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A pan-cancer analysis of the oncogenic role of ATP binding cassette subfamily E member 1 (ABCE1) in human tumors

An observational study

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Abstract

ATP-binding-cassette subfamily E member 1 (ABCE1) has been identified as an essential component of RNA translation and cell proliferation. However, studies on its role in pan-cancer are limited. Here, we aimed to characterize ABCE1 expression and its potential biological functions in cancer. ABCE1 expression was analyzed using RNA-seq data from The Cancer Genome Atlas (TCGA), the Genotype-Tissue Expression (GTEx) database, and the Clinical Proteomic Tumor Analysis Consortium database. The prognostic value of ABCE1 was analyzed using clinical survival data from TCGA. We downloaded the immune cell infiltration score of TCGA samples from published articles and online databases and performed a correlation analysis between immune cell infiltration levels, chemokines/chemokine receptors, and ABCE1 expression. We further assessed the association between ABCE1-correlated genes and their functions in pancreatic adenocarcinoma (PAAD). In general, ABCE1 gene expression was upregulated in most tumors. There were significant strong correlations between ABCE1 expression and tumor-infiltrating cells in cancers. Furthermore, RNA transport and ribosome biogenesis were significantly related to ABCE1 expression in PAAD. Our study revealed that ABCE1 may serve as a potential prognostic and immunological pan-cancer biomarker. Moreover, ABCE1 may be used in the development of a novel target for PAAD.

Abbreviations: ABCE1 = ATP-binding cassette subfamily E member 1, CESC = carcinoma and endocervical adenocarcinoma, COAD = colon adenocarcinoma, DC = dendritic cell, DEG = differentially expressed gene, DSS = disease-specific survival, GTEx = Genotype-Tissue Expression database, HNSC = head and neck squamous cell carcinoma, KEGG = Kyoto encyclopedia of genes and genomes, HR = hazard ratio, LGG = lower grade glioma, LIHC = liver hepatocellular carcinoma, LUAD = lung adenocarcinoma, NK = naïve killer, OS = overall survival, PAAD = pancreatic adenocarcinoma, PAAD = pancreatic adenocarcinoma, PFI = progression-free interval, ROC = receiver operating characteristic, TCGA = The Cancer Genome Atlas, TILs = tumor-infiltrating cells, TME = tumor microenvironment.

Keywords: ABCE1, biomarker, PAAD, pan cancer, prognosis

1. Introduction

In the central dogma proposed by Francis Crick, the translation is a vital step that describes how the genetic code is converted into amino acids. This cyclical process consists of initiation, elongation, termination, and ribosome recycling stages.[1] Ribosome recycling is an integral step of mRNA translation and surveillance at the core of ribosome-based quality control, protein homeostasis, and ribosome-related diseases.[2–4]

The ATP-binding cassette (ABC) protein ABCE1 facilitates ribosome recycling by splitting archaeal and eukaryotic ribosomes into large and small subunits.[5,6] ABCE1 contains 2 ABC transporter domains and 2 4Fe-4S ferredoxin-type domains, which are extremely sensitive to the redox environment. ABCE1 has been linked to diverse functions: innate immunity, HIV capsid assembly, tissue homeostasis, and ribosome biogenesis.[7–11] Several results demonstrated the role of ABCE1 in tumors. In lung squamous cell carcinoma, the tissue level of ABCE1 was positively correlated with lncRNA FAM201A, which induces

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Our study is based on open source data, so the authors declare that there are no ethical issues and other competing interests.

The datasets generated and analyzed during this study are available in the public databases TCGA and GTEx. Additional data related to this paper may be requested from the corresponding author.

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tumor cell migration and invasion.[12] In lung adenocarcinoma (LUAD), ABCE1 promoted A549 cell growth and was correlated with clinical stage.[13] In addition, ABCE1-mediated translation constitutes a critical process in the progression of N-MYC-driven and c-MYC-driven cancers.[14] However, the prognostic value of ABCE1 in cancer has seldomly been analyzed and compared systematically.

In this study, using the Cancer Genome Atlas (TCGA) datasets and Genotype-Tissue Expression (GTEx) databases, we evaluated the expression of ABCE1 and its association with the prognosis of patients with cancer. We further examined the association between ABCE1 gene expression with the immune cell infiltration, correlated chemokines, and chemokine receptors in pan-cancer. Further, we analyzed the ABCE1 coexpressed gene functions in pancreatic adenocarcinoma (PAAD). Our results provide novel insights into the functional role of ABCE1 in pan-cancer, offering a potential antitumor strategy.

2. Material and methods

2.1. Data processing and expression analysis

To obtain standardized clinical data of cancer patients, as well as a large sample size for each cancer type, we chose TCGA database (http://cancergenome.nih.gov/abouttcga). The GTEx database was used to evaluate tissue-specific gene expression and regulation in normal tissue samples.

Although all cancers are molecularly distinct, many share common driver mutations. Pan-cancer analysis involves assessing frequently mutated genes and other genomic abnormalities common to many different cancers, regardless of tumor origin. The mRNA expression data of ABCE1 in multiple cancers was downloaded from the TCGA pan-cancer dataset, and patients' clinical data in the specific tumor was downloaded from the respective dataset. For protein expression levels between normal and tumor tissues, the Clinical Proteomic Tumor Analysis Consortium (CPTAC) datasets were used. For RNA-seq data, expression levels were transcripts per million normalized. Expression data for all chemokines were Log2 transformed. The gene expression data in TCGA might not be normally distributed. So the nonparametric Wilcoxon rank-sum test that compares 2 paired groups was conducted on these tumor types to calculate the gene expression differences and analyze these differences to establish if they are statistically significantly different from one another. R 3.6.3 was used to integrate the original data and verify the results analyzed by the website database. All applied online web tools were introduced below.

2.2. Survival analysis

Overall survival (OS) is a common clinical indicator in prognoses prediction. The relationship between ABCE1 gene expression and patients' OS interval in 21 cancers was visualized with a heatmap, and the hazard ratios (HRs) of ABCE1 in patients' disease-specific survival (DSS) and progression-free interval (PFI) were visualized with forest plots. The HR with corresponding 95% confidence intervals and log-rank P-values were calculated via univariate survival analysis. The Kaplan–Meier survival analysis was conducted via R packages "survminer" and "survival."

The time ROC analysis was performed by R packages "timeROC" and "ggplot2" to compare the predictive accuracy of gene and risk scores. The area under the receiver operating characteristic curves (AUC) ranging from 0 to 1, indicates the significance of ABCE1 expression in differentiating cancer tissues from normal tissues.

