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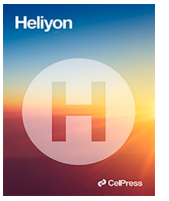

Review article

Golgi scaffold protein PAQR11 in pan-cancer landscape: A comprehensive bioinformatics exploration of expression patterns, prognostic significance, and potential immunological function

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ABSTRACT

Background: The progestin and adipoQ receptor family member, PAQR11, is recognized for its roles in vesicle trafficking, mitogenic signaling, and metastatic spread, positioning it as a crucial regulator in cancer biology. PAQR11 influences lipid metabolism and susceptibility to ferroptosis in cancer cells. This study aims to investigate the prognostic significance of PAQR11, its relevance to immune responses, and its association with drug sensitivity across various cancer types. By elucidating these aspects, the research seeks to assess PAQR11's potential as a biomarker and therapeutic target in oncology.

Methods: We conducted a comprehensive bioinformatics analysis using publicly available pan-cancer datasets from TCGA, GEO, UALCAN, TIMER, GEPIA2, KM plotter, and TISIDB. This analysis encompassed gene expression profiles across 33 cancer types, with a focus on PAQR11's expression patterns, prognostic significance, and immunological relevance. In addition, the study explored the correlation between PAQR11 expression and drug sensitivity, alongside its molecular and pathological characteristics in various tumors.

Results: Our findings demonstrate elevated PAQR11 expression levels across multiple cancer types, which significantly correlate with patient prognostic outcomes. The analysis further revealed PAQR11's involvement in immunological and epigenetic processes, underscoring its critical role in cancer progression and treatment response. Notably, a strong correlation between PAQR11 expression and drug sensitivity was identified, suggesting its potential influence on the initiation and progression of various cancers and highlighting its promise as a therapeutic target.

Conclusions: The comprehensive analysis of PAQR11 underscores its significance as a biomarker for cancer prognosis and its role in regulating immunological and epigenetic processes. These findings offer valuable insights that could inform early detection strategies and the development of novel therapeutic approaches. Further exploration and validation of PAQR11 are essential, highlighting the need for its integration into future oncological research and treatment strategy development.

Trial registration: Not applicable.

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1. Background

The rising incidence of malignant tumors has increasingly become a critical factor affecting human life expectancy and quality of life [1,2]. Cancer imposes a substantial societal and economic burden, with lung, breast, and prostate cancers among the leading contributors [3]. A significant challenge remains in the early diagnosis and treatment of cancer, as nearly 50 % of cases are diagnosed at advanced stages [4]. Despite the development of novel anti-tumor therapies over the past decade, including a variety of immunotherapies and targeted therapies, many patients exhibit poor drug sensitivity or develop resistance, rendering these treatments ineffective [5]. Therefore, it is imperative to conduct extensive research to identify key driver genes and their downstream pathways. Such investigations will not only promote the development of more effective treatment strategies but also deepen our understanding of therapeutic targets and potential biomarkers in tumors.

PAQR11, also known as monocyte-to-macrophage differentiation-associated (MMD), is a relatively understudied member of the progestin and adipoQ receptor (PAQR) family. It functions as a critical scaffold protein within the endomembrane system, facilitating vesicle trafficking, mitogenic signaling, and the promotion of metastatic spread [6,7]. PAQR11's biological activity is reportedly mediated through the activation of Ras signaling pathways [6]. Additionally, elevated PAQR11 expression levels have been observed in mature macrophages [8], and its role in macrophage activation has been demonstrated in in vitro studies [9]. More recently, PAQR11 was identified as a key regulator of lipid metabolism, particularly in enhancing ferroptosis susceptibility in ovarian and renal cancer cells [10].

The discovery of genetic commonalities and differences across various cancers has been facilitated by advancements in genetics and cancer genomics technologies, which have underscored the importance of key gene alterations, mutations in signaling pathways, and immunological changes in cancer development. Analyzing pan-cancer data offers substantial insights into the detection and treatment of multiple cancer types [11]. The publicly available pan-cancer dataset from The Cancer Genome Atlas (TCGA) provides gene expression profiles across 33 distinct cancer types, serving as a critical resource for cross-cancer studies on the molecular and pathological characteristics of tumors, as well as patient-related clinical features [12]. Recent comprehensive analyses of various cancers using the TCGA database have identified significant molecular alterations at the genomic, transcriptomic, and proteomic levels in both cancerous and normal tissues, further advancing our understanding of tumor biology.

Currently, only a limited number of studies have explored the relationship between PAQR11 and cancer characteristics in individual cancer types. While the pan-cancer expression of PAQR11 and its impact on clinical prognosis remain insufficiently elucidated, previous research indicates a potential link between PAQR11 and the initiation and progression of cancer [13]. Further comprehensive studies are needed to fully understand PAQR11's role across various cancers and its implications for prognosis and therapeutic strategies.

In this study, we conducted a comprehensive and systematic examination of PAQR11 using bioinformatics approaches, focusing on its expression patterns, prognostic significance, and immunological relevance. Additionally, a strong correlation between PAQR11 expression and drug sensitivity was observed. By analyzing PAQR11 across multiple cancer types, this research provides a novel perspective on its role in cancer biology. The analysis uncovers important insights into the immunological and epigenetic processes associated with PAQR11, presenting potential avenues for early cancer detection and the development of innovative therapeutic strategies.

2. Methods

2.1. TIMER, GEPIA2, and CCLE

The pan-cancer cell line expression was assessed using the Cancer Cell Line Encyclopedia (CCLE) dataset [14], accessible at https://sites.broadinstitute.org/ccle/. An expression matrix was constructed using R version 4.2.2, and data visualization was performed using the ggplot2 package.

The TIMER web tool (https://cistrome.shinyapps.io/timer/) [15] serves as a comprehensive resource that leverages TCGA data to measure immune cell infiltration levels in various tumor tissues and to examine differences in gene expression between tumor and normal tissues. In this study, the "DiffExp module" was used to analyze the differential expression of PAQR11 across tumor and adjacent normal tissues in multiple cancer types. Additionally, the "Gene module" was employed to investigate the relationship between PAQR11 expression and the extent of immune cell infiltration, providing insights into its potential role in modulating tumor-immune interactions.

The GEPIA2 web tool (http://gepia2.cancer-pku.cn/#index) consolidates data from the TCGA and GTEx datasets to facilitate differential expression analyses [16]. in this study, a log2 transformation was applied to the expression values after adding 1 to the transcripts per million (TPM) values. Statistical significance was evaluated using an unpaired two-sample *t*-test, with a threshold of $P < 0.01$. The relationship between PAQR11 expression and both overall survival (OS) and disease-free survival (DFS) was assessed using GEPIA2, with PAQR11 expression dichotomized at the median value. Survival analyses were performed using the Log-rank test (Mantel–Cox test), and Cox proportional hazard ratios with 95 % confidence intervals were incorporated into the survival plots to provide a comprehensive assessment of the prognostic significance of PAQR11.

2.2. Prognoscan and KM plotter

The PrognoScan website (http://dna00.bio.kyutech.ac.jp/PrognoScan/index.html) [17] serves as a comprehensive resource for

investigating the relationships between gene expression patterns and clinical outcomes, with a particular focus on overall survival (OS) and disease-free survival (DFS). This tool allows researchers to explore the prognostic significance of specific genes across various cancer types, facilitating the identification of potential biomarkers linked to patient outcomes.

The KM plotter tool was utilized to explore the association between PAQR11 expression and overall survival (OS) across multiple cancer types. The log-rank test was applied to compare survival rates between groups, with a significance threshold set at $P < 0.05$. Cutoff values for grouping were determined by calculating all possible values between the lower and upper quartiles, and the optimal threshold was selected for analysis.

2.3. Tisidb

The TISIDB database, available at http://cis.hku.hk/TISIDB/, integrates various data types to provide insights into tumor-immune interactions [18]. In this study, the TISIDB platform was utilized to examine the relationship between PAQR11 expression and immune subtypes across a wide range of cancer types. The analysis was conducted using the Pearson correlation coefficient, with statistical significance set at a threshold of $P < 0.05$.

2.4. Sangerbox

Sangerbox functions as an online analytical tool that integrates data from both the TCGA and GTEx datasets [19]. This platform sources its data primarily from the University of California, Santa Cruz (UCSC) via the Xenabrowser platform, which is accessible at https://xenabrowser.net/, for online data analysis. In this study, Sangerbox was used to analyze the association between PAQR11 expression and various factors, including immune checkpoint genes, tumor mutation burden, microsatellite instability, and ESTIMATE scores in tumor specimens.

