



Comprehensive pan-cancer analysis: essential role of ABCB family genes in cancer

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Background: The adenosine triphosphate-binding-cassette (ABC) transporter orchestrates the transmembrane transport of diverse substrates with the aid of ATP as an energy source. ABC transporter constitutes a widespread superfamily of transporters prominently present on the cellular membrane of organisms. Advancements in understanding have unveiled additional roles beyond mere intracellular or extracellular transport functions for the ABC protein family, encompassing involvement in DNA repair, protein translation, and gene expression regulation. Yet its role in tumors is still unknown.

Methods: This study drew support from multiple databases, including Gene Expression Omnibus (GEO), European Genome-phenome Archive (EGA), The Cancer Genome Atlas (TCGA), and employed multidimensional bioinformatics analyses, incorporating online databases and the R-project. Through a comprehensive analysis, we seek to discern transcriptional-level disparities among genes and their consequential impacts on prognosis, tumor microenvironment (TME), stemness score, immune subtypes, clinical characteristics, and drug sensitivity across human cancers.

Results: ABC transporter subfamily B (ABCB) family genes exhibited heightened expression across diverse tumors, demonstrating a significant correlation with overall prognosis in pan-cancer contexts. Notably, gene expression levels manifested substantial associations with TME, stemness score, immune subtypes, clinical characteristics, and drug sensitivity in specific cancers, including kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), and pancreatic adenocarcinoma (PAAD). Within this subset, transporter associated with antigen processing 1 (*TAP1*), *TAP2*, and *ABCB6* emerged as noteworthy oncogenes.

Conclusions: The outcomes of this study contribute to a comprehensive understanding of the implications of ABCB family genes in tumor progression, offering insights into potential therapeutic targets for cancer. Notably, the identification of *ABCB6* as a significant oncogene suggests promising avenues for targeted therapies in KIRP, LIHC, and PAAD.

Keywords: ATP-binding-cassette transporter (ABC transporter); pan-cancer; prognosis; tumor microenvironment (TME); drug sensitivity

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Introduction

The global incidence and mortality rates of cancer have experienced a notable escalation (1). Presently, cancer has surpassed infectious diseases, emerging as a preeminent threat to human health, a trend accentuated by advancements in socioeconomic conditions (2). According to World Health Organization (WHO) estimates, cancer ranks among the top two leading causes of death in 112 countries worldwide (1). The underlying causative factors are multifaceted, encompassing rapid population growth, demographic aging, and shifts in lifestyle patterns (3,4). In the pathogenesis of cancer, which involves genetic and environmental determinants, investigations into environmental factors have exhibited considerable advancement, leading to the identification of various carcinogens (5). Nevertheless, a consensus prevails that

individual genetic factors play a more pivotal role in the pathogenesis of cancer (6). Indeed, the accrual of genetic alterations *in vivo* constitutes the foundational basis for the occurrence of cancer (7).

The evolution of cancer treatment spans several centuries, witnessing advancements; however, contemporary first-line modalities still predominantly encompass surgery, radiotherapy, and chemotherapy. In recent years, the rapid strides in molecular biology and immunology have engendered transformative breakthroughs, notably in the realms of targeted therapies and immune checkpoint inhibitors. This progress signifies a paradigm shift in cancer treatment from nonselective agents to precise targeted medicine (8-10). Exemplifying this shift, inhibitors targeting epidermal growth factor receptor mutations, such as afatinib and erlotinib, have demonstrated efficacy in decelerating the progression of non-small cell lung cancer, ovarian epithelial cancer and osteosarcoma (11-14). Currently, a limited subset of targeted therapies tailored for specific tumor types has garnered success. Consequently, the crux of targeted therapy lies in the identification of pertinent target genes, enabling the precise modulation of tumor cells while preserving normal cell integrity (9,15,16).

The ATP-binding cassette (ABC) transporter constitutes a widespread superfamily of transporters prominently present on the cellular membrane of organisms. Functioning with the aid of ATP as an energy source, this protein orchestrates the transmembrane transport of diverse substrates (17). Virtually all molecules endowed with physiological functions serve as transport substrates for ABC proteins (18-20). Traditionally associated with drug resistance in extant literature, ABC transporters have been recognized for their role in mediating the efflux of chemotherapeutic drugs (21,22). Advancements in understanding have unveiled additional roles beyond mere intracellular or extracellular transport functions for the ABC protein family, encompassing involvement in DNA repair, protein translation, and gene expression regulation. Yet its role in tumors is still unknown. Through our research, we found that the level of *TAP1*, *TAP2* and *ABCB6* gene expression was significantly correlated with tumor microenvironment, immune subtypes and clinical characteristics in KIRP, LIHC and PAAD. The structural attributes and specific functionalities of these transporters underscore their relevance to a spectrum of physiological processes, including antigen presentation, lipid transport, nutrient uptake, and stem cell formation (18,20). Consequently, the implication arises that ABC transporters are intricately linked to various human diseases (23).

Of particular interest is the ABC transporter subfamily B

Highlight box

Key findings

- Certain oncogenes may elude detection through singular omics analysis methodologies. Nevertheless, through the integration of multiple databases, we have successfully identified several oncogenes within the ABC transporter subfamily B (ABCB) family gene. The upregulation of ABCB family genes serves as a notable indicator of an unfavorable prognosis in various cancers, with particular emphasis on *ABCB6* in kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), and pancreatic adenocarcinoma (PAAD).

What is known and what is new?

- The ATP-binding cassette (ABC) transporter constitutes a widespread superfamily of transporters prominently present on the cellular membrane of organisms. Functioning with the aid of ATP as an energy source, this protein orchestrates the transmembrane transport of diverse substrates. Advancements in understanding have unveiled additional roles beyond mere intracellular or extracellular transport functions for the ABC protein family, encompassing involvement in DNA repair, protein translation, and gene expression regulation. Yet its role in tumors is still unknown.
- Through our research, we found that the level of *TAP1*, *TAP2* and *ABCB6* gene expression was significantly correlated with tumor microenvironment, immune subtypes and clinical characteristics in KIRP, LIHC and PAAD.

What is the implication, and what should change now?

- ABCB family genes exhibit elevated expression levels and a notable association with the prognosis across various cancers. The results enhance our comprehension of the critical function that genes of the ABCB family serve in tumor development and provide important perspectives for pinpointing prospective therapeutic targets within cancer research.

(ABCB) family, predominantly implicated in drug resistance, as well as processes involving polypeptide, phospholipid, iron, and cholate transport. This family exhibits heightened expression in tissues such as the liver, small intestine, ovary, and testis, with 11 discernible subtypes, *ABCB1–ABCB11*. Research has established correlations between certain members of the ABCB family—such as transporter associated with antigen processing 1 (*TAP1*, also named *ABCB2*), *TAP2* (also named *ABCB3*), associated with immunodeficiency disease, *ABCB4* linked to progressive familial intrahepatic cholestasis and *ABCB6* associated with hepatocellular carcinoma (25-27). Notably, these diseases demonstrate close associations with the initiation and progression of various neoplastic conditions within the body. Current investigations further indicate that mutations in ABCB genes are closely tied to colorectal tumors, melanoma, hematological tumors, and similar afflictions (28-30). However, the precise and nuanced role of the ABCB family genes in diverse pathological conditions remains unclear, necessitating further exploration.

Our investigation involved a comprehensive analysis of the prognostic significance of the ABCB family gene across a spectrum of cancers, utilizing multiple databases including The Cancer Genome Atlas (TCGA), Kaplan-Meier Plotter, and Gene Expression Profiling Interactive Analysis (GEPIA). Additionally, we conducted an in-depth assessment of the associations between the expression levels of the ABCB gene family and various aspects of the tumor microenvironment (TME), stemness score, immune subtypes, clinical characteristics, and drug sensitivity. Noteworthy emphasis was placed on specific cancer types, namely, kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), and pancreatic adenocarcinoma (PAAD). Cancer abbreviations are summarized in [Table S1](#).

Methods

Analysis of differential ABCB family expression genes in pan-cancer

In our investigation, we accessed original data encompassing gene expressions, clinical characteristics, immune subtypes, survival data and stemness scores for 33 types of human cancer from UCSC Xena (<https://xena.ucsc.edu/>). ID (identification for genes) transitions were facilitated using R-package “BioMart”. Through reading and integrating with R software, the expression levels of ABCB family genes

in pan-cancer are extracted (FPKM value). Wilcoxon Test is used to detect expression differences between ABCB family genes in cancers, with significance denoted by “*”, “**” and “***” indicating P values of <0.05, <0.01, and <0.001, respectively. Visualization tools such as “ggpubr”, “pheatmap”, and “corrplot” were utilized to generate box plots, heatmaps, and correlation plots, respectively. Regarding the definition of expression level: the gene expression level (FPKM value) after unified processing and normalization is a continuous variable. It is arranged from low to high, and the median value is used as the cutoff point. Below this value is defined as low expression, otherwise, it is defined as high expression. In the heatmap, we use color to distinguish low and high expression groups, with red representing the high expression group and green representing the low expression group, while the cutoff value is black. At the same time, the depth of the color represents the degree of high or low expression. The correlations within ABCB genes were characterized by Spearman analysis. When the absolute value of the Spearman correlation coefficient between genes exceeds 0.3, the pair of genes is generally considered to be related. The R package “corrplot” completes the visualization of correlation analysis. The correlation coefficient’s value is indicated by the circle’s size, while the colors signify whether the correlation is positive or negative.

Subsequently, based on the extraction of ABCB family gene expression in the previous step, the tissues were divided into tumor groups and normal tissue groups according to their source, and then the gene expression differences and statistical significance were calculated through statistical analysis. Specifically, R-package “limma” with built-in relevant statistical algorithms and functions was employed to execute the differential analysis between tumor and normal tissue.

Correlation between pan-cancer survival and ABCB family gene expression

For the examination of the correlation between pan-cancer survival data and ABCB family gene expression, overall survival (OS) data from TCGA databases were extracted for comprehensive analysis. The Kaplan-Meier method and log-rank test were applied to assess OS. Patients were categorized into low and high expression groups based on the median expression level. The R-packages “survminer” and “survival” to conduct Kaplan-Meier analysis were employed to delineate survival curve which link the different

expression groups with clinical outcome. R packages “forest plot” were employed to visualize survival analysis outcome and construct Cox model and forest plots. Additionally, online databases (Kaplan-Meier Plotter, GEPIA) were utilized to further verify the relationship between gene expression and OS across pan-cancers. The analysis covered diverse original data sources, including Gene Expression Omnibus (GEO, <https://www.ncbi.nlm.nih.gov/geo/>), European Genome-phenome Archive (EGA, <https://www.ebi.ac.uk/ega/>), and TCGA. The Human Protein Atlas (<https://www.proteinatlas.org/>) was consulted to validate protein expression status in tumor and paired normal tissues.

Dependence analysis between stemness score, TME and ABCB family gene expression

Furthermore, in the investigation of the dependence between stemness score, TME, and ABCB family gene expression, RNA stemness score (RNAss) is an index calculated based on expression data, and DNA stemness score (DNAss) is an index calculated based on methylation data. The index ranges between 0 and 1. A value close to 1 indicates that the lower the degree of cell differentiation, the stronger the stem cell characteristics. The Spearman’s method was utilized to analyze the correlation of ABCB genes with DNAss/RNAss via the “cor.test” command. R-packages “estimate” and “limma” were employed to calculate stromal and immune scores which could predict the content of stromal and immune cells and represent tumor purity and immune infiltrating characteristics across pan-cancer tissues (based on ABCB family gene expression). Spearman’s method was also employed to assess the connection between stromal/immune scores and ABCB expression level. The assessment of TME and stemness scores involved the use of R-packages “reshape2”, “ggpubr”, “ggplot2”, and “limma”, with “corrplot” utilized for the visualization of the results.

Correlation between drug sensitivity, immune subtype, clinical character and ABCB family gene expression

For our investigation into drug sensitivity, data were acquired from the CellMiner database (31) (<https://discover.nci.nih.gov/cellminer/home.do>). The CellMiner database, primarily derived from the 60 types of cancer cell lines (also called NCI-60 cell line) cataloged by the National Cancer Institute’s Center for Cancer Research, is the predominant cancer cell sample set for testing

anticancer drugs. It facilitates queries for data on 22,379 confirmed genes and 20,503 compounds analyzed within the NCI-60 cell line. These anticancer drugs include multiple drugs approved by the US Food and Drug Administration (FDA), as well as drug molecules in clinical trials. We extracted the expression of ABCB gene in NCI-60 cell line from the database and performed correlation analysis with the sensitivity of anti-cancer drugs. To perform drug sensitivity correlation analysis, we utilized R-packages “impute”, “limma”, and “ggpubr”. These tools facilitated the examination of the relationships between drug sensitivity and ABCB family gene expression. Furthermore, for the correlation analysis between ABCB family gene expression and immune subtypes, as well as clinical characteristics, we employed R-packages “limma” and “reshape2”. Thorsson and colleagues integrated the immune genomic data from over 10,000 TCGA tumor patients to classify six immune subtypes. These are: wound healing (C1), IFN- γ dominant (C2), inflammatory (C3), lymphocyte depleted (C4), immunologically quiet (C5), and TGF- β dominant (C6). Each subtype is distinct, marked by variations in macrophage or lymphocyte signatures, Th1 to Th2 cell ratios, levels of intratumor heterogeneity, aneuploidy, neoantigen load, cellular proliferation rates, immunomodulatory gene expression, and prognostic outcomes (32). These analyses allowed us to explore potential associations between the expression patterns of ABCB family genes and immune subtype classification, as well as various clinical features.

