


CD155-Prognostic and Immunotherapeutic Implications Based on Multiple Analyses of Databases Across 33 Human Cancers

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Hongpan Zhang, MD¹, Zhihao Yang, MD² , Guobo Du, MD¹,
Lu Cao, MD¹, and BangXian Tan, MD¹

Abstract

Growing evidence has suggested that CD155 participates in the regulation of many biological processes ranging cell growth, invasion, and migration from regulation of immune responses in most malignances. However, the impact of prognostic value and CD155-related immune response on the survival in multiple cancers remains incompletely clear. In our study, we assessed the prognostic significance and immune-associated mechanism of CD155 based on data from multiple databases and methods, including UCSC Xena, Oncomine, Prognoscan. We identified that CD155 was commonly upregulated in most human cancers, and High expression of CD155 was closely correlated with unfavorable clinical outcomes in 10/33 of human cancers, while CD155 at low level was responsible for better survival in KICH and PAAD. More intriguingly, CD155 expression had a significant interaction with immune function in several tumors by analyzing Tumor mutational burden and microsatellite in stability, immune score and stromal score. The correlation between immune infiltration and CD155 expression also indicated that CD155 expression positively correlated with CD4⁺ T cells in Head and Neck squamous cell carcinoma, Lung adenocarcinoma and Colon adenocarcinoma, while had inversely interaction with CD8⁺ T in Kidney renal clear cell carcinoma and Head and Neck squamous cell carcinoma as well as Tregs in Skin Cutaneous Melanoma, Head and Neck squamous cell carcinoma and Bladder Urothelial Carcinoma. These findings indicate CD155 correlates with cancer immunotherapy function. In conclusions, our observations revealed CD155 might function as immune-associated system in the development of human cancers, and acted as a promising prognostic and therapeutic target against human cancers.

Keywords

CD155, prognostic value, immunotherapy, human cancers

Abbreviation

ACC, Adrenocortical carcinoma; BLCA, Bladder Urothelial Carcinoma; BRCA, Breast invasive carcinoma; CESC, Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, Cholangio carcinoma; COAD, Colon adenocarcinoma; DLBC, Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; ESCA, Esophageal carcinoma; GBM, Glioblastoma multiforme; HNSC, Head and Neck squamous cell carcinoma; KICH, Kidney Chromophobe; KIRC, Kidney renal clear cell carcinoma; KIRP, Kidney renal papillary cell carcinoma; LAML, Acute Myeloid Leukemia; LGG, Brain Lower Grade Glioma; LIHC, Liver hepatocellular carcinoma; LUAD, Lung adenocarcinoma; TME, tumor microenvironment; OS, overall survival; DSS, Disease-specific survival; LUSC, Lung squamous cell carcinoma; MESO, Mesothelioma; OV, Ovarian serous cystadenocarcinoma; PAAD, Pancreatic adenocarcinoma; PCPG, Pheochromocytoma and Paraganglioma; PRAD, Prostate adenocarcinoma; READ, Rectum

¹ Department of Oncology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, People's Republic of China

² BaoTou Medical College, Inner Mongolia University of Science and Technology, Baotou, People's Republic of China

Corresponding Author:

BangXian Tan, MD, Department of Oncology, Affiliated Hospital, North Sichuan Medical College, No. 63, Wenhua Road, Shunqing District, Nanchong City, Sichuan Province 637000, People's Republic of China.

Email: tbx_nsmc@126.com



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; TMB, Tumor mutational burden; MSI, microsatellite in stability; DFI, Disease-free interval; PFI, Progression-free interval

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Introduction

Cancer is one of main causes of morbidity and mortality globally among people in both high-income countries and less developed countries.¹⁻⁴ Based on agency for Research on Cancer (IARC), there may be an increase in 22 million cancer cases and 13 million cancer-related deaths in 2030.⁵ Recently, immunotherapy has reported to be now a remarkably effective therapeutic approach for anti-tumor.⁶⁻¹¹ However, the impact of immune response on the survival of multiple cancers remains incompletely clear; therefore, it is crucial to identify immune-related prognostic biomarkers.

Poliovirus receptor (PVR, CD155), a member of the immunoglobulin (Ig) superfamily, participates in the regulation of many biological processes ranging cell growth, invasion, and migration from cell adhesion, and modulation of immune responses in the development of malignancies.¹²⁻¹⁵ PVR is significantly upregulated in most human cancers, and its high activity tightly correlates with poor prognosis.¹⁶⁻¹⁸ Recently, PVR, which has been identified by receptors expressed on T and NK cells, is also recognized as a promising immunotherapy target.¹⁹⁻²² It has been proposed that in the tumor microenvironment the balance between CD155/DNAM-1 and CD155/TIGIT/CD96 contrasting signals contributes to modulate NK cell effector functions.²³⁻²⁷ These results display that CD155 has functionally indispensable roles in T and NK cells. However, the deeper mechanisms understanding of CD155 in tumor progression deserves further explored.

In this present study, we investigated the expression profiling and prognostic value of CD155 in multiple types of cancer based on several databases and identified the interaction of CD155 with Tumor mutational burden (TMB), microsatellite in stability (MSI), immune score, stromal score and tumor-infiltrating immune cells in the different tumor microenvironments.

Material and Methods

Patients and Specimens

The RNA-Seq FPKM data, somatic mutation data, and corresponding clinical data with multiple human cancers of The Cancer Genome Atlas (TCGA) were obtained from UCSC Xena (<https://xena.ucsc.edu/>).²⁸ We collected expression profile data of gene in 33 solid tumors, more than 10000 samples from TCGA project.

OncoPrint Database Analysis

We used the OncoPrint database, which included 715 gene expression datasets from 86,733 cancers and normal samples, to examine different expression of CD155 in distinct types of malignancies (<http://www.oncoPrint.org>).²⁹ The results obtained from the database are set up with threshold of p -value < 0.05 , fold change > 1.5 , and gene ranking of Top 10%.

Survival Analysis and Clinical Correlation Analysis

The Survival package of R was utilized to identify the prognosis value of CD155 involved with different types of malignancies.³⁰ This test was based on the Kaplan-Meier method and Univariate Cox regression analysis, respectively. Hazard ratio (HRs) and 95% confidence intervals (CIs) were applied with describe the relative risk. $P < 0.05$ was considered as a statistical difference. Clinical stage was used to analyze the correlation between gene expression and clinical characteristics.

PrognScan Database Analysis

The interaction between survival time of patients in human cancers and elevated CD155 expression was determined by the PrognScan database (<http://www.abren.net/PrognScan/>).³¹ Hazard ratio (H.R.s) and 95% confidence intervals (CIs) were used to describe the relative risk. Corrected P -value < 0.05 was regarded as a statistically significant difference.