To validate the prognostic relevance of PAQR11, Cox proportional hazard regression models were employed. The association between PAQR11 expression and multiple clinical outcomes was evaluated using the Log-rank test on the Sangerbox platform, with hazard ratios (HR) and 95 % confidence intervals (CI) computed via Cox proportional hazards regression. The clinical outcomes analyzed included overall survival (OS), disease-specific survival (DSS), disease-free interval (DFI), and progression-free interval (PFI) in patients with various malignancies. Expression values were normalized using a $\log2(x + 0.001)$ transformation. Correlation analysis was subsequently performed using the Pearson correlation coefficient to further investigate the relationships between PAQR11 expression and clinical outcomes.

2.5. Ualcan

The UALCAN web portal (http://ualcan.path.uab.edu) serves as a comprehensive resource offering extensive and interactive data analysis, leveraging information from The Cancer Genome Atlas (TCGA) to enable detailed exploration of various tumor types [20]. In this study, UALCAN was used to investigate differences in PAQR11 promoter methylation levels between tumor and normal tissues. Promoter methylation degrees were quantified using beta values, and statistical comparisons were performed using the Student's t-test to identify significant variations.

2.6. Cbioportal

The cBioPortal platform (https://www.cbioportal.org) provides a robust resource for exploring multi-dimensional cancer genomic datasets, primarily derived from the TCGA [21]. In this study, PAQR11 gene mutations across various malignancies were thoroughly analyzed, including detailed summaries of gene mutations and visualizations of pan-oncogenic mutations.

2.7. Gsca

The GSCA platform (http://bioinfo.life.hust.edu.cn/GSCA/#/) integrates drug sensitivity data with transcriptomic information from cancer cell lines, drawing primarily from the GDSC (Genomics of Drug Sensitivity in Cancer) and CTRP (Cancer Therapeutics Response Portal) databases [22]. In this research, Generalized Structured Component Analysis (GSCA) was used to investigate the prevalence of deleterious mutations in the PAQR11 gene across various cancer types. Additionally, the study explored the relationship between PAQR11 expression and copy number variations (CNV). Further analysis examined the connection between PAQR11 expression levels and drug responsiveness, covering a wide array of chemotherapeutic agents. Spearman correlation coefficients were used to assess the relationship between expression levels and drug sensitivity, while t-tests were employed to evaluate the statistical significance of differences between groups.

2.8. Cellminer

CellMiner (https://discover.nci.nih.gov/cellminer/home.do) is a specialized software tool designed to facilitate the integration and analysis of pharmacological data across 60 different cancer cell lines [23]. In this study, the datasets used were the Processed RNA sequencing data and the Developmental Therapeutics Program NCI-60, both sourced from the CellMiner database. Statistical analyses and graphical visualizations were performed using the R programming language. The focus of this study was on drugs that have either

gained approval from the U.S. Food and Drug Administration (FDA) or undergone extensive clinical evaluations.

2.9. Analysis of PAQR11 copy number alterations (CNA) and single nucleotide variants (SNV)

To investigate the relationship between PAQR11 expression and copy number alterations (CNA) in breast cancer, we analyzed data across molecular subtypes, including HER2-positive, luminal A, luminal B, and triple-negative breast cancer (TNBC). Bar plots were generated using R software (version X.X) to visualize the PAQR11 CNA counts, with pairwise comparisons assessed by Student's t-test. Statistical significance was indicated by *P < 0.05, **P < 0.01, and ***P < 0.001.

Additionally, PAQR11 single nucleotide variant (SNV) frequency in uterine corpus endometrial carcinoma (UCEC) was analyzed using TCGA data. A total of 475 patients were stratified into microsatellite stable (MSS, n = 358) and microsatellite instability (MSI, n = 117) groups based on their MSI NABTIS scores. Bar plots were generated using R software, and a chi-squared test was employed to evaluate differences in SNV frequency between the MSS and MSI groups.

3. Results

3.1. Elevated expression of PAQR11 in tumors compared to normal tissues

Firstly, we examined the expression levels of PAQR11 across various tumor cell lines (Fig. 1A). The analysis revealed differential expression, with notably high PAQR11 expression in liver hepatocellular carcinoma (LIHC) cell lines and low expression in mesothelioma (MESO) cell lines.

Subsequently, we compared PAQR11 expression between tumor and normal tissues. Differential expression analysis, conducted using the GEPIA2 web tool, indicated that PAQR11 is significantly overexpressed in nine tumor types compared to normal tissues, while being underexpressed in breast cancer (BRCA) (Fig. 1B). Collectively, these findings highlight the broadly elevated expression of PAQR11 in a variety of tumors, suggesting its potential role in cancer biology.

3.2. Pan-cancer prognostic significance of PAQR11

To assess the pan-cancer prognostic significance of PAQR11, we conducted a series of analyses. Using GEPIA2, we found that high PAQR11 expression significantly correlated with poorer overall survival (OS) in stomach adenocarcinoma (STAD), prostate adenocarcinoma (PRAD), LIHC, acute myeloid leukemia (LAML), and kidney renal papillary cell carcinoma (KIRP) (Fig. 1C). Notably, patients with high PAQR11 expression exhibited shorter median survival times and worse OS. Similarly, Kaplan-Meier plotter results supported these findings, showing that high PAQR11 expression was associated with significantly worse OS in head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), KIRP, LIHC, lung adenocarcinoma (LUAD), pheochromocytoma and paraganglioma (PCPG), STAD, thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC). Thus, PAQR11 was identified as a prognostic risk factor for these cancers. Conversely, in esophageal squamous cell carcinoma (ESCC) and rectum adenocarcinoma (READ), high PAQR11 expression correlated with prolonged OS, indicating that PAQR11 may act as a protective factor in these cancers (Fig. S1)

Next, we utilized the Sangerbox online tool, which applies the R package 'surv' Coxph function, to construct Cox proportional hazard regression models. Across 39 tumor types, we found significant associations between PAQR11 expression and OS, disease-specific survival (DSS), disease-free interval (DFI), and progression-free interval (PFI). High PAQR11 expression was associated with poor OS in eight cancer types, including esophagogastric junction adenocarcinoma (STES), bladder urothelial carcinoma (BLCA), STAD, LAML, glioblastoma multiforme and lower-grade glioma (GBMLGG), the pan-kidney cohort (KIPAN), LIHC, and KIRP (Fig. 2A). Similarly, PAQR11 expression impacted patient DSS, DFI, and PFI (Fig. 2B–D).

Additionally, we used PrognoScan to analyze the relationship between PAQR11 expression and survival in GEO datasets. High PAQR11 expression was associated with inferior OS in lung, bladder, and brain cancers. He high expression group also demonstrated worse OS in lung and breast cancers and poorer disease-free survival (DFS) in breast and colorectal cancers. However, in brain and soft tissue cancers, PAQR11 appeared to function as a protective factor for survival. These comparisons were statistically significant, with further details provided in Table 1.

Collectively, these results suggest that PAQR11 expression significantly influences the prognosis of patients across a wide range of cancer types, acting as either a risk or protective factor depending on the tumor context.

3.3. PAQR11 genetic alterations are prevalent across various tumor tissues

Alterations in PAQR11 across various cancers were analyzed using cBioPortal. Our findings indicated that PAQR11 gene alterations were present in approximately 5 % of the cancer patients analyzed (Fig. S2), with gene amplification being the most common alteration. Additionally, missense mutations in the PAQR11 gene were detected in a specific subset of patients. A comprehensive pan-cancer analysis revealed that the highest frequency of PAQR11 amplifications occurred in pancreatic neuroendocrine tumors (Fig. 3A). In melanoma, colorectal adenocarcinoma, and hepatocellular carcinoma, mutations were identified in a subset of patients, while deep deletions were observed in breast invasive ductal carcinoma, uterine endometrioid carcinoma, pancreatic adenocarcinoma, and prostate adenocarcinoma (Fig. 3A).