Statistical analysis

Gene expression data from the TCGA, GTEx, and EGA databases were analyzed using Student’s *t*-test. Wilcoxon test was employed for comparing gene expression differences between normal and tumor tissues and the Kruskal-Wallis test was for comparing expression in pan-cancer. OS was calculated using the Kaplan-Meier method, and survival curves were compared using log-rank tests. Pearson analysis was performed to evaluate the correlation between ABCB expression levels with other factors (DNAss/RNAss, immune/stromal scores). All statistical analysis was conducted using R software (version 3.6.1). A P value <0.05 was considered statistically significant.

Ethical statement

The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013).

Results

The expression levels of ABCB family gene in pan-cancers

The findings of our investigation revealed that the expression levels of *TAP1*, *TAP2*, and *ABCB7* were notably elevated across pan-cancers, closely followed by *ABCB6*, *ABCB8*, and *ABCB10*. Conversely, the gene expression levels of *ABCB5* and *ABCB11* were observed to be comparatively diminished (Figure 1A). Consequently, these two genes, namely *ABCB5* and *ABCB11*, were excluded from subsequent analyses. Further examination delineated that the expression levels of *TAP1* and *TAP2* reached their zenith in cholangiocarcinoma (CHOL), while *ABCB7* exhibited its highest expression in glioblastoma multiforme (GBM). In contrast to other family members, the expression level of *ABCB1* was observed to be lower, particularly evident in kidney chromophobe (KICH) and kidney renal clear cell carcinoma (KIRC). Overall, the ABCB gene family manifested heightened expression in pan-cancers except *ABCB1* (Figure 1B). Furthermore, *TAP1* and *TAP2* emerged as the genes displaying the highest positive correlation, with a correlation coefficient of 0.85. Upon excluding the genes with low expression abundance, *ABCB5* and *ABCB11*, the most negative correlation was observed between *ABCB4* and *ABCB9*, with a correlation coefficient of -0.18 (Figure 1C).

In our effort to assess the variance in the transcriptional levels of family genes, we employed R-packages within the R software framework to analyze RNA sequencing data from the TCGA database. Our investigation unveiled that *ABCB1* exhibited lower expression in tumor tissues compared to adjacent tissues across multiple cancer types, including bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), head and neck squamous cell carcinoma (HNSC), KICH, KIRC, lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), uterine corpus endometrial carcinoma (UCEC) and rectum adenocarcinoma (READ) (Figure 2A). Simultaneously, our analysis indicated that *TAP1* exhibited a state of elevated expression in several cancer types, including esophageal carcinoma (ESCA), prostate adenocarcinoma (PRAD), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), KIRP and UCEC, BLCA, BRCA, CHOL, COAD, GBM, HNSC, KIRC, LIHC, LUAD and READ (Figure 2B). The examination further revealed that *TAP2* demonstrated higher expression levels in KICH,

BLCA, CHOL, COAD, ESCA, GBM, HNSC, KIRC, KIRP, LIHC, PRAD, READ, and STAD. However, it exhibited lower expression specifically in KICH (Figure 2C). Our analysis indicated that *ABCB4* exhibited elevated expression levels in BRCA, GBM, KIRC, KIRP, LUAD, and LUSC. Conversely, a lower expression of *ABCB4* was observed in BLCA, CHOL, COAD, HNSC, KICH, READ, UCEC and LIHC (Figure 2D). The examination revealed that *ABCB6* demonstrated higher expression levels in COAD, ESCA, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, and UCEC. Conversely, it exhibited lower expression in KICH and THCA (Figure 2E). The analysis unveiled that *ABCB7* exhibited higher expression levels in CHOL, COAD, GBM, KICH, KIRC, LIHC, LUAD, LUSC, and STAD. Conversely, it demonstrated lower expression in BRCA, KIRP, and UCEC (Figure 2F). Our investigation found that *ABCB8* displayed higher expression levels in BLCA, BRCA, CHOL, COAD, ESCA, HNSC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, and UCEC. Conversely, it demonstrated lower expression in KIRC and THCA (Figure 2G). Our examination revealed that *ABCB9* exhibited higher expression levels in BLCA, BRCA, CHOL, ESCA, HNSC, KICH, LIHC, LUAD, LUSC, READ, STAD, THCA, and UCEC. Conversely, it displayed lower expression in GBM, KIRC, and PRAD (Figure 2H). Our analysis demonstrated that *ABCB10* exhibited higher expression levels in BRCA, CHOL, ESCA, GBM, KIRC, LIHC, LUAD, LUSC, and STAD. Conversely, it displayed lower expression in KICH, KIRP, THCA, and UCEC (Figure 2I). The details of overexpression and low expression status of ABCB genes in cancers were summarized in Table S2.

Correlation analysis of the expression levels of ABCB family gene and prognosis in pan-cancers

In the pursuit of verifying the prognostic value of the ABCB gene family, various databases were employed. Kaplan-Meier survival curves, derived from TCGA datasets, illuminated the association between ABCB family genes and the prognosis of diverse cancers. Generally, higher expression levels of ABCB family genes were linked to a poorer prognosis in patients, with the exception of *ABCB1*, which played a protective role in skin cutaneous melanoma (SKCM), sarcoma (SARC), KIRC, HNSC, COAD, LUAD, PAAD (Figure 3A-3G). Specifically, *TAP1* demonstrated a detrimental role in three cancers—uveveal melanoma (UVM), lower grade glioma (LGG) and PAAD—while playing a

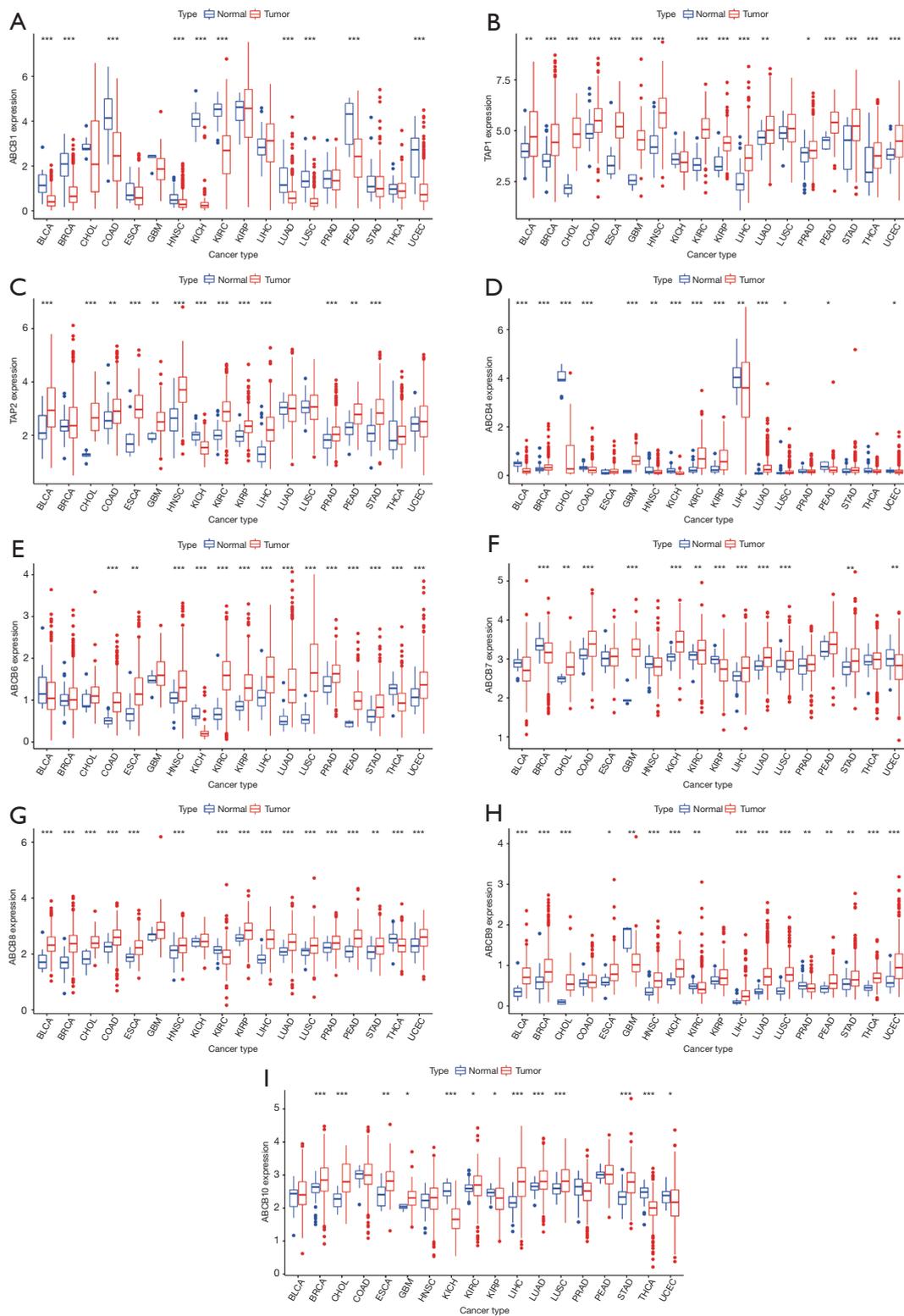


Figure 2 ABCB family gene expression levels in tumor tissues their matched adjacent tissues in different cancer types. (A) *ABCB1*, (B) *TAP1*, (C) *TAP2*, (D) *ABCB4*, (E) *ABCB6*, (F) *ABCB7*, (G) *ABCB8*, (H) *ABCB9*, (I) *ABCB10*. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. The abbreviations of the cancer name can be found in [Table S1](#). ABCB, ABC transporter subfamily B; TAP, transporter associated with antigen processing.

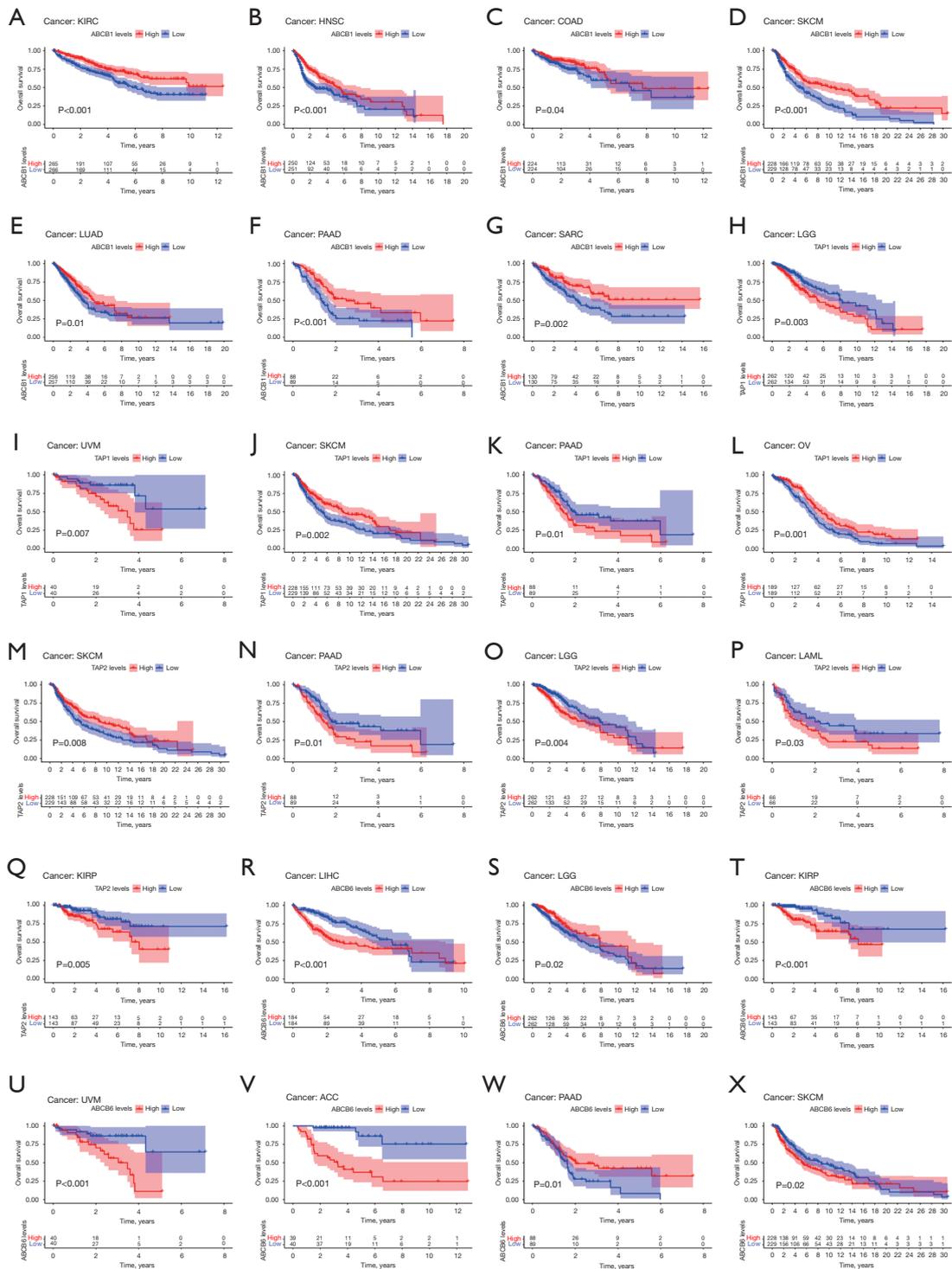


Figure 3 Correlation analysis of the expression levels of ABCB family gene and prognosis by Kaplan-Meier survival curves in pan-cancers. (A-G: *ABCB1*; H-L: *TAP1*; M-Q: *TAP2*; R-X: *ABCB6*). (A) KIRC (n=531); (B) HNSC (n=501); (C) COAD (n=448); (D) SKCM (n=457); (E) LUAD (n=513); (F) PAAD (n=177); (G) SARC (n=260); (H) LGG (n=524); (I) UVM (n=80); (J) SKCM (n=457); (K) PAAD (n=177); (L) OV (n=378); (M) SKCM (n=457); (N) PAAD (n=177); (O) LGG (n=524); (P) LAML (n=132); (Q) KIRP (n=286); (R) LIHC (n=368); (S) LGG (n=524); (T) KIRP (n=286); (U) UVM (n=80); (V) ACC (n=79); (W) PAAD (n=177); (X) SKCM (n=457). The abbreviations of the cancer name can be found in [Table S1](#). ABCB, ABC transporter subfamily B; TAP, transporter associated with antigen processing.

protective role in ovarian serous cystadenocarcinoma (OV) and SKCM (Figure 3H-3L). *TAP2* exhibited a detrimental role in four cancers—acute myeloid leukemia (LAML), brain LGG, KIRP, and PAAD—while exerting a protective role in SKCM (Figure 3M-3Q). *ABCB4* displayed a detrimental role in adrenocortical carcinoma (ACC), UVM, LGG, READ, and STAD, while concurrently having a protective role in KIRC, PAAD, and SKCM (Figure S1). *ABCB6* was detrimental in SKCM, UVM, ACC, KIRP, LIHC, and PAAD, and had a protective role in LGG (Figure 3R-3X). *ABCB7* has a protective role in GBM and KIRC (Figure S1). *ABCB8* exhibited a detrimental role in GBM, KIRC, LGG, SKCM, THCA, and UVM, with a protective role in lymphoid neoplasm diffuse large B-cell lymphoma (DLBC) (Figure S1). *ABCB9* had a detrimental role in thymoma (THYM), KIRC, LGG, THCA and UVM, and a protective role in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) (Figure S1). *ABCB10* played a protective role in mesothelioma (MESO), ACC, and ESCA, with additional protective roles in HNSC and KIRC (Figure S1).

