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Research article

Deciphering the multidimensional impact of *IGFBP1* expression on cancer prognosis, genetic alterations, and cellular functionality: A comprehensive Pan-cancer analysis

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ABSTRACT

Objectives: IGF-binding protein 1 (*IGFBP1*) is a key regulator of insulin-like growth factors, impacting biological processes, including cancer progression and prognosis.
Materials and methods: This study investigates genetic alterations affecting IGFBP1 expression in tumors using data from The Cancer Genome Atlas (TCGA) PanCancer Atlas via cBioPortal. We analyzed samples from 32 cancer types for mutation sites, including deep deletions, amplifications, and mutations. RNA-seq data were normalized using log2(value + 1). Statistical analyses, including survival outcomes, were conducted using R packages like ggplot2, stats, and car. Kaplan-Meier survival curves and log-rank tests assessed overall survival (OS) and progression-free survival (PFS). Univariate Cox regression was used to develop nomogram models for OS. Functional consequences of IGFBP1 mutations were explored through protein structure, stability, and IGF interaction analyses. Protein-protein interaction networks and functional enrichment were analyzed using GEPIA2, STRING, and Cytoscape. Gene Ontology (GO), KEGG, and Gene Set Enrichment Analysis (GSEA) provided insights into affected biological pathways.
Results: Pan-cancer analysis revealed diverse expression patterns, including significant upregulation in cutaneous melanoma (SKCM) and downregulation in lung adenocarcinoma (LUAD) and stomach adenocarcinoma (STAD). Specifically, elevated IGFBP1 expression in SKCM patients led to a 25 % improvement in 5-year survival. In contrast, higher *IGFBP1* levels in LUAD and OV patients resulted in a 30 % and 20 % decrease in survival, respectively. Elevated *IGFBP1* levels are significantly linked to advanced tumor stage and grade in OV and LUAD, affecting prognostic outcomes. Nomogram models for OV, SKCM, LUAD, and STAD showed *IGFBP1*'s predictive strength with AUC values ranging from 0.70 to 0.85, indicating its diagnostic potential. Genetic analyses revealed mutations in IGFBP1 in 12 % of STAD cases and 10 % of UCEC cases, indicating significant genetic variation. Immune analysis showed that high *IGFBP1* expression significantly influenced immune cell infiltration, particularly macrophages and $CD8^+$ T cells, thereby affecting survival in LUAD and OV. Functional enrichment and gene set enrichment analysis identified

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IGFBP1 involvement in crucial pathways, such as cell cycle regulation, immune response, and PD-1 signaling, highlighting its biological impact. Additionally, *IGFBP1* expression delineates distinct molecular and immune subtypes, correlating with specific cancer behaviors and immune patterns. *Conclusions:* These findings highlight IGFBP1's potential as a biomarker and therapeutic target, particularly for immunoregulation and cancer subtype stratification.

1. Introduction

Cancer, a complex group of diseases characterized by uncontrolled cell growth, is a major global health challenge that causes significant morbidity and mortality. It is responsible for an estimated 19.3 million new cases and 10 million deaths in 2020, with projections suggesting an increase to 28.4 million cases by 2040 [1]. The genetic and phenotypic heterogeneity of the disease complicates treatment and often results in variable patient outcomes. Despite advancements in surgery, chemotherapy, and other treatments, these treatments frequently fall short of a cure and can lead to severe side effects. This highlights the urgent need to develop more effective therapies to improve clinical outcomes, reduce side effects, and decrease mortality rates, underscoring the critical need for ongoing and enhanced cancer research. Genetic diagnosis has revolutionized the field of oncology by providing unparalleled insights into the molecular underpinnings of cancer [2]. Among myriad biomarkers and molecular signatures, Insulin-like Growth Factor Binding Protein 1 (IGFBP1) has emerged as a focal point of research because of its nuanced role in cancer progression [3]. Genetic diagnostic techniques, including high-throughput sequencing and gene expression profiling, have facilitated detailed studies on IGFBP1, uncovering its intricate interactions with the cellular pathways involved in cancer [4,5].

Despite strides in understanding the molecular landscapes of various cancers, the relationship between IGFBP1 and cancer remains unclear [6]. Current research has revealed conflicting evidence regarding IGFBP1's role as a tumor suppressor in some contexts [7–10] and as a promoter of cancer in others [11,12]. These paradoxical roles underscore the intricate balance of cellular processes regulated by IGFBP1, including cell growth, apoptosis, and interactions with the Insulin-like Growth Factor (IGF) axis [13]. Additionally, a correlation was found between *IGFBP1* expression and the infiltration of myeloid-derived suppressor cells [12]. Nevertheless, substantial gaps persist in our understanding of how IGFBP1 modulates the tumor microenvironment and whether it can be utilized as a therapeutic agent.

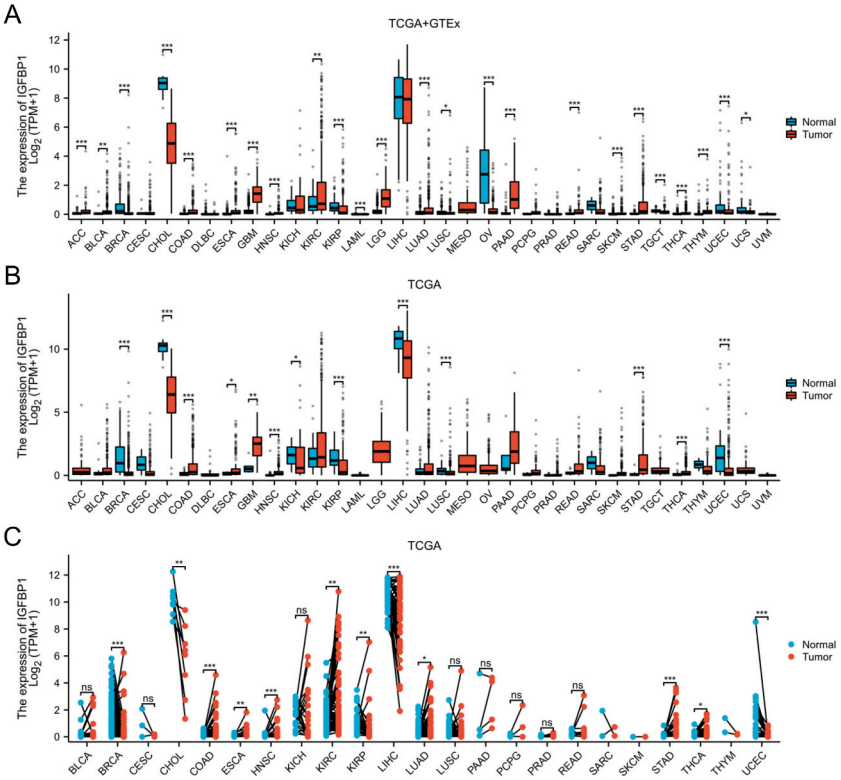

Fig. 1. Pan-Cancer *IGFBP1* mRNA Expression. (A) *IGFBP1* mRNA expression in samples from TCGA_ GTEx in 33 cancers. (B) *IGFBP1* mRNA expression in cancers from TCGA in 33 cancers. (C) *IGFBP1* expression in 23 tumor-matched samples from the TCGA.(*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

This study addresses these gaps by conducting a comprehensive analysis of the association between *IGFBP1* and cancer. By leveraging advanced genetic diagnostic methods, we sought to elucidate the variations in IGFBP1 expression patterns across different types of cancer, assess its prognostic significance, and investigate its interaction with key signaling pathways and the tumor microenvironment. Through this endeavor, we aspire to elucidate ambiguous roles of IGFBP1 in oncogenesis, providing novel insights that could guide the development of targeted cancer therapies and enhance patient outcomes.

2. Results

This study examined the expression of IGFBP1 in various cancer types using standardized TCGA_GTEx data. The results revealed differential expression of IGFBP1 across the majority of tumors, with some demonstrating high expression levels and others showing low expression levels (Fig. 1A), consistent with the TCGA findings (Fig. 1B). Additionally, IGFBP1 expression was evaluated in 23 distinct tumor types using paired TCGA samples (Fig. 1C).

The HPA database demonstrated predominant RNA expression of *IGFBP1* in 30 cell lines (Fig. 2A), including gastric (Fig. 2B), liver (Fig. 2C), ovarian (Fig. 2D), pancreatic, and bile duct cancers.

2.1. Correlations between IGFBP1 expression and clinical parameters

We investigated the relationship between the clinicopathological features and *IGFBP1* expression. The results showed that gender and *IGFBP1* expression were significantly correlated in KIRC and LUAD (Fig. 3A and H). Moreover, the expression of *IGFBP1* in KIRC, ESCA, LUAD, and LGG correlated with tumor size (Fig. 3B), lymph node metastasis (Fig. 3C–F), distant metastasis (Fig. 3D), pathological stage (Fig. 3E–G, J), and WHO grade (Fig. 3K), which are important indicators of tumor prognosis.

Specifically, male patients in KIRC and LUAD showed high expression of IGFBP1. Meanwhile, higher T stage (T3&T4), N stage (N1&N2&N3), M stage (M1), and pathological stage III&IV of KIRC showed higher expression. In ESCA, N stage (N1&N2&N3) and pathological stage III&IV showed higher expression; LUAD also had higher expression in pathological stage III&IV, while in LGG, G3 grade showed higher expression.

2.2. Relationship between IGFBP1 expression and Pan-cancer prognosis

As depicted in Fig. 4A, we investigated the relationship between *IGFBP1* expression and OS in different types of cancer. Enhanced *IGFBP1* expression was associated with a longer OS in SKCM (Fig. 4E), whereas increased *IGFBP1* expression was associated with a shorter OS in LUAD (Fig. 4B), STAD (Fig. 4C), and OV (Fig. 4D). We examined the relationship between DSS and *IGFBP1* expression (Fig. 4F). High *IGFBP1* expression predicted better DSS in SKCM (Fig. 4J) but was associated with worse DSS in KIRC (Fig. 4G), LIHC (Fig. 4H), and OV (Fig. 4I). Finally, we investigated the correlation between PFI and *IGFBP1* expression (Fig. 4K). A higher PFI in THCA (Fig. 4N) correlated with high *IGFBP1* expression, whereas a lower PFI was observed in PAAD (Fig. 4M) and KIRC (Fig. 4L).

We investigated the relationship between IGFBP1 expression and OS in different cancer types (Fig. 4). Enhanced IGFBP1 expression was associated with longer OS in SKCM (Fig. 4E), with a HR of 0.69 (95 % CI: 0.52–0.90, $p = 0.007$). In contrast, increased IGFBP1 expression was associated with shorter OS in LUAD (Fig. 4B, HR = 1.46, 95 % CI: 1.02–2.16, $p = 0.037$), STAD (Fig. 4C, HR = 1.49, 95 % CI: 1.16–1.92, $p = 0.002$), and OV (Fig. 4D, HR = 1.36, 95 % CI: 1.05–1.76, $p = 0.018$).

In terms of DSS, high IGFBP1 expression predicted better DSS in SKCM (Fig. 4J, HR = 0.65, 95 % CI: 0.48–0.87, $p = 0.003$), but was associated with worse DSS in KIRC (Fig. 4G, HR = 1.37, 95 % CI: 1.08–1.61, $p = 0.003$), LIHC (Fig. 4H, HR = 1.48, 95 % CI: 1.12–1.96, $p = 0.003$), and OV (Fig. 4I, HR = 1.49, 95 % CI: 1.16–1.92, $p = 0.002$).

