



# Comprehensive multi-omics analysis of CD36 in pan-cancers: Evaluating role in prognosis, immune microenvironment, and therapeutic response



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## ABSTRACT

Cluster of differentiation-36 (CD36) is involved in cellular adhesion, lipid metabolism, immunity, and inflammation. Multiple studies have enlightened the regulatory roles of CD36 in metabolic reprogramming, metastasis, chemoresistance, stemness, immune modulation, senescence, inflammation, and angiogenesis. However, its role in tumorigenesis is still unclear and context-dependent. We performed a comprehensive pan-cancer analysis of CD36 by using data from TCGA, integrating transcriptomic, proteomic, methylation, mutational, immune infiltration, immunotherapy, and drug sensitivity datasets. Expression patterns, clinical associations, prognostic potential, immune interactions, and therapeutic implications were systematically evaluated. We also evaluated CD36-related molecular pathways and immune signatures in cancer by a comprehensive GSEA analysis. We found that CD36 expression pattern is dysregulated in multiple cancer types, whereas higher expression correlated with poor prognosis in LGG, BRCA, CESC, and LAML. CD36 mRNA showed inverse correlations with methylation levels. GSEA analysis revealed cancer-type-dependent association of CD36 with hallmark pathways, whereas multiple cancer types showed positive correlation with immune and inflammation-related pathways and negative correlation with cell cycle-related pathways. CD36 expression correlated with macrophage infiltration, immune regulators, and immunotherapy outcomes, including T-cell dysfunction and Immune checkpoint blockade (ICB) response. Moreover, drug sensitivity analyses revealed significant associations between CD36 and anticancer compound responses. This study provides a comprehensive and context-dependent landscape of CD36, establishing its oncogenic and immune-regulatory roles. Our findings highlight the potential of CD36 in prognosis, tumor microenvironment, and therapeutic sensitivity, while experimental validation is required to prove therapeutic relevance in cancer therapy and immunotherapy.

## 1. Introduction

Cancers are the leading cause of mortality worldwide due to their malignant and heterogeneous nature [1]. American Cancer Society of

United States reported more than 2 million new cancer cases and more than half a million cancer-caused deaths in 2024 [2]. National Cancer Center (NCC), China, 2022, reported around 5 million new cancer cases with more than 2 million deaths mostly caused by thyroid, liver, stomach, and lung cancers [3]. The effective diagnosis or prognosis with potential screening is a prerequisite to reducing the mortality ratio

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## Abbreviations

ACC	Adrenocortical carcinoma
APCs	Antigen presenting cells
BLCA	Bladder urothelial carcinoma
BRCA	Breast invasive carcinoma
CD36	Cluster of differentiation-36
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL	Cholangiocarcinoma
CNA	Copy number alteration
COAD	Colon adenocarcinoma
DLBC	Diffuse large B-cell lymphoma
ESCA	Esophageal carcinoma
FDR	False discovery rate
GBM	Glioblastoma multiforme
GDC	Genomic Data Commons
HLA	Human leukocyte antigen
HNSC	Head and neck squamous cell carcinoma
HRD	Homologous recombination deficiency
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
LOH	Loss of heterozygosity
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
M	Metastasis
MATH	Mutant-allele tumor heterogeneity
MDSCs	Myeloid-derived suppressor cells
MESO	Mesothelioma
MHC	Major histocompatibility
MSI	Microsatellite instability
N	Nodes
NEO	Neoantigen
NES	Normalized enrichment score
OV	Ovarian serous cystadenocarcinoma
PAAD	Pancreatic adenocarcinoma
PCPG	Pheochromocytoma and Paraganglioma
PRAD	Prostate adenocarcinoma
READ	Rectum adenocarcinoma
ROC	Receiver operating characteristic
SARC	Sarcoma
SKCM	Skin cutaneous melanoma
STAD	Stomach adenocarcinoma
T	Tumor
TGCT	Testicular germ cell tumors
THCA	Thyroid carcinoma
THYM	Thymoma
TILs	Tumor infiltrating lymphocytes
TIME	Tumor immune microenvironment
TMB	Tumor mutational burden
TME	Tumor microenvironment
UCEC	Uterine corpus endometrial carcinoma
UCS	Uterine carcinosarcoma
UVM	Uveal melanoma

associated with cancers, which is still a key challenge in China [4]. Cancer treatment and management have been revolutionized by numerous advancements in exploring molecular mechanisms of tumors with their microenvironment and utilization of single or combination therapy of novel therapeutic agents. There are still multiple challenges in effective treatment of cancers including financial or social constraints, toxicity profiles, limited patient data, and clinical or therapeutic failure [5]. Evaluation or exploration of novel cancer biomarkers is the advanced approach in oncology to improve cancer diagnosis and treatment in solid tumors at molecular level [6]. Moreover, Chimeric Antigen Receptor T (CAR-T) cell therapy and targeted therapies such as immune-inhibitory checkpoints are the novel dimensions in cancer treatment which has shown potential to deal with heterogeneity of cancers but still it's a major challenge [7,8]. Therefore, discovery or evaluation of novel biomarkers may provide an effective roadmap to improve diagnosis, prognosis, and treatment of cancers. "Pan-cancers Study" is the most critical and comprehensive approach to explore the various aspects of a novel biomarker which provides an in-depth role in

cancer biology with associated molecular pathways and therapeutic potential [9–11].

CD36, a multifunctional transmembrane glycoprotein regulating fatty acid metabolism, immune activation, and angiogenesis, has emerged as both a prognostic biomarker and therapeutic target in hematological cancers, with ongoing preclinical and clinical investigations [12]. Currently, CD36 has proven to be a key player in the progression of leukemia, such as acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) [13]. Emerging evidence demonstrates that CD36 promotes cancer progression through its role in fatty acid uptake and metabolic reprogramming, especially enhancing tumor cell proliferation, metastasis, and cancer stem-like properties, across several malignancies, including breast, oral, and hepatocellular carcinoma [14,15]. Furthermore, overexpression of CD36 has been linked to poor prognosis and immunosuppressive tumor microenvironments, positioning CD36 as a compelling therapeutic target with ongoing preclinical exploration using antibodies, inhibitors, and genetic models [16,17].

Evaluation of CD36 correlation and association in different cancers with immunogenicity and prognosis is the aim of this study. We adopted a comprehensive multi-omics pan-cancer approach to explore CD36's contribution to cancer biology and its clinical potential.

## 2. Materials and methods

### 2.1. Collection of datasets

We downloaded the expression of all 33 cancers from UCSC Xena ([xenabrowser.net/](http://xenabrowser.net/)). Human Protein Atlas (HPA) database ([www.proteinatlas.org/](http://www.proteinatlas.org/)) was utilized to acquire immunohistochemistry of CD36. To evaluate correlation of CD36 expression with different tumor characteristics, we obtained pan-cancer data for tumor mutational burden (TMB), microsatellite instability (MSI), mutant-allele tumor heterogeneity (MATH), neoantigen load (NEO), tumor purity, genomic ploidy, homologous recombination deficiency (HRD), and loss of heterozygosity (LOH) from the TCGA database and previously published studies [18,19]. The TISIDB ([cis.hku.hk/TISIDB/index.php](http://cis.hku.hk/TISIDB/index.php)) database was selected to fetch data on molecular subtypes of cancers. In addition, somatic mutation data (Level 4 SNV) of all TCGA cohorts were downloaded from Genomic Data Commons (GDC) portal (<https://portal.gdc.cancer.gov/>), processed by MuTect 2 algorithm [20]. The cancer immunity cycle data were obtained from TIP database ([biocc.hrbmu.edu.cn/TIP/](http://biocc.hrbmu.edu.cn/TIP/)).

### 2.2. Expression landscape of CD36

We used TCGA and GTEx combined datasets with normalized expressions as  $(\log_2(\text{TPM}+1))$  to explore the differential CD36 expression in cancerous versus normal tissues. CD36 differential expression between tumor and adjacent normal tissues was analyzed by TIMER 2.0 ([timer.cistrome.org/](http://timer.cistrome.org/)) across various cancer types with the "Gene\_DE" module and Wilcoxon rank-sum test for statistical significance. For cancers with less or no normal tissues, we used GEPIA2 ([gepia2.cancer-pku.cn/#analysis](http://gepia2.cancer-pku.cn/#analysis)) and "Expression analysis-Box Plots" component to analyze CD36 differential expression by using Match TCGA normal and GTEx data, 0.01 as p-value cutoff, and 1 as  $\log_2\text{FC}$  [21]. Moreover, TCGA-TARGET-GTEx (PANCAN) was downloaded from USCS, and CD36 (ENSG00000135218) expression was extracted across all samples. We further normalized the expressions as  $[\log_2(x+0.001)]$  and examined differential expression of CD36 among each cancer type. For expression analysis of CD36 total protein, we used CPTAC datasets from UALCAN ([ualcan.path.uab.edu/analysis-prot.html](http://ualcan.path.uab.edu/analysis-prot.html)) [22].