2.3. Immune cell infiltration

The immune correlates between ABCE1 expression in cancers and immune system was elucidated using TISIDB (http://cis.hku.hk/TISIDB/) tool. The immune cell infiltration scores were downloaded from TCGA. Patients were divided into 2 groups for each tumor based on the median ABCE1 expression level (high and low ABCE1 expression) to compare the extent of immune. The correlation of ABCE1 with levels of immune cell infiltration, including dendritic cells (DCs), B cells, macrophages, naïve killer (NK) cells and T cells, was detected in 7 cancers using the R package "GSVA" and assessed by Spearman correlation analysis.

2.4. Gene set enrichment analyses

To better understand the carcinogenesis of ABCE1, correlation analyses of ABCE1 with all genes were performed using TCGA data. Pearson's correlation coefficients were calculated. Genes correlated with ABCE1 ($P < .05$) were selected for gene set enrichment analysis. "ClusterProfiler" package was employed to conduct Gene Ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) analysis. In the differentially expressed gene (DEG) screen, $ABCE1^{high}$ group and $ABCE1^{low}$ group were compared with the criteria set of $|\log_2 FC| > 1$, adjusted $P < .05$. In the enrichment results, adjusted $P < .05$ is considered to be significantly enriched.

2.5. Statistical analyses

All the data are normalized by log2 transformation and presented as means ± standard error (SD). Comparisons of normal tissue and cancer tissue were used with the Wilcoxon rank-sum test. The Student's *t* test was adopted to compare the different expression levels of ABCE1 in tumor tissues and normal tissues. R 3.6.2. *P* value < 0.05 was set as the significance threshold for all statistical analyses.

2.6. Ethical statement

All the data used in this study was open-access data from online databases, so the ethical approval was not necessary in our research.

3. Results

3.1. ABCE1 expression data in pan-cancer tissues

To compare the expression of ABCE1 in human cancers, we used the GTEx and TCGA databases to analyze the mRNA levels in normal and tumor tissues. Analysis of ABCE1 gene expression revealed up-regulation of this gene in tumor tissues from bladder urothelial carcinoma ($n = 433$), breast invasive carcinoma ($n = 1222$), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC, $n = 309$), cholangiocarcinoma ($n = 45$), colon adenocarcinoma (COAD, n = 521), lymphoid neoplasm diffuse large B-cell lymphoma ($n = 48$), esophageal carcinoma ($n = 173$), glioblastoma multiforme ($n = 174$), head and neck squamous cell carcinoma (HNSC, $n = 546$), kidney renal clear cell carcinoma ($n = 611$), brain lower grade glioma (LGG, $n = 529$), liver hepatocellular carcinoma (LIHC, n = 424), lung adenocarcinoma (LUAD, n = 594), lung squamous cell carcinoma ($n = 551$), pancreatic adenocarcinoma (PAAD, $n = 182$), prostate adenocarcinoma ($n = 551$), skin cutaneous melanoma ($n = 472$), stomach adenocarcinoma ($n = 407$), testicular germ cell tumors ($n = 156$) and thymoma ($n = 121$) (Fig. 1A). For paired tumors in the TCGA dataset, ABCE1 mRNA level was upregulated in bladder urothelial carcinoma, breast invasive carcinoma, cholangiocarcinoma, esophageal carcinoma, HNSC, kidney renal clear cell carcinoma, LIHC, LUAD, lung squamous cell carcinoma, prostate adenocarcinoma, and stomach adenocarcinoma, relative to adjacent normal tissues (Fig. 1B).

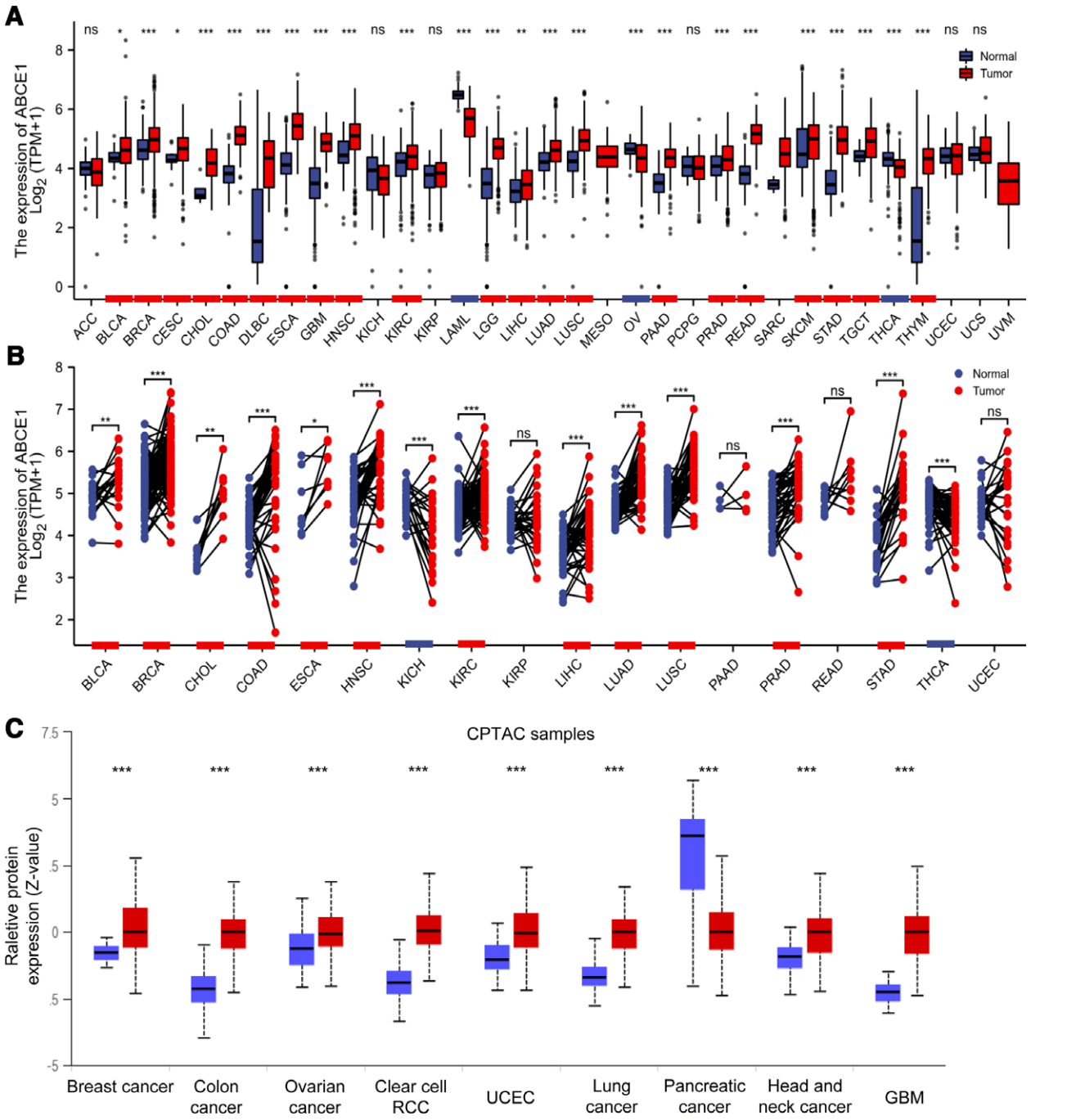

Figure 1. Expression of ABCE1 gene in different tumors and grades. (A) Gene expression status of ABCE1 in the unpaired normal and tumor tissues based on GTEx and TCGA databases. (B) The expression profiles of ABCE1 gene in paired tumor and normal tissues across different cancers from a TCGA dataset. (C) The protein expression level of ABCE1 protein between normal tissue and primary tissue based on the CPTAC dataset. Clear cell RCC, clear cell renal cell carcinoma. *** $P < .001$.