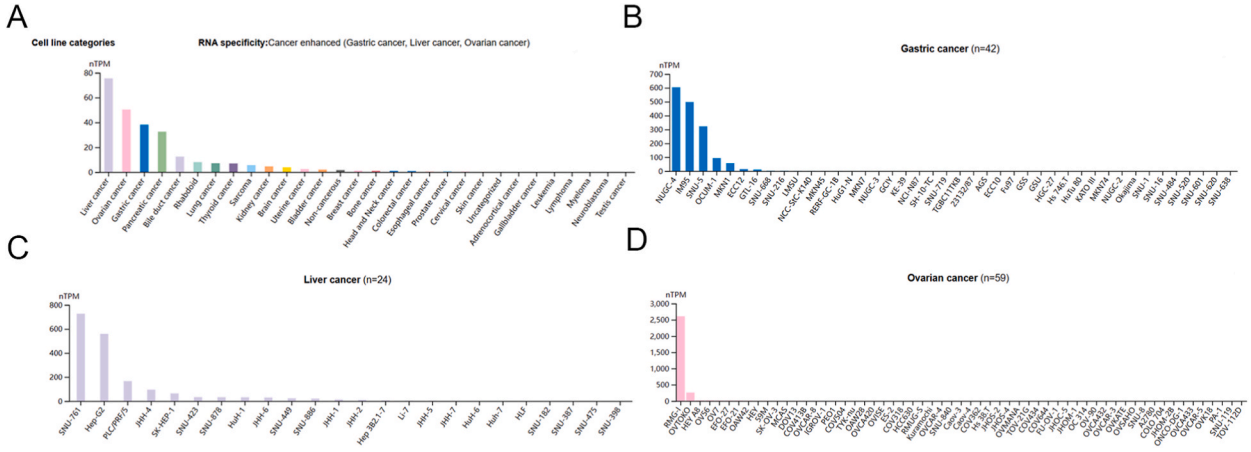

Fig. 2. RNA Expression Profile of *IGFBP1* in Various Cell Lines. (A) 30 cancers (B) Gastric cancer. (C) Liver cancer. (D) Ovarian cancer.

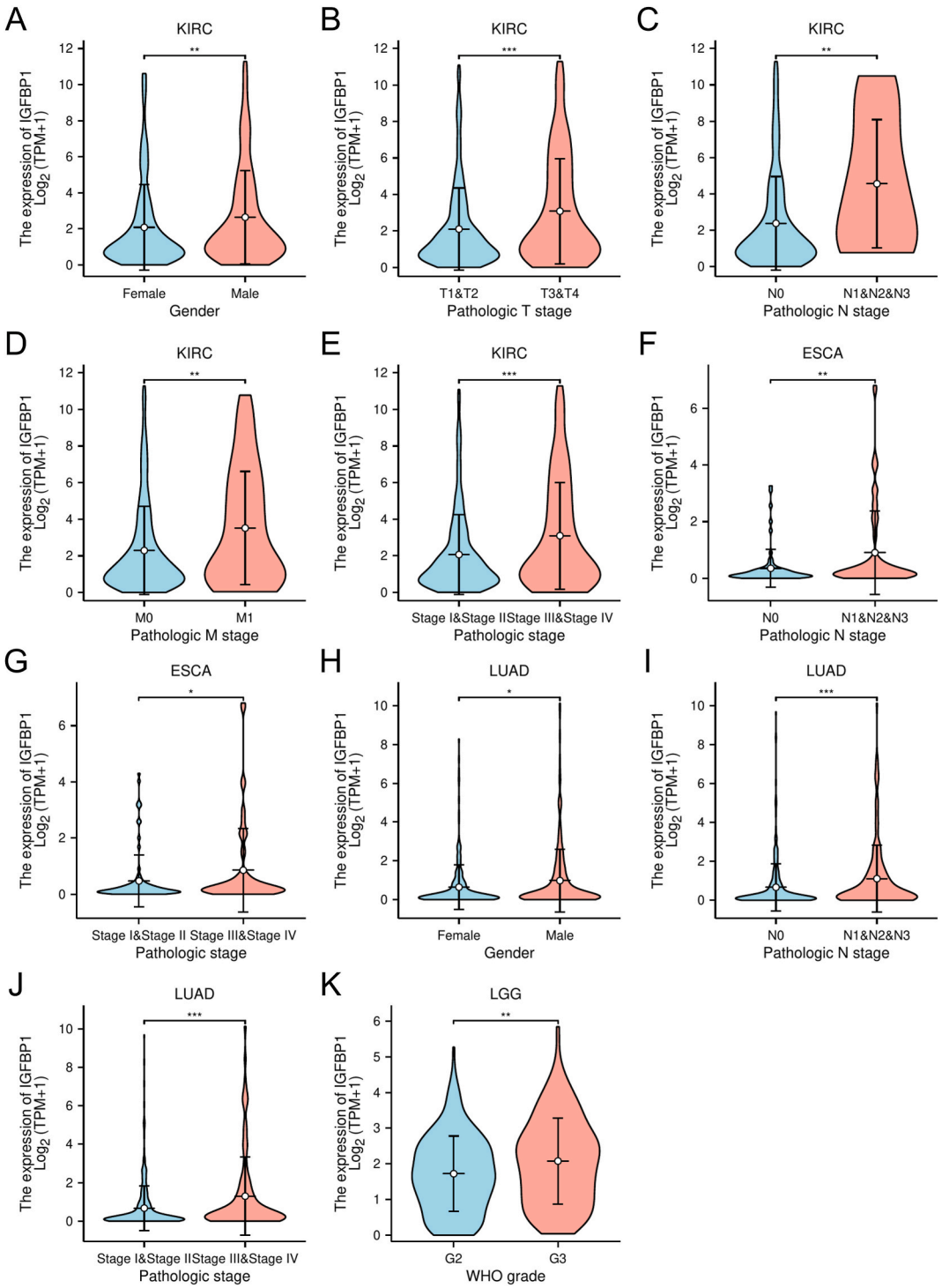

Fig. 3. Correlation of *IGFBP1* Expression with Clinicopathological Parameters. (A–E) In KIRC, the expression of *IGFBP1* was linked with pathologic stage, T stage, N stage, M stage, and gender. (F–G) N stage and pathological stage in ESCA were associated with *IGFBP1* expression. (H–J) In LUAD, there was a correlation between *IGFBP1* expression, pathological stage, and N stage. *IGFBP1* expression (J–L) was linked to the WHO grade in LGG.

In addition, the study of PFI showed that higher PFI in THCA (Fig. 4N, HR = 0.55, 95 % CI: 0.31–0.94, p = 0.028) was associated with high expression of IGFBP1, while PAAD (Fig. 4M, HR = 1.36, 95 % CI: 1.05–1.76, p = 0.018) and KIRC (Fig. 4L, HR = 1.49, 95 % CI: 1.17–2.11, $p < 0.001$) had lower PFI.

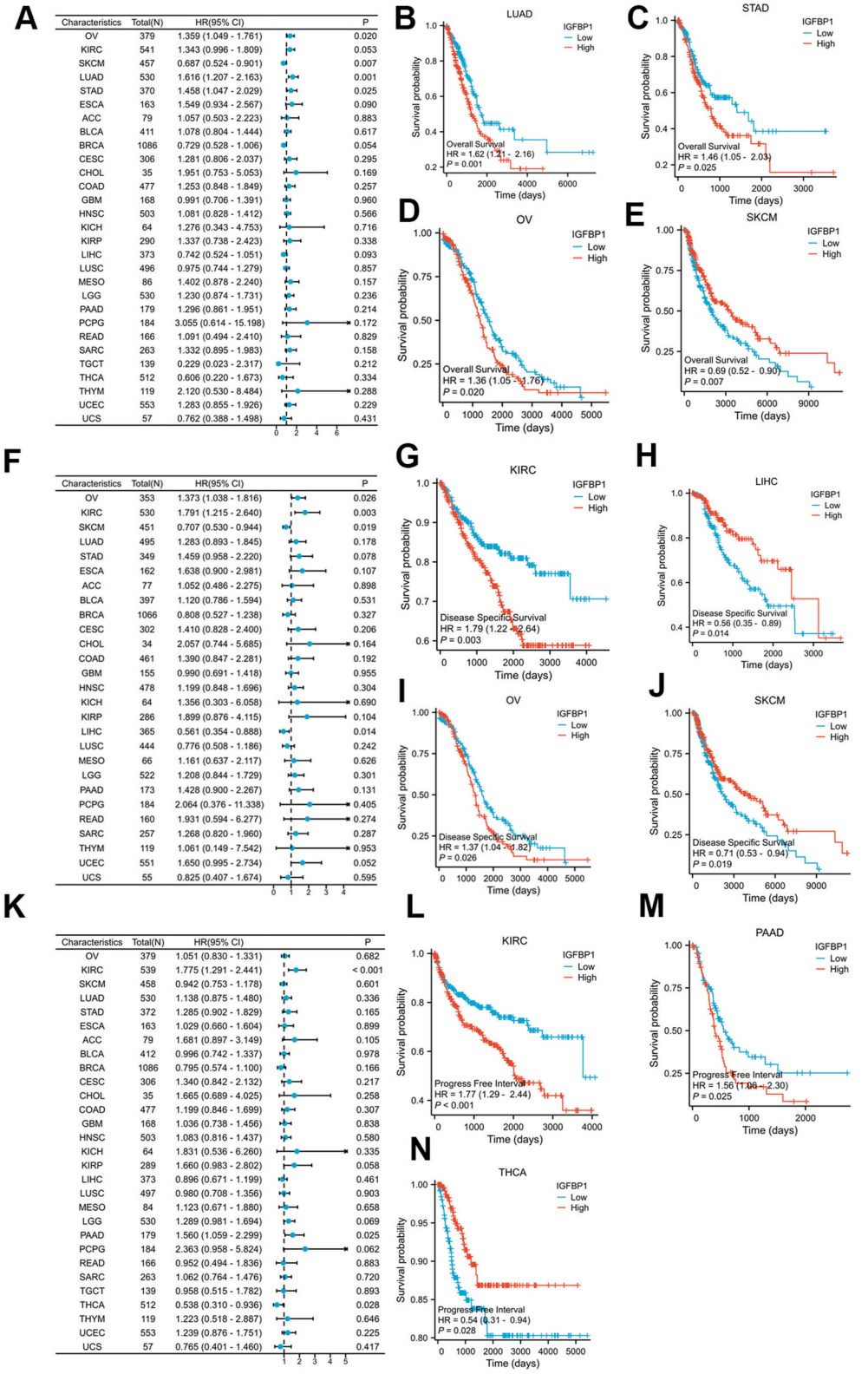

Fig. 4. OS, DSS and PFI in Pan-Cancer and *IGFBP1* Expression. (A) Forest plot of OS in patients with cancer. (B–E) OS in OV, SKCM, STAD, and LUAD. (F) Forest plot of DSS in different cancer types. (G–J) DSS in KIRC, LIHC, OV, and SKCM, respectively. (K) Forest plot of PFI in different cancer types. (L–N) PFI in KIRC, PAAD, and THCA. (OS: Overall Survival; DSS: Disease-Specific Survival, PFI: Progression-Free Interval).

