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Analysis

Identification of gasdermin B function in the progression of renal clear cell carcinoma by a pan-cancer analysis

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Abstract
The Gasdermin (GSDM) protein family is critically involved in pyroptosis, which participates in the onset and progression of human malignancies. The exact role and impact of the GSDM family genes in various malignancies, particularly renal clear cell carcinoma (KIRC), is still uncertain. The present results indicated GSDMB gene expression significantly upregulated in individuals with KIRC, whose diagnostic effectiveness was confirmed through ROC analysis. Kaplan–Meier analysis also revealed KIRC patients had poor survival prognosis. The high expression of GSDMB served as an independent risk factor for overall survival (OS) in KIRC, based on multivariate cox analysis for confirmation. A nomogram based on GSDMB expression and clinical characteristics displayed remarkable diagnostic effectiveness for KIRC. Collectively, these findings may shed light on functions of GSDM family genes in tumor progression and offer new directions for future research into their potential as therapeutic targets in various types of tumors. Furthermore, the outcomes of this research highlighted that the prediction of treatment responses in KIRC patients may get improved through in-depth exploration into the impact of GSDMB expression on individuals with KIRC patients.

Keywords Pan-cancer · Gasdermin · Prognosis · Progression · Kidney renal clear cell carcinoma

1 Introduction

Cancer, as one of the major causes of mortality, greatly hinders the efforts to increase life expectancy globally [1, 2]. The Global Cancer Statistics reports that there were about 19.3 million new cancer diagnoses, and the disease caused 10 million deaths. Scientists predict the global cancer burden to rise by 47% to 28.4 million cases by 2040 [3], largely due to the increasing risk factors related to aging, globalization, and rising socioeconomic conditions [4, 5]. Cancer is a genetic disease caused by the aggregation of molecular modifications and mutations in the genome of somatic cells [6]. To improve the timely diagnosis and prognosis of the disease, identifying survival biomarkers has become significant [7].

Advances in DNA sequencing technology have facilitated deeper insights into the identification of potentially druggable cancer genes, especially those that underpin disease phenotype, prognosis, drug susceptibility, and resistance to chemotherapy [8]. Personalized treatments can be developed by understanding the unique molecular patterns of

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everyone's cancer. In many cases, cancer progression is driven by the accumulated mutations that lead to altered expression of proteins or signaling pathways.

The human Gasdermins (GSDMs) is a multi-functional protein family composed of six segments: Gasdermin A, B, C, D, E, and Pejvakin (encoded by GSDMA to GSDME and PJVK) [9, 10]. Five out of six members, excluding Pejvakin, have a pore-forming N-terminal domain that is crucial in executing pyroptosis [11]. Pyroptosis has a significant function in the progression of cancer, with evidence suggesting it triggers GSDMD-dependent caspase-1 inflammasome pathways and other GSDM-dependent non-inflammasome signaling pathways [12]. In recent years, research has revealed new information about the GSDM protein family. Reports show that GSDMA expression levels are elevated in the gastrointestinal tract and skin, but lowered in primary gastric cancer [13]. Additionally, GSMDC is overexpressed in metastatic melanoma cells, and its knockdown has been linked to the inhibition of colorectal cancer cell line growth and a good prognosis [14]. However, GSDMC expression has been suppressed in many esophageal squamous cell carcinomas (ESCCs) and may also act as a tumor-suppressing gene. In contrast, GSDMB serves as a driver of tumor progression, and its increased expression level has been linked to poor survival rates, increased metastasis, and poor responses to HER2-targeted therapy in HER2-positive breast cancer [15]. Despite these findings, there is still limited research available on the comprehensive impact of the GSDM family across different kinds of cancer.

In this report, the predictive significance of Gasdermins genes in pan-cancer was systematically analyzed with a series of online databases, including Kaplan–Meier Plotter, The Cancer Genome Atlas (TCGA), and PrognoScan. In addition, this research highlighted the underlying relationship between the GSDM gene family expression and immune subtypes as well as susceptibility to drugs in pan-cancer. Finally, per various databases and bioinformatics modalities, the GSDM genes' expression profile and predictive significance were assessed, particularly the correlation between GSDMB and KIRC.

These findings may clearly demonstrate the functions of Gasdermin genes in the onset and advancement of cancer. This information can lead to in-depth research on GSDM genes as possible therapeutic targets for various types of tumors. This research primarily focused on the expression of GSDMB in KIRC and its prognostic and therapeutic impact. The differentially expressed genes among individuals with KIRC having high- and low- GSDMB expression levels, and their potential and mechanisms were also analyzed.

2 Methods

2.1 Patients and samples

The clinical information, immune subtype, stemness score (RNA and DNA), and transcriptome RNA-seq data of 33 types of malignancies were retrieved from the UCSC (https://xena.ucsc.edu/) [16]. The drug response was evaluated using Cancer (GDSC) database [17]. The expression profile of the Gasdermin family genes and their significance were analyzed with the aid of the TCGA pan-cancer dataset and the Perl software.

2.2 Differential expression analysis

The "Wilcoxon test" was applied to observe the differential expression of Gasdermin family genes in distinct types of malignancies. The results are indicated by asterisks, with "*" representing $P < 0.05$, "**" representing a $P < 0.01$, and "***" representing a $P < 0.001$. Moreover, a box plot and heatmap were created by means of the R-packages "ggpubr" and "pheatmap", respectively. The link between the expression profile of each Gasdermin gene was analyzed using the R package "corrplot."

2.3 Prognosis analysis

To observe the link between the expression of the Gasdermin family genes and clinical endpoints, the follow-up data of each sample was retrieved from the TCGA database. The overall survival (OS), which is the duration between initial diagnosis and death, was analyzed utilizing the Kaplan–Meier survival curve ($P < 0.05$) [18].

Each tumor type was classified into high-expression and low- expression groups using the median of Gasdermin genes expression. The survival curves were then generated as per the expression levels of all GSDM genes, using R-packages "survminer" and "survival". Moreover, cox regression analysis was applied to assess the link between Gasdermin genes

and the overall prognosis of pan-cancer. Finally, the results were visualized through forest plot with the help of the R-packages "survival" and "forestplot".

Furthermore, the link between Gasdermin family genes expression and survival outcomes in pan-cancer was further validated utilizing online databases, Kaplan–Meier Plotter and PrognoScan [19]. The clinical outcomes that were considered included overall survival (OS), relapse-free survival (RFS), Disease-Free Survival (DFS), and Distant Metastasis-Free Survival (DMFS). RFS refers to the time until any recurrence or death from any cause [20] DFS is the time elapsed from the beginning of randomization to the disease recurrence or death for any reason [21]. DMFS represents the time from the start of randomization to the development of any distant metastasis or death [22]. The expression profile of the Gasdermin family genes was assessed in PrognoScan using all microarray datasets. A COX analysis was conducted with a P-value < 0.05 as the cutoff. The Kaplan–Meier Plotter dataset was also utilized to evaluate the impact of Gasdermin genes on survival in 21 diverse categories of cancer.

2.4 GO enrichment and KEGG pathway analysis

Gene Ontology and KEGG pathway analyses were conducted using the "clusterProfiler" package.

2.5 Immune infiltration analysis

The immune infiltration and tumor purity in pan-cancer tissues were assessed by estimating the stromal and immune scores (for the stromal/immune cells infiltrating) through the ESTIMATE algorithm [23]. The link between the expression of Gasdermin family genes and DNA and RNA stemness score (RNAs and DNAs) was determined using Spearman correlation. The link between the expression of Gasdermin genes and the tumor microenvironment (TME) and stemness in certain cancers was analyzed by applying the R-packages "ggpubr", "ggplot2" "reshape2", and "limma".

2.6 Chemotherapy sensitivity

To observe the link between GSDM genes expression and drug susceptibility, data was obtained from the CellMiner™ database (Version: 2020.3, database: 2.4.2, https://discover.nci.nih.gov/cellminer/home.do) [24, 25]. Data processing and results visualization were conducted using R "limma", packages.

The Pearson correlation analysis was employed to identify genes that are linked to GSDMB in the TCGA dataset, with criteria of ($|r| > 0.5$, $P < 0.05$). These related genes were then imported into String to construct functional protein association networks, and hub genes were identified in Cytoscape 3.8.2.

2.7 Statistical analysis

The Mann–Whitney U or student t-test was conducted to make a comparison between two groups, and one-way ANOVA and Kruskal–Wallis were used for multiple-group comparisons. The Kaplan–Meier analysis was used to compare the survival curves of two groups. The hazard ratio (HR) and 95% confidence interval (CI) were calculated by means of the univariate and multivariate Cox regression. A nomograph was developed to predict the overall survival of patients. The receiver operating characteristic curve was utilized to assess the diagnostic and risk assessment of GSDMB for KIRC. All analyses were achieved based on R software 4.1. A bilateral P-value < 0.05 indicated the significance level unless specified otherwise.

