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ORIGINAL ARTICLE

Oncogenic Role of *GLMN* in Liver Hepatocellular Carcinoma

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Abstract

Liver cancer, particularly liver hepatocellular carcinoma (LIHC), is one of the most lethal malignancies worldwide with increasing incidence rates. This study investigated the role of the *GLMN* (*Glomulin)* gene in the progression of liver cancer and its potential as a diagnostic biomarker and therapeutic target. Using data from TCGA, GEPIA, and CPTAC databases, we analysed and compared *GLMN* expression levels between liver cancer tissues and normal tissues and explored the correlation between *GLMN* expression and patient survival outcomes. Our results showed that *GLMN* was significantly overexpressed in LIHC, and higher expression was associated with poor overall survival and disease-free survival. Additionally, we found a positive correlation between GLMN expression and CD8+ T cell infiltration, suggesting its involvement in the regulation of the tumour immune microenvironment. Gene enrichment analysis revealed that *GLMN* is involved in ubiquitin-mediated proteolysis and cell cycle regulation, highlighting its role in cancer progression. These findings suggest that GLMN may serve as a prognostic marker and therapeutic target for liver cancer.

Key words : *GLMN (Glomulin*) gene ; liver hepatocellular carcinoma (LIHC) ; CD8+ T-cell infiltration ; Ubiquitin-mediated proteolysis ; Targeted therapy

Introduction

Cancer has become a major cause of human death. It is a common disease that poses a threat to human health and affects people's quality of life. According to the World Health Organization (WHO), cancer caused approximately 10 million deaths worldwide in 2020[1]1, and patients with liver cancer had one of the lowest survival rates (18%). The incidence of liver cancer is increasing globally, and according to the latest cancer statistics, it is the fastest-growing malignancy in men, with an annual growth rate of 2%–3%. Liver cancer can be classified into primary and secondary tumors. Primary liver cancer (PLC) can be further subdivided into hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and other rare types[2]. Since the pathogenesis and exact molecular mechanisms of liver cancer are not fully understood, early detection of liver cancer and appropriate treatment can significantly improve the cure rate. Therefore, there is an urgent need to identify disease-specific biomarkers for early diagnosis and localization of cancer, which can help in improving the cure rates and patient survival[3]. Since gene expression is involved in almost all biological processes, identifying a specific biomarker gene has become a promising approach for early cancer diagnosis.

The *GLMN (Glomulin)* gene is one of the genes that has garnered increasing attention in cancer research in recent years. This gene encodes a phosphorylated protein that is a member of the Skp1-Cullin-F-box-like complex. This protein is primarily involved in regulating angiogenesis and

cell growth and remains relatively stable in normal tissues. Currently, research on the role of *GLMN* in liver cancer is in its early stages. It has been reported that abnormal *GLMN* expression may promote the growth and spread of liver cancer by affecting the tumour microenvironment. Its high expression in tumour-associated macrophages and the tumour vasculature makes it a potential diagnostic marker and therapeutic target[4]. However, theoretical knowledge regarding the role of the *GLMN* gene in liver cancer progression is still insufficient. Therefore, this study aimed to investigate the correlation between *GLMN* expression and progression of liver hepatocellular carcinoma (LIHC) to provide a theoretical basis for using *GLMN* as a potential diagnostic marker and therapeutic target. We hope that our findings will pave the way for future research on novel liver cancer treatments.

2. Materials and Methods

2.1 Gene Expression Analysis

We used the TIMER2.0 tool (http://timer.cistrome.org/) to analyze GLMN expression in different tumors and normal tissues. In the "Exploration" section under "Gene_DE," we entered "GLMN" and clicked submit. The system displayed the differences in GLMN expression between various tumors, tumor subtypes, and normal tissues. Next, we used the GEPIA tool (http://gepia2.cancer-pku.cn/#index) and navigated to the "Box Plot" option in the "Expression DIY" section of the "Expression Analysis" module. We entered the gene "GLMN," selected the tumor name "LICH" in "Datasets Selection," set the P-value cutoff to "0.01" and |Log2FC| cutoff to "1," and chose "Match TCGA normal and GTEx data." After clicking "plot," we obtained the differences in GLMN expression between LIHC and normal tissues, with data from the TCGA+GTEx databases. Finally, we accessed the "Stage Plot" option in the "Expression DIY" section, entered the gene "GLMN," selected the tumor name "LICH" in "Datasets Selection," and clicked "plot," resulting in a violin plot showing GLMN expression at different pathological stages of LIHC in the TCGA database. The box plots or violin plots were generated using log2 [TPM (transcripts per million) +1] transformed expression data.