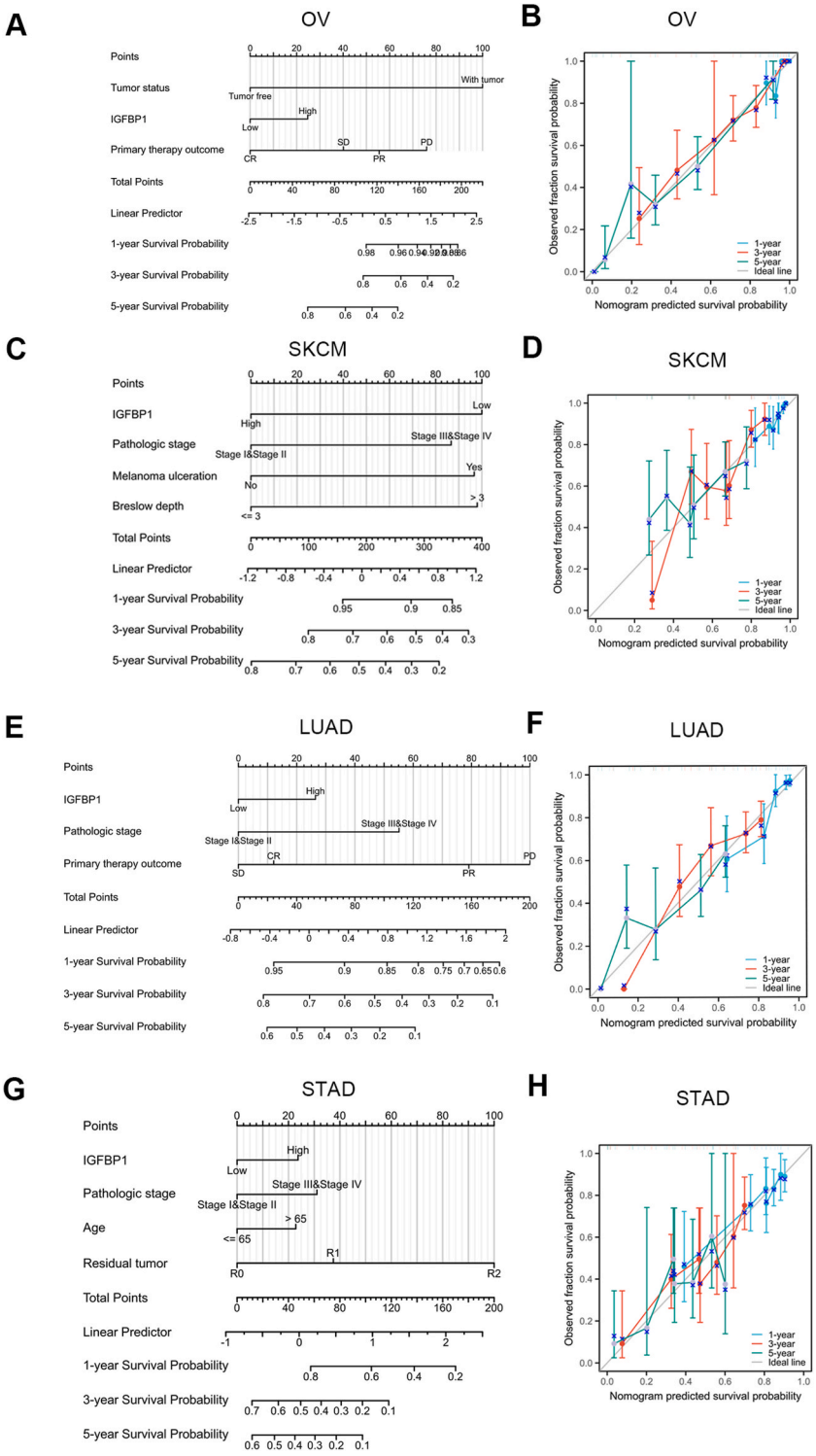

Fig. 5. Nomogram Models and Calibration Curves for OS. (A, C, E, G) Nomogram models for OS in OV, SKCM, LUAD, and STAD (B, D, F, H). At 1, 3, and 5 years, nomogram models for OV, SKCM, LUAD, and STAD were assessed using calibration curves.

2.3. Construction and evaluation of nomogram models

We conducted univariate and multivariate Cox regression analyses of OS to thoroughly assess the effect of *IGFBP1* expression on the prognosis of specific cancers (Tables S1–S4). Nomogram models for OS demonstrated strong predictive abilities for OV (Fig. 5A), SKCM (Fig. 5C), LUAD (Fig. 5E), and STAD (Fig. 5G), indicating a significant influence of *IGFBP1* on prognosis. These nomogram models

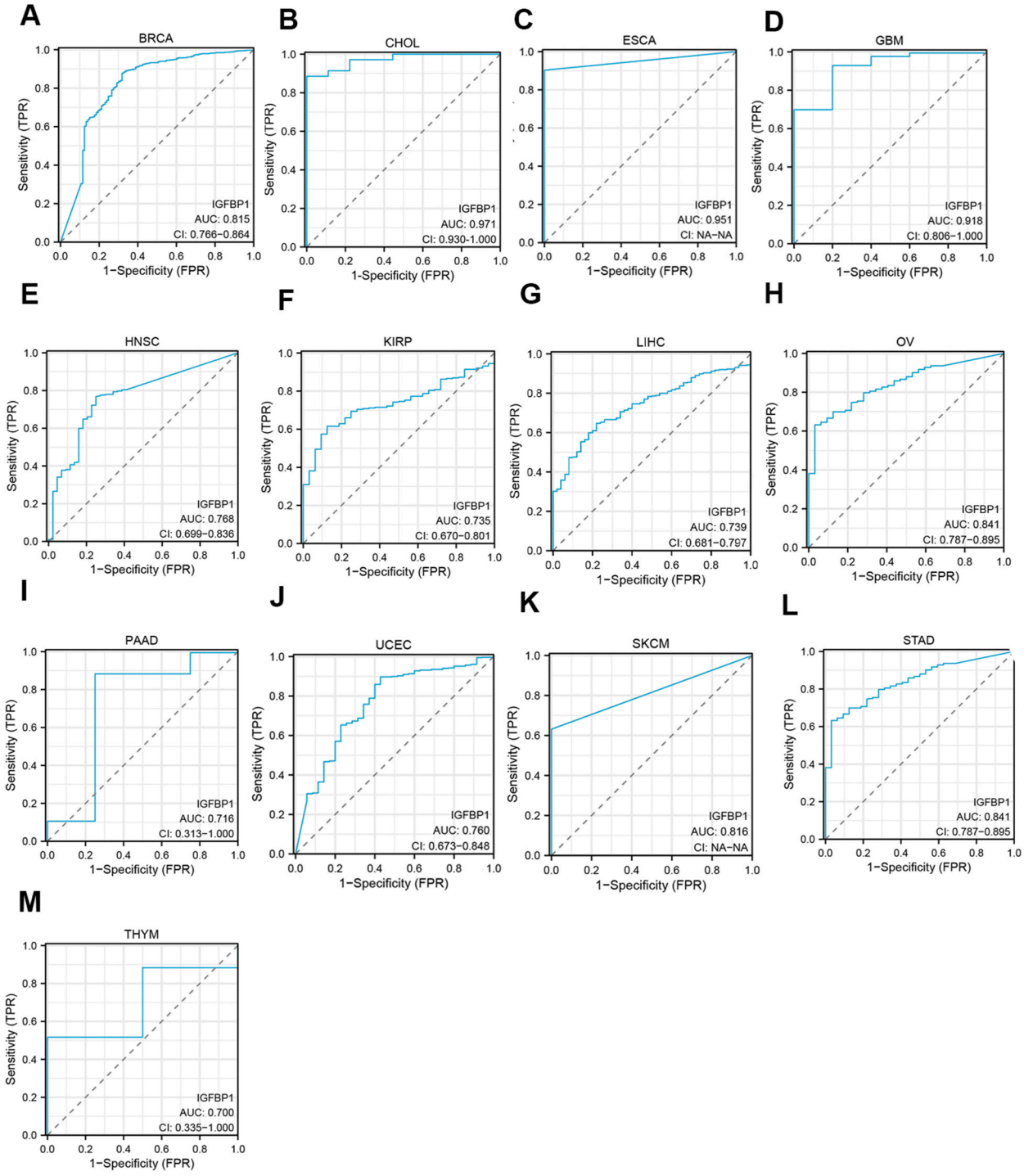

Fig. 6. *IGFBP1* ROC Curve in 13 cancer cases. BRCA, CHOL, ESCA, DBM, HNSC, KIRP, LIHC, OV, PAAD, UCEC, SKCM, STAD, THYM (A–M) (AUC >0.7). (ROC: receiver operator characteristic curve).

exhibited high accuracy, as evidenced by the calibration curves for survival projections at one, three, and five years (Fig. 5B–D, F, and H).

2.4. Diagnostic value of IGFBP1

Fig. 6A–M shows that *IGFBP1* exhibited significant diagnostic efficacy across a wide range of cancer types. Interestingly, in 13 tumors, the Area Under the Curve (AUC) exceeded 0.7, including BRCA (AUC = 0.815), CHOL (AUC = 0.971), ESCA (AUC = 0.951), GBM (AUC = 0.918), HNSC (AUC = 0.768), KIRP (AUC = 0.735), LIHC (AUC = 0.739), OV (AUC = 0.841), PAAD (AUC = 0.716), UCEC (AUC = 0.760), SKCM (AUC = 0.816), STAD (AUC = 0.841), and THYM (AUC = 0.7), indicating a notably high diagnostic value.

2.5. Genetic alteration of IGFBP1

We investigated the genetic alterations affecting *IGFBP1* expression in tumors using the cBioPortal web application. Our study included 10,967 samples from all 32 studies in TCGA PanCancer Atlas. We identified 67 mutation sites between amino acids 0 and 259, with 12 truncating and 55 missense mutations. The most frequently observed mutation was R177Q (Fig. 7A). The three most common types of mutations are deep deletions, amplifications, and mutations. *IGFBP1* mutations were predominantly found in STAD, UCEC, LUAD, ESCA, SKCM, HNSC, DLBL, LUSC, and BUCA (Fig. 7B). Among the 32 malignancies examined, BRCA, DLBC, ESCA, LUAD, MESO, PAAD, and SKCM exhibited significant deletions in *IGFBP1* mRNA expression (Fig. 7C).

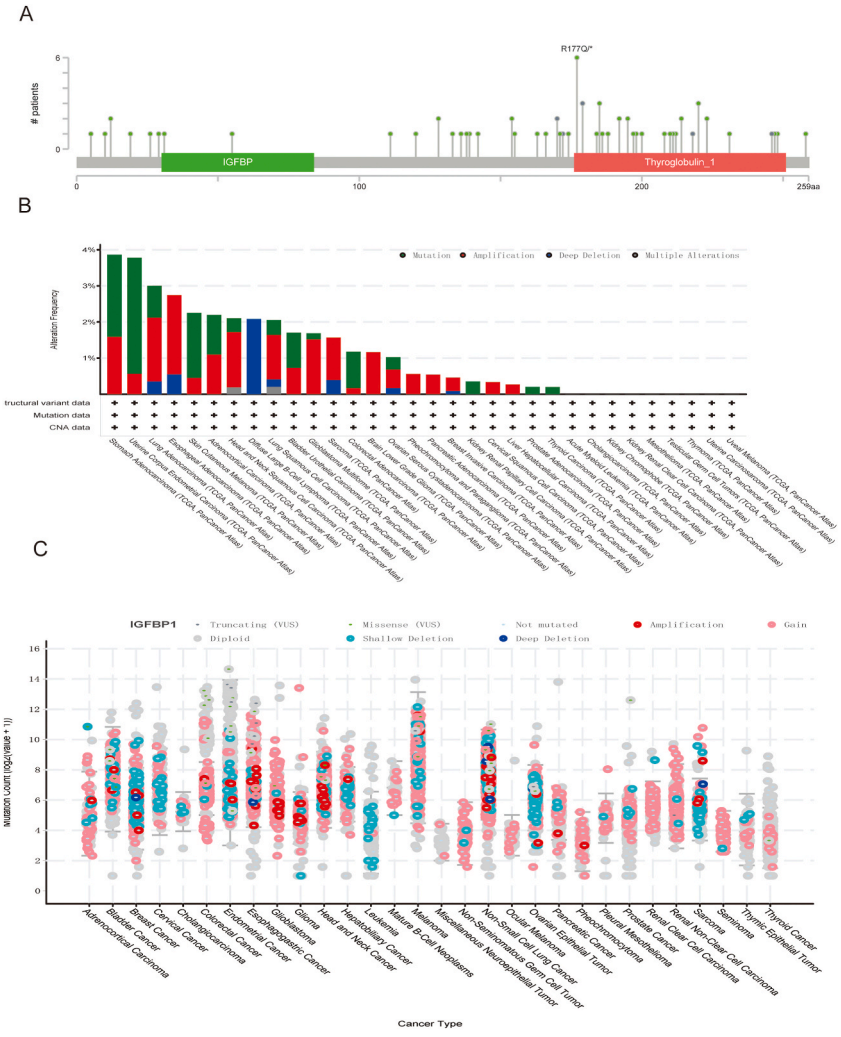

Fig. 7. Genetic Alterations in *IGFBP1* (A) Schematic depicting mutations in *IGFBP1* throughout several protein domains. (B) Bar graph displaying mutations in *IGFBP1*. (C) *IGFBP1* mutation counts and types.