3 Results

3.1 The landscape of gasdermin family genes in *pan-cancer*

The differentially expressions of Gasdermin family genes in cancers were presented in Fig. 1A. GSDMA, GSDMB, GSDMC, GSDMD, GSDME and PJVK were significantly upregulated in BLCA, BRCA, COAD, ESCA, GBM, KICH, KIRC, KIRP, LIHC, LUAD, PRAD, and READ. GSDME was significantly down-regulated in HNSC and THCA. CNV affected the mRNA expression of Gasdermin family genes in cancers. GSDMD expression was positively associated with CNV in most cancers (Fig. 1B). GSDMB, GSDME, GSDMC, and PJVK showed positive association with CNV in KIRP, CESC, LUSC, ESCA, LUAD, HNSC, BRCA,

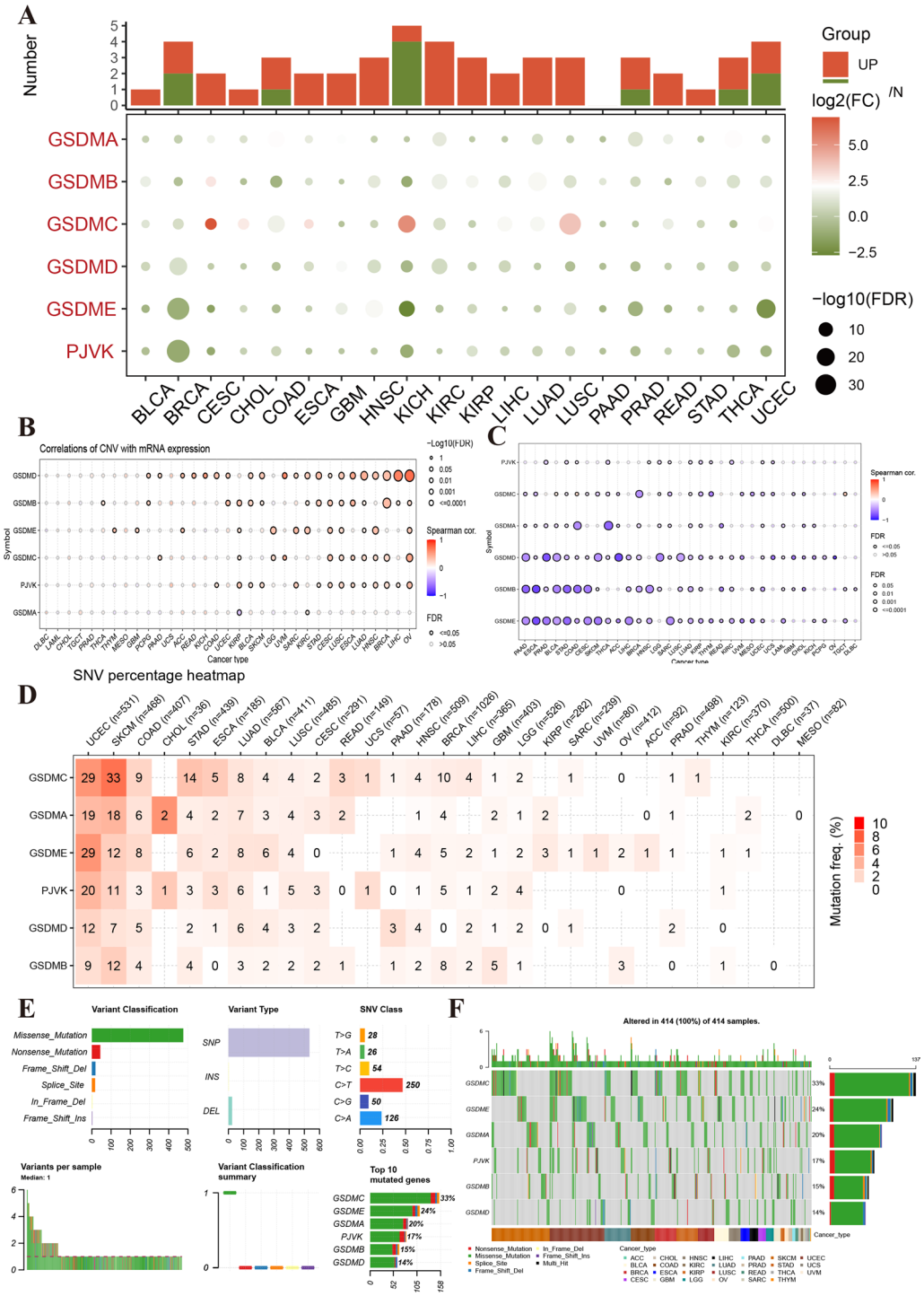

Fig. 1 Expression levels and correlations of Gasdermin family genes in pan-cancer. **A** Elevated or decreased expression levels of Gasdermin family genes in whole cancers. **B** Heatmap plots shows the correlations of CNV with mRNA expression of Gasdermin family genes in specific cancers. **C** Correlations between methylation and mRNA expression of inputted genes in the specific cancers. **D** Profile of SNV of Gasdermin family genes in specific cancers. **E** Variant classification and type of Gasdermin family genes in cancers. **F** Gene alteration levels of Gasdermin family genes in cancers

and OV. GSDMA was only positively associated with GSDMA in KIRP and KIRC. The methylation levels significantly affected the mRNA expression of Gasdermin family. As shown in Fig. 1C, five Gasdermin family genes were negatively associated with methylation levels in cancers (Fig. 1C). All five genes showed high single nucleotide variants (SNV) in UCEC, SKCM, COAD, STAD, ESCA, LUAD, BLCA, and LUSC (Fig. 1D). The Fig. 1E and F showed the variant classification and type and gene

alteration frequency. The missense mutation was main variant classification followed by nonsense, frame shirt del and splice site. T > G and T > A were primary variant type of SNP. All gene alteration frequencies were 33% for GSDMC, 24% for GSDME, 20% for GSDMA, 17% for PJVK, 15% for GSDMB, and 14% for GSDMD.

3.2 Prognostic value of gasdermin family genes in *pan-cancer*

Subsequently, the prognosis-predictive value of the Gasdermin family genes was further explored through the analysis of multiple databases. As indicated by K-M survival curves, the Gasdermin family gene expression is linked to the prognosis of many cancer types (Supplementary material 1). The macroscopic analysis revealed that in many cases, a lower expression level of GSDM genes was linked to a higher survival rate, such as individuals with KIRC, KICH, and Uveal Melanoma (UVM) having better overall survival. However, the opposite was seen in patients with BLCA and Skin Cutaneous Melanoma (SKCM), where enhanced expression of GSDM genes was linked to better OS. More specifically, for distinct types of malignancies, the expression of GSDMB genes had variable impacts on patient survival. For example, the higher expression level of the GSDMB gene was linked to lower OS in individuals with KIRC (N = 530, P < 0.001). Contrarily, higher GSDMB expression was favorable for the OS in individuals with BLCA (P < 0.001), SKCM (P = 0.011), and Uterine Carcinosarcoma (UCS) (P = 0.026). The expression of GSDMC has a positive impact on the overall survival of COAD (P = 0.031) and LGG (P = 0.007) but a negative impact on the OS in individuals with BRCA (P = 0.014), KICH (N = 64, P = 0.031), KIRC (P = 0.007), Pancreatic adenocarcinoma (PAAD) (P = 0.046), and Uveal Melanoma (UVM) (P = 0.007). The expression of GSDMD had a positive impact on the OS in BLCA individuals (P = 0.007), SKCM (P = 0.030), and UCEC (P = 0.047) but a negative impact on the OS in UVM individuals (P = 0.007) and Brain Lower Grade Glioma (LGG) (P < 0.001). The expression of GSDME had a positive impact on the OS in Adrenocortical carcinoma (ACC) individuals (P = 0.005), but a negative impact on the OS in KIRC individuals (P = 0.002), LIHC (P = 0.001), and STAD (N = 350, P = 0.040). Higher expression of PVJK had a positive impact on the OS in Acute Myeloid Leukemia (LAML) individuals (P = 0.002), Mesothelioma (MESO) (P = 0.010), PAAD (P = 0.037) and Sarcoma (SARC) (P = 0.005) but a negative impact on the OS in KIRC individuals (P < 0.001).

Additionally, a predictive evaluation was conducted as per the Hazard Ratio in pan-cancer using COX regression analysis. The outcomes indicated that GSDMA had a unfavored impact on OS of KIRC, but a favor impact in KP, LAML, MESO, and SARC (Fig. 2A). GSDMB had a negative impact on OS of HNSC, KICH, KIRC, LIHC, and UCEC, but favor impact in ACC and KIRP (Fig. 2B). GSDMC had a negative impact on LIHC, PAAD, SKCM, and THCA (Fig. 2C). Moreover, GSDMD acted as a high-risk factor in ACC, KIRC, LGG, and UVM and as a low-risk factor in KIRP and SKCM (Fig. 2D). GSDME played a role as an adverse factor in KIRC and LIHC (Fig. 2E). Ultimately, PVJK served as an unsatisfying factor in KICH and SCKM (Fig. 2F).

Likewise, the link between GSDM family gene expression and the prognosis of cancers was elucidated in the PrognoScan database using the GEO dataset. Specific results are showcased in Table 1. Specifically, GSDMB served a negative predictive role in Breast cancer (DFS, DMFS & RFS) and soft tissue cancer (DMFS) but a positive prognosis-predictive role in Colorectal cancer (DFS and OS), Lung cancer (OS & RFS), Brain cancer (OS), Blood cancer (OS) and Skin cancer (OS). GSDMC played a negative prognosis-predictive role in Breast cancer (DFS, DMFS & RFS) and Lung cancer (OS). GSDMD served as a good prognostic factor in Breast cancer (DMFS & RFS) and Ovarian cancer (DFS & OS) but a poor prognostic factor in Eye cancer (DMFS), Brain cancer (OS), Blood cancer (OS) and Lung cancer (RFS).

3.3 Correlations of GSDM genes with tumor microenvironment, stemness score, and immune status

In order to find out the correlation between the expression of GSDM genes and immune subtypes, correlation analysis was carried out [26]. As a milieu comprising immune components, tumor vessels, extracellular matrix, malignant cells, and signaling molecules, tumor microenvironment (TME) heterogeneity is crucial for the advancement, metastasis, and clinical prognosis of tumors [27]. Thus, further immune infiltration analysis was carried out to observe the link between the expression of GSDM family genes and TME in pan-cancer using the ESTIMATE algorithm. The outcomes of this research exposed that GSDM family genes have a significant association (positive/negative) with stromal and immune scores in pan-cancer. On the other hand, GSDM gene expression correlates significantly with RNAs and DNAs in pan-cancer (Fig. 3). Figure 4 showed the correlations of GSVA scores of GSDM family genes with immune cell infiltration levels in cancers. We found that NK cells, Th1, CD8 T cells, cytotoxic and exhausted cells showed positive associations with GSVA score in most cancers. CD8 naïve, Neutrophil, Th17, central memory CD4 naïve, and B cells showed negative associations with GSVA score in most cancers.