### 2.3. CD36 mutation and methylation analysis

We selected "TCGA Pan-Cancer Atlas Studies" from cBioPortal ([www.cbioportal.org/](http://www.cbioportal.org/)) to conduct CD36 genetic mutations analysis [23]. We

chose “Cancer Types Summary” module to extract findings of CD36 related to copy number alteration (CNA), types of mutations, and alteration frequencies across 33 TCGA tumors [23,24]. Pearson and Spearman correlation tests were employed to evaluate correlation between CD36 and CNA. We determined 20 genes that showed highest mutation ratio in a group with CD36 mutation as compared to wild-type group. CD36 methylation status was explored by using SMART database ([www.bioinfo-zs.com/smartapp/](http://www.bioinfo-zs.com/smartapp/)) [25]. It provided an association between CD36 expression and various methylation probes in 33 cancer types. To identify the CD36 role in tumorigenesis, we also evaluated its relation with different genomic or tumor microenvironment factors, including HRD, LOH, ploidy, purity, NEO, MSI, and TMB [18,19,26]. To express CD36's relation with Mutant-allele tumor heterogeneity (MATH) across all cancers, we used Mftools; R package with function of infer-Heterogeneity to compute MATH scores.

#### 2.4. CD36 prognostic evaluation in pan-cancer

The prognostic value of CD36 across 33 TCGA cancer types was assessed using Kaplan-Meier survival analysis. Patients were stratified into high-CD36 and low-CD36 expression groups based on median levels, and overall survival (OS), progression-free interval (PFI), disease-specific survival (DSS), and disease-free interval (DFI) were evaluated. Log-rank tests were applied to determine statistical significance. Receiver operating characteristic (ROC) curve analysis was also used to explore diagnostic and prognostic potential of CD36 in all cancers by calculating AUC with pROC package. We considered only those cancers having more than 0.7 AUC.

#### 2.5. Immune infiltration analysis

We applied ESTIMATE R package on expression data to compute estimate, immune, and stromal scores of all cancer patients and further analyzed correlation with CD36 by using Pearson test [27]. Correlation significance was determined using a p-value threshold of 0.05. We used multiple algorithms available in TIMER2 to evaluate correlation between CD36 and various immune cells, and used heatmap package to construct a heat map. FDR-adjusted  $P < 0.05$  as a threshold was used for significance. CD36 interaction in **tumor immune microenvironment (TIME) was investigated by exploring its relation with immune receptors**, major histocompatibility complex (MHC), chemokines, and immune stimulators or inhibitors by using TISIDB ([cis.hku.hk/TISIDB/](http://cis.hku.hk/TISIDB/)) database [28]. Statistical significance was determined by applying  $P < 0.05$  as a significant threshold.

#### 2.6. CD36 functional enrichment analysis

Patients of all cancer types were categorized into high and low CD36 groups based on median expression. We used GSEA-MSigDB ([www.gsea-msigdb.org/gsea/msigdb](http://www.gsea-msigdb.org/gsea/msigdb)) database to download the standard cancer Hallmark gene set (*h.all.v2024.1.Hs.symbols.gmt*) and computed their false discovery rate (FDR) and normalized enrichment score (NES) by GSEA. Benjamini-Hochberg (BH) FDR correction was used to control multiple testing. Pathways with FDR-adjusted  $P < 0.05$  were considered significant. The  $-\log_{10}(\text{FDR})$  values were scaled and used to determine bubble size, while NES were capped at  $\pm 3$ . A dot plot was generated by using ggplot 2 (v: 3.5.2) R package to visualize the results. Furthermore, fourteen tumor-related functional states were downloaded by using CancerSEA ([biocc.hrbmu.edu.cn/CancerSEA/goDownload](http://biocc.hrbmu.edu.cn/CancerSEA/goDownload)) while z scores were computed by z-score algorithm of singscore (v: 1.29.0) R package [29]. The statistical correlation between CD36 and z scores of all functional states was evaluated by using Pearson test.

#### 2.7. CD36 and immunotherapy response

TIDE database ([tide.dfci.harvard.edu](http://tide.dfci.harvard.edu)) was utilized to investigate

relationship of CD36 with immunotherapy, which determines the prospects of cancer immune evasion by using expression profiles [30, 31]. CD36 association with dysfunction of T cells and impact of T cells on immunotherapy in different cohorts was evaluated by another module, “Regulator Prioritization”. Our analysis proved a strong role of CD36 in immunity and its possible impact on outcomes of ICB treatment. CD36 expression was also investigated in various murine tumor models with or without ICB treatment in responders and non-responders by using TIMSO ([tismo.cistrome.org/](http://tismo.cistrome.org/)) database [32]. Anti-PD1, Anti-PDL1, Anti-PDL2, and Anti-CTL4 are included in ICB treatments. Wald test using DESeq2 (FDR  $\leq 0.05$ ) was applied to statistically evaluate differences among responder, non-responder, and baseline groups. Table 1 describes the detailed information about tumor models. Moreover, differences in CD36 expression in different cell lines were also examined before and after cytokine treatment. Moreover, to evaluate the association between CD36 expression and immunotherapy prognosis, Kaplan-Meier plotter (<https://kmplot.com>), was used.

#### 2.8. Drug sensitivity analysis

We obtained dose-response values as AUC from CTRP, PRISM, GDSC1, and GDSC2 datasets and IC50 values of antagonists from both GDSC datasets and performed Spearman correlation to assess CD36 correlation with AUC. The positive and negative correlations with high CD36 expression indicate drug resistance and sensitivity, respectively.

#### 2.9. Statistical analysis

All statistical analyses were performed with R software version 4.0.5 along with online databases. Kruskal-Wallis test was used to investigate variation among different sample groups, while unpaired Wilcoxon rank sum test was used for pairwise comparisons. Pearson and Spearman correlation tests were applied to evaluate correlation between CD36 expression and different tumor variables. Log-rank tests were performed for Kaplan-Meier survival analysis. FDR (False Discovery Rate) correction was applied to adjust for multiple hypothesis testing in immune infiltration analysis and GSEA, with an FDR-adjusted p-value threshold for significance. Statistical significance was determined at  $*P < 0.05$ ,  $**P < 0.01$ , and  $***P < 0.001$ .

### 3. Results

#### 3.1. Dysregulated CD36 expression in pan-cancers

The aim of study is to investigate oncogenic ability of CD36 in various cancers as a significant prognostic factor and a noteworthy contribution to immunogenicity. Almost twenty cancer types revealed dysregulated expression of CD36, analyzed by TIMER2 and GEPIA2, including UCEC, THCA, STAD, SKCM, READ, PRAD, PAAD, LUSC, LUAD, LIHC, LAML, KIRP, KIRC, HNSC, GBM, COAD, CHOL, BRCA, and BLCA (Fig. 1A–B). Paired analysis also depicted a similar dysregulated pattern of CD36 expression across multiple-type cancers (Fig. 1C). An