2.6. Relationship between different functional states and IGFBP1

We investigated the functional status of *IGFBP1* across diverse cancer types using CancerSEA, a platform that enables exploration of the relationship between *IGFBP1* and various functional states of cancer cells at the single-cell level. Our study revealed a positive correlation between hypoxia, metastasis, and *IGFBP1* expression. Conversely, negative correlations were observed between invasion, epithelial-to-mesenchymal transition (EMT), DNA damage, apoptosis, and DNA repair (Fig. 8A). Subsequently, we examined the association between *IGFBP1* expression and the functional status of specific cancers. Our findings demonstrate a positive correlation between *IGFBP1* and metastasis, as well as hypoxia, in OV and BRCA. Conversely, *IGFBP1* expression was negatively correlated with apoptosis in UM and with EMT, invasion, DNA damage, and repair in GBM (Fig. 8B–E).

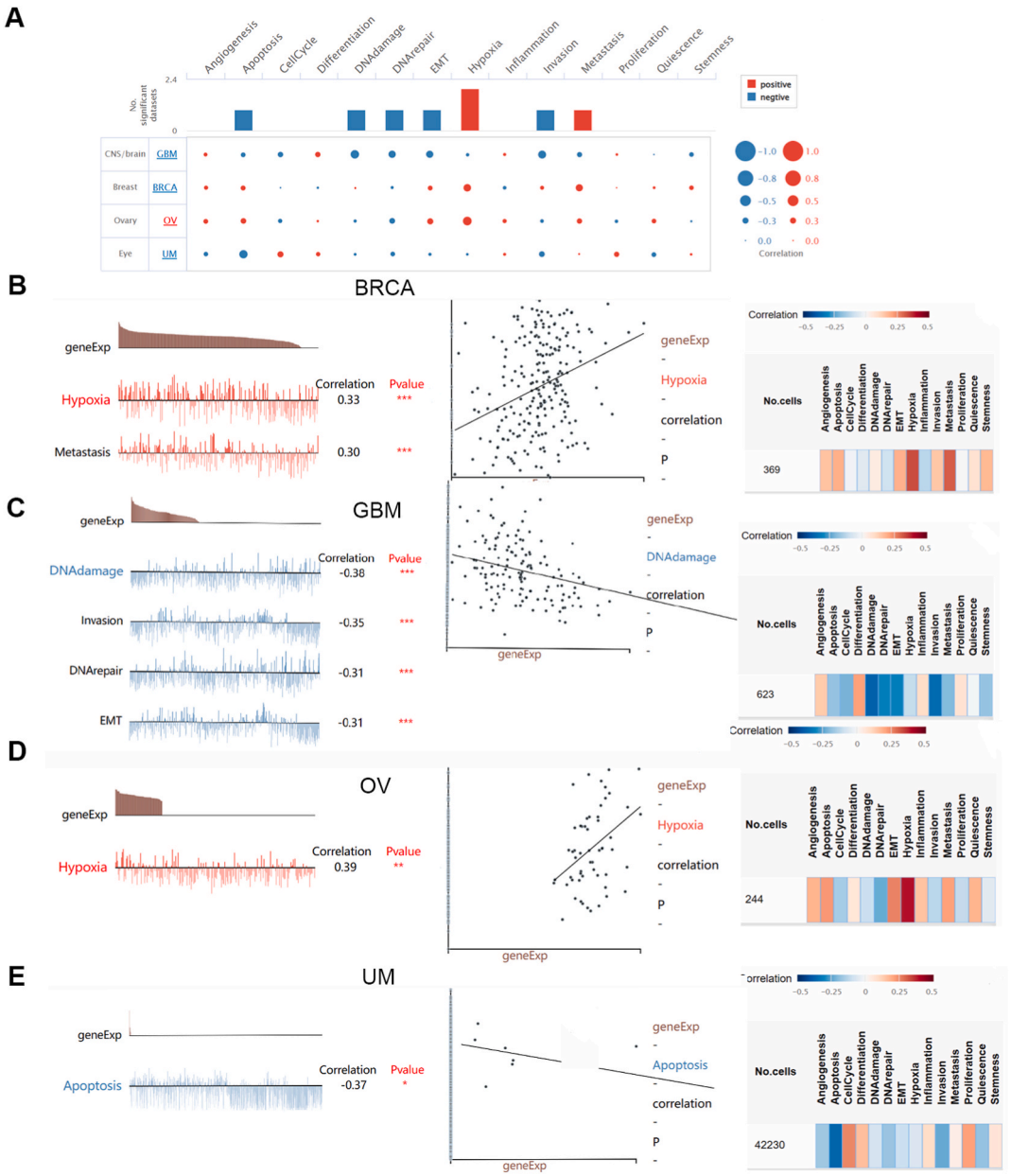

Fig. 8. Correlation of *IGFBP1* with Functional State in Four Cancers. (A) The interactive bubble chart presents the correlation of *IGFBP1* with the functional state in 4 cancers. Correlation of *IGFBP1* with the functional state in (B) BRCA, (C) GBM, (D) OV, and (E) UM. The X-axis represents the different gene sets.

2.7. Functional enrichment analysis of IGFBP1-Related genes by GEPIA2 database

To gain a deeper understanding of the biological function of *IGFBP1* in tumor formation, we selected the top 100 genes most significantly associated with *IGFBP1* from the GEPIA2 database (Table S5). Subsequently, we used STRING to construct a PPI network based on these genes (Fig. 9A). GO analysis (Fig. 9B) revealed that genes linked to *IGFBP1* are implicated in various biological processes, including "coagulation," "regulation of blood coagulation," and "hemostasis regulation." Moreover, these genes are associated with the formation of "blood microparticles," "endoplasmic reticulum lumen," and "collagen-containing extracellular matrix." Molecular processes involving "enzyme inhibitor activity," "peptidase inhibitor activity," and "endopeptidase inhibitor activity" endopeptidase inhibitor activity are also associated with *IGFBP1*-associated genes. Additionally, KEGG pathway analysis (Fig. 9C) suggested that these 100 genes might be involved in pathways such as the "PPAR signaling pathway," "Biosynthesis of amino acids," and "Pyruvate metabolism," among others.

Furthermore, GSEA was employed to elucidate the biological function of *IGFBP1* in five tumor types (KIRC, LUAD, OV, SKCM, and STAD), where *IGFBP1* expression was linked to prognosis. The results indicated that *IGFBP1* is predominantly associated with cell cycle checkpoints, DNA methylation, and the PD-1 signaling pathway (Fig. 9D–H).

The significant enrichment of IGFBP1-related genes during cell migration and adhesion suggests their involvement in the metastatic mechanism of tumors. These processes are crucial for the dissemination of tumor cells from the primary site to distant organs, facilitating the emergence of an invasive phenotype and metastasis. Furthermore, analysis revealed a significant enrichment of IGFBP1-related genes in signaling pathways that stimulate cell proliferation and survival. The activation of these pathways is associated with the uncontrolled proliferation and apoptosis resistance of tumor cells, thereby contributing to tumor progression. Angiogenesis is essential for tumor growth and metastasis, as it supplies nutrients and oxygen to tumor cells. The enrichment in angiogenesis-related signaling pathways suggests that IGFBP1 may play a pivotal.

2.8. IGFBP1-associated genes and PPI network using STRING database and functional enrichment analysis

We utilized a predetermined threshold and conducted a STRING database query to identify 50 genes strongly associated with

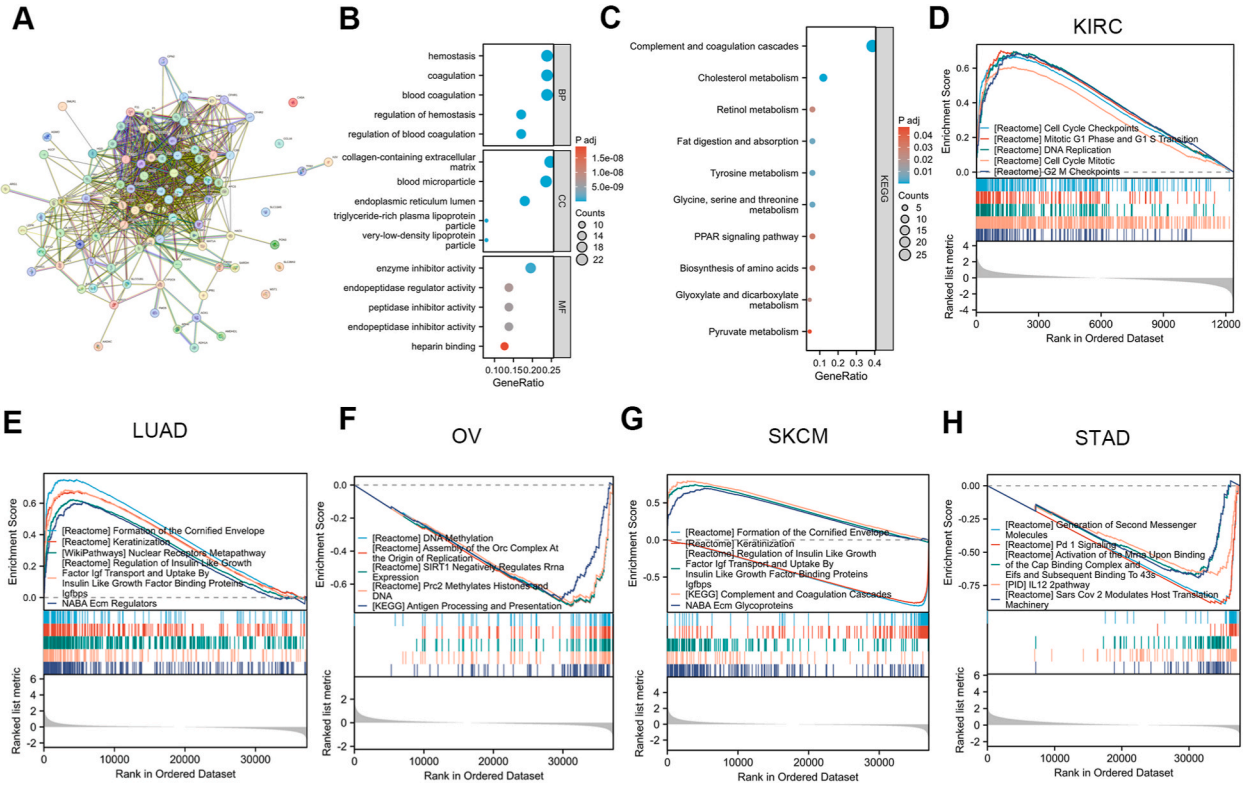

Fig. 9. Functional Enrichment Analysis of *IGFBP1*-**Related Genes from GEPIA2 Database.** (A) A Protein-Protein Interaction (PPI) network on the STRING website was created using 100 *IGFBP1*-related genes from the GEPIA2 database. (B) GO enrichment analysis using 100 genes linked to *IGFBP1*, GO enrichment analysis (BP, CC, and MF). (C) KEGG pathway analysis of the one hundred *IGFBP1*-related genes. Based on the differential expression analysis in KIRC, LUAD, OV, SKCM, and STAD, respectively, (D–H) GSEA (PPI: Protein-Protein Interaction; KEGG: Kyoto Encyclopedia of Genes and Genomes; GSEA: Gene Set Enrichment Analysis; GO: Gene Ontology; BP: Biological Process; CC: Cellular Component; MF: Molecular Function).