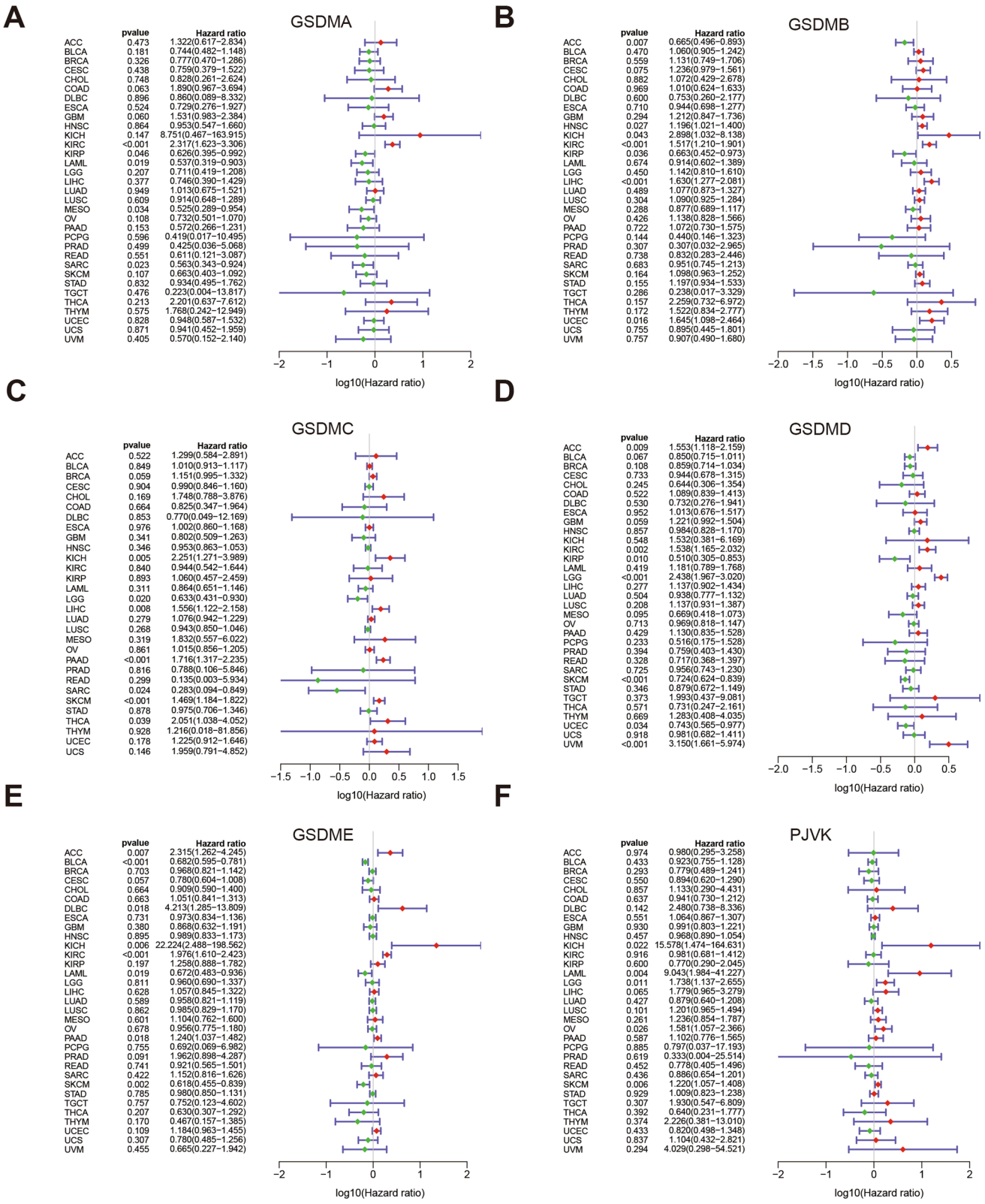

Fig. 2 Forest plots presented hazard ratios of Gasdermin family genes for different cancers. **A** GSDMA. **B** GSDMB. **C** GSDMC. **D** GSDMD. **E** GSDME. **F** PJVK

Table 1 Prognostic value of GADMB, GSDMC and GSDMD in some cancers from GEO dataset

Geene	Dataset	Cancer type	Endpoint	N	P	HR [95% CI]
GSDMB	GSE4922	Breast cancer	DFS	249	0.00208544	1.33 [1.11–1.59]
GSDMB	GSE4922	Breast cancer	DFS	249	0.0146086	1.41 [1.07–1.87]
GSDMD	GSE26712	Ovarian cancer	DFS	185	0.0109129	0.65 [0.47–0.91]
GSDMB	GSE3494	Breast cancer	DFS	236	0.0205455	1.31 [1.04–1.64]
GSDMB	GSE17537	Colorectal cancer	DFS	49	0.036561	0.03 [0.00–0.80]
GSDMC	GSE3494	Breast cancer	DFS	236	0.0154773	2.82 [1.22–6.52]
GSDMB	GSE9195	Breast cancer	DMFS	77	0.00071899	2.85 [1.55–5.24]
GSDMB	GSE9195	Breast cancer	DMFS	77	0.00491419	2.61 [1.34–5.11]
GSDMB	GSE7390	Breast cancer	DMFS	198	0.040751	1.14 [1.01–1.29]
GSDMC	GSE6532	Breast cancer	DMFS	87	0.000652564	4.76 [1.94–11.66]
GSDMC	GSE19615	Breast cancer	DMFS	115	0.00681196	8.14 [1.78–37.16]
GSDMD	GSE22138	Eye cancer	DMFS	63	0.00200447	1.74 [1.22–2.47]
GSDMD	GSE19615	Breast cancer	DMFS	115	0.033728	0.17 [0.03–0.87]
GSDMB	GSE30929	Soft tissue cancer	DMFS	140	0.0199126	2.62 [1.16–5.89]
GSDMB	GSE31210	Lung cancer	OS	204	0.000135344	0.36 [0.21–0.61]
GSDMB	GSE12945	Colorectal cancer	OS	62	0.00377267	0.44 [0.25–0.77]
GSDMB	GSE3141	Lung cancer	OS	111	0.00467108	0.70 [0.55–0.90]
GSDMB	GSE17537	Colorectal cancer	OS	55	0.0215324	0.05 [0.00–0.64]
GSDMB	GSE4412	Brain cancer	OS	74	0.0329973	0.68 [0.47–0.97]
GSDMB	GSE5122	Blood cancer	OS	58	0.034422	0.72 [0.53–0.98]
GSDMB	GSE8970	Blood cancer	OS	34	0.0435993	0.72 [0.53–0.99]
GSDMB	GSE19234	Skin cancer	OS	38	0.0467965	0.18 [0.03–0.98]
GSDMC	GSE11117	Lung cancer	OS	41	0.0150055	1.47 [1.08–2.01]
GSDMC	GSE31210	Lung cancer	OS	204	0.0166793	2.47 [1.18–5.19]
GSDMD	GSE4412	Brain cancer	OS	74	0.000521696	1.93 [1.33–2.79]
GSDMD	GSE26712	Ovarian cancer	OS	185	0.00722748	0.61 [0.42–0.87]
GSDMD	GSE4271	Brain cancer	OS	77	0.0254763	1.42 [1.04–1.93]
GSDMD	GSE12417	Blood cancer	OS	163	0.0348238	1.87 [1.05–3.34]
GSDMB	GSE31210	Lung cancer	RFS	204	0.00373091	0.54 [0.36–0.82]
GSDMB	GSE9195	Breast cancer	RFS	77	0.00865616	2.21 [1.22–4.00]
GSDMB	GSE9195	Breast cancer	RFS	77	0.0277648	2.00 [1.08–3.69]
GSDMB	GSE12276	Breast cancer	RFS	204	0.0410039	1.16 [1.01–1.34]
GSDMC	GSE6532	Breast cancer	RFS	87	0.000652564	4.76 [1.94–11.66]
GSDMC	GSE12276	Breast cancer	RFS	204	0.00139909	1.39 [1.14–1.70]
GSDMC	GSE1379	Breast cancer	RFS	60	0.0151312	1.49 [1.08–2.06]
GSDMD	GSE31210	Lung cancer	RFS	204	0.0171171	3.03 [1.22–7.56]
GSDMD	GSE1378	Breast cancer	RFS	60	0.0221833	0.51 [0.29–0.91]
GSDMD	GSE12276	Breast cancer	RFS	204	0.0239815	0.72 [0.54–0.96]

3.4 Drug susceptibility of GSDM genes in *pan-cancer*

For the purpose of determining the possible association between the expression of GSDM family genes and drug susceptibility in various cancers from the CellMiner™ database, correlation analysis was made using the R software. The results demonstrated that GSDMA expression had a positive link to Dexrazoxane drug susceptibility, while GSDMB had a positive link to Nelarabine, Fluphenazine, and Perifosine drug susceptibility. GSDMC expression was negatively linked to Ixazomib citrate, Midostaurin, Bortezomib, Pralatrexate, AT-13387, Vismodegib, and Vincristine and was positively linked to Gefitnib and Lificguat. GSDMD demonstrated a positive link to the susceptibility to Fludarabine, Cladribine, and 5-fluoro deoxy uridine 10. All the results are illustrated in Fig. 5A and 5B.