2.2 Survival Prognosis Analysis

We continued using the GEPIA 2 tool. First, in the "Expression Analysis" module, we navigated to "Survival Analysis." We entered the gene "GLMN," selected "LICH" in "Datasets Selection," and set "Cutoff-High(%)" and "Cutoff-Low(%)" both to 50. Under "Methods," we selected "Overall Survival" and "Disease-Free Survival (RFS)" to obtain survival plots for high and low GLMN expression groups. Additionally, we used the same method in the "Survival Map" section to generate significance plots for overall survival and disease-free survival.

2.3 Gene Mutation Analysis

In this step, we used the cBioPortal website (https://www.cbioportal.org/). We located and selected "Liver Hepatocellular Carcinoma (TCGA, PanCancer Atlas)" from the list, clicked "Query By Gene," and entered "GLMN." In the "Cancer Type Summary," we observed the mutation frequency, mutation types, and CNA (copy number alterations) results for LIHC. In the "Mutations" module, we displayed the mutation site information for GLMN on the protein structure diagram.

2.4 Immune Infiltration Analysis

We used the TIMER 2.0 tool again. In the "Immune" module, we entered the gene "GLMN" and selected "CD8+ T cells" and "cancer-associated fibroblasts" in the "Immune Infiltrates" section. We used algorithms including TIMER, MCPCOUNTER, CIBERSORT-ABS, QUANTISEQ, EPIC, and XCELL to estimate immune infiltration levels. P-values and partial correlation (cor) values were obtained through Spearman rank correlation tests (adjusted for purity). The data were presented as heatmaps and scatter plots.

2.5 GLMN-Related Gene Enrichment Analysis

We first used the STRING website (https://string-db.org/) to query for protein-protein interactions, using the single protein name "GLMN" and species "Homo sapiens." We then set the following parameters: minimum required interaction score ["low confidence (0.150)"], network edges' meaning ("evidence"), maximum number of interactions shown in the first layer ("no more than 50 interactors"), and active interaction sources ("experiments"). This provided

us with GLMN-binding proteins based on existing experimental data.

We obtained the top 100 target genes related to GLMN based on LIHC and normal tissue datasets using the "Similar Gene Detection" module in GEPIA 2.

We also performed pairwise Pearson correlation analysis between GLMN and selected genes using the "Correlation Analysis" module in GEPIA 2, displaying log2 TPM values in scatter plots and providing P-values and correlation coefficients (R).

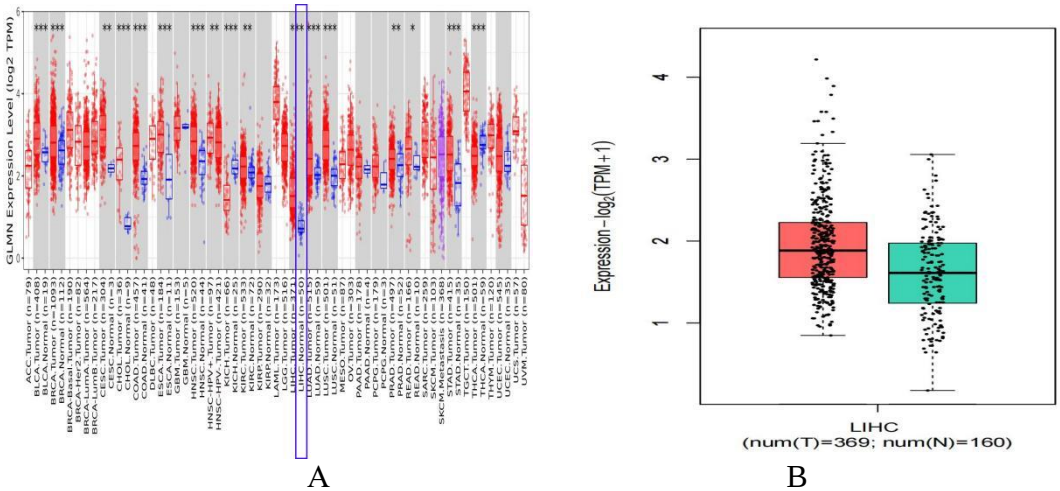
Additionally, we used the "Gene_Corr" module in TIMER 2 to generate heatmap data for selected genes, including partial correlation (cor) and P-values from Spearman rank correlation tests, adjusted for purity.