Further insights were gained through Cox analysis (Figure S2, Table S3), GEPIA (Figure S3) and Kaplan-Meier plotter database (Figure S4), culminating in a summarized table (Table 1). In Figure S2, correlation analysis was done between the expression levels of ABCB family gene and prognosis by the Cox method in pan-cancers. Results manifested that *ABCB1* takes a protective role in PAAD, HNSC, KIRC, LUAD, SKCM and SARC. *TAP1* had a detrimental role in LGG, UVM, PAAD, but took a protective role in SKCM and OV. *TAP2* took a detrimental role in LGG, LAML, KIRP, PAAD but had a protective in SKCM. *ABCB6* displayed a detrimental role in SKCM, UVM, ACC, KIRP, LIHC and PAAD but owned a protective role in LGG. With regard to GEPIA analysis, *ABCB1* manifested a protective role in CESC, KIRC, LUAD and PAAD. Meanwhile, *TAP1* exhibited a detrimental role in LGG, OV, SKCM and UVM. *TAP2* also played a detrimental role in LAML, LGG, KIRP and PAAD. *ABCB6* had a detrimental role in ACC, KIRP, LIHC, SKCM, and UVM (Figure S3). In Kaplan-Meier plotter database, *ABCB1* played a detrimental role in LIHC and *TAP2* manifested a detrimental role in KIRP and PAAD. Meanwhile, *ABCB6* displayed a detrimental role in KIRC, KIRP and LIHC (Figure S4). Notably, three consistent prognostic results were observed across all methods—KIRP, LIHC, and PAAD.

Correlation analysis of the expression levels of ABCB family gene and TME, stemness scores in pan-cancers

The TME plays a pivotal role in the initiation and progression of tumors, influencing cellular heterogeneity, drug resistance, and subsequent tumor development and metastasis (33). In our quest to understand the correlation between gene expression levels and the TME, we employed the ESTIMATE algorithm to quantify the stromal and immune scores across various cancers. This allowed us to explore tumor purity (represented by stromal score) and the presence of infiltrating immune cells (represented by immune score) in pan-cancer tissues. Our research indicated a notable correlation, either positive or negative, between the expression of ABCB genes and RNAss (Figure 4A) as well as DNAss (Figure 4B) in pan-cancers. Similarly, the expression levels of ABCB family genes exhibited significant positive or negative correlations with stromal scores (Figure 4C) and immune scores (Figure 4D). These results illuminated the intricate relationship between ABCB gene expression and the composition of the TME across a spectrum of cancers.

Correlation analysis of the expression levels of ABCB family gene and TME, stemness scores in selected cancers

Our exploration delved deeper into the correlation between gene expression levels within the ABCB gene family and the TME as well as stemness scores in specific cancers—KIRP, LIHC, and PAAD. In the context of KIRP, the results indicated a positive correlation between the expression levels of *ABCB6* and *ABCB7* with RNAss. Conversely, *ABCB1*, *TAP2*, *ABCB4*, and *ABCB9* exhibited a negative correlation with RNAss. Examining the association with DNAss in KIRP, *TAP2* and *ABCB9* demonstrated a positive correlation, while *ABCB1* exhibited a negative correlation. Regarding stromal scores, the expression levels of *TAP1* and *TAP2* were found to be positively associated. Moreover, *TAP1* and *TAP2* exhibited a positive correlation with immune scores, while *ABCB1*, *ABCB7*, and *ABCB10* displayed a negative correlation with immune scores in KIRP. The exploration extended to ESTIMATE scores, revealing a positive correlation between the expression levels of *TAP1* and *TAP2*, and a negative correlation with *ABCB1* and *ABCB10* in KIRP (Figure 5A).

In the context of LIHC, our analysis revealed that the expression level of *ABCB6* exhibited a positive correlation

Table 1 Correlation analysis of the expression levels of ABCB family gene and prognosis by multiple methods in pan-cancers

Gene	Role	OS			
		TCGA (Kaplan-Meier)	TCGA (Cox)	Kaplan-Meier plotter	GEPIA
<i>ABCB1</i>	Detrimental	–	–	LIHC	–
	Protective	PAAD, COAD, HNSC, KIRC, LUAD, SKCM, SARC	SKCM, KIRC, HNSC, PAAD, MESO, LUAD	–	CESC, KIRC, LUAD, PAAD
<i>TAP1</i>	Detrimental	LGG, UVM, PAAD	LUAD, UVM, KIRP, PAAD, LGG, THYM	–	LGG, OV, SKCM, UVM
	Protective	OV, SKCM	REA, SKCM, STAD, OV	–	–
<i>TAP2</i>	Detrimental	LGG, LAML, KIRP, PAAD	LUAD, LAML, UVM, LGG, ACC, KIRP, PAAD	KIRP, PAAD	LAML, LGG, KIRP, PAAD
	Protective	SKCM	SKCM	–	–
<i>ABCB4</i>	Detrimental	UVM, ACC, LGG, READ, STAD	LGG, UVM, ACC, KICH, THCA, DLBC	KIRP, STAD, THCA	ACC, LGG
	Protective	KIRC, PAAD, SKCM	KIRC, PAAD, SKCM, HNSC, SARC	–	HNSC, PAAD
<i>ABCB6</i>	Detrimental	SKCM, UVM, ACC, KIRP, LIHC, PAAD	ACC, KIRP, LIHC, UVM, SKCM, KIRC, COAD, KICH	KIRC, KIRP, LIHC	ACC, KIRP, LIHC, SKCM, UVM
	Protective	LGG	PAAD, LGG	–	–
<i>ABCB7</i>	Detrimental	UCEC	LGG, ESCA, UCEC, SARC, BRCA	BRCA, HNSC, PAAD, SARC, UCEC	–
	Protective	GBM, KIRC	KIRC, MESO, GBM, SKCM	–	GBM, KIRC, MESO
<i>ABCB8</i>	Detrimental	GBM, KIRC, LGG, SKCM, THCA, UVM	UVM, KIRC, LGG, KICH, GBM, SKCM	KIRC, LIHC, THCA	ACC, KICH, LGG, SKCM, UVM
	Protective	DLBC	DLBC, HNSC, KIRP, PAAD	–	DLBC
<i>ABCB9</i>	Detrimental	KIRC, LGG, THCA, THYM, UVM	KIRC, LGG, THYM, KIRP, UVM, DLBC, BLCA, KICH	BLCA, BRCA, KIRC, LIHC, SARC, THCA	BLCA, BRCA, DLBC, LGG, THCA, UVM
	Protective	CESC	–	–	–
<i>ABCB10</i>	Detrimental	MESO, ACC, ESCA	PCPG, ACC, MESO	BLCA, CESC, PCPG	ACC, CESC, LUAD, MESO, PCPG
	Protective	HNSC, KIRC	KIRC	–	–

The abbreviations of the cancer name can be found in [Table S1](#). ABCB, ABC transporter subfamily B; OS, overall survival; TCGA, The Cancer Genome Atlas; GEPIA, Gene Expression Profiling Interactive Analysis.

with RNAss, while *ABCB4* displayed a negative correlation with RNAss. Examining DNAss, the expression levels of *ABCB1*, *ABCB4*, *ABCB6*, and *ABCB7* were found to be positively correlated. Moving on to stromal scores, the expression levels of *TAP1* and *TAP2* were positively related, and *ABCB6* showed a negative correlation with stromal scores in LIHC. In terms of immune scores, *TAP1* and *TAP2* exhibited a positive correlation, while *ABCB4*, *ABCB6*, and *ABCB10* displayed a negative correlation with

immune scores in LIHC. The exploration extended to ESTIMATE scores, revealing a positive correlation between the expression levels of *TAP1* and *TAP2*, and a negative correlation with *ABCB4*, *ABCB6*, and *ABCB10* in LIHC (*Figure 5B*).

In the context of PAAD, the analysis indicated that the expression level of *ABCB6* exhibited a positive correlation with RNAss, while *ABCB1* and *ABCB4* displayed a negative correlation with RNAss. Examining DNAss, *ABCB1* and

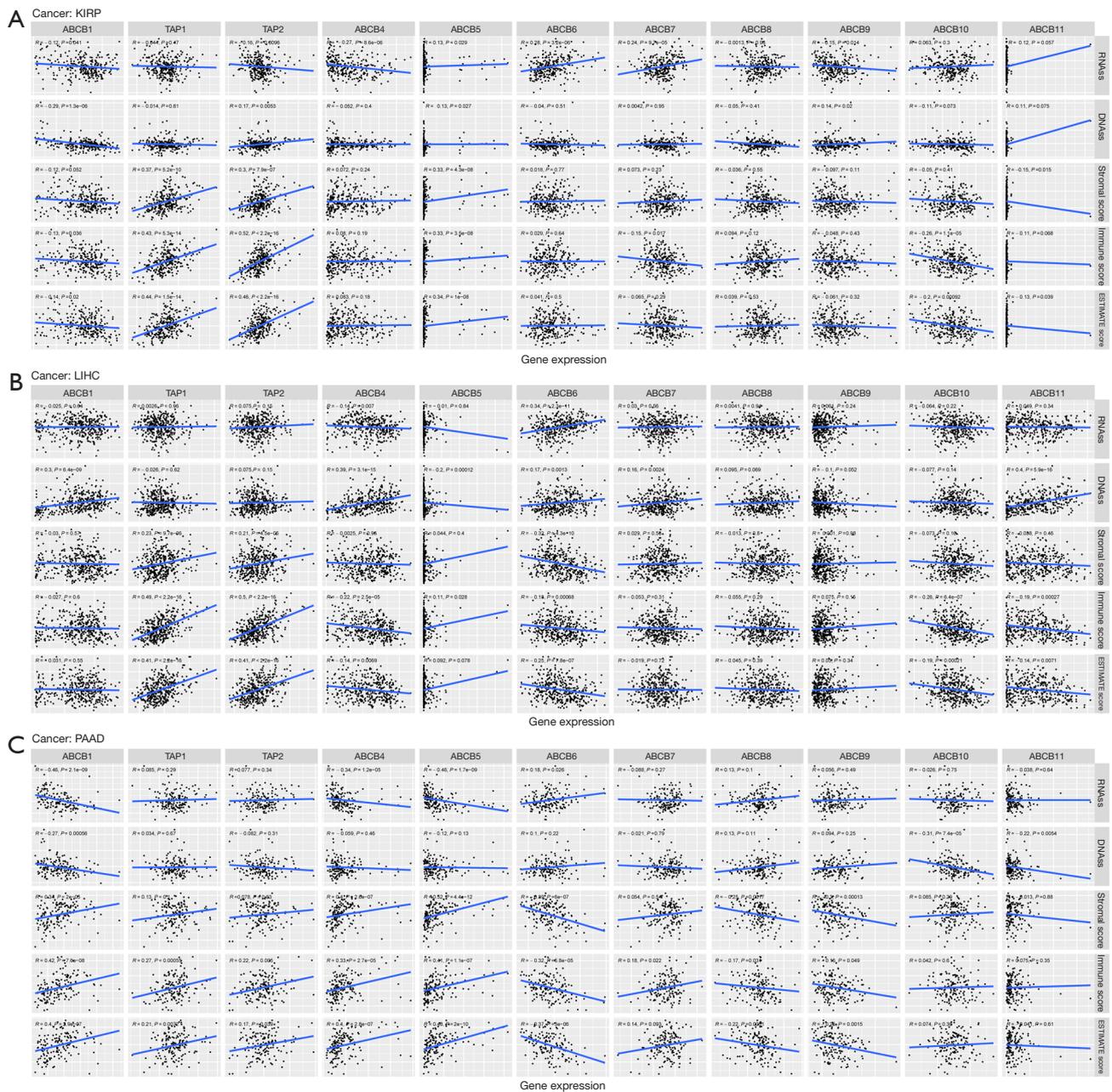


Figure 5 Correlation analysis of the expression levels of ABCB family gene and TME, stemness scores in (A) KIRP, (B) LIHC, (C) PAAD. X-axis represents expression levels of genes, Y-axis represents TME and stemness score index. A P value less than 0.05 indicates a significant association with the respective index. The correlation coefficient, denoted as “R”, signifies the nature of the correlation: a positive or negative number indicates a positive or negative correlation, respectively. The abbreviations of the cancer name can be found in Table S1. ABCB, ABC transporter subfamily B; TME, tumor microenvironment; RNAss, RNA stemness score; DNAss, DNA stemness score.

