using TCGA and GTEx data for tumors without normal control. It was found that POC1A was overexpressed in 27 of 33 cancer types, including ACC, BLCA, BRCA, CESC, CHOL, COAD, DLBC, ESCA, GBM, HNSC, KICH, KIRP, LGG, LIHC, LUAD, LUSC, OV, PAAD, PRAD, READ, SARC, SKCM, STAD, THCA, THYM, UCEC, and UCS. However, POC1A was under-expressed in three tumor types, including LAML, PCPG, and TGCT (**Figure 1B**). The correlation between POC1A expression and tumor pathological staging in the TCGA cohort was further explored. The results demonstrated that POC1A expression was elevated with the increase of tumor stages in ACC, BRCA, HNSC, KICH, KIRC, KIRP, LUAD, LUSC, and PAAD (**Figure 2A-I**).

Gene alteration of POC1A in pan-cancer

Mutation and copy number alteration (CNA) influence gene expression. Thus, mutations and CNA of POC1A we assessed. The highest alteration frequency of POC1A (>7%) was observed in undifferentiated stomach adenocarcinoma patients, in which “Mutation” was the primary type (**Figure 3A**). The expression of POC1A was positively correlated with can in 23 of 33 tumor types and negatively correlated in KIRP (**Figure 3B**), indicating that high CNA was one of the main reasons for the high expression of POC1A in pan-cancer.

High expression of POC1A is associated with poor prognosis in pan-cancer

To explore the prognostic value of POC1A in pan-cancer, the Kaplan-Meier survival analysis and UniCox analysis were used. The best cut-off value was used to distinguish the high and low expression groups of POC1A. Kaplan-Meier survival analysis revealed that high expression of POC1A was associated with worse OS in ACC, BLCA, CHOL, KICH, KIRC, KIRP, LAML, LGG, LIHC, LUAD, MESO, PAAD, PCPG, PRAD, SARC, and SKCM (**Figure 4**). UniCox analysis showed that POC1A was a risk factor for OS in ACC, DLBC, KICH, KIRC, KIRP, LGG, LIHC, LUAD, MESO, PAAD, PCPG, PRAD, READ, SKCM, and THYM (**Figure 5A**). The prognostic value of POC1A for DSS, DFI, and PFI in pan-cancer was also analyzed and the results are shown in **Figure 5B-D**. All these results suggested that high expression of POC1A was associated with poor prognosis and might be a potential prognostic biomarker in pan-cancer.

POC1A is correlated with tumor immune infiltration and microenvironment in pan-cancer

The amount of tumor-infiltrating lymphocytes is an important predictor of prognosis in cancer patients and their response to immunotherapy. The StromalScore, ImmuneScore, and ESTIMATEScore of the tumor tissue were calculated using the R language “estimate” package, and their correlation with POC1A expression was evaluated. The results showed that POC1A was negatively correlated with StromalScore and ImmuneScore in most tumors and positively correlated with tumor purity (**Figure 6A**). By exploring the correlation between POC1A expression and immune cell infiltration using the immune cell infiltration data from the ImmuCellAI database, it was found that POC1A was positively correlated with nTreg cells in most tumors and negatively correlated with immune killer cells, such as activated natural killer (NK) cells, CD4 T cells, and CD8 T cells in pan-cancer (**Figure 6B**). Similarly, results of data from the TIMER2 database showed that POC1A was negatively correlated with CD8 T cells and NK cells in most tumors (**Figure 7**).

POC1A expression is associated with immune checkpoint genes

Immune checkpoint genes are important targets of immunotherapy. Five immune checkpoint genes were identified and the relationship between POC1A expression and immune checkpoint gene expression in pan-cancer was analyzed. The results revealed that the expression of POC1A was positively correlated with immune checkpoints in several tumors (**Figure 8**), suggesting that immune cells are inhibited. The correlation between POC1A expression and immune regulatory genes was further analyzed. The results showed that the POC1A gene has a potential immunomodulatory effect in most tumors (**Figure 9**).

POC1A expression is correlated with TMB and MSI in pan-cancer

The TMB of each tumor sample was calculated, and the relationship between POC1A expression and TMB was analyzed using Spearman's rank correlation coefficient. The results are shown in **Figure 10A**. The expression levels of POC1A were significantly positively correlated with TMB in BLCA, BRCA, COAD, GBM, KICH, LGG, LIHC, LUAD, LUSC, PAAD, PRAD, SKCM, SARC, STAD, UCEC, UCS, and UVM, and inversely correlated with TMB in THYM. The correlation between POC1A expression and MSI was also analyzed using Spearman's rank correlation coefficient, and the results are shown in **Figure 10B**. Notably, the expression levels of POC1A were significantly positively correlated with MSI in BLCA, COAD, ESCA, HNSC, KIRC, LIHC, MESO, SARC, STAD, and UCEC, and inversely correlated with MSI in READ.

GSEA analysis of POC1A

Based on the Reactome database, genes correlating with POC1A ($P<0.05$) were ranked and subjected to GSEA analysis in pan-cancer. The analysis was performed using the R package "clusterProfiler". The top 20 results of each tumor identified by this analysis are shown in **Figure 11**. POC1A was positively correlated with cell cycle-related and immune-related pathways in various tumors, which is consistent with the previous conclusion that the POC1A has an immune regulatory function.

Drug sensitivity analysis

The correlation between POC1A1 and IC_{50} of 192 anti-cancer drugs was analyzed. It was discovered that patients with high POC1A expression might be resistant to most anti-cancer drugs, such as vincristine, oxaliplatin, carmustine, etc. (**Figure 12**, **Supplementary Table 1**).

Discussion

The centrosome is an organelle that plays a key role in the process of cell division and can regulate the process of the cell cycle(Mittal et al.,2020). Several studies have confirmed that centrosome amplification is found in virtually all cancer types and has been linked to chromosomal instability (CIN) and tumorigenesis(Cosenza et al.,2016,Pihan et al.,1998,Godinho et al.,2014). Therefore, abnormal regulation of the centrosome is a hallmark of cancer(Chan et al.,2011). Lopes et al. studied Barrett's esophagus patients and found that before the cells began to transform into cancer cells, they initially accumulated in the centrosomes, and centrosome expansion promoted the occurrence of esophageal cancer(Lopes et al.,2018). As an important component of the centrosome, POC1A is known to be a regulator of the cell cycle. Lu et al. found that POC1A can be used as a potential biomarker for the poor prognosis of gastric cancer(Lu et al.,2020). However, the role of POC1A in pan-cancer is uncertain. Therefore, the present study systematically analyzed the relation between POC1A expression and prognosis, tumor immunity microenvironment, immune checkpoint gene, tumor mutation burden (TMB), microsatellite instability (MSI), and drug sensitivity in 33 different tumors using the TCGA database.

The results showed that POC1A was significantly highly expressed in 27 of 33 cancer types. Reduced POC1A expression was only observed in LAML, PCPG, and TGCT. It was also found that the expression of POC1A increased with the increase of tumor stage in nine tumor types (**Figure 2A-I**). Moreover, high expression of POC1A was significantly associated with poor OS, DSS, DFI, and PFI in various tumors. All these results indicate that POC1A is an important oncogene and could be a potential biomarker for the poor prognosis of pan-cancer.