Tumor Mutational Burden (TMB) and Microsatellite in Stability (MSI) Analysis

TMB and MSI have also been recognized as biomarkers in the response of anti-PD1/PD-L1 monotherapy outcomes.³² TMB of each patient was calculated by somatic mutation data of 33 cancers. MSI data download from the research of Bonneville etc.³³

CD155 Modulate the Tumor Microenvironment in Human Cancers

The tumor microenvironment of 33 kinds of cancer were evaluated by the "ESTIMATE" R package.³⁴ CIBERSORT (<https://cibersort.stanford.edu/>) was utilized by performing integrative analysis between tumor-infiltrating immune cells and CD155 expression in human cancers.³⁵

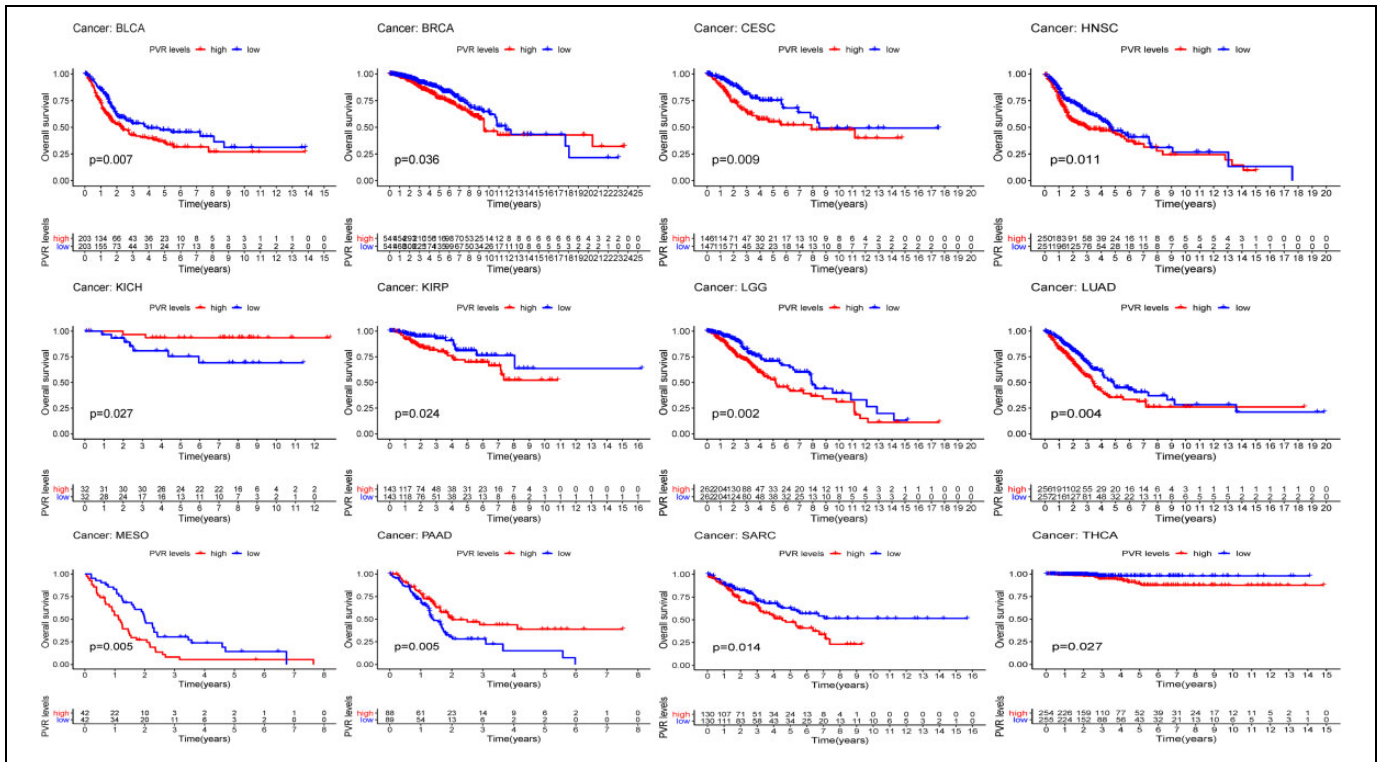


Figure 2. Prognostic value of CD155 of pan-cancer by Kaplan-Meier method in overall survival.

0.036, 0.009, 0.011, 0.024, 0.002, 0.004, 0.005, 0.014, 0.027, respectively), while high expression of CD155 was significantly associated with a favorable prognosis in KICH and PAAD patients ($P = 0.027, 0.005$; Figure 2). The univariate Cox regression analysis shown that overexpressing CD155 possessed a high risk in ACC, BLCA, CESC, HNSC, KIRP, LGG, LUAD, MESO, PRAD, SARC, THCA, ($HR = 1.9, 95\%CI:1.164-3.104, P = 0.010$; $HR = 1.31, 95\%CI:1.102-1.575, P = 0.003$; $HR = 1.51, 95\%CI:1.160-1.957, P = 0.002$; $HR = 1.39, 95\%CI:1.140-1.695, P = 0.001$; $HR = 2.42, 95\%CI:1.660-3.529, P < 0.001$; $HR = 2.183, 95\%CI:1.539-3.097, P < 0.001$; $HR = 1.45, 95\%CI:1.187-1.773, P = <0.001$, $HR = 1.525, 95\%CI:1.149-2.025, P = 0.004$; $HR = 5.07, 95\%CI:1.379-18.696, P = 0.015$; $HR = 1.31, 95\%CI:1.07-1.693, P = 0.037$; $HR = 4.39, 95\%CI:1.266-15.222, P = 0.020$, respectively; Table 1).

Except for OS, the trend of DSS, DFI and PFI was consistent with above results (Figures 3 and 4). Additionally, Overview of these results was seen from above figures, there is an apparent heterogeneity among multiple human cancers. This analysis indicated that CD155 might be a worse prognostic factor in multiple cancers. Moreover, the prognostic value of CD155 in cancer patients has also been confirmed in the PrognosScan database (Table 2).

Significance of CD 155 in Different Stages of Distinct Cancers

To further confirm the prognostic value of CD155, we investigated differential expression of CD155 in different tumor stages.

Table 1. Univariate Cox Regression Analysis.

Cancer	HR	HR.95L	HR.95H	P value
KIRP	2.420	1.660	3.529	0.000
LGG	2.183	1.539	3.097	0.000
LUAD	1.451	1.187	1.773	0.000
HNSC	1.390	1.140	1.695	0.001
CESC	1.506	1.160	1.957	0.002
BLCA	1.317	1.102	1.575	0.003
MESO	1.525	1.149	2.025	0.004
ACC	1.901	1.164	3.104	0.010
PRAD	5.078	1.379	18.696	0.015
THCA	4.391	1.266	15.222	0.020
PAAD	0.660	0.464	0.938	0.021
SARC	1.312	1.017	1.693	0.037
KIRC	1.276	0.980	1.662	0.070
BRCA	1.203	0.984	1.470	0.071
ESCA	1.354	0.967	1.894	0.077
UCS	1.567	0.934	2.627	0.089
GBM	1.278	0.930	1.756	0.131
LUSC	1.156	0.953	1.401	0.140
UVM	2.029	0.732	5.626	0.174
KICH	0.545	0.202	1.474	0.232
DLBC	0.433	0.104	1.796	0.249
COAD	1.203	0.814	1.779	0.354
SKCM	1.086	0.906	1.301	0.374
PCPG	1.796	0.481	6.714	0.384
OV	1.075	0.908	1.274	0.400
LIHC	1.109	0.840	1.464	0.465
TGCT	0.676	0.160	2.857	0.594
THYM	0.668	0.123	3.611	0.639
UCEC	0.958	0.702	1.308	0.789
STAD	1.025	0.833	1.261	0.814
CHOL	0.937	0.540	1.627	0.818
LAML	1.019	0.828	1.254	0.860
READ	0.958	0.408	2.247	0.921

