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Comprehensive Bioinformatics Analysis Reveals GAPDH As A Prognostic Biomarker In Liver Hepatocellular Carcinoma And Head And Neck Squamous Cell Carcinoma

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Abstract
Liver hepatocellular carcinoma (LIHC) and head and neck squamous cell carcinoma (HNSC) are aggressive cancers with high morbidity and mortality. Identifying reliable biomarkers for early diagnosis, prognosis, and therapeutic targeting is crucial. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is traditionally known as a glycolytic enzyme but is increasingly recognized for its role in cancer biology. This study investigates the expression and promoter methylation of GAPDH in LIHC and HNSC, utilizing data from the UALCAN and GEPIA2 databases. Our results show that GAPDH expression is significantly upregulated in primary tumor tissues compared to normal tissues in both LIHC and HNSC. This upregulation is associated with reduced promoter methylation, suggesting hypomethylation as a potential mechanism. Furthermore, the validation of these findings across different cancer stages indicates that GAPDH expression increases from stage I to stage III in both cancer types, with a decrease in stage IV for LIHC and high variability in HNSC. Promoter methylation levels are consistently lower in tumor samples compared to normal tissues, with increased gene body methylation. Mutational analysis via the cBioPortal database reveals that GAPDH alterations are more frequent in HNSC than in LIHC, though they do not significantly impact overall survival. Kaplan-Meier survival curves from the KM plotter tool indicate that high GAPDH expression correlates with worse overall survival and relapse-free survival in LIHC, whereas in HNSC, high GAPDH expression affects overall survival but not relapse-free survival. Protein-protein interaction network and gene enrichment analyses highlight GAPDH's involvement in metabolic processes, protein synthesis, and extracellular interactions. Drug sensitivity analysis shows a positive correlation between GAPDH expression and resistance to multiple therapeutic agents, suggesting GAPDH as a potential biomarker for predicting drug sensitivity. Overall, these findings underscore the potential of GAPDH as a diagnostic, prognostic, and therapeutic target in LIHC and HNSC.

Keywords: Cancer: LIHC: HNSC: GAPDH: Diagnosis

Introduction

Cancer, a leading cause of morbidity and mortality worldwide, encompasses a group of diseases characterized by the uncontrolled growth and spread of abnormal cells [1-5]. Despite significant advances in cancer research, the disease remains a formidable challenge due to its complex nature and the multitude of factors involved in its onset and progression [6, 7]. Among the various types of cancer, liver hepatocellular carcinoma (LIHC) and head and neck squamous cell carcinoma (HNSC) are particularly prevalent and deadly [8]. LIHC is the most common type of primary liver cancer, accounting for approximately 75% of all liver cancer cases [9]. It typically arises in the context of chronic liver disease, including hepatitis B or C infection, alcoholic liver disease, and non-alcoholic steatohepatitis [10]. LIHC is a major global health problem,

especially in regions with high rates of hepatitis B and C infections, such as East Asia and sub-Saharan Africa [11]. The prognosis for LIHC patients remains poor, with a five-year survival rate of less than 20%, primarily due to late-stage diagnosis and limited therapeutic options [12]. Head and neck squamous cell carcinoma (HNSC) includes cancers of the oral cavity, pharynx, and larynx. It is the sixth most common cancer worldwide, with tobacco use, alcohol consumption, and human papillomavirus (HPV) infection being significant risk factors [13]. Despite advances in surgery, radiation therapy, and chemotherapy, the overall survival rate for HNSC has not improved significantly over the past few decades. The aggressive nature of the disease and the potential for recurrence and metastasis contribute to the high mortality associated with HNSC.
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a key enzyme in the glycolytic pathway, traditionally known for its role in cellular energy metabolism [14]. Recent studies, however, have revealed that GAPDH has multifunctional roles beyond glycolysis, including involvement in DNA repair, apoptosis, and cellular signaling [15, 16]. Emerging evidence suggests that GAPDH may play a significant role in cancer development and progression. Overexpression of GAPDH has been observed in various human cancers, including breast, lung, and prostate cancers, indicating its potential as a diagnostic and prognostic biomarker [17, 18]. In our study, we aim to elucidate the diagnostic, prognostic, and therapeutic importance of GAPDH genes in LIHC and HNSC using multi-omics in silico analyses. By integrating data from genomics, transcriptomics, proteomics, and metabolomics, we seek to provide a comprehensive understanding of the role of GAPDH in these cancers. This approach will enable us to identify novel biomarkers and potential therapeutic targets, ultimately contributing to the development of more effective strategies for the management of LIHC and HNSC.