Furthermore, high CNA of POC1A was positively correlated with POC1A mRNA expression. Chromosome deletion of POC1A was the most marked in gastric cancer, and chromosome amplification was the most significant in seminoma. These results suggest a low level of POC1A mutation in pan-cancer and a high correlation between CNV and POC1A expression.

Recent studies have demonstrated that the immunosuppressive microenvironment is one of the reasons for the poor prognosis of tumor patients(Nakamura et al.,2020,Wang et al.,2021, Phuengkham et al.,2019, Yang et al.,2020). Therefore, we explored the correlation between POC1A and the immune microenvironment in pan-cancer using two different immune cell infiltration data. It was found that POC1A expression was negatively correlated with ImmuneScore and StromalScore and positively correlated with tumor purity in most tumors. Besides, the infiltration levels of immune killer cells, such as activated NK cells, CD4 T cells, and CD8 T cells, were negatively associated with POC1A expression in pan-cancer. However, immunosuppressive cells, such as

nTregs and iTregs, were positively correlated with POC1A expression based on two different analytical methods. The correlation between POC1A expression and the immune checkpoint gene was further evaluated. The results showed that POC1A was positively correlated with an immune checkpoint in various tumors, suggesting that immune cells were inhibited. Moreover, the correlation between POC1A expression and immunomodulatory genes was investigated, and the results showed that POC1A had potential immunomodulatory effects in most tumors (**Figure 9A-D**). Collectively, these results suggest that high expression of POC1A is associated with the immunosuppressive tumor microenvironment. POC1A expression was also significantly positively correlated with TMB and MSI in most tumors, suggesting that patients with high POC1A expression may be more sensitive to immunotherapy. Given the role and prognostic value of POC1A in pan-cancer, the possible biological function and associated signal pathway of POC1A in pan-cancer were further predicted using GSEA analysis. Our GSEA results suggested that POC1A was positively correlated with cell cycle-related and immune-related pathways in various tumors. Taken together, these results suggest that the POC1A gene may have an immunomodulatory function, and tumor patients with high expression of POC1A may be in an immunosuppressive state.

Additionally, the correlation between POC1A1 and IC_{50} of 192 anti-cancer drugs was performed and the results showed that patients with high POC1A expression might be resistant to most anti-cancer drugs, including vincristine, oxaliplatin, carmustine, which provides a new idea and direction for the study of the mechanism of chemoresistance.

Conclusion

To the best of our knowledge, this is the first study to perform more comprehensive bioinformatics analysis of POC1A in pan-cancer. The results identified POC1A as a potential prognostic biomarker and therapeutic target of pan-cancer. Importantly, it was found that high expression of POC1A was associated with immunosuppressive tumor microenvironment and immune checkpoint genes. We speculated that POC1A may be a novel potential biomarker for screening sensitive patients for immunotherapy.

Abbreviations

ACC: Adrenocortical carcinoma; BLCA: Bladder Urothelial Carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; 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: Lower Grade Glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin Cutaneous Melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular Germ Cell Tumor; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine Corpus Endometrial Carcinoma; UCS: Uterine Carcinosarcoma; UVM: Uveal Melanoma.

Declarations

Data availability statement

Publicly available datasets were analyzed in this study. The datasets analyzed during the current study are available in the TCGA(https://xenabrowser.net/datapages/)、GTEx(https://xenabrowser.net/datapages/),ImmuCellAI(http://bioinfo.life.hust.edu.cn/ImmuCellAI#!/),TIMER2(http://timer.comp-genomics.org/), cBioportal(https://www.cbioportal.org/) and GDSC(https://www.cancerrxgene.org/).

Conflict of Interest

The authors declare that there is no conflict of interest.

Author contributions

Zhao Qi conducted bioinformatics analysis, and Zhao Qi and Gao Shuping wrote and completed the manuscript. All authors have contributed to the article and approved the final manuscript.

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Figures

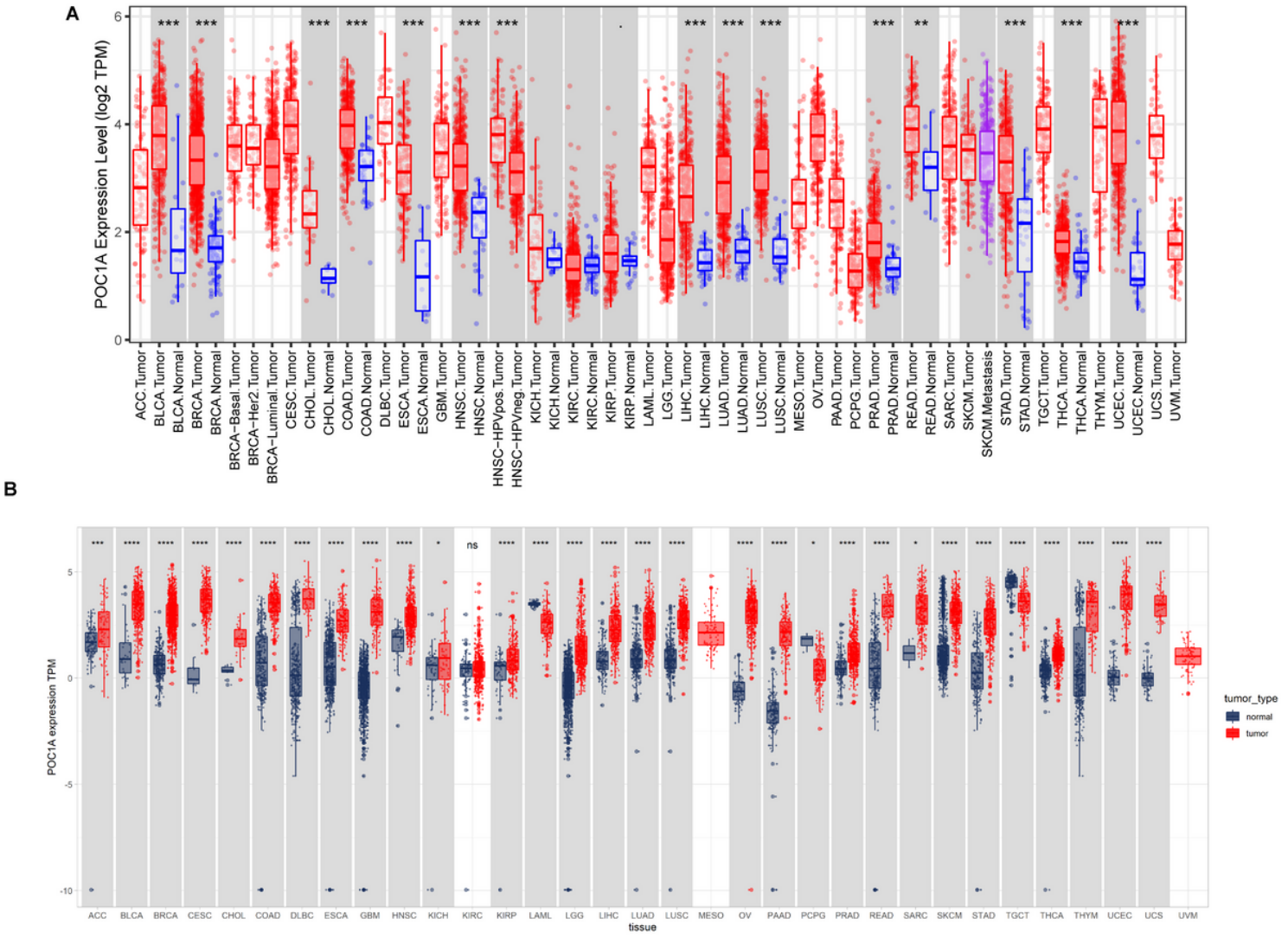

Figure 1

Expression of POC1A in pan-cancer. (A) Expression analysis of POC1A in pan-cancer using the TIMER2 database. (B) POC1A expression in tumor tissues and normal tissues from the TCGA and GTEx cohorts. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