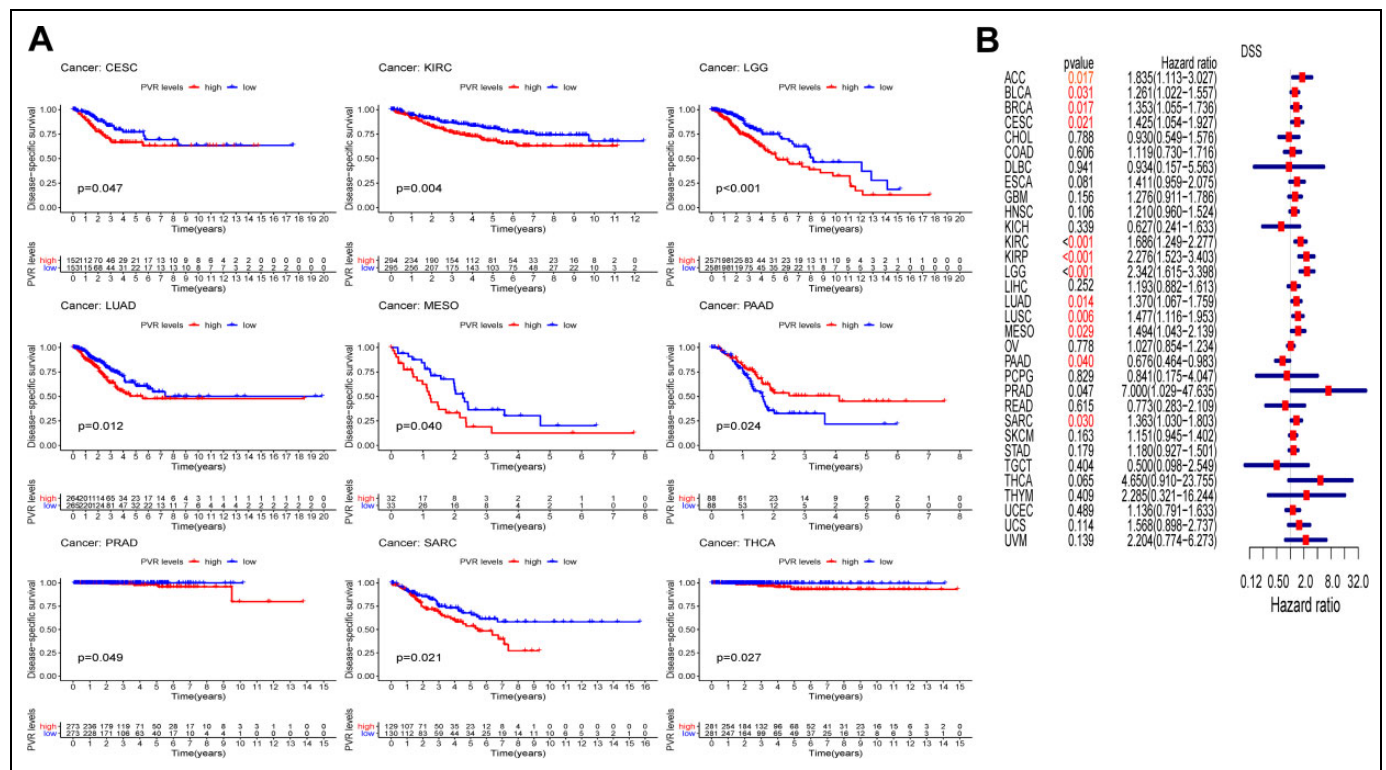


Figure 3. Prognostic value of CD155 in Disease-specific survival. A, Kaplan-Meier plots show the result of pan-cancer Disease-specific survival analysis. B, Forest plot shows the result of pan-cancer Disease-specific survival analysis of CD155.

As shown in Figure 5, the expression level of CD155 was significantly different in the clinical stages of various tumors. Therefore, CD155 might affect the prognosis of distinct cancers.

Estimation of Tumor Mutational Burden (TMB) and Microsatellite in Stability (MSI)

We found that CD155 expression level had a significant correlation with the TMB in these tumors by Pearson's correlation test (ACC $r = 0.287$, BRCA $r = 0.149$, COAD $r = -0.140$, ESCA $r = 0.246$, KIRP $r = -0.168$, LGG $r = 0.237$, LIHC $r = 0.104$, LUAD $r = 0.247$, OV $r = 0.135$, SARC $r = 0.268$, SKCM $r = 0.094$, THYM $r = 0.341$, UCEC $r = 0.360$, UCS $r = 0.397$; Figure 6A). On the other hand, it has a significant correlation with MSI in these cancers (BRCA $r = 0.071$, COAD $r = -0.157$, KICH $r = 0.32$, LUSC $r = 0.113$, PAAD $r = 0.216$, READ $r = -0.19$, SARC $r = 0.130$, UCEC $r = 0.265$, UVM $r = 0.281$; Figure 6B).

CD155 Modulate the Immune Infiltration of Tumor Microenvironment in Human Cancers

After identifying the immunotherapy potential of CD155, we further observed that these genes expression in many cancers were significantly correlated with the immune score and stromal score (Figure 7 and Supplement Figure 1). More importantly, we investigated the correlation between immune

infiltration and CD155 expression (Figure 8 Supplement Figure 2). As seen from above figures, CD155 expression level had a strongly positive correlation with CD4+ T cells in HNSC, LUAD and COAD as well as NK cells in HNSC, while inversely interaction with CD8+ T in KIRC and HNSC as well as Tregs in SKCM, HNSC and BLCA. Collectively, these findings indicate that CD155 correlates with cancer immunotherapy function.

Functional Analysis

To identify the molecular mechanisms underlying the prognostic performance of CD155, we performed Gene Set Enrichment Analysis. As seen from Figure 9, GSEA analysis was performed to participate in the modulation of gene ontological (GO) enrichment and KEGG analysis. As shown in Table 3, the enrichment results were that the common GO functional categories ($P < 0.05$) were obviously enriched in humoral immune response, immune receptor activity, immunoglobulin-complex-circulating, and T cell and B cell related functions, while KEGG analysis exhibited that the fundamental pathway functional categories ($P < 0.05$) were significantly clustered in natural killer cell mediated cytotoxicity, pathways in cancer, regulation of Autophagy, Cytokine-cytokine receptor interaction, and cell cycle (Table 3). These results suggested that CD155 might affect multiple patients with poor prognosis by biological processes and pathways above.