Methodology

UALCAN database

UALCAN is an accessible, user-friendly web resource for analyzing cancer data from The Cancer Genome Atlas (TCGA) and MET500 [19]. It provides comprehensive analysis options for exploring gene expression, promoter methylation, and survival data across various cancer types. Researchers can easily compare cancerous and normal tissue samples, investigate the effects of different clinicopathological features, and identify potential biomarkers. UALCAN's intuitive interface enables the generation of publication-quality plots and statistical analyses, making it a valuable tool for cancer genomics research. By facilitating the interpretation of large-scale data, UALCAN significantly advances our understanding of cancer biology and supports the development of targeted therapies. In this study, UALCAN database was used to analyze the expression and promoter methylation levels of GAPDH.

GEPIA2 database

GEPIA2 (Gene Expression Profiling Interactive Analysis 2) is a powerful online tool for analyzing RNA sequencing expression data from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) projects [20]. It offers extensive features for differential expression analysis, survival analysis, correlation analysis, and similar gene detection. Researchers can explore gene expression across various cancer types and normal tissues, assess prognostic significance, and visualize results through customizable, high-quality plots. GEPIA2 is known for its user-friendly interface, allowing both novice and experienced researchers to perform complex bioinformatics analyses with ease, thereby facilitating the discovery of novel biomarkers and therapeutic targets in cancer research. Herein, we used GEPIA2 for the expression validation of GAPDH using the additional cancer patient cohorts.

OncoDB

OncoDB, short for Oncogenomic Database, is a comprehensive repository that consolidates oncogenomic data from various cancer studies [21]. It serves as a centralized resource for researchers to access and analyze molecular profiles, genetic mutations, and clinical annotations across different cancer types. OncoDB facilitates the exploration of oncogenomic landscapes, enabling the identification of potential driver mutations, biomarkers, and therapeutic targets. By integrating diverse datasets and providing analytical tools, OncoDB supports translational research efforts aimed at understanding cancer biology and improving patient outcomes through personalized treatment approaches. OncoDB was used in this study to validate promoter methylation level of GAPDH.

cBioPortal

cBioPortal is a widely used open-access platform that facilitates exploration and analysis of complex cancer genomics data [22]. It aggregates molecular profiles from cancer studies, offering researchers and clinicians valuable insights into genetic alterations, clinical outcomes, and therapeutic implications. With user-friendly tools for visualizing data and integrating diverse datasets, cBioPortal empowers researchers to uncover patterns, identify potential biomarkers, and advance understanding of cancer biology, ultimately aiding in the development of personalized treatment strategies. In this study, cBioPortal database was utilized for the mutational analysis of GAPDH.

Kaplan Meier (KM) plotter tool

The KM plotter tool is a valuable resource in oncology research, providing Kaplan-Meier survival plots based on gene expression data [23]. It enables researchers to assess the impact of specific genes on patient survival across various cancer types. By integrating large datasets from public repositories, KM plotter allows for robust statistical analysis and visualization, aiding in the identification of prognostic biomarkers and potential therapeutic targets. This tool plays a crucial role in advancing precision medicine by facilitating evidence-based decisions in clinical and translational research. In the current work, this tool was used to analyze the prognostic importance of GAPDH.

Gene Set Cancer Analysis (GSCA)

GSCA is a computational method used in cancer research to explore the association between gene sets and cancer phenotypes [24]. It integrates genomic data to identify gene sets that are significantly correlated with cancer-related outcomes such as survival or drug response. By analyzing patterns across multiple datasets, GSCA helps uncover molecular pathways and biological processes crucial in cancer development and progression. This approach aids in prioritizing therapeutic targets and understanding the complex interplay between genes and disease phenotypes, contributing to the advancement of personalized medicine strategies. Herein, GSCA was utilized for the drug sensitivity analysis of GAPDH.