However, its expression was downregulated in kidney chromophobe ($n = 89$) and thyroid carcinoma ($n = 568$), relative to adjacent normal tissues (Fig. 1B). Results of the CPTAC dataset revealed that ABCE1 protein expressed at higher levels in most primary tissues, while it was down-regulated in pancreatic cancer (Fig. 1C). These findings suggested that ABCE1 was upregulated in most cancers in both mRNA and protein levels.

3.2. Impact of ABCE1 on pan-cancer prognosis

To investigate the association of ABCE1 expression with the prognosis of cancers, we further used Cox proportional hazards model to evaluate the relationship of ABCE1 level with the OS of patients in TCGA database. Results of Kaplan–Meier OS analysis revealed that high ABCE1 level was significantly linked to worse OS in patients with CESC, HNSC, LGG, LIHC, LUAD, and PAAD (HR = 1.80, $P = .007$) (Fig. 2). While low ABCE1 levels correlated to worse OS in COAD patients (Fig. 2). Moreover, The DSS) and PFI analysis confirmed that ABCE1 acts as a protective factor for patients with COAD, and a risk factor for patients with CESC, LUAD and PAAD (Fig. 3A). Specifically, these analysis demonstrated that ABCE1 held the highest risk score in PAAD patients. We further evaluated the expression of ABCE1 in different tumor stages, in which ABCE1

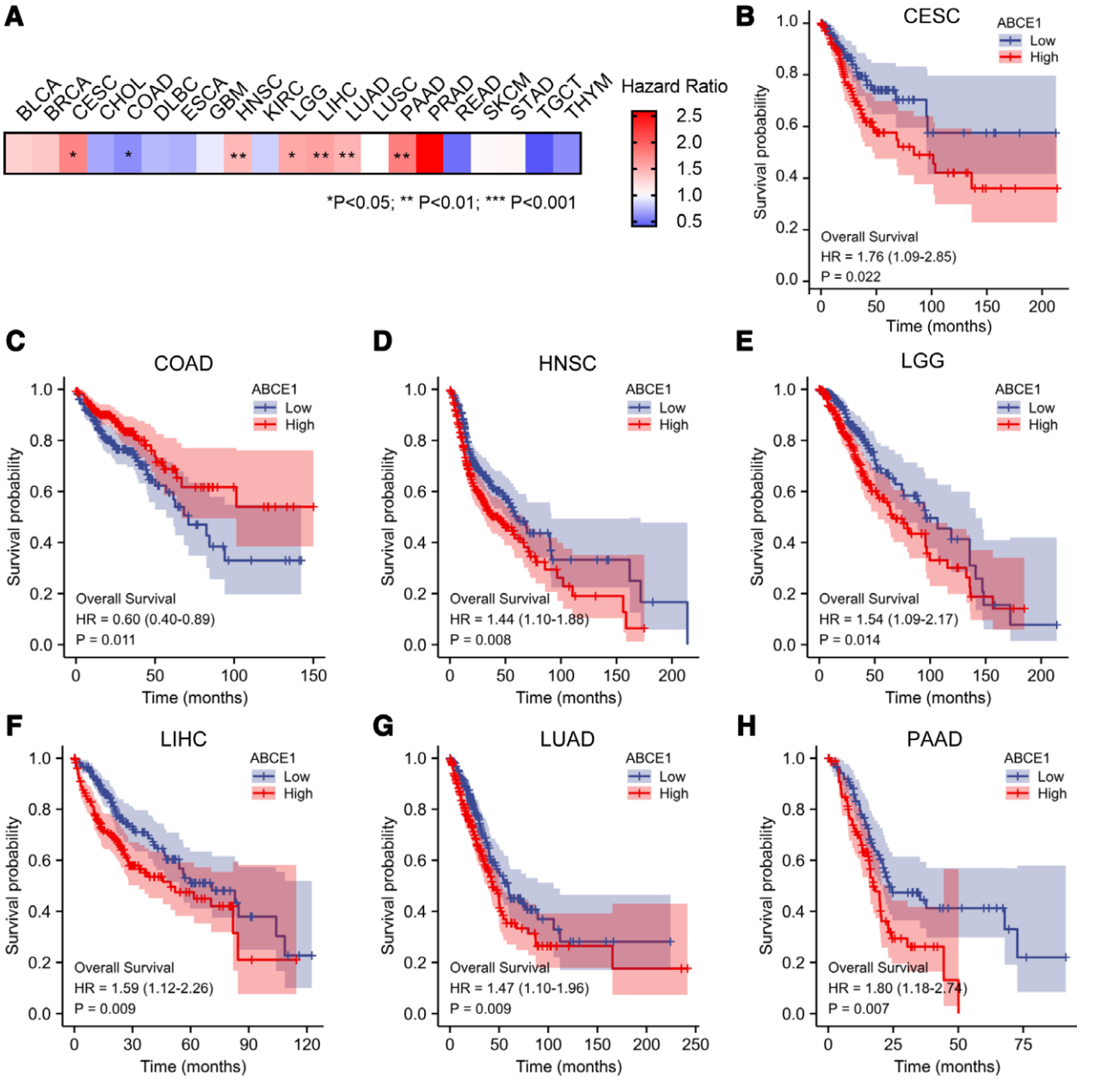

Figure 2. Relationship between ABCE1 level and overall survival (OS). (A) Heatmap showing Hazard ratio of ABCE1 in OS after Cox analysis. (B–H) Kaplan–Meier curves showing OS in CESC, COAD, HNSC, LGG, LIHC, LUAD, and PAAD. Only significant results were shown. COAD = colon adenocarcinoma, HNSC = head and neck squamous cell carcinoma, LGG = lower grade glioma, LIHC = liver hepatocellular carcinoma, LUAD = lung adenocarcinoma, PAAD = pancreatic adenocarcinoma.

expression level was not significantly changed in CESC, COAD, and PAAD (Figs. 3B, C, and H). However, ABCE1 was up-regulated in higher grades/stages in HNSC, LGG, LIHC, and LUAD than that in lower grades/stages (Fig. 3D–G).