IGFBP1, leading to the construction of a protein-protein interaction (PPI) network (Fig. 10A–B). The top ten hub genes identified within this network were *INS*, *IGFBP1*, *AKT1*, *IGF1*, *LEP*, *TP53*, *IL6*, *IGF1R*, *IGFBP3*, and *ADIPOQ* (Fig. 10C). Subsequently, using PathLinker plugins, we successfully reconstructed the signaling circuit involving these 10 hub genes (Fig. 10D). Subsequently, KEGG and GO enrichment analyses were performed. The top three GO terms enriched in biological processes were insulin-like growth factor I binding, hormone activity, and insulin receptor binding. Prominent cellular component terms encompassed endoplasmic reticulum lumen, plasma membrane signaling receptor complex, and secretory granule lumen. Notable molecular function terms included cellular response to peptides, response to peptides, and insulin-like growth factor receptor signaling pathway. Additionally, the top KEGG pathways identified were longevity-regulating, AMPK signaling, and prostate cancer pathways (Fig. 10E).

2.9. GSEA functional enrichment analysis

The GSEA results for the eight cancers associated with prognosis are presented in Fig. 11A–H. These findings encompass pathways, including PD1 signaling, B cell receptor (BCR) signaling, *CD22*-mediated BCR regulation, biological oxidation, TCR signaling via BCR, fatty acid metabolism, Fceri-mediated MAPK activation, and the PI3KCI pathway, among others. The presence of these common enrichment pathways suggests a strong association between *IGFBP1,* immunity, and energy metabolism in various malignancies.

2.10. Correlation of IGFBP1 expression and tumor immune microenvironment

The immunological microenvironment of the tumor plays a crucial role in the onset and progression of cancer. To investigate the relationship between immune cells and *IGFBP1* expression across various cancer types, we conducted a correlation study using TIMER 2.0. The heat maps in Fig. 12A, B, 12C, and 12D illustrate the correlations between *IGFBP1* expression and B cells, $CD4^+$ T cells, $CD8^+$ T cells, and macrophages, respectively. The following specific correlations were observed: IGFBP1 expression was negatively associated with B cells in CHOL and positively with UCS; IGFBP1 expression was negatively associated with $CD4^+$ T cells in TGCT and positively with ESCA; IGFBP1 expression was negatively associated with $CD8^+$ T cells in CHOL and positively with MESO; and IGFBP1 expression was negatively associated with macrophages in CESC and positively with MESO.

2.11. Influence of IGFBP1 expression and immunological infiltration on overall survival

To elucidate the impact of immune cell infiltration on tumor prognosis, we utilized TIMER 2.0 to examine the combined effects of *IGFBP1* expression and immune cell infiltration on overall survival (OS). The data presented in Fig. 13A–D suggest that B cell infiltration may influence the prognosis of OV and SKCM. Moreover, there appeared to be a correlation between OS and infiltration of

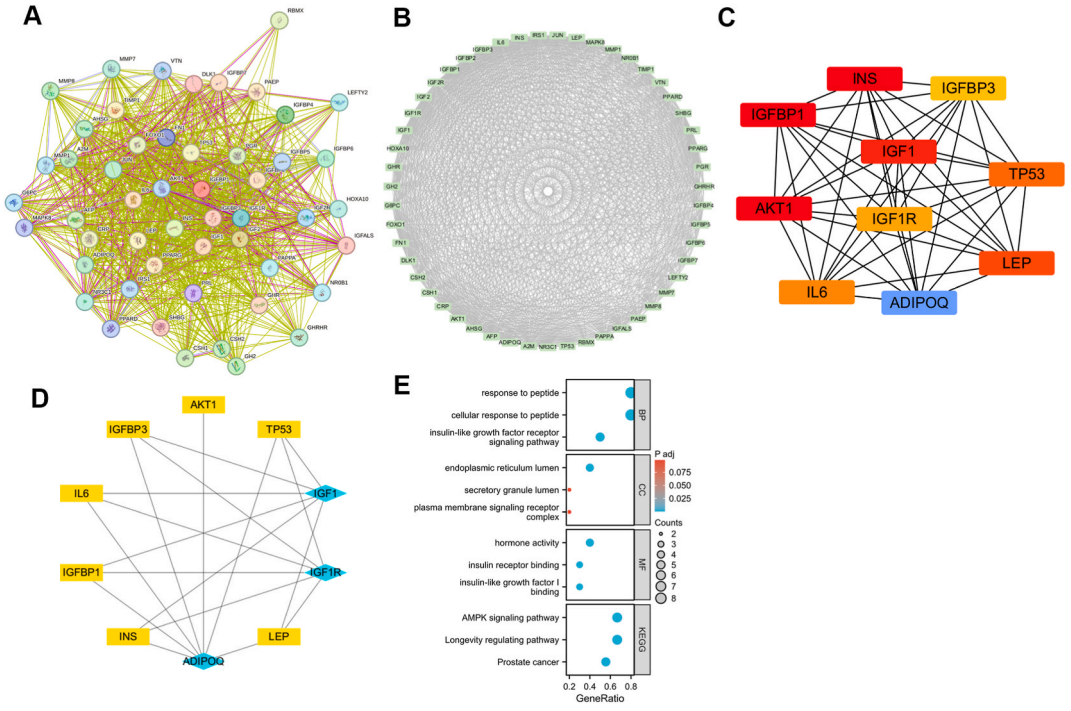

Fig. 10. PPI network of 50 genes associated with *IGFBP1* using the STRING database and functional enrichment analysis. (A–B) Show the *IGFBP1* PPI network. The top ten hub genes of the PPI network are highlighted in (C). (D) Signaling pathway that was rebuilt using the ten hub genes. (E) KEGG pathway and GO enrichment analyses of 50 genes.

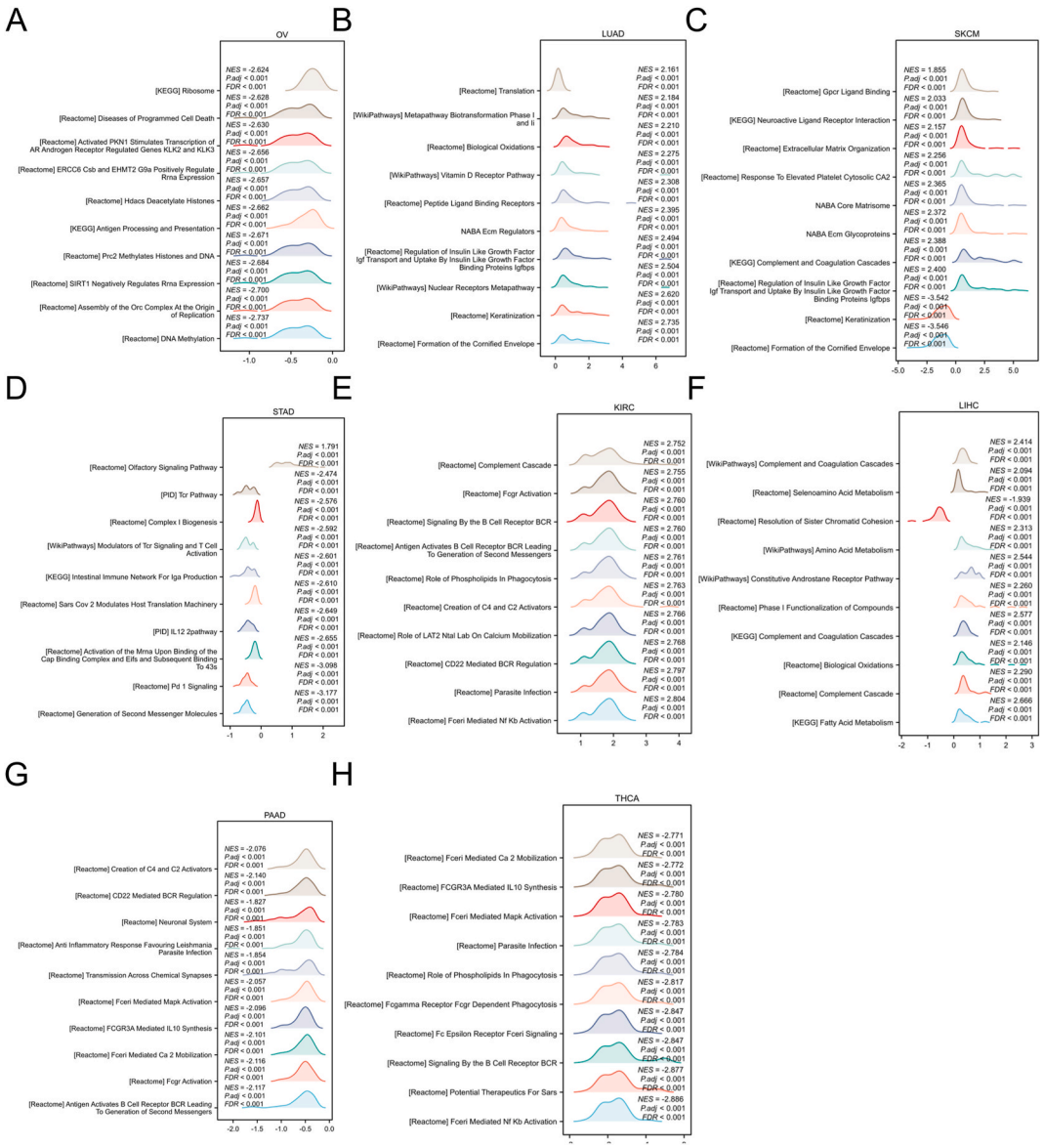

Fig. 11. *IGFBP1* Expression in Eight Malignancies using GSEA Functional Enrichment Analysis. In OV, LUAD, SKCM, STAD, KIRC, LIHC, PAAD, and THYM(A-H), the top 10 GSEA functional enrichment pathways of *IGFBP1*.

$CD4^+$ and $CD8^+$ T cells in LUAD and SKCM (Fig. 13E–L). Additionally, macrophage infiltration was associated with the prognosis of OV, LUAD, SKCM, and STAD (Fig. 13M−P). Importantly, the impact of immune cells on tumor prognosis varies depending on the level of *IGFBP1* expression, indicating the dependency of immune cell function on *IGFBP1* expression levels.

2.12. Different molecular and immune subtypes of cancer associated with IGFBP1 expression

Using the TIDIB database, we analyzed IGFBP1 expression across various molecular and immunological subtypes of malignancies associated with prognosis. The results revealed notable variations in IGFBP1 expression among 4 molecular subtypes of cancer ($P < 0.05$): STAD (five subtypes), BRCA (five subtypes), ESCA (five subtypes), LGG (six subtypes), and LIHC (three subtypes) (Fig. 14A–F). Additionally, significant expression changes of IGFBP1 were observed in KIRC in the context of immunological subtypes ($P < 0.05$) (Fig. 14G–L).