Results

Expression and promoter methylation landscape of GAPDH in LIHC and HNSC tissues specimens

The Figure 1 illustrates the expression and promoter methylation levels of GAPDH in LIHC and HNSC tissues compared to normal tissues sourced from the UALCAN database. In LIHC, GAPDH expression is significantly ($p<0.5$) higher in primary tumor samples than in normal tissues, indicating upregulation (Figure 1A). This upregulation is accompanied by slightly lower promoter methylation levels in the tumor samples, suggesting hypomethylation as a potential mechanism for increased GAPDH expression (Figure 1C). Similarly, in HNSC, GAPDH expression is elevated in primary tumor samples relative to normal tissues (Figure 1B), though the difference is less pronounced than in LIHC. Promoter methylation levels in HNSC tumors are also reduced compared to normal tissues, albeit to a lesser extent (Figure 1D). These findings suggest that GAPDH upregulation in both cancers is associated with reduced promoter methylation, highlighting GAPDH's potential as a diagnostic and prognostic biomarker and a possible therapeutic target.

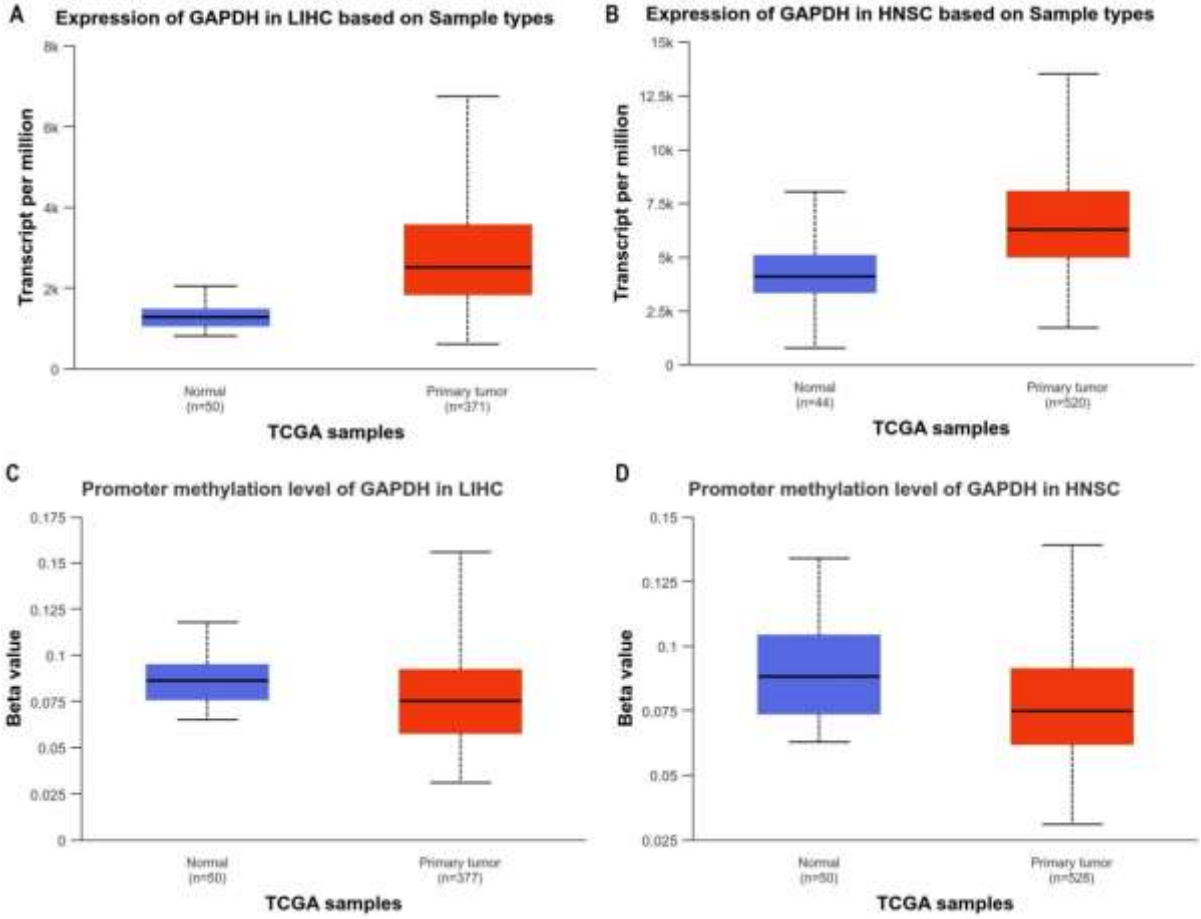

Figure 1: Expression and promoter analysis results of GAPDH in LIHC and HNSC samplesvia the UALCAN. (A) Expression analysis results. (B) Promoter methylation analysis results. P-value < 0.05.