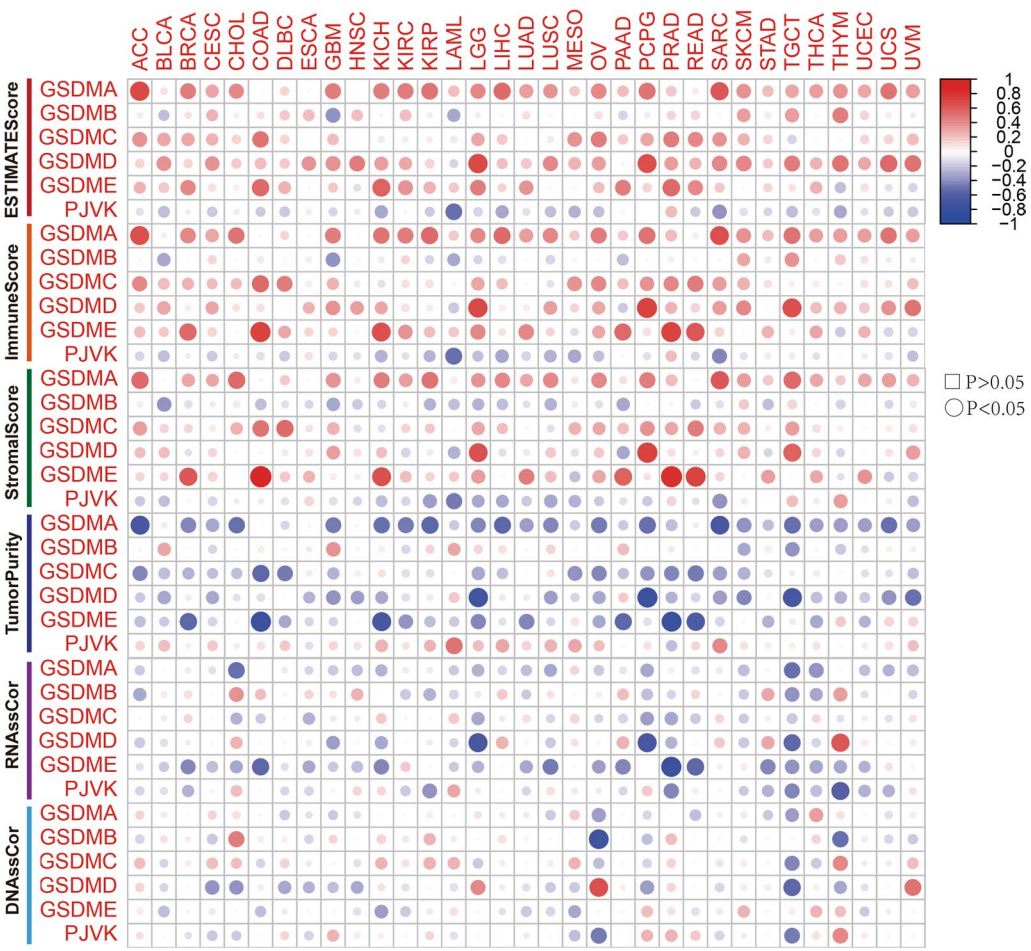

Fig. 3 Correlations of Gasdermin family genes with tumor microenvironment, tumor purity, and tumor stem cells characteristics (The larger dots indicate smaller P values, while blank grids signify that the P value is greater than 0.05)

3.5 High GSDMB is correlated with clinical features in KIRC

The KIRC tissues were compared to adjacent healthy tissues in order to investigate the expression of GSDMB in KIRC patients. The outcomes highlighted that GSDMB overexpressed in KIRC tissues ($p = 2.835*e^{-4}$, Fig. 6A). The receiver operating curve (ROC) was generated to inspect the effectiveness of the differential expression of GSDMB in distinguishing normal and KIRC tissues. The area under the curve (AUC) of GSDMB was 0.813 (Fig. 6B), which indicated significant diagnostic value and thus a potential biomarker for KIRC therapy.

Furthermore, the GSDMB expression and its clinical characteristics in individuals with KIRC were assessed. The clinical and GSDMB expression data of 520 individuals were collected from the TCGA database. The individuals with KIRC were categorized into high- and low-GSDMB expression groups according to the mean expression (Table 2). The outcomes revealed that high GSDMB expression was linked to histologic grade ($p = 0.0071$, Fig. 6C), pathologic stage ($p = 0.00016$, Fig. 6D), T stage (T1-2 vs T3-4, $p = 0.00027$, Fig. 6E), and M stage ($p = 0.031$, Fig. 6F). The results suggested that high GSDMB expression correlated with T ($p = 0.028$), M ($p = 0.008$), and pharmaceutical ($p = 0.002$) (Table 2).

3.6 Prognosis and clinical value of GSDMB in KIRC

In the survival analysis of KIRC from the TCGA dataset, the results demonstrated that high GSDMB expression had a significant link to poor OS ($p < 0.001$, Fig. 7A); poor PFI ($p = 0.016$, Fig. 7B); unsatisfying DFI ($p < 0.022$, Fig. 7C) and poor DSS ($p < 0.001$, Fig. 7D). Subsequently, univariate cox regression analysis indicated high GSDMB expression was remarkably linked to poor OS (hazard ratio [HR] = 1.339, 95% CI 1.234–1.452, Fig. 7E). Multivariate cox regression analysis highlighted

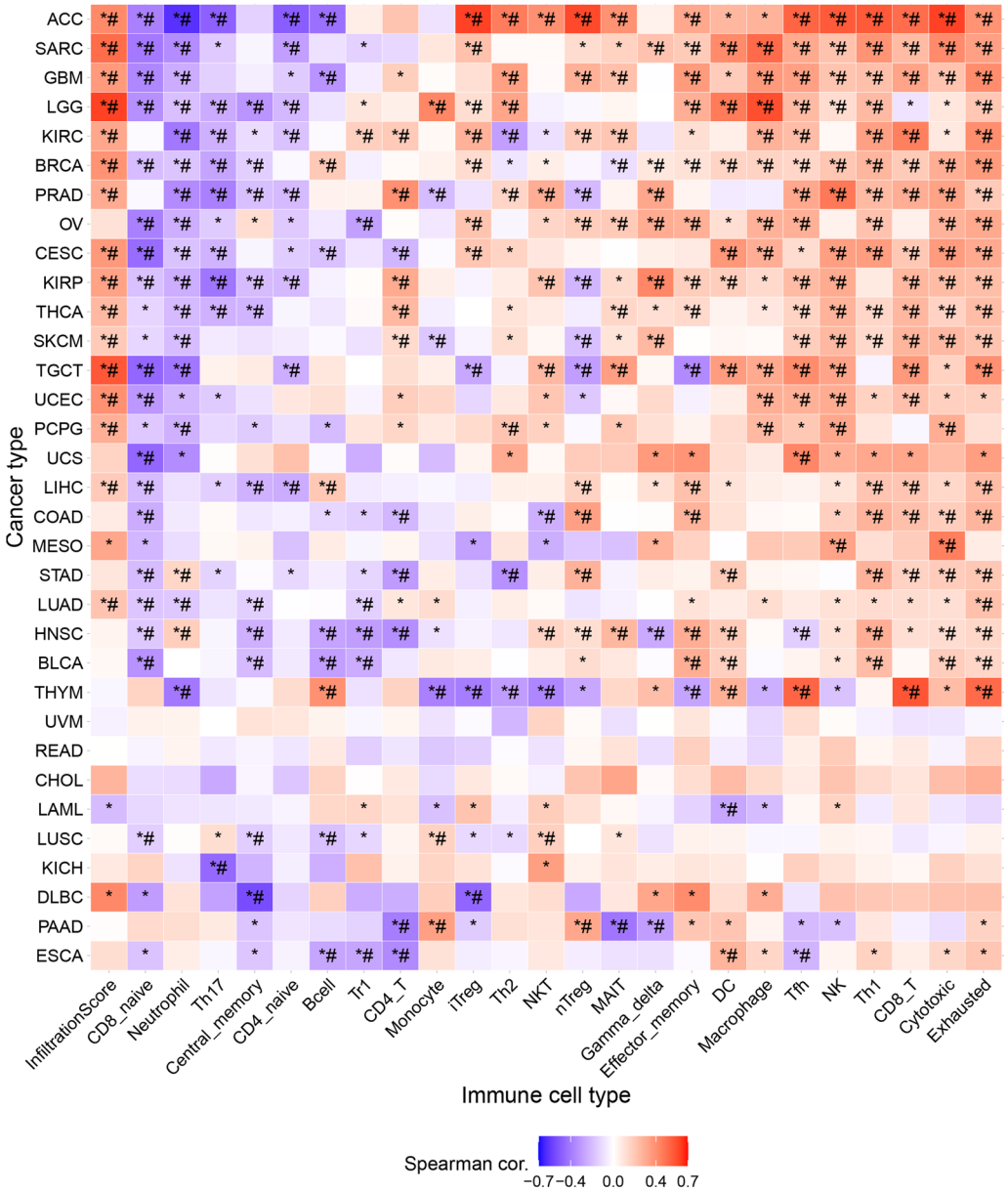

Fig. 4 Correlation of Gasdermin family genes with immune cell infiltrations levels in different cancers

that high GSDMB expression served as an independent prognostic factor for OS in individuals with KIRC (HR = 1.202, 95% CI 1.099–1.315, Fig. 7F).

Furthermore, to predict the 1-, 3-, and 5-year OS in KIRC patients from the TCGA dataset, the nomogram was developed using age, grade, stage, radiation, pharmaceutical, and GSDMB expression (Fig. 8A). The ROC analysis verified that the AUC at 3 years was 0.923 (Fig. 8B). Overall, the nomogram model provided a terrific calibration method for predicting 3-year OS (Fig. 8C).