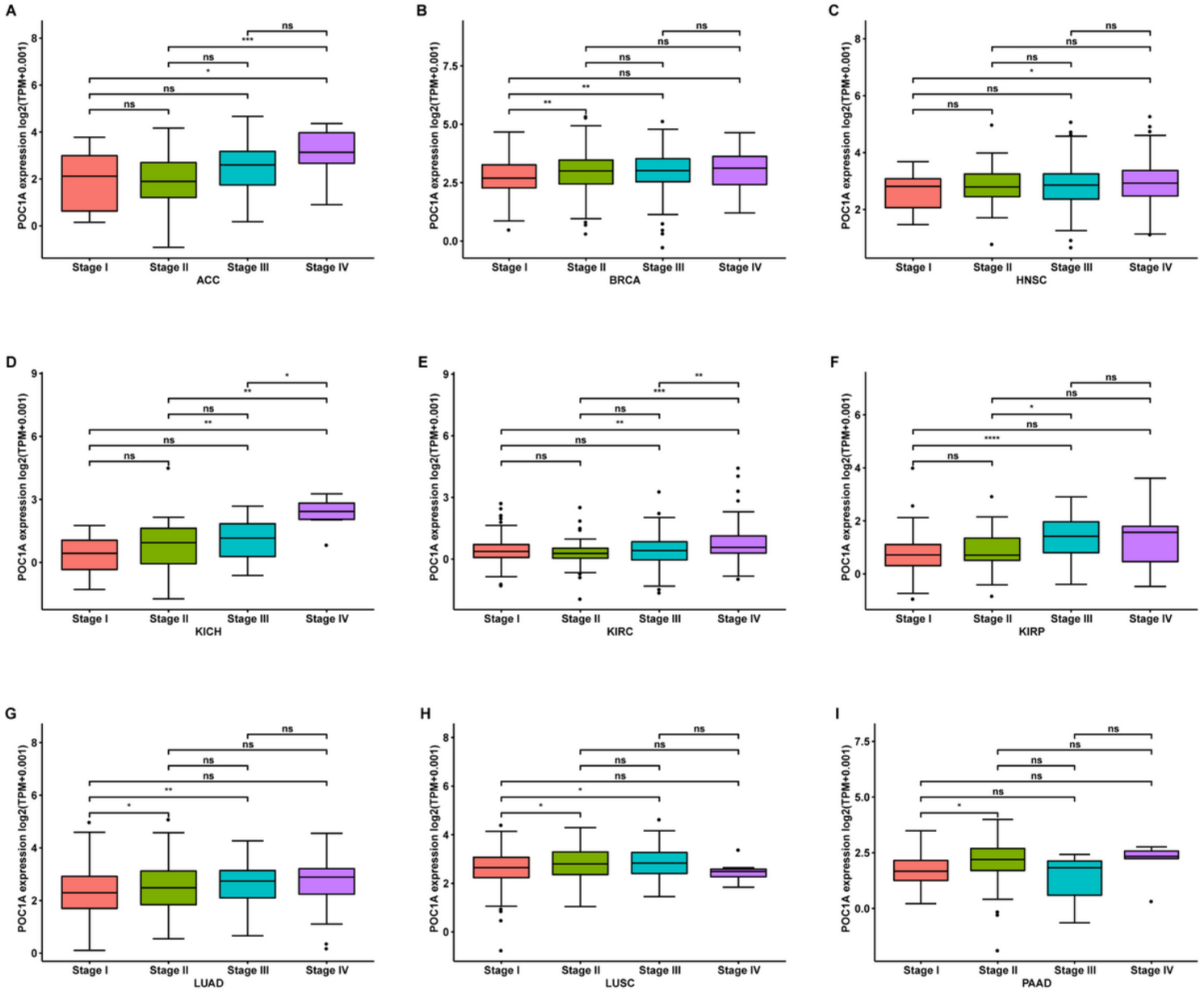

Figure 2

Expression of POC1A at various tumor stages. (A-I) POC1A expression at various tumor stages in indicated tumor types. *P<0.05, **P<0.01, ***P<0.001, **** <0.0001.