To evaluate the predictive prognosis value of ABCE1 gene expression levels for cancers, we performed the receiver operating characteristic (ROC) curve analysis using the TCGA dataset. The AUC was adopted to evaluate the prediction accuracy of ABCE1 for cancers. For COAD, HNSC, LGG, LIHC, LUAD, and PAAD, ABCE1 had good prediction abilities as the areas under the curves were all larger than 0.5 (Fig. 4). However, for CESC (Figure S1A, Supplemental Digital Content, http://links.lww.com/MD/H956), the prognostic prediction ability of ABCE1 was poor. Time-dependent ROC indicated that ABCE1 performed the best predictive effect on the risk of PAAD patients, especially at the 3-year stage (1 year, AUC = 0.606; 2 years, AUC = 0.617; 3 years, AUC = 0.659) (Figure S1B–H, Supplemental Digital Content, http://links.lww.com/MD/H956)). These results indicated the appreciable reliability of ABCE1 as a biomarker for COAD, HNSC, LGG, LIHC, LUAD, and PAAD prognosis, and PAAD had the best accuracy among these cancers.

3.3. Correlation between ABCE1 expression and immune characteristics

To explore the relationship between ABCE1 and tumor-Infiltrating lymphocytes (TILs), we conducted the landscape heatmap using the TISIDB database. The pan-cancer dataset in TISIDB includes 30 cancers. The correlation between ABCE1 expression and immune system was analyzed in pan-cancer dataset (Fig. 5A) and individual cancer dataset (Figures 5 and 6), respectively. As shown in Fig. 5A, the relations between ABCE1 expression and

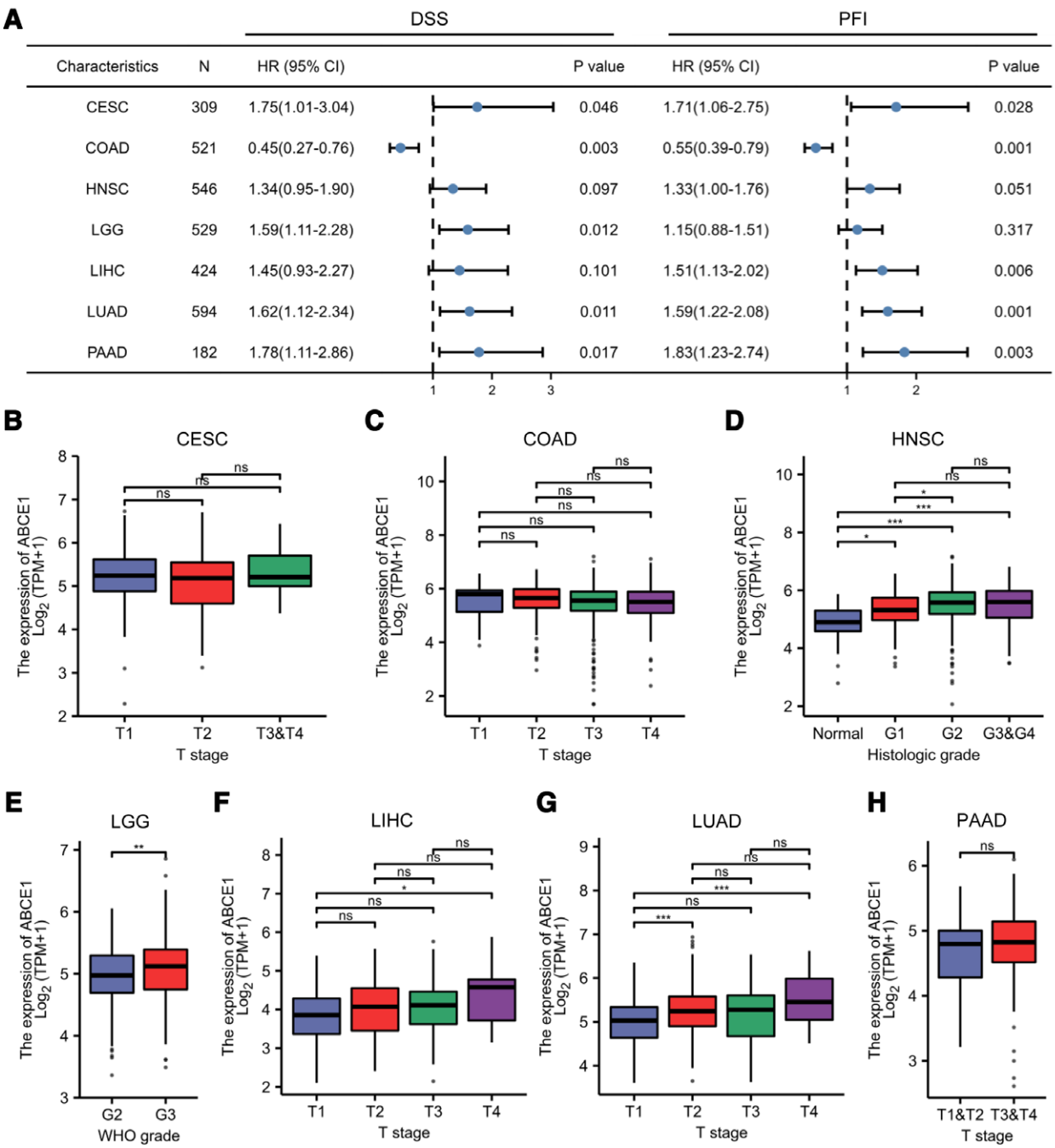

Figure 3. Prognostic value of ABCE1 based TCGA dataset. (A) Forest plots showing survival Univariate Cox Regression analysis of the risk factor for cancer patients in both DSS and PFI. (B-H) Associations of BCAT1 expression and patients' clinical stage in CESC (B), COAD (C), HNSC (D), LGG (E), LIHC (F), LUAD (G), and PAAD (H). *P* value was based on the Wilcoxon test. COAD = colon adenocarcinoma, HNSC = head and neck squamous cell carcinoma, LGG = lower grade glioma, LIHC = liver hepatocellular carcinoma, LUAD = lung adenocarcinoma, PAAD = pancreatic adenocarcinoma.

abundance of 28 TILs in pan-cancer were exhibited. Due to the potential prognostic value of ABCE1 in COAD, HNSC, LGG, LIHC, LUAD, and PAAD, the immune characteristics in these cancers were analyzed. In COAD, ABCE1 gene expression was negatively correlated with the infiltration of NK cells and DC, while appreciably positively correlated with that of Macrophages (Fig. 5B). In HNSC, ABCE1 gene expression was negatively correlated with the infiltration of DC, B cells, and T cells (Fig. 5C). In LGG, ABCE1 gene expression was negatively correlated with the infiltration of NK cells and Macrophages, while positively correlated with that of DC (Fig. 6A). In LIHC, ABCE1 gene expression was negatively correlated with the infiltration of DC, and positively correlated with that of macrophages (Fig. 6B). In LUAD, ABCE1 gene expression was negatively correlated with the infiltration of 4 TILs, including NK cells, DC, B cells, and T cells (Fig. 6C). In PAAD, ABCE1 gene expression was positively correlated with the infiltration of macrophages (Fig. 6D). Accordingly, these results strongly suggested that ABCE1 gene may play a crucial role in tumor immunity.