Expression and promoter methylation level validation of GAPDH using additional TCGA LIHC and HNSC cohorts

The Figure 2 presents data on GAPDH expression and promoter methylation validation across different cancer stages in LIHC and HNSC via GEPIA2 database. The box plots in Figure 2A show significantly higher expression levels of GAPDH in tumor tissues (LIHC: n=369, HNSC: n=519) compared to normal tissues (LIHC: n=50, HNSC: n=44), with asterisks indicating statistical significance ($p<0.05$). This consistent upregulation across both cancer types underscores the potential role of GAPDH in tumorigenesis. Violin plots in Figure 2B depict GAPDH expression levels across different stages of LIHC and HNSC. In LIHC, GAPDH expression increases from stage I to stage III, with a slight decrease in stage IV, and an overall F value of 4.07 ($p<0.01$), indicating significant variability across stages. Similarly, HNSC shows increased GAPDH expression from stage I to stage III, with stage IV showing the highest variability, supported by an F value of 4.34 ($p<0.01$). These patterns suggest that GAPDH expression may correlate with cancer progression and severity. Line plots in Figure 2C

illustrate the promoter and gene body methylation levels of GAPDH in both cancer types. For LIHC, the red line representing tumor samples (n=371) shows reduced promoter methylation compared to normal samples (n=41), with a notable increase in methylation within the gene body region. In HNSC, similar trends are observed with tumor samples (n=520) showing reduced promoter methylation compared to normal samples (n=20), again accompanied by higher methylation in the gene body. These findings suggest that hypomethylation of the GAPDH promoter might contribute to its upregulated expression in both LIHC and HNSC, while gene body methylation changes may further influence its role in cancer biology.