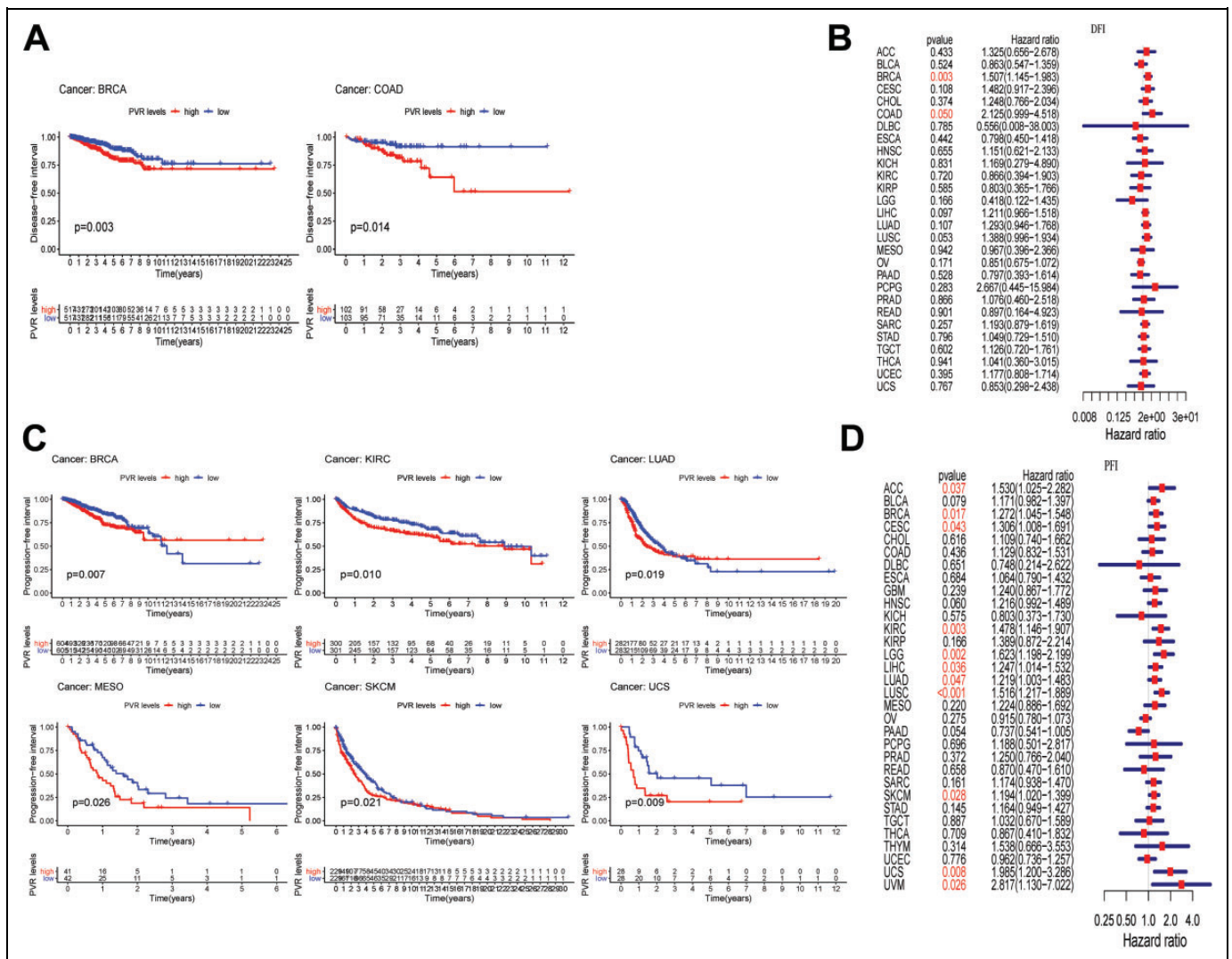


Figure 4. Prognostic value of CD155 in Disease-free interval and Progression-free interval analysis. A and C, Survival curves show the result of pan-cancer Disease-free interval and Progression-free interval analysis of CD155. B and D, Forest plots show the result of pan-cancer Disease-free interval and Progression-free interval analysis of CD155.

Discussion

Cancer immunotherapy has been one of the most effectively therapeutic approach for cancer therapy.³⁸⁻⁴¹ CD155 (PVR/nccl5), a member of the nectin-like family of adhesion molecules, is widely overexpressed across most malignances and has been linked to unfavorable clinical outcomes.^{17,42-45} Intriguingly, previous results reported on literature are almost similar to ours. Meanwhile, CD155 has been shown to play important tumor cell-extrinsic roles by modulating the function of tumor-infiltrating lymphocytes via interactions with both stimulatory and inhibitory receptors on T and NK cells.^{19,46} Overall, our study explores insights in understanding the potential role of CD155 in tumor immunotherapy and its use as a cancer biomarker.

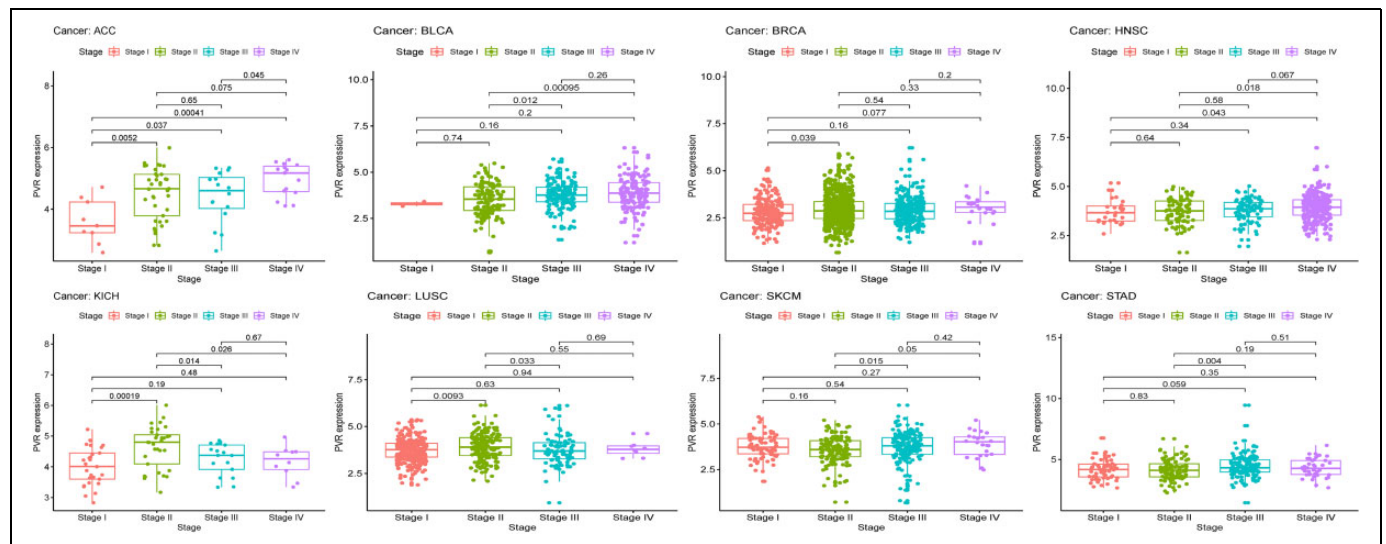
In our present study, for the first time, we identified that the CD155 is significantly elevated in 33 tumors based on the

TCGA datasets, which is consistent with studies in hepatocellular carcinoma,⁴⁷ Pancreatic Cancer,^{18,48} and colorectal carcinoma.⁴⁹ Next, KM plotter analysis and Univariate Cox regression analysis revealed that the higher expression of CD155 were remarkably correlated with its worse OS, DSS, DFI and PFI in many cancers, indicating a diagnostic and therapeutic role in the initiation of these cancers.

Another study associated with immune function is that CD155 expression in malignances is closely correlated with TMB and MSI, especially for BRCA, COAD and UCEC, indicating that CD155 may serve as a biomarker predicting anti-PD1/PD-L1 monotherapy outcomes⁵⁰⁻⁵³ in these cancers. The immune score, stromal score has also significantly interaction with CD155 in BLCA, BRCA, CESC, HNSC, KIRC, LUAD, and SKCM. In reviewing reports, the stromal and immune cells has indispensable roles in driving TME of multiple cancers.^{34,54} These consequences further confirm that CD155

Table 2. The Prognostic Value of CD155 in Human Cancer in the PrognScan Database.