To further investigate the connection between ABCE1 gene expression and immune cell trafficking, we analyzed the correlations with chemokine receptors and chemokines using TISIB database (Figure S2–S5, Supplemental Digital Content, http://links.lww.com/MD/H957: http://links.lww.com/MD/H958: http://links.lww.com/MD/H959: http://links.lww.com/MD/H960). Specifically, the results showed that ABCE1 expression

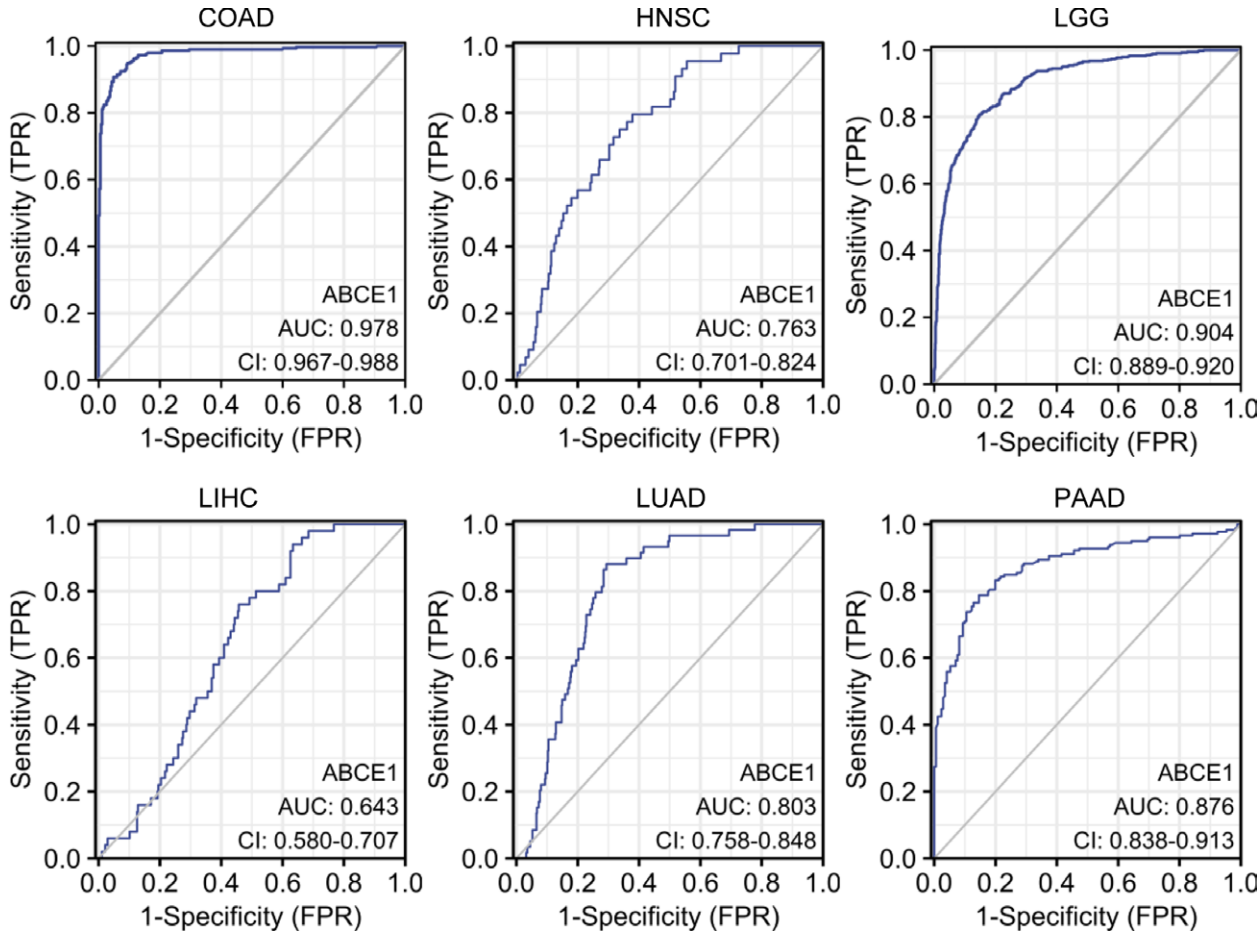

Figure 4. Receiver operating characteristic (ROC) curves for detecting the ability of ABCE1 gene expression in cancer diagnosis. AUC = area under the curves.

was negatively correlated with chemokine receptor CCR10 in most cancers (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/H957, Figure S3, http://links.lww.com/MD/H958). Moreover, the relations between ABCE1 expression and abundance of 41 chemokines in pan-cancer were exhibited. (Figure S4, Supplemental Digital Content, http://links.lww.com/MD/H959).

3.4. Function of ABCE1 coexpression networks in PAAD

The above results identified significant associations between ABCE1 expression and the prognosis of cancers. Since ABCE1 has the best prognosis prediction accuracy in PAAD (Figs. 2 and 3), we analyzed the DEG networks of ABCE1 in TCGA to investigate the biological function of ABCE1, and PAAD was chosen as an example to illustrate the potential effect. The top 50 genes positively correlated with ABCE1 in PAAD were displayed in a heat map (Fig. 7A). Next, we perform a series of enrichment analyses to determine the correlated gene ontology (GO) terms and KEGG pathways. Results of the biological process categories from GO analysis showed ABCE1 and its coexpression genes mainly linked to the catalytic activity acting on RNA, helicase activity, ribonucleoprotein complex binding, ribosome biogenesis, nuclear transport, nucleocytoplasmic transport, and rRNA metabolic process (Fig. 7B). KEGG pathway enrichment analysis revealed that upregulated DEGs were primarily involved in RNA transport, ubiquitin mediated proteolysis, spliceosome, and ribosome biogenesis in eukaryotes (Fig. 7C).

In terms of tumor microenvironment (TME), ABCE1 gene expression was positively correlated with the infiltration of T helper cells, Tcm, Th1 cells, Th2 cells, Neutrophils and Macrophages, while negatively correlated with pDC and NK CD56 bright cells (Fig. 7D). In addition, chemokines CCL3, CCL15, CCL17, CCL22, and CX3CL1, chemokine receptors CCR1, CCR8, CCR10, and CXCR1, were associated with ABCE1 gene expression (Figure S5, Supplemental Digital Content, http://links.lww.com/MD/H960). These results suggested that ABCE1 expression might play an essential role in PAAD by regulating ribosome biogenesis, RNA transport and the immune response of TME.