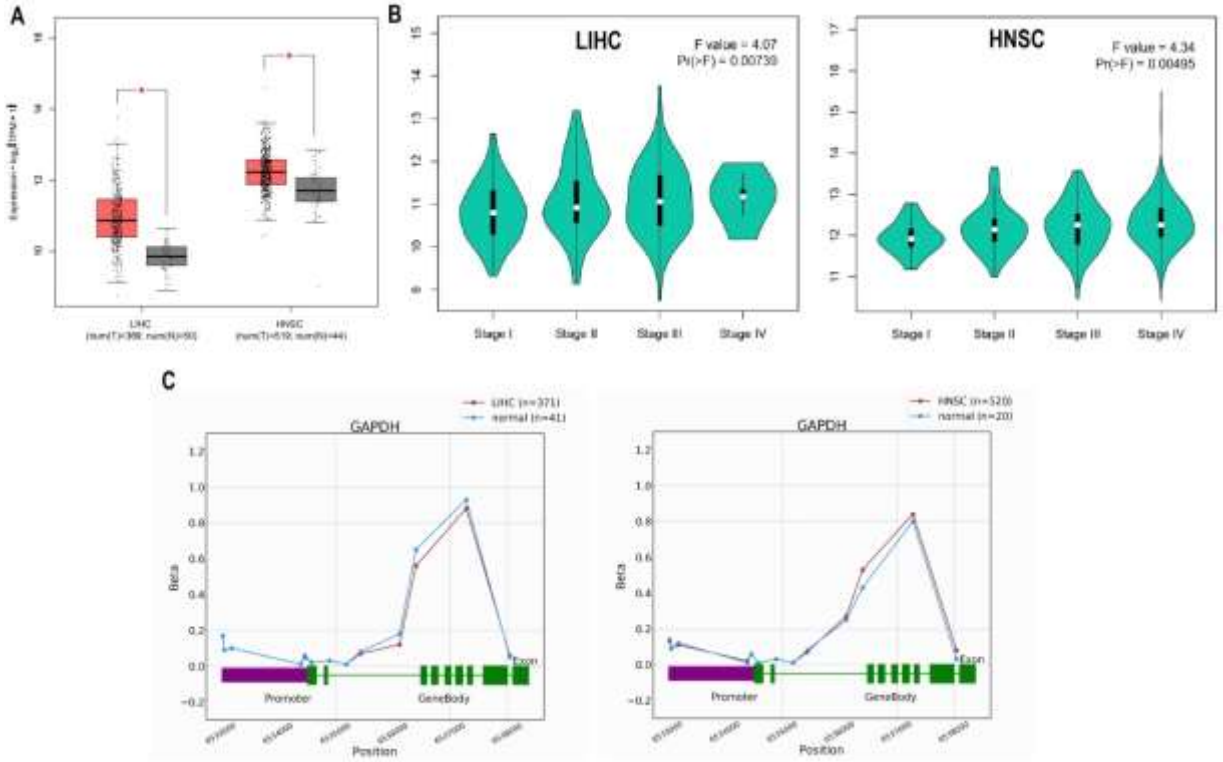

Figure 2: Expression and promoter methylation validation of GAPDH using additional LIHC and HNSC cohorts via GEPIA2 and OncoDB. (A) Expression across normal and LIHC and HNSC samples. (B) Expression across different stages of LIHC and HNSC. (C) Promoter methylation analysis of GAPDH across LIHC and HNSC samples paired with controls. P-value < 0.05.

Mutational analysis of GAPDH in LIHC and HNSC tissues specimens

The Figure 3 provides insights into genetic alterations of GAPDH and their impact on survival in LIHC and HNSC tissue samples via the cBioPortal database. In LIHC, 0.5% of the cases exhibit GAPDH amplification with no other alterations reported (Figure 3A), while in HNSC, 1.8% of the cases show genetic alterations in GAPDH, including amplifications, missense mutations, and structural variants of unknown significance (Figure 3A). This suggests that GAPDH alterations are more frequent in HNSC than in LIHC. The Kaplan-Meier survival curve compares overall survival between HNSC patients with altered GAPDH and those with unaltered GAPDH, with a log-rank test p-value of 0.695 indicating no significant difference in overall survival between the two groups (Figure 3B). These findings suggest that while GAPDH alterations exist in a subset of HNSC patients, they do not significantly impact overall survival, indicating that GAPDH alterations alone may not be a strong prognostic marker for survival outcomes in these cancers