To further investigate the relationship between PAQR11 expression and copy number variations (CNV), we used the GSCA

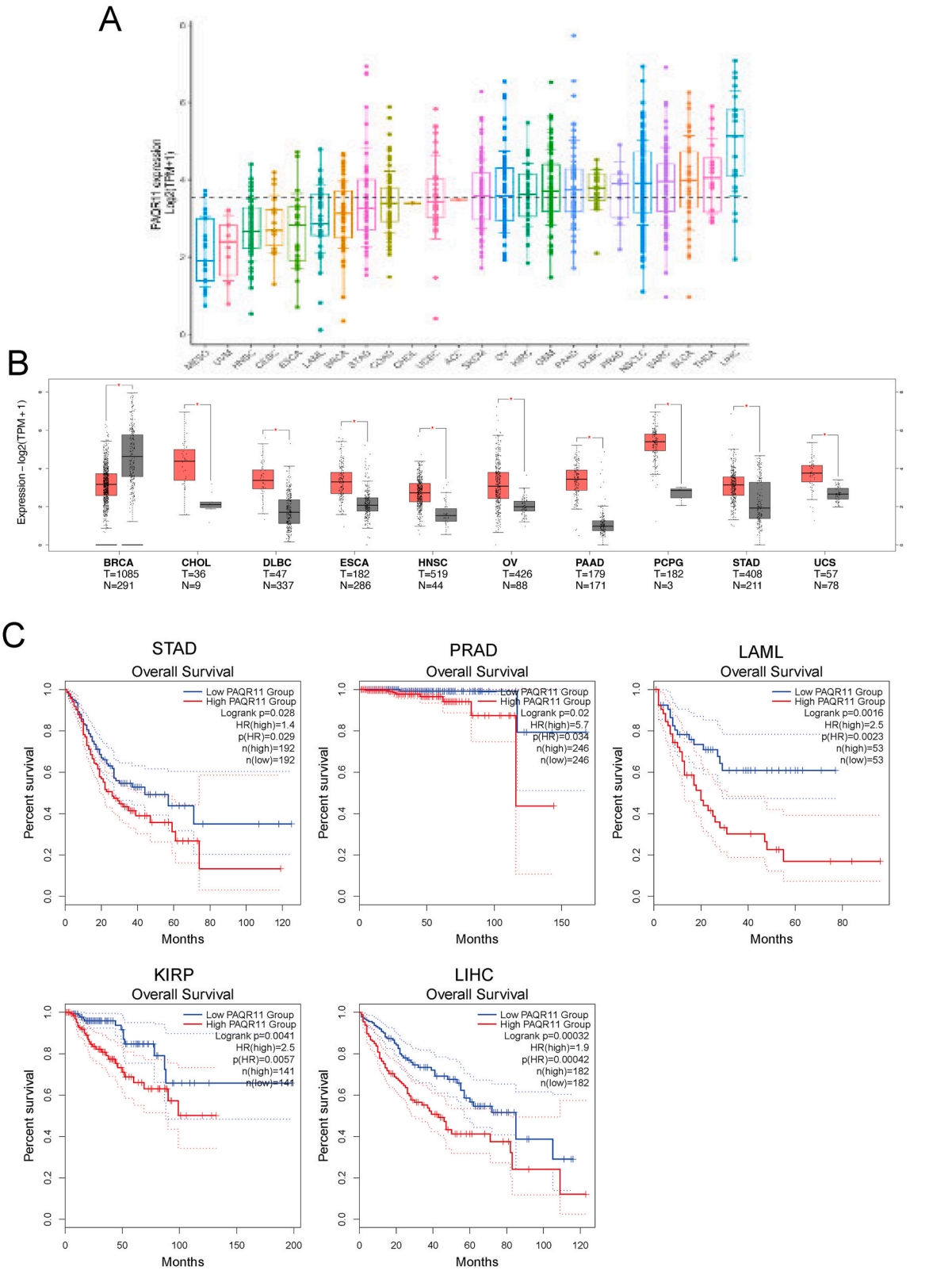

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Fig. 1. Pa-cancer analysis of PAQR11 expression and prognosis. **A:** exhibits the expression levels of PAQR11 in various cancer cell lines, utilizing data extracted from the CCLE database. **B:** The differences in PAQR11 expression between tumor and normal tissues were analyzed using the GEPIA2 database. An unpaired two-sample *t*-test was employed to assess statistical significance, with a p-value threshold set at 0.01. In the visualization, red represents tumor tissues, while blue indicates normal tissues. Statistically significant differences are marked with an asterisk (*P < 0.01). **C:** The Kaplan-Meier survival curve was used to analyze human cancers, with groups segregated into high and low PAQR11 expression based on the median cutoff value, as assessed by the GEPIA2 database. Statistical significance was determined using the logrank test to calculate the P-value.

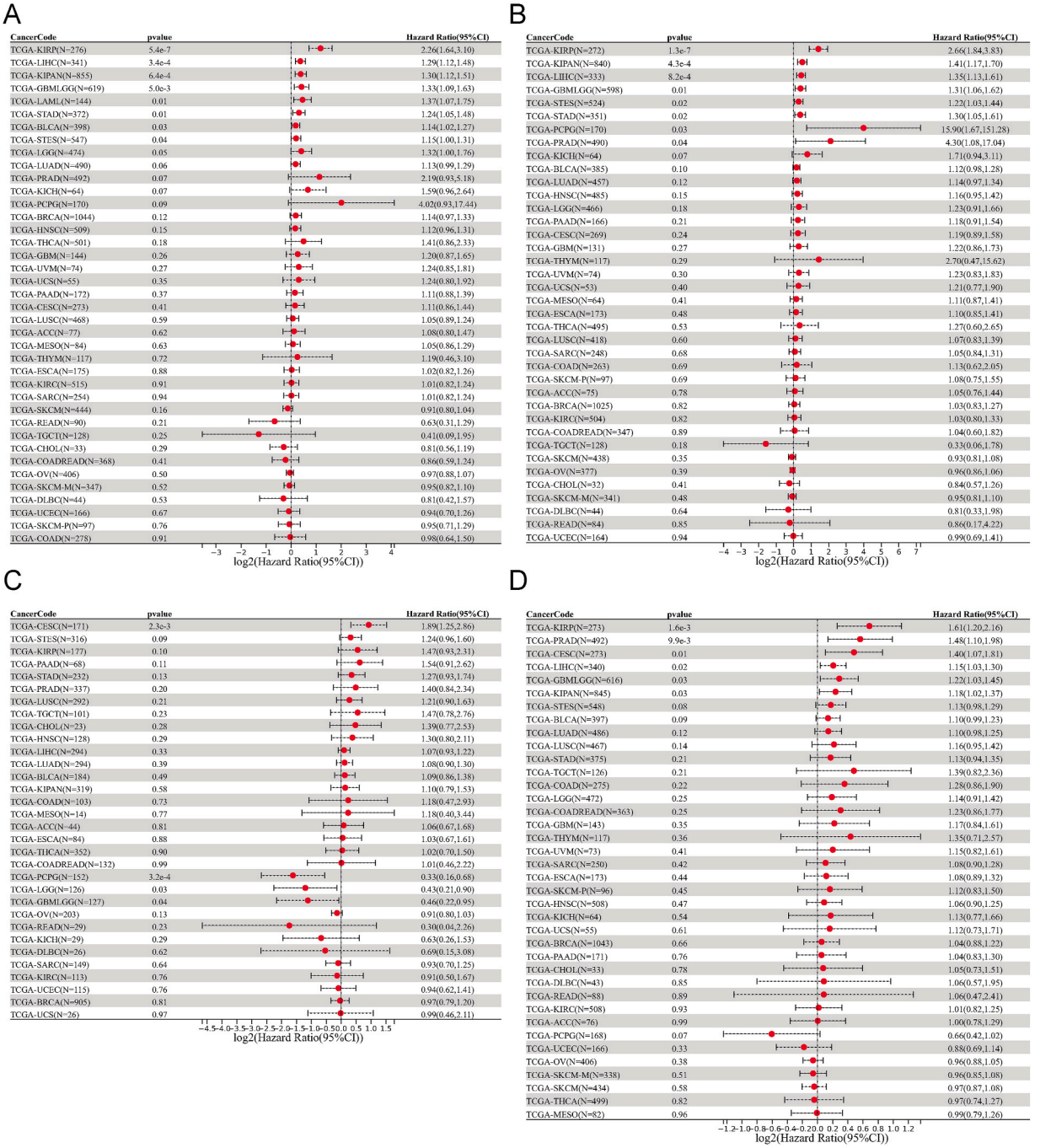

Fig. 2. Analysis of the correlation between PAQR11 expression and **A** (Overall Survival, OS), **B** (Disease-Specific Survival, DSS), **C** (Disease-Free Interval, DFI), and **D** (Progression-Free Interval, PFI) was conducted using Cox proportional hazard regression models. Hazard ratios (HR) with 95 % confidence intervals were calculated, and statistical significance was assessed using the Log-rank test. The results are presented as forest plots.

Table 1
Analysis of the prognosis of PAQR11 across different cancer types was executed using the PrognoScan database.