4. Discussion

Over the past few decades, despite huge improvements in cancer therapy combined surgery with novel targeted therapies, immunotherapeutic drugs, advanced chemotherapy, and radiotherapy, there is still limited success in cancer treatment.[15] Translational control is crucial to cancer development and progression, directing both global control of protein synthesis and selective translation of specific mRNAs that promote tumor cell survival, angiogenesis, transformation, invasion, and metastasis.[16] As first reported in glioblastoma multiforme, the existing mRNA translational control has more extensive influence than the transcription changes downstream of aberrant signaling pathways in cancer pathogenesis.[17,18] Therefore, members of the mRNA translation process might play essential roles in tumor prognosis.

As a member of the ATP-binding cassette transporter family, ABCE1 regulates varieties of biological processes including viral infection, cell proliferation, and antiapoptosis.[7,19,20] Previous research has reported that ABCE1 plays a vital role in lung cancer progression and metastasis.[20] In gastric cancer, patients with the lower ABCE1 expression had significantly

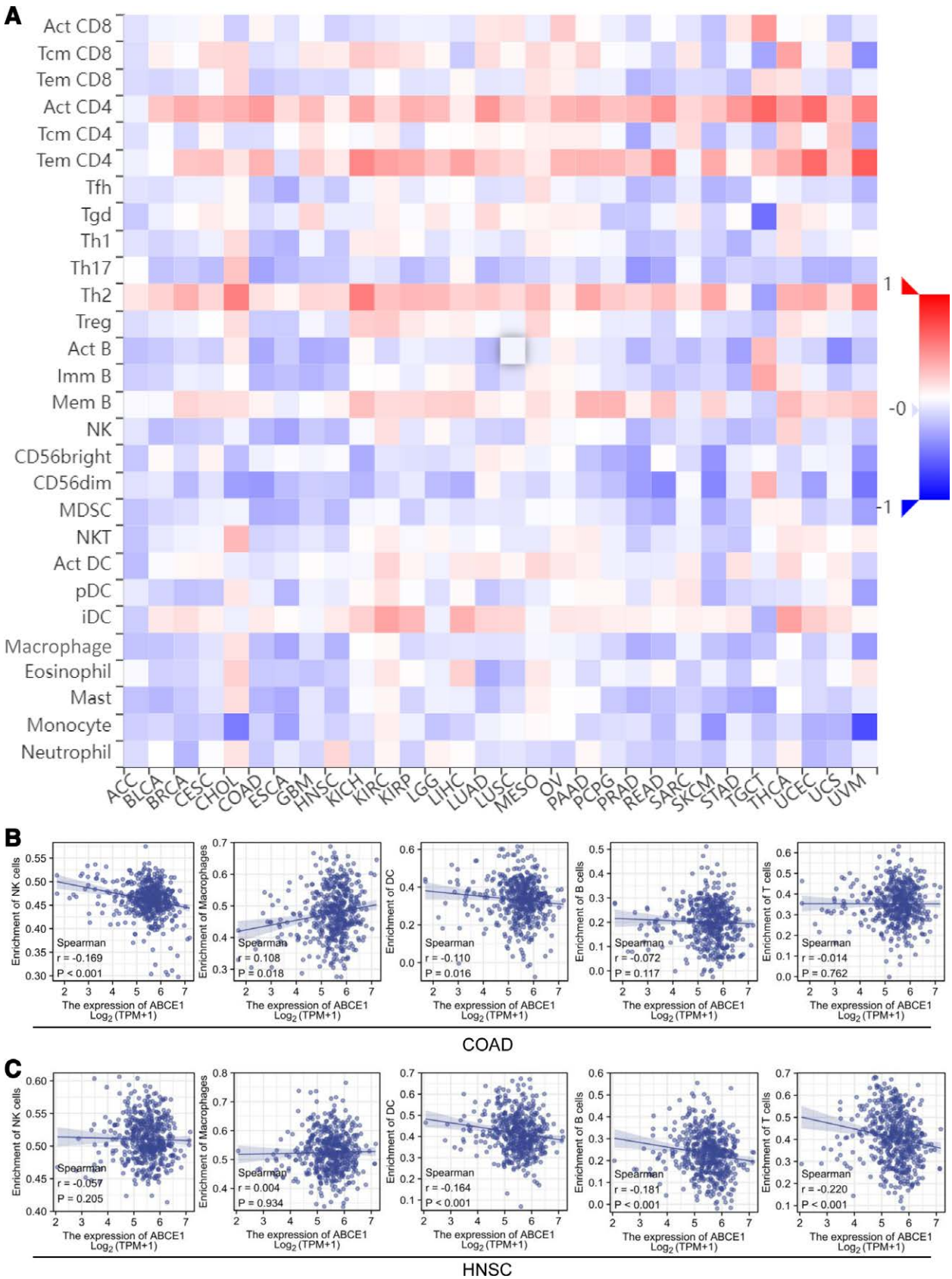

Figure 5. Correlation analysis of ABCE1 expression with immune infiltration cells. (A) The landscape of the relationship between ABCE1 and chemokine receptors in pan-cancers based on the TISIDB database (red means positive correlation and blue means negative correlation). (B, C) Correlation analysis of ABCE1 and infiltrating levels of NK, macrophages, DC, B cells and T cells in COAD (B) and HNSC (C). COAD = colon adenocarcinoma, HNSC = head and neck squamous cell carcinoma.