**Table 1**  
Murine tumor models.

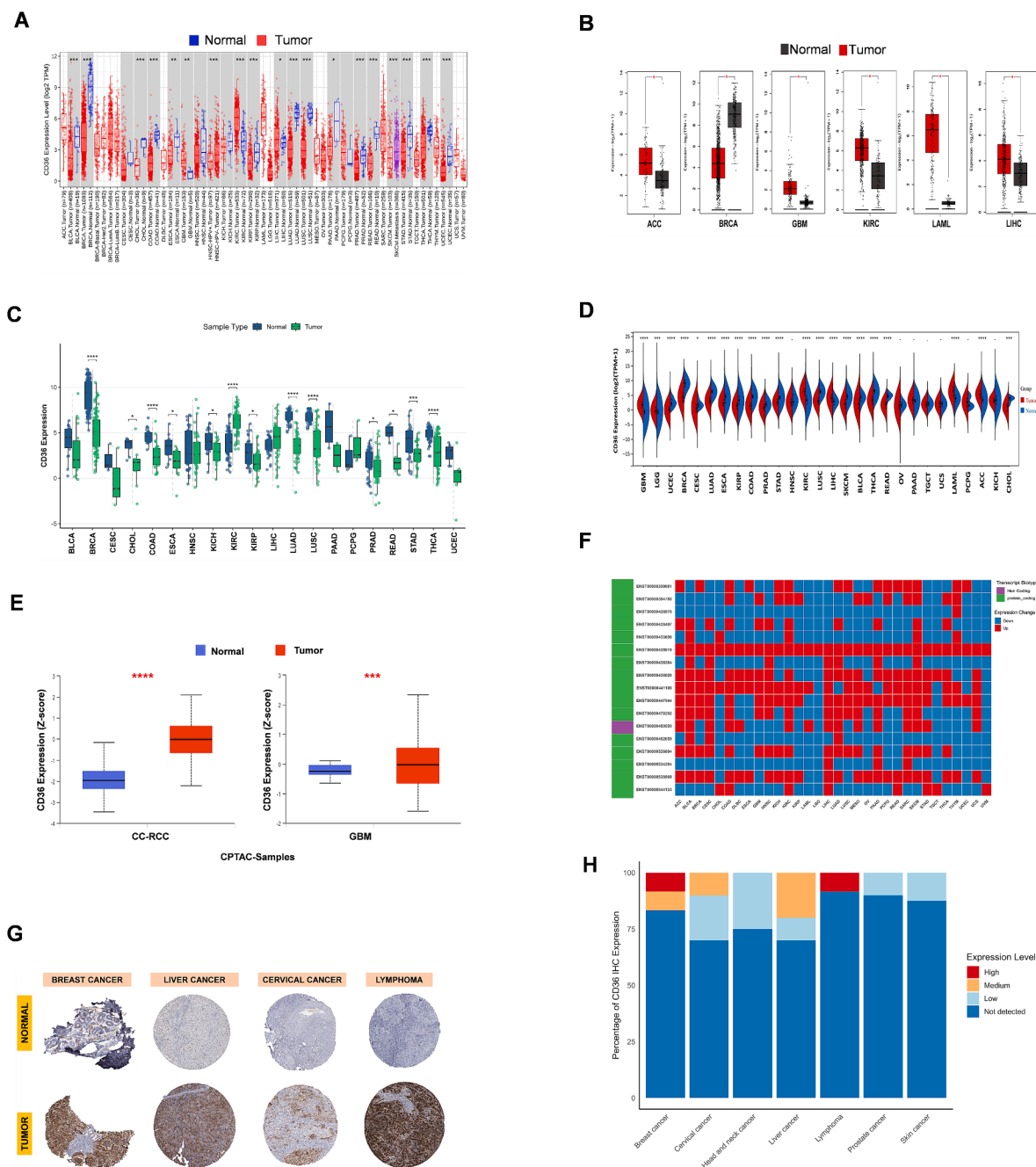
Cancer Type	Tumor Model
Mammary cancer	4T1, E0771, EMT6, T11, KP25L, p53-2225L, p53-2336R
Colorectal carcinoma	CT26, MC38
Gastric adenocarcinoma	YTN16
HNSC	MOC22
Hepatocellular carcinoma	BNL-MEA
Lung carcinoma	LLC
Melanoma	B16, YUMM1.7, D3UV2, D4M.3A.3
Sarcoma	402230

integrated analysis of combined samples of GTEx and TCGA datasets showed significantly differential expression of CD36 in various cancers when compared to normal and tumor samples (Fig. 1D). Furthermore, we noticed upregulation of CD36 protein in CC-RCC and GBM in CPTAC samples obtained from UALCAN (Fig. 1E). Multiple cancer types enclosed sufficient CD36 transcripts upregulation (ENST00000435819) (Fig. 1F). Immunohistochemistry (IHC) staining of CD36 from HPA database revealed significant expression in various tumorous tissues, including breast, liver, cervical, and lymphoma (Fig. 1G). Based on staining intensity, breast cancer and lymphoma tissues exhibited high CD36 expression, while medium in cervical and liver cancers (Fig. 1H). These findings indicate that CD36 protein is frequently upregulated in a

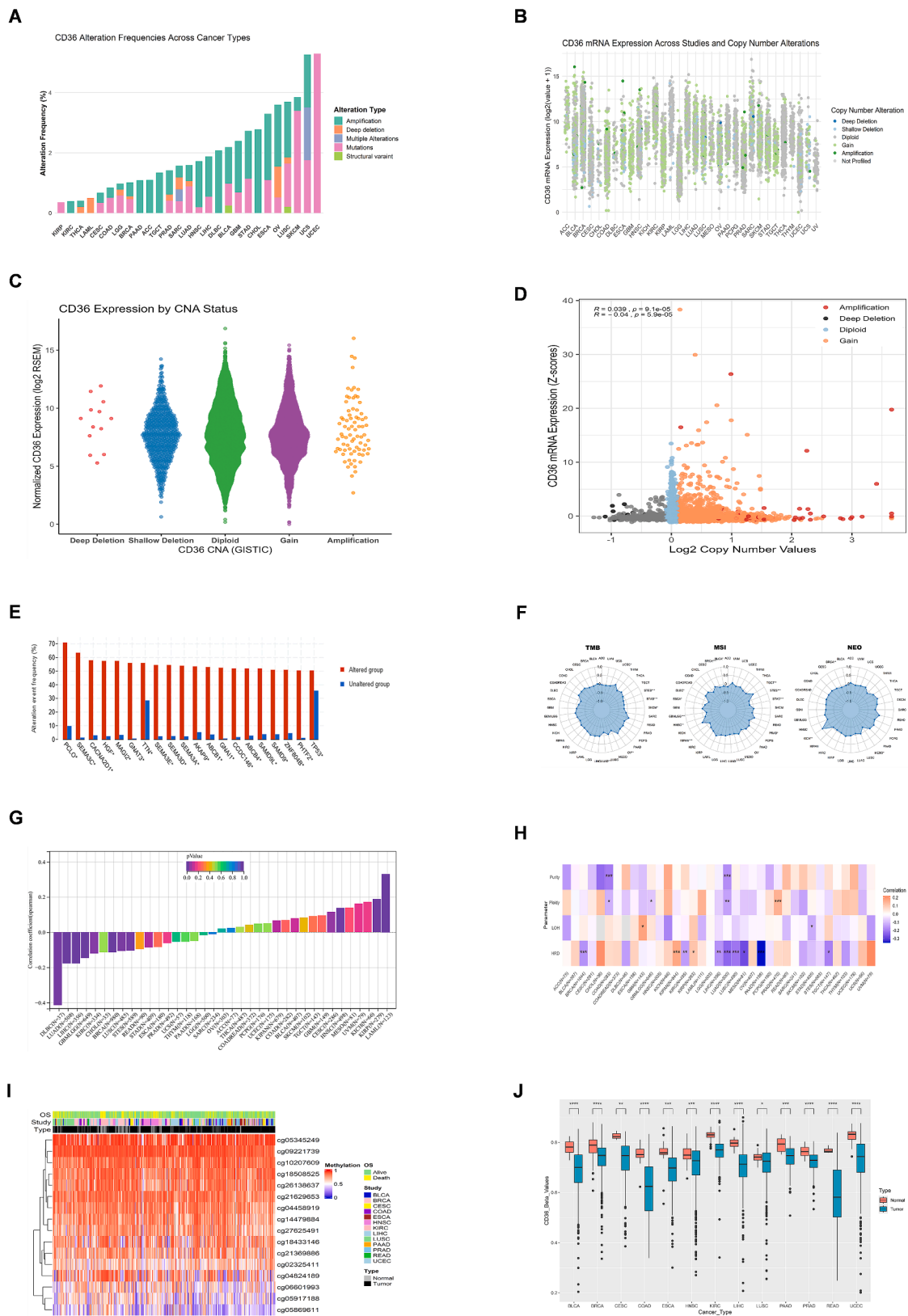
subset of cancers, supporting its potential role as an oncogenic marker. There was also a constructive relation found between CD36 expression and clinical attributes, including Stages, Grades, Metastasis (M), Nodes (N), and Tumor (T) in various cancers (Fig. S1A–E). Molecular subtypes of cancers also exhibited a remarkable correlation with CD36 (Fig. S2).