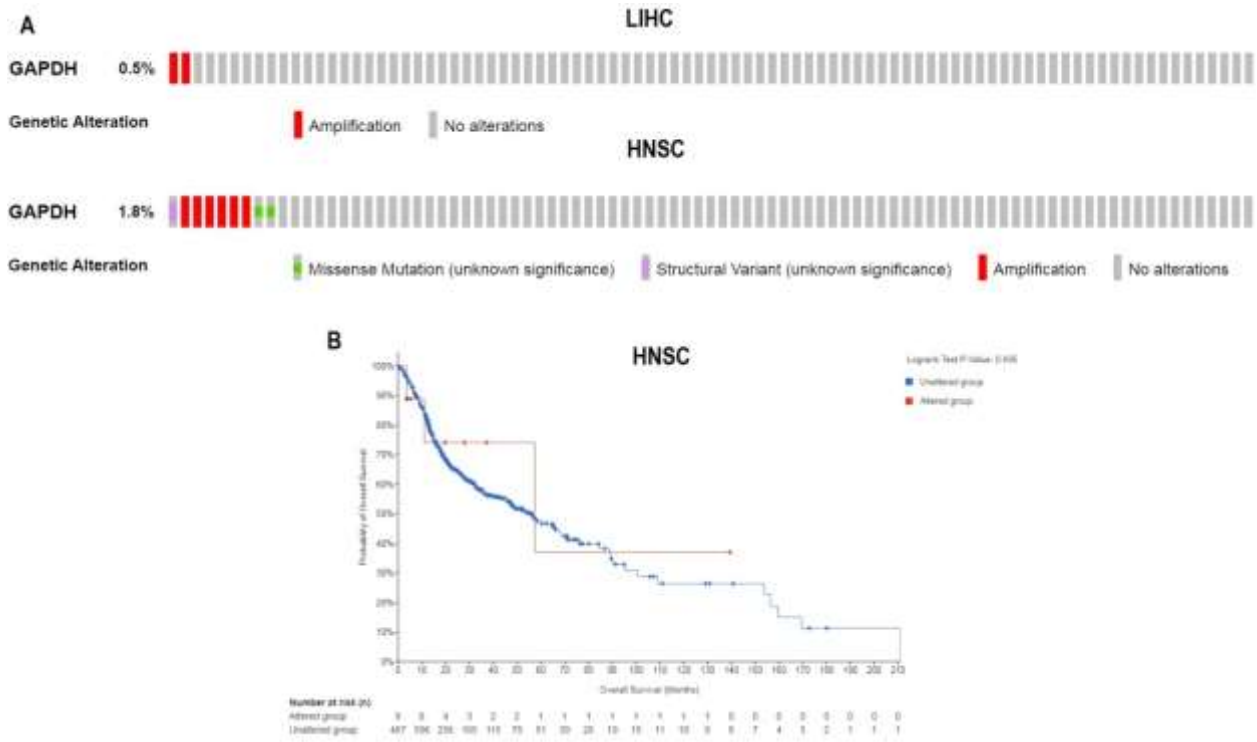

Figure 3: Mutational analysis of GAPDH across LIHC and HNSC samples via cBioPortal. (A) Mutational frequencies across LIHC and HNSC samples. (B) Effect of the observed mutations on the survival of LIHC patients. P-value < 0.05.

Prognostic significance of GAPDH in LIHC and HNSC

The Kaplan-Meier survival curves in Figure 4 sourced from the KM plotter tool illustrate the association between GAPDH expression levels and patient outcomes in LIHC and HNSC. In Figure 4A, the left plot shows overall survival (OS) for LIHC patients, with high GAPDH expression correlating with significantly worse survival (HR = 2.43, 95% CI: 1.69-3.51, log-rank P = 8.7e-07). The right plot in Figure 4A displays OS for HNSC patients, where high GAPDH expression also predicts poorer survival (HR = 1.63, 95% CI: 1.17-2.29, log-rank P = 0.0038). In Figure 4B, the left plot represents relapse-free survival (RFS) for LIHC patients, indicating that high GAPDH expression is associated with a significantly higher risk of relapse (HR = 1.75, 95% CI: 1.25-2.46, log-rank P = 0.001). Conversely, the right plot in Figure 4B shows RFS for HNSC patients, where high GAPDH expression does not significantly affect relapse-free survival (HR = 1.54, 95% CI: 0.73-3.29, log-rank P = 0.26). These results collectively suggest that high GAPDH expression is a negative prognostic marker for both OS and RFS in LIHC, whereas its impact on survival in HNSC is significant for OS but not for RFS.