DATASET	CANCER TYPE	ENDPOINT	PROBE ID	CORRECTED _P_-VALUE	ln(HRhigh/HRlow)	COX _P_-VALUE	ln (HR)	HR [95 % CIlow - CIupp]
GSE31210	Lung cancer	Relapse Free Survival	203414_at	0.000322	1.45	0.000138	0.92	2.51 [1.56–4.03]
GSE2658	Blood cancer	Disease Specific Survival	244523_at	0.000495	0.89	0.001264	0.62	1.87 [1.28–2.73]
GSE17537	Colorectal cancer	Disease Free Survival	203414_at	0.001449	2.5	0.00003	1.92	6.83 [2.77–16.85]
GSE6532-GPL570	Breast cancer	Relapse Free Survival	244523_at	0.005401	1.42	0.067175	0.47	1.60 [0.97–2.65]
GSE6532-GPL570	Breast cancer	Distant Metastasis Free Survival	244523_at	0.005401	1.42	0.067175	0.47	1.60 [0.97–2.65]
GSE31210	Lung cancer	Overall Survival	203414_at	0.006242	1.77	0.006834	0.87	2.38 [1.27–4.48]
GSE4922-GPL97	Breast cancer	Disease Free Survival	244523_at	0.006509	0.84	0.079793	0.43	1.53 [0.95–2.48]
GSE13507	Bladder cancer	Disease Specific Survival	ILMN_1733937	0.010726	1.25	0.01318	0.37	1.45 [1.08–1.95]
GSE7696	Brain cancer	Overall Survival	203414_at	0.010932	−1.25	0.025347	−0.49	0.61 [0.40–0.94]
GSE2990	Breast cancer	Distant Metastasis Free Survival	203414_at	0.012369	1.28	0.282437	0.24	1.28 [0.82–1.99]
GSE8894	Lung cancer	Relapse Free Survival	203414_at	0.014561	0.82	0.004119	0.47	1.60 [1.16–2.19]
GSE30929	Soft tissue cancer	Distant Recurrence Free Survival	203414_at	0.015907	−1.07	0.002319	−0.45	0.64 [0.48–0.85]
GSE4412-GPL96	Brain cancer	Overall Survival	203414_at	0.019058	0.97	0.002918	1.18	3.27 [1.50–7.13]
GSE14333	Colorectal cancer	Disease Free Survival	203414_at	0.025924	0.95	0.414217	0.26	1.30 [0.70–2.42]
GSE4716-GPL3694	Lung cancer	Overall Survival	1686	0.029211	1.59	0.01865	1.8	6.07 [1.35–27.28]
GSE2990	Breast cancer	Relapse Free Survival	203414_at	0.042601	0.87	0.197135	0.22	1.25 [0.89–1.75]

platform. A significant correlation between PAQR11 expression and CNV was observed in 16 tumor types, with the strongest positive correlation observed in breast cancer (BRCA) (Fig. 3B). A deeper analysis of different molecular subtypes of BRCA revealed that PAQR11 CNVs were associated with specific subtypes. The HER2 subtype exhibited the highest frequency of PAQR11 CNAs, while triple-negative breast cancer (TNBC) showed the least (Fig. 3C).

In addition, we analyzed the frequency of single nucleotide variants (SNV) of PAQR11 across various tumors, finding that the highest SNV frequency occurred in UCEC (Fig. 3D). We further stratified the 475 TCGA-UCEC patients based on their MSI NABTIS Score into the Microsatellite Stable (MSS) group ($n = 358$, MSI NABTIS Score <0.4) and the Microsatellite Instability (MSI) group ($n = 117$, MSI NABTIS Score >0.6). A comparison of SNV proportions between the groups revealed no statistically significant difference ($p = 0.753$) (Fig. 3E).

Collectively, these results suggest that PAQR11 alterations, including amplifications, CNVs, and SNVs, are prevalent across multiple tumor types. These alterations may play a crucial role in regulating tumorigenesis and proliferation, highlighting the potential importance of PAQR11 in cancer development and progression.

3.4. Pan-cancer analysis of PAQR11 promoter methylation

DNA methylation plays a critical role in tumor development, metastasis, and progression [24,25]. Epigenetic methylation is instrumental in regulating tumor proliferation and metastasis [26–28], and it can also serve as a biomarker for monitoring the effectiveness of interventions aimed at reducing tumor risk [29]. Additionally, DNA methyltransferases have become key targets in epigenetic cancer drug therapy research [30,31].

o assess the methylation levels of the PAQR11 promoter across different tumors, we utilized the UALCAN platform. The analysis revealed that PAQR11 promoter methylation levels were significantly elevated in READ, KIRC, and colon adenocarcinoma (COAD) compared to normal tissues (Fig. 4A). In contrast, promoter methylation levels were significantly lower in PRAD, UCEC, THCA, Lung squamous cell carcinoma (LUSC), LUAD, LIHC, HNSC, cervical squamous cell carcinoma (CESC), and BLCA compared to normal tissues (Fig. 4B).

Urther analysis using UALCAN data showed that in tumors with reduced PAQR11 promoter methylation, including HNSC, LIHC, LUAD, and LUSC, PAQR11 expression was significantly higher than in normal tissues. This suggests that promoter hypomethylation may contribute to PAQR11 overexpression in these cancers (Fig. S3). However, no significant correlation between PAQR11 promoter methylation and its expression levels was found across the tumor samples analyzed (Fig. S4). These findings indicate that PAQR11 promoter methylation varies significantly among different tumor types, and this differential methylation may contribute to MMD upregulation in certain cancers.

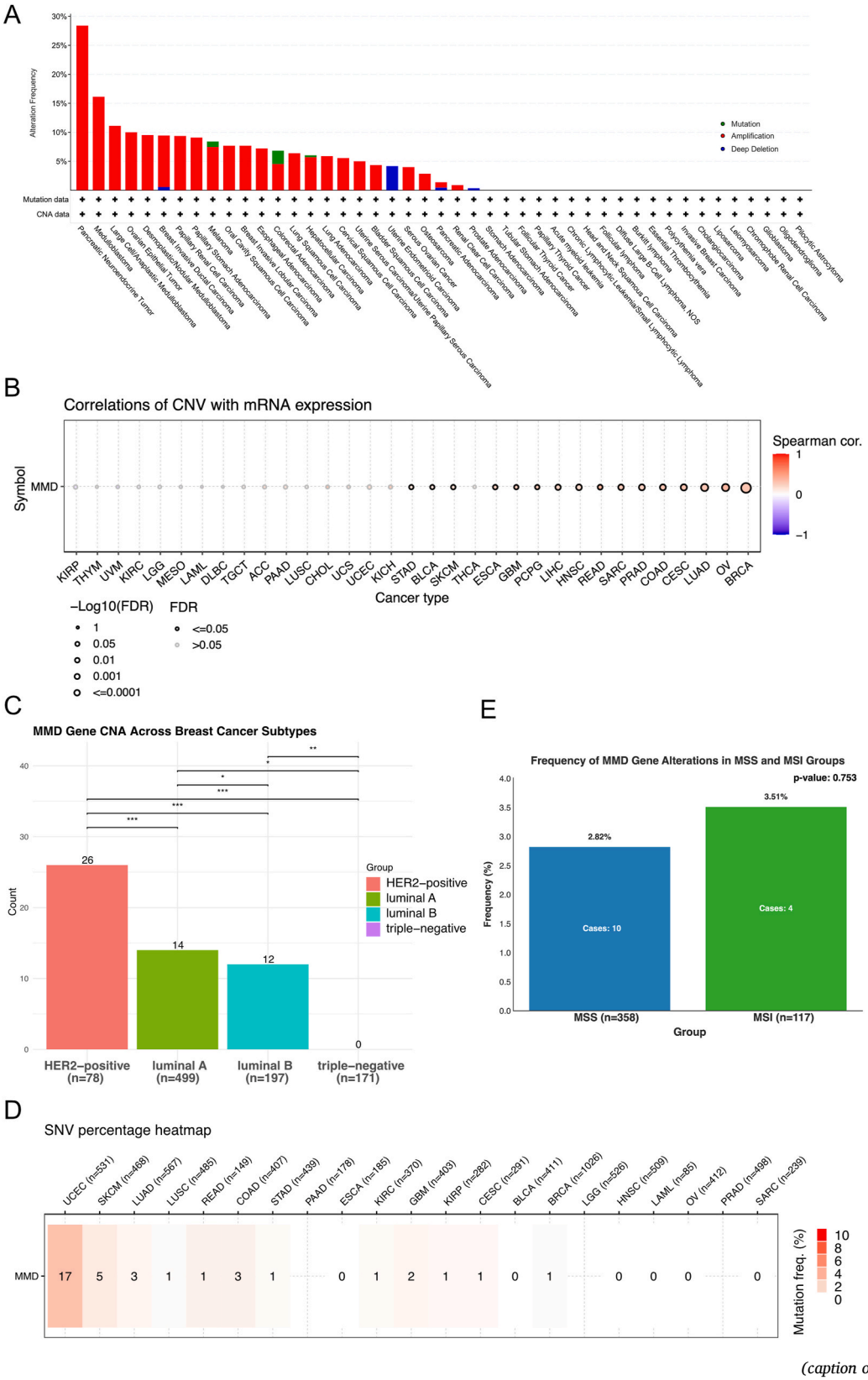

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Fig. 3. Pan-cancer analysis focusing on the genomic alterations associated with PAQR11. **A**: The landscape of PAQR11 genetic alterations was generated utilizing the cBioPortal database. **B:** An analysis was conducted to examine the correlation between PAQR11 expression and CNV across different tumors, utilizing the GSCA website. **C:** Association of PAQR11 Copy Number Alterations (CNA) with molecular subtypes of breast cancer. Pairwise comparisons between subtypes were assessed using a *t*-test, with statistical significance indicated as *P < 0.05, **P < 0.01, and ***P < 0.001. **D:** The GSCA website was employed to investigate the prevalence of SNVs within the PAQR11 gene across various tumor samples. **E:** Comparison of single nucleotide variants (SNVs) in TCGA UCEC patients stratified by MSI NABTIS score into microsatellite stable (MSS, n = 358) and microsatellite instability (MSI, n = 117) groups. The frequency of SNVs between the two groups was analyzed using a chi-squared test to assess statistical significance, with p-values reported.