### 3.2. CD36 mRNA expression regulation by epigenetic changes

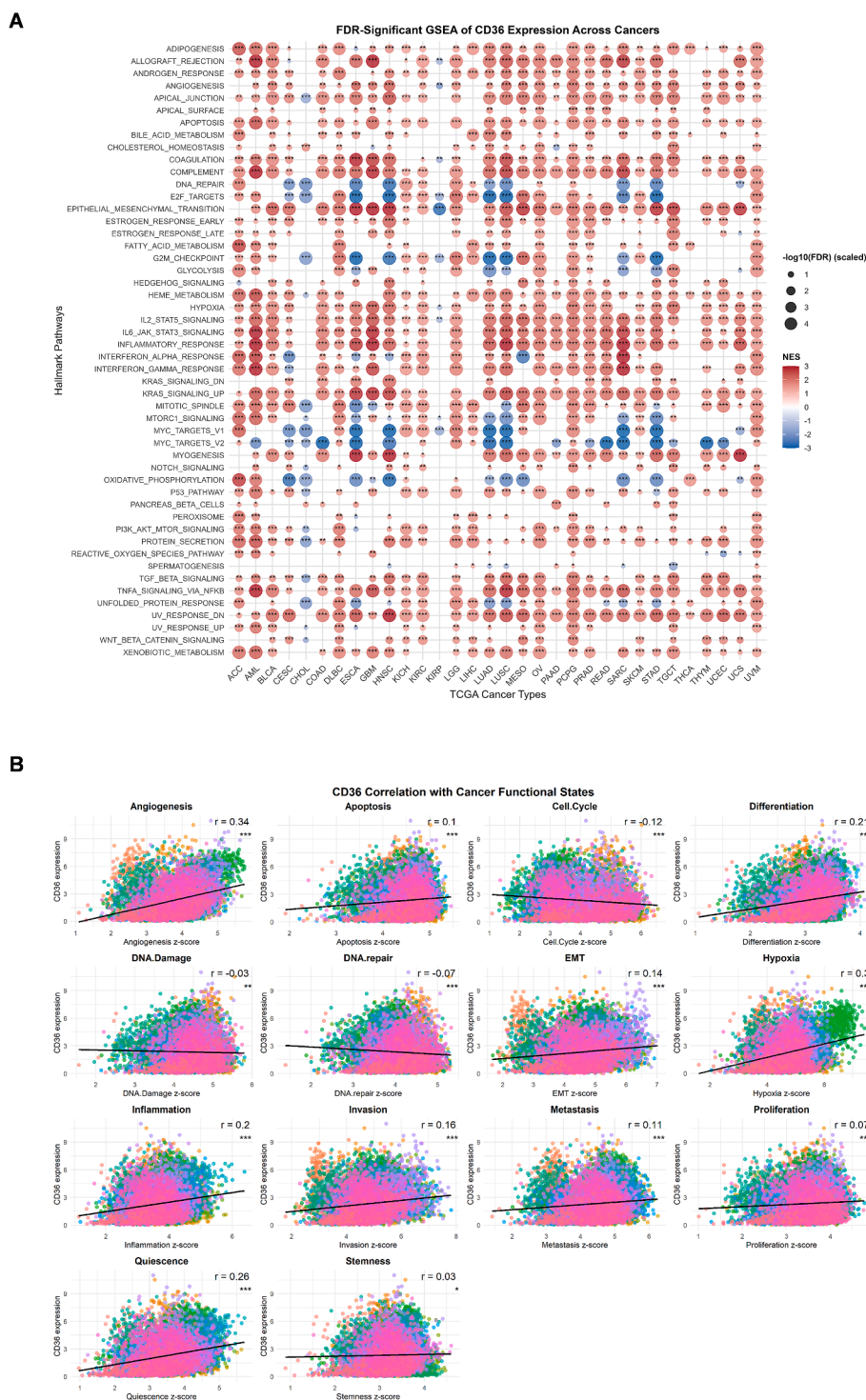
CD36 mutation analysis from cBioPortal database indicated amplification as the most frequent alteration in multiple cancer types, including LIHC, PAAD, TGCT, DLBC, BLCA, OV, HNSC, ACC, KIRC, GBM, and CHOL, whereas UCEC, SKCM, and KIRP also exhibited high



**Fig. 1.** Expression landscape of CD36 in pan-cancer. (A–B) CD36 differential expression based on TCGA normal and tumor samples; (C) CD36 differential expression based on TCGA paired samples; (D) Combined TCGA and GTEx datasets to evaluate the transcript expression level of CD36; (E) CD36 protein expression levels between normal and tumor samples, analyzed by UALCAN; (F) CD36 transcript expression levels in combined TCGA and GTEx datasets; (G) CD36 protein differential expression based on IHC results of HPA database. (H) Staining based CD36 IHC expression in cancers. Data were presented as mean  $\pm$  SD. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .



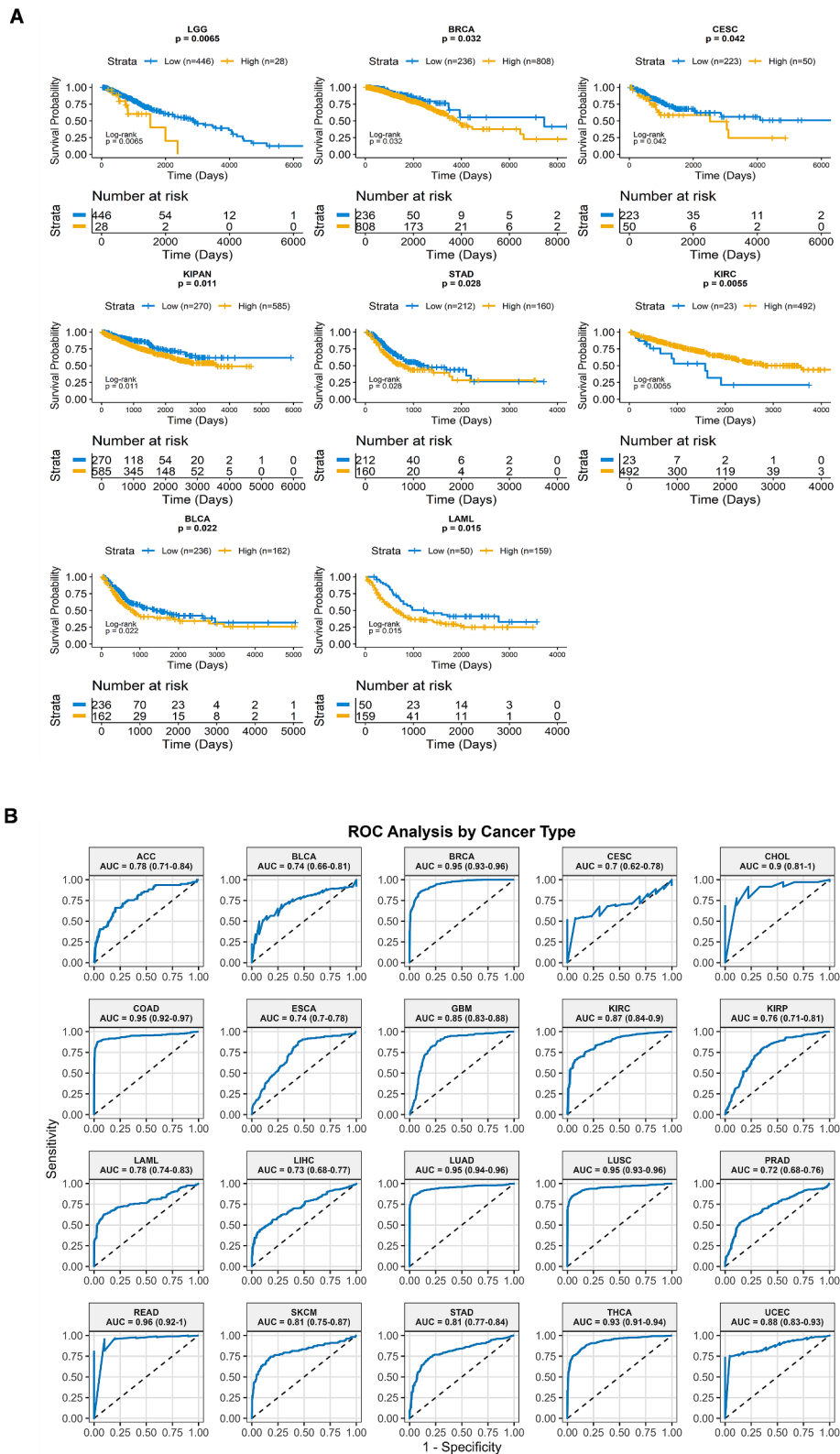
**Fig. 2. Genetic and epigenetic alterations of CD36 in pan-cancer.** (A) CD36 alteration frequencies in pan-cancer; (B-D) CD36 expression and CNA in pan-cancer; (E) Top 20 genes with significant difference in mutation rate between CD36 altered and unaltered groups; (F) Correlation between CD36 expression and TMB, MSI, and NEO in pan-cancer; (G) Correlation between CD36 expression and MATH in pan-cancer; (H) Correlation between CD36 and HRD, LOH, Purity, and Ploidy in pan-cancer; (I) Levels of CD36 methylation probes in pan-cancer; (J) Differences in CD36 methylation levels between normal and tumor tissues in pan-cancer. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , \*\*\*\* $P < 0.0001$ .