Table 2 Correlation analysis of the expression levels of ABCB family gene and TME in selected cancers

Cancer	TME	Positive	Negative
KIRP	RNAss	<i>ABCB6, ABCB7</i>	<i>ABCB1, TAP2, ABCB4, ABCB9</i>
	DNAss	<i>TAP2, ABCB9</i>	<i>ABCB1</i>
	Stromal scores	<i>TAP1, TAP2</i>	–
	Immune scores	<i>TAP1, TAP2</i>	<i>ABCB1, ABCB7, ABCB10</i>
	ESTIMATE scores	<i>TAP1, TAP2</i>	<i>ABCB1, ABCB10</i>
LIHC	RNAss	<i>ABCB6</i>	<i>ABCB4</i>
	DNAss	<i>ABCB1, ABCB4, ABCB6, ABCB7</i>	–
	Stromal scores	<i>TAP1, TAP2</i>	<i>ABCB6</i>
	Immune scores	<i>TAP1, TAP2</i>	<i>ABCB4, ABCB6, ABCB10</i>
	ESTIMATE scores	<i>TAP1, TAP2</i>	<i>ABCB4, ABCB6, ABCB10</i>
PAAD	RNAss	<i>ABCB6</i>	<i>ABCB1, ABCB4</i>
	DNAss	–	<i>ABCB1, ABCB10</i>
	Stromal scores	<i>ABCB1, ABCB4</i>	<i>ABCB6, ABCB8</i>
	Immune scores	<i>ABCB1, TAP1, TAP2, ABCB4, ABCB7</i>	<i>ABCB6, ABCB8, ABCB9</i>
	ESTIMATE scores	<i>ABCB1, TAP1, TAP2, ABCB4</i>	<i>ABCB6, ABCB8, ABCB9</i>

The abbreviations of the cancer name can be found in [Table S1](#). ABCB, ABC transporter subfamily B; TME, tumor microenvironment; RNAss, RNA stemness score; DNAss, DNA stemness score.

extended to ESTIMATE scores, revealing a positive correlation between the expression levels of *ABCB1*, *TAP1*, *TAP2*, and *ABCB4*, and a negative correlation with *ABCB6*, *ABCB8*, and *ABCB9* in PAAD (*Figure 5C*). Detailed correlation analyses of ABCB gene expression levels and stromal/immune scores, stemness scores in KIRP, LIHC and PAAD are summarized in *Table 2*.

Correlation analysis of the expression levels of ABCB family gene and immune subtypes

In the analysis of immune subtypes in KIRP, LIHC, and PAAD, six immune subtypes, including C1 (wound healing), C2 (IFN- γ dominant), C3 (inflammatory), C4 (lymphocyte depleted), C5 (immunologically quiet), and C6 (TGF- β dominant), were considered (32). C1 (wound healing) exhibited elevated angiogenic gene expression, high cellular proliferation, and a Th2 cell-biased adaptive immune infiltrate. C2 (IFN- γ Dominant) demonstrated the most pronounced M1/M2 macrophage polarization and CD8 signal, sharing the highest T cell receptor (TCR) diversity with C6. This subtype also presented a high proliferation rate, potentially overriding an emerging Type

I immune response. C3 (inflammatory) was characterized by increased Th17 and Th1 gene levels, low to moderate tumor proliferation, and, in conjunction with C5, the least aneuploidy and somatic copy number alterations among the subtypes. C4 (lymphocyte depleted) showed a significant macrophage presence, subdued Th1 activity, and an elevated M2 response. C5 (immunologically quiet) had the minimal lymphocyte and maximal macrophage responses, predominantly M2 macrophages. Lastly, C6 (TGF- β dominant), a diverse group of mixed tumors not specifically categorized in any TCGA subtype, had the strongest TGF- β signature and a balanced distribution of Type I and II T cells (32). This classification serves as the foundation for immunoassays. Our analysis aimed to explore potential crosstalk between ABCB family genes and immune subtypes in these specific cancers. In KIRP, the results revealed that the expressions of *TAP1*, *TAP2*, *ABCB6*, and *ABCB7* were associated with immune subtypes (*Figure 6A*). Specifically, *TAP1* and *TAP2* were found to be more expressed in C2, while *ABCB6* was more expressed in C1 and C2 in KIRP (*Figure 6A*). Moving on to LIHC, the analysis indicated that the expression of *TAP1*, *TAP2*, *ABCB6*, *ABCB4*, *ABCB1*, and *ABCB10* was associated with

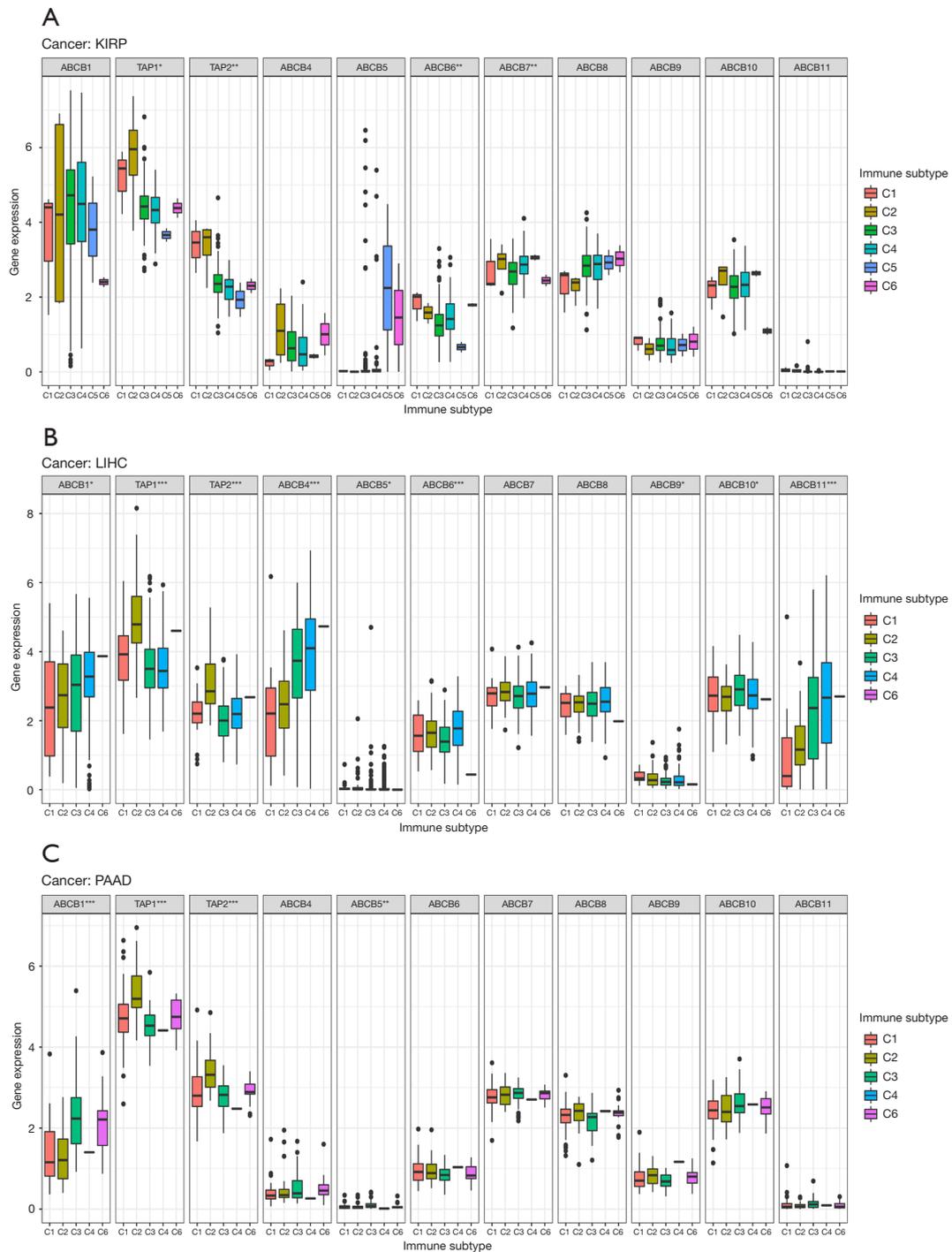


Figure 6 Correlation analysis of the expression levels of ABCB family gene and immune subtypes in (A) KIRP, (B) LIHC, (C) PAAD. C1, wound healing; C2, IFN- γ dominant; C3, inflammatory; C4, lymphocyte depleted; C5, immunologically quiet; C6, TGF- β dominant. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. The abbreviations of the cancer name can be found in [Table S1](#). ABCB, ABC transporter subfamily B; IFN, interferons; TGF, transforming growth factor.

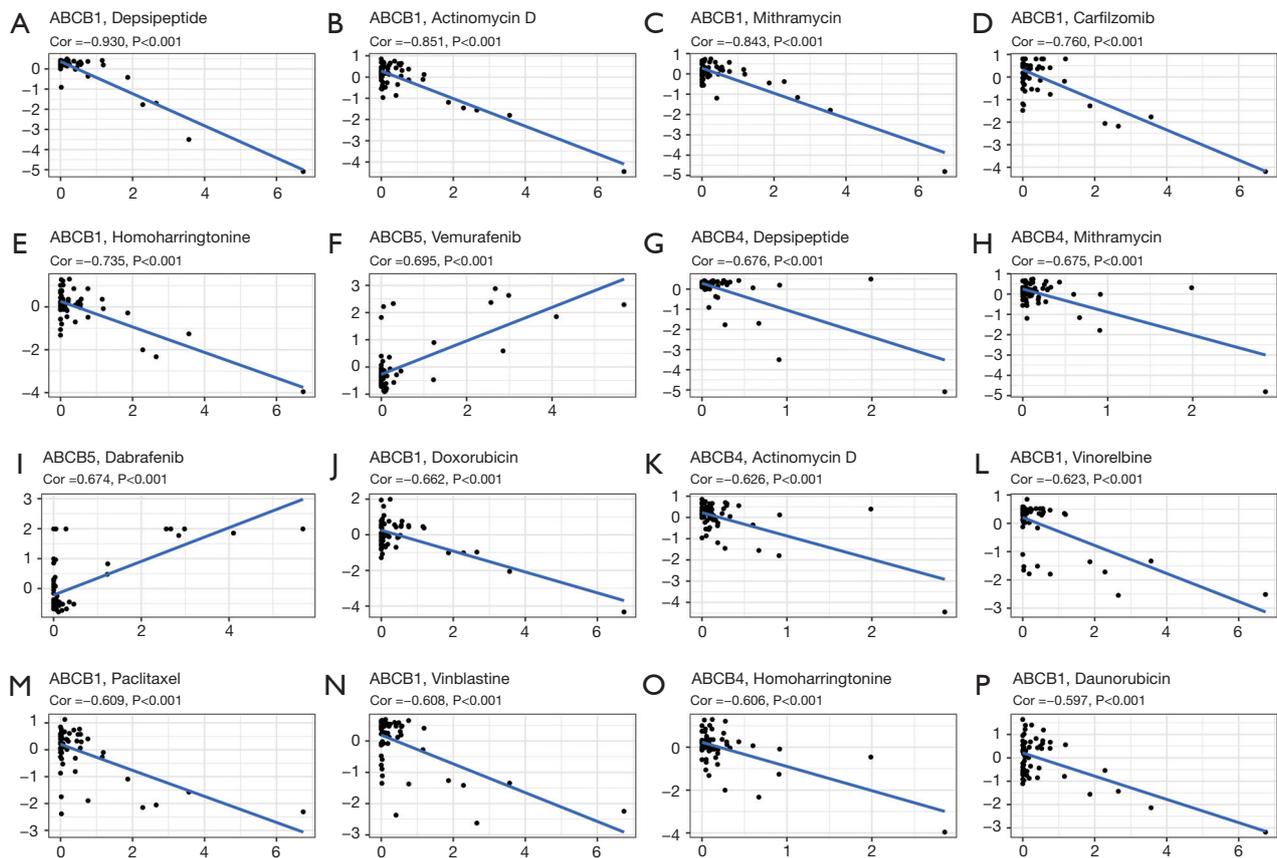


Figure 7 Correlation analysis of the expression levels of ABCB family gene and drug sensitivity in pan-cancers. The expression level of *ABCB1* gene was negatively correlated to following drug sensitivity: (A) depsipeptide; (B) actinomycin D; (C) mithramycin; (D) carfilzomib; (E) homoharringtonine; (J) doxorubicin; (L) vinorelbine; (M) paclitaxel; (N) vinblastine; (P) daunorubicin. The expression level of *ABCB4* gene was negatively correlated to following drug sensitivity: (G) depsipeptide; (H) mithramycin; (K) actinomycin D; (O) homoharringtonine. The *ABCB5* was positively correlated with vemurafenib (F) and dabrafenib (I). ABCB, ABC transporter subfamily B.

immune subtypes (Figure 6B). *TAP1* and *TAP2* were more expressed in C2, while *ABCB6* was more expressed in C2 and C4 in LIHC (Figure 6B). In PAAD, the results showed that the expression levels of *TAP1*, *TAP2*, and *ABCB1* were associated with immune subtypes (Figure 6C). Consistent with KIRP and LIHC, *TAP1* and *TAP2* were found to be more expressed in C2 in PAAD (Figure 6C). Combining the expression levels of ABCB family genes with the results of immune subtypes across pan-cancers, *TAP1* and *TAP2* were consistently found to be more expressed in C2 (Figure S5). This research illuminates the possible interactions between ABCB family genes and immune subtypes within certain cancer classifications.