2.13. Immunogenomic analyses of IGFBP1

IGFBP1 was positively correlated with chemokines in ACC, PAAD, UCS, and BLCA, and negatively correlated with ESCA, OV, and

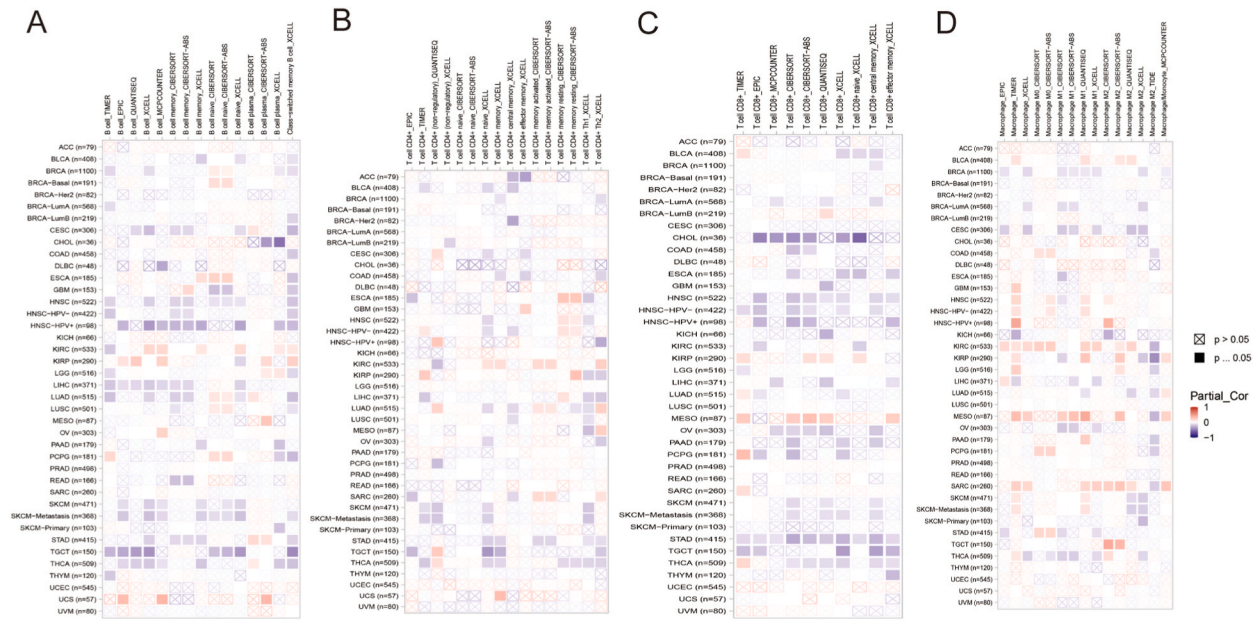

Fig. 12. Correlation Between *IGFBP1* Expression and Immune Cell Infiltration. Panels (A–D) display heatmaps illustrating the correlations observed in the TIMER2 database between *IGFBP1* expression and four distinct immune cell types: B cells, $CD4^+$ T cells, $CD8^+$ T cells, and macrophages, respectively.

STAD (Fig. 15A) according to the TIDIB database. Additionally, In ACC, GBM, KIRC, KIRP, MESO, SARC, UCEC, and UCS, *IGFBP1* exhibited a positive connection with immunoinhibitors; in contrast, OV, STAD, and LIHC showed a negative correlation (Fig. 15B). Moreover, *IGFBP1* was negatively associated with immunostimulators in CESC, CHOL, LIHC, OV, and STAD and positively correlated with them in KIRC, MESO, SARC, UCEC, and UCS (Fig. 15C). Regarding lymphocytes, *IGFBP1* negatively correlated with CESC, KICH, READ, OV, and STAD, and positively correlated with ACC, GBM, KIRC, KIRP, MESO, SARC, UCEC, and UCS (Fig. 15D). Furthermore, *IGFBP1* was negatively associated with the majority of MHC molecules in CESC, CHOL, LUAD, OV, and STAD but was positively associated with the majority of MHC molecules in ACC, GBM, LGG, MESO, SARC, UCEC, and UCS (Fig. 15E). In terms of receptors, Fig. 15F shows that *IGFBP1* had a positive connection with the majority of receptors in KIRP, KIRC, MESO, and UCS and a negative association with them in CESC, LIHC, OV, and PAAD.

3. Discussion

The insufficiency of current cancer diagnostics and treatments accentuates the need for advanced research to improve therapeutic efficacy and patient prognosis, necessitating a deeper understanding of the disease mechanisms. *IGFBP1*, which plays a pivotal role in oncogenesis, emergeshas emerged as a crucial research target and promises significant insights for therapeutic advancement. This study aimed to elucidate *IGFBP1*'s role in cancer, bridge critical research gaps, and highlight the potential of its outcomes in refining clinical strategies and enhancing prognostic accuracy.

The variable expression of *IGFBP1* across different cancer types, with some tumors showing high levels and others showing low levels, aligns with the standardized TCGA and GTEx data, indicating that *IGFBP1* plays a significant role in the oncogenesis of diverse cancers. This differential expression suggests that *IGFBP1* may be integral to the distinct pathways of cancer development and progression. The association of *IGFBP1* expression with clinicopathological parameters in cancers such as KIRC, ESCA, LUAD, and LGG, which correlates with pathological staging, tumor staging, and WHO grading, underscores its potential impact on tumor behavior and patient prognosis. In KIRC, *IGFBP1* expression is linked to various stages of tumor development and sex, while in LGG, it correlates with the WHO grade, indicating its influence on tumor aggressiveness and outcome.

Furthermore, the relationship between *IGFBP1* expression levels and survival metrics such as OS, DSS, and PFI revealed its prognostic value. High *IGFBP1* expression was associated with longer OS in SKCM, but predicted shorter OS in LUAD, STAD, and OV, highlighting its dual role and importance as a prognostic biomarker. These findings suggest that *IGFBP1* function and its impact on survival outcomes vary considerably across different types of cancer, reflecting its complex role in cancer biology. The substantial diagnostic efficacy of *IGFBP1* in cancers, such as BRCA, CHOL, and ESCA, with ROC AUC values exceeding 0.7, underscores its potential as a biomarker. An AUC above 0.7 indicates good diagnostic performance, highlighting *IGFBP1*'s prospective utility in cancer detection.

Functional enrichment analysis of 100 *IGFBP1*-related genes derived from the GEPIA2 database revealed their involvement in biological processes such as the regulation of blood coagulation. This analysis offers deeper insights into *IGFBP1*'s role in tumorigenesis by elucidating the biological pathways involving these genes. A protein-protein interaction network constructed using the

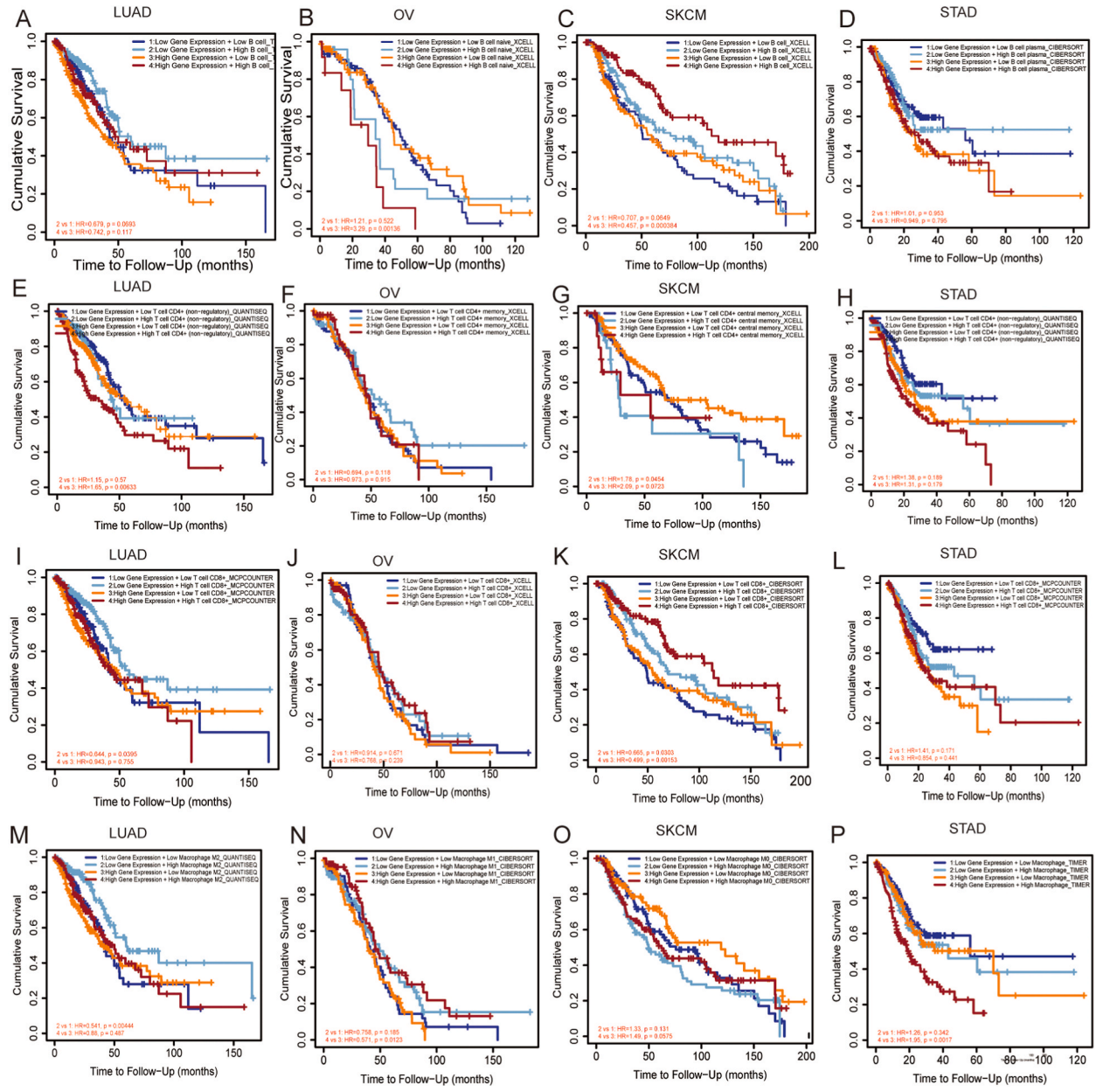

Fig. 13. Influence of Immune Cell Infiltration on Overall Survival. OS was associated with *IGFBP1* expression. (A–D) The effects of B cell infiltration on OS at different levels of *IGFBP1* expression in LUAD, OV, SKCM, and STAD. (E–H) The effects of $CD4^+$ T cell infiltration on OS at various *IGFBP1* expression levels in LUAD, OV, SKCM, and STAD. (I–L) Analysis of the expression of $CD8^+$ T cells at different *IGFBP1* levels and its influence on OS in LUAD, OV, SKCM, and STAD. (M − P) Analysis of the expression of macrophages at varying *IGFBP1* levels and their impact on OS in LUAD, OV, SKCM, and STAD.

STRING database identified ten hub genes, including *INS* and *IGFBP3*, which are pivotal for network integrity and functionality. These hub genes, central to the network architecture, play critical roles in understanding the mechanistic pathways of tumor development. *INS*, which is involved in insulin signaling pathways, is associated with cancer metabolism and growth [20]. Similarly, the role of *IGFBP3*, another member of the *IGFBP* family, can be explored in the context of its interaction with *IGFBP1* and its collective impact on tumor biology [21].