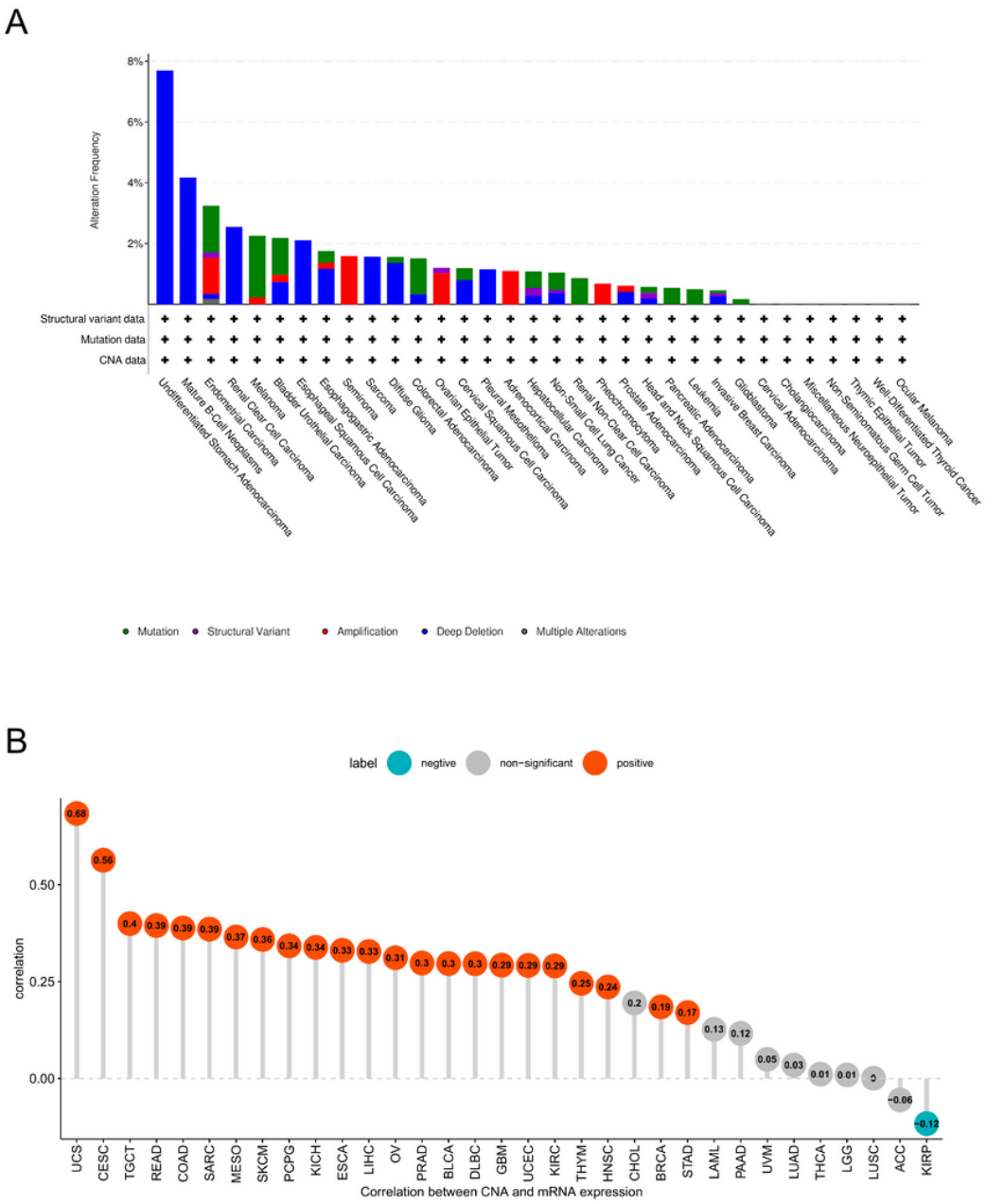

Figure 3

Gene alteration of POC1A. (A) Mutation and CNA status of POC1A in TCGA pan-cancer. (B) Correlation between POC1A expression and CNA.

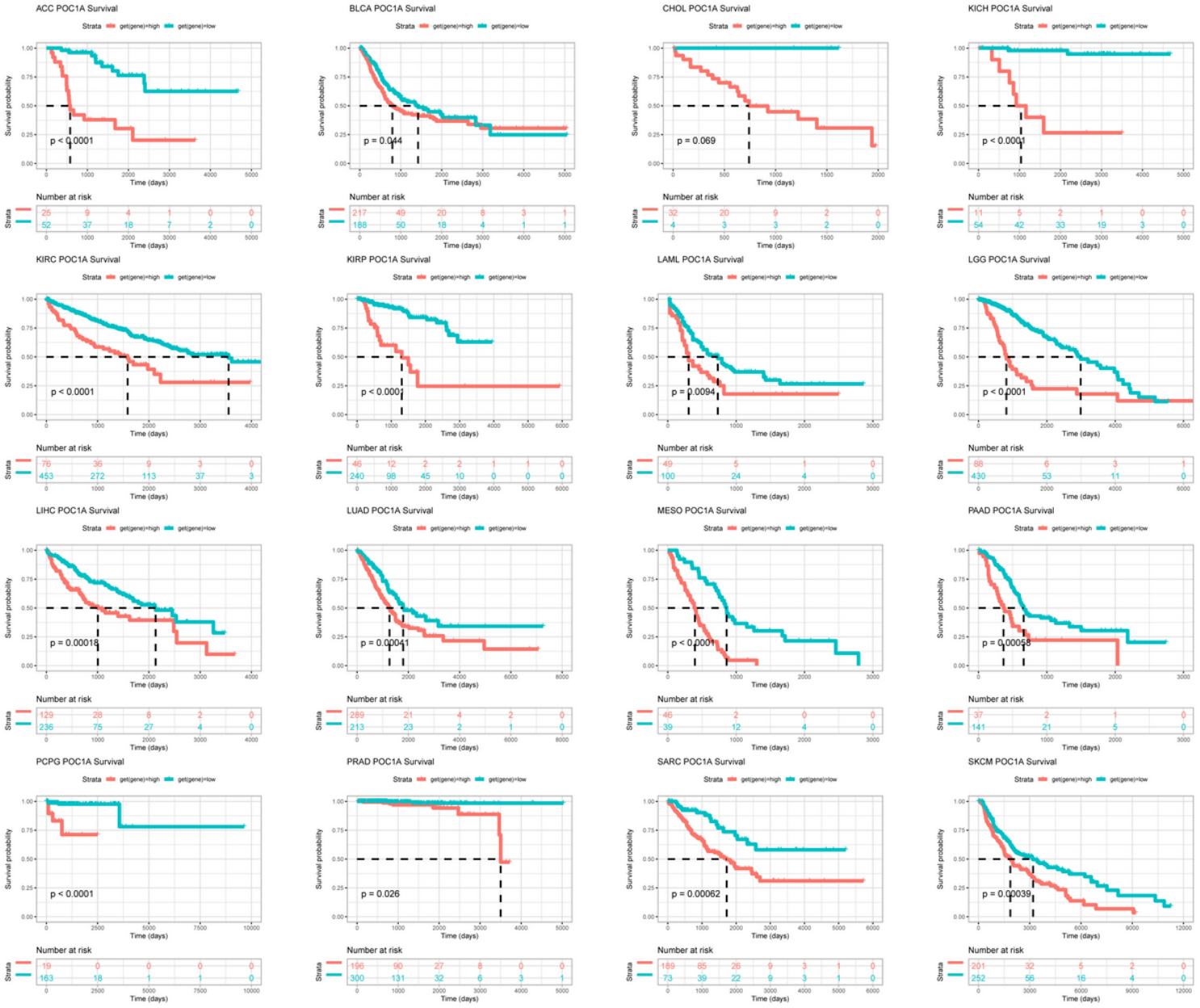

Figure 4

Prognostic value of POC1A. Kaplan-Meier overall survival analysis of POC1A in TCGA pan-cancer in indicated tumor types.