3.7 Function and pathway analysis of GSDMB in KIRC

To investigate the potential interaction network of the differential expression genes in high- and low-GSDMB expression groups, PPI analysis was carried out. The results showed that many genes were correlated with GSDMB in KIRC (Fig. 9A). To further explore the specific molecular function and signaling pathways of the genes correlated with GSDMB, GO and KEGG enrichment analyses were carried out. The results of GO enrichment analysis showed genes

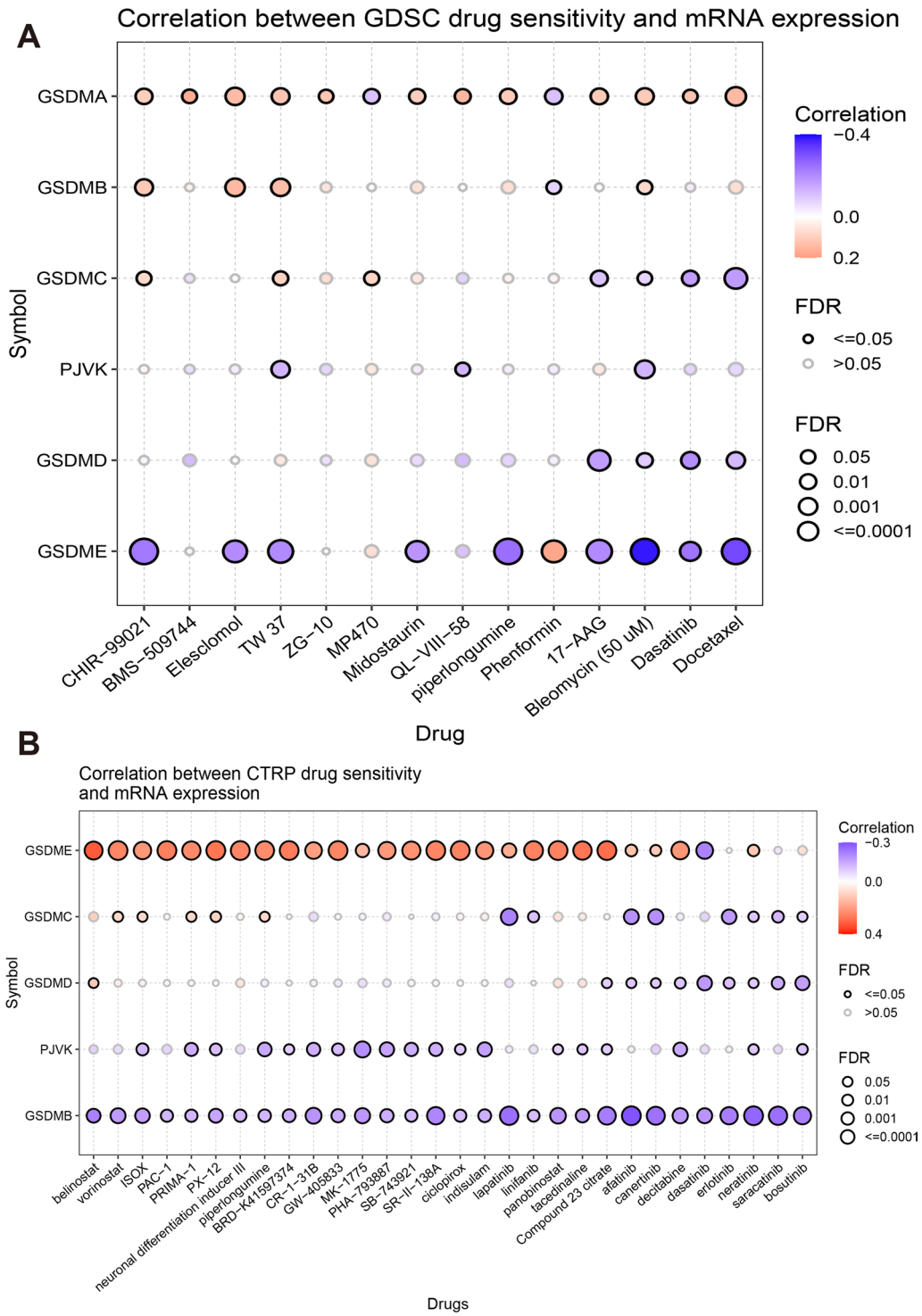

Fig. 5 Drug sensitivity analysis of Gasdermin family genes in whole cancers. **A** GDSC drug sensitivity and mRNA expression. **B** CTRP drug sensitivity and mRNA expression

correlated with GSDMB were mainly enriched in RNA splicing (Fig. 9B). KEGG enrichment also indicated a remarkable involvement of GSDMB in spliceosomes (Fig. 9C).

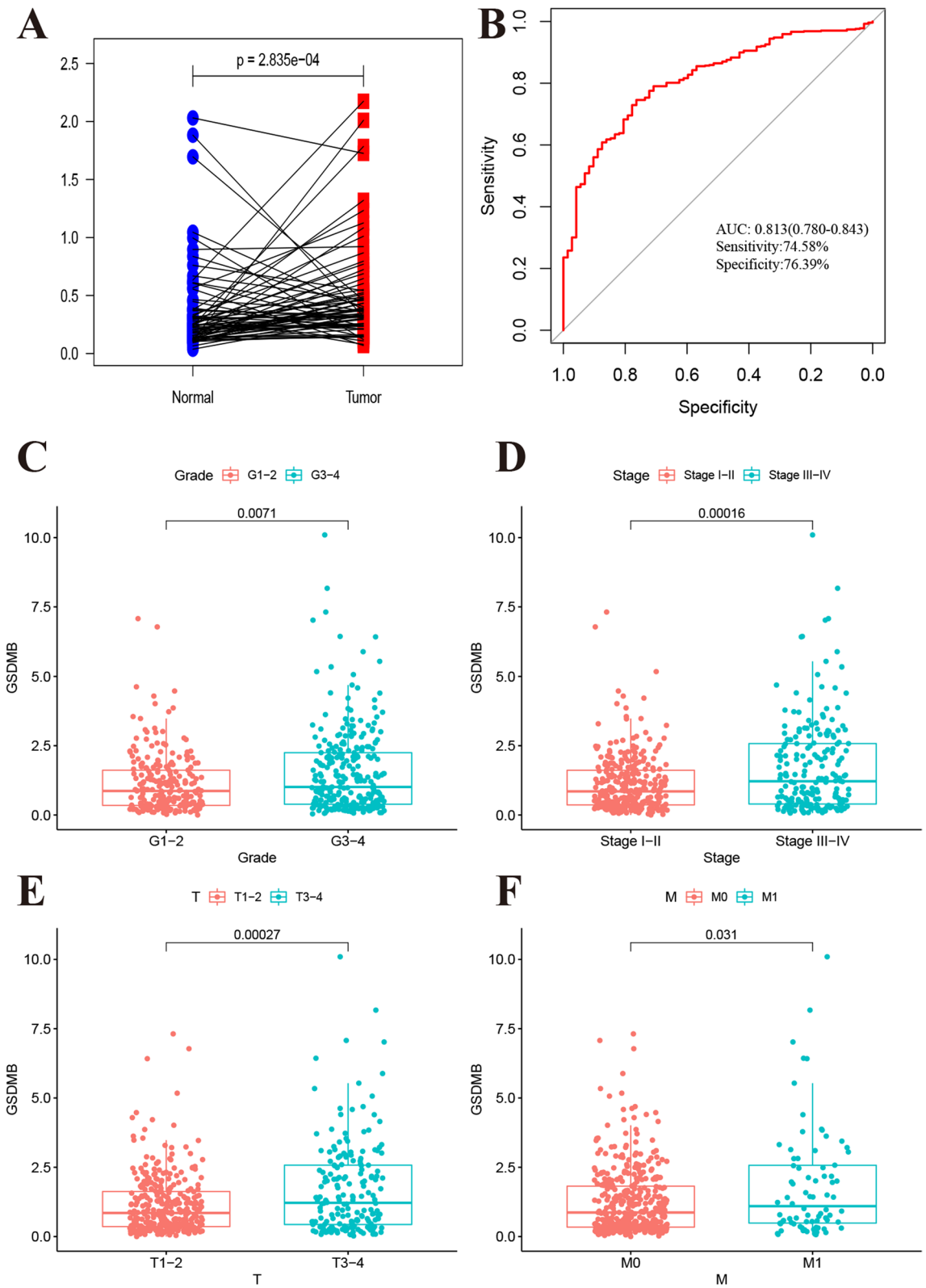

Fig. 6 Differential expression and correlation of GSDMB with clinical characteristic. **A** GSDMB is elevated in KIRC tissue. **B** Receiver operating characteristics of GSDMB for diagnosing KIRC. **C**–**F** The expression of GSDMB is associated with clinical grade and stage