IGFBP1 is a multifunctional protein that influences cell proliferation, apoptosis, and migration. Its expression levels in various cancers can be modulated by multiple factors, including the tumor microenvironment and the activity of distinct signaling pathways. In cutaneous melanoma (SKCM), the upregulation of IGFBP1 may be linked to its role in promoting cell proliferation and tumor growth by augmenting the availability of insulin-like growth factor (IGF), which aids tumor cells in adapting and surviving within a specific

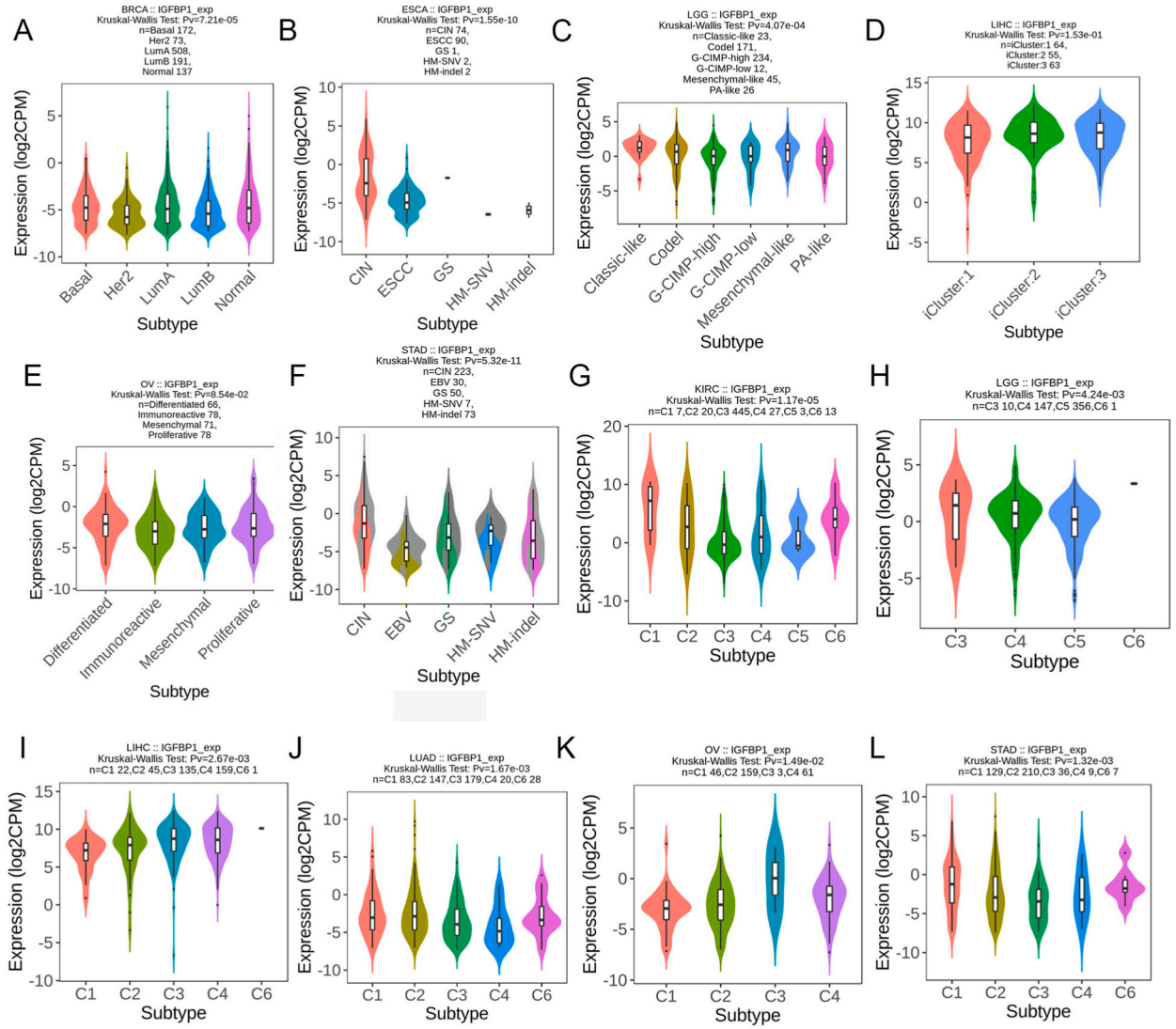

Fig. 14. *IGFBP1* Expression and Immune and Molecular Subtype Correlations in Six Cancer Types: BRCA, ESCA, LGG, LIHC, OV, and STAD(A-F), and immune subtypes in 6 cancers: KIRC, LGG, LIHC, LUAD, OV, and STAD (G–L) ($p < 0.05$).

microenvironment [22,23]. Furthermore, the upregulation of IGFBP1 may be associated with immune regulation, enabling tumor cells to evade immune system attack. Conversely, the downregulation of IGFBP1 in lung adenocarcinoma (LUAD) may indicate its tumor suppressor function [24]. IGFBP1 can inhibit the IGF signaling pathway by sequestering IGF, thereby reducing cell proliferation and promoting apoptosis. In these cancers, other cell growth-promoting signaling pathways, such as the PI3K/AKT and MAPK pathways, may be more active. Consequently, inhibiting IGFBP1 could be advantageous for cancer cell proliferation. Additionally, genetic and epigenetic regulatory mechanisms, including DNA methylation, alterations in transcription factor activity, and the regulation of noncoding RNA, can also influence IGFBP1 expression. Thus, the expression pattern of IGFBP1 across different cancers reflects its complex and varied biological functions. The upregulation or downregulation of IGFBP1 may correspond to its pro-oncogenic or anti-oncogenic effects within the tumor microenvironment, respectively. These differences are likely determined by the intracellular and extracellular signaling environments and the genetic regulatory mechanisms unique to specific cancer types.

IGFBP1 harbors several critical domains, such as the IGF-binding domain and the heparin-binding domain. Mutations within these domains can compromise the protein's capacity to bind IGFs, thereby modulating their availability and activity. Disruption of the heparin-binding domain may perturb the protein's interaction with extracellular matrix components, thereby influencing cell adhesion and migration.

The interaction of IGFBP1 with various cellular proteins and components is pivotal for its proper function. Such mutations can disrupt these interactions, thereby potentially modulating signaling pathways. For instance, IGFBP1's engagement with integrins and other cell surface receptors is indispensable for mediating cell adhesion and migration. Disruption of these interactions may result in

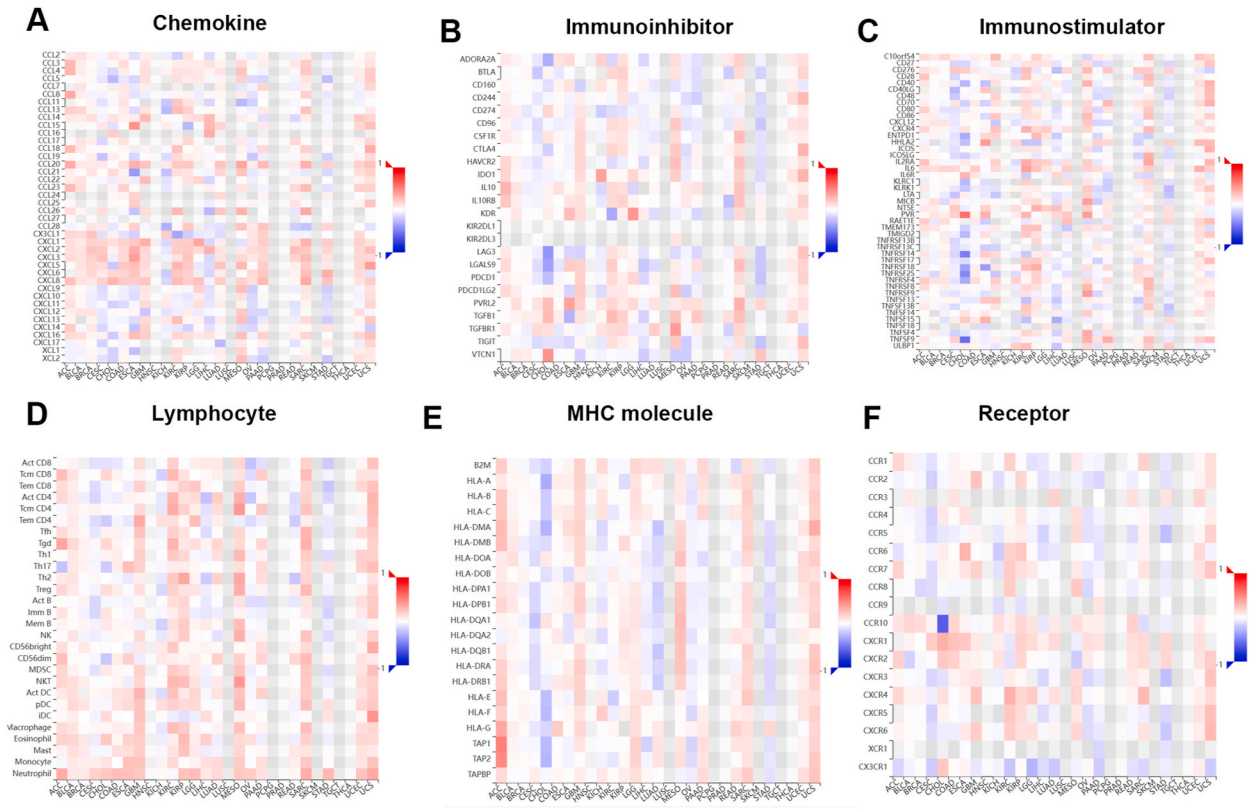

Fig. 15. Relationship Between *IGFBP1* and Genes Linked to Immunoregulation in 33 Different Cancer Types. (A) chemokines, (B) immunoinhibitors, (C) immunostimulators, (D) lymphocytes, (E) MHC molecules, and (F) receptors. (MHC: major histocompatibility complex).

abnormal cell behavior, which could contribute to tumor progression and metastasis.

GSEA has identified pathways such as *PD-1* signaling, which are likely to be prevalent across multiple malignancies and are affected by *IGFBP1*. The *PD-1* signaling pathway, which is vital for immune checkpoint regulation [25], offers insight into *IGFBP1*'s role in cancer immune evasion. The similarity of these pathways indicates that *IGFBP1* modulates immune responses and energy metabolism across various tumor types.

A detailed exploration of the genetic alterations affecting *IGFBP1* has revealed a diverse array of mutations, shedding light on its intricate involvement in the genomic landscape of cancers. Leveraging CancerSEA to probe *IGFBP1*'s correlation between various functional states of cancer cells, including metastasis and hypoxia, has yielded invaluable insights into its underlying biological mechanisms.

Hypoxic conditions facilitate the invasiveness and survival of tumor cells. Targeting IGFBP1 could potentially reduce tumor cell survival and metastasis by modulating the hypoxia response pathway. IGFBP1 expression is inversely associated with invasion and epithelial-mesenchymal transition (EMT) in glioblastoma multiforme (GBM). Invasion and EMT are critical processes enabling tumor cells to gain migratory and metastatic potential. Modulating IGFBP1 expression may influence EMT and invasion status, thereby inhibiting tumor progression.

The TIMER2 database revealed that *IGFBP1* expression is correlated with immune cells, such as B cells, $CD4^+$ T cells, $CD8^+$ T cells, and macrophages across cancers. Elevated *IGFBP1* levels in certain breast cancers are associated with an increased number of M2 macrophages and decreased survival rates. In colorectal cancer, higher *IGFBP1* levels are correlated with more regulatory T cells, aiding in immune evasion. Patients with lung adenocarcinoma with high *IGFBP1* expression had a median survival of 22 months, compared to 36 months in those with lower expression. In melanoma, high *IGFBP1* levels correspond to fewer $CD8^+$ T cells, affecting the treatment response. These insights underscore *IGFBP1*'s impact on the immune microenvironment and its pivotal role in cancer prognosis and therapy. Investigating *IGFBP1*'s effect on immune infiltration offers a deeper understanding of its function in immune regulation within tumors [26]. IGFBP1 expression is also linked to the expansion of regulatory T cells and myeloid suppressor cells. By inhibiting IGFBP1 expression, the proliferation of these immunosuppressive cells can be diminished, thereby reducing tumors' ability to evade immune responses. Furthermore, IGFBP1 may modulate the secretion of inhibitory cytokines (e.g., TGF-β, IL-10) and chemokines (e.g., CCL2, CXCL8). Targeting the IGFBP1 pathway is anticipated to enhance the tumor immune microenvironment and bolster the efficacy of immunotherapy by modulating the balance of these factors. Future research should assess the potential of IGFBP1 as a predictive biomarker and therapeutic target for immunotherapy. It should also investigate the clinical outcomes of combining immune checkpoint inhibitors with IGFBP1-targeted therapy and elucidate the mechanisms by which IGFBP1 influences

the immune microenvironment and immune cell function. This will provide a theoretical foundation for the development of novel immunotherapy protocols.

In addition, our study revealed that IGFBP1 possesses significant diagnostic and prognostic value across various cancer types, imparting substantial clinical relevance. Initially, IGFBP1 is anticipated to emerge as an effective biomarker for early cancer detection, with the potential to enhance detection sensitivity and specificity via non-invasive blood tests. Furthermore, IGFBP1 expression levels can serve as a tool for patient stratification, aiding in the identification of high-risk and low-risk individuals. This enables the implementation of personalized monitoring and treatment strategies. Moreover, IGFBP1 expression can guide treatment selection and may be employed to predict treatment responsiveness, facilitating the development of targeted therapeutic agents. Consequently, investigating the clinical application potential of IGFBP1 holds great importance for enhancing the early detection, precise treatment, and comprehensive management of cancer.