Correlation analysis of the expression levels of ABCB family gene and drug sensitivity in pan-cancers

In our investigation of the relationship between ABCB gene expression levels and the sensitivity of clinical drugs, we utilized the CellMiner database for correlation analysis (Figure 7). The findings revealed that the expression level of *ABCB1* gene was negatively correlated with the drug sensitivity of depsipeptide, actinomycin D, mithramycin, carfilzomib, homoharringtonine, doxorubicin, vinorelbine, paclitaxel, vinblastine, and daunorubicin. Similarly, the expression of *ABCB4* gene showed a negative correlation with depsipeptide, mithramycin, actinomycin D, and

homoharringtonine. The *ABCB5* was positively correlated with vemurafenib and dabrafenib.

Correlation analysis of the expression levels of ABCB family gene with clinical characteristics in selected cancers and protein expression status

The relationships between ABCB family gene and clinical characteristics are shown in *Figure 8*. The results showed that the expression levels of *ABCB1* and *TAP2* genes was positively correlated with patients' age in LIHC and PAAD, respectively, as well as *ABCB10* in KIRP. Moreover, the expression level of *ABCB6* gene was positively correlated with clinical stage in KIRP and LIHC. *TAP1* gene was found positively correlated with tumor grade in LIHC. *TAP1*, *TAP2* genes were positively correlated with tumor grade in PAAD, however, the expression level of *TAP1* gene was negatively correlated with clinical stage in PAAD. Besides, the expression levels of *ABCB1*, *ABCB4*, *ABCB6* and *ABCB7*, *ABCB8*, *ABCB9*, *ABCB10* were found to correlate with gender differences in LIHC and KIRP, respectively. In KIRP, *TAP1*, *TAP2* and *ABCB6* manifested lower expression status in normal tissue, at the same time, they showed higher expression status in KIRP tumor tissue (*Figure 9A-9F*).

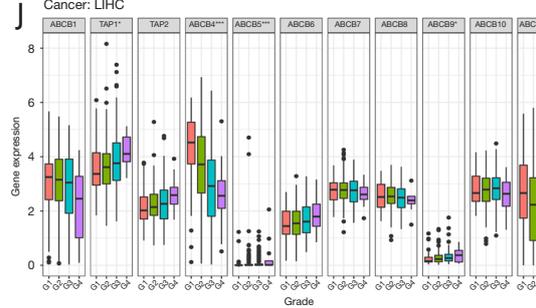
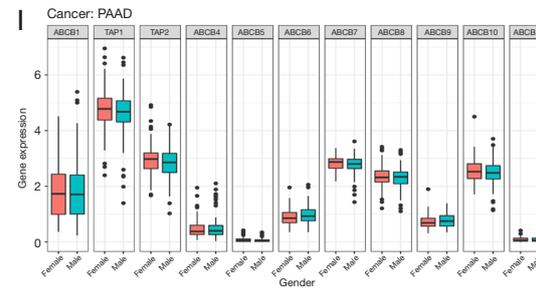
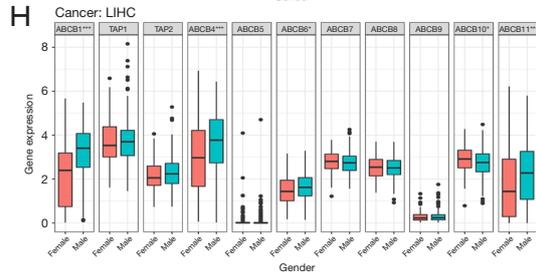
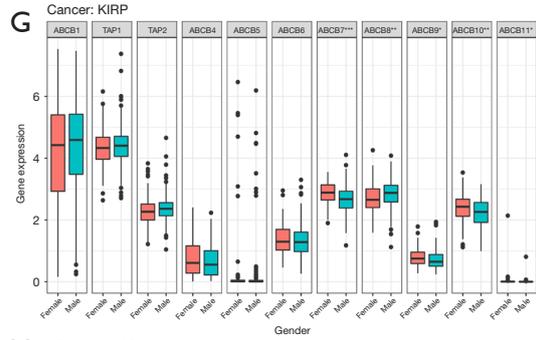
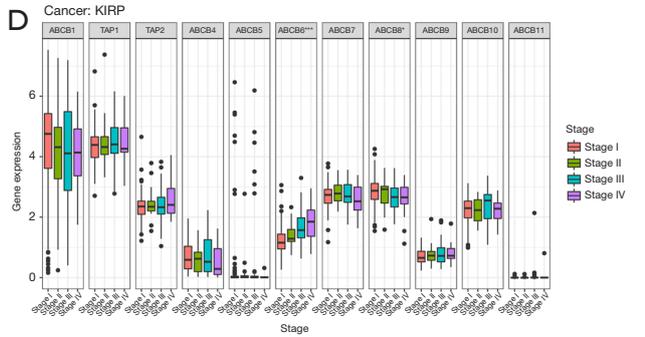
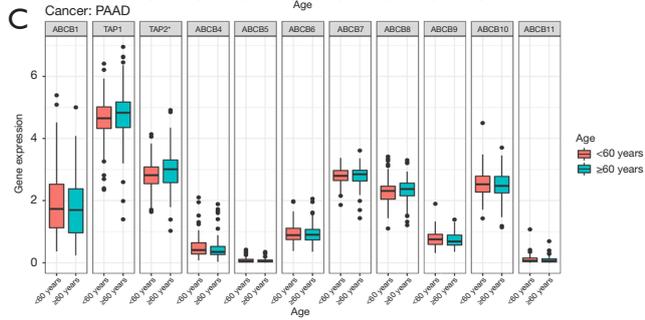
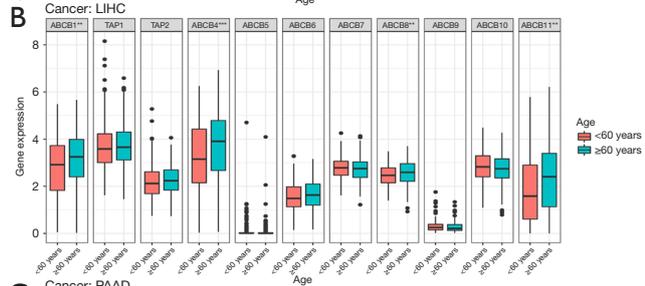
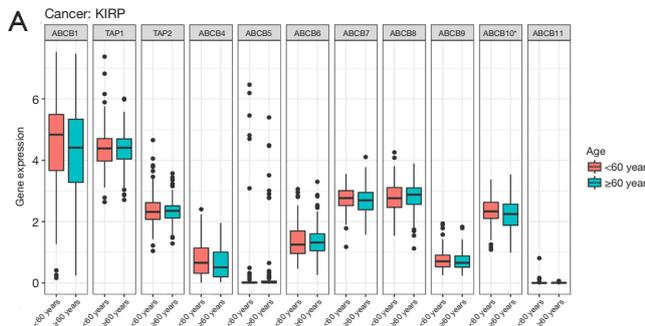
Discussion

Our investigation delved into the expression status of ABCB genes across 10,327 pairs of tumors and their corresponding adjacent samples from 33 types of human primary cancers, utilizing independent datasets from TCGA. Previous research has highlighted the close association of ABCB genes with various human diseases, particularly in the context of cancer occurrence (34-36). In general, tumors with differential expression of ABCB genes exhibit a higher expression level in the majority of tumor types, although there is a smaller percentage in which they show lower expression. This complexity in expression patterns underscores the intricate role of ABCB genes in the landscape of diverse human cancers. To the best of our knowledge, this study represents the inaugural endeavor to substantiate the elevated expression status of the ABCB gene across a spectrum of pan-cancers. Consequently, the research furnishes substantial evidence for prognostic predictions in the realm of pan-cancers by elucidating the expression status of ABCB genes. Moreover, this investigation holds the promise of contributing significantly

to the prospective advancement of targeting therapeutic modalities aimed at the ABCB family gene.

Our investigation established a correlation between the expression levels of ABCB genes and the prognosis of KIRP, LIHC, and PAAD. The consistency of prognostic outcomes across diverse databases and statistical algorithms reinforces the robustness of our findings in relation to these three cancers. A positive correlation was observed between increased expression levels of *TAP2* and *ABCB6* genes and a concomitant decrease in overall survival rates in KIRP, LIHC, and PAAD. This aligns with findings from Zhao *et al.*'s report, which indicated that the gene expression of *ABCB6* is associated with diminished treatment response and unfavorable outcomes in glioma (37). *ABCB6* exhibits elevated expression levels in hepatocellular carcinoma, and its expression serves as a predictive indicator for hepatitis C-related hepatocellular carcinoma. Moreover, it has been elucidated that *ABCB6* exerts regulatory control over the growth and proliferation of tumor cells through its targeting of the cell cycle (27).

In the course of our investigation, we observed an association between *TAP1* and the prognosis of OV, LGG, and other entities. Contrary findings from other studies have indicated that heightened *TAP1* expression is correlated with adverse clinical outcomes, encompassing diminished OS, increased likelihood of local recurrence, drug resistance, and treatment failure in conditions such as hepatocellular carcinoma and breast cancer (38,39). Nevertheless, it is noteworthy to acknowledge the existence of inconsistent data regarding the expression of ABCB genes and the survival duration of TCGA cancers across various databases. These disparities may stem from variations in sample composition and algorithmic methodologies employed in distinct databases. Notably, within the entire family of genes studied, the expression levels of *TAP1* and *TAP2* exhibited the most pronounced correlation. High expression of this TAP complex enhances MHC I assembly, increases drug efflux, and decreases drug sensitivity, ultimately contributing to drug resistance. Simultaneously, it also elevates tumor stemness, impacting patient survival. As per our analytical outcomes, *TAP2* manifested a negative correlation with the prognosis of cancers across multiple databases. Research has demonstrated that the overexpression of the *TAP2* gene may serve as an indicator of aggressive breast tumors (39). Consequently, the association between the *TAP2* gene and the aforementioned three diseases merits further experimental exploration. In summary, our investigations underscore the utility of ABCB family genes as significant



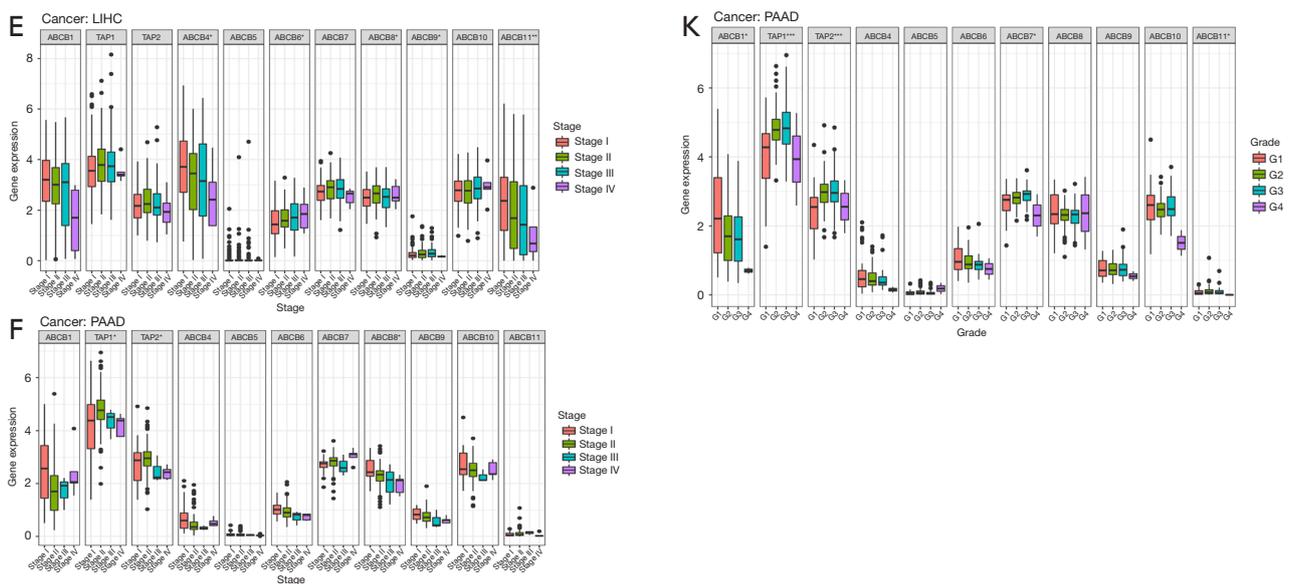


Figure 8 Correlation analysis of the expression levels of ABCB family gene and clinical characteristics in selected cancers. (A-C) The association between the expression level of ABCB family genes and patient ages in KIRP, LIHC, PAAD, respectively. (D-F) The relationship between ABCB family gene expression levels and the clinical stages of patients in KIRP, LIHC, and PAAD is examined, respectively. (G-I) The link between ABCB family gene expression and patient gender within the KIRP, LIHC, and PAAD, respectively. (J,K) The association between the expression level of ABCB family genes and patients’ tumor grades in LIHC, PAAD, respectively. *, P<0.05; **, P<0.01; ***, P<0.001. The abbreviations of the cancer name can be found in Table S1. ABCB, ABC transporter subfamily B.

biomarkers for prognostic predictions in tumors, with particular emphasis on *TAP2* and *ABCB6*.