Dataset	Cancer type	Endpoint	P-value	HR [95% CI-low CI-upp]
GSE17536	Colorectal cancer	Disease Specific Survival	0.00	0.15 [0.03-0.68]
GSE13507	Bladder cancer	Disease Specific Survival	0.00	2.26 [1.44-3.55]
GSE17537	Colorectal cancer	Disease Specific Survival	0.02	0.07 [0.01-0.58]
GSE1456-GPL96	Breast cancer	Disease Specific Survival	0.04	2.74 [1.20-6.25]
GSE1456-GPL96	Breast cancer	Disease Specific Survival	0.04	1.84 [1.06-3.19]
GSE22138	Eye cancer	Distant Metastasis Free Survival	0.02	0.00 [0.00-0.97]
GSE11121	Breast cancer	Distant Metastasis Free Survival	0.02	0.43 [0.25-0.71]
GSE19615	Breast cancer	Distant Metastasis Free Survival	0.04	7.72 [1.72-34.64]
GSE30929	Soft tissue cancer	Distant Recurrence Free Survival	0.00	2.05 [1.22-3.44]
GSE12417-GPL570	Blood cancer	Overall Survival	0.00	4.97 [1.74-14.19]
GSE19234	Skin cancer	Overall Survival	0.00	10.16 [2.99-34.52]
jacob-00182-HLM	Lung cancer	Overall Survival	0.00	1.89 [1.05-3.41]
GSE17536	Colorectal cancer	Overall Survival	0.00	0.26 [0.07-0.98]
jacob-00182-UM	Lung cancer	Overall Survival	0.00	3.34 [1.51-7.43]
GSE31210	Lung cancer	Overall Survival	0.01	2.45 [1.28-4.68]
GSE9893	Breast cancer	Overall Survival	0.01	0.76 [0.63-0.92]
GSE16581	Brain cancer	Overall Survival	0.01	84.38 [2.38-2998.10]
GSE1456-GPL96	Breast cancer	Overall Survival	0.01	2.26 [1.11-4.62]
GSE19234	Skin cancer	Overall Survival	0.01	2.67 [1.41-5.06]
GSE13507	Bladder cancer	Overall Survival	0.01	1.54 [1.12-2.11]
GSE3141	Lung cancer	Overall Survival	0.02	1.70 [1.17-2.46]
GSE5287	Bladder cancer	Overall Survival	0.02	1.82 [1.00-3.30]
GSE19234	Skin cancer	Overall Survival	0.02	11.80 [3.01-46.28]
GSE4573	Lung cancer	Overall Survival	0.02	2.29 [1.23-4.27]
GSE12276	Breast cancer	Relapse Free Survival	0.00	1.47 [1.15-1.88]
GSE1456-GPL96	Breast cancer	Relapse Free Survival	0.01	2.25 [1.10-4.60]
GSE31210	Lung cancer	Relapse Free Survival	0.02	2.09 [1.34-3.27]
GSE8894	Lung cancer	Relapse Free Survival	0.02	1.90 [1.11-3.26]
GSE1456-GPL96	Breast cancer	Relapse Free Survival	0.04	4.63 [1.34-16.03]

**Figure 5.** The boxplot shows the correlation between the expression of PVR and the pathological grade in ACC, BLCA, BRCA, HNSC, KICH, LUSC, SKCM and STAD. The label at the top of the picture corresponds to the pathological stage of the patient.

plays a vitally significant part in the tumor progression by immune system. Lastly, results of immune infiltration demonstrate that CD155 expression level in diverse immune infiltration cell has a strongly positive correlation with CD4+ T cells

in HNSC, LUAD and COAD as well as NK cells in HNSC, while inversely interaction with CD8+ T (KIRC and HNSC) and Tregs (SCKM, HNSC and BLCA). There is also evidence that CD155/CD226 interaction can attenuate the generation of

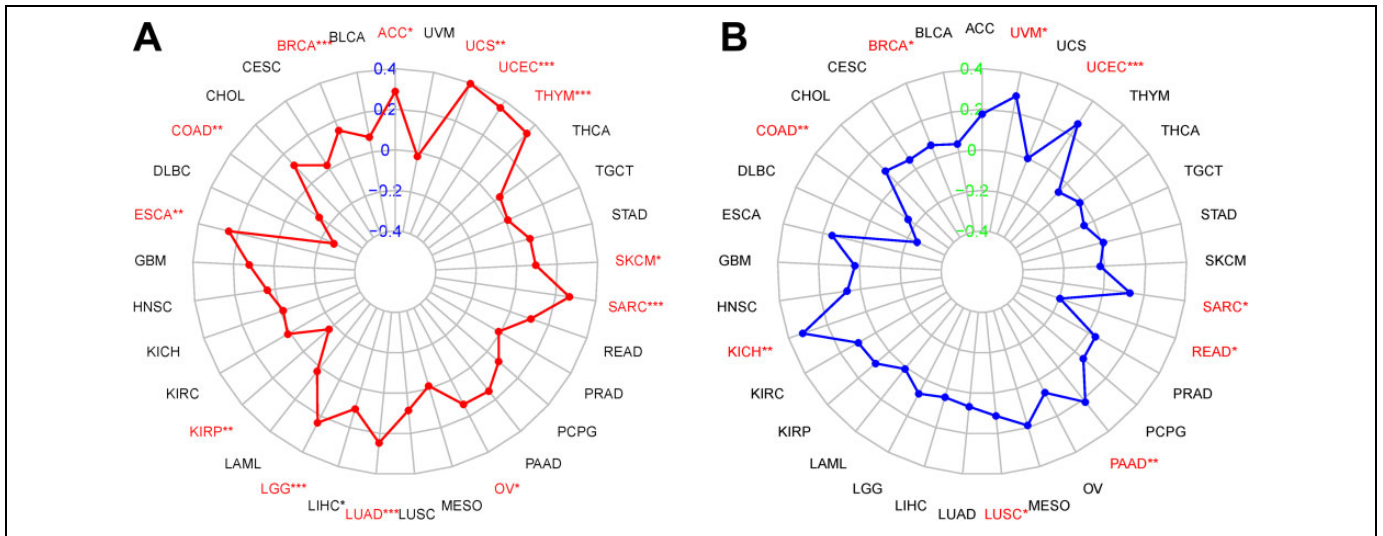


Figure 6. The radar plots show the correlation between the expression of PVR and the TMB, MSI. A, The expression of PVR associated with TMB in ACC, BRCA, COAD, ESCA, KIRC, LGG, LUAD, OV, SARC, SKCM, THYM, UCEC, UCS. B, The expression of PVR associated with MSI in BRCA, COAD, KICH, LUSC, PAAD, READ, SARC, UCEC, UVM. Significant Codes: *** ≤ 0.001 ** ≤ 0.01 * ≤ 0.05 .