Table 2 Association between GSDMB expression and clinical characteristics

Parameters	level	GSDMB		*P*
		High expression	Low expression	
Age (%)	< = 60	142 (54.6)	120 (46.2)	0.065
	> 60	118 (45.4)	140 (53.8)	
Sex (%)	Female	96 (36.9)	84 (32.3)	0.311
	Male	164 (63.1)	176 (67.7)	
Smoking (%)	NO	141 (54.2)	120 (46.2)	0.079
	Yes	119 (45.8)	140 (53.8)	
Grade (%)	G1	7 (2.7)	6 (2.3)	0.258
	G2	103 (39.6)	123 (47.3)	
	G3	107 (41.2)	100 (38.5)	
	G4	43 (16.5)	31 (11.9)	
Stage (%)	Stage I	115 (44.2)	145 (55.8)	0.053
	Stage II	30 (11.5)	25 (9.6)	
	Stage III	72 (27.7)	51 (19.6)	
	Stage IV	43 (16.5)	39 (15.0)	
T (%)	T1	116 (44.6)	148 (56.9)	0.028
	T2	37 (14.2)	30 (11.5)	
	T3	99 (38.1)	79 (30.4)	
	T4	8 (3.1)	3 (1.2)	
M (%)	M0	196 (75.4)	216 (83.1)	0.008
	M1	41 (15.8)	37 (14.2)	
	MX	23 (8.8)	7 (2.7)	
N (%)	N0	122 (46.9)	113 (43.5)	0.254
	N1	10 (3.8)	5 (1.9)	
	NX	128 (49.2)	142 (54.6)	
Radiation (%)	NO	260 (100.0)	255 (98.1)	0.072
	YES	0 (0.0)	5 (1.9)	
Pharmaceutical (%)	NO	211 (81.2)	236 (90.8)	0.002
	YES	49 (18.8)	24 (9.2)	

3.8 Correlations of GSDM genes with immune status and stemness score in KIRC

A correlation analysis demonstrated the possible correlation in KIRC between the GSDM family gene expression and immune types, stemness scores, or TME. The results highlighted that GSDMA, GSDMC, GSDMD, and GSDME were linked to immune subtypes in KIRC (Fig. 10A). These results were supported by further analysis indicating that GSDMA and GSDME were highly expressed in C6 but lowly expressed in C5. GSDMD exhibited a higher expression in C2 and a lower expression in C5. Different from other GSDM genes, GSDMC uniquely exhibited a higher expression in C5. Further results of correlation analysis in KIRC (Fig. 10B) indicated that GSDMB ($R=-0.15$, $p=0.0087$) and PVJK ($R=-0.12$, $p=0.029$) were negatively linked to RNAs, and contrarily, GSDME ($R=0.22$, $p=8.4*e-5$) was positively linked to RNAs. GSDME ($R=-0.19$, $p=0.0069$) was also negatively linked to DNAs. Regarding TME, GSDMA and GSDME had a positive link to stromal, immune, and ESTIMATE scores ($p<0.05$). GSDMB was positively linked to immune score ($R=0.22$, $p=7.1*e-5$) but negatively linked to stromal score ($R=-0.12$, $p=0.03$). GSDMC had a negative link to stromal score ($R=0.14$, $p=0.015$), immune score ($R=0.097$, $p=0.088$), and ESTIMATE score ($R=0.14$, $p=0.014$). GSDMD correlated with stromal score negatively ($R=-0.2$, $p=0.00044$) but immune score ($R=0.28$, $p=5.1*e-7$) and ESTIMATE score ($R=-0.085$, $p=0.14$) positively. PVJK was negatively associated with stromal score ($R=-0.24$, $p=2.2*e-5$) and ESTIMATE score ($R=-0.16$, $p=0.0046$).

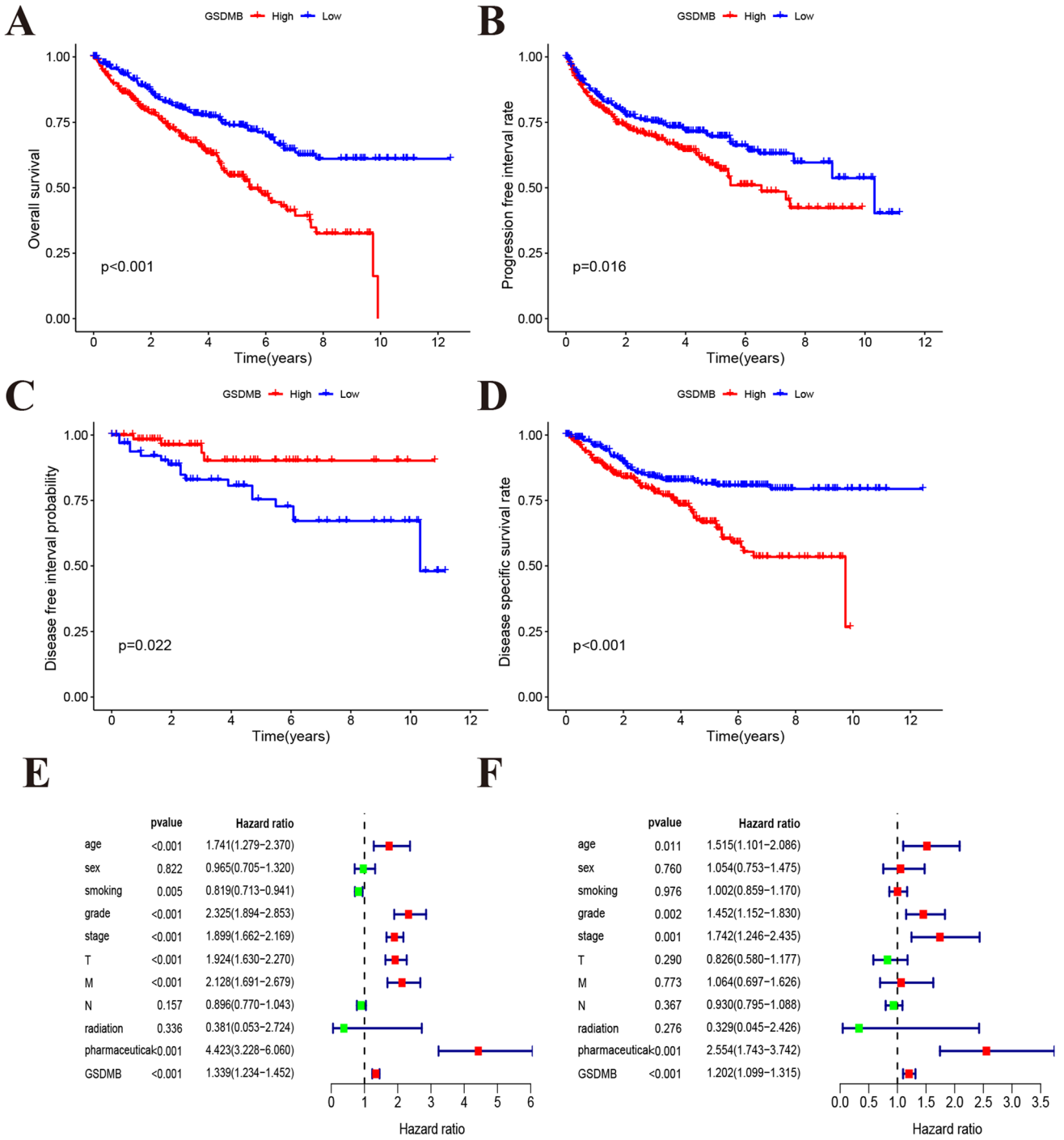

Fig. 7 GSDMB is an independent prognosis factor in KIRC. **A**–**D** Highly expressed GSDMB is associated with OS, PFI DFI and DSS. **E** Univariate cox regression of GSDMB for OS. **F** Multivariate cox regression of GSDMB for OS

4 Discussion

Throughout this research, we comprehensively investigated the expression of the Gasdermin gene family (GSDMA to GSDME and PJVK) using TCGA data of 33 various human cancers with corresponding normal tissues. Previous studies have provided cues for the significant role of GSDM family proteins in pyroptosis through the pore-forming function, which participates in tumor pathogenesis and progression [28, 29]. Consistent with the previous reports,