Sokolov employed the logistic regression algorithm to conduct an analysis encompassing transcriptome data, methyl groups, and transcription factor binding sites (40). The terms RNAss denote gene expression, while DNAss reflect epigenetic characteristics. Additionally, a heightened stemness index signifies an active state of cancer stem cells and dedifferentiation. Consequently, the stemness score is intricately associated with tumor pathology, clinical prognosis, and the TME. Notably, the stemness score holds promise as a potential target for anticancer therapy. Our research indicates a notable correlation, either positive or negative, between ABCB gene expression and RNAss, DNAss across various cancers, especially noted in KIRP, PAAD, and LIHC. Additionally, *ABCB6* gene exhibited a notably positive correlation with DNAss stemness scores in the aforementioned three types of tumors. This observation provides comprehensive evidence supporting the activation of tumor stem cells through the heightened expression of the *ABCB6* gene. Furthermore, this aligns with the findings from our prior study, indicating a negative correlation between *ABCB6* expression and cancer prognosis. Taken

together, these results underscore the characterization of *ABCB6* as an oncogene, implicating its role in promoting unfavorable outcomes in cancer.

The study further examined the link between ABCB family genes and the TME. The ESTIMATE algorithm, leveraging single-sample gene set enrichment analysis, was employed to quantify infiltrating stromal and immune cells and estimate tumor purity (41). Elevated scores on these parameters signify increased presence of stromal and immune cells, coupled with reduced tumor purity. Understanding potential therapeutic targets holds the promise of steering the TME towards a tumor-suppressive state (42).

The influence of the immune microenvironment on treatment outcomes and patient survival is readily apparent (43). This microenvironment encompasses infiltrating immune cells, diverse immune regulatory factors, and stromal cells surrounding tumor sites. Theoretically, tumor cells will create an immunosuppressive microenvironment and inhibit immune cells from playing the role of immune surveillance and immune clearance, thereby conducive to tumor proliferation and metastasis. But at the same time, the activation of immune microenvironment can also enhance the function of

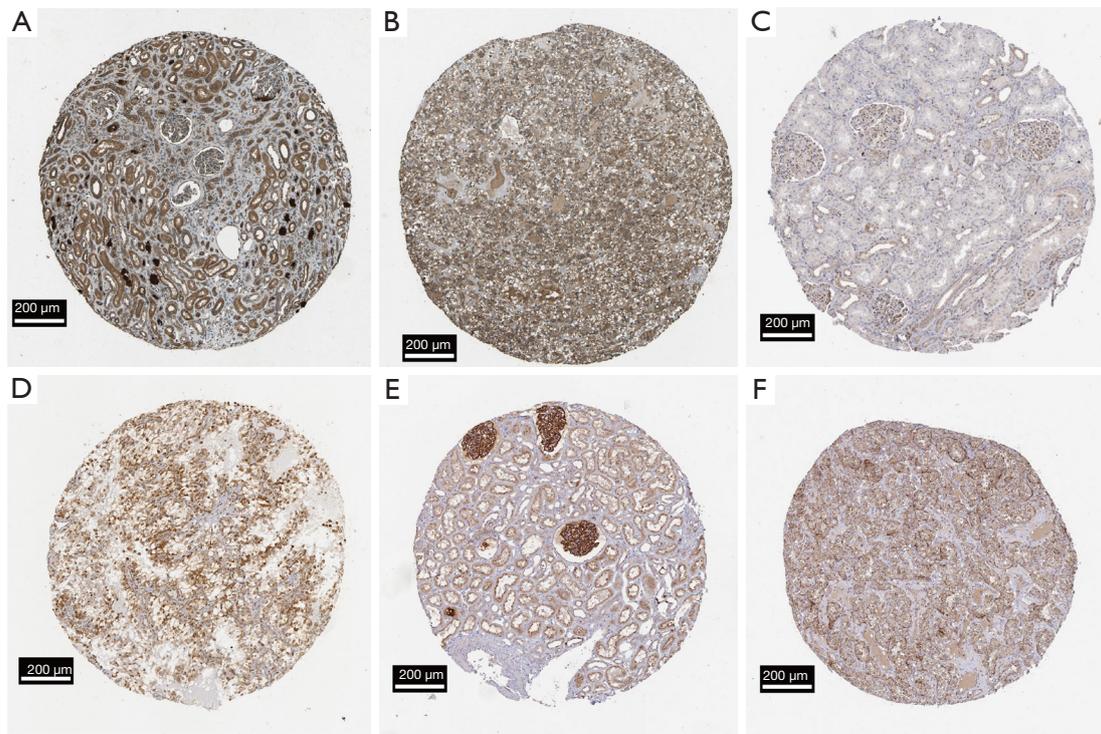


Figure 9 TAP1, TAP2 and ABCB6 protein expression statuses in tumor and paired normal tissues in KIRP. (A) TAP1 protein status in normal renal tissue. (B) TAP1 protein status in tumor renal tissue. (C) TAP2 protein status in normal renal tissue. (D) TAP2 protein status in tumor renal tissue. (E) ABCB6 protein status in normal renal tissue. (F) ABCB6 protein status in tumor renal tissue. The scale bars of 200 μm is located in the lower left corner of each tissue section photo (immunohistochemistry staining). The images can be obtained from Human Protein Atlas database (<https://www.proteinatlas.org/>). The links to the individual normal and tumor tissues of each protein are provided for TAP1 (<https://www.proteinatlas.org/ENSG00000168394-TAP1/tissue/kidney#img>; <https://www.proteinatlas.org/ENSG00000168394-TAP1/pathology/renal+cancer#img>), TAP2 (<https://www.proteinatlas.org/ENSG00000204267-TAP2/tissue/kidney#img>; <https://www.proteinatlas.org/ENSG00000204267-TAP2/pathology/renal+cancer#img>), and ABCB6 (<https://www.proteinatlas.org/ENSG00000115657-ABCB6/tissue/kidney#img>; <https://www.proteinatlas.org/ENSG00000115657-ABCB6/pathology/renal+cancer#img>), respectively. ABCB, ABC transporter subfamily B; TAP, transporter associated with antigen processing; KIRP, kidney renal papillary cell carcinoma. ure 9 TAP1, TAP2 and ABCB6 protein expression statuses in tumor and paired normal tissues in KIRP. (A) TAP1 protein status in normal renal tissue. (B) TAP1 protein status in tumor renal tissue. (C) TAP2 protein status in normal renal tissue. (D) TAP2 protein status in tumor renal tissue. (E) ABCB6 protein status in normal renal tissue. (F) ABCB6 protein status in tumor renal tissue. The scale bars of 200 μm is located in the lower left corner of each tissue section photo (immunohistochemistry staining). The images can be obtained from Human Protein Atlas database (<https://www.proteinatlas.org/>). The links to the individual normal and tumor tissues of each protein are provided for TAP1 (<https://www.proteinatlas.org/ENSG00000168394-TAP1/tissue/kidney#img>; <https://www.proteinatlas.org/ENSG00000168394-TAP1/pathology/renal+cancer#img>), TAP2 (<https://www.proteinatlas.org/ENSG00000204267-TAP2/tissue/kidney#img>; <https://www.proteinatlas.org/ENSG00000204267-TAP2/pathology/renal+cancer#img>), and ABCB6 (<https://www.proteinatlas.org/ENSG00000115657-ABCB6/tissue/kidney#img>; <https://www.proteinatlas.org/ENSG00000115657-ABCB6/pathology/renal+cancer#img>), respectively. ABCB, ABC transporter subfamily B; TAP, transporter associated with antigen processing; KIRP, kidney renal papillary cell carcinoma.

immune cells to kill tumor cells, including stimulating and upregulating immune presentation functions by immune regulatory factors, increasing the differentiation of cytotoxic T cells, etc. (44). Under such an immune background,

drug treatments that modulate immune function are poised to amplify the tumor-killing effect. An immune-promoting microenvironment correlates with improved response to drug therapy and a more favorable prognosis.

In conjunction with the findings in our article, the ABCB gene—encoding a transport protein on the cell membrane—merits attention. As a highly conserved housekeeping gene, ABCB governs material transport functions critical to the immune microenvironment. Our analysis reveals a close association between ABCB gene expression, DNA/RNA stemness, tumor purity, and immune profiling. Thus, ABCB gene expression significantly influences the immune context, treatment response, and overall prognosis.

Notably, our findings indicated a significant correlation between TME and gene expression in the aforementioned three tumors. Specifically, the results of this study revealed a negative correlation between TME-related scores and the expression of *ABCB6* in LIHC and PAAD. This implies that heightened expression of the *ABCB6* gene is associated with increased tumor purity in cancers, providing further substantiation for our assertion that *ABCB6* functions as an oncogene.

Delving further into the analysis, we investigated the association between ABCB family genes and immune subtypes in KIRP, PAAD, and LIHC. The findings revealed that, whether across pan-cancers or within the specified three tumors, the genes *TAP1* and *TAP2* exhibited higher expression in the C2 immune subtype. The C2 immune subtype is characterized by IFN-aggregation, marked by increased infiltration of CD8⁺ lymphocytes and a higher polarization ratio of M1 macrophages, indicating heightened immune activity (32). These results imply the potential development of targeted drugs based on *TAP1* and *TAP2*, which could effectively operate through the C2 immune subtype.

Additionally, we delved into the potential associations between the gene expressions of the ABCB family and drug sensitivity across various tumor cell lines utilizing data from the CellMiner database. The underlying methodology of the CellMiner database involves subjecting 60 cancer cell lines (NCI-60 cell line set) to treatment with 20,503 analyzed compounds, followed by the assessment of genetic changes in more than 20,000 genes within these cell lines. Given the diverse array of compounds within this database, it is noteworthy that the identified drugs associated with sensitivity to the ABCB gene may not necessarily align with those commonly employed in clinical settings. For a better clinical practice, we screened the drugs in CellMiner, leaving only those drugs that have been approved by the FDA or have entered the clinical trial stage. Our investigation revealed that the expressions of *ABCB1* and *ABCB4* hold particular significance in guiding

clinical drug usage. The results demonstrated that *ABCB1* contributed to increased drug resistance against paclitaxel, vinblastine, and daunorubicin. This observation aligns with the well-established role of *ABCB1* as a drug resistance gene mediating drug efflux. However, our results presented an intriguing divergence, indicating a positive correlation between the expression level of *ABCB1* gene and the prognosis of numerous cancers. In other words, higher expression levels of *ABCB1* gene were associated with better patient prognosis. This incongruity might be attributed to the fact that the drug sensitivity database utilized in our study was derived from cell lines, while the survival data was sourced from clinical patients. Further exploration is warranted to elucidate the specific function of the *ABCB1* gene in this context.

Examining clinical characteristics, our analysis revealed a notable positive correlation between *ABCB6* gene expression and clinical stage in KIRP and LIHC, this finding aligns with our earlier prognostic and expression analysis, as a more aggressive clinical stage typically leads to a poorer prognosis. Indeed, corroborating studies have demonstrated that the upregulation of *ABCB6* gene expression is linked to the progression of prostate cancer and melanoma (45,46). This observed phenomenon may be attributed to the high expression of *ABCB6*, which potentially contributes to heme biosynthesis in tumors (47,48). In both LIHC and PAAD, a positive correlation was identified between the expression levels of *TAP1* and *TAP2* genes and tumor grade. This observation might be linked to the drug resistance function of the *TAP1* gene, particularly evident in hepatocellular carcinoma (35). In KIRP, the expression statuses of *TAP1*, *TAP2*, and *ABCB6* proteins were concordant, with higher protein expression observed in tumor tissue. These findings align with our gene expression results in *Figure 2B, 2C, 2E* and our overall survival analysis results in *Figure 3Q, 3T*.

This research supplied comprehensive insights into the expression status of ABCB family genes in pan-cancers and elucidated the correlation between gene expression and prognosis, along with subsequent TME and immune analyses, making it possess certain clinical significance. There are inherent limitations that cannot be overlooked. Firstly, our data were obtained from public databases, lacking further *in vivo* or *in vitro* experiments, which we intend to conduct in the future. Additionally, the molecular mechanisms and downstream pathways of the identified oncogenes—*TAP1*, *TAP2*, and *ABCB6*—remain unclear and warrant exploration through subsequent experiments.

Conclusions

ABCB family genes exhibit elevated expression levels and exhibit a notable association with the prognosis across various cancers. Specifically, the expression levels of *TAP1*, *TAP2*, and *ABCB6* genes demonstrated significant correlations with the TME, immune subtypes, and clinical characteristics in KIRP, LIHC, and PAAD, with a heightened emphasis on the intricate dynamics observed in KIRP. The results enhance our comprehension of the critical function that ABCB family genes serve in tumor development and provide important perspectives for pinpointing prospective therapeutic targets in oncology studies.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-2050/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Table S1 Abbreviations for the name of cancers

Abbreviations	Full names
ACC	Adrenocortical carcinoma
BLCA	Bladder urothelial carcinoma
BRCA	Breast invasive carcinoma
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL	Cholangiocarcinoma
COAD	Colon adenocarcinoma
DLBC	Lymphoid neoplasm diffuse large b-cell lymphoma
ESCA	Esophageal carcinoma
GBM	Glioblastoma multiforme
HNSC	Head and neck squamous cell carcinoma
KICH	Kidney chromophobe
KIRC	Kidney renal clear cell carcinoma
KIRP	Kidney renal papillary cell carcinoma
LAML	Acute myeloid leukemia
LGG	Brain lower grade glioma
LUSC	Lung squamous cell carcinoma
LIHC	Liver hepatocellular carcinoma
LUAD	Lung adenocarcinoma
MESO	Mesothelioma
OV	Ovarian serous cystadenocarcinoma
PRAD	Prostate adenocarcinoma
PAAD	Pancreatic adenocarcinoma
PCPG	Pheochromocytoma and paraganglioma
READ	Rectum adenocarcinoma
STAD	Stomach adenocarcinoma
SARC	Sarcoma
SKCM	Skin cutaneous melanoma
TGCT	Testicular germ cell tumors
THCA	Thyroid carcinoma
THYM	Thymoma
UCEC	Uterine corpus endometrial carcinoma
UVM	Uveal melanoma
UCS	Uterine carcinosarcoma