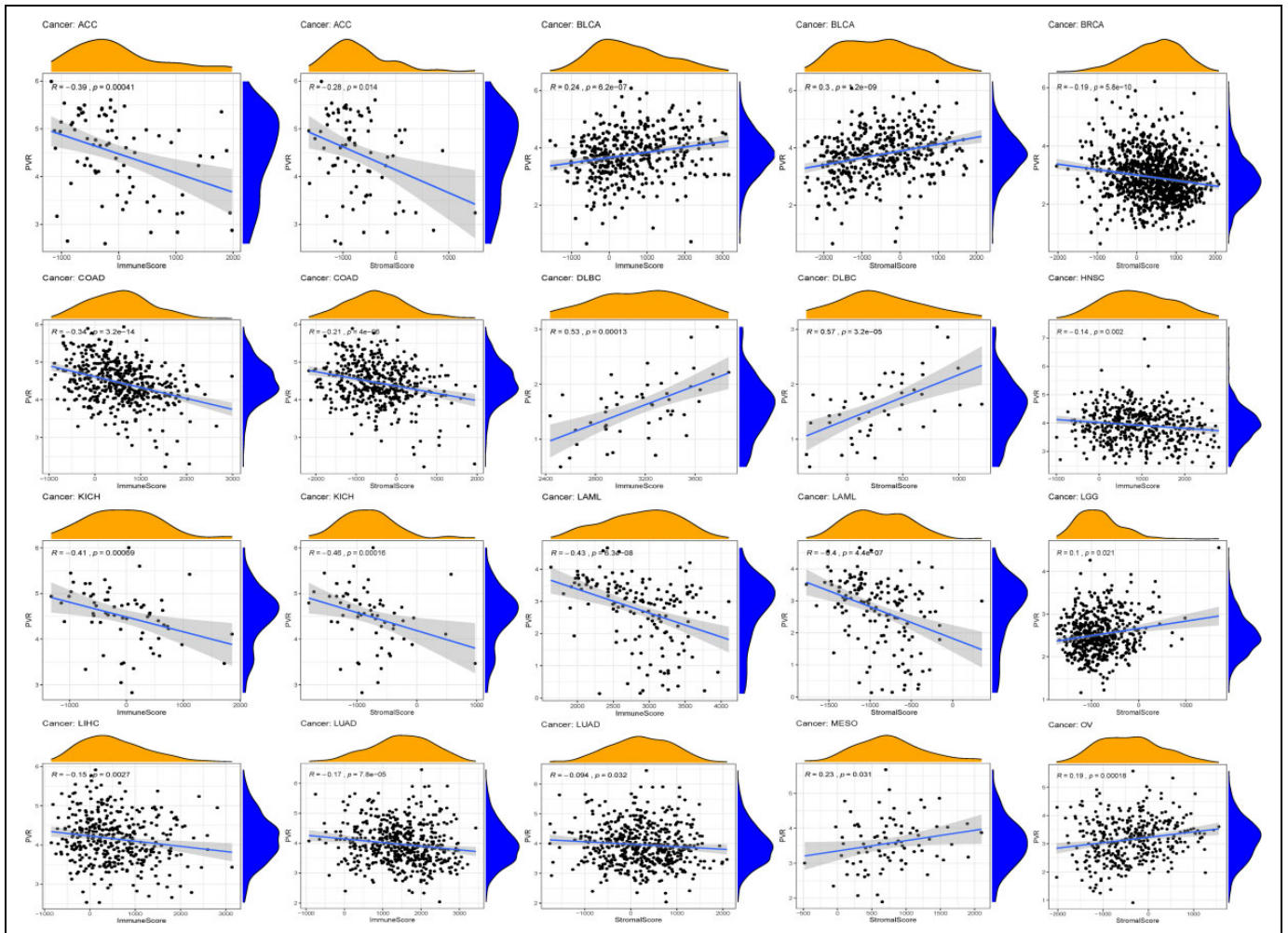


Figure 7. The expression level of PVR was correlated with immune score and stromal score in human TME.

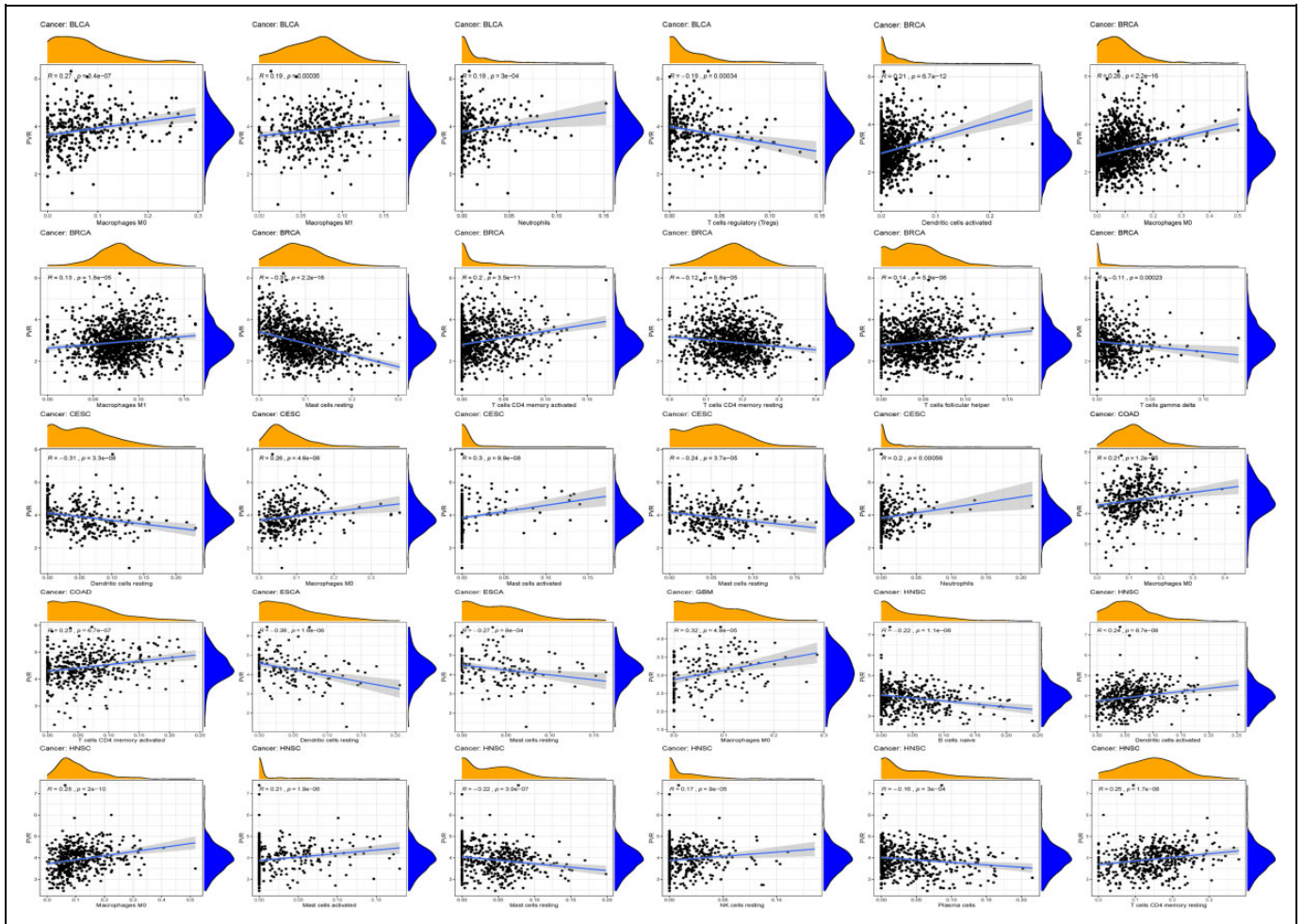


Figure 8. The expression level of PVR was correlated with immune cell infiltration in human cancer.

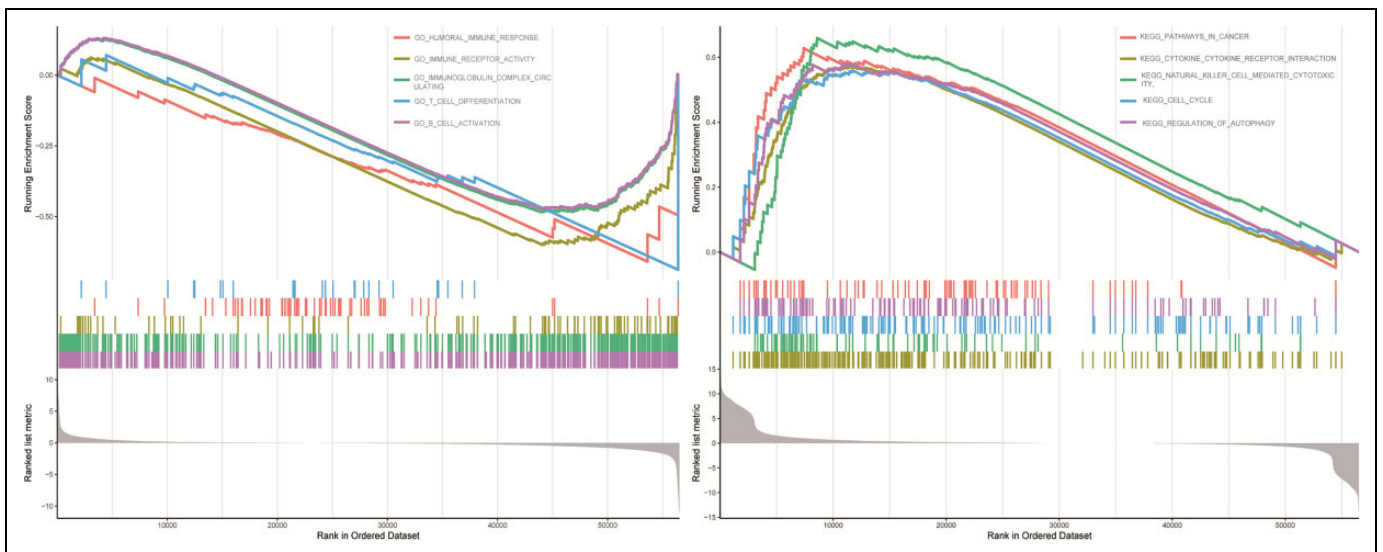


Figure 9. GSEA analysis of CD155 in human cancer.