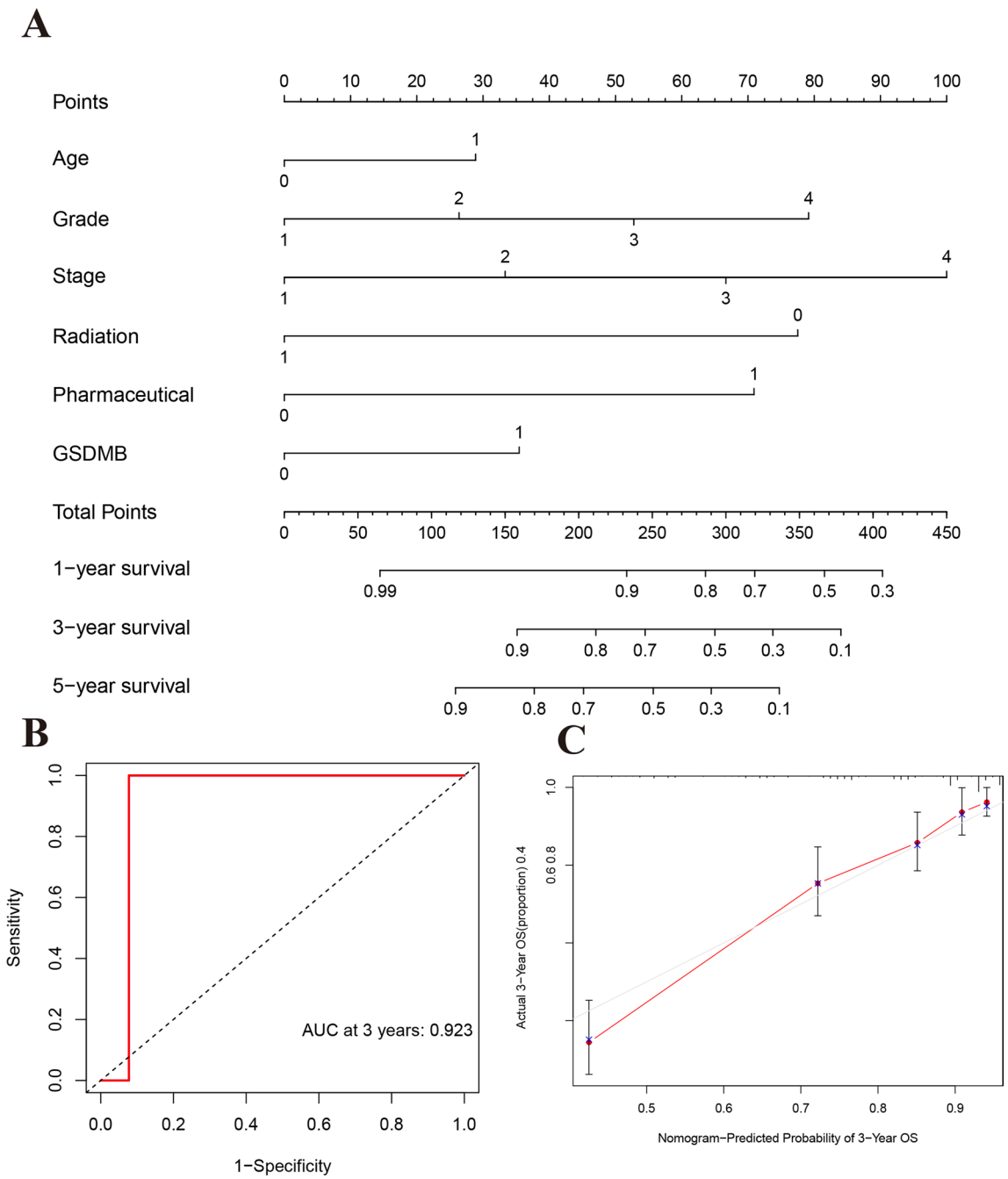

Fig. 8 Establishment and validation of nomogram model based on prognostic signature genes. **A** Nomogram model established in KIRC patients. **B** AUC of GSDMB for predicting 3-year overall survival. **C** The 3-year calibration curves in the KIRC

the present statistics derived from TCGA highlighted that GSDMA expression was enhanced in nine tumor types, compared to the control tissues. GSDMB was upregulated in eleven types of cancer, whereas it was downregulated in three tumor types. GSDMC possessed a higher expression in twelve tumor types. GSDMD was found to be more prevalent in thirteen types of cancer, with a lower expression in KICH and PRAD. GSDME exhibited higher expression in seven tumor types and lower expression in four tumor types. PVJK expression was upregulated in six tumor types and downregulated in five. Consequently, this research shed light on the potential roles of GSDM family genes as biomarkers or therapeutic targets for pan-cancer prognosis research.

This preliminary research also illuminated the correlation between GSDM family gene expression level and pan-cancer prognosis using various databases. The results were consistent and highlighted that the high expression level of GSDMB

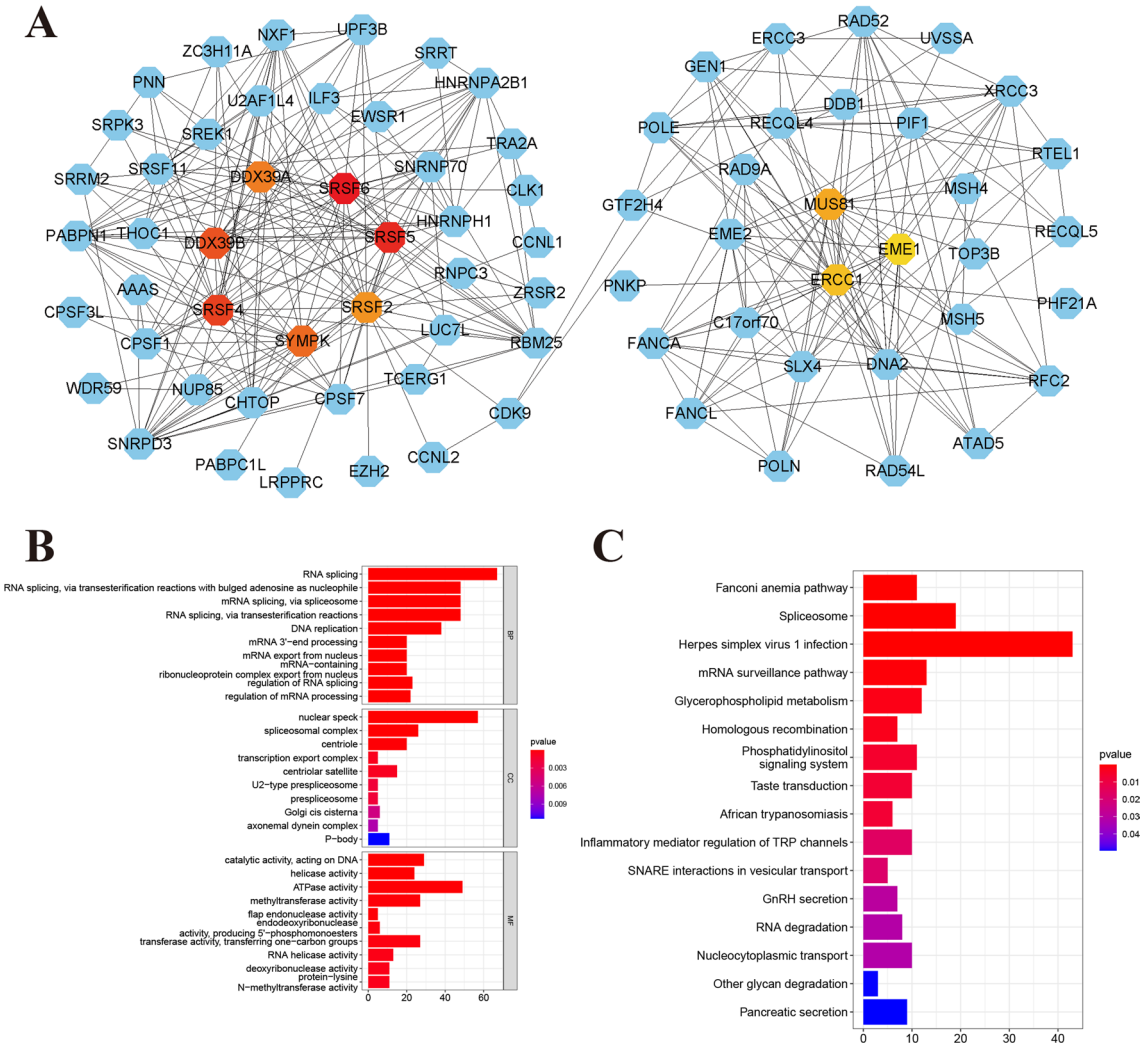

Fig. 9 Function analysis of GSDMB in KIRC. **A** PPI of genes correlated with GSDMB. **B** Functional enrichment of genes correlated with GSDMB. **C** KEGG pathway analysis of genes correlated with GSDMB

was significantly associated with poor OS in KIRC. Previous studies have revealed the involvement of GSDMB in the progression of a limited number of tumors [30]. However, only few reports investigated its potentially detrimental effects on the OS of individuals with KIRC [31, 32], which were consistent with our findings. We also found that GSDM genes served as good prognostic factors in some types of cancer, while they were poor prognostic factors in other types of cancer. Their function is similar in these cancers. But they predict different outcome of the cancers. This reason could be that genes have dual roles. Some genes were suppressor genes in some cancers but oncogene in other cancer. Different cancers have different occurrence mechanisms. These genes exert different function roles in different cancer occurrence or progression. That is why these genes predict different outcomes in cancers. Collectively, these studies suggested that GSDM family genes can serve as a pan-cancer prognostic marker, especially GSDMB for KIRC.

Another major finding of this research was that GSDM gene expression is associated with immune subtypes (C1-C6), TME, and stemness score in pan-cancer. The findings of this report revealed that the expression of all GSDM genes was linked to each immune subtype. Especially, GSDMA, GSDMB, GSDMC, and GSDMD were upregulated in C1, C2, and C6, which may be related to the regulation of STAT2 and STAT4. However, GSDME and PVJK were upregulated in C5, which exhibits the highest macrophage response, especially M2 macrophages [33]. Similarly, immune infiltration analysis revealed that GSDM family genes have a considerable link to immune infiltration scores of nearly all kinds of tumor types. This may corroborate recent research finding that pyroptosis mediated by GSDM can alter antitumor immunity [34].

Additionally, tumor stemness was strongly negatively linked to GSDM gene expression in most cancer types, including KIRC. Stemness is the potential of primitive cells to self-renew and differentiates [35]. The two tumor stemness