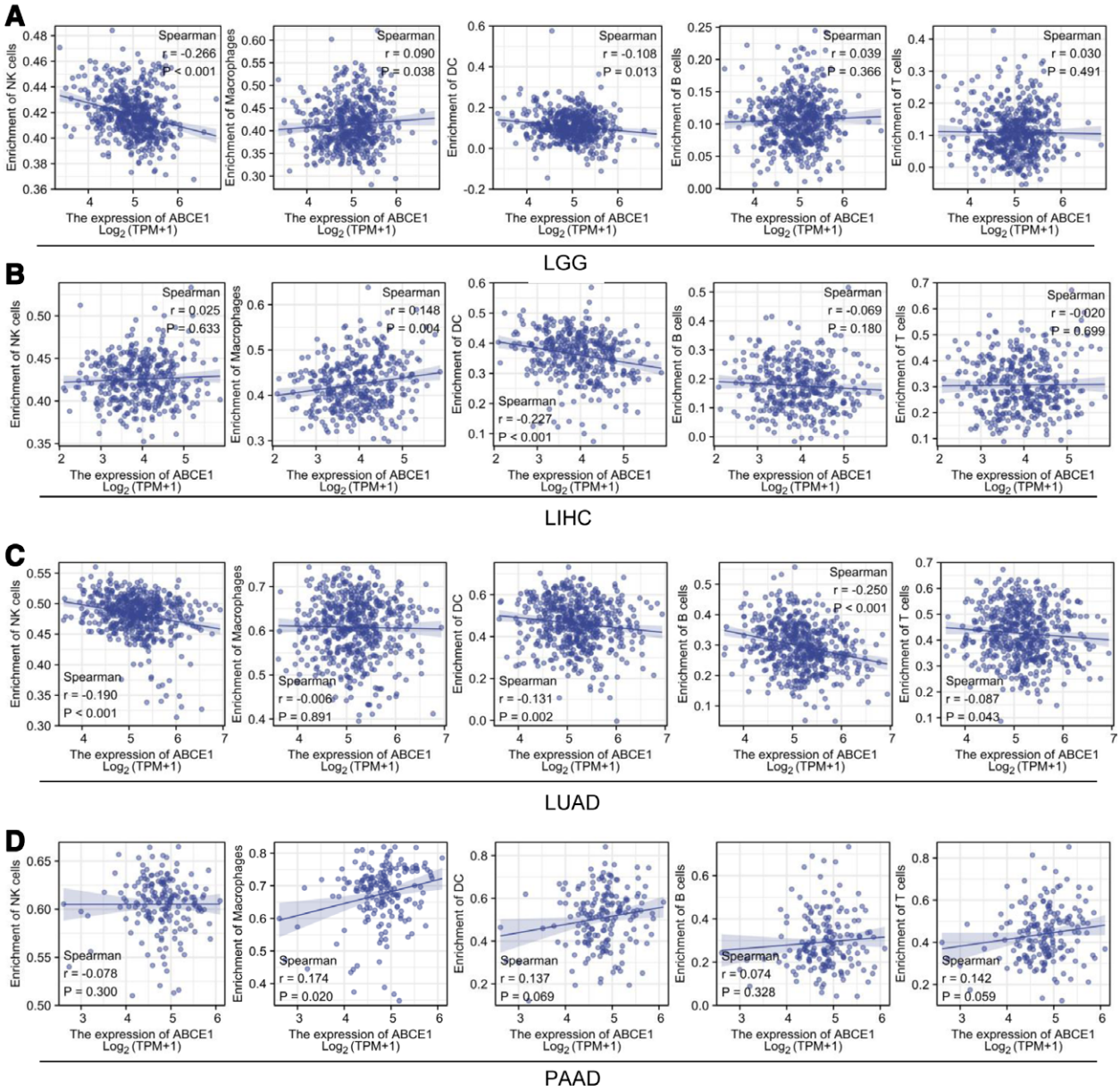

Figure 6. Relevance between ABCE1 expression with infiltration levels of 5 immune cells. (A–D) Correlations between ABCE1 expression with TILs in LGG (A), LIHC (B), LUAD (C), and PAAD (D). TIL = tumor-infiltrating cells, LGG = lower grade glioma, LIHC = liver hepatocellular carcinoma, LUAD = lung adenocarcinoma, PAAD = pancreatic adenocarcinoma.

better disease-free survival.[21] Suppression of ABCE1-mediated mRNA translation also limits neuroblastoma progression driven by the N-MYC transcription factor.[14] These studies indicated that ABCE1 might be a promising biomarker and antitumor target. However, no systematic studies on ABCE1 in pan-cancer have been reported.

Considering the limited researches had been performed regarding ABCE1 in cancer, we performed an integrated bioinformatics analysis using TCGA, GTEx, CPTAC, and TISIB databases. In the first step, we evaluated the expression and prognostic significance of ABCE1 in the TCGA pan-cancer database. Results showed that ABCE1 mRNA level was high in 20 tumors, but low in 3 tumors (Fig. 1A). The expression of ABCE1 in lung cancer has been found to tightly regulated by lncRNA FAM201A, transcription factor N-MYC and miR-299-3p.[12,14,22] In various cancers, metabolic profile changes dramatically, and the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway is highly responsive to these changes, promoting the translation of *MYC*.[23–26] Therefore, the different expression patterns of ABCE1 in cancers might be related with these upstream factors.

Next, the relationship between ABCE1 gene expression and tumor prognosis was explored. To screen the cancer in which ABCE1 is an independent prognosis factor, we conducted the univariate Cox regression analyses based on TCGA. Possible confounders are patient age and sex, which may influence the clinical outcome of cancers. However, the relationship between ABCE1 gene expression level with these confounders is unclear, so we focused on the role of ABCE1 in the screening process. In CESC, HNSC, LGG, LIHC, LUAD, and PAAD, high ABCE1 expression patients had a worse prognosis (Fig. 2). For DSS, univariate Cox regression analysis revealed that ABCE1 acts as a risk factor for patients with CESC, LGG, LUAD, and PAAD, and a protective factor for patients with COAD (Fig. 3A). Meanwhile, the PFI analysis showed that high ABCE1 mRNA levels indicated worse prognosis in CESC, LIHC, LUAD, PAAD,