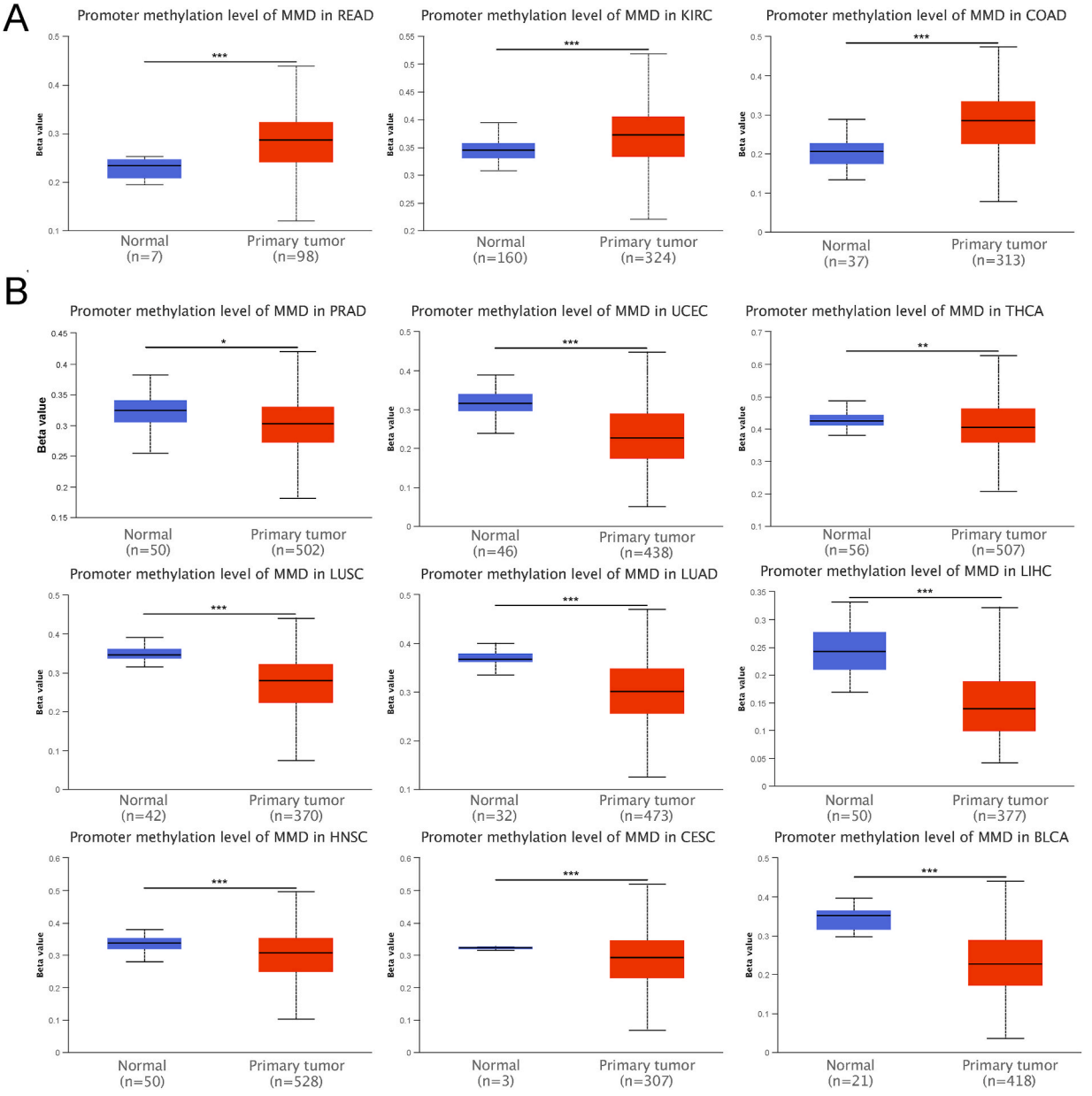

Fig. 4. DNA promoter methylation levels between normal and cancerous tissues were analyzed and compared using the UALCAN database. Statistical significance was determined via Student's t-test, with * indicating P < 0.05, ** indicating P < 0.01, and *** indicating P < 0.001. **A:** The methylation levels of the PAQR11 promoter were observed to be significantly elevated in cancerous tissues in comparison to normal tissues. **B:** The methylation levels of the PAQR11 promoter were significantly higher in normal tissues compared to cancerous tissues.

Subsequently, Sangerbox was employed to investigate the correlation between PAQR11 expression and three RNA modification marker genes associated with m1A, m5C, and m6A modifications (Fig. S5). The analysis revealed that the expression of most of these RNA modification marker genes was positively correlated with PAQR11. Based on these findings, we hypothesize that PAQR11 may play a role in regulating tumorigenesis through epigenetic mechanisms, potentially influencing tumor progression via its interaction with RNA modification processes.

3.5. PAQR11 expression is correlated with pan-cancer immune subtypes

Initially, we conducted a differential expression analysis using the TCGA pan-cancer dataset, dividing patients into two groups based on the median expression level of PAQR11. This analysis identified 33,741 differentially expressed genes (DEGs), of which 87 DEGs met the statistical significance criteria of $p < 0.05$, $q < 0.05$, and $|LogFC| > 1$ (Table S1 A subsequent KEGG pathway enrichment analysis revealed significant differences in three immune-related pathways that may be regulated by PAQR11 (Fig. 5A), prompting further exploration into the relationship between PAQR11 and anti-tumor immunity.

The immune subtypes within tumors provide critical insights into the immune status of different cancer types and are instrumental in guiding immunotherapy strategies. These subtypes reflect the characteristics of the tumor microenvironment across different tumors [32,33], with six recognized immune subtypes (C1 to C6), each representing a distinct immunological state [34].

Using the TISIDB immunological platform, we analyzed the relationship between PAQR11 expression and immune subtypes across 20 tumor types (Fig. 5B). The analysis revealed varying levels of PAQR11 expression across different immune subtypes within the same tumor. For example, in STAD and sarcoma (SARC), PAQR11 expression was higher in the C6 subtype (TGF-β dominant) and lower in the C1 subtype (wound healing). In KIRP, PAQR11 expression was significantly higher in the C1 and C2 subtypes (IFN-γ dominant) compared to other subtypes.