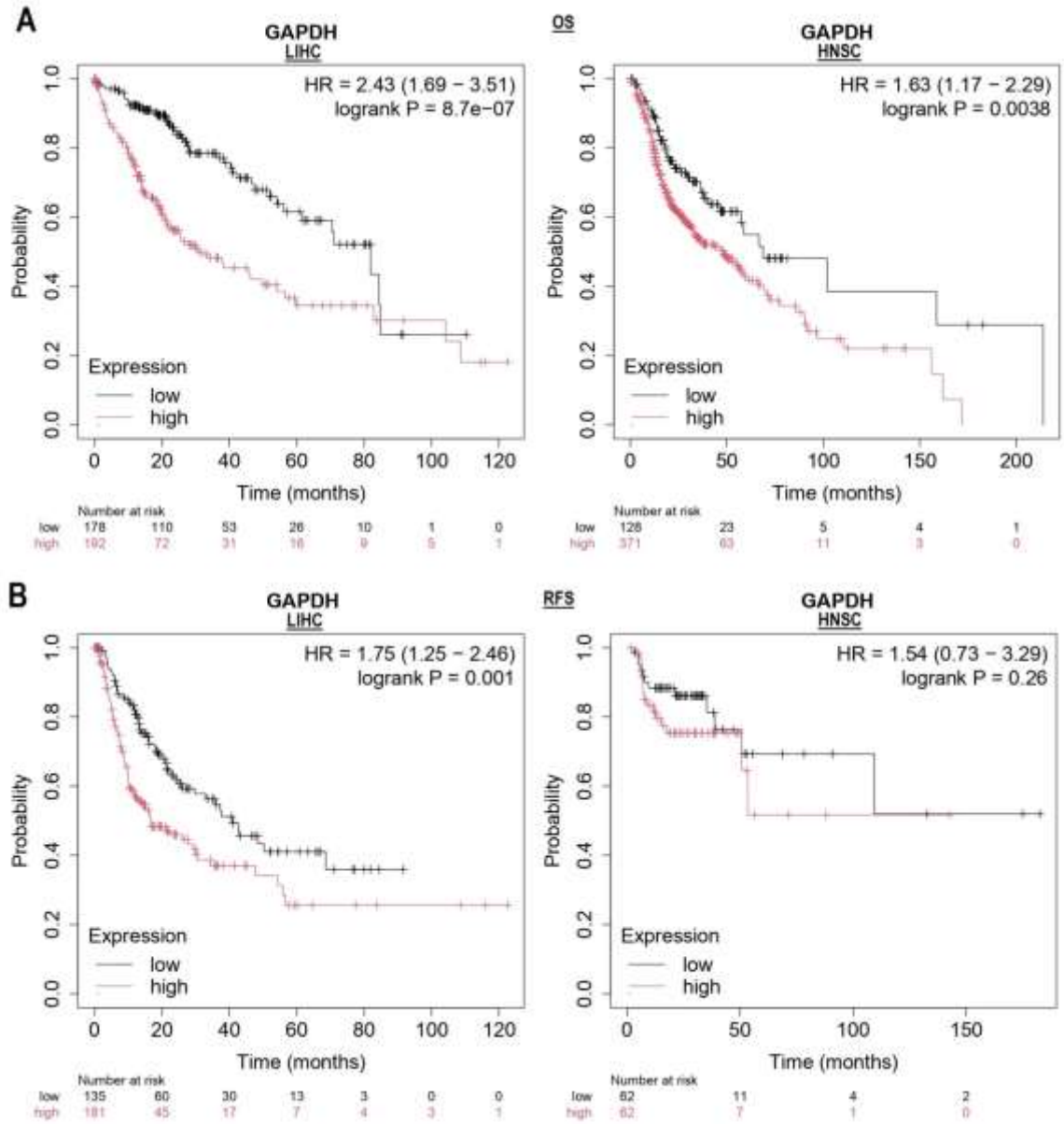

Figure 4: Survival analysis of GAPDH across LIHC and HNSC patients using KM plotter tool. (A) OS. (B) RFS. P-value < 0.05.

Protein-protein interaction (PPI) network and gene enrichment analysis of GAPDH-associated genes

The provided Figure 5 illustrates the PPI network and enrichment analysis for GAPDH and its interacting partners. Figure 5A depicts a PPI network highlighting GAPDH's extensive interactions with various proteins, including EPRS1, SYNCRIP, RPL13A, SIAH1, ENO1, GPI, TPI1, ALDOA, and PGK1/2. Figure 5B, C, D, and E present the results of gene enrichment analyses for these interactions. Figure 5B focuses on cellular components, indicating significant enrichment in complexes such as the GAIT complex, sperm fibrous sheath, aminoacyl-tRNA synthetase multienzyme complex, and various extracellular vesicles and regions, with particularly high fold enrichment in the GAIT complex. Figure 5C details the enrichment of molecular functions, showing prominent activities such as phosphotransferase activity, fructose-bisphosphate aldolase activity, carbon-oxygen lyase activity, and several binding activities, including those for fructose, ADP, and tubulin. Figures 5D and E present biological processes and KEGG pathways, respectively, with a strong emphasis on metabolic processes. In Figure 5D, processes like glycolytic process, ATP generation from ADP, and various nucleotide metabolic processes show high fold enrichment. Similarly, Figure 5E highlights KEGG pathways such as glycolysis/gluconeogenesis, biosynthesis of amino acids, fructose and mannose metabolism, and the HIF-1 signaling pathway, all of which demonstrate significant enrichment. These results collectively suggest that GAPDH and its interacting proteins are involved in a wide array of cellular functions, particularly those related to metabolism, protein synthesis, and extracellular interactions, underlining GAPDH's multifaceted role in cellular physiology.