Table 3. Gene Set Enrichment Analysis of CD155 in Human Cancer.

Description	Set size	Enrichment score	P value
GO_HUMORAL_IMMUNE_RESPONSE	348	-0.49312	0.034483
GO_HUMORAL_IMMUNE_RESPONSE_MEDIATED_BY_CIRCULATING_IMMUNOGLOBULIN	143	-0.73306	0.02381
GO_IMMUNE_RECEPTOR_ACTIVITY	126	-0.54154	0.022222
GO_IMMUNE_RESPONSE_REGULATING_CELL_SURFACE_RECEPTOR_SIGNALING_PATHWAY	491	-0.59137	0.038462
GO_IMMUNOGLOBULIN_COMPLEX	140	-0.78863	0.02381
GO_IMMUNOGLOBULIN_COMPLEX_CIRCULATING	65	-0.81986	0.022727
GO_IMMUNOGLOBULIN_PRODUCTION	202	-0.67177	0.026316
GO_IMMUNOGLOBULIN_RECEPTOR_BINDING	69	-0.81328	0.022222
GO_T_CELL_DIFFERENTIATION	239	-0.41371	0.027778
GO_T_CELL_PROLIFERATION	186	-0.45498	0.027027
GO_T_CELL_RECEPTOR_COMPLEX	125	-0.58827	0.02381
GO_T_CELL_RECEPTOR_SIGNALING_PATHWAY	199	-0.4518	0.027778
GO_B_CELL_ACTIVATION	306	-0.4548	0.030303
GO_B_CELL_MEDIATED_IMMUNITY	215	-0.69932	0.027027
GO_B_CELL_RECEPTOR_SIGNALING_PATHWAY	118	-0.74546	0.02439
KEGG_PATHWAYS_IN_CANCER	325	0.417665	0.036145
KEGG_MAPK_SIGNALING_PATHWAY	267	0.437298	0.039474
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	264	0.404767	0.045455
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	132	0.502204	0.03
KEGG_CELL_CYCLE	124	0.473067	0.019231
KEGG_ECM_RECEPTOR_INTERACTION	84	0.574433	0.014085
KEGG_FATTY_ACID_METABOLISM	42	-0.69405	0.021277
KEGG_REGULATION_OF_AUTOPHAGY	35	0.806302	0.027027
KEGG_PRIMARY_IMMUNODEFICIENCY	35	-0.62109	0.042553

CD8+ T cells by regulating NK T-cell differentiation.⁵⁵ In addition, the inhibition of TIGIT/CD155 signaling in HNSC significantly impeded the immunosuppression of Tregs by inactivating the output of suppressive cytokines.⁵⁶ However, this was not consistent with our predicting analysis in HNSC, suggesting that the underlying mechanism possibly needs to be further explored. Together, our studies provide possible mechanisms, which explain why CD155 expression correlates with cancer immune modulation.

In addition, by performing functional enrichment analysis, we can identify its underlying functions and previously predict unappreciated biological processes associated with human cancers. The functional analysis result of CD155-related genes indicated that it was relevant to humoral immune response, immune receptor activity, natural killer cell mediated cytotoxicity, pathways in cancer, regulation of Autophagy, Cytokine-cytokine receptor interaction, which also contribute to validate immune-related mechanisms by which CD155 can promote carcinogenesis and progression of tumor.

The above results show that the association between poor prognosis and cancer patients may be mainly because of lower immune repose and inhibited immune reactive in TME, which can promote overcome tumor immune suppression and enhance anti-tumor immunity. According to these changes, most tumors with malignance may benefit from immunotherapy and chemotherapy. However, some limitations are supposed to be highlighted in our investigation. First, the biological function of 7 identified genes, especially the association with immunofiltration, should be verified in the assays.

Next, only limited data can be used for performance assessment, and it is necessary to collect more data of the robustness of CD115 in the future.

In summary, for the first time, we comprehensively explore the correlation between CD155 expression and prognostic potential among 33 tumors. Our findings also revealed that CD155 might function as immune-associated biomarker in the development of human cancers. Consequently, CD155 could be used as a promising prognostic biomarker and potential novel therapeutic target against human cancers.

Authors' Note

Hongpan Zhang and Zhihao Yang conceived, designed and wrote the study. Zhang Hongpan and Yang Zhihao contributed equally. Du Guobo and Cao Lu contributed to the revision and statistical analysis of the background of the article. Tan Bangxian finally revised the article and provided financial support for the publication of the article. The data used in our study were obtained from public databases UCSC, TCGA, ONCOMINE, and PrognoScan, therefore, ethical approval was not required.

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Declaration of Conflicting Interests

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ORCID iD

Zhihao Yang, MD  <https://orcid.org/0000-0002-6134-5737>

Supplemental Material

Supplemental material for this article is available online.