Table S2 The expression status of ABCB family gene in pan-cancers

Gene	Less expressed	More expressed
<i>ABCB1</i>	BLCA, BRCA, COAD, HNSC, KICH, KIRC, LUAD, LUSC, READ	–
<i>TAP1</i>	–	BLCA, BRCA, CHOL, COAD, ESCA, GBM, HNSC, KIRC, LIHC, LUAD, PRAD, READ, STAD, THCA, UCEC
<i>TAP2</i>	KICH	BLCA, CHOL, COAD, ESCA, GBM, HNSC, KICH, KIRC, KIRP, LIHC, PAAD, READ, STAD
<i>ABCB4</i>	BLCA, CHOL, COAD, HNSC, KICH, LIHC	BRCA, GBM, KIRC, KIRP, LUAD, LUSC
<i>ABCB6</i>	KICH, THCA	COAD, ESCA, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, UCEC
<i>ABCB7</i>	BRCA, KIRP, UCEC	CHOL, COAD, GBM, KICH, KIRC, LIHC, LUAD, LUSC, STAD
<i>ABCB8</i>	KIRC, THCA	BLCA, BRCA, CHOL, COAD, ESCA, HNSC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, THCA, UCEC
<i>ABCB9</i>	GBM, KIRC, PRAD	BLCA, BRCA, CHOL, ESCA, HNSC, KICH, KIRC, LIHC, LUAD, LUSC, READ, STAD, THCA, UCEC
<i>ABCB10</i>	KICH, KIRP, THCA, UCEC	BRCA, CHOL, ESCA, GBM, KIRC, LIHC, LUAD, LUSC, STAD

Table S3 Correlation analysis of the expression levels of ABCB family gene and prognosis by the Cox method in pan-cancers

Gene	Cancer	HR	HR.95L	HR.95H	p value	
<i>ABCB1</i>	SKCM	0.506332666	0.380835888	0.673184372	2.83E-06	
	KIRC	0.757179895	0.666890778	0.859693089	1.76E-05	
	HNSC	0.419286417	0.258552638	0.679943165	0.000425	
	PAAD	0.76118578	0.622652387	0.930541349	0.00776	
	MESO	0.718810699	0.542195927	0.952955923	0.021738	
	LUAD	0.679694991	0.467726812	0.987724607	0.042895	
<i>TAP1</i>	LGG	1.756764227	1.442467046	2.139543194	2.11E-08	
	SKCM	0.819058885	0.743928259	0.901777084	4.78E-05	
	PAAD	1.623012844	1.245608647	2.114765899	0.000335	
	UVM	1.485761762	1.182426037	1.866914245	0.000678	
	OV	0.860877575	0.775648288	0.955471972	0.004858	
	READ	0.590340328	0.405927656	0.858531557	0.005812	
	KIRP	1.621457085	1.079494157	2.435513951	0.019887	
	STAD	0.848342441	0.728477278	0.987930467	0.034327	
	LUAD	1.153245521	1.005538093	1.322650271	0.041456	
	THYM	2.178785654	1.028036917	4.617642468	0.042142	
	<i>TAP2</i>	SKCM	0.790009119	0.685577258	0.910348763	0.00112
		LUAD	1.275723095	1.055082157	1.542504916	0.011958
		LAML	1.512436042	1.0044652	2.277294207	0.047558
UVM		1.682400619	1.104321197	2.563087488	0.015438	
LGG		1.784730845	1.304538615	2.441678729	0.000292	
PAAD		1.845435753	1.320843087	2.578378274	0.00033	
ACC		1.850014973	1.103924268	3.100353438	0.019529	
<i>ABCB4</i>	KIRP	2.733970366	1.568825931	4.764450801	0.000387	
	LGG	3.782840051	2.432093711	5.883769524	3.56E-09	
	UVM	8.877375054	3.393019404	23.22644773	8.60E-06	
	KIRC	0.584743963	0.431750268	0.791952031	0.000526	
	ACC	1.34455089	1.110299426	1.628224832	0.002436	
	PAAD	0.317149307	0.14851189	0.677276972	0.003011	
	SKCM	0.833447926	0.721493978	0.962773725	0.013307	
	KICH	342.4169754	3.116445632	37622.79175	0.014931	
	HNSC	0.344914138	0.124749218	0.953639344	0.040223	
	SARC	0.648581076	0.423320933	0.993708035	0.046706	
	THCA	9.379386829	1.032026439	85.24287165	0.046816	
	DLBC	2.095817042	1.007178845	4.361141119	0.047805	
	<i>ABCB5</i>	LGG	3722217.424	3380.97322	4.10E+09	2.30E-05
READ		877484.0544	133.0000867	5.79E+09	0.00229	
STAD		3.30141668	1.302204197	8.369925484	0.01186	
<i>ABCB6</i>	ACC	4.759736206	2.607018129	8.69003882	3.78E-07	
	KIRP	2.47334617	1.580995768	3.869359679	7.31E-05	
	LIHC	1.726669545	1.304538358	2.285396746	0.000134	
	UVM	5.310152265	2.160803111	13.04964665	0.000273	
	PAAD	0.424354355	2.12E-01	8.48E-01	0.015216	
	LGG	0.600161802	0.390097715	0.9233435	0.020189	
	SKCM	1.350347018	1.036480424	1.759258571	0.026052	
	KIRC	1.360396127	1.02E+00	1.82E+00	0.036844	
	COAD	1.613133478	1.020254083	2.550540751	0.040781	
	KICH	6.183381897	1.00E+00	3.82E+01	0.049844	

Table S3 (continued)

Table S3 (continued)

Gene	Cancer	HR	HR.95L	HR.95H	p value
ABCB7	KIRC	4.27E-01	3.10E-01	5.87E-01	1.69E-07
	LGG	2.804835156	1.686236748	4.665477884	7.11E-05
	MESO	0.400234169	0.233279458	0.686675934	0.000885
	GBM	0.478226102	0.270087979	0.846761882	0.011387
	ESCA	2.333591989	1.205520383	4.517262127	0.011917
	UCEC	1.64E+00	1.09E+00	2.47E+00	0.01764
	SARC	1.58252596	1.062509154	2.357051141	0.023929
	SKCM	0.762817077	0.600582109	0.968876503	0.026478
	BRCA	1.508454217	1.028011379	2.213432818	0.035626
ABCB8	UVM	8.091592972	2.937960138	22.28548849	5.23E-05
	KIRC	1.933627638	1.350551578	2.768436175	0.000317
	LGG	2.145793233	1.382050882	3.331591233	0.00067
	DLBC	0.027337909	0.002218313	0.336905229	0.00497
	HNSC	0.619868296	0.443558758	0.866258861	0.005098
	KIRP	0.366934101	0.181795501	0.740615879	0.005143
	PAAD	0.548069726	0.345630327	0.869080059	0.010573
	KICH	11.38994331	1.627728014	79.70054425	0.014256
	GBM	1.396919964	1.062294381	1.836953504	0.016734
	SKCM	1.261567992	1.000035126	1.591497897	0.049965
	ABCB9	KIRC	2.098469521	1.447242528	3.042734197
LGG		1.87E+00	1.23E+00	2.86E+00	0.003735
THYM		3.86768459	1.539484068	9.716881388	0.004003
KIRP		2.662616087	1.202310512	5.896583584	0.015772
PCPG		16.04910866	1.588531432	162.145919	0.018665
UVM		4.221433297	1.260967704	14.13239929	0.019486
DLBC		6.511585171	1.31522793	32.23832195	0.021692
BLCA		1.649441667	1.02243904	2.660948678	0.040276
ABCB10	KIRC	8.280304695	1.070303442	64.05981998	0.042862
	KIRC	0.583764941	0.43799616	0.778046789	0.000241
	PCPG	14.6519283	2.650409767	80.99841982	0.002089
	ACC	2.987619312	1.468152649	6.079660149	0.002534
	MESO	1.965655913	1.102767895	3.503732007	0.021924
ABCB11	LGG	6.781550297	2.159670495	21.29464867	0.001042
	KICH	1071118.999	81.06868827	14152145966	0.004133
	SKCM	0.001883742	8.21E-06	0.432314817	0.023677

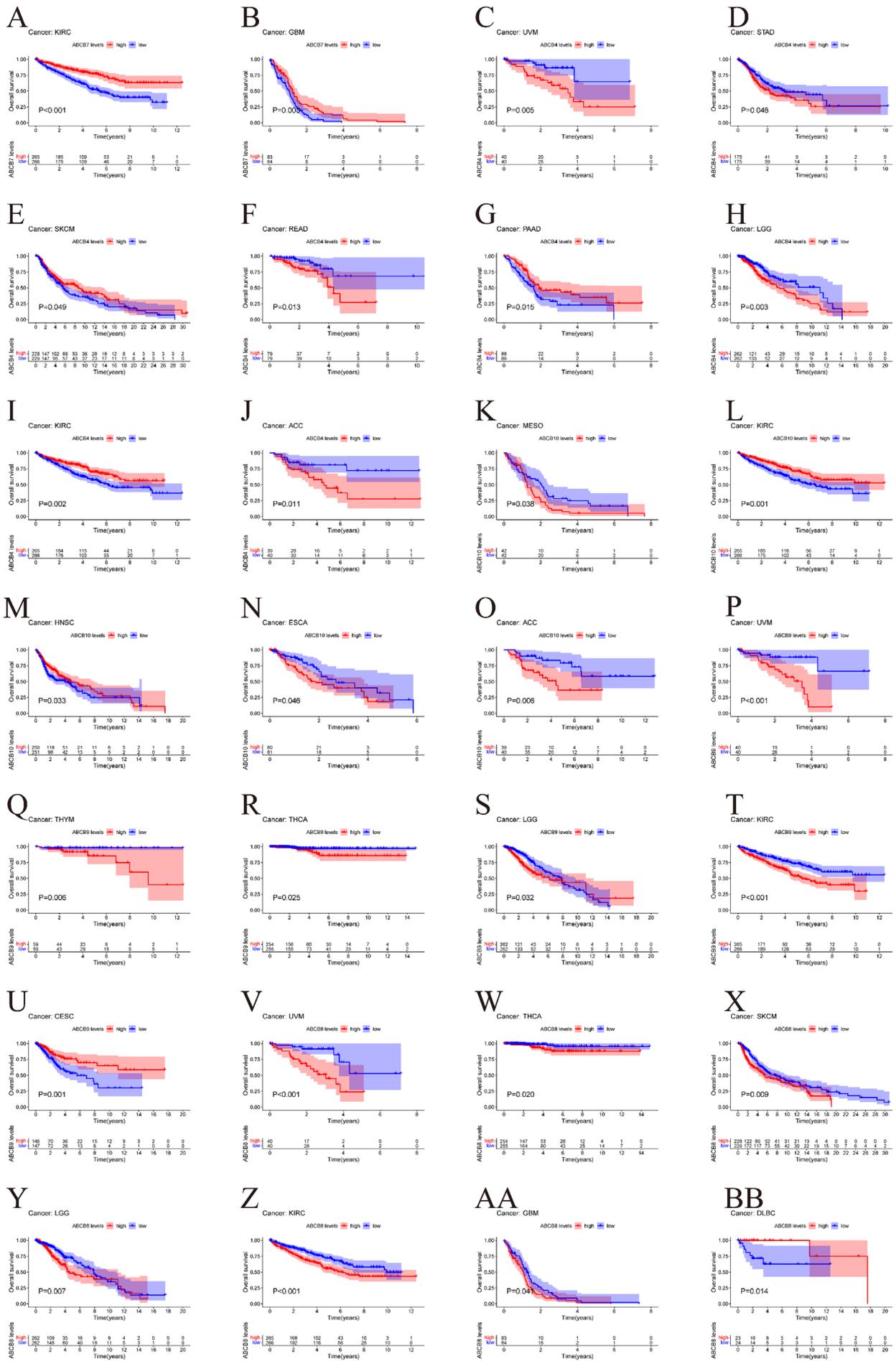


Figure S1 Correlation analysis of the expression levels of ABCB family gene and prognosis by Kaplan-Meier survival curves in pan-cancers. (A) KIRC (n=531); (B) GBM (n=167); (C) UVM (n=80); (D) STAD (n=350); (E) SKCM (n=457); (F) READ (n=158); (G) PAAD (n=177); (H) LGG (n=524); (I) KIRC (n=531); (J) ACC (n=79); (K) MESO (n=84); (L) KIRC (n=531); (M) HNSC (n=501); (N) ESCA (n=161); (O) ACC (n=79); (P) UVM (n=80); (Q) THYM (n=118); (R) THCA (n=509); (S) LGG (n=524); (T) KIRC (n=531); (U) CESC (n=293); (V) UVM (n=80); (W) THCA (n=509); (X) SKCM (n=457); (Y) LGG (n=524); (Z) KIRC (n=531); (AA) SKCM (n=167); (BB) DLBC (n=47).