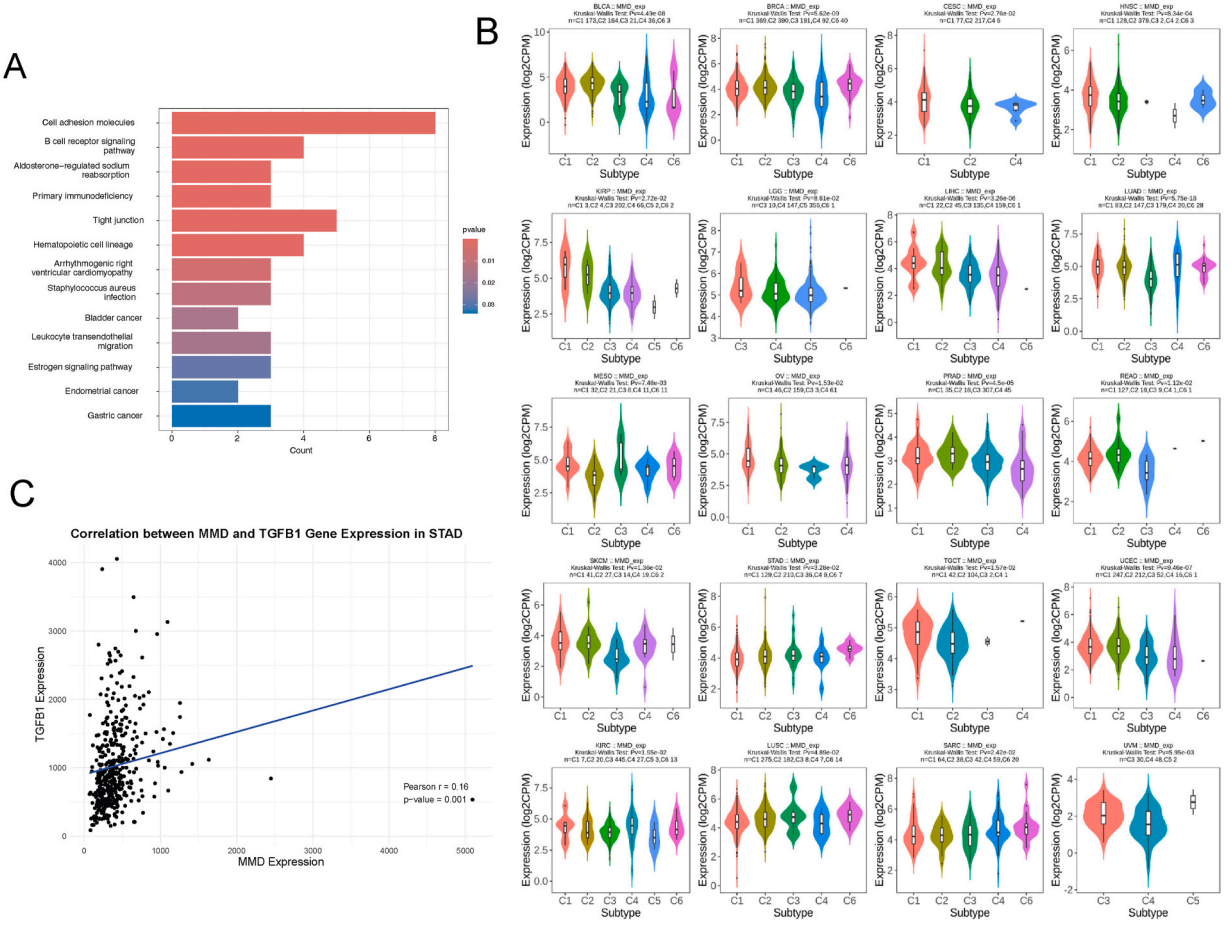

Fig. 5. Pan-cancer analysis of PAQR11 effects on the tumor immune microenvironment. **A:** KEGG Pathway Enrichment Analysis of 87 Statistically Significant Differentially Expressed Genes (DEGs) in TCGA-Pancancer Dataset, Highlighting Three Immune-Related Pathways Potentially Regulated by PAQR11. **B:** The association between PAQR11 expression and six immune subtypes across pan-cancer was investigated, encompassing subtypes C1 through C6. **C:** Analysis of TCGA-STAD data examining the correlation between PAQR11 and TGFB1 expression. Pearson's correlation coefficient was used to evaluate the relationship, and statistical significance was assessed using the corresponding p-value.

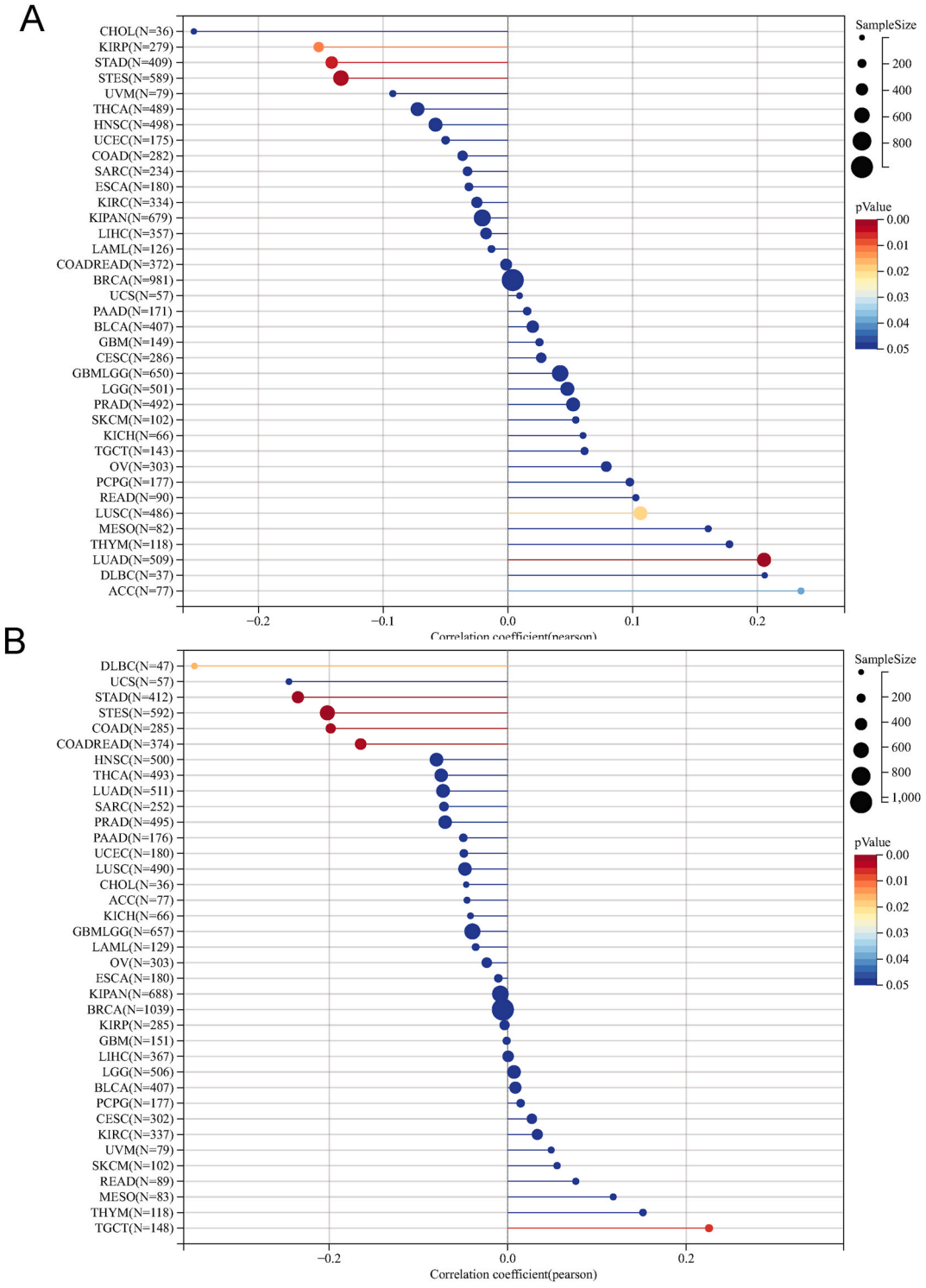

Fig. 6. Correlation analysis of PAQR11 expression with tumor mutational burden, microsatellite instability, and stromal score. **A**: The relationship between PAQR11 expression and Tumor Mutational Burden (TMB) was analyzed across multiple cancer types. **B:** The correlation between PAQR11 expression and Microsatellite Instability (MSI) was investigated. **C:** The association between PAQR11 expression and stromal score across various cancers was assessed using Pearson's correlation analysis.

Given the elevated PAQR11 expression in the C6 (TGF-β dominant) subtype in STAD and the known role of TGF-β in the pathogenesis and progression of gastric cancer [35], we conducted further analysis using TCGA-STAD data. This revealed a statistically significant positive correlation between PAQR11 and TGFB1 expression (Fig. 5C), suggesting that the TGF-β pathway may play a key role in the influence of PAQR11 on gastric cancer progression.

These findings suggest that PAQR11 expression is linked to immune subtypes and may play an important role in modulating the tumor-immune microenvironment, potentially influencing tumor progression and responses to immunotherapy.

3.6. Correlations between PAQR11 expression and key biomarkers in the tumor microenvironment

Tumor Mutational Burden (TMB) and Microsatellite Instability (MSI) are key biomarkers of the tumor microenvironment [36,37]. To investigate the immune-related role of PAQR11 in the tumor microenvironment, we calculated the Pearson correlation coefficient between PAQR11 expression and TMB, MSI, tumor purity, and immune checkpoint-related genes across pan-cancer types using the Sangerbox tool.

PAQR11 exhibited significant correlations with TMB in five cancers, showing a positive correlation in two tumors (LUAD, LUSC), and a negative correlation in three tumors (KIRP, STAD, STES) (Fig. 6A). For MSI, PAQR11 was significantly negatively correlated in five cancers, including diffuse large B-cell lymphoma (DLBC), STAD, STES, COAD, and COADREAD (colon/rectum adenocarcinoma esophageal carcinoma), while showing a positive correlation in testicular germ cell tumors (TGCT) (Fig. 6B).