**Fig. 3. Functional pathways associated with CD36. (A)** GSEA-based comprehensive analyses to evaluate CD36 potential functions in pan-cancers; **(B)** Correlation between CD36 and 14 cancer functional states (CancerSEA database) in pan-cancer. \* $FDR < 0.05$ , \*\* $FDR < 0.01$ , \*\*\* $FDR < 0.001$ .

mutations. However, deep deletion was also observed in LUSC, OV, LUAD, SARC, PAAD, BRCA, LGG, LAML, and THCA, while structural variants were seen in BLCA and LUSC (Fig. 2A). CD36 correlation with mutations and CNA was also examined by using cBioPortal. We noticed sufficient CD36 mutation counts in different cancers such as gain or missense, shallow and deep deletions, and amplification (Fig. 2B). Moreover, high CD36 mRNA levels were associated with amplification, diploid, and gains while low in deep or shallow deletions (Fig. 2C).

Multiple tumors exhibited positive correlation between CD36 and CNA (Fig. 2D). The most frequently mutated genes found in altered CD36 groups are TP53, PHTF2, ZNF804B, SAMD9, SAMD9L, ABCB4, CCDC146, GNAI1, ABCB1, AKAP9, SEMA3A, SEMA3D, SEMA3E, TTN, GNAT3, MAGI2, HGF, CANCA2D1, SEMA3C and PCLO (Fig. 2E). CD36 proved a significant association with all genomic instability markers including HRD, ploidy, purity, LOH, MATH, NEO, MSI and TMB which provokes CD36 contribution in genomic modulations (Fig. 2F-H). CD36



**Fig. 4. Prognostic significance of CD36 in pan-cancer. (A)** KM curve to evaluate the association between CD36 and overall survival in pan-cancer; **(B)** ROC Analysis of CD36 expression in tumor versus normal group, predicting CD36 diagnostic potential in pan-cancers.

methylation analysis revealed lower methylation levels in several cancers, particularly in BLCA, LIHC, and UCEC (Fig. 2I–J). Furthermore, CD36 methylation showed a negative correlation with its mRNA levels across various cancers (Fig. S3A).

### 3.3. CD36 is associated with different cancer-related pathways

To evaluate CD36's role in cancer-related pathways, we performed an extensive GSEA analysis of 33 cancers. Multiple cancer types exhibited significant positive association of CD36 in multiple immune

**Table 2**

Diagnostic performance of CD36 in pan-cancers: AUC and 95% confidence intervals.

Cancer Type	AUC	CI (Lower-Upper)	Performance
READ	0.965217391	0.914–0.996	Excellent
LUAD	0.950691345	0.935–0.964	Excellent
LUSC	0.949268105	0.933–0.963	Excellent
BRCA	0.946753161	0.934–0.958	Excellent
COAD	0.945827364	0.923–0.966	Excellent
THCA	0.925157908	0.907–0.941	Excellent
CHOL	0.907407407	0.790–0.981	Excellent
UCEC	0.878502415	0.823–0.923	Very Good
KIRC	0.870493598	0.842–0.898	Very Good
GBM	0.853654369	0.823–0.879	Very Good
SKCM	0.809741549	0.749–0.866	Very Good
STAD	0.807893743	0.773–0.841	Very Good
LAML	0.782915387	0.735–0.831	Good
ACC	0.779474432	0.706–0.840	Good
KIRP	0.758778729	0.712–0.805	Good
ESCA	0.738451963	0.699–0.778	Good
BLCA	0.736179361	0.656–0.804	Good
LIHC	0.725681741	0.681–0.769	Good
PRAD	0.719235114	0.675–0.759	Good

and inflammation-related pathways, including IL2/STAT5 signaling, IL6/JAK/STAT3 signaling, TNF $\alpha$ /NF- $\kappa$ B signaling, inflammatory response, interferon response, EMT, complement, apoptosis, allograft rejection and adipogenesis (Fig. 3A). Conversely, CD36 showed negative correlation with proliferation and cell cycle pathways including oxidative phosphorylation, DNA repair, MYC targets V1 or V2, G2M checkpoints and E2F targets. However, some pathways illustrated cancer-type-specific patterns, which indicate heterogeneous nature of CD36 to oncogenic pathways. This finding suggests that CD36 acts as a multifaceted regulator, impacting immune, metabolic, and inflammatory signaling in a context-dependent manner. We also observed a strong constructive relationship between CD36 and tumor-related functional states such as stemness ( $r = 0.03$ ), quiescence ( $r = 0.26$ ), proliferation ( $r = 0.07$ ), metastasis ( $r = 0.11$ ), invasion ( $r = 0.16$ ), inflammation ( $r = 0.2$ ), hypoxia ( $r = 0.3$ ), EMT ( $r = 0.14$ ), differentiation ( $r = 0.21$ ), apoptosis ( $r = 0.1$ ), and angiogenesis ( $r = 0.34$ ) (Fig. 3B).

### 3.4. CD36 as a diagnostic or prognostic factor in pan-cancers

Kaplan-Meier (KM) survival analysis revealed that prognostic significance of CD36 expression is dependent on cancer type. High CD36 expression was significantly associated with poor overall survival (OS) in LGG, BRCA, CESC, KIPAN, and LAML (Fig. 4A). In terms of progression-free interval (PFI), patients with elevated CD36 had reduced survival in KIRP and KIPAN (Fig. S3B). Disease-specific survival (DSS) analysis also indicated lower survival probability with high CD36 expression for LGG and KIRP patients (Fig. S3C), while disease-free interval (DFI) analysis showed that increased CD36 expression predicted shorter survival in LUAD and ESCA (Fig. S3D). Collectively, these findings suggest that CD36 acts as a context-dependent prognostic biomarker, exerting tumor-promoting effects in certain malignancies such as glioma, breast, and renal cancers. Although CD36 has a context-dependent role, its differential expression across pan-cancer types suggests diagnostic and prognostic significance, aiding in patient stratification and the prediction of treatment outcomes.

ROC curve analysis demonstrated strong diagnostic performance of CD36 expression across multiple cancer types, with AUC values exceeding 0.7 for each cancer type. The AUC values and 95% confidence intervals (CIs) for each cancer type are presented in Fig. 4B and summarized in Table 2. For each cancer type, the 95% CIs for AUC values are non-overlapping, supporting robust diagnostic performance of CD36 expression across these cancers. The performance of the diagnostic test was excellent for BRCA, LUAD, LUSC, COAD, CHOL, and THCA, with AUC values consistently above 0.9. These findings reinforce CD36's

diagnostic potential across multiple malignancies. TIDE database supported that hypomethylation of CD36 is associated with poor prognosis in SARC, DLBC, SKCM, and BRCA (Fig. S3E).

### 3.5. CD36 is correlated with immune regulators

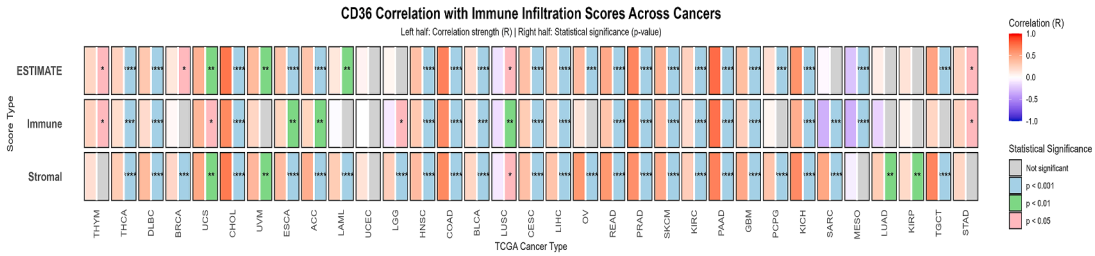
CD36 expression displayed strongest positive correlation with immune, stromal, and ESTIMATE scores in PAAD, PRAD, COAD, and CHOL (Fig. 5A), with  $P < 0.001$ . Moreover, significant positive correlations were observed in GBM, KICH, KIRC, READ, SKCM, LIHC, CESC, BLCA, and HNSC. CD36 has also shown a positive relation with different immune regulators in all cancers, which provokes its immune regulatory role in immunotherapy. Major histocompatibility complex (MHC) molecules, specifically human leukocyte antigen (HLA) family, have shown a remarkable positive association with CD36, proposing potential for antigen processing and presentation (Fig. S4A). CD36 expression is positively associated with key chemokines, including CXCL8, CXCL12, CCL2, and CCL5 (Fig. S4B). These associations suggest that CD36 may contribute to tumor progression by enhancing chemokine-mediated immune cell recruitment and inflammatory signaling. CD36 displayed strong positive correlations with immune receptors such as CCR1, CCR2, CCR4, CXCR1, and CXCR2, indicating its potential role in amplifying chemokine-receptor interactions and shaping immune cell trafficking within the tumor microenvironment (Fig. S4C). CD36 also exhibited positive correlations with several immunostimulators, including C10orf54, CXCL12, ENTPD1, CD28, and TNFSF18, suggesting that it may contribute to immune activation pathways and modulation of antitumor immune responses in the tumor microenvironment (Fig. S4D). CD36 further showed positive correlations with key immunoinhibitors, including KDR, ADORA2A, PDCD1LG2, IL10, CSF1R, HAVCR2, TGFBI, and TGFBR1. These associations indicate that CD36 may also promote an immunosuppressive tumor microenvironment, potentially facilitating immune evasion (Fig. S4E).