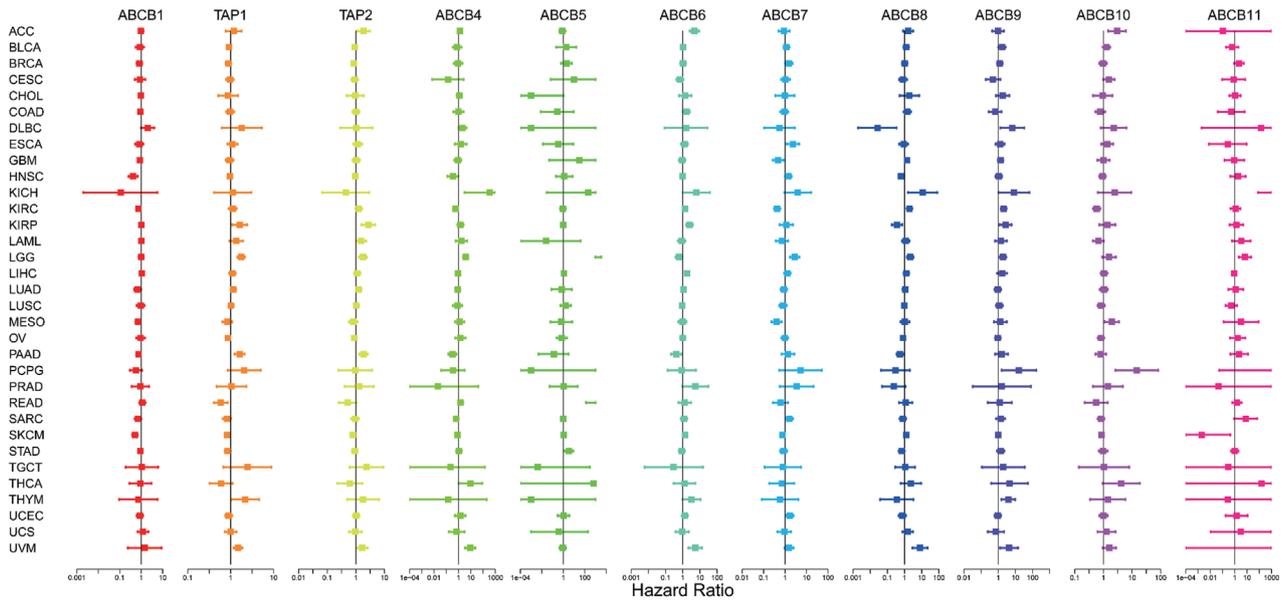


Figure S2 Correlation analysis of the expression levels of ABCB family gene and prognosis by the Cox method in pan-cancers. The lines of different colors represent the risk value of each gene in the corresponding cancer. hazard ratio <1 or hazard ratio >1 represents low or high risk respectively.

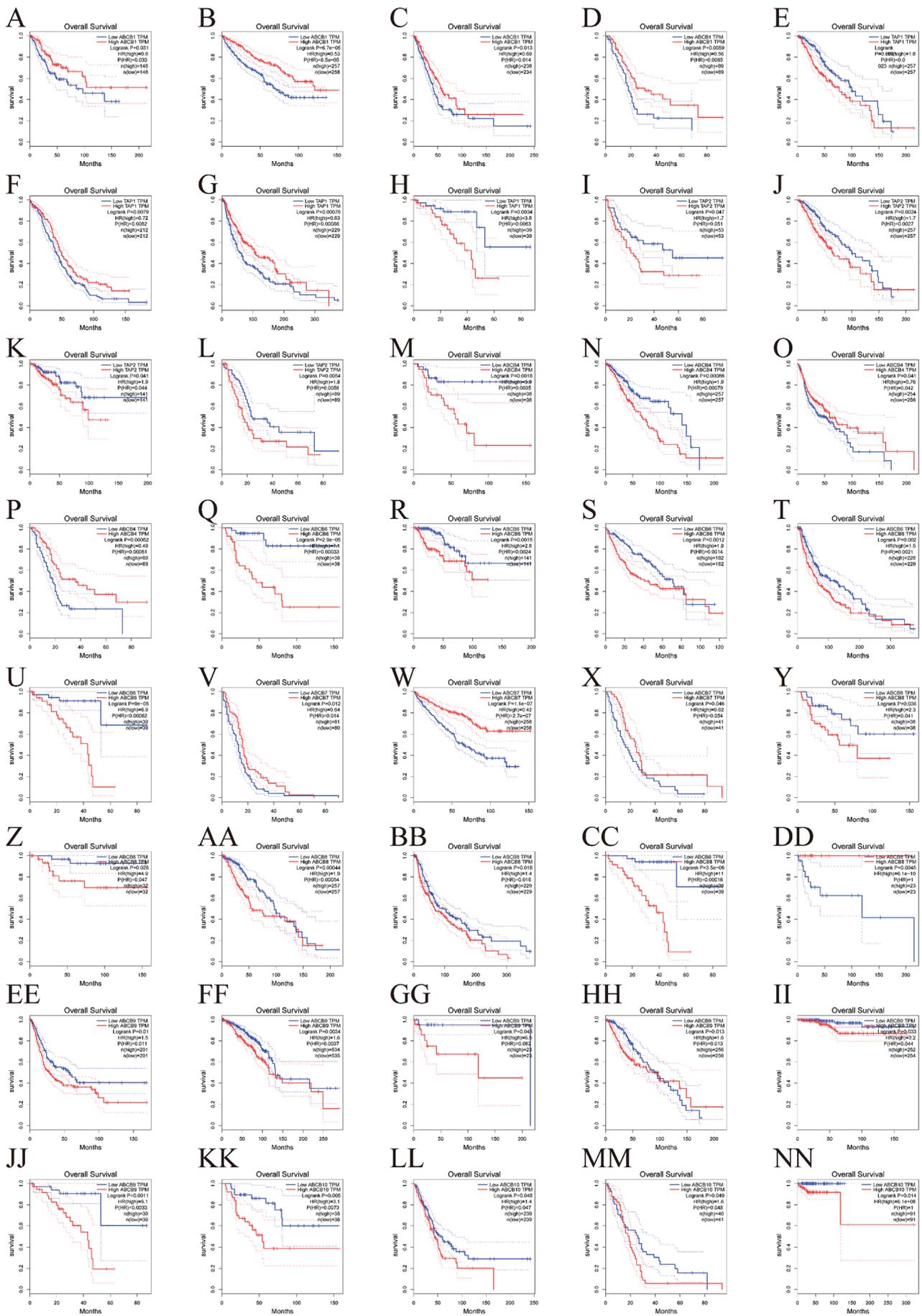


Figure S3 Correlation analysis of the expression levels of ABCB family gene and prognosis by GEPIA database in pan-cancers. (A) CESC in ABCB1, (B) KIRC in ABCB1, (C) LUAD in ABCB1, (D) PAAD in ABCB1, (E) LGG in TAP1, (F) OV in TAP1, (G) SKCM in TAP1, (H) UVM in TAP1, (I) LAML in TAP2, (J) LGG in TAP2, (K) KIRP in TAP2, (L) PAAD in TAP2, (M) ACC in ABCB4, (N) LGG in ABCB4, (O) HNSC in ABCB4, (P) PAAD in ABCB4, (Q) ACC in ABCB6, (R) KIRP in ABCB6, (S) LIHC in ABCB6, (T) SKCM in ABCB6, (U) UVM in ABCB6, (V) GBM in ABCB7, (W) KIRC in ABCB7, (X) MESO in ABCB7, (Y) ACC in ABCB8, (Z) KICH in ABCB8, (AA) LGG in ABCB8, (BB) SKCM in ABCB8, (CC) UVM in ABCB8, (DD) DLBC in ABCB8, (EE) BLCA in ABCB9, (FF) BRCA in ABCB9, (GG) DLBC in ABCB9, (HH) LGG in ABCB9, (II) THCA in ABCB9, (JJ) UVM in ABCB9, (KK) ACC in ABCB10, (LL) LUAD in ABCB10, (MM) MESO in ABCB10, (NN) PCPG in ABCB10.

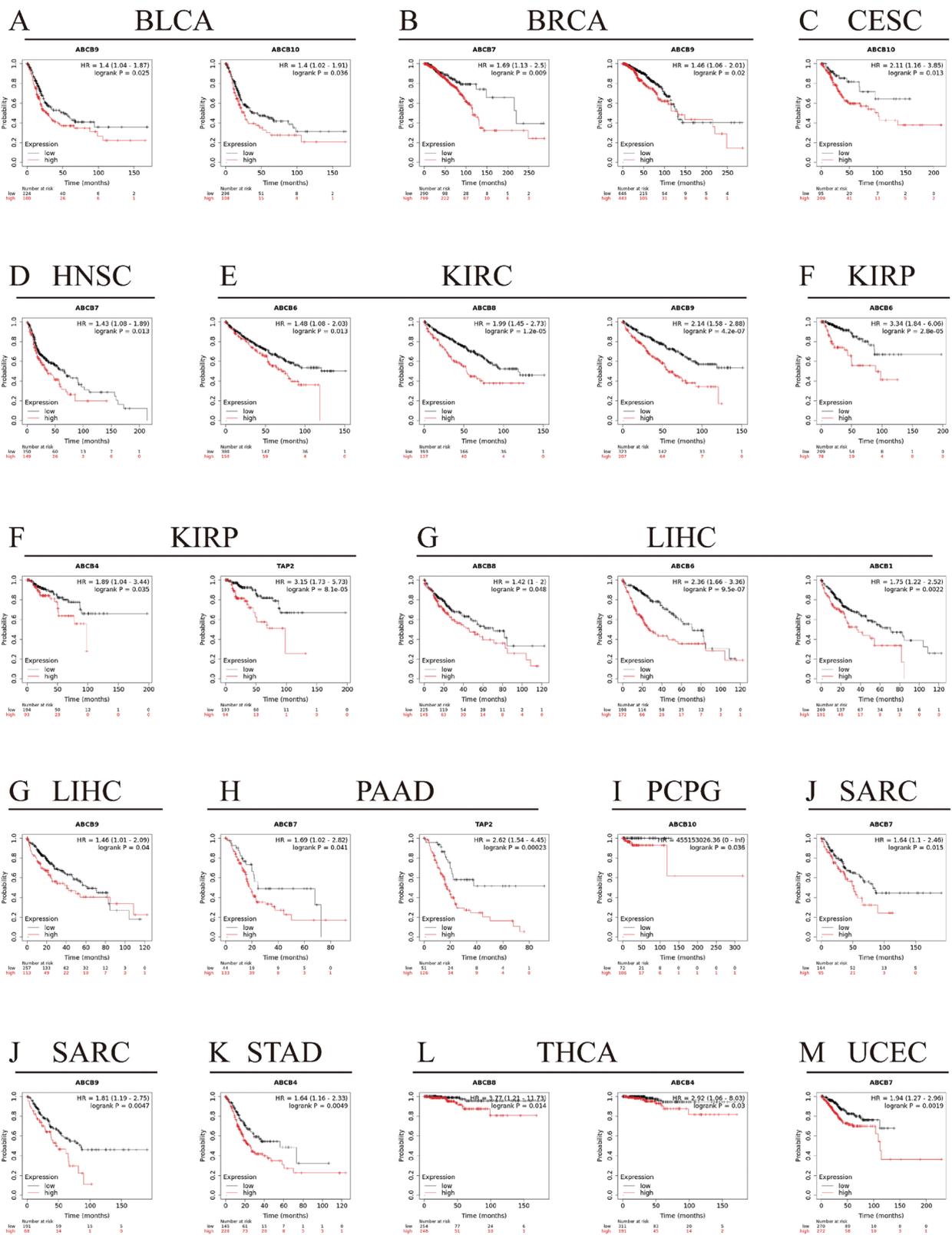


Figure S4 Correlation analysis of the expression levels of ABCB family gene and prognosis by Kaplan-Meier Plotter database in pan-cancers. (A) ABCB9, ABCB10 in BLCA; (B) ABCB7, ABCB9 in BRCA; (C) ABCB10 in CESC; (D) ABCB7 in HNSC; (E) ABCB6, ABCB8, ABCB9 in KIRC; (F) TAP2, ABCB4, ABCB6 in KIRP; (G) ABCB1, ABCB6, ABCB8, ABCB9 in LIHC; (H) TAP2, ABCB7 in PAAD; (I) ABCB10 in PCPG; (J) ABCB7, ABCB9 in SARC; (K) ABCB4 in STAD; (L) ABCB4, ABCB8 in THCA; (M) ABCB7 in UCEC.

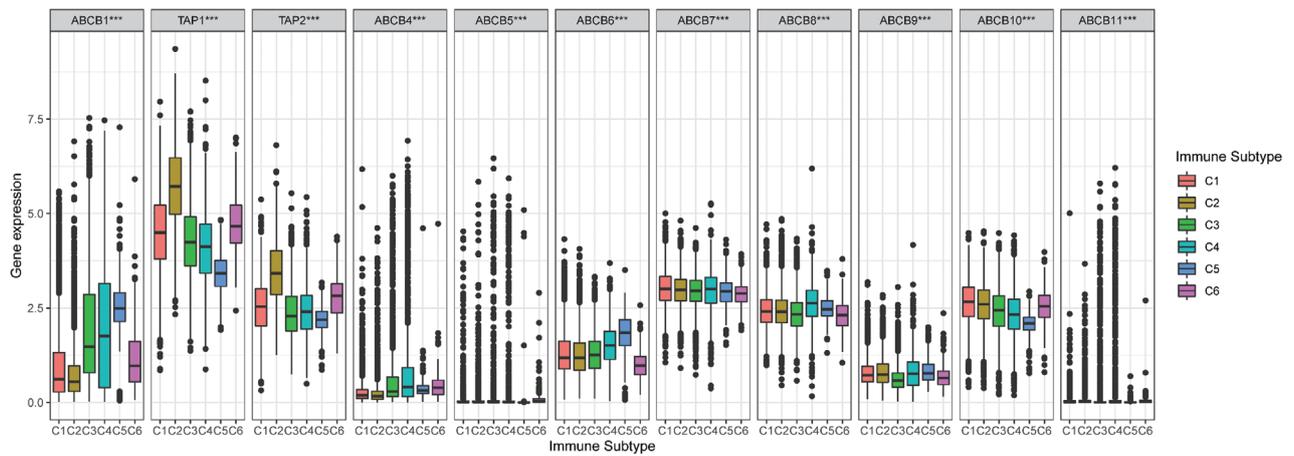


Figure S5 Correlation analysis of the expression levels of ABCB family gene and immune subtypes in pan-cancers. C1, wound healing; C2, IFN-g dominant; C3, inflammatory; C4, lymphocyte depleted; C5, immunologically quiet; C6, TGF-b dominant. *, P<0.05; **, P<0.01; ***, P<0.001.