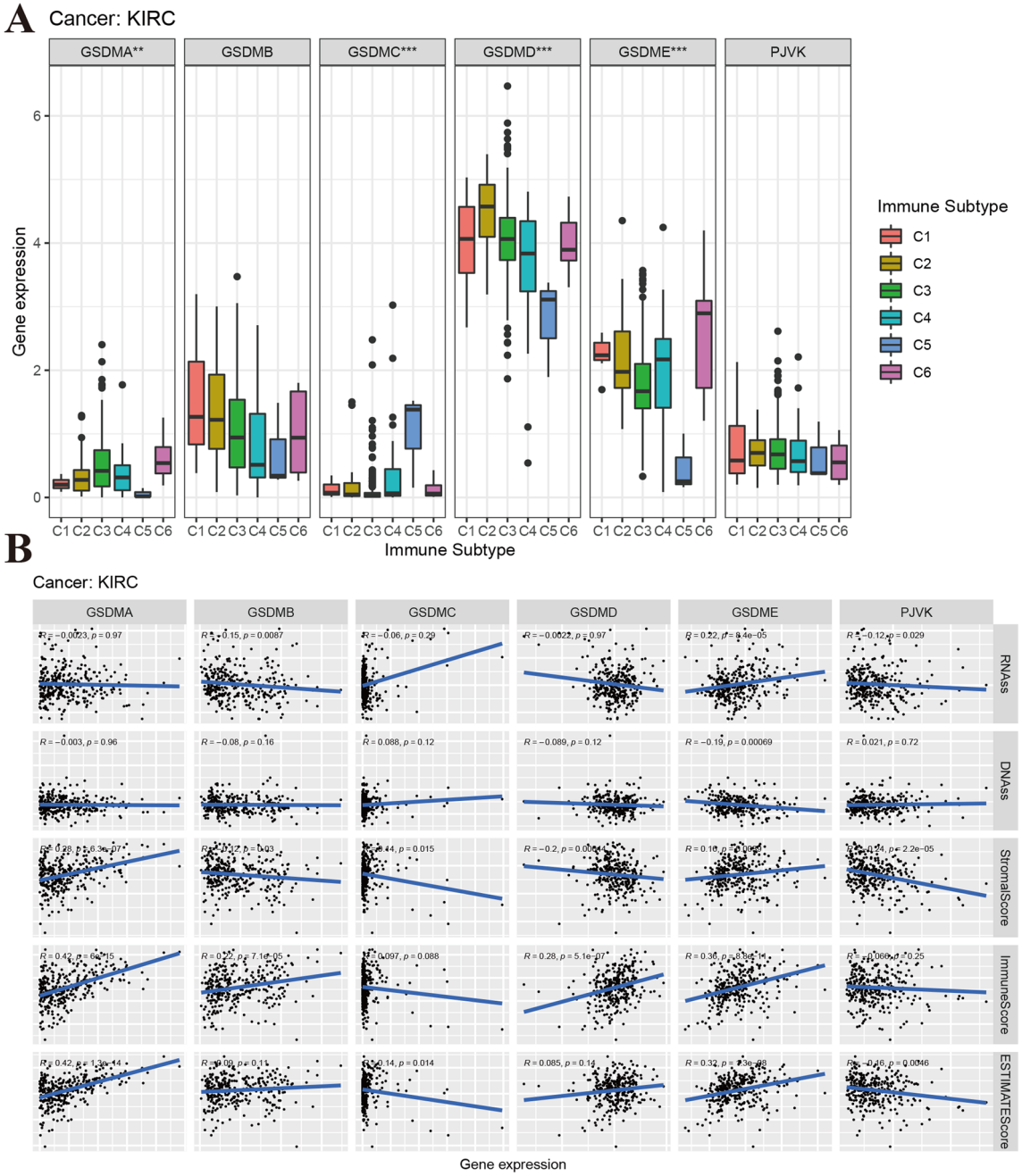

Fig. 10 Correlation of Gasdermin family genes with immune subtype, tumor microenvironment and stemness score in KIRC. **A** Differential expression of Gasdermin family genes among different immune subtype in KIRC. **B** correlation of Gasdermin family genes with stromal score, immune score, RNA stemness score and DNA stemness score in KIRC

indices, including both RNA and DNA stemness scores (mRNAsi and mDNAsi), were initially derived from cross-platform analysis by applying One-Class Logistic Regression (OCLR) based on a machine-learning algorithm [36]. To our knowledge, the two tumor stemness indices comprise RNAsi/RNAss (indicating mRNA gene expression) and DNAsi/DNAss (indicating epigenetic signature). The stemness index not only correlates with biological processes in stem cells but greater tumor dedifferentiation as well, which may contribute to the aggressiveness or recurrence of metastatic tumors. Moreover, recent studies have demonstrated that tumor stemness indices were associated with the immune microenvironment, intratumor heterogeneity, PD-L1 expression levels, and drug response [37]. According to previous reports, a lower stemness index was associated with upregulated leukocyte fraction and increased levels of PD-L1 expression [38]. Therefore, it is reasonable to predict the tumor types which are negatively correlated with GSDM gene expression are

more sensitive to immune checkpoint blockade therapy, owing to sufficient immune infiltration and the upregulation of PD-L1-correlated gene pathways [39]. In addition, the association of GSDM gene expression with immune subtypes, TME, and stemness score in KIRC was highlighted in this research. The results revealed that the expression of four GSDM genes (GSDMA, GSDMC, GSDMD, and GSDME) is associated with immune subtypes (C1-C6) in KIRC. More specifically, the GSDMA and GSDME were positively correlated with C6 (TGF-β Dominant) in KIRC, which may be related to the latest finding that DPF3a regulates KIRC metastasis by modulating TGF-β signaling, which upregulated in KIRC patients with metastases [40]. GSDMA, GSDMD, and GSDME exhibited a negative correlation with C5 (Immunologically Quiet) in KIRC, which could represent low-level macrophage response, in accordance with recent studies that Hepcidin antimicrobial peptide (HAMP) expression level was upregulated in KIRC, and positively related to the immune infiltration level of macrophages [41]. However, an in-depth understanding of the tumor stemness might lead to a promising biomarker for immunotherapy intervention for the treatment of cancer [42].

Furthermore, the potential relationship between GSDM gene expression and susceptibility to drugs was observed in 33 distinct human cancer cell lines from the CellMiner™ database. The CellMiner™ database serves as an integrated database, particularly developed for oncology research, which enables researchers of integrating and studying molecular and pharmacological data of NCI-60 tumor cell lines [43]. NCI-60, comprising sixty diverse tumor cell lines, has been utilized since 1990, by the National Cancer Institute's Developmental Therapeutics Program to screen over one hundred thousand compounds and natural products [44]. The outcomes illustrated that GSDMA expression was positively correlated with susceptibility to Dexrazoxane, while GSDMB was positively correlated with susceptibility to Nelarabine, Fluphenazine, and Perifosine. GSDMC expression was negatively associated with Ixazomib citrate, Midostaurin, Bortezomib, Pralatrexate, AT-13387, Vismodegib, and Vincristine, and was positively correlated with Gefitnib and Lificguat. GSDMD demonstrated a positive correlation with susceptibility to Fludarabine, Cladribine, and 5-fluoro deoxy uridine 10. The above results confirmed that GSDM gene expression level in cancer cells is related to the susceptibility to certain drugs, and the evaluation of GSDM gene expression will have a special guiding significance for the clinical therapy selection of drugs.

Furthermore, the differential expression and prognostic significance of GSDMB were observed in KIRC through cox regression, survival analysis, and immune infiltration analysis (including cox regression, survival analysis, and immune infiltration analysis). GSDMB expression was observed to be significantly higher in KIRC tissues than in normal tissues. The ROC analysis confirmed the effectiveness of GSDMB differential expression in distinguishing KIRC samples from normal tissues, with the AUC of GSDMB equaling up to 0.813. Moreover, the results demonstrated high GSDMB expression was related to clinicopathologic characteristics of KIRC, including histologic grade, pathologic stage, T classification, M classification, and pharmaceutical. K-M survival plotter analysis also showed KIRC patients with highly expressed GSDMB presented unsatisfying OS, PFI, DSS, and DFI ($p < 0.05$). The multivariate cox regression analysis indicated that high GSDMB expression served as an independent prognostic factor for OS in KIRC patients. Collectively, the results showed that high GSDMB expression was correlated with advanced KIRC, which signified GSDMB had significant diagnostic value and a potential biomarker for prognosis and therapy for KIRC.

Owing to the prognostic value of GSDMB, a nomogram was constructed to predict the 1, 3, and 5-year OS in KIRC patients from the TCGA dataset. For verification, the 3-year receiver operating curve and a calibration curve were drawn. They both revealed good diagnostic effectiveness of the nomogram, which can provide a basis for clinical physicians to improve the accuracy of identifying individuals at a high risk of developing KIRC.

Moreover, PPI and gene enrichment analyses were carried out on the differentially expressed genes in high- and low-GSDMB expression groups to analyze their potential interaction networks, molecular functions, and signaling pathways. The results revealed that the differential genes correlated with GSDMB are related to RNA splicing and spliceosomes.

In the present study, pan-cancer analysis of the GSDM family genes was performed to investigate their correlation with survival, tumor microenvironment, and therapeutic targets. The study found that high GSDMB expression served as an independent prognostic factor for overall survival in individuals with KIRC. However, this study has some limitations. Firstly, this research relied primarily on public databases and bioinformatics tools and did not include in vivo and in vitro experiments to support the findings. Moreover, confounding factors may have led to some biases. Despite these limitations, the positive results of this study provide a foundation for future investigation into the cellular or molecular mechanisms of GSDM family genes in different types of tumors. Secondly, the study was not able to determine if the GSDM genes affect the survival prognosis through the immune microenvironment, despite the significant correlation between stromal and immune components in TME in KIRC patients. Therefore, further research that examines GSDM gene expression and immune infiltration in KIRC patients may provide further insights. Lastly, although the enrichment analysis revealed RNA splicing-associated biological processes, additional research is needed to explore the biological mechanisms of GSDMB in KIRC.

5 Conclusions

Collectively, the present study utilized computational methods to examine the expression profiles of the Gasdermin family genes, which were linked to the prognosis of many types of tumors, particularly in KIRC, and were linked to the TME and stemness score in pan-cancers. Additionally, the expression of GSDM genes in cancer cells was correlated with susceptibility to specific drugs. Furthermore, overexpression of Gasdermin B was associated with poor prognosis in KIRC and identified as an independent prognostic factor in individuals with KIRC. The nomogram based on GSDMB expression and clinical characteristics demonstrated promising diagnostic efficacy. These findings could pave the way for further research into the Gasdermin family genes as potential prognostic and therapeutic targets in pan-cancer, especially in KIRC.

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Author contributions LYY designed this study and directed the research group in all aspects, including planning, execution, and analysis of the study. TXY drafted the manuscript. LZZ collected the data. LZZ provided the statistical software, performed the data analysis, LZZ and LYY arranged the Figures and Tables. LYY revised the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability All data used in this study are publicly available from the following sources: TCGA database: https://portal.gdc.cancer.gov/; GTEx project: https://gtexportal.org/.

Declarations

Ethics approval and content to participate The ethic approval is not applicable because the data is from public platform.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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