Immune infiltration analysis of CD36 in pan-cancers revealed strong positive association with multiple immune cells such as macrophages, monocytes, DCs, NKs, and B cells, evaluated by using various algorithms (Fig. 5B). Furthermore, Immune subtype analysis showed that CD36 expression was high in C6 (TGF- $\beta$  Dominant) and C3 (Inflammatory) immune subtypes across various cancer types (Fig. 5C). Given that cancer immune cycle determines the tumor immune response, we investigated CD36 expression in cancer immune cycle that depicted positive relation of high CD36 expression with Step1 and Step 4 across almost all cancers as described in Table 3 (Fig. 5D). CD36 is strongly linked to immune regulation, as evidenced by its association with diverse immune infiltrates, enrichment in TGF- $\beta$ -dominant and inflammatory subtypes, and correlation with key steps of the cancer immune cycle, highlighting its role in remodeling the tumor-immune microenvironment. CD36 also demonstrated positive correlations with immune checkpoint molecules, including C10orf54, EDNRB, TLR4, ENTPD1, IL10, and IL2RA, suggesting that it may contribute to immune escape mechanisms by engaging checkpoint pathways in the tumor microenvironment (Fig. 5E).

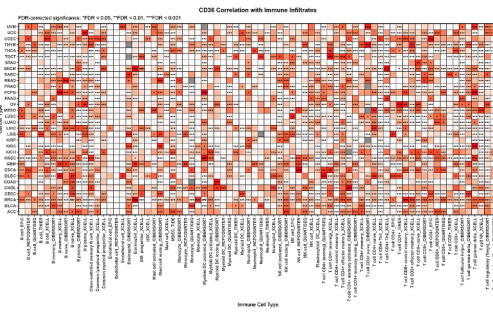
### 3.6. CD36 association with immunotherapy

CD36 exhibited notably high expression in TCGA Endometrial cancer (based on T cell dysfunction scores in the core dataset), in the ICB\_Zhao2019\_PD1 cohort (as indicated by normalized Z-scores derived from Cox proportional hazards regression in the immunotherapy dataset), and in TAM M2 cells (based on normalized expression levels in immune-suppressive cell types) (Fig. 6A). However, lower CD36 expression was found in MDSC, Pan 2018 Pme11, ICB\_Miao2018\_ICB, and METABRIC cohorts. *In-vivo* murine tumor models described CD36's potential to respond to immunotherapy in various cohorts (Fig. 6B–C). CD36 also reported response to *in-vitro* cytokines (IFN $\gamma$ ) treatment in 4T1-XW33589424 cell line (Fig. 6D). TIDE database revealed a positive

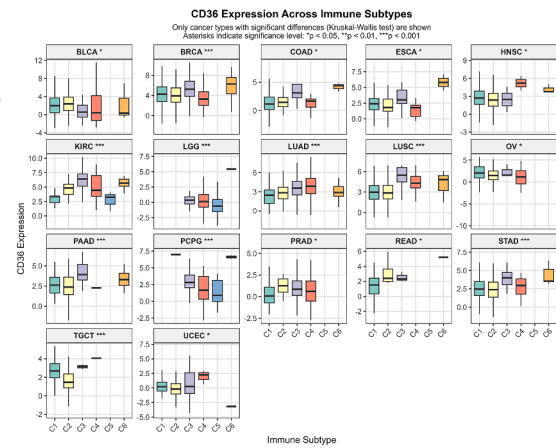
**A**



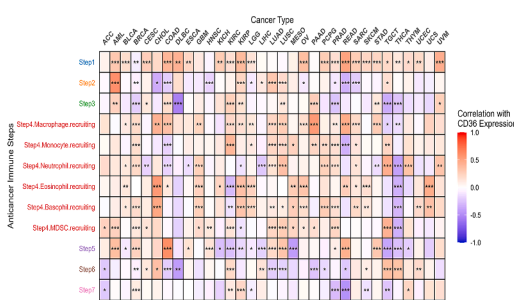
**B**



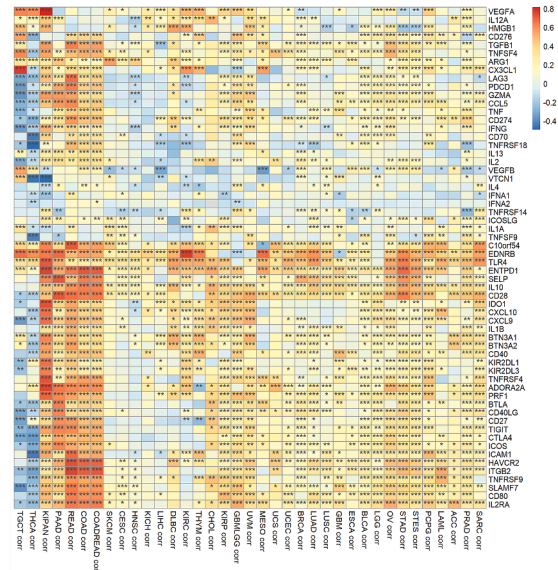
**C**



**D**



**E**



**Fig. 5. Association of CD36 with immune infiltration.** (A) Correlation between CD36 and Immune, Stromal, and ESTIMATE Scores based on the ESTIMATE algorithm; \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . (B) CD36 correlation with various immune cells across TCGA cancers by using different algorithms (CIBERSOT, X-cell, QUANTISEQ, TIMER, EPIC, TIDE) \* $FDR < 0.05$ , \*\* $FDR < 0.01$ , \*\*\* $FDR < 0.001$ . (C) Difference in pan-cancer immune subtypes between CD36 high expression and low expression group; C1= Wound healing, C2= IFN-gamma Dominant, C3= Inflammatory, C4= Lymphocyte Depleted, C5= Immunologically Quiet, C6= TGF-beta Dominant; \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . (D) Correlation between CD36 expression and anticancer immune steps in pan-cancer; (E) Correlation between CD36 expression and immune checkpoints. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

relation between CD36 and CTL activity in different immunotherapy cohorts, as shown in Table 4. Elevated CD36 expression showed prolonged progression-free survival and overall survival during Anti-PD-L1, Anti-CTLA4, and Anti-PD1 therapies (Fig. 6E).

Drug sensitivity analysis showed diversity in relation to CD36

expression and drug sensitivity based on CTRP, PRISM, and GDSC datasets (Fig. 7A–F). CD36 was negatively associated with multiple drugs, which suggests that high CD36 expression is responsible for high drug sensitivity.

**Table 3**  
Cancer immunity cycle.

Steps	Description
Step 1	Release of cancer cell antigens
Step 2	Cancer antigen presentation
Step 3	Priming and activation
Step 4	Trafficking of immune cells to tumors
Step 5	Infiltration of immune cells into tumors
Step 6	Recognition of cancer cells by T cells
Step 7	Killing of cancer cells

#### 4. Discussion

CD36 is a multifunctional scavenger receptor and fatty acid transporter that has shown a significant role in cancers through its involvement in lipid metabolism, immune modulation, and cellular adhesion. Beyond classical role of lipid uptake and fatty acid oxidation (FAO) in metastasis and therapy resistance, CD36 also contributes to angiogenesis, T-cell metabolism, and macrophage polarization, positioning it as a bridge between intrinsic and microenvironment of tumor cells [33]. Recently, CD36-dependent metastatic potential was observed in CD36<sup>+</sup> metastasis-initiating cells, fueled by dietary lipids. Interestingly, blocking of CD36 with neutralizing antibodies completely inhibits metastasis in pre-clinical models [34]. Similarly, CD36-mediated uptake of oxidized low-density lipoproteins (OxLDL) in CD8<sup>+</sup> tumor infiltrating lymphocytes (TILs) induced lipid peroxidation and promoted intratumoral CD8<sup>+</sup> T cell dysfunction [35]. Such findings highlight CD36 as a key regulator in immune crosstalk and cancer progression. We advance the understanding of CD36's oncogenic role through a comprehensive multi-omics analysis of 33 cancer types, integrating clinical and molecular data with robust multiple-testing correction.