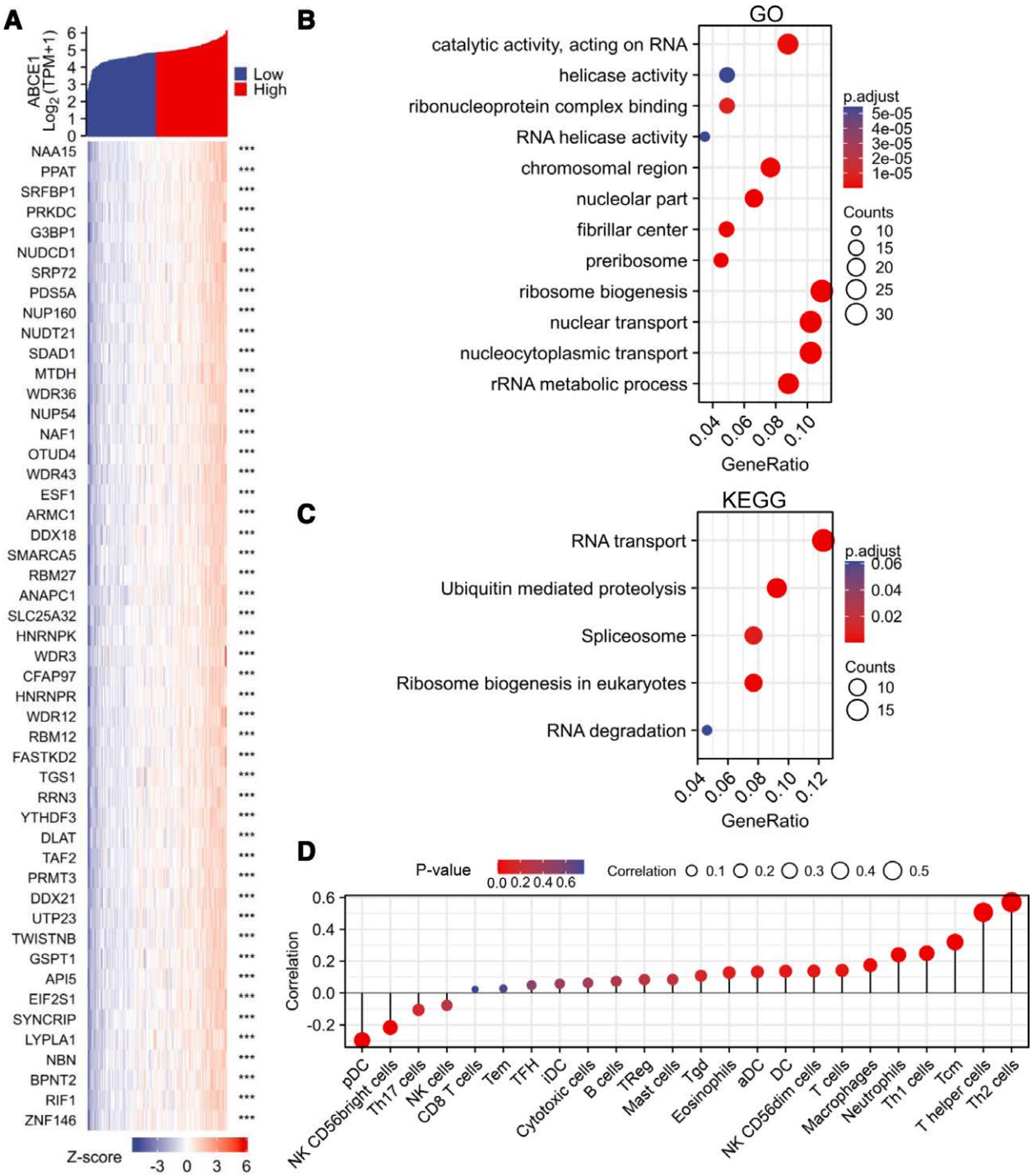

Figure 7. Enrichment analysis of ABCE1 expression-correlated DEmRNAs in PAAD. (A) Clustering analysis heatmap of DEmRNAs between the expression of ABCE1high and ABCE1low in TCGA-PAAD dataset. (B, C) GO enrichment (B) and KEGG enrichment (C) analysis of ABCE1 gene expression-correlated upregulated pathway. (D) Correlations between the infiltration of immune cells and the expression of ABCE1 in PAAD. aDC = activated DC; iDC = immature DC; pDC = plasmacytoid DC; Tcm = T central memory; Tem = T effector memory; Tfh = T follicular helper; Tgd = T gamma delta. PAAD = pancreatic adenocarcinoma.

and better prognosis in COAD (Fig. 3A). Simultaneously, ROC curves confirmed that ABCE1 can be a prognostic biomarker (Fig. 4). As an important negative regulator of 2-5A/RNase L pathway, ABCE1 regulates RNA stability, so it might be involved in tumor cell proliferation.[27] Recent evidence has shown that the ectopic expression of ABCE1 promoted the viability and invasive capacity of lung cancer cells.[28] Therefore, the reason why ABCE1 affects patients' survival differently might be its different expression levels among cancers. What's more, ABCE1 correlates with different immune cells in each tumor (Figs. 5 and 6), which may contribute to its different roles among these cancers. These results indicated that ABCE1 mainly promotes oncogenesis and tumor progression in most human cancers.

Chemokines control the migration and positioning of immune cells in tissues through their interaction with chemokine receptors.[29] This process is critical for different immune cell subsets recruitment and the antitumor function of immune system.[30] Our results demonstrated that ABCE1 expression was correlated with tumor-infiltrating immune cells according to the TISIDB database.

Moreover, high ABCE1 gene expression was significantly correlated with less CCR10 expression in pan-cancer (Figure S3, Supplemental Digital Content, http://links.lww.com/MD/H958). CCR10 is mainly expressed by T_{reg} cells, and responses to CCL28, which promotes T_{reg} cell's migration to certain tumor microenvironments.[31,32] These results demonstrated that ABCE1 had a strong association with TILs and was essential in the TME.

Considering the prognosis prediction accuracy of ABCE1, we analyzed the ABCE1 coexpression gene function in PAAD. Pancreatic cancer, including PAAD, is one of the most lethal human malignant tumors with a devastating prognosis,[33] which makes novel biomarker detection urgent. In this research, elevated ABCE1 mRNA level PAAD was detected. However, at the protein level, ABCE1 was down-regulated in pancreatic cancer, according to the CPTAC database (Fig. 1C). This might be due to the translation regulation or post-translation modification. Higher ABCE1 gene expression correlated with worse prognosis in OS, DSS, and PFI (Figs. 2 and 3), suggesting that the trend of ABCE1 mRNA level in PAAD was consistent with the majority of tumors. Coexpression gene function enrichment showed that ABCE1 mainly participate in processes of RNA catalytic activity, helicase activity, ribonucleoprotein complex binding, ribosome biogenesis, nuclear transport, nucleocytoplasmic transport, rRNA metabolic process, RNA transport, ubiquitin-mediated proteolysis, spliceosome, and ribosome biogenesis in eukaryotes (Fig. 7), similar to previous studies.

The significant advantage of our research is the comprehensive analysis which revealed that ABCE1 was an independent prognostic factor for CESC, LGG, LUAD, PAAD, and COAD. We demonstrates a high gene expression of ABCE1 in most cancer for the first time, which improves the understanding of the pathogenesis of ABCE1 in human cancer. Comprehensive assessment of ABCE1 in TME revealed its potential role as a prognosis biomarker and its immunoregulation effect. We also found the relationship between high expression of ABCE1 and poor OS in PAAD might associated with ribosome biogenesis. However, we did not verify the prognostic ability of ABCE1 in protein expression level; therefore, the predictive value of ABCE1 in clinical tumor sections needs to be verified by other researches. This study serves as a cornerstone to further reveal the biochemistry mechanisms involving ABCE1 in development of various tumors. As an alternative therapeutic approach, targeting ABCE1 may shed new light for tumor immune therapy.

Author contribution

J.Y. and H.M. conceived and designed the study. J.Y., H.M., J.H., M.W., B.Y., S.G., and Z.D. processed the data. J.Y. analyzed the data and wrote the manuscript. All authors discussed the results and commented on the manuscript.

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Validation: Ji He, Min Wang, Bo Yu, Shaonan Ge, Zhibo Dai.
Writing—original draft: Jihong Yu.
Writing—review and editing: Jihong Yu.

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