We used the "Draw Venn Diagram" tool, an interactive Venn diagram viewer, to perform cross-analysis and observe overlapping genes interacting with GLMN. We combined these two datasets for KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis. We uploaded the gene lists to the DAVID database (Database for Annotation, Visualization, and Integrated Discovery), using "OFFICIAL_GENE_SYMBOL" and species "Homo sapiens" to obtain functional annotation chart data. Finally, we visualized the enriched pathways using the "ggplot2" R package (https://cran.r-project.org/web/packages/ggplot2/index.html).
We also performed Gene Ontology (GO) enrichment analysis using the "clusterProfiler" R package (http://www.bioconductor.org/packages/release/bioc/html/clusterProfiler.html), covering biological processes (BP), cellular components (CC), and molecular functions (MF). We visualized them as cnetplots using the cnetplot function (colorEdge = TRUE, node_label = "ALL", circular = TRUE). The analysis was conducted using RStudio software (https://posit.co). A two-tailed P<0.05 was considered statistically significant.

Results

1. Gene Expression Analysis

We used the TIMER2 method to analyse the expression levels of the *GLMN* gene across various cancer types in TCGA dataset. As shown in Figure 1A, *GLMN* expression in LIHC tumour tissues was significantly higher than that in the corresponding control tissues (P<0.001). On comparing GLMN expression between normal tissues and LIHC tissues using the GTEx database, it was found that the median expression of *GLMN* was higher in LIHC tissues than in normal tissues (Fig.1B). Using the CPTAC database, we found that the expression of GLMN protein was higher in LIHC tissues than in normal tissues (P<0.001) (Fig.1C). Furthermore, violin plots indicated significant differences in GLMN expression levels across different stages of LIHC (P<0.01), with a noticeable decrease in Stage IV (Fig.1D).



A B

Figure1

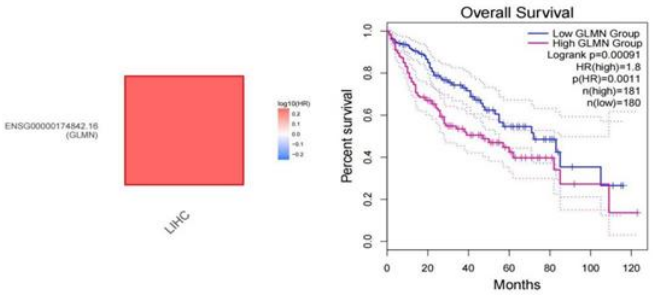
Fig.1 Expression of the *GLMN* gene in different tumours and pathological stages. A: Expression of the *GLMN* gene across different cancers and specific cancer subtypes was analysed using

TIMER2.* P<0.05;** P<0.01;*** P<0.001. B: Box plot data showing the expression of *GLMN* in liver hepatocellular carcinoma (LIHC) tissues from TCGA database and corresponding normal tissues from the GTEx database as a control.* P<0.05. C: Expression of GLMN protein between normal tissues and LIHC tissues based on the CPTAC dataset. D: Violin plots showing the expression levels of the *GLMN* gene by the pathological stage (Stage I, II, III, and IV) of LIHC based on TCGA data. Log2 (TPM + 1) was applied for log-scale.）

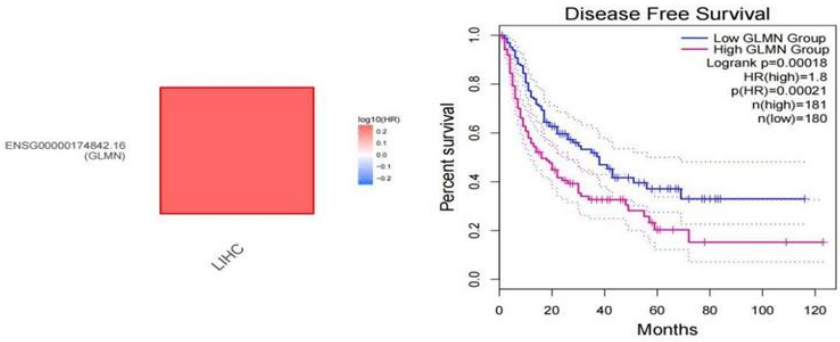
2. **Survival Analysis**

3. We divided the LIHC cases into high-expression and low-expression groups based on *GLMN* expression levels and primarily used TCGA and GEO datasets to investigate the correlation between *GLMN* expression and prognosis of patients with LIHC. Figure 2A shows that *GLMN* expression was positively correlated with overall survival in patients with LIHC (P<0.05). Kaplan-Meier survival curves were used to compare overall survival between patients in the *GLMN* high- and low-expression groups. It was found that the overall survival rate of the *GLMN* high-expression group was lower than that of the low-expression group, especially in the later stages of follow-up when the gap widened. Patients in the high-expression group had shorter survival times and higher mortality rates. There was a significant difference in survival rates between the high-expression and low-expression groups (P=0.00091), with high *GLMN* expression significantly affecting overall survival (P<0.05). The hazard ratio (HR; high-expression group)was 1.8, indicating that patients in the high-expression group had a 1.8 times higher risk of death than those in the low-expression group. Figure 2B shows that *GLMN* was also positively correlated with disease-free survival in patients with LIHC (P<0.05). The disease-free survival rate in the high expression group was significantly lower than that in the low expression group (P<0.001). Over time, the probability of remaining disease-free increased in the low expression group. The HR (high-expression group) was 1.8, indicating that patients in the high-expression group had a 1.8 times higher risk of disease progression than those in the low-expression group.

Fig2



A



B

(Fig. 2 Correlation between GLMN gene expression and survival of patients with LIHC in TCGA. We used the GEPIA2 tool to evaluate overall survival (A) and disease-free survival (B) of patients with LIHC in TCGA by GLMN gene expression. The survival map and Kaplan-Meier curves with positive results are shown.)

4. **Genetic Mutation Analysis**

5. We studied the genetic alteration status of GLMN in LIHC samples from TCGA cohort. As shown in Figure 3A, only 0.27% of the 369 LIHC samples exhibited gene amplification. Figure 3B demonstrates that no mutations were found at any amino acid sites in the GLMN protein.

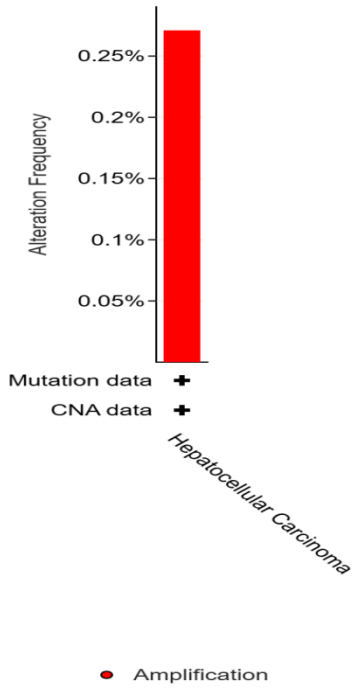


Figure A

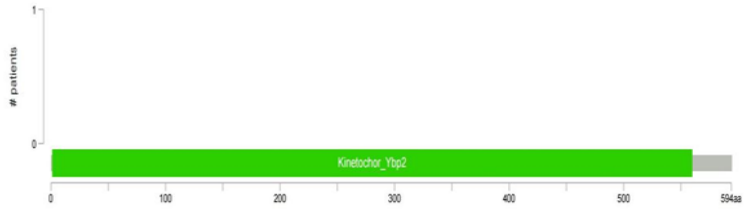


Figure B

(Fig. 3 Mutation analysis of *GLMN* in LIHC. We used the cBioPortal tool to analyse the mutation status of *GLMN* in LIHC. A: Alteration frequency by the mutation type. B: Mutation sites.)

6. **Immune Infiltration Analysis**

7. We explored the potential relationship between *GLMN* expression and infiltration levels of different immune cells in LIHC using various algorithms (Fig. 4A). GLMN expression was negatively correlated with cancer-associated fibroblasts (as measured by the XCELL algorithm) (Rho = -0.157, P<0.01), suggesting that higher GLMN expression may be associated with decreased fibroblast infiltration. Conversely, cancer-associated fibroblasts (as measured using the EPIC algorithm) showed a positive correlation with GLMN expression (Rho = 0.175, P<0.01). GLMN expression was also positively correlated with CD8+ T cell infiltration (Rho = 0.172-0.303, P<0.05) (Fig. 4B).

A

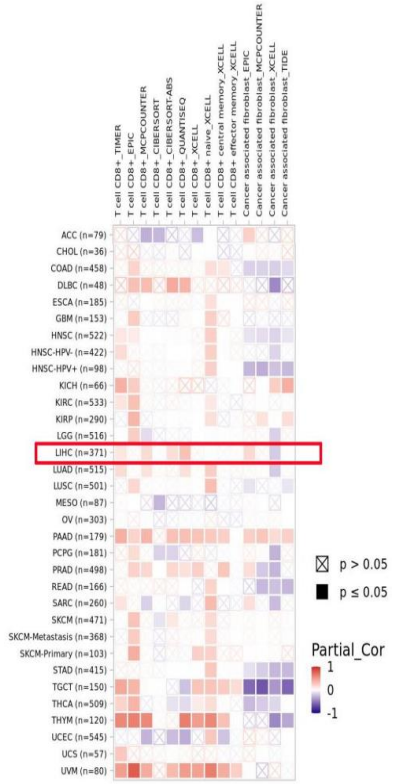


Fig4 A

Fig. 4A: Correlation analysis between *GLMN* expression and immune infiltration of cancer-associated fibroblasts and CD8+ T cells.）

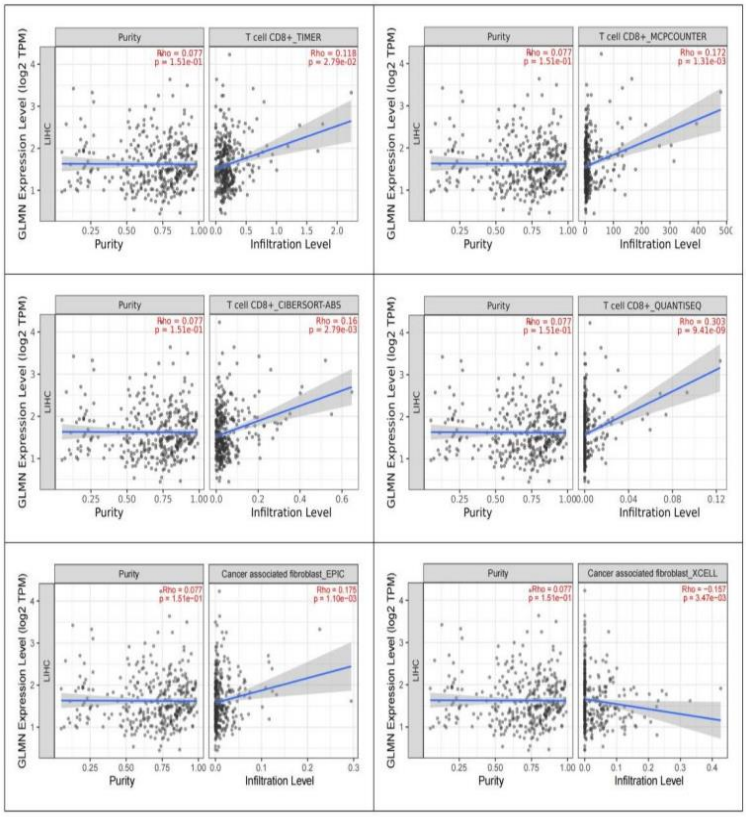


Fig4 B

Fig. 4B: *GLMN* expression was negatively correlated with cancer-associated fibroblasts using XCELL and positively correlated with cancer-associated fibroblasts using EPIC.）

5.***GLMN*-Related Gene Enrichment Analysis** Using the STRING tool, we obtained the protein-protein interaction network of *GLMN* (Fig. 5A). The GEPIA2 tool was used to identify the top 100 genes associated with *GLMN* expression. Figure 5B shows that GLMN expression was positively correlated with *C1orf52* (R=0.82), *RPF1* (R=0.77), *MTF2* (R=0.76), *ITGB3BP* (R=0.75), and *NASP* (R=0.75; all P<0.001). Heatmap data also confirmed that *GLMN* expression was positively correlated with these five genes (P<0.05) (Fig. 5C).

Venn diagram analysis revealed no common members between the two groups (Fig. 5D). We combined the two datasets for KEGG and GO enrichment analyses. Figure 5E shows that *GLMN* was involved in multiple pathways of liver cancer, with the most significant enrichment observed in the ubiquitin-mediated proteolysis pathway. Other notable pathways include the cell cycle and spliceosome pathways, whereas pathways such as eukaryotic ribosome biogenesis were also significantly enriched. Figure 5F illustrates the molecular functions of different proteins and their interaction networks, including protein–macromolecule adapter activity, enzyme-substrate adapter activity, ubiquitin ligase-substrate adapter activity, FK506-binding activity, and macrolide binding.

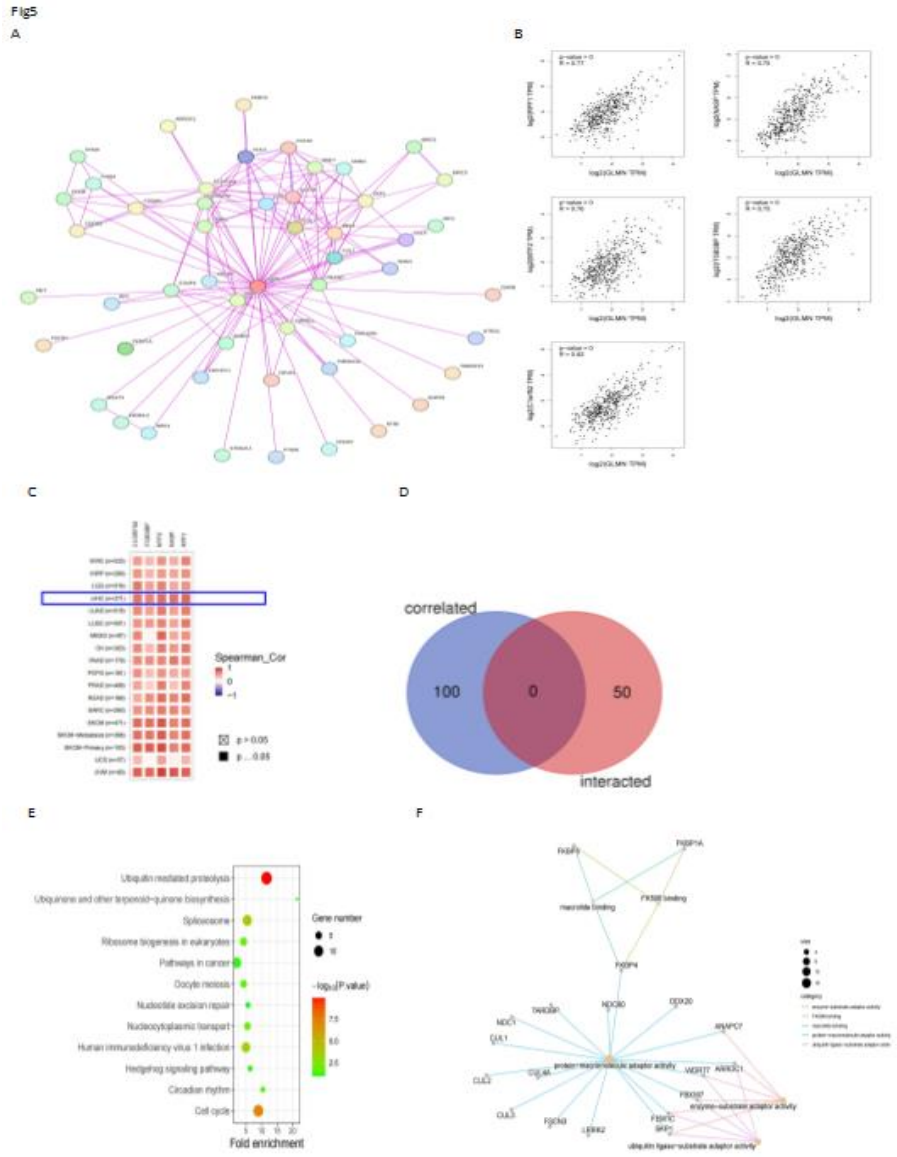


Fig. 5: *GLMN*-related gene enrichment analysis. A: We first obtained the GLMN-binding proteins using the STRING tool. B: Using the GEPIA2 approach, we identified the top 100 GLMN-correlated

genes based on the LIHC dataset and analysed the correlation between the expression of *GLMN* and the selected genes, including *C1orf52, RPF1, MTF2, ITGB3BP,* and *NASP*. C: The corresponding heatmap data of LIHC are displayed. D: An intersection analysis of the GLMN-binding and correlated genes was conducted. E: Based on the *GLMN*-binding and interacting genes, KEGG pathway analysis was performed. F: The cnetplot for the molecular function data derived from GO analysis is shown.）

Discussion

The *GLMN* gene shows high expression in several cancers, suggesting that it may play a role in various types of cancer. However, its significant upregulation in LIHC is particularly notable, highlighting its potential as a biomarker for liver cancer. High *GLMN* expression may facilitate the initiation, progression, or metastasis of LIHC. This gene plays an important role in disease progression, and tends to have a low expression in the late stages. This suggests that advanced liver cancer treatment may require more targeted or personalized strategies. The trend of low *GLMN* expression in late-stage liver cancer indicates changes in the biological characteristics of the cancer. In the early stages, high *GLMN* expression may promote tumour cell proliferation; however, in the late stages, cancer cells may rely more on other oncogenic mechanisms, reducing their dependence on *GLMN*-related pathways. Clinically, this indicates that early stage tumours may respond well to *GLMN*-targeted therapies, whereas more complex treatment strategies may be required for late-stage tumours. This shift is helpful not only for predicting cancer prognosis but also for guiding the development of personalized treatment strategies.

GLMN likely promotes liver cancer progression, and patients with high *GLMN* expression tend to have a worse prognosis. This suggests that *GLMN* could serve as potential prognostic marker, and patients with high expression may require closer monitoring or more aggressive treatment interventions. Mutations in the *GLMN* gene are concentrated in the Kinetochor_Ybp2 region, which may be an important functional domain of the GLMN protein. Although *GLMN* mutations are rare, the presence of gene amplification suggests that *GLMN* promotes cancer development via gene amplification in some patients with liver cancer. This finding further supports *GLMN* as a potential therapeutic target for liver cancer, particularly in patients with gene amplification.

The infiltration levels of cancer-associated fibroblasts (CAF) may influence *GLMN* expression, or act in tandem with *GLMN* to regulate certain processes in the tumour microenvironment. *GLMN* expression levels may be closely related with CD8+ T cell infiltration in the immune microenvironment, suggesting its role in immune surveillance or tumour immune evasion. Thus, *GLMN* may regulate the activity or recruitment mechanisms of CD8+ T cells in the tumour microenvironment. One possible mechanism is that *GLMN* promote CD8+ T cell activation or migration by regulating signal transduction in tumour cells or surrounding stromal cells, thereby enhancing the anti-tumour immune response. Studies have shown[5] that in some tumours, CD8+ T-cell infiltration is insufficient or functionally exhausted owing to an immunosuppressive microenvironment (e.g., due to the role of CAFs), leading to tumour immune evasion. However, the positive correlation between *GLMN* expression and CD8+ T cell infiltration suggests that *GLMN* may mitigate this immunosuppressive effect or promote effective CD8+ T cell infiltration, thereby enhancing the tumour immune response[6]. Thus, *GLMN* could potentially serve as a biomarker for predicting the efficacy of immunotherapy. Since CD8+ T cell activity is closely related to the effectiveness of many immune checkpoint inhibitors, *GLMN* expression may help in predicting the response of patients with LIHC to immunotherapy.

GLMN and five other genes (*PRPF8, ANSP*, *MTF2*, *TCBBP1*,and *CNOT2*) may participate in the same biological processes or functions in the same signalling pathways, particularly the *CNOT2* gene. These genes may be involved in liver cancer-related processes through common molecular mechanisms such as gene expression regulation, RNA splicing, and transcription regulation. These processes are critical in liver cancer because tumour development often involves dysregulated gene networks and abnormal gene expression. Thus, these genes may influence the initiation and progression of cancer

by regulating cell proliferation, apoptosis, invasion, and metastasis.

Ubiquitin-mediated proteolysis (UPS) plays a key role in many cancers including LIHC. Studies have shown that ubiquitination regulates critical processes such as the cell cycle, apoptosis, autophagy, and DNA repair. Dysregulation of UPS can lead to uncontrolled cancer cell proliferation and tumour progression. The importance of UPS in liver cancer treatment has been extensively studied[78], and proteasome inhibitors such as bortezomib [9] have been identified that can inhibit liver cancer cell proliferation by disrupting protein degradation pathways. UPS is a critical mechanism for regulating protein stability, and if *GLMN* regulates key protein stability via the UPS, its abnormal expression or amplification may affect the degradation of key proteins in cancer cells, promoting cancer progression. For example, *GLMN* amplification may disrupt ubiquitination, leading to the abnormal stabilization of cancer-related proteins (such as cell cycle regulators or DNA repair proteins), allowing cells to evade apoptosis and accelerate tumour progression. Thus, *GLMN* may be an important regulator of this pathway and potential therapeutic target in liver cancer.

Similarly, *GLMN* may accelerate liver cancer progression by affecting cell cycle regulation. The cell cycle pathway is crucial for cell proliferation and division. Clinically, CDK4/6 inhibitors that target cell cycle regulation[10] have been used to treat various cancers. Therefore, exploring the regulatory role of *GLMN* in the cell cycle may provide new strategies for the treatment of liver cancer. Cell cycle regulation is fundamental to tumourigenesis, and many gene mutations identified in LIHC are associated with cell cycle regulation, leading to rapid cancer cell proliferation and evasion of apoptotic signals.

Spliceosome is a crucial molecular machine for RNA precursor processing, and is responsible for removing introns and connecting exons. In LIHC, abnormal RNA splicing is associated with cancer cell proliferation and evasion of apoptosis, making spliceosome inhibition a potential therapeutic approach[11].

Ribosome biogenesis in eukaryotes is a core process in protein synthesis. Dysregulated ribosome biogenesis is closely linked to tumourigenesis, especially in MYC-upregulated cancers, such as LIHC. Studies have shown that the failure of key checkpoints in ribosome biogenesis can trigger p53-mediated tumour-suppressive mechanisms, inhibiting cancer progression[12].

In summary, the *GLMN* gene is a potential therapeutic target for liver cancer. Our findings provide new diagnostic and therapeutic insights into LIHC, which may improve patient survival and pave the way for personalized treatment approaches.

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CRediT authorship contribution statement

Yan piao: Conceptualization, Data curation, Validation, Writing – original draft, Writing – review & editing.

Han Wang: Data curation, Investigation, Writing – original draft, Writing – review & editing.

Guangze jin: Data curation, Writing – original draft, Writing – review & editing.

Zhezhu Han: Writing – review & editing.

Chengri Jin: Writing – review & editing.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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