A key finding of our study is the heterogeneous expression of CD36 across pan-cancers and its cancer-type-dependent clinical associations. CD36 high expression was correlated with poor overall survival in LGG, BRCA, and LAML, while better overall survival was observed in KIRC, CHOL, and SARC. This heterogeneity of CD36 is biologically acceptable because of its diverse cellular functions. CD36-mediated long-chain fatty acid uptake (LCFA) promotes metastasis and invasion in epithelial tumor cells, whereas it regulates angiogenesis and vascular fatty-acid (FA) transport in endothelial cells [33]. Within the immune compartment, CD36-driven lipid accumulation polarizes macrophages toward an immunosuppressive M2 phenotype [15]. Consequently, CD36-mediated lipid-driven immunosuppression and tumor proliferation contribute to poor prognosis in certain cancers, whereas its association with immune-inflamed or metabolically distinct microenvironments may underlie protective effects in others. Our methylation analysis revealed that CD36 methylation levels are significantly lower among different cancers, such as BLCA, COAD, READ, and UCEC. We also noticed that CD36 mRNA expression is inversely proportional to methylation in multiple cancers, which endorsed a significant correlation between reduced CD36 methylation and poor prognosis. Hypermethylated CD36 caused cell cycle arrest, induced apoptosis, and inhibited cell migration in lung cancer cells which influenced proliferation [36].

GSEA provides mechanistic insight into the heterogeneity and context-dependent role of CD36. CD36 showed positive correlations with immune and inflammatory pathways but negative associations with proliferative and cell cycle-related pathways across multiple cancer types. This suggests that CD36 may regulate immune-metabolic crosstalk. In some cancers, CD36-driven lipid uptake promotes immune suppression and EMT, whereas in others it appears to limit unchecked proliferation and immune infiltration. Previous cancer-specific studies substantiate this context-dependent behavior. For example, CD36 interacts with TGF- $\beta$  to promote EMT in cervical cancer [37], while CD36-mediated fatty-acid metabolism in gastric cancer drives metastasis [38]. Our findings extend these observations into a unified pan-cancer framework.

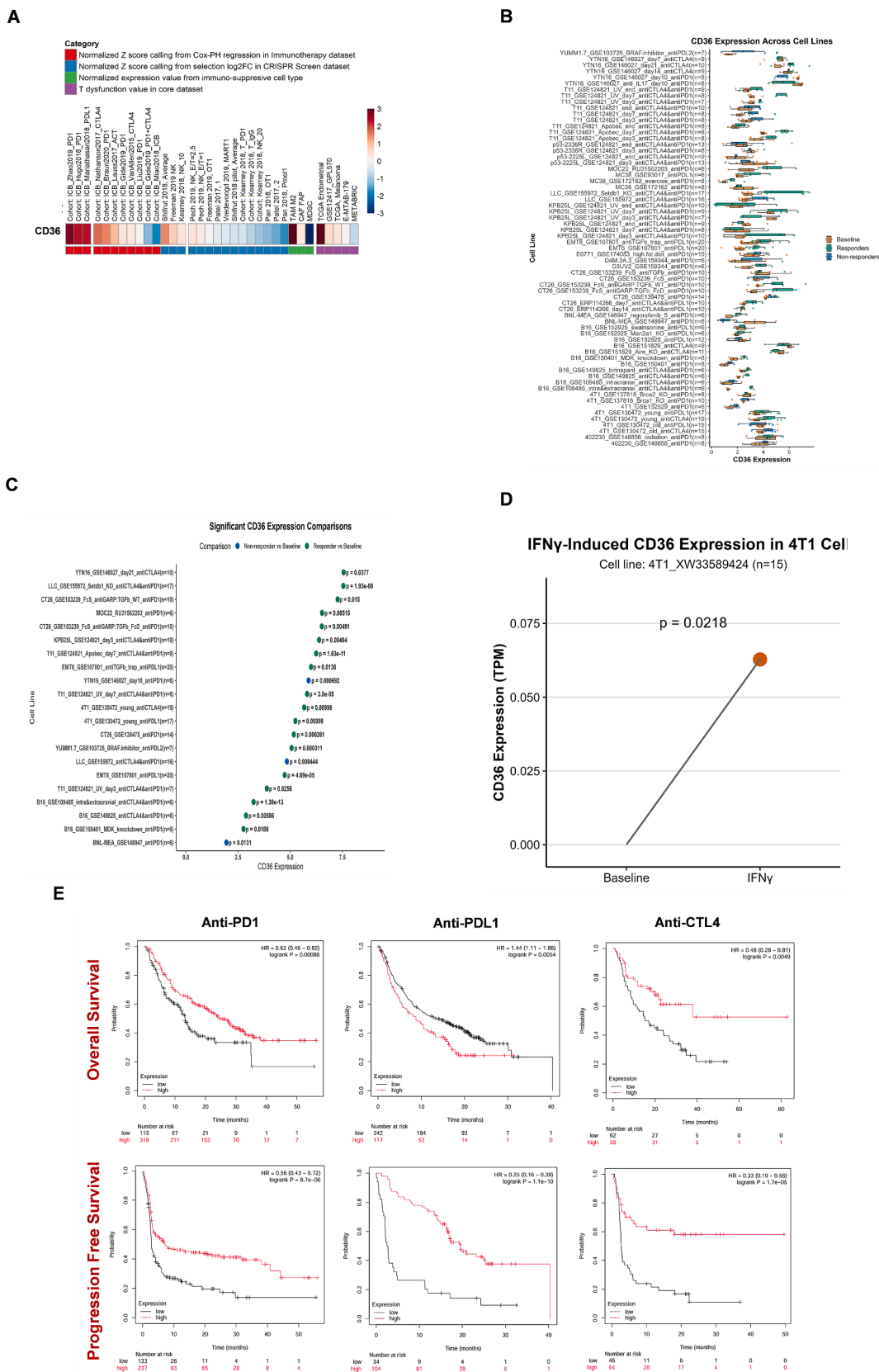
In our study, another notable paradox was observed: high CD36 expression was correlated with T-cell dysfunction scores, yet was also associated with improved outcomes under ICB in different cohorts. This can be interpreted within context of T-cell state hierarchies. T cell-infiltrated tumors often exhibit dysfunction and exhaustion signatures due to chronic antigen exposure. Such tumors contain terminally exhausted T-cells and also progenitor-like exhausted cells (TCF1<sup>+</sup>PD-1<sup>+</sup>) with proliferative potential that can be reactivated by PD-1/PD-L1 therapy [39,40]. Therefore, tumors with high dysfunction scores may remain ICB-responsive because of this progenitor pool. CD36 positive correlation with cytotoxic T-lymphocyte (CTL) activity in different immunotherapy cohorts is consistent with this model. Mechanistically, CD36-driven lipid stress may accelerate terminal T-cell dysfunction, whereas abundance of progenitor versus terminally exhausted subsets, together with stromal modulators, e.g., TGF- $\beta$ , possibly dictates the ICB responsiveness of CD36-high tumors.

Our findings demonstrate a significant positive association between CD36 and various immune features, underscoring its immune-regulatory role across pan-cancers. CD36 association with HLA family of MHC molecules suggests a potential role in antigen presentation, consistent with previous findings of CD36's interaction with CD1 antigen-presenting molecules [41]. CD36 has also been reported to regulate immune cell metabolism via influencing antigen presentation and handling [15]. The association of CD36 with chemokines and their receptors highlights its role in chemokine-mediated immune cell recruitment, which aligns with established mechanisms of macrophage and monocyte recruitment and polarization within the tumor microenvironment (TME) [15,42]. This chemokine-receptor interaction promotes tumor-associated myeloid populations, such as immunosuppressive macrophages. Similarly, CD36's linkage to immune stimulators (CD28, TNFSF18, ENTPD1) and immune inhibitors (PD-L2, TGFB1, HAVCR2, CSF1R) suggests the coexistence of activating and suppressive signals within an inflamed but immunosuppressive TME [43,44]. Furthermore, CD36 enrichment in TGF- $\beta$ -dominant and inflammatory immune subtypes, along with its correlation with multiple steps of the cancer immunity cycle, strengthens its proposed role in shaping immune infiltration patterns. Emerging evidence elaborates the immune-metabolic crosstalk driven by CD36 in the tumor microenvironment (TME). In tumor-infiltrating CD8<sup>+</sup> T cells, CD36 can provoke lipid peroxidation and ferroptosis, impairing cytokine production and cytotoxic function. Notably, genetic ablation of CD36 in CD8<sup>+</sup> T cells restores antitumor activity and synergizes with anti-PD-1 therapy [45]. Similarly, in hepatocellular carcinoma models, the CD36 inhibitor SSO combined with anti-PD-1 enhances T cell responses and tumor control [46,47]. CD36 also supports intertumoral Treg survival via PPAR- $\beta$ -mediated mitochondrial fitness; deletion of CD36 in Tregs boosts anti-tumor immunity, particularly when combined with ICBs [16,45].