To enhance diagnostic accuracy further, investigating the synergistic application of IGFBP1 with additional biomarkers or imaging techniques can yield a more nuanced understanding of tumor characteristics, thereby augmenting the detection rate and classification precision of cancer. For instance, we intend to integrate IGFBP1 with imaging modalities like computed tomography (CT) or magnetic resonance imaging (MRI) in the near future. This combination may offer superior sensitivity and specificity for the early detection of tumor lesions and their staging. Additionally, by synthesizing the findings from multiple biomarkers (including, but not limited to, CEA and CA-125), a comprehensive diagnostic model can be constructed to facilitate more precise early screening and diagnosis across a range of cancer types.

Although this comprehensive analysis provides valuable insights into *IGFBP1*'s involvement in cancer, several limitations should be acknowledged. First, the retrospective nature of TCGA-based analysis may introduce selection bias, thereby limiting the generalizability of the findings to broader populations [14]. Secondly, the functional mechanisms underlying *IGFBP1*'s diverse roles of in different cancer types remain unexplored, necessitating further mechanistic studies to fully elucidate its biological significance. Lastly, the study primarily relied on mRNA expression data, which might not fully capture *IGFBP1*'s post-translational modifications and interactions in the tumor microenvironment, potentially overlooking crucial aspects of its functionality [27,28].

Future studies on *IGFBP1* should address these limitations by incorporating prospective studies, functional assays, and multi-omics approaches to provide a more comprehensive understanding of *IGFBP1*'s role in cancer. Specifically, efforts should focus on elucidating the mechanistic pathways through which *IGFBP1* influences cancer progression, metastasis, and patient prognosis. Secondly, investigating *IGFBP1*'s interacts with other proteins and plays a role in the tumor microenvironment, particularly its impact on immune infiltration and response to therapy [28]. Third, we assessed the therapeutic potential of targeting *IGFBP1*, including the development of inhibitors and antibodies to modulate its activity in cancer cells [29]. We intend to pursue further research in the future, employing gene editing technologies like CRISPR to systematically investigate the specific functions and underlying mechanisms of IGFBP1 within critical pathways. This will be achieved through targeted knockout or overexpression studies.

In conclusion, this study highlights *IGFBP1*'s critical role in cancer biology and its potential use as a prognostic marker. Overcoming the current research limitations and pursuing further studies will enhance our understanding of *IGFBP1*'s complex function in cancer development. Additionally, this study sets the stage for further investigation into *IGFBP1*'s capacity to improve cancer diagnosis, prognosis, and treatment approaches.

4. Materials and Methods

4.1. Data gathering

The Cancer Genome Atlas (TCGA) (https://portal.gdc.cancer.gov/) [14] provides extensive molecular profiles and clinical data across 33 cancer types using the TCGA_GTEx dataset hosted on the UC Santa Cruz (UCSC) Xena platform (https://xena.ucsc.edu/) [15]. These types include Adrenocortical Carcinoma (ACC), Bladder Urothelial Carcinoma (BLCA), Breast Invasive Carcinoma (BRCA), Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (CESC), Cholangiocarcinoma (CHOL), Colon Adenocarcinoma (COAD), Lymphoid Neoplasm Diffuse Large B-cell Lymphoma (DLBC), Esophageal Carcinoma (ESCA), Glioblastoma Multiforme (GBM), Head and Neck Squamous Cell Carcinoma (HNSC), Kidney Chromophobe (KICH), Kidney Renal Clear Cell Carcinoma (KIRC), Kidney Renal Papillary Cell Carcinoma (KIRP), Acute Myeloid Leukemia (LAML), Brain Lower Grade Glioma (LGG), Liver Hepatocellular Carcinoma (LIHC), Lung Adenocarcinoma (LUAD), Lung Squamous Cell Carcinoma (LUSC), Mesothelioma (MESO), Ovarian Serous Cystadenocarcinoma (OV), Pancreatic Adenocarcinoma (PAAD), Pheochromocytoma and Paraganglioma (PCPG), Prostate Adenocarcinoma (PRAD), Rectum Adenocarcinoma (READ), Sarcoma (SARC), Skin Cutaneous Melanoma (SKCM), Stomach Adenocarcinoma (STAD), Testicular Germ Cell Tumors (TGCT), Thyroid Carcinoma (THCA), Thymoma (THYM), Uterine Corpus Endometrial Carcinoma (UCEC), Uterine Carcinosarcoma (UCS), Uveal Melanoma (UVM). For expression data acquisition, RNA-seq data for these 33 cancer projects were downloaded and organized from TCGA database using the STAR pipeline, with the data extracted in the TPM format. Data processing involved the application of the log2(value + 1) transformation method to normalize the RNA-seq data. In the data analysis, R programming language was employed, utilizing packages such as ggplot2 (version 3.3.6) for data visualization, stats (version 4.2.1) for statistical analysis, and car (version 3.1-0) for advanced linear modeling. As the study adhered to protocols established by TCGA and UCSC, it was exempt from requiring ethical approval and patient informed consent.

4.2. IGFBP1 expression analysis

In the analysis of *IGFBP1* expression in TCGA samples, including TCGA and GTEx samples, as well as TCGA paired samples, we

evaluated the mRNA expression levels in malignant and normal tissues. Additionally, the mRNA expression of *IGFBP1* in various cell lines was obtained from the Human Protein Atlas (HPA) website (https://www.proteinatlas.org/).

4.3. Relationship between clinical characteristics and IGFBP1 expression

The methodology for acquiring clinical pathology data closely mirrors that used to obtain the expression data. Data unrelated to clinical information were systematically discarded during the acquisition process. Additionally, the association between important clinical features and *IGFBP1* expression was investigated in cancer types in which *IGFBP1* could affect patient outcomes. This investigation included an analysis of *IGFBP1* expression with respect to sex, pathological stage, and T, N, and M stages, with the aim of uncovering any significant associations that could inform patient management strategies.

4.4. Prognosis analysis

The data filtering strategy involved removing normal samples and non-clinical information and retaining only datasets containing survival information. Subsequently, the data were processed using log2 transformation (log2(value + 1)). Using data from The TCGA database, this study assessed the correlation between *IGFBP1* expression and clinical outcomes, including overall survival (OS), progression-free interval (PFI), and disease-specific survival (DSS), across various cancer types. The Kaplan-Meier method, along with the log-rank test, was employed, and survival curves with a significance level below 0.05 were emphasized. Furthermore, cancers exhibiting a potential prognostic impact of *IGFBP1* were chosen to construct receiver operating characteristic (ROC) curves. This analysis utilizes R packages including survival (version 3.3.1), survminer (version 0.4.9), ggplot2 (version 3.3.6), and pROC (version 1.18.0).

4.5. Creation and assessment of the nomogram models

For the nomogram models, cancers affected by *IGFBP1* expression in terms of OS, PFI, and DSS were subjected to univariate Cox regression analysis with a focus on OS. Tumors showing p-values below 0.05 and sample sizes exceeding 300 were selected to develop nomogram models, proving to be an effective approach for predicting OS in individual cases. The predictive accuracy of the models was then evaluated using calibration curves over one, three, and five-year periods.

The nomogram and calibration plot were created using the R package survival (version 3.3.1) and rms (version 6.3-0). The processing included proportional hazard hypothesis testing and Cox regression analysis using the survival package. Furthermore, the rms package was employed to build nomogram-related models, conduct calibration analyses, and visualize the results.

4.6. Analysis of genetic alterations

In this study, we used cBioPortal (https://www.cbioportal.org/) for Cancer Genomics to examine genetic alterations in *IGFBP1* [16]. Specifically, we utilized the "mutations" module to identify the locations of mutations, and the "mRNA vs. study" and "cancer types summary and mutations" modules facilitated the exploration of somatic mutation frequency and genomic details of *IGFBP1* mutations across various cancer types.

4.7. Relationship between IGFBP1 and cancer cell functionality

We used CancerSEA (http://biocc.hrbmu.edu.cn/CancerSEA/home.jsp), which is a comprehensive database designed to investigate the functional state of cancer cells at the single-cell level [17]. Focusing on the average association between *IGFBP1* expression and various functional states across four cancer types, we explored the functional implications of *IGFBP1* expression in diverse malignancies.

4.8. Protein-protein interaction network and functional enrichment analysis

The GEPIA2 database was used to identify 100 *IGFBP1*-related genes with expression patterns most similar to those of *IGFBP1*. Potential protein interactions with *IGFBP1* were determined and integrated into the STRING database (https://string-db. org). Subsequently, a PPI network investigation was conducted using the acquired relevant genes, with the significance threshold set at a confidence score exceeding 0.7. The resulting data were loaded into Cytoscape (v3.8.2) (https://cytoscape.org/) for visualization and further analysis.

Enrichment studies of genes closely interacting with *IGFBP1* were performed using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG). Following conversion of the input molecule IDs, the clusterProfiler package was employed to conduct enrichment analysis. Subsequently, the GOPlot package was used to calculate the corresponding z-scores for each enrichment entry, using the molecular values provided. The cut-off level for significance was established at p-value <0.05.

Gene Set Enrichment Analysis (GSEA) was conducted using the "clusterProfiler" package to investigate biological pathway differences between high- and low-*IGFBP1* groups. P-value below 0.05 and a false discovery rate (FDR) below 0.05 were considered indicative of significantly altered pathways. Each analysis included 1000 permutations of the gene set. The results of the GSEA were visualized using the R "ggplot2″ package.

4.9. Immune infiltration analysis

TIDIB (Tumor-Immune Database) is a database that specifically collects and organizes tumor-immune related data, aiming to help researchers better understand tumors and the mechanisms of their interaction with the immune system. The TIDIB database collects publicly available high-throughput sequencing data, including gene expression data, transcriptome data, proteome data, and immunology-related sequencing data.

Using TIMER, TIDE, and other algorithms, we explored the association between *IGFBP1* expression and various immune cell types, including B cells, macrophages, $CD8^+$ T cells, and $CD4^+$ T cells, using Tumor Immune Estimation Resource 2.0 (TIMER2.0), accessible at http://timer.cistrome.org/ [18]. Furthermore, a comprehensive analysis was conducted to assess the impact of immune cell infiltration on overall survival (OS) following the classification of *IGFBP1* expression across different cancer types.

We also used the TISIDB database (http://cis.hku.hk/TISIDB/index.php) to explore the association between *IGFBP1* expression and the molecular or immunological subtypes [19]. Furthermore, we investigated the correlations between *IGFBP1* expression and MHC molecules, chemokine receptors, chemokines, immunoinhibitors, immunostimulators, and tumor-infiltrating lymphocytes.

5. Statistical analysis

Correlations between the two groups were assessed using the Spearman rank test, and differences between groups were compared using the Wilcoxon rank-sum test. Factors influencing prognosis were determined using univariate and multivariate Cox proportional hazard regression analyses. Survival analysis was conducted using Kaplan-Meier analysis with the log-rank test. Statistical analyses were performed using R (version 4.2.1), with significance set at $p < 0.05$ (*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Data availability

The data were obtained from publicly accessible databases, including The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) project and so on.

CRediT authorship contribution statement

Zengwu Yao: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Junping Han:** Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jinhui Wu:** Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Miaomiao Li:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ruyue Chen:** Writing – review & editing, Software, Resources, Methodology, Formal analysis, Data curation. **Mi Jian:** Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zhensong Yang:** Visualization, Validation, Supervision, Software, Methodology, Investigation. **Xixun Wang:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Yifei Zhang:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation. **Jinchen Hu:** Writing – review & editing, Supervision, Software, Resources, Funding acquisition, Conceptualization. **Lixin Jiang:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37402.

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