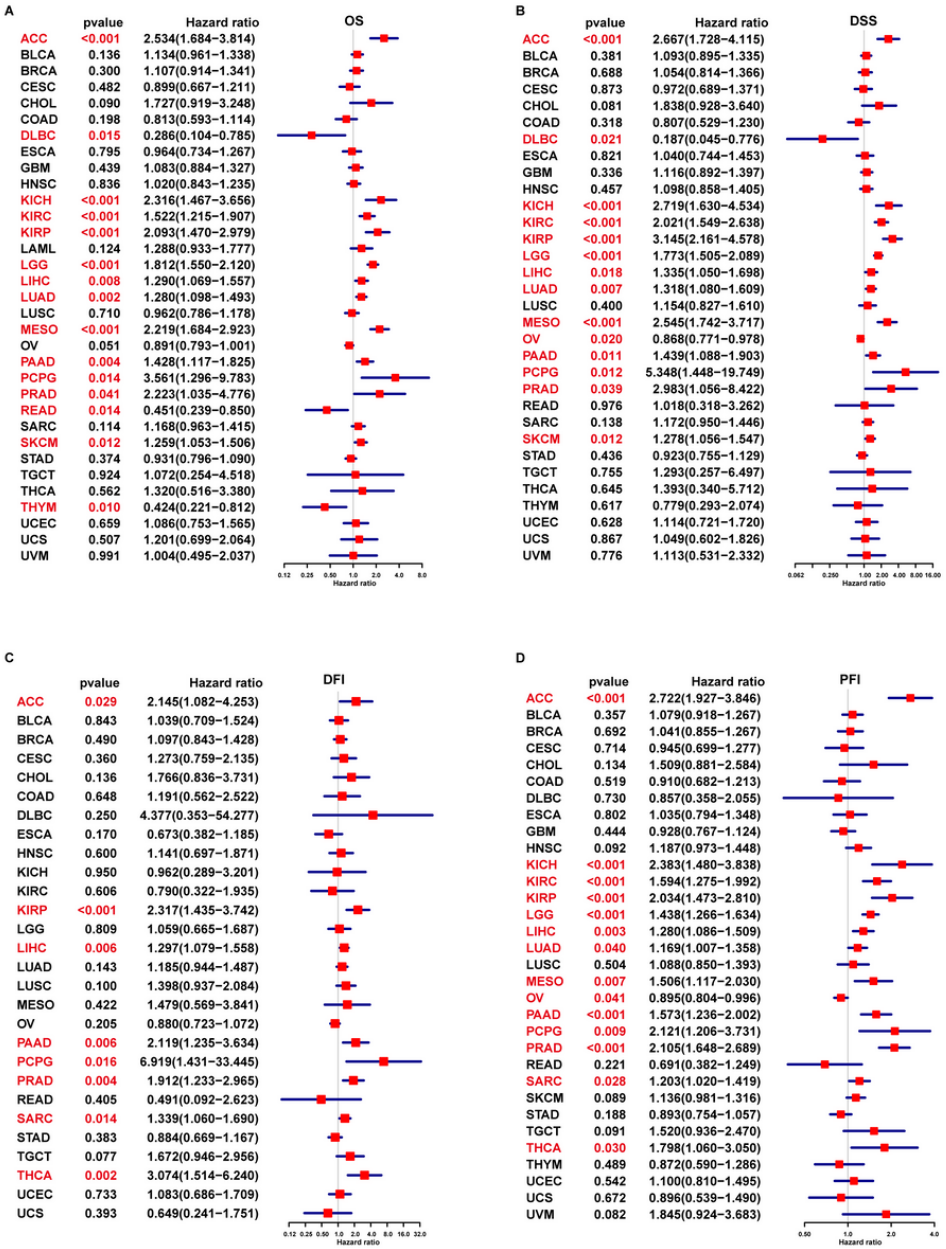

Figure 5

UniCox analysis of POC1A. (A) UniCox overall survival (OS)analysis of POC1A in TCGA pan-cancer. (B) UniCox disease-specific survival (DSS) analysis of POC1A in TCGA pan-cancer. (C) UniCox disease-free interval (DFI) analysis of POC1A in TCGA pan-cancer. (D) The UniCox progression-free interval (PFI) analysis of POC1A in TCGA pan-cancer. The red color represents significant results (P<0.05).

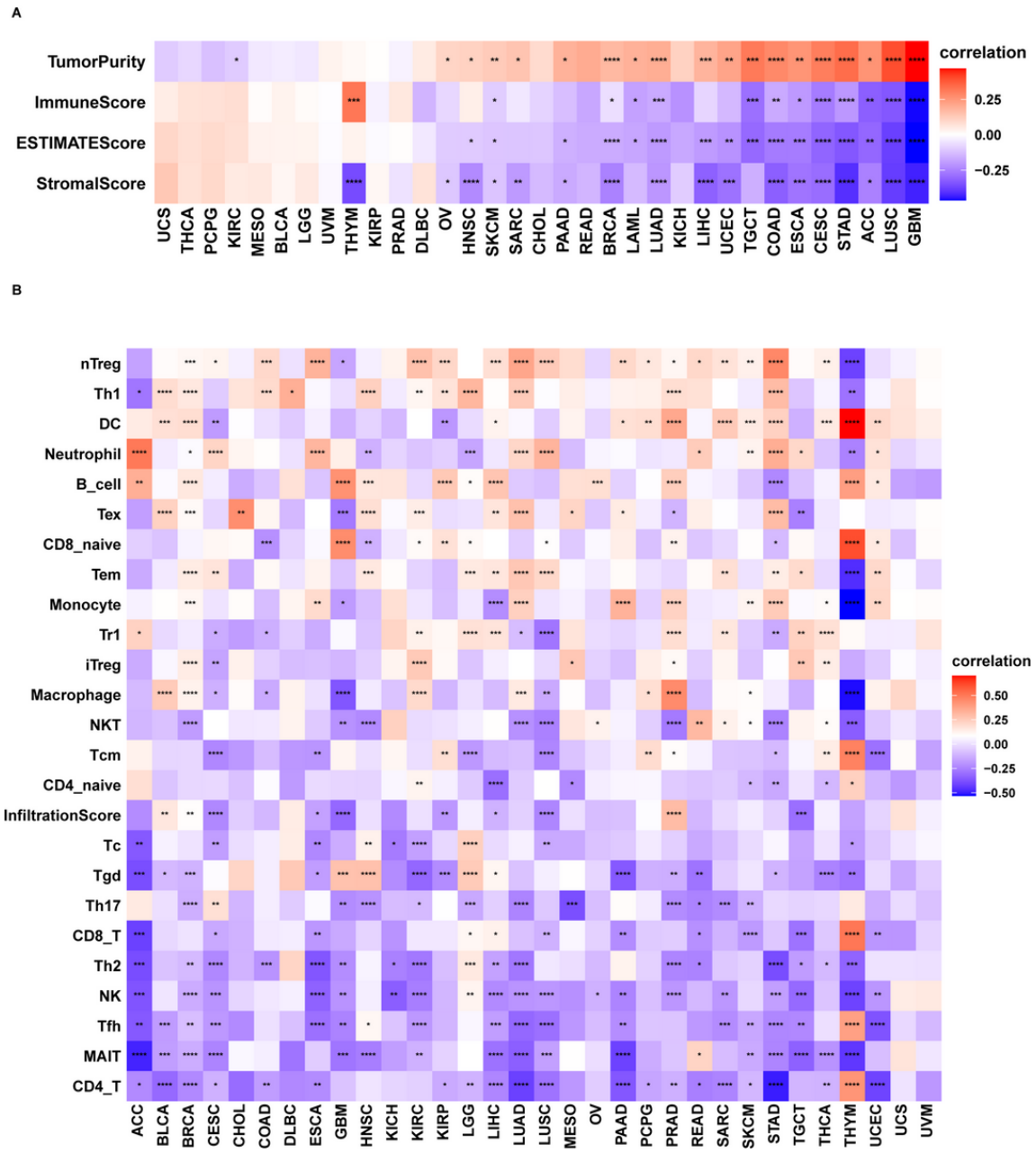

Figure 6

Immune infiltration analysis based on data from the ImmuCellAI database. (A) Correlation between POC1A expression and immune cell infiltration in LUAD. (B) Relationship between POC1A expression and tumor purity, StromalScore, ImmuneScore, and ESTIMATEscore. Red represents positive correlation and blue represents negative correlation; the darker the color, the stronger the correlation. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

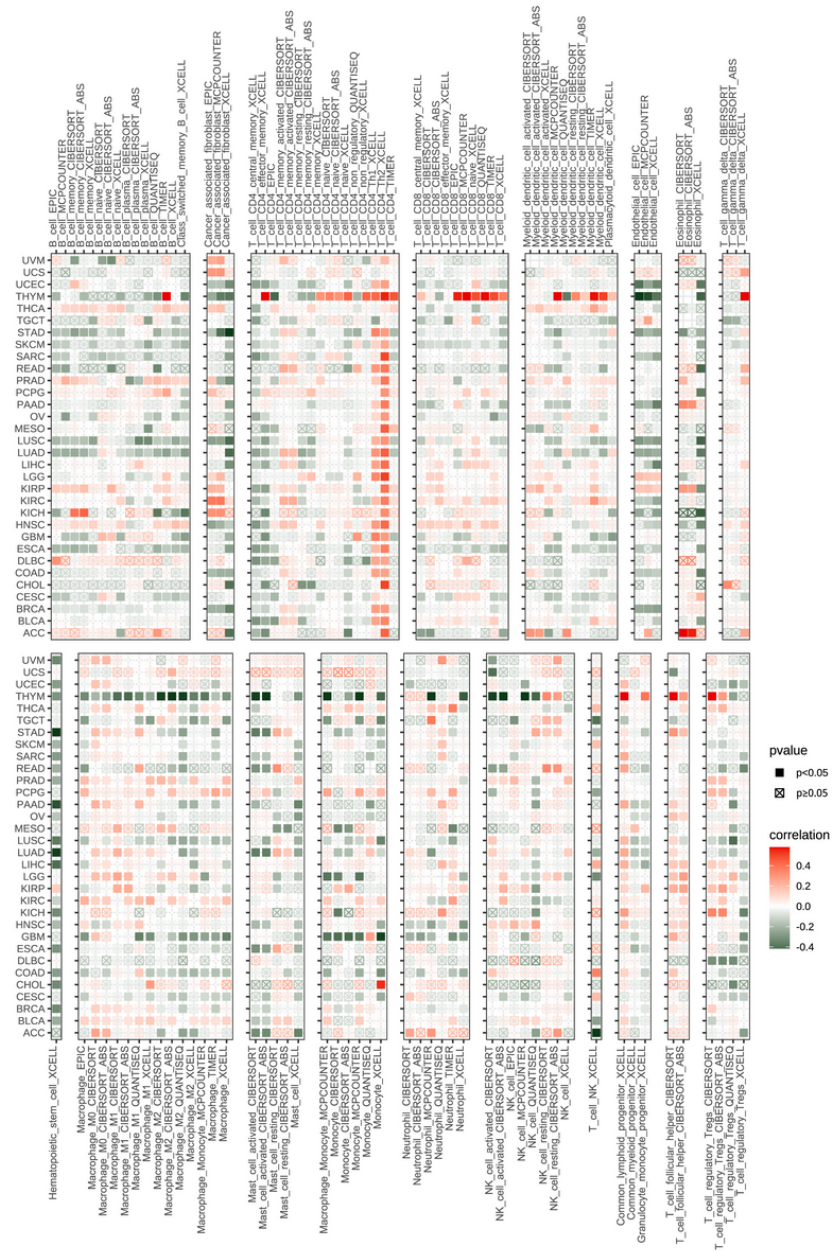

Figure 7

Immune infiltration analysis based on data from the TIMER2 database.

The relationship between POC1A expression and infiltration levels of immune cells in pan-cancer. Red represents positive correlation and the green represents negative correlation; the darker the color, the stronger the correlation. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

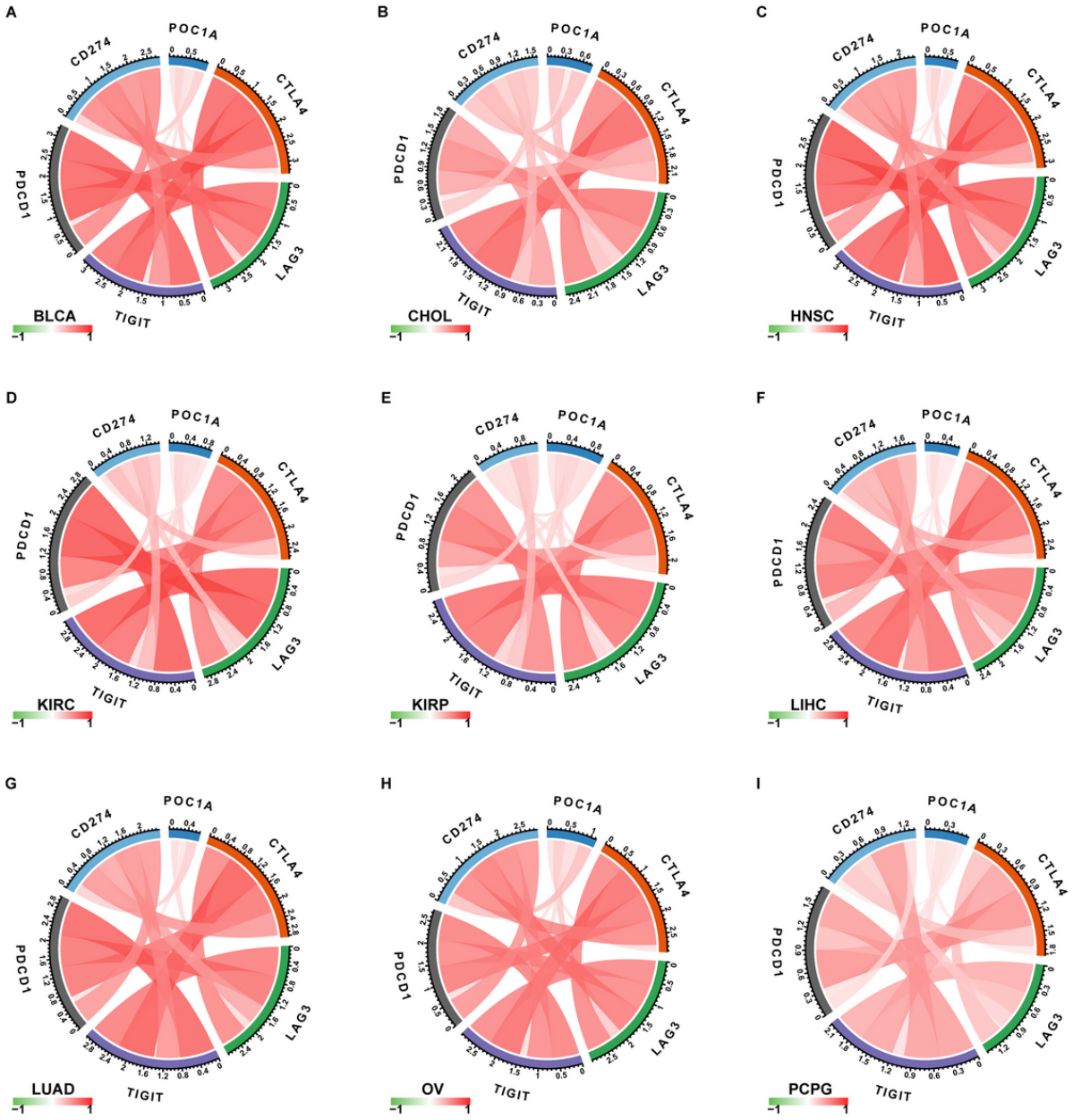

Figure 8

Correlation between POC1A expression and immune checkpoint genes.

The correlation between POC1A expression and immune checkpoint genes in pan-cancer. Red lines represent positive correlation, green lines represent negative correlation, and the darker the color, the stronger the correlation.

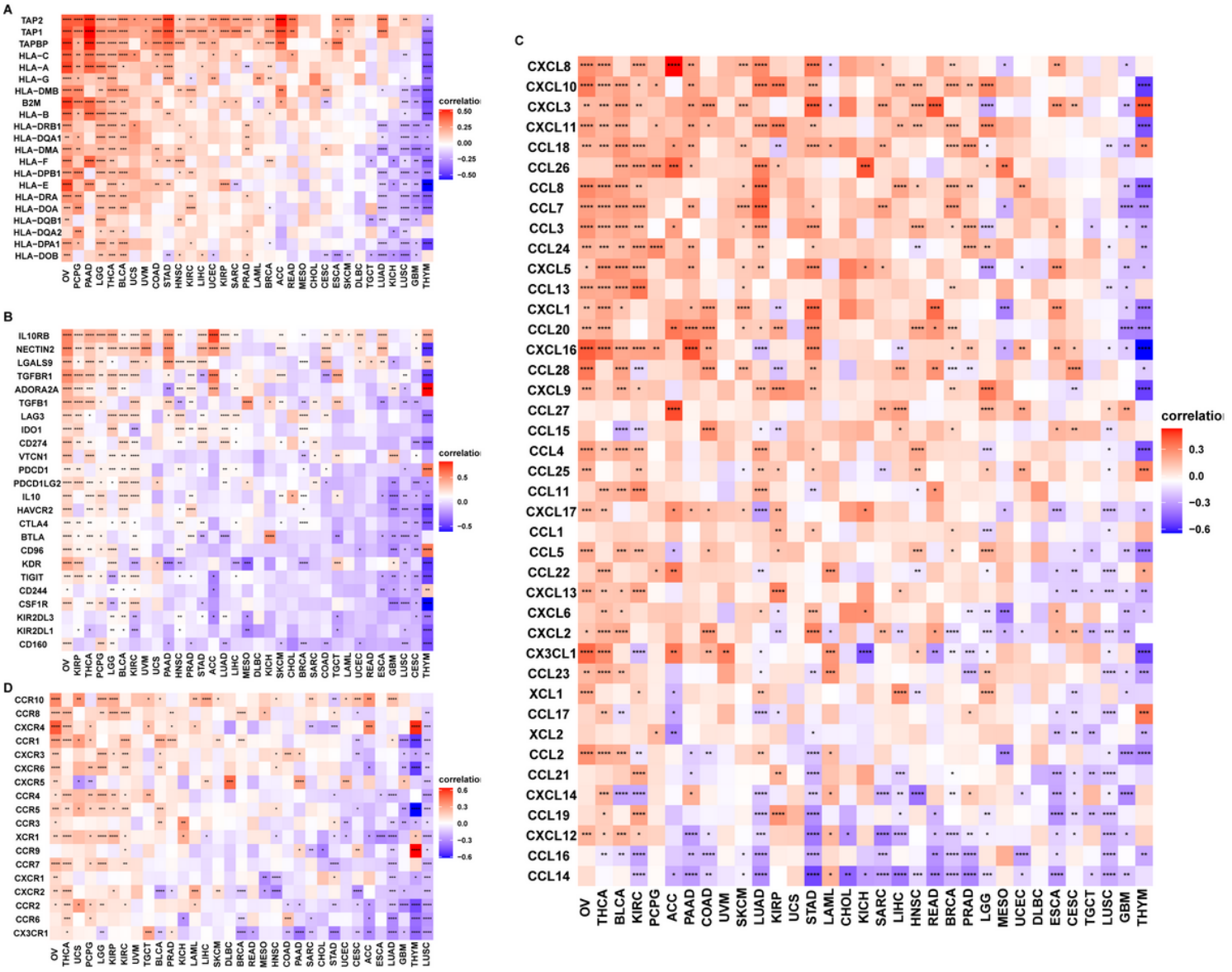

Figure 9

Correlation between POC1A and immunomodulatory genes. (A) Heatmap representing the correlation between POC1A expression and MHC genes. (B) Heatmap of the correlation between POC1A expression and immunosuppressive status-related genes. (C) Heatmap representing the correlation between POC1A expression and chemokine genes. (D) Heatmap representing the correlation between POC1A expression and chemokine receptor genes. Pearson's correlation coefficient was calculated using R software.

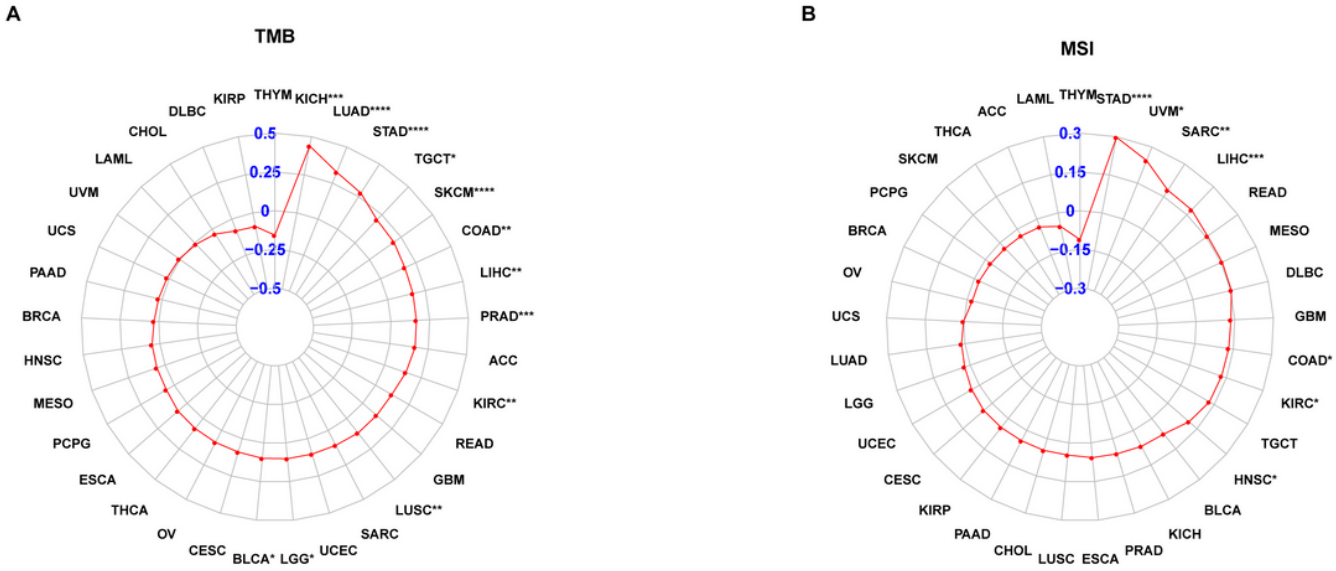

Figure 10

Correlation between POC1A expression and tumor mutation burden (TMB) and microsatellite instability (MSI). (A-B) Radar plots of the correlation of POC1A expression with TMB (A) and MSI (B) in pan-cancer. The red dot shows the correlation coefficient. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

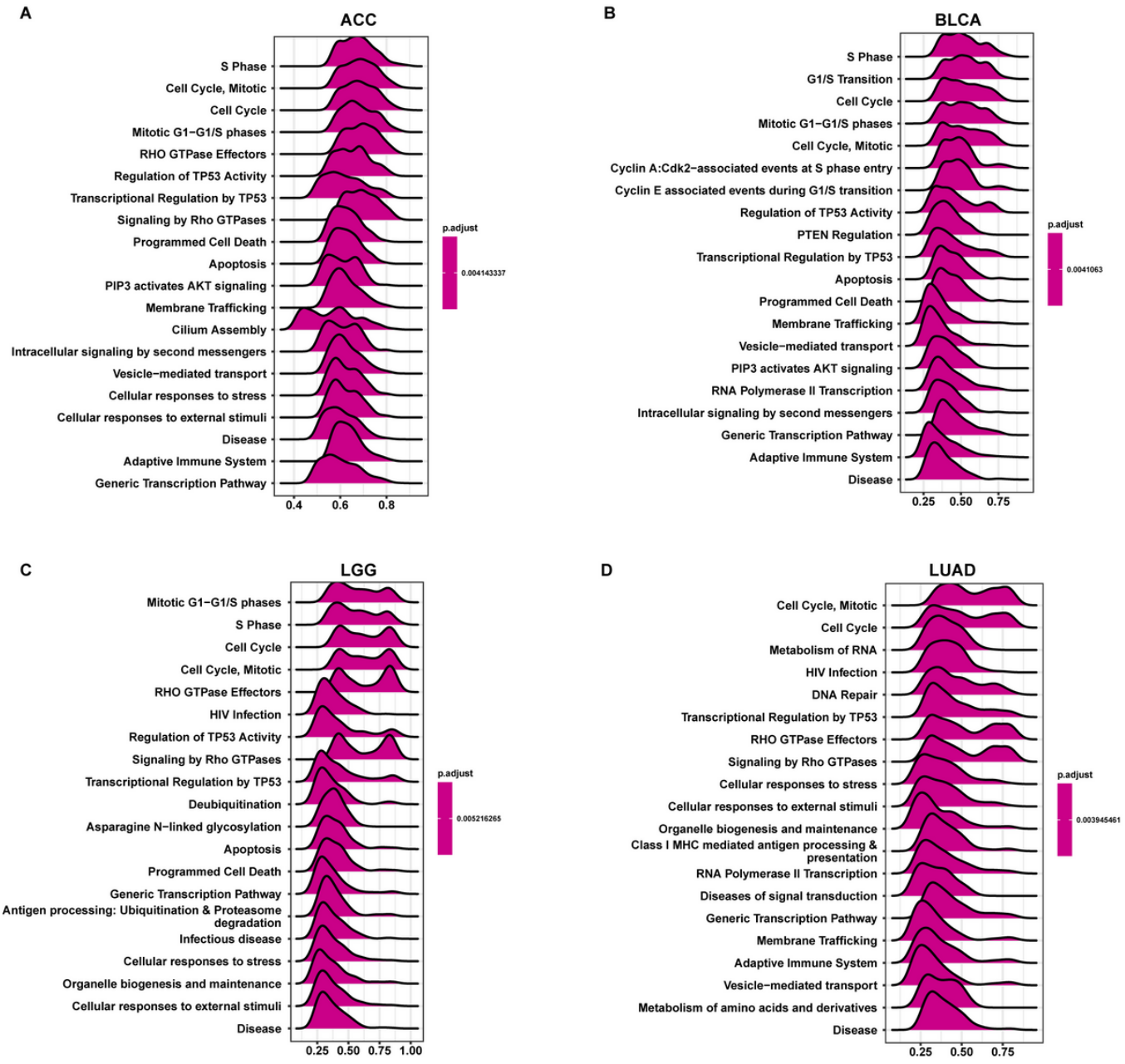

Figure 11

GSEA analysis of POC1A in pan-cancer. (A-D) The top 20 genes of indicated tumor types identified by GSEA (NES ≥ 1.5, adjusted P-value <0.05). Red indicates cell cycle-related or immune regulation-related pathways.

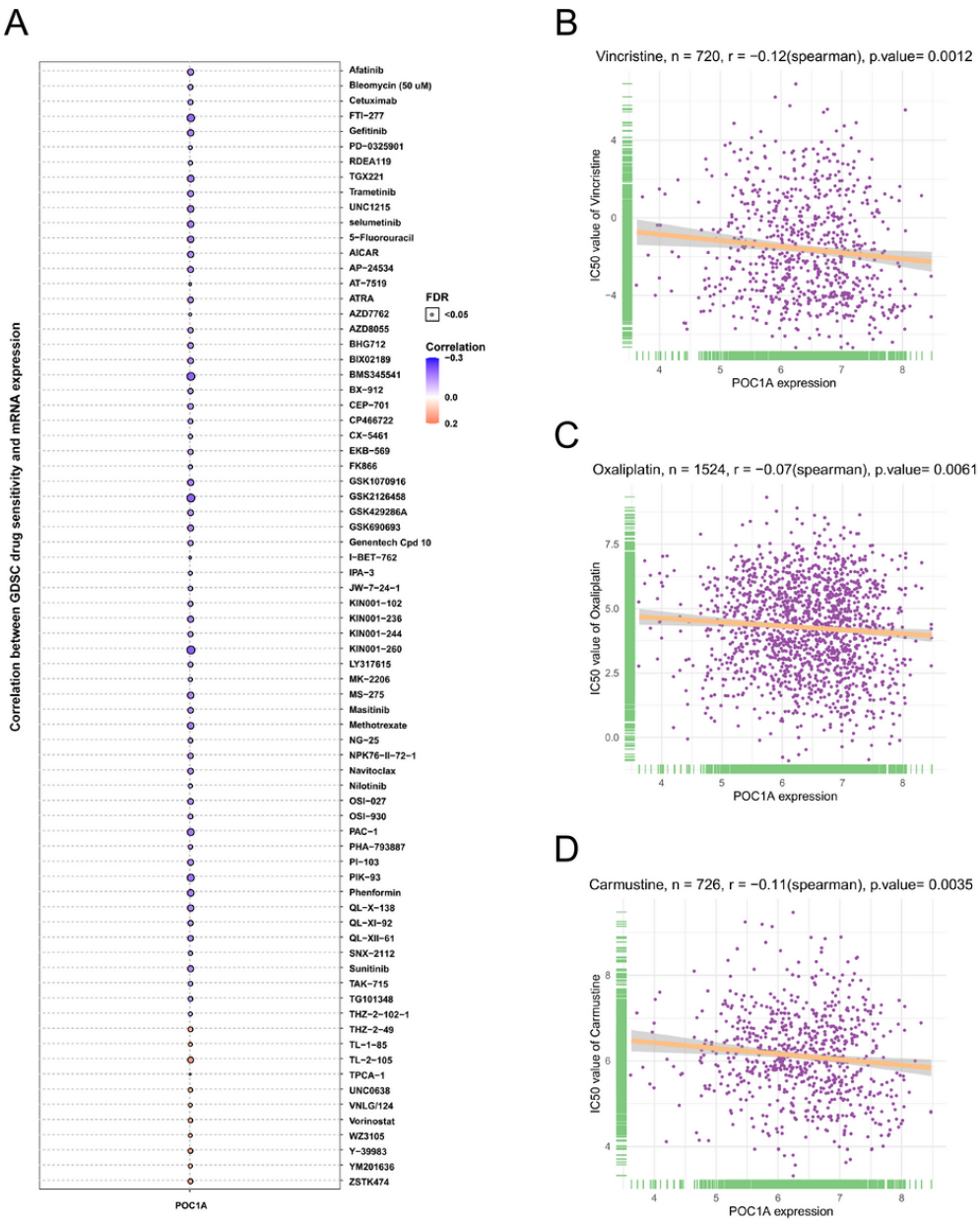

Figure 12

Correlation between POC1A expression and IC_{50} values of anti-cancer drugs. The correlation between POC1A expression and IC_{50} values of indicated anti-cancer drugs.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.csv