We also explored the relationship between PAQR11 expression and tumor purity, finding significant correlations in 23 tumors. A negative correlation was observed in cancers such as BLCA, READ, uveal melanoma (UVM), DLBC, and glioblastoma multiforme (GBM), etc., whereas a positive correlation was found in TGCT and CESC (Fig. S6).

Additionally, we analyzed the correlation between PAQR11 and previously reported immune checkpoint-related genes [34] and observed a significant positive correlation in the majority of tumors (Fig. S7).

These findings suggest that PAQR11 is intricately linked with various biomarkers of the tumor microenvironment, including TMB, MSI, tumor purity, and immune checkpoint genes. This highlights the potential of PAQR11 as a promising target for tumor immunotherapy.

3.7. The role of PAQR11 in regulating the immune microenvironment across various cancer types

The ESTIMATE algorithm (Estimation of Stromal and Immune cells in Malignant Tumors using Expression data) enables researchers to estimate stromal cell presence and immune cell infiltration in tumor tissues. To explore the relationship between PAQR11 expression and the tumor microenvironment, we analyzed correlations between stromal scores, immune scores, ESTIMATE scores, and PAQR11 expression levels.

In 39 tumor types analyzed, significant correlations between PAQR11 expression and stromal scores were found in 26 tumor types, with 25 showing positive correlations (Fig. S8). Similarly, PAQR11 was significantly correlated with immune scores in 26 cancer types, including 20 with positive correlations (Fig. S9). Furthermore, PAQR11 expression levels were significantly associated with ESTIMATE scores in 29 cancers, with 24 displaying positive correlations (Fig. S10).

We also investigated the correlation between PAQR11 expression and the infiltration of six immune cell types: B cells, $CD8^+$ T cells, $CD4^+$ T cells, neutrophils, dendritic cells, and macrophages. Significant correlations between PAQR11 expression and immune cell infiltration were observed in PRAD, KIRC, KIRP, LIHC, and Pancreatic Adenocarcinoma (PAAD) (Fig. S11).

Overall, these immunological analyses indicate that PAQR11 plays a role in influencing the infiltration of various immune cells into tumors, thereby modulating the tumor immune microenvironment. This suggests that PAQR11 could serve as a key regulator of immune dynamics across multiple cancer types, highlighting its potential as a target for immunotherapy.

3.8. Association between PAQR11 expression and drug sensitivity

Drug resistance remains a major challenge in effectively treating cancer patients [38], often resulting from gene dysregulation [39,40]. To explore the relationship between PAQR11 expression and drug sensitivity, we utilized the GSCA platform to analyze data from the GDSC and CTRP databases.

From the GDSC database, PAQR11 expression showed significant positive correlations with sensitivity to several drugs, including 17-AAG, CCT007903, CP724714, EHT 1864, Gefitinib, Lapatinib, QL-VIII-58, ZG-10, and Phenformin (Fig. 7A). In contrast, the CTRP database revealed significant negative correlations between PAQR11 expression and sensitivity to drugs such as BRD-K61166597, GSK2636771, ML210, ML320, cucurbitacin I, cytochalasin B, marinopyrrole A, navitoclax, ABT-737, BRD-K88742110, PRIMA-1, and epigallocatechin-3-monogallate (Fig. 7B).

Further analysis of PAQR11 and drug IC50 values using the CellMiner database identified 20 significant associations. Among these, PAQR11 expression was negatively correlated with the IC50 of 12 drugs, including colchicine, azacitidine, fluorouracil, and vincristine, among others (Fig. 7C).

These findings suggest that abnormal expression of PAQR11 may contribute to the development of drug resistance in various tumors. This highlights PAQR11 as a potential biomarker for predicting drug sensitivity, offering a promising avenue for precision therapy and improving personalized treatment strategies.

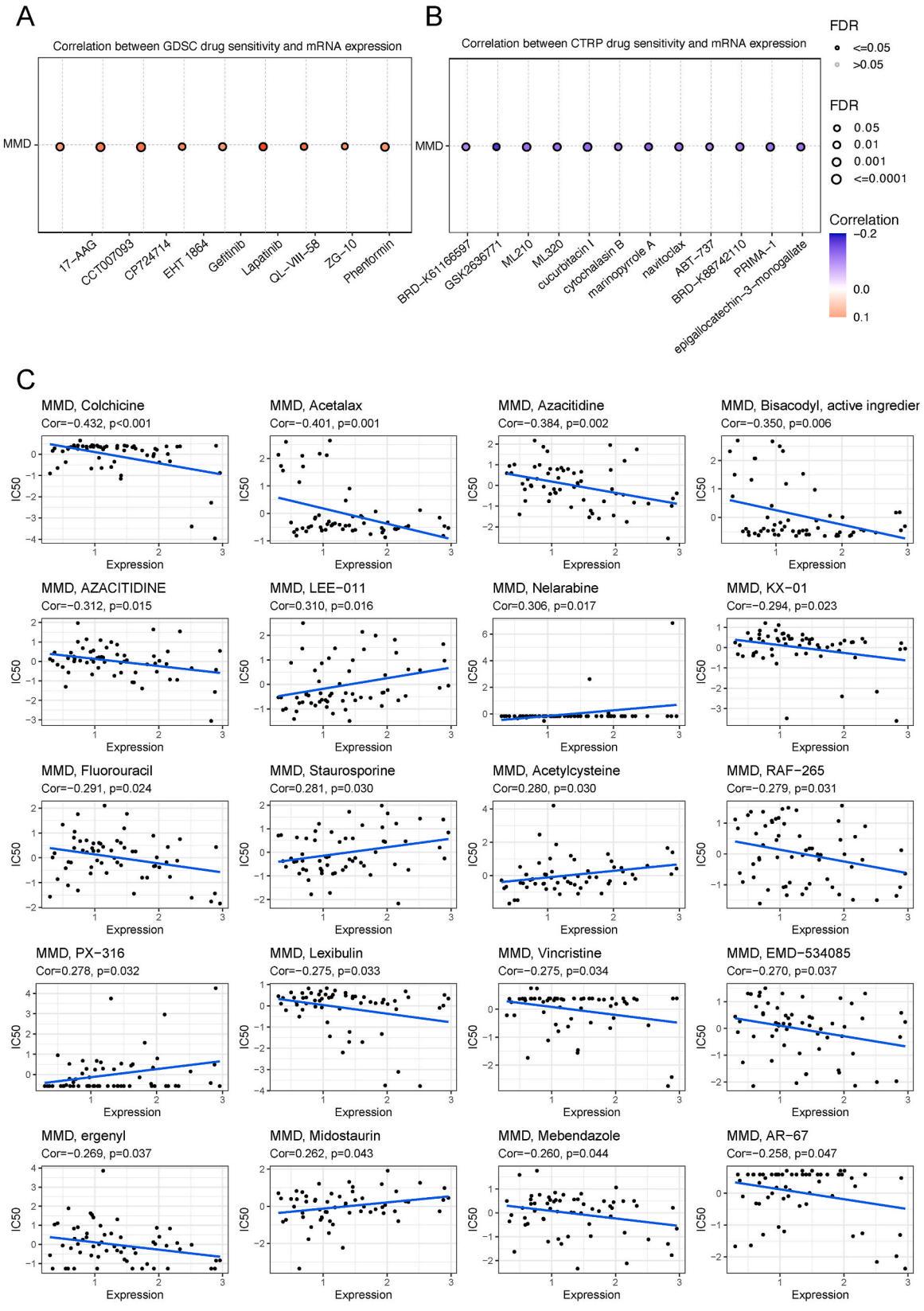

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Fig. 7. Correlation analysis to investigate the association between the expression of PAQR11 and drug sensitivity. The correlation between drug sensitivity and PAQR11 (MMD) mRNA expression was assessed utilizing **A** (GDSC database) and **B** (CTRP database). **C:** A correlation analysis was conducted to investigate the relationship between PAQR11 expression and drug IC50 values. Pearson's correlation coefficient was used to assess the strength and direction of these associations, with statistical significance determined by the corresponding p-values.

4. Discussion

Cancer continues to pose a formidable global health challenge, affecting millions worldwide [2,41]. Early diagnosis remains difficult, and late-stage metastasis significantly contributes to its status as the leading cause of mortality [42]. Over time, cancer research has evolved from basic pathological diagnoses to uncovering its genetic and molecular foundations. The rapidly growing field of oncology has identified numerous molecular targets, each playing a role in tumorigenesis, progression, and therapeutic responses. This study focuses on PAQR11, a relatively underexplored molecular entity, and its role across various cancers. Our findings highlight PAQR11's significance in cancer biology and its potential therapeutic implications.