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.
- Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: good or bad news from the 2018 global cancer statistics? *Cancer Commun (Lond).* 2019;39(1):22.
- Fidler MM, Bray F, Soerjomataram I. The global cancer burden and human development: a review. *Scand J Public Health.* 2018; 46(1):27-36.
- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65(2): 87-108.
- Goodman J, Lynch H. Improving the international agency for research on cancer's consideration of mechanistic evidence. *Toxicol Appl Pharmacol.* 2017;319:39-46.
- Granier C, Karaki S, Roussel H, et al. Cancer immunotherapy: rational and recent breakthroughs. *Rev Med Interne.* 2016;37(10): 694-700.
- O'Donnell JS, Teng MWL, Smyth MJ. Cancer immunoediting and resistance to T cell-based immunotherapy. *Nat Rev Clin Oncol.* 2019;16(3):151-167.
- Koo SL, Wang WW, Toh HC. Cancer immunotherapy—the target is precisely on the cancer and also not. *Ann Acad Med Singap.* 2018;47(9):381-387.
- Yang Y. Cancer immunotherapy: harnessing the immune system to battle cancer. *J Clin Invest.* 2015;125(9):3335-3337.
- Baxeveanis CN, Perez SA, Papamichail M. Cancer immunotherapy. *Cancer Immunol Immunother.* 2009;46(4):167-189.
- Xu F, Chen JX, Yang XB, et al. Analysis of lung adenocarcinoma subtypes based on immune signatures identifies clinical implications for cancer therapy. *Mol Ther Oncolytics.* 2020;17:241-249.
- Kucan Brlic P, Lenac Rovis T, Cinamon G, Tsukerman P, Mandelboim O, Jonjic S. Targeting PVR (CD155) and its receptors in anti-tumor therapy. *Cell Mol Immunol.* 2019;16(1):40-52.
- Sloan KE, Stewart JK, Treloar AF, Matthews RT, Jay DG. CD155/PVR enhances glioma cell dispersal by regulating adhesion signaling and focal adhesion dynamics. *Cancer Res.* 2005; 65(23):10930-10937.
- Zhuo B, Li Y, Gu F, et al. Overexpression of CD155 relates to metastasis and invasion in osteosarcoma. *Oncol Lett.* 2018;15(5): 7312-7318.
- Xu Y, Cui G, Jiang Z, Li N, Zhang X. Survival analysis with regard to PD-L1 and CD155 expression in human small cell lung cancer and a comparison with associated receptors. *Oncol Lett.* 2019;17(3):2960-2968.
- Fang L, Zhao F, Iwanowycz S, et al. Anticancer activity of emodin is associated with downregulation of CD155. *Int Immunopharmacol.* 2019;75:105763.
- Zhang J, Zhu Y, Wang Q, et al. Poliovirus receptor CD155 is up-regulated in muscle-invasive bladder cancer and predicts poor prognosis. *Urol Oncol.* 2020;38(2):41. e11-41. e18.
- Nishiwada S, Sho M, Yasuda S, et al. Clinical significance of CD155 expression in human pancreatic cancer. *Anticancer Res.* 2015;35(4):2287-2297.
- O'Donnell JS, Madore J, Li XY, Smyth MJ. Tumor intrinsic and extrinsic immune functions of CD155. *Semin Cancer Biol.* 2019; 65:189-196.
- Gao J, Zheng Q, Xin N, Wang W, Zhao C. CD155, an onco-immunologic molecule in human tumors. *Cancer Sci.* 2017; 108(10):1934-1938.
- Triki H, Charfi S, Bouzidi L, et al. CD155 expression in human breast cancer: clinical significance and relevance to natural killer cell infiltration. *Life Sci.* 2019;231:116543.
- Lupo KB, Matosevic S. CD155 immunoregulation as a target for natural killer cell immunotherapy in glioblastoma. *J Hematol Oncol.* 2020;13(1):76.
- Egelkamp J, Chichelnitskiy E, Kühne JF, et al. Back signaling of HLA class I molecules and T/NK cell receptor ligands in epithelial cells reflects the rejection-specific microenvironment in renal allograft biopsies. *Am J Transplant.* 2019;19(10):2692-2704.
- Hoogi S, Eisenberg V, Mayer S, Shamul A, Barliya T, Cohen CJ. A TIGIT-based chimeric co-stimulatory switch receptor improves T-cell anti-tumor function. *J Immunother Cancer.* 2019; 7(1):243.
- Chauvin JM, Ka M, Pagliano O, et al. IL15 stimulation with TIGIT blockade reverses CD155-mediated NK-cell dysfunction in melanoma. *Clin Cancer Res.* 2020;26(20):5520-5533.
- Hill GR, Koyama M. Cytokines and costimulation in acute graft-versus-host disease. *Blood.* 2020;136(4):418-428.
- Chauvin JM, Zarour HM. TIGIT in cancer immunotherapy. *J Immunother Cancer.* 2020;8(2):e000957.
- Lee CM, Barber GP, Casper J, et al. UCSC genome browser enters 20th year. *Nucleic Acids Res.* 2020;48(D1):D756-D761.
- Rhodes DR, Kalyana-Sundaram S, Mahavisno V, et al. OncoPrint 3.0: genes, pathways, and networks in a collection of 18,000 cancer gene expression profiles. *Neoplasia.* 2007;9(2):166-180.
- Rizvi AA, Karaesmen E, Morgan M, et al. Gwasurvivr: an R package for genome-wide survival analysis. *Bioinformatics.* 2019;35(11):1968-1970.
- Mizuno H, Kitada K, Nakai K, Sarai A. PrognoScan: a new database for meta-analysis of the prognostic value of genes. *BMC Med Genomics.* 2009;2:18.
- Filipovic A, Miller G, Bolen J. Progress toward identifying exact proxies for predicting response to immunotherapies. *Front Cell Dev Biol.* 2020;8:155.
- Bonneville R, Krook MA, Kautto EA, et al. Landscape of microsatellite instability across 39 cancer types. *JCO Precis Oncol.* 2017;(1):1-15.

34. Yoshihara K, Shahmoradgoli M, Martínez E, et al. Inferring tumour purity and stromal and immune cell admixture from expression data. *Nat Commun.* 2013;4(1):2612.
35. Newman AM, Liu CL, Green MR, et al. Robust enumeration of cell subsets from tissue expression profiles. *Nat Methods.* 2015; 12(5):453-457.
36. Kuleshov MV, Diaz JEL, Flamholz ZN, et al. Modenrichr: a suite of gene set enrichment analysis tools for model organisms. *Nucleic Acids Res.* 2019;47(W1):W183-W190.
37. Reimand J, Isserlin R, Voisin V, et al. Pathway enrichment analysis and visualization of omics data using g: profiler, GSEA, Cytoscape and EnrichmentMap. *Nat Protoc.* 2019;14(2):482-517.
38. Abbott M, Ustoyev Y. Cancer and the immune system: the history and background of immunotherapy. *Semin Oncol Nurs.* 2019; 35(5):150923.
39. Lohmueller J, Finn OJ. Current modalities in cancer immunotherapy: immunomodulatory antibodies, CARs and vaccines. *Pharmacol Ther.* 2017;178:31-47.
40. Riley RS, June CH, Langer R, Mitchell MJ. Delivery technologies for cancer immunotherapy. *Nat Rev Drug Discov.* 2019;18(3): 175-196.
41. Helmy KY, Patel SA, Nahas GR, Rameshwar P. Cancer immunotherapy: accomplishments to date and future promise. *Ther Deliv.* 2013;4(10):1307-1320.
42. Molfetta R, Zitti B, Lecce M, et al. CD155: a multi-functional molecule in tumor progression. *Int J Mol Sci.* 2020;21(3):992.
43. Yong H, Cheng R, Li X, et al. CD155 expression and its prognostic value in postoperative patients with breast cancer. *Biomed Pharmacother.* 2019;115:108884.
44. Huang DW, Huang M, Lin XS, Huang Q. CD155 expression and its correlation with clinicopathologic characteristics, angiogenesis, and prognosis in human cholangiocarcinoma. *Onco Targets Ther.* 2017;10:3817-3825.
45. Atsumi S, Matsumine A, Toyoda H, Niimi R, Iino T, Sudo A. Prognostic significance of CD155 mRNA expression in soft tissue sarcomas. *Oncol Lett.* 2013;5(6):1771-1776.
46. Anderson AC, Joller N, Kuchroo VK. Lag-3, Tim-3, and TIGIT: co-inhibitory receptors with specialized functions in immune regulation. *Immunity.* 2016;44(5):989-1004.
47. Duan X, Liu J, Cui J, et al. Expression of TIGIT/CD155 and correlations with clinical pathological features in human hepatocellular carcinoma. *Mol Med Rep.* 2019;20(4):3773-3781.
48. Brooks J, Fleischmann-Mundt B, Woller N, et al. Perioperative, spatiotemporally coordinated activation of T and NK cells prevents recurrence of pancreatic cancer. *Cancer Res.* 2018;78(2):475-488.
49. Masson D, Jarry A, Baurly B, et al. Overexpression of the CD155 gene in human colorectal carcinoma. *Gut.* 2001;49(2):236-240.
50. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther.* 2017;16(11):2598-2608.
51. Huang AC, Postow MA, Orlowski RJ, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature.* 2017;545(7652):60-65.
52. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science.* 2017;357(6349):409-413.
53. Ott PA, Bang YJ, Piha-Paul SA, et al. T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. *J Clin Onco.* 2019;37(4):318-327.
54. Liu W, Ye H, Liu YF, et al. Transcriptome-derived stromal and immune scores infer clinical outcomes of patients with cancer. *Oncol Lett.* 2018;15(4):4351-4357.
55. Georgiev H, Ravens I, Shibuya A, Förster R, Bernhardt G. CD155/CD226-interaction impacts on the generation of innate CD8(+) thymocytes by regulating iNKT-cell differentiation. *Eur J Immunol.* 2016;46(4):993-1003.
56. Wu L, Mao L, Liu JF, et al. Blockade of TIGIT/CD155 signaling reverses T-cell exhaustion and enhances antitumor capability in head and neck squamous cell carcinoma. *Cancer Immunol Res.* 2019;7(10):1700-1713.