Immunotherapy cohorts' analysis by using TIDE, TIMSO, and KM plotter databases further exhibited context-dependence of CD36 biology. CD36 was enriched in T-cell dysfunction, while positively correlated with cytotoxic T lymphocyte (CTL) activity and improved progression-free and overall survival during anti-PD-1, anti-PD-L1, and anti-CTLA-4 therapies. These findings were supported by TISMO murine models, which represented a significant response of immunotherapy to CD36. Although these associations are based on survival and bulk transcriptomic data and require mechanistic evaluation, they still suggest a dual role of CD36, which is consistent with emerging evidence that progenitor-like exhausted T cells (TCF1<sup>+</sup>PD-1<sup>+</sup>) can sustain ICB responsiveness in otherwise dysfunctional T-cell contexts [48].

#### 5. Limitation

This study is based on bulk transcriptomics and genomic profiles and includes correlations that define CD36-mediated roles in various cancers that require *in-vitro* and *in-vivo* functional validation. Specifically, immunotherapy analysis was performed on publicly available cohorts, which require clinical validation.



**Fig. 6.** CD36 correlation with immunotherapy response. (A) Correlation between CD36 and T cell dysfunction and outcomes using ICB treatment; (B-C) CD36 expression comparison across different tumor models and ICB treatments, between pre- and post-ICB treatment and responders and non-responders; (D) CD36 response to IFN $\gamma$  treatment in 4T1\_XW33589424; (E) Correlation between CD36 expression and pan-cancer immunotherapy prognosis (KM-plot database).

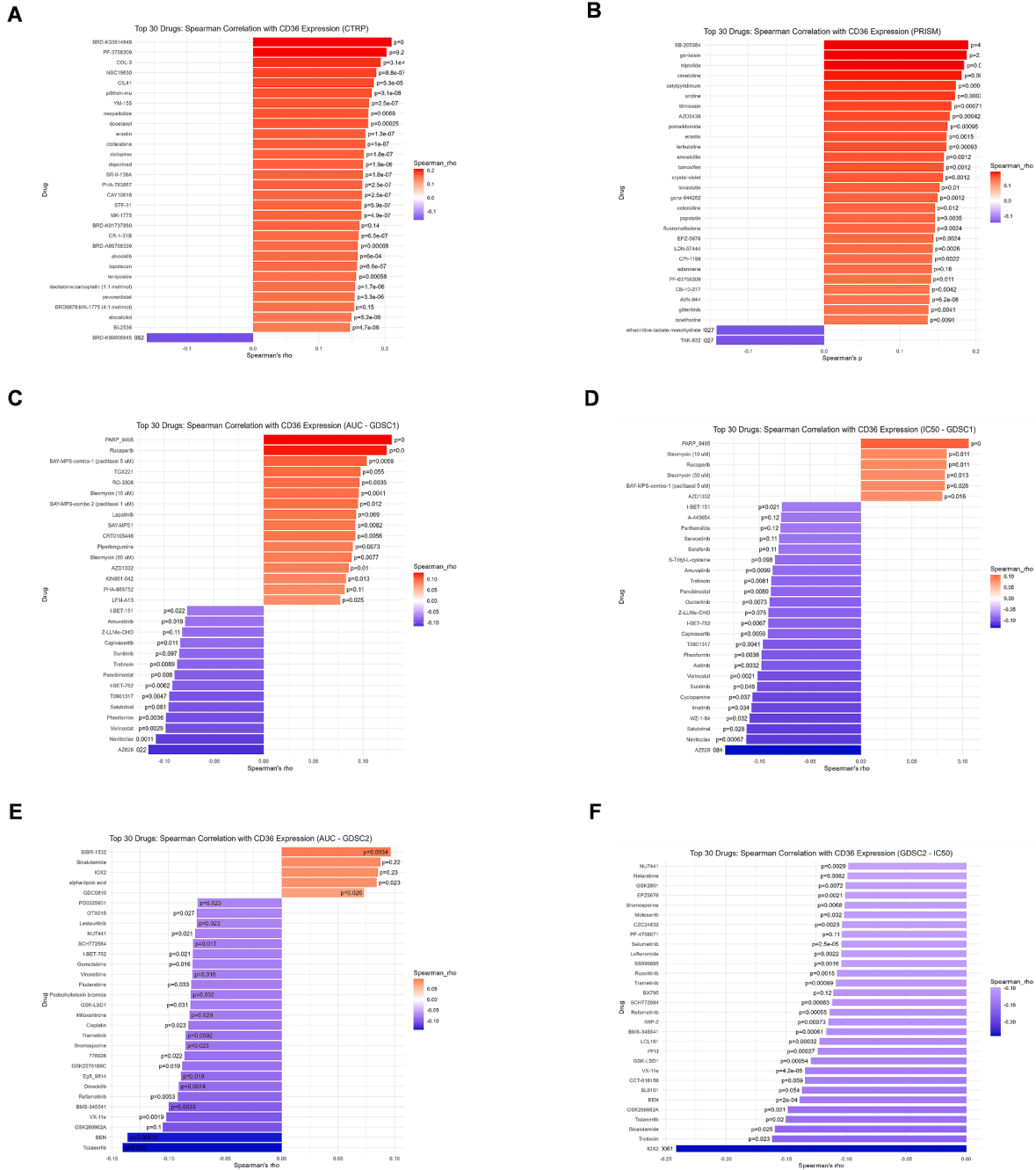
**Table 4**  
Correlation between CD36 expression and CTL in immunotherapy (TIDE database).

Cohort	Cancer	CTL Cor.	P_value	Sig.
Zhao2019_PD1	Glioblastoma	0.559	0.02947017	*
Zhao2019_PD1	Glioblastoma	0.49 <sup>†</sup>	0.041488715	*
Riaz2017_PD1	Melanoma	0.321	0.005510093	**
Mariathasan2018_PDL1	Bladder	0.217	0.046204859	*
Riaz2017_PD1	Melanoma	0.2	0.045880081	*
Gide2019_PD1	Melanoma	0.184	0.011189544	*
Braun2020_PD1	Kidney	0.133	0.025362686	*
Braun2020_PD1	Kidney	0.133	0.005163894	**
VanAllen2015_CTL4	Melanoma	0.113	0.033464151	*
Gide2019_PD1+CTLA4	Melanoma	-0.35	0.029626814	*

\*P < 0.05, \*\*P < 0.01.

**6. Conclusion**

Conclusively, this comprehensive multi-omics pan-cancer analysis reveals the heterogeneous and cancer-type-dependent role of CD36, integrating immune modulation, metabolic regulation, and therapeutic response. CD36 displayed both tumor-promoting and immune-inflamed associations, with dual links to prognosis and immunotherapy outcomes that emphasize its context-dependent functions in the tumor microenvironment. GSEA also illustrated cancer-type dependent enrichment of CD36 in cancer pathways, particularly immune and inflammatory pathways, while showing an inverse relation with proliferative and cell cycle pathways. Additionally, drug sensitivity analyses demonstrated significant correlations between CD36 expression and responses to



**Fig. 7.** CD36 correlation with drug response based on CTRP, PRISM, and GDSC databases. (A) Spearman correlation between CD36 expression and drugs AUC from CTRP database; (B) Spearman correlation between CD36 expression and drugs AUC from PRISM database; (C) Spearman correlation between CD36 expression and drugs AUC from GDSC1 database; (D) Spearman correlation between CD36 expression and drugs IC50 from GDSC1 database; (E) Spearman correlation between CD36 expression and drugs AUC from GDSC2 database; (F) Spearman correlation between CD36 expression and drugs IC50 from GDSC2 database.

various anticancer drugs. Collectively, these findings underscore the novelty of CD36 as a metabolic-immune regulator in cancer and point toward future mechanistic studies to define its therapeutic potential.

### CRedit authorship contribution statement

**Muhammad Sameer Ashaq:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Shengsong Wang:** Validation, Data curation. **Meiqi Guo:** Validation. **Lingling Wang:** Validation. **Zhuoran Li:** Validation. **Yi Wang:** Validation. **Yufeng Huang:** Validation. **Yuan Li:** Writing – review & editing, Conceptualization. **Baobing Zhao:** Writing – review & editing, Supervision, Conceptualization.

### Ethics approval

Not applicable.

### Declaration of generative AI in scientific writing

Not applicable.

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### Data availability

Data will be available on request.

### Conflict of interest

The authors declare no competing financial interests and personal relationship that could have appeared to influence the work reported in this manuscript.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pscia.2025.100097>.

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