To identify valuable molecular targets and common patterns in tumor development, we used bioinformatics methods to analyze gene expression differences across cancers at the transcriptomic level. Analyzing PAQR11 using pan-cancer data from the TCGA databases, we observed that PAQR11 expression was notably elevated in nine tumors, underscoring its importance. Particularly, PAQR11 overexpression in liver hepatocellular carcinoma (LIHC) is significant given the liver's susceptibility to oncogenic stimuli due to its metabolic functions [43]. Conversely, PAQR11's reduced expression in mesothelioma—a cancer typically associated with asbestos exposure [44]—may suggest a protective role or a downstream effect of primary oncogenic events. The underexpression of PAQR11 in BRCA is intriguing and warrants further investigation, especially given BRCA's multifactorial etiology.

The prognostic implications of PAQR11 are profound. Elevated PAQR11 has been linked to epithelial-mesenchymal transition (EMT) and poorer survival rates in several cancers, possibly due to its role in Golgi compaction mediated by ZEB1 [7]. Our study found that high PAQR11 expression correlated with unfavorable outcomes in nine tumor types, including stomach adenocarcinoma and prostate adenocarcinoma, consistent with previous studies suggesting its potential as a prognostic marker. Interestingly, in rectal adenocarcinoma and esophageal carcinoma, higher PAQR11 expression was associated with better survival outcomes, which might reflect the unique genetic, epigenetic, and environmental factors influencing different cancers. This duality calls for further research into PAQR11's mechanisms of action and its influence on cancer prognosis.

The epigenetic regulation of PAQR11, especially through promoter methylation, provides further insights into its role in cancer. DNA methylation is a critical epigenetic modification often associated with gene silencing and is a hallmark of many cancers [45]. Our analysis revealed distinct methylation patterns in PAQR11 across different tumors, suggesting that epigenetic mechanisms may regulate its activity in specific tumor microenvironments.

The tumor microenvironment (TME), composed of various cell types, plays a key role in tumor progression, metastasis, and therapeutic responses [46]. Our findings suggest that PAQR11 significantly influences the immune microenvironment. Its expression varied across different immune subtypes, indicating its potential role in modulating the immune landscape of tumors. Furthermore, correlations between PAQR11 expression and the infiltration of immune cells emphasize its role in shaping immune responses, possibly by recruiting or suppressing specific cell types.

We also explored the relationship between PAQR11 and key indicators of the TME, such as tumor mutational burden (TMB) and microsatellite instability (MSI). High TMB is associated with greater efficacy of immune checkpoint blockade therapy [47], while MSI serves as a biomarker for immunotherapy [48]. In STAD patients, higher PAQR11 expression correlated with lower TMB and MSI, potentially indicating reduced immunotherapy efficacy. Furthermore, our analysis demonstrated a negative correlation between PAQR11 and tumor purity in the majority of tumor types, a factor known to be associated with poorer survival outcomes [49,50]. These correlations suggest that PAQR11 may influence immune responses and tumor progression through its effects on the TME.

One of the most critical findings of this study is the correlation between PAQR11 expression and drug sensitivity. The observed associations with multiple drugs underscore PAQR11's potential as a therapeutic target. Furthermore, previous studies have shown that high PAQR11 expression increases tumor cell sensitivity to ferroptosis inducers [10], and its link to drug resistance in various tumors could provide insight into the mechanisms behind drug resistance. Understanding these relationships may pave the way for more effective precision therapies tailored to individual patients based on their PAQR11 expression levels.

Despite the comprehensive analysis of PAQR11 across multiple databases, this study has certain limitations. Firstly, the sequencing data derived from various databases may contain inherent biases, potentially leading to systematic errors. Secondly, although bioinformatics analyses provide valuable insights, they are inherently subject to potential biases and require further experimental validation. Therefore, additional in vivo and in vitro studies are essential to confirm the proposed functions of PAQR11 and to elucidate its precise mechanisms.

Although our data suggest that PAQR11 is highly expressed in several tumors, and we have examined its potential as a biomarker and its various roles in cancer biology, the underlying molecular mechanisms remain unclear. Future research is crucial to advance our understanding of PAQR11's role in tumorigenesis and to determine its full potential as a therapeutic target. Further experimental investigations could provide critical insights into how PAQR11 contributes to cancer progression and response to treatment, which may ultimately inform the development of targeted therapies.

5. Conclusion

In conclusion, PAQR11 emerges as a key player in oncology, with significant implications for cancer initiation, progression, and therapeutic response. The diverse expression of PAQR11 across various cancers, its association with prognosis, and its influence on the tumor microenvironment—as demonstrated in our study—highlight its pivotal role in cancer biology. As the field of oncology advances toward personalized medicine, understanding the molecular complexities of targets like PAQR11 will be essential for developing customized therapeutic strategies, ultimately improving patient outcomes. Future research into PAQR11's mechanisms and therapeutic potential will be critical to leveraging its role for more effective cancer treatments.

CRediT authorship contribution statement

Zhu Liu: Writing – original draft, Investigation, Formal analysis, Data curation. **Zhi-Qiang Ling:** Writing – review & editing, Validation, Project administration, Funding acquisition, Conceptualization.

Ethical approval statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Zhejiang Cancer Hospital (IRB-2023-245, Scientific research). All data analysis were performed in accordance with relevant guidelines and regulations.

Data availability statement

Transcriptome data and related clinical data are available in the Genomic Data Commons Data Portal (DGC) repository, https://portal.gdc.cancer.gov/

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Zhu Liu drafted the manuscript. Zhi-Qiang Ling was the overall principle investigators of this project, who designed the article and obtained financial support, were responsible for the manuscript design, oversaw the entire manuscript, and revised and synthesized the paper. All authors provided input into figures and table and have seen and approved the final manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Zhi-Qiang Ling reports financial support, administrative support, article publishing charges, statistical analysis, and writing assistance were provided by National Natural Science Foundation of China (32271238, 81972908). Zhi-Qiang Ling reports financial support, administrative support, article publishing charges, statistical analysis, and writing assistance were provided by National Health Commission Science Research Fund-Zhejiang Provincial Health Key Science and Technology Plan Project (WKJ-ZJ-2117). Zhi-Qiang Ling reports financial support, administrative support, article publishing charges, statistical analysis, and writing assistance were provided by Zhejiang Province Health Leader Talent (Zjwjw2021-40). Zhi-Qiang Ling reports financial support, administrative support, article publishing charges, statistical analysis, and writing assistance were provided by Zhejiang Provincial Public Welfare Technology Research Plan Project (LGD20H160003, LY20H160005 and LGF21H160010). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e41724.

List of Abbreviations

PAQR11	Progestin and adipoQ receptor family member 11
MMD	Monocyte To macrophage differentiation associated
TCGA	The cancer genome atlas

GEO Gene expression omnibus
UALCAN The University of ALabama at Birmingham CANcer data analysis Portal
GEPIA2 Gene expression profiling interactive analysis 2
KM plotter Kaplan-Meier plotter
OS Overall survival
DFS Disease-free survival
UC University of California
SC Santa Cruz
ESTIMATE Estimation of stromal and immune cells in MAlignant tumor tissues using expression data
DSS Disease-specific survival
DFI Disease-free interval
PFI Progression-free period
GDSC Genomics of drug sensitivity in cancer
CTRP Cancer therapies response portal
GSCA Generalized structured component analysis
CNV Copy number variations
RNA Ribonucleic acid
FDA Food and drug administration
LIHC Liver hepatocellular carcinoma
MESO Mesothelioma
BRCA Breast cancer
STAD Stomach adenocarcinoma
PRAD Prostate adenocarcinoma
LAML Acute myeloid leukemia
KIRP Kidney renal papillary cell carcinoma
HNSC Head and neck squamous cell carcinoma
KIRC Kidney renal clear cell carcinoma
LUAD Lung adenocarcinoma
PCPG Pheochromocytoma and paraganglioma
THCA Thyroid carcinoma
UCEC Uterine corpus endometrial carcinoma
ESCC Esophageal squamous cell carcinoma
READ Rectum adenocarcinoma
STES Esophagogastric junction adenocarcinoma
BLCA Bladder urothelial carcinoma
GBMLGG Glioblastoma multiforme and lower-grade glioma
KIPAN Pan-kidney cohort
SNV Single nucleotide variants
COAD Colon adenocarcinoma
LUSC Lung squamous cell carcinoma
CESC Cervical squamous cell carcinoma and endocervical adenocarcinoma
SARC Sarcoma
TMB Tumor mutational burden
MSI Microsatellite instability
DLBC Lymphoid neoplasm diffuse large B-cell lymphoma
COADREAD Colon adenocarcinoma/rectum adenocarcinoma esophageal carcinoma
TGCT Testicular germ cell tumors
UVM Uveal melanoma
GBM Glioblastoma multiforme
PAAD Pancreatic adenocarcinoma
IC50 Half maximal inhibitory concentration
EMT Epithelial-mesenchymal transition
DNA Deoxyribonucleic acid
Mb Mutations per million bases

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