Scientific Publications

World Journal of Cancer and Oncology Research, 2025, 4, 6136
www.scipublications.com/journal/index.php/wjcor
DOI: 10.31586/wjcor.2025.6136

Article

Bioinformatic Analysis of GCN1 as a Novel Diagnostic and Prognostic Biomarker in Hepatocellular Carcinoma and Preliminary Exploration of Its Molecular Mechanisms

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Abstract:

Background: Hepatocellular carcinoma (HCC) faces significant challenges in early diagnosis and prognostic assessment, necessitating novel molecular biomarkers. The role of GCN1 in tumorigenesis remains unclear, warranting systematic investigation of its clinical value. **Methods:** Utilizing multi-omics data from 164 HCC patients in the TCGA database, we comprehensively evaluated the diagnostic and prognostic value of GCN1 through differential expression analysis, Cox proportional hazards regression, and gene set enrichment analysis (GSEA). **Results:** GCN1 expression was significantly upregulated in tumor tissues (P<0.001), with ROC analysis demonstrating an AUC of 0.921 (95% CI: 0.893-0.950) for discriminating tumor from normal tissue. Clinical correlation analysis revealed that high GCN1 expression significantly associated with advanced T stage (OR=1.941, P=0.002) and AFP levels >400 ng/ml (OR=3.697, P<0.001). Multivariate survival analysis confirmed its independent prognostic value (HR=1.454, P=0.038). Functional analysis indicated GCN1 promotes tumor progression by regulating cell cycle (NES=2.385) and axon guidance (NES=2.307) pathways. **Conclusion:** This study first elucidates the dual clinical value of GCN1 in HCC, providing a theoretical foundation for developing novel diagnostic biomarkers and prognostic evaluation systems. Future research should validate its molecular mechanisms and explore potential targeted therapies.

Keywords: Hepatocellular carcinoma (HCC), GCN1 gene, biomarker, TCGA database

How to cite this paper:
Wei, M., Ke, C., & Wu, S. (2025). Bioinformatic Analysis of GCN1 as a Novel Diagnostic and Prognostic Biomarker in Hepatocellular Carcinoma and Preliminary Exploration of Its Molecular Mechanisms. *World Journal of Cancer and Oncology Research, 4*(1), 1-9.
DOI: 10.31586/wjcor.2025.6136

Academic Editor:
Mohamed Kotb El-Sayed

Received: June 3, 2025
Revised: July 15, 2025
Accepted: July 27, 2025
Published: July 30, 2025

1. Introduction

Hepatocellular carcinoma (HCC) ranks as the third leading cause of cancer-related deaths globally, claiming over 800,000 lives annually [1]. Despite advances in surgical resection and targeted therapies, the 5-year survival rate remains below 18%, primarily due to diagnostic challenges (only 30% of patients present with resectable disease at diagnosis) and high postoperative recurrence rates (70%) [2]. This critical clinical landscape underscores the urgent need for novel biomarkers to optimize diagnosis and treatment.

GCN1 (General Control Nonderepressible 1), an evolutionarily conserved stress response regulator, has recently garnered attention in oncology research. Studies demonstrate its role in promoting tumor angiogenesis via mTORC1 signaling in colorectal cancer [3] and mediating chemoresistance in lung cancer [4]. Notably, GCN1 exhibits unique cell cycle regulatory functions during liver regeneration [5], suggesting potential

significance in HCC pathogenesis. However, systematic investigations elucidating GCN1's expression patterns and clinical relevance in HCC are lacking.

This study establishes a multidimensional analytical framework using clinical-genomic data from 164 HCC patients in The Cancer Genome Atlas (TCGA). Our strategy encompasses: 1) differential expression analysis to identify tumor-specific expression of GCN1; 2) logistic regression modeling to assess clinicopathological correlations; 3) Cox proportional hazards modeling to determine prognostic value; and 4) Gene Set Enrichment Analysis (GSEA) to explore underlying molecular pathways. This integrated multi-omics approach addresses limitations of conventional single-dimension studies, offering a novel paradigm for biomarker discovery [6].

Our work systematically reveals the dual diagnostic and prognostic significance of GCN1 in HCC and uncovers its association with cell cycle regulatory pathways, providing new directions for mechanistic research. The findings not only offer a potential biomarker for precision HCC management but also advance our understanding of molecular networks driving HCC pathogenesis.

2. Methods

2.1. Data Source and Patient Inclusion

The clinical and transcriptomic data used in this study were obtained from the Liver Hepatocellular Carcinoma (LIHC) project of The Cancer Genome Atlas (TCGA) database. A total of 164 hepatocellular carcinoma (HCC) patients were included. Their clinicopathological characteristics included pathological stage (T, N, M), gender, age, body mass index (BMI), alpha-fetoprotein (AFP) level, albumin level, prothrombin time, vascular invasion status, and others. Patients lacking key clinical data were excluded to ensure the accuracy and completeness of the study results.

2.2. Gene Expression Analysis

RNA sequencing data (in FPKM format) from tumor tissues and matched normal tissues in the TCGA-LIHC cohort were downloaded to analyze the expression level of the GCN1 gene in liver cancer versus normal tissues. Data preprocessing and normalization were conducted using R software (v4.2.1). The Wilcoxon rank-sum test was used to assess the differential expression of GCN1 between tumor and normal tissues, and the paired Wilcoxon test was applied for paired sample analysis.

2.3. Evaluation of the Diagnostic Value of GCN1

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic efficacy of GCN1 in distinguishing tumor tissues from normal tissues in the TCGA-LIHC cohort. The area under the curve (AUC) and its 95% confidence interval (CI) were calculated to assess its potential as a diagnostic biomarker for hepatocellular carcinoma.

2.4. Clinical Correlation Analysis

Based on the median expression level, patients were divided into high and low GCN1 expression groups. Differences in clinical variables between the two expression groups were compared. Univariate logistic regression analysis was used to explore the association between GCN1 expression and various clinical parameters (such as T stage, AFP, gender, age, etc.). The results were expressed as odds ratio (OR), 95% confidence interval (CI), and P-value, with $P < 0.05$ considered statistically significant.

2.5. Survival Analysis

Overall survival (OS) was used as the endpoint event. A Cox proportional hazards regression model was constructed to analyze the relationship between clinical variables,

GCN1 expression, and prognosis. First, univariate Cox regression analysis was performed to identify variables significantly associated with survival ($P < 0.05$). These variables were then included in a multivariate Cox regression model to evaluate their independent prognostic value. Results were expressed as hazard ratio (HR), 95% CI, and P-value. Kaplan–Meier survival curves were plotted to demonstrate survival differences between high and low GCN1 expression groups, and differences were compared using the log-rank test.

2.6. Differential Expression Analysis and Functional Annotation

Based on GCN1 expression levels, differential gene expression (DEGs) analysis was performed between the high and low expression groups using the "DESeq2" package. The screening criteria were set as $|\log2 \text{ Fold Change}| > 1.5$ and adjusted P-value < 0.05. A volcano plot was generated using the "ggplot2" package, and a heatmap of DEGs was created using the "pheatmap" package. Further, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, as well as Gene Set Enrichment Analysis (GSEA), were conducted on the DEGs. GO/KEGG analyses were performed using the cluster Profiler package. For GSEA, the c2.cp.kegg.v7.5.1.symbols.gmt gene set from the MSigDB database was used to assess KEGG pathways significantly enriched in the high GCN1 expression group. The significance threshold was set at FDR < 0.25 and a significant Normalized Enrichment Score (NES).

3. Results

3.1. Clinical Characteristics of HCC Patients, GCN1 Expression in HCC, and Its Diagnostic Efficacy

This study conducted a systematic analysis based on data from 164 HCC patients in the TCGA-LIHC cohort. As shown in Table 1, the baseline characteristics of the patients presented typical epidemiological features of HCC: males accounted for 67.1% (110/164), and patients over 60 years old accounted for 44.5% (73/164). Pathological staging showed that early-stage cases (T1) accounted for 61.6% (101 cases), while late-stage cases (T2–T4) accounted for 38.4% (63 cases). Notably, the proportion of metastatic disease was relatively low (only 3 cases with M1, accounting for 1.8%), which is related to the inclusion criteria that prioritized surgically resected cases. Serological index analysis showed that 75% of patients (123 cases) had AFP ≤400 ng/ml, and 78% (128 cases) had albumin ≥3.5 g/dl, suggesting that most patients had liver function classified as Child-Pugh class A. This study revealed key molecular features of GCN1 in hepatocellular carcinoma through multidimensional analysis. As shown in Figure 1A, analysis based on the TCGA-LIHC cohort demonstrated that the expression level of GCN1 in liver cancer tissues was significantly higher than in normal liver tissues, and this difference was further validated in paired sample analysis (Figure 1B). Evaluation of diagnostic efficacy showed that GCN1 exhibited excellent performance in distinguishing liver cancer from normal tissues. ROC curve analysis indicated that the AUC value reached 0.921 (95% CI: 0.893–0.950), significantly superior to the traditional biomarker AFP.

Table 1. Baseline Characteristics

Characteristics	overall
Pathologic T stage, n (%)	
T1	101 (61.6%)
T2&T3&T4	63 (38.4%)
Pathologic N stage, n (%)	
N0	163 (99.4%)

Characteristics	overall
N1	1 (0.6%)
Pathologic M stage, n (%)	
M0	161 (98.2%)
M1	3 (1.8%)
Gender, n (%)	
Male	110 (67.1%)
Female	54 (32.9%)
Age, n (%)	
<= 60	91 (55.5%)
> 60	73 (44.5%)
BMI, n (%)	
<= 25	95 (57.9%)
> 25	69 (42.1%)
AFP (ng/ml), n (%)	
<= 400	123 (75%)
> 400	41 (25%)
Albumin(g/dl), n (%)	
< 3.5	36 (22%)
>= 3.5	128 (78%)
Prothrombin time, n (%)	
<= 4	130 (79.3%)
> 4	34 (20.7%)
Vascular invasion, n (%)	
No	111 (67.7%)
Yes	53 (32.3%)

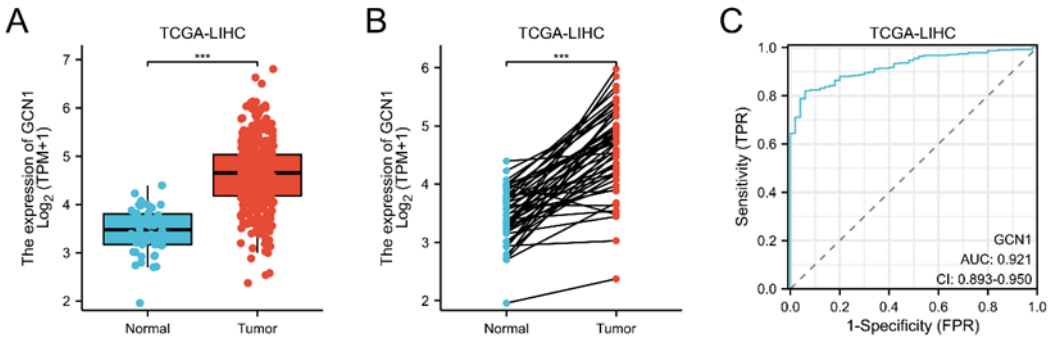

Figure 1. GCN1 Expression in Hepatocellular Carcinoma Tissues Versus Normal Tissues and Its Diagnostic Efficacy. A. GCN1 gene expression levels in the TCGA-LIHC cohort show significantly higher expression in tumor tissues compared to normal tissues ($P < 0.001$). B. In paired samples from the TCGA-LIHC cohort, tumor tissues also exhibited significantly higher GCN1 expression than adjacent non-tumorous tissues ($P < 0.001$). C. The ROC curve evaluated the ability of GCN1 to distinguish tumor tissues from normal tissues in the TCGA-LIHC cohort.

3.2. Association Between GCN1 Expression Levels and Clinicopathological Features

This study revealed the systematic association between GCN1 expression levels and clinicopathological features using a univariate logistic regression model (Table 2). The results showed that advanced T stage (T2–T4 vs. T1) significantly increased the likelihood of high GCN1 expression (OR = 1.941, 95% CI: 1.285–2.933, P = 0.002). Among serological

indicators, patients with AFP >400 ng/ml had a 3.7-fold increased risk of high GCN1 expression (OR = 3.697, 95% CI: 2.014–6.785, P < 0.001).It is noteworthy that the biological correlation between GCN1 expression and tumor progression was validated across multiple dimensions: GCN1 expression levels increased progressively from normal tissues to T4-stage tumors (Figure 2A); the median GCN1 expression level in the AFP >400 ng/ml group was significantly higher than that in the AFP ≤400 ng/ml group (Mann-Whitney U test, P = 0.0001) (Figure 2B).Other variables, including N/M stage, demographic characteristics, and liver function indicators, did not show statistically significant associations with GCN1 expression (all P > 0.05).

Table 2. Univariate Logistic Regression Analysis

Characteristics	Total (N)	OR (95% CI)	P value
Pathologic T stage (T2&T3&T4 vs. T1)	371	1.941 (1.285 – 2.933)	**0.002**
Pathologic N stage (N1 vs. N0)	258	2.687 (0.276 – 26.173)	0.395
Pathologic M stage (M1 vs. M0)	272	0.314 (0.032 – 3.057)	0.318
Gender (Female vs. Male)	374	1.375 (0.890 – 2.125)	0.151
Age (> 60 vs. <= 60)	373	0.816 (0.543 – 1.225)	0.326
BMI (> 25 vs. <= 25)	337	0.739 (0.481 – 1.135)	0.167
AFP (ng/ml) (> 400 vs. <= 400)	280	3.697 (2.014 – 6.785)	**< 0.001**
Albumin(g/dl) (>= 3.5 vs. < 3.5)	300	1.254 (0.728 – 2.159)	0.414
Prothrombin time (> 4 vs. <= 4)	297	1.119 (0.681 – 1.839)	0.658
Vascular invasion (Yes vs. No)	318	1.459 (0.917 – 2.320)	0.111

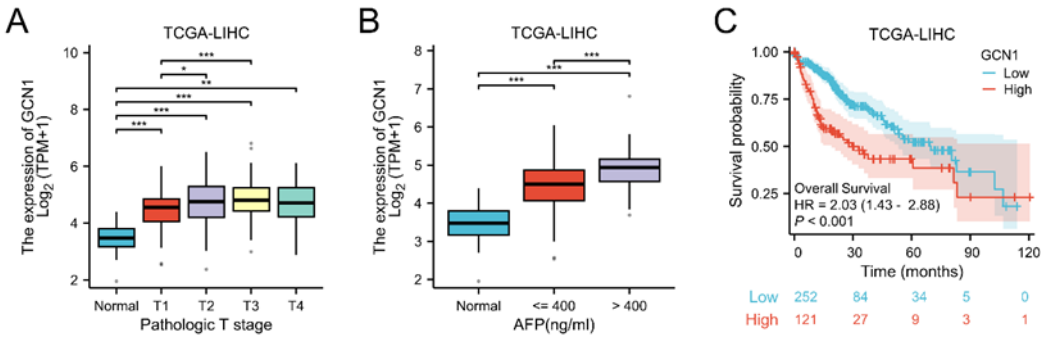

Figure 2. Clinical relevance analysis of GCN1 gene expression in liver hepatocellular carcinoma (LIHC). A. Association between GCN1 expression and tumor stage (Pathologic T stage). B. Association between GCN1 expression and AFP (alpha-fetoprotein) levels. C. Association between GCN1 expression and overall survival (OS).

3.3. Survival Analysis Results

GCN1 expression levels were significantly associated with the prognosis of hepatocellular carcinoma patients. In univariate Cox regression analysis, advanced T stage (T2–T4 vs. T1, HR = 2.126, 95% CI: 1.481–3.052, P < 0.001), distant metastasis (M1 vs. M0, HR = 4.077, 95% CI: 1.281–12.973, P = 0.017), and high GCN1 expression (HR = 1.604, 95% CI: 1.133–2.271, P = 0.008) were identified as significant prognostic factors (Table 3).In the multivariate model, after adjusting for T stage and M stage, high GCN1 expression remained an independent prognostic factor (HR = 1.454, 95% CI: 1.021–2.070, P = 0.038), with a hazard ratio comparable to that of T stage (HR = 2.010, 95% CI: 1.395–2.897, P < 0.001).Kaplan–Meier survival curves visually demonstrated the prognostic stratification ability of GCN1. As shown in Figure 2C, the median survival time in the high-expression

group was significantly lower than in the low-expression group, with a hazard ratio of 2.03 (95% CI: 1.43–2.88).

Table 3. Univariate and Multivariate Cox Regression Results

Characteristics	HR (95% CI)	P value
a.		
Pathologic T stage (T2&T3&T4VS.T1)	2.126 (1.481 - 3.052)	< 0.001
Pathologic N stage (N1 VS. N0)	2.029 (0.497 - 8.281)	0.324
Pathologic M stage (M1 VS. M0)	4.077 (1.281 - 12.973)	0.017
Gender (Female VS. Male)	1.261 (0.885 - 1.796)	0.200
Age (> 60 VS.<= 60)	1.205 (0.850 - 1.708)	0.295
BMI (> 25 VS.<= 25)	0.798 (0.550 - 1.158)	0.235
AFP (ng/ml) (> 400 VS.<= 400)	1.075 (0.658 - 1.759)	0.772
Albumin(g/dl) (>= 3.5 VS.< 3.5)	0.897 (0.549 - 1.464)	0.662
Prothrombin time (> 4 VS.<= 4)	1.335 (0.881 - 2.023)	0.174
Vascular invasion (Yes VS. No)	1.344 (0.887 - 2.035)	0.163
GCN1 expression (High VS. Low)	1.604 (1.133 - 2.271)	0.008
b.		
Pathologic T stage (T2&T3&T4VS.T1)	2.010 (1.395 - 2.897)	< 0.001
GCN1 expression (High VS. Low)	1.454 (1.021 - 2.070)	0.038

3.4. Differential Expression Analysis and Functional Annotation Results

Differential expression analysis revealed a large number of significantly differentially expressed genes between the high and low GCN1 expression groups (Figure 3A), with a total of 991 differentially expressed genes—851 upregulated and 140 downregulated—suggesting that GCN1 may play a role in regulating various upstream and downstream genes. The heatmap (Figure 3B) displays the top five most upregulated and top five most downregulated differentially expressed genes between the high and low GCN1 expression groups. Several genes associated with tumor development or tissue differentiation (such as LGALS14, MAGEA4, CEACAM7) were significantly upregulated in the high GCN1 expression group, further suggesting its involvement in tumor progression or specific biological pathways. GO/KEGG functional enrichment analysis (Figure 3C) showed that the differentially expressed genes were mainly involved in auditory organ development, sensory organ morphogenesis, and ion channel activity, indicating that GCN1 may be associated with cellular sensing and signal transduction functions. GSEA analysis (Figures 3D-F) further revealed significant enrichment of high GCN1 expression in: Cell cycle (NES = 2.385), suggesting that GCN1 may promote cell proliferation; Neuroactive ligand-receptor interaction (NES = 2.069); and Axon guidance pathway (NES = 2.307), indicating that GCN1 may also play a regulatory role in neuro-related signaling pathways.

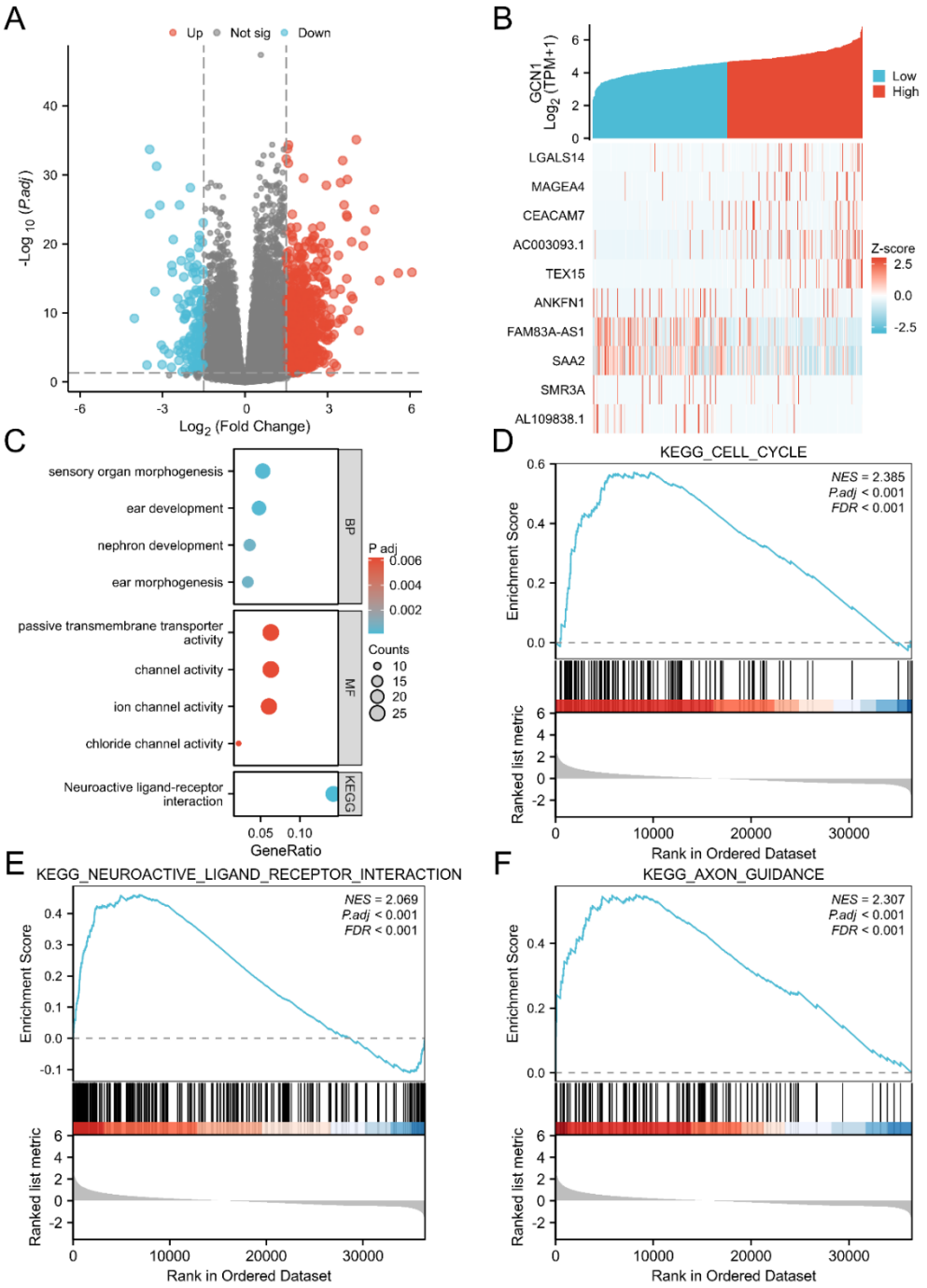

Figure 3. Differential expression analysis and functional enrichment results related to GCN1. A. Volcano plot showing differentially expressed genes (DEGs) between high and low GCN1 expression groups. B. Heatmap of Z-score normalized expression levels of DEGs, highlighting representative significantly upregulated and downregulated genes. Samples are grouped based on high or low GCN1 expression. C. GO and KEGG enrichment analysis results. D-F. GSEA results showing KEGG pathways significantly enriched in samples with high GCN1 expression.

4. Discussion

Hepatocellular carcinoma (HCC), as the third leading cause of cancer-related deaths worldwide [7], requires an in-depth understanding of its molecular mechanisms to improve clinical diagnosis and treatment. This study systematically reveals for the first time the diagnostic and prognostic value of the GCN1 gene in HCC. The main findings

include: GCN1 is specifically overexpressed in tumor tissues and significantly correlated with clinical staging; it demonstrates excellent diagnostic performance (AUC = 0.921) and possesses independent prognostic value (HR = 1.454); it may promote tumor progression by regulating pathways such as the cell cycle. These findings provide new insights for molecular subtyping and precision treatment of HCC.

From the molecular mechanism perspective, analysis of TCGA data shows that the high expression pattern of GCN1 is highly consistent with oncogene expression profiles in pan-cancer studies [8]. Notably, its diagnostic performance is significantly better than that of the traditional biomarker AFP and superior to recently reported markers GP73 (AUC = 0.85) and DKK1 (AUC = 0.87) [9]. This high specificity may stem from the low baseline expression of GCN1 in normal liver tissue and is closely related to epigenetic remodeling in the early stages of liver cancer development [10]. We further found that GCN1 expression is strongly positively correlated with T stage (OR = 1.941) and AFP levels (OR = 3.697), suggesting its potential involvement in the invasive biological behavior of HCC [11].

In terms of prognostic evaluation, multivariate Cox analysis confirmed the independent prognostic value of GCN1 (HR = 1.454), consistent with the characteristics of key oncogenic driver genes [12]. Functional enrichment analysis showed significant association with the cell cycle pathway (NES = 2.385), complementing the known abnormal activation mechanisms of the CDK4/6 pathway in liver cancer cells [13]. Particularly noteworthy is the enrichment of the axon guidance pathway (NES = 2.307), which may explain the neural infiltration features seen in some HCC cases [14]. Differential expression of the cancer-testis antigen MAGEA4 suggests that GCN1 may be involved in immune evasion mechanisms, which aligns with recent studies on PD-1/PD-L1 inhibitor resistance [15].

This study is the first to clarify the dual clinical value of GCN1 in HCC, providing a theoretical basis for the development of novel diagnostic biomarkers and prognostic evaluation systems. However, there are limitations: first, the sample bias in the TCGA database may affect the generalizability of the results and requires validation in multi-center cohorts; second, the lack of protein-level verification and spatial transcriptomics analysis makes it difficult to fully assess tumor heterogeneity; moreover, the specific mechanisms of GCN1 need to be elucidated through experimental approaches such as CRISPR/Cas9 gene editing models [16]. It is worth noting that the interaction between immune cells and tumor cells in the liver cancer microenvironment may influence GCN1 expression, which will be an important direction for future research.

5. Conclusion

In summary, this study is the first to comprehensively elucidate the diagnostic and prognostic significance of GCN1 in hepatocellular carcinoma. GCN1 is markedly overexpressed in tumor tissues and correlates strongly with clinical stage and AFP levels, demonstrating superior diagnostic performance compared to traditional biomarkers. Its independent prognostic value and potential involvement in key oncogenic pathways, such as the cell cycle and axon guidance, highlight its relevance in HCC progression. Moreover, the association of GCN1 with immune evasion markers like MAGEA4 suggests a possible role in immunotherapy resistance. While these findings provide a solid foundation for developing GCN1 as a novel biomarker and therapeutic target, further validation in multi-center cohorts and mechanistic studies are warranted to fully clarify its biological function and clinical utility in HCC.

Funding:

This work was supported by Clinical and Research Foundation of The Seventh Affiliated Hospital, Sun Yat-sen University (NO. ZSQYLCKYJJ202319).

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