Diagnostic, Prognostic, and Immunological Roles of CD177 in Cervical Cancer

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Abstract

Background.

CD177, an indicator of prognosis in diverse cancers, is involved in the physiological processes of various tumor cells, and acts as an immune molecule with novel functions in cancer pathogenesis. However, the diagnostic, prognostic and immunological role of CD177 in cervical cancer remains unclear.

Methods.

Utilizing publicly available databases and integrating several bioinformatics analysis methods, we evaluated the expression level of CD177 in cervical cancer by GENT2, HPA and GEO databases. The Kaplan–Meier Plotter database, Xena Shiny and the constructed of a nomogram were clearly demonstrated its prognostic value for patients. Gene set enrichment analysis explored the relationship between CD177 and cervical cancer immune responses and immune cells infiltration level. In addition, we investigated the association between CD177 expression and stromalscore, immunescore, immune checkpoint and drug sensitivity by TCGA RNA-seq data.

Results.

CD177 was apparently expressed at low levels in cervical cancer and predicted a poor survival rate for patients. CD177 significantly activated immune-related signaling pathways and had a positive relationship with immune cell infiltration level. The high CD177 expression group possessed the high stromalscore and immunescore. CD177 had potential interactions with CTLA4, CD27, BLTA, CD200R1, CD80, NRP1, TNFRSF25, TIGIT, ICOS and TNFSF9 checkpoint markers. And CD177 expression was positively relevant with drug sensitivity for Lapatinib, Belinostat, ATRA, Gefitinib, Navitoclax and Tamoxifen.

Significance.

These findings may shed light on the vital role of CD177 in cervical cancer diagnosis, prognosis, and immunological function, and it may be a promising predictor and potential factor for cervical cancer patients.

Introduction

Cervical cancer is the fourth leading cause of cancer-related death in women, with 604,000 new cases and 342,000 deaths in 2020 worldwide (Sung et al. 2021). The five-year survival rate of early-stage patients is significantly prolonged by surgery and adjuvant radiation and chemotherapy, but outcomes for patients given a diagnosis of metastatic and recurrent disease are poor (Rosen et al. 2017). PD-1/PD-L1

immune checkpoint inhibitors can be used in advanced PD-L1 positive patients (Wendel Naumann and Leath 2020). However, patients have a response rate of 10–25% to such treatment (Otter et al. 2019). Consequently, new insights into immune molecule and cell interactions in the tumor microenvironment may be helpful to explore more immunotherapy targets and improve the immune effectiveness for advanced cervical cancer patients (Mandal and Chan 2016).

CD177 (also known as NB1, HNA-2a, or PRV1) is a glycophosphatidylinositol (GPI)-linked extracellular membrane protein, expressed on the plasma membrane and specific granules of neutrophils (Kissel et al. 2001, Kluz et al. 2020, Silvestre-Roig et al. 2019). Approximately 50% of all circulating neutrophils in humans express the CD177 protein (Silvestre-Roig et al. 2016). CD177 exerts its biological functions by modulating human neutrophil migration, acting as a flow cytometry marker for myelodysplastic syndrome, and presenting antigens in immune diseases on the neutrophil surface (Alayed et al. 2020, Bai et al. 2017, Eulenberg-Gustavus et al. 2017). At present, CD177 has been extensively studied in immune diseases, such as kawasaki disease, rheumatoid arthritis, allergic asthmatic subjects, and inflammatory bowel disease.

In the field of oncology, CD177 also plays a double-edged role in affecting the clinical significance and prognostic value in multiple cancers. The higher expression of CD177 significantly correlated with the poor prognosis of ovarian cancer and pancreatic ductal adenocarcinoma but correlated with a good prognosis of breast cancer (Jiang et al. 2020, Kluz, Kolb, Xie, Borcherding, Liu, Luo, Kim, Wang, Zhang, Li, Stipp, Gibson-Corley, Zhao, Qi, Bellizzi, Tao, Sugg, Weigel, Zhou, Shen and Zhang 2020, Moreira et al. 2018). More importantly, recent research has revealed that CD177 could enhance the inhibitory function of tumor-infiltrating Treg cells in the tumor microenvironment, and blocking CD177 with antibodies in CD177 + tumor-infiltrating cells may serve as a new antitumor immunotherapy target (Kim et al. 2021). However, the data about the prognostic values and immune functions of the CD177 gene and its protein in the developing of cervical cancer has never been reported.

Due to the rapid development of biological databases in recent years, we comprehensively explored the diagnosis, prognosis, and immunological function of CD177 by performing a variety of bioinformatical analysis in cervical cancer, including screening for CD177 expression level and prognostic value, investigating the molecular biological function, evaluating the potential association between tumor-infiltrating lymphocytes, stromalscore, immunescore, immune checkpoint and drug sensitivity. From our study, we hypothesized that CD177 might be a prognostic biomarker in cervical cancer, these might contribute to the further understanding of the role of CD177 in cervical cancer.

Materials & Methods

CD177 mRNA and protein expression

We searched GENT2 (http://gent2.appex.kr/gent2/) and HPA (https://www.proteinatlas.org/) databases to get the expression of mRNA and protein in pancancer. We also obtained mRNA expression datasets

from the GEO database (https://www.ncbi.nlm.nih.gov/geo/)(Li et al. 2019, Park et al. 2019). GSE6791 (including 20 cervical cancers and 8 controls), GSE9750 (including 33 cervical cancers and 21 controls) and GSE63514 (including 28 cervical cancers and 24 controls) were downloaded from GPL96 ([HG-U133A] Affymetrix Human Genome U133A Array) and GPL570 ([HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array) platforms. Background correction, standardization and expression value calculation were performed by using the limma, dplyer, and ggplot2 packages of R software (version: x64 4.1.2). |Fold-change (FC)| and adjusted p value < 0.05 were considered statistically significant.

Survival analysis

We assessed the overall survival (OS) and progress-free survival (PFS) in the high and low CD177 expression groups in the Kaplan–Meier Plotter database https://kmplot.com/analysis/)(Győrffy 2021). Besides, the Xena Shiny was (https://shiny.hiplot.com.cn/ucsc-xena-shiny/) investigated to illuminate the impact of CD177 on the 33 different types of cancers, and the disease-free interval (DFI) and progression-free interval (PFI) were also affirmed the impact of CD177 on cervical cancer(Wang et al. 2021).

The Cancer Genome Atlas (TCGA)

TCGA database molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types (https://portal.gdc.cancer.gov/). We downloaded cervical cancer RNA-seq data from TCGA database, using limma, dplyr, corrplot, ggplot2, vioplot and ggpubr packages in R software (version: x64 4.1.2) to construct the survival nomogram and CD177 coexpression circos plot. GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment were performed to analysis the influence of CD177-related genes for signal pathways in cervical cancer patients. Furthermore, we estimated the stromalscore, immunescore and estimatescore in cervical cancer immune microenvironment. And the relationship between immune checkpoints and drug sensitivity with CD177 also verified from TCGA data.

Coexpression gene networks and protein-protein interaction network

The LinkedOmics (http://linkedomics.org/admin.php) database was used to plot the heatmap of top 50 positively and negatively CD177 correlated genes in cervical cancer(Vasaikar et al. 2018). The protein-protein interaction network was constructed by analyzing the STRING database (https://string-db.org/) to further clear the CD177 protein function.

Immune infiltration analysis

TISIDB (http://cis.hku.hk/TISIDB/) can clarify the function of a specific gene in tumor–immune interplay, and generate testable hypotheses and high quality figures for publication (Ru et al. 2019). TIMER(https://cistrome.shinyapps.io/timer/) is a comprehensive resource for the systematic analysis of immune infiltrates across diverse cancer types (Li et al. 2016, Li et al. 2017). We made use of the two databases to explore the critical influencing of CD177 expression for the immune status of the tumor microenvironment.

Statistical analysis

The survival outcomes of K-M plotters were demonstrated with HR and p value by a log-rank test. Correlations between CD177 expression and its related genes were analyzed by the Pearson correlation test in LinkedOmics. The infiltration level for each SCNA category was compared with the normal level using a two-sided Wilcoxon rank-sum test in the TIMER database.

Results

The expression pattern of CD177 from a pancancer and cervical cancer perspective

To evaluate the expression of CD177 across various tumor types, we conducted pancancer analysis in the GENT2 database. The results revealed that the mRNA expression of CD177 in cervical cancer, breast cancer, colon cancer, kidney cancer and esophageal cancer was lower. Notably, CD177 had low expression in cervical cancer, with a P value of 0.004 and log2FC of -0.570 (Fig. 1A and Supplementary data 1). Subsequently, we examined the protein expression of CD177 in different human organs and tissues, which principally expressed in the oral mucosa, colon, rectum, cervix, appendix, bone marrow, esophagus, liver, placenta, skin, spleen, and tonsil in the HPA database (Fig. 1B). We also downloaded the gene expression profile datasets GSE6791, GSE9750 and GSE63514 from the GEO database. We could discover that the expression level of CD177 was apparently down-regulated in cervical cancer (Fig. 1C). The above results demonstrated that CD177 was expressed at low levels in cervical cancer and may be a potential novel prognostic biomarker.

Prognostic values of CD177 expression in cervical cancer

To assess how CD177 affects the prognosis of cancer patients, a prognosis analysis was done using Xena Shiny. The molecular profile Cox analysis in TCGA showed that CD177 was as a protective factor (log (Hazard Ratio) < 0, P value < 0.05) in READ, HNSC and CESC (Fig. 2A). Then we evaluated the prognostic value of CD177 in cervical cancer using the Kaplan–Meier plotter database, which illustrated that the OS (log-rank P = 0.00073) and PFS (log-rank P = 0.0047) for patients with high CD177 levels was significantly longer than that for patients with the low expression (Fig. 2B-C). To validate these findings, we proceeded to investigate the impact of CD177 on DFI and PFI for cervical cancer patients. The high CD177 expression was attributed to a prolonged DFI and PFI for patients. These results implied that low CD177 expression was associated with a worse prognosis in cervical cancer. To further forecast the survival time of cervical cancer patients, a nomogram was constructed by using age, grade, T stage, N stage, M stage and CD177 levels as indicators to forecast one, three-, and five- year overall survival in cervical cancer patients. The sample with a higher score had a worse prognosis (Fig. 3A). Calibration curves showing the desirable predictions of the nomograms for one, three-, and five- year clinical outcomes (Fig. 3B).

CD177 coexpression gene networks and protein-protein interaction network

To gain insight into the potential contributors of CD177 that may facilitate its function during the carcinogenic process, the online database LinkedOmics was used to explore CD177 coexpression genes. The top 50 positively and negatively correlated genes were presented in the heatmaps of Fig. 4A. Moreover, circos plot derived from genes identified by the TCGA database, we confirmed a significantly positive correlation existed between CD177 with SPRR3, TMPRSS11F, CNFN, IL36RN, PRSS27 and KRT78, and a significantly negative correlation existed between CD177 with TAF9, ZNF354A, NUDCD2, PFDN1 and SCMH1 (Fig. 4B). Afterwards, we conducted the STRING database to further investigate the protein-protein interaction network (Fig. 4C). The PPI network was composed of 31 nodes and 99 edges. The 20 colored nodes represented query proteins and first shell of interactors, the 10 white nodes represented second shell of interactors. According to the analysis above, we can easily retrieve the interactions between CD177 with other coexpression genes and proteins, which is beneficial to better understand the complicated regulatory networks of human beings.

The differentially expressed genes and CD177-related gene enrichment analysis

To further investigate the function of CD177 in cervical cancer, we divided TCGA RNA-seq data into CD177 low expression group and CD177 high expression group.

The differentially expressed genes (DGEs) in the two groups were presented in the heatmap (Fig. 5A). The GO analysis data showed that DGEs mainly located in plasma membrane and participated in the activation of immune functions, most of the DGEs were associated with cytokine – mediated signaling pathway, humoral immune response, antimicrobial humoral response, and inflammatory response to antigenic stimulus (Fig. 5B-C). And the KEGG pathways revealed that CD177 enrichment in the regulation of immune effector process, cell killing, response to chemokine, positive regulation of leukocyte mediated immunity, and regulation of dendritic cell chemotaxis (Fig. 5D-E). To further explore the relationship between the enriched pathways, we performed Gene Set Enrichment Analysis (GSEA) analysis, we observed the pathways including chemokine-signaling, cytokine-cytokine-receptor-interaction, hematopoietic-cell-lineage and melanoma were upregulated in the CD177 high expression group, but the pathway of primary-immunodeficiency were upregulated in the CD177 low expression group (Fig. 5F). All these results indicated that expression of CD177 might be involved in the immune activation and innate and adaptive immune responses.

Correlations between CD177 expression and immune infiltration in cervical cancer

We had demonstrated the relevance of CD177 and immune regulation in cervical cancer, in order to clarify the correlations between CD177 expression and immune infiltration in cervical cancer. We split the CD177

expression into high and low expression groups using the ESTIMATE algorithm, we estimated the stromalscore ranging from − 2434.48 to 806.9, the immunescore ranging from − 1221.7 to 3398.3, and ESTIMATEScore ranging from − 3271.3 to 3983.5 (Supplementary data 2). These results manifested that there was a statistically significant difference in the two groups, the stromal cells and immune cells infiltration level in the CD177 high expression group elevated than that in the low expression group (Fig. 6A). We determined the correlation between CD177 and the abundance of tumor-infiltrating lymphocytes using Xena Shiny. The relationship of CD177 expression between the different immune cells is shown in Fig. 6B. According to the landscape, we found that CD177 was moderately correlated with tumor-infiltrating lymphocytes in 33 types of cancers. The expression of CD177 was significantly correlated with the abundance of lymphocytes in CESC, including activated CD8 + central memory T cell, CD4 + Th1 T cell, CD4 + effector memory T cell, natural killer cell, actived myeloid dendritic cell, monocyte, macrophage, and B cell (Fig. 6B). These data verified that CD177 may regulate the level of immune cells infiltration in cervical cancer.

CD177 was a critical factor influencing the immune status of the tumor microenvironment

To verify the reliability and authenticity of the results, we applied the spearman correlation test to evaluation the correlation between the abundance of immune cells and CD177 expression level. Following analysis found that CD177 expression level was positively correlated with actived CD4 + T cell (r = 0.118, P = 0.0397), actived CD8 + T cell (r = 0.13, P = 0.0229), actived DC cell (r = 0.154, P = 0.00693), immune B cell (r = 0.254, P = 7.56e-06), macrophage cell (r = 0.268, P = 2.2e-06), memory B cell (r = 0.15, P = 0.00873), monocyte (r = 0.139, P = 0.0147), NK cell (r = 0.22, P = 0.000112), and Th1 cell (r = 0.234, P = 3.74e-05) (Fig. 7A). Additionally, the somatic copy number alterations (SCNA) of CD177 markedly regulated the degree of immune infiltration of CD4 + T cell, CD8 + T cell, neutrophil, and dendritic cell in cervical cancer (Fig. 6B).

Relationship between immune checkpoint and CD177

Nextly, correlation test was validated to further explored the relationship between immune checkpoint and CD177. We selected 47 common immune checkpoint genes (Supplementary data 3). We found that CD177 was positively correlated with CTLA4, CD27, BLTA, CD200R1, CD80, TNFRSF25, TIGIT, ICOS and TNFSF9 checkpoint markers (Fig. 8). Collectively, these results suggested that a potential interaction of CD177 with known immune checkpoints in cervical cancer.

Analysis of drug sensitivity to the CD177 gene

At last, to clarify the potential correlation between CD177 expression and drug sensitivity in cervical cancer. We observed a significant difference in IC50 (half maximal inhibitory concentration) between CD177 high and low expression groups. The IC50 of antineoplastic drugs and targeted drugs in CD177 high expression group was much lower than that in the CD177 low expression group, including Lapatinib, Belinostat, ATRA, Gefitinib, Navitoclax and Tamoxifen (Fig. 9). Therefore, CD177 expression was positively relevant with drug sensitivity.

Discussion

CD177 is a membrane surface immune molecule of neutrophils, and previous studies have demonstrated that it can influence prognosis in different types of cancers. In breast cancer, CD177 acts as a tumor suppressor and expresses at lower levels to predict the poor prognosis, regulating the Wnt/β-Catenin signaling pathway to inhibit tumor cell proliferation, invasion, and migration (Kluz, Kolb, Xie, Borcherding, Liu, Luo, Kim, Wang, Zhang, Li, Stipp, Gibson-Corley, Zhao, Qi, Bellizzi, Tao, Sugg, Weigel, Zhou, Shen and Zhang 2020). However, in epithelial ovarian cancer, the expression of CD177 was highly increased and positively related to the malignant degree, which is a predictor marker for poor prognosis (Jiang, Chen, Zhang, Zhou and Wu 2020). Therefore, to clarify the correlation between the prognostic value and expression of CD177 in cervical cancer, we used several authoritative databases including GENT2, HPA, GEO, Kaplan–Meier plotter, and Xena Shiny. We determined that CD177 was low expressed in cervical cancer tissues, and as a protective factor, low CD177 expression predicted poor prognosis for patients. Meanwhile, we forecast one, three-, and five- year overall survival in cervical cancer patients by constructing a nomogram. Taken together, the imbalance of CD177 expression seems to have a vital role in carcinogenesis. However, the effect of changes in the expression level of CD177 during carcinogenesis is still ambiguous.

To confirm molecular contributors of CD177 that may facilitate its function during the carcinogenic process in cervical cancer, the gene coexpression networks and protein-protein interaction network were created. We identified the top 50 genes that were positively and negatively associated with CD177. And CD177 was discovered to be relevant to the genes, including TAF9, ZNF354A, NUDCD2, PFDN1, SCMH1, SPRR3, CNFN, TMPRSS11F, IL36RN, PRSS27 and KRT78. For most of these genes, several findings have been manifested that they are involved in transcription, cell cycle progression, growth control and cell migration. For example, PFDN1 can promote gastric cancer metastasis via the activation of Wnt/β-catenin pathway(Zhou et al. 2020). Expression of SPRR3 is associated with tumor cell proliferation and invasion in glioblastoma multiforme(Liu et al. 2014). For most of the proteins in the protein-protein interaction network, including PECAM1, PRTN3, CNTN5, CNTN6, KCNIP3, PLAUR, LYPD3, PROCR, ZNF575, ZNF706, PLNLYP, and LYPD5, they were mostly enriched involved in transcriptional regulation, host defense system of polymorphonuclear leukocytes, proliferation of cancer cells, and cells adhesion. These physiological and pathological processes play a crucial role in the development of cervical cancer

To further investigate the function of CD177 in cervical cancer, we divided TCGA RNA-seq data into CD177 low and high expression groups. Functional enrichment analysis indicated that CD177 participated in the activation of immune functions. The immune system is a critical regulator of biology, and the destruction of immune balance is involved in the occurrence and progression of diseases. It has been reported that CD177 influences the function and homeostasis of tumor-infiltrating Treg cells, and targeting CD177 + TI Treg cells may be another immunotherapy approach (Kim, Borcherding, Ahmed, Voigt, Vishwakarma, Kolb, Kluz, Pandey, De, Drashansky, Helm, Zhang, Gibson-Corley, Klesney-Tait, Zhu, Lu, Lu, Huang, Xiang, Cheng, Wang, Wang, Tang, Hu, Wang, Liu, Li, Zhuang, Avram, Zhou, Bacher, Zheng, Wu, Zakharia and Zhang 2021). Meanwhile, tumor CD177 + neutrophil infiltration has been associated

with resistance to antiangiogenic treatment in colorectal cancer, which specifically revealed that CD177 serves as a therapeutic target for tumor resistance (Schiffmann et al. 2019). Nevertheless, the immune functions of CD177 in cervical cancer have not been reported. We first found that CD177 positively regulated the immunological processes in cervical cancer. Activation of cytokine – mediated signaling pathway, humoral immune response, antimicrobial humoral response, and inflammatory response to antigenic stimulus may play important antitumor roles in the cervical cancer immune microenvironment.

Activation of the immune system depends on tumor-infiltrating lymphocytes. Tumor-infiltrating lymphocytes account for a large proportion of the TME and will have an impact on the clinical outcomes of tumor patients (Zhang and Zhang 2020). A better understanding of tumor-infiltrating lymphocytes will provide the ability to predict and guide immunotherapy response. Therefore, to further explore the tumor-infiltrating lymphocytes affected by CD177 in cervical cancer, a pancancer correlation analysis showed that CD177 was moderately associated with tumor-infiltrating lymphocytes in 33 types of cancers, we found that activated CD8 + central memory T cell, CD4 + Th1 T cell, CD4 + effector memory T cell, natural killer cell, actived myeloid dendritic cell, monocyte, macrophage, and B cell were positively correlated with the expression of CD177 using Xena Shiny. Moreover, the spearman correlation test confirmed the significant positive correlation between CD177 and the infiltration level, including CD4 + T cell, actived CD8 + T cell, actived DC cell, immune B cell, macrophage cell, memory B cell, monocyte, NK cell, and Th1 cell. These results further demonstrated the relevance of the CD177 expression level to the level of infiltrating immune cells. In addition, somatic copy number alterations (SCNAs) play a key role in activating oncogenes and inactivating tumor suppressors, which are also useful diagnostic markers for numerous cancer types (Luo et al. 2020, Zack et al. 2013). We found that the copy number alterations of CD177 could affect the infiltration level of CD4 + T cells, CD8 + T cells, neutrophils, and dendritic cells. Together, these results all suggested that CD177 was closely correlated with immune infiltrates in cervical cancer.

Cervical cancer patients have a poor prognosis when tumor metastasis and recurrence occur (Cohen et al. 2020). PD-1/PD-L1 immunotherapy has provided another option for advanced PD1/PD-L1-positive patients (Odiase et al. 2021). However, the 10–25% response rate of PD-1/PD-L1 checkpoint inhibitors for cervical cancer patients means that more therapeutic targets and prognostic biomarkers must be identified to increase the therapeutic response (Otter, Chatterjee, Stewart and Michael 2019).

In our current research, we found that CD177 was positively correlated with CTLA4, CD27, BLTA, CD200R1, CD80, TNFRSF25, TIGIT, ICOS and TNFSF9 checkpoint markers. The relationships implicated the role of CD177 in regulating tumor immunology in cervical cancer. These novel findings suggested the substantial progress in CD177 was involved in the regulation of immune functions in cervical cancer.

In addition, we investigated the association of CD177 with drug sensitivity. The results indicated that cervical cancer patients were more sensitive to the antineoplastic drugs and targeted drugs including Lapatinib, Belinostat, ATRA, Gefitinib, Navitoclax and Tamoxifen. As a potent EGFR inhibitor, Lapatinib play a more effective role in advanced or metastatic breast cancer(Bilancia et al. 2007). But Monk B J et

al. reported that there was no evidence to support the use of Lapatinib to enhance the survival for recurrent and advanced cervical cancer patients(Monk and Pandite 2011). That might imply the low CD177 expression in cervical cancer is more resistant to chemotherapy drugs than high CD177 group.

Belinostat as an anticancer drug has been approved for some T-cell lymphoma, but there was no study has confirmed Belinostat(Eckschlager et al. 2017). CD177 expression may have particular guiding significance for the clinical selection of Belinostat for cervical cancer patients. Several study have demonstrated that all-trans retinoic acid (ATRA) enhance anti-PD-L1 efficacy in cervical cancer(Liang et al. 2022). Therefore, the combination of ATRA and anti-PD-L1 in CD177 high expression cervical cancer patients may overcome the low anti-PD-L1 antibody response in cervical cancer treatment. Gefitinib and Navitoclax as targeted drugs have been approved for non-small-cell lung cancer(Hosomi et al. 2020, Zhang et al. 2020). More clinical research needs to be explored to prove the effectiveness of Gefitinib and Navitoclax in cervical cancer, but CD177 may provide a good prognostic target in the future research.

However, our study has certain limitations. The effects of CD177 on the progression and prognosis of cervical cancer need further experimental study verification, and the role of CD177 in determining the clinical outcome of immunotherapy remains to be further investigated.

Conclusions

In our study, we found that CD177 was notably downregulated in cervical cancer and low expression of CD177 predicted poor prognosis for cervical cancer patients. Moreover, CD177 was positively related to immune-associated pathways and tumor-infiltrating lymphocytes, and could be a promising prognostic target through its interaction with infiltrating immune cells and immune checkpoint. And its drugs sensitivity has particular guiding significance for the clinical selection for cervical cancer patients.

Abbreviation List

GO Gene Ontology

KEGG Kyoto Encyclopedia of Genes and Genomes

GSEA Gene set enrichment analysis

TCGA The Cancer Genome Atlas

OS Overall survival

PFS Progress-free survival

PFI Progression-free interval

DFI Disease-free interval

DEGs Differentially expressed genes

SCNA Somatic copy number alterations

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 Brain 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 Tumors

THCA Thyroid carcinoma

THYM Thymoma

UCEC Uterine Corpus Endometrial Carcinoma

UCS Uterine Carcinosarcoma

UVM Uveal Melanoma

Declarations

Data availability

Public datasets were obtained from GENT2 (http://gent2.appex.kr/gent2/), HPA (https://www.proteinatlas.org/), GEO database (https://www.ncbi.nlm.nih.gov/geo/) Kaplan–Meier Plotter websites (https://kmplot.com/analysis/), Xena Shiny (https://shiny.hiplot.com.cn/ucsc-xena-shiny/), TCGA (https://portal.gdc.cancer.gov/), LinkedOmics (http://linkedomics.org/admin.php), STRING database (https://string-db.org/), TISIDB (http://cis.hku.hk/TISIDB/) and TIMER (https://cistrome.shinyapps.io/timer/).

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Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [WL], [WL], [YL], [TL], [YW], [DF] and [FS]. The first draft of the manuscript was written by [WL] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

References

1. Alayed K, Meyerson JB, Osei ES, Blidaru G, Schlegelmilch J, Johnson M, Meyerson HJ. 2020. CD177 Enhances the Detection of Myelodysplastic Syndrome by Flow Cytometry. Am J Clin Pathol.153:554–565.
2. Bai M, Grieshaber-Bouyer R, Wang J, Schmider AB, Wilson ZS, Zeng L, Halyabar O, Godin MD, Nguyen HN, Levescot A, et al. 2017. CD177 modulates human neutrophil migration through activation-mediated integrin and chemoreceptor regulation. Blood.130:2092–2100.
3. Bilancia D, Rosati G, Dinota A, Germano D, Romano R, Manzione L. 2007. Lapatinib in breast cancer. Ann Oncol.18 Suppl 6:vi26-vi30.
4. Cohen AC, Roane BM, Leath CA. 2020. Novel Therapeutics for Recurrent Cervical Cancer: Moving Towards Personalized Therapy. Drugs.80:217–227.
5. Eckschlager T, Plch J, Stiborova M, Hrabeta J. 2017. Histone Deacetylase Inhibitors as Anticancer Drugs. Int J Mol Sci.18.
6. Eulenberg-Gustavus C, Bähring S, Maass PG, Luft FC, Kettritz R. 2017. Gene silencing and a novel monoallelic expression pattern in distinct CD177 neutrophil subsets. J Exp Med.214:2089–2101.
7. Győrffy B. 2021. Survival analysis across the entire transcriptome identifies biomarkers with the highest prognostic power in breast cancer. Comput Struct Biotechnol J.19:4101–4109.
8. Hosomi Y, Morita S, Sugawara S, Kato T, Fukuhara T, Gemma A, Takahashi K, Fujita Y, Harada T, Minato K, et al. 2020. Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non-Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study. J Clin Oncol.38:115–123.
9. Jiang J, Chen Y, Zhang M, Zhou H, Wu H. 2020. Relationship between CD177 and the vasculogenic mimicry, clinicopathological parameters, and prognosis of epithelial ovarian cancer. Ann Palliat Med.9:3985–3992.
10. Kim M-C, Borcherding N, Ahmed KK, Voigt AP, Vishwakarma A, Kolb R, Kluz PN, Pandey G, De U, Drashansky T, et al. 2021. CD177 modulates the function and homeostasis of tumor-infiltrating regulatory T cells. Nat Commun.12:5764.
11. Kissel K, Santoso S, Hofmann C, Stroncek D, Bux J. 2001. Molecular basis of the neutrophil glycoprotein NB1 (CD177) involved in the pathogenesis of immune neutropenias and transfusion reactions. Eur J Immunol.31:1301–1309.
12. Kluz PN, Kolb R, Xie Q, Borcherding N, Liu Q, Luo Y, Kim M-C, Wang L, Zhang Y, Li W, et al. 2020. Cancer cell-intrinsic function of CD177 in attenuating β-catenin signaling. Oncogene.39:2877–2889.
13. Li B, Severson E, Pignon J-C, Zhao H, Li T, Novak J, Jiang P, Shen H, Aster JC, Rodig S, et al. 2016. Comprehensive analyses of tumor immunity: implications for cancer immunotherapy. Genome Biol.17:174.

14. Li T, Fan J, Wang B, Traugh N, Chen Q, Liu JS, Li B, Liu XS. 2017. TIMER: A Web Server for Comprehensive Analysis of Tumor-Infiltrating Immune Cells. Cancer Res.77:e108-e110.
15. Li Y, Liu C, Li B, Hong S, Min J, Hu M, Tang J, Wang T, Yang L, Hong L. 2019. Electrical stimulation activates calpain 2 and subsequently upregulates collagens via the integrin β1/TGF-β1 signaling pathway. Cell Signal.59:141–151.
16. Liang Y, Wang W, Zhu X, Yu M, Zhou C. 2022. Inhibition of myeloid-derived suppressive cell function with all-trans retinoic acid enhanced anti-PD-L1 efficacy in cervical cancer. Sci Rep.12:9619.
17. Liu Q, Zhang C, Ma G, Zhang Q. 2014. Expression of SPRR3 is associated with tumor cell proliferation and invasion in glioblastoma multiforme. Oncol Lett.7:427–432.
18. Luo H, Xu X, Yang J, Wang K, Wang C, Yang P, Cai H. 2020. Genome-wide somatic copy number alteration analysis and database construction for cervical cancer. Mol Genet Genomics.295:765–773.
19. Mandal R, Chan TA. 2016. Personalized Oncology Meets Immunology: The Path toward Precision Immunotherapy. Cancer Discov.6:703–713.
20. Monk BJ, Pandite LN. 2011. Survival data from a phase II, open-label study of pazopanib or lapatinib monotherapy in patients with advanced and recurrent cervical cancer. J Clin Oncol.29:4845.
21. Moreira LF, Maino MM, Garbin HI, Da Natividade GR, Volkweis BS, Kulczynski JU. 2018. CD117 Expression in Squamous Cell Carcinoma of the Oesophagus. Anticancer Res.38:3929–3933.
22. Odiase O, Noah-Vermillion L, Simone BA, Aridgides PD. 2021. The Incorporation of Immunotherapy and Targeted Therapy Into Chemoradiation for Cervical Cancer: A Focused Review. Front Oncol.11:663749.
23. Otter SJ, Chatterjee J, Stewart AJ, Michael A. 2019. The Role of Biomarkers for the Prediction of Response to Checkpoint Immunotherapy and the Rationale for the Use of Checkpoint Immunotherapy in Cervical Cancer. Clin Oncol (R Coll Radiol).31:834–843.
24. Park S-J, Yoon B-H, Kim S-K, Kim S-Y. 2019. GENT2: an updated gene expression database for normal and tumor tissues. BMC Med Genomics.12:101.
25. Rosen VM, Guerra I, McCormack M, Nogueira-Rodrigues A, Sasse A, Munk VC, Shang A. 2017. Systematic Review and Network Meta-Analysis of Bevacizumab Plus First-Line Topotecan-Paclitaxel or Cisplatin-Paclitaxel Versus Non-Bevacizumab-Containing Therapies in Persistent, Recurrent, or Metastatic Cervical Cancer. Int J Gynecol Cancer.27:1237–1246.
26. Ru B, Wong CN, Tong Y, Zhong JY, Zhong SSW, Wu WC, Chu KC, Wong CY, Lau CY, Chen I, et al. 2019. TISIDB: an integrated repository portal for tumor-immune system interactions. Bioinformatics. Oct 15;35:4200–4202. Epub 2019/03/25.
27. Schiffmann LM, Fritsch M, Gebauer F, Günther SD, Stair NR, Seeger JM, Thangarajah F, Dieplinger G, Bludau M, Alakus H, et al. 2019. Tumour-infiltrating neutrophils counteract anti-VEGF therapy in metastatic colorectal cancer. Br J Cancer.120:69–78.
28. Silvestre-Roig C, Fridlender ZG, Glogauer M, Scapini P. 2019. Neutrophil Diversity in Health and Disease. Trends Immunol.40:565–583.

29. Silvestre-Roig C, Hidalgo A, Soehnlein O. 2016. Neutrophil heterogeneity: implications for homeostasis and pathogenesis. Blood.127:2173–2181.
30. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. 2021. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin.71:209–249.
31. Vasaikar SV, Straub P, Wang J, Zhang B. 2018. LinkedOmics: analyzing multi-omics data within and across 32 cancer types. Nucleic Acids Res.46:D956-D963.
32. Wang S, Xiong Y, Zhao L, Gu K, Li Y, Zhao F, Li J, Wang M, Wang H, Tao Z, et al. 2021. UCSCXenaShiny: An R/CRAN Package for Interactive Analysis of UCSC Xena Data. Bioinformatics (Oxford, England).
33. Wendel Naumann R, Leath CA. 2020. Advances in immunotherapy for cervical cancer. Curr Opin Oncol.32:481–487.
34. Zack TI, Schumacher SE, Carter SL, Cherniack AD, Saksena G, Tabak B, Lawrence MS, Zhsng C-Z, Wala J, Mermel CH, et al. 2013. Pan-cancer patterns of somatic copy number alteration. Nat Genet.45:1134–1140.
35. Zhang X, Zhang R, Chen H, Wang L, Ren C, Pataer A, Wu S, Meng QH, Ha MJ, Morris J, et al. 2020. KRT-232 and navitoclax enhance trametinib's anti-Cancer activity in non-small cell lung cancer patient-derived xenografts with KRAS mutations. Am J Cancer Res.10:4464–4475.
36. Zhang Y, Zhang Z. 2020. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol.17:807–821.
37. Zhou C, Guo Z, Xu L, Jiang H, Sun P, Zhu X, Mu X. 2020. PFND1 Predicts Poor Prognosis of Gastric Cancer and Promotes Cell Metastasis by Activating the Wnt/β-Catenin Pathway. Onco Targets Ther.13:3177–3186.

Figures

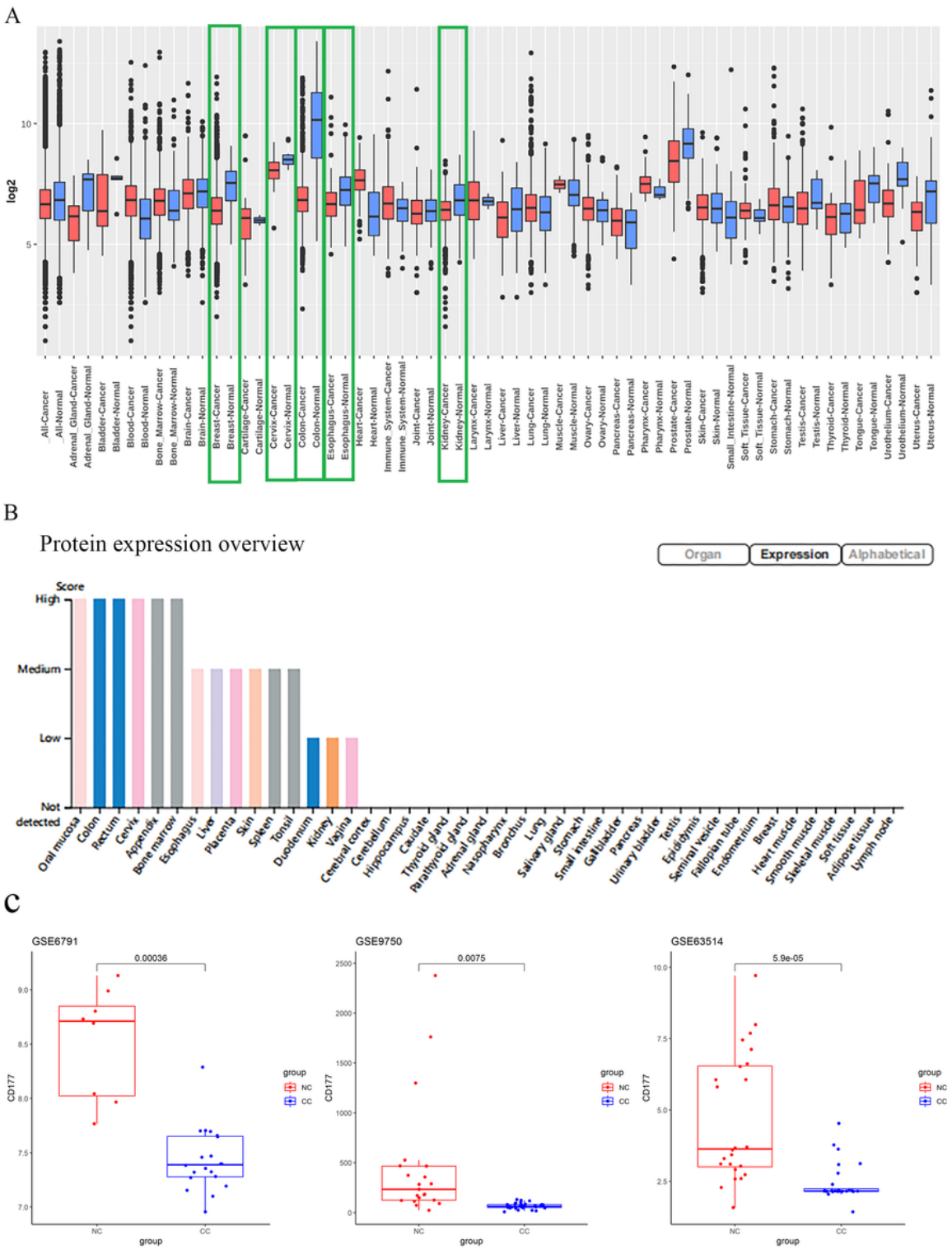

Figure 1

The Expression Pattern of CD177 from a Pancancer and Cervical Cancer Perspective. (A) The mRNA expression of CD177 in various types of normal (blue) and cancer (red) tissues. (B) The protein expression of CD177 in different human organs and tissues. (C) The mRNA expression of CD177 in GSE6791, GSE9750 and GSE63514 datasets with cutoff criteria of |logFC| > 1.0 and adj P < 0.05. CC, cervical cancer; NC, normal cervix.

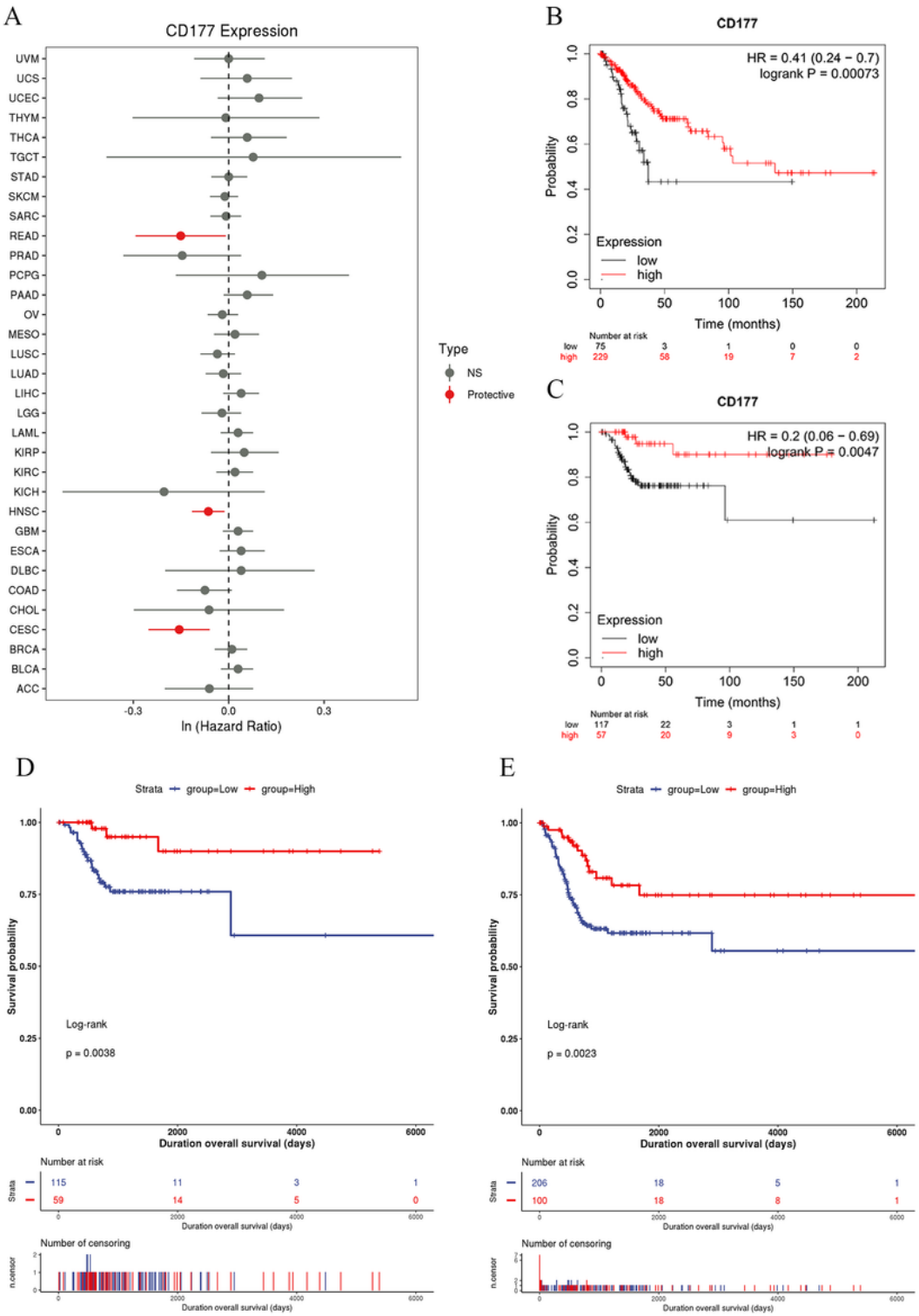

Figure 2

Prognostic values of CD177 expression in cervical cancer. (A) Forest plot of prognosis analysis for high- and low- CD177 gene expression in different cancer types. (B-C) Survival curves of OS and PFS by the Kaplan–Meier plotter database. (D-E) Survival curve of DFI and PFI in high- and low- CD177 patients by the Xean Shiny.

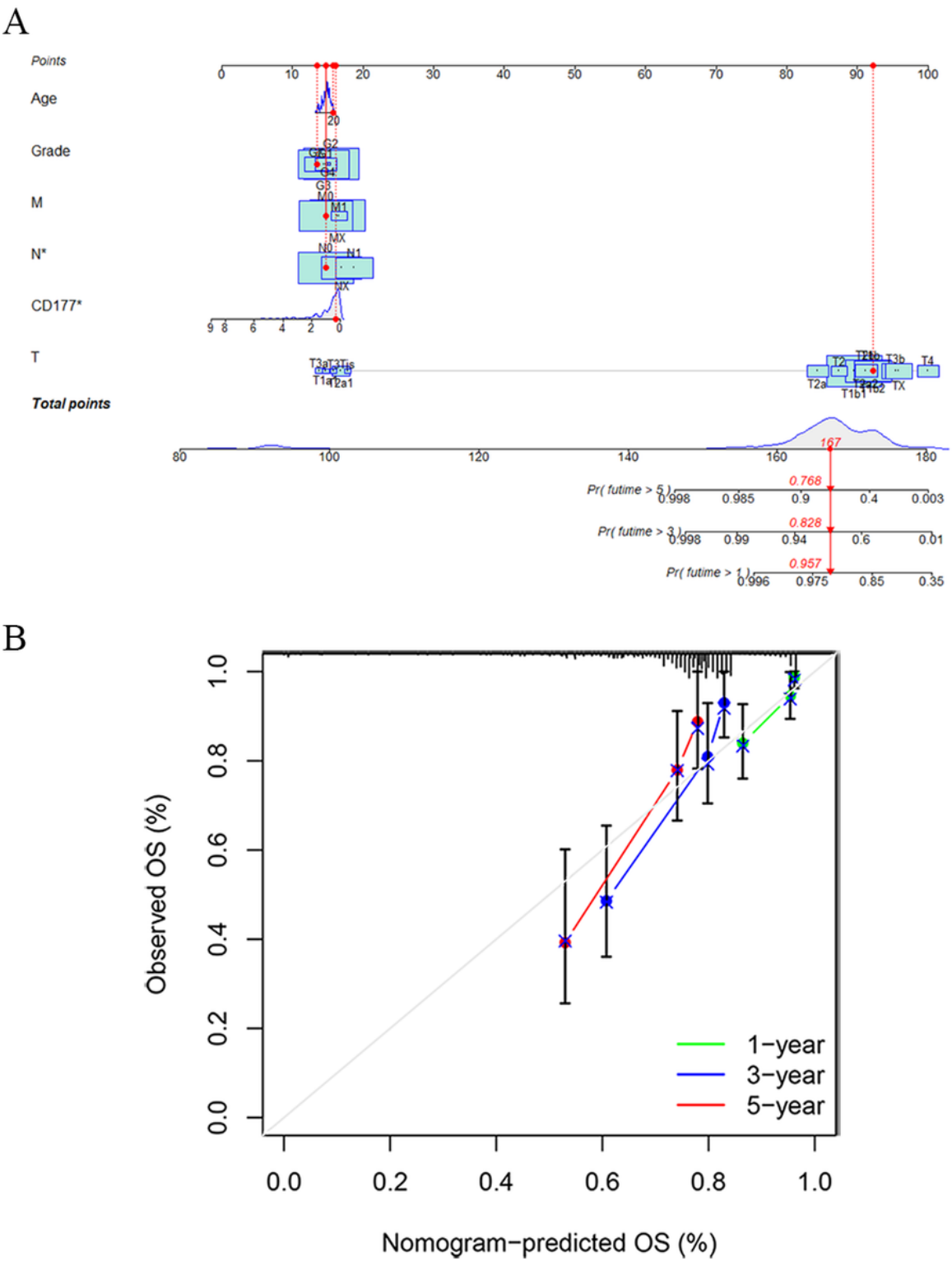

Figure 3

Survival of cervical cancer patients is predicted by constructing a nomogram. (A) A nomogram for forecasting the probability of cervical cancer patients after one, three, and five years was displayed. (B) Calibration plots validaed the efficiency of nomograms for overall survival.

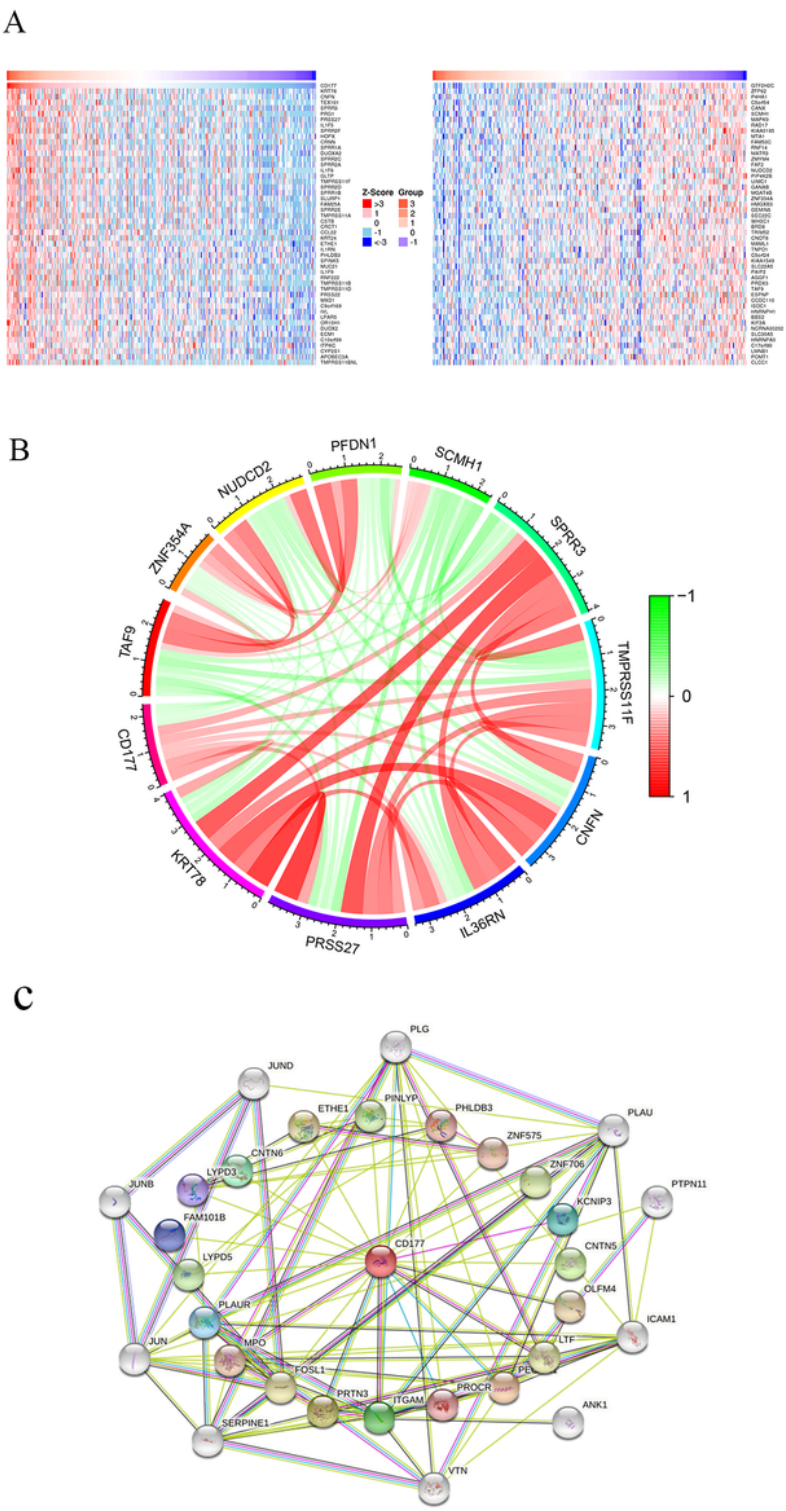

Figure 4

CD177 coexpression gene networks and protein-protein interaction network.

(A) Heatmaps showing the top 50 positively and negatively correlated genes with CD177. (B) The circos plot of significantly positive and negative correlated genes with CD177 identified by the TCGA database. (C) The protein-protein interaction network about CD177 evaluated by STRING database.

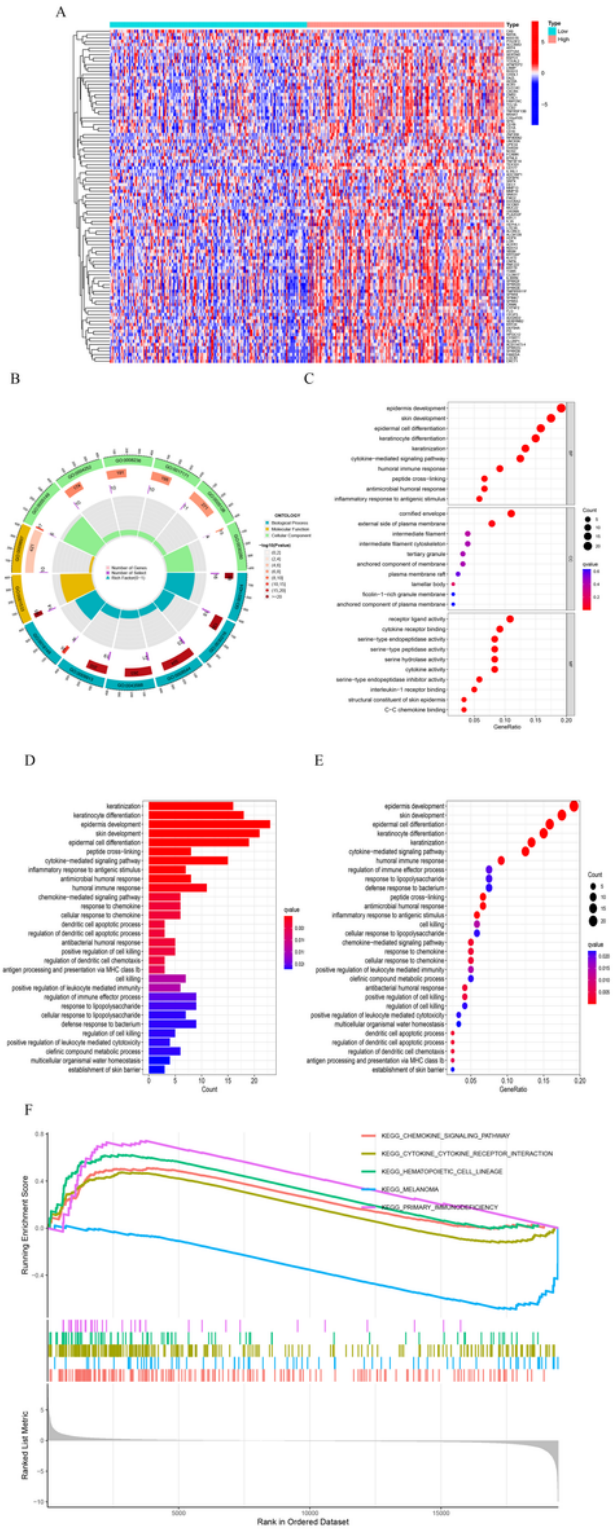

Figure 5

The Functions of CD177 and its Related Genes in Cervical Cancer.

(A) The heatmap showing the differentially expressed genes in the CD177 low and high expression groups. (B-C) GO enrichment analysis of CD177-associated DGEs. (D-E) KEGG enrichment analysis of

CD177-associated DGEs. (F) GSEA of CD177-associated DGEs in the CD177 low and high expression groups.

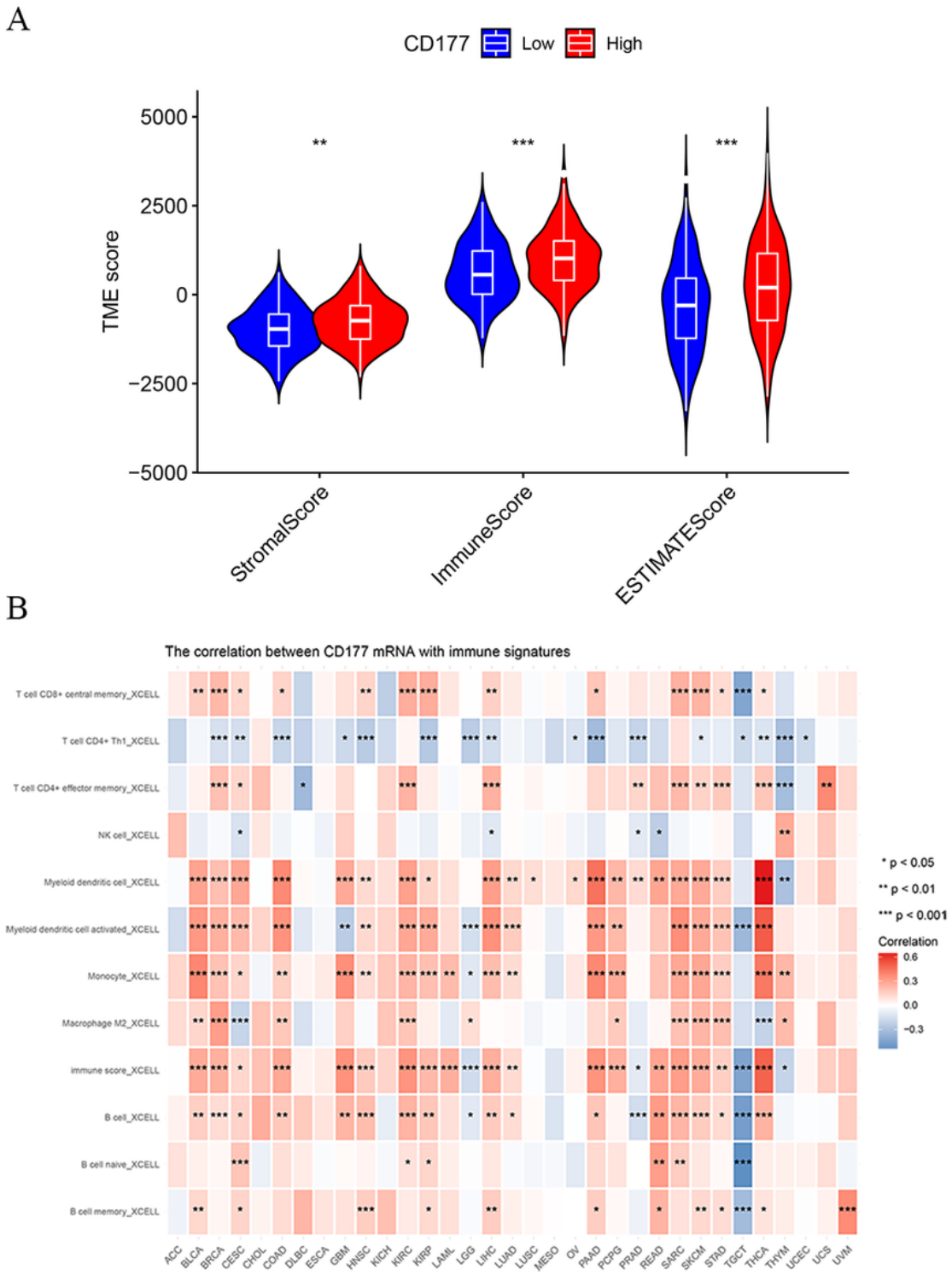

Figure 6

Correlation between Immune infiltration and CD177 in Cervical Cancer. (A) The violin plot showed the significance of stromalscore, immunescore and ESTIMATEScore in the high and low CD177 expression

groups. (B) The correlation between CD177 mRNA with immune signatures in the 33 different types of cancers (red is positively correlated and blue is negatively correlated). * P < 0.05,

** P < 0.01, *** P < 0.001

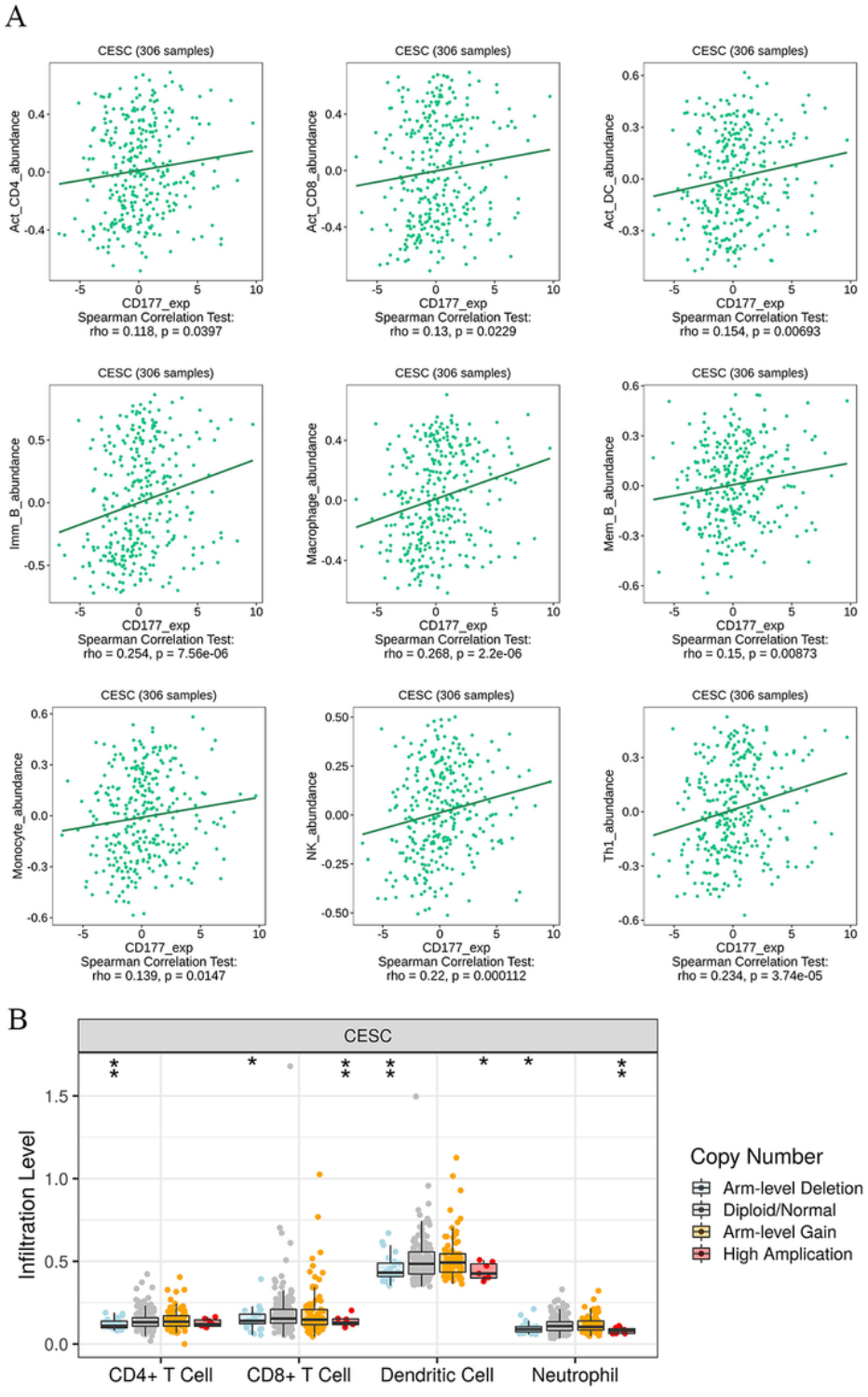

Figure 7

CD177 influenced the abundance of immune cells and somatic copy number alterations in cervical cancer microenvironment. (A) Scatter plot showing the relationship between the 13 abundance of immune cells and the expression of CD177. (B) Tumor infiltration levels in cervical cancer with different SCNAs by using GISTIC 2.0.

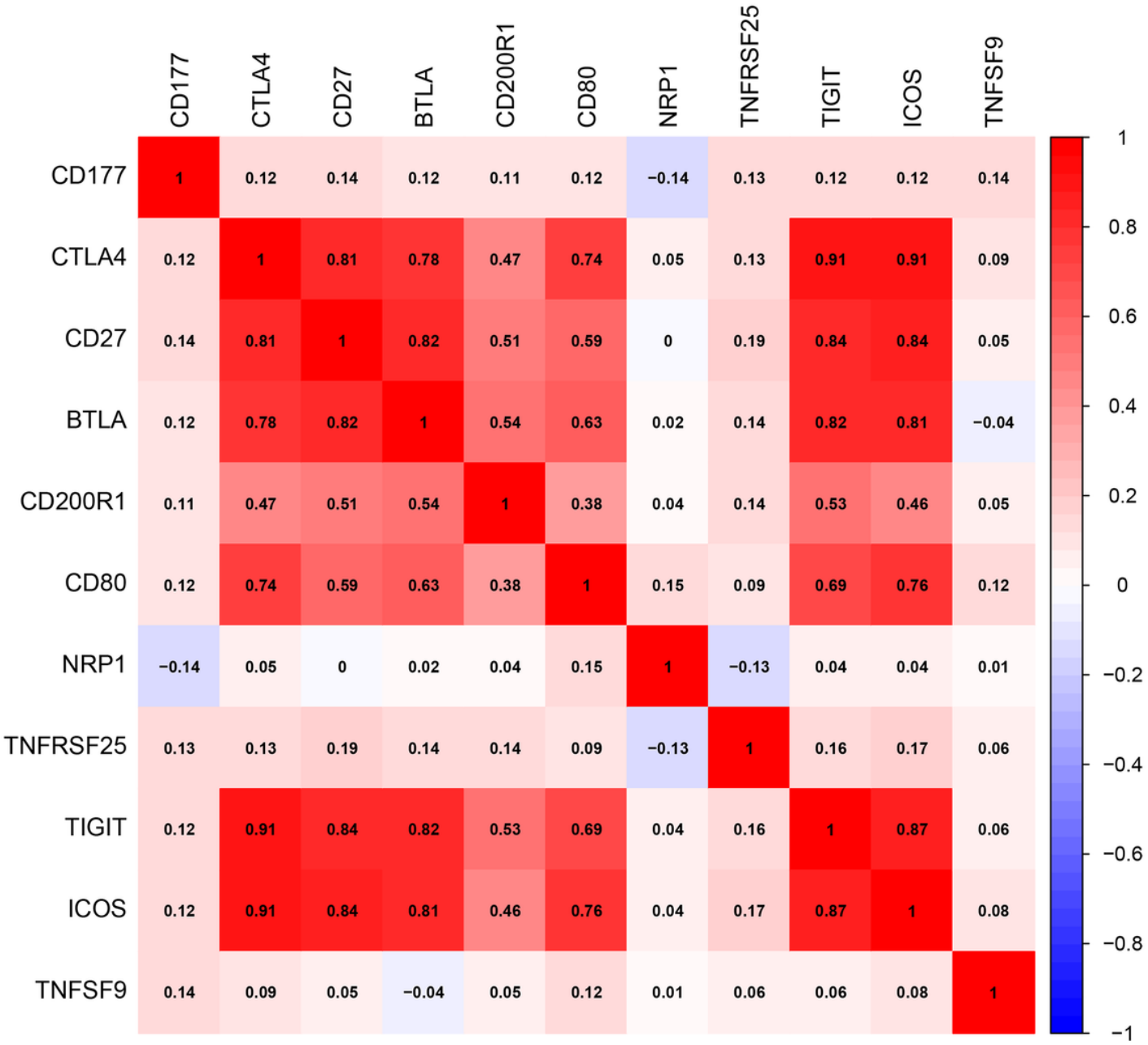

Figure 8

Relationship between immune checkpoint and CD177 in cervical cancer. Heatmap of the relationship between immune checkpoint and CD177 in cervical cancer. Red indicated positive correlations while blue indicated negative. Numbers represented correlation coefficients.

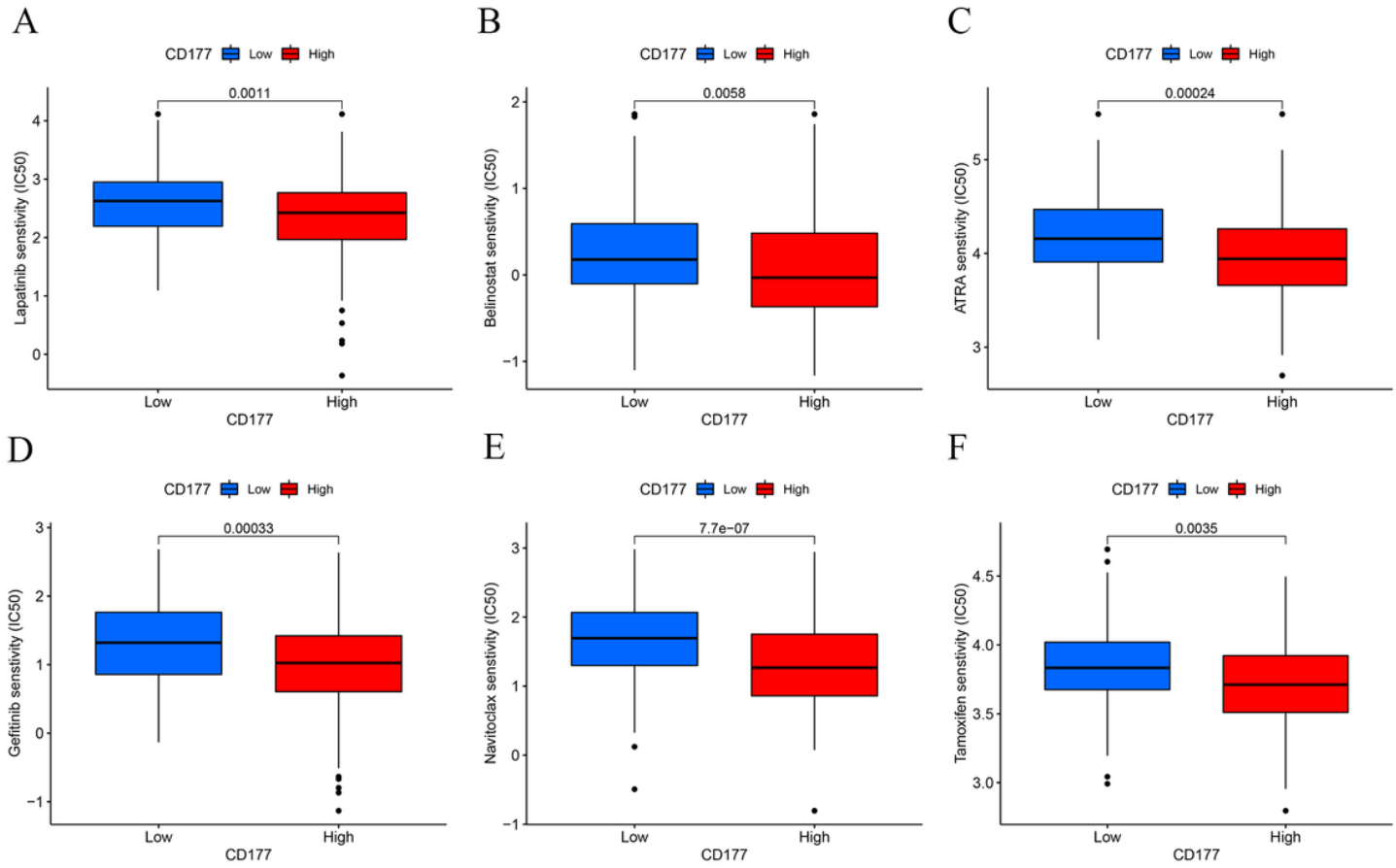

Figure 9

Analysis of drug sensitivity to the CD177 gene. CD177 expression was positively relevant with drug sensitivity, including Lapatinib, Belinostat, ATRA, Gefitinib, Navitoclax and Tamoxifen.

Supplementary Files

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

- SupplementaryData1.xlsx
- SupplementaryData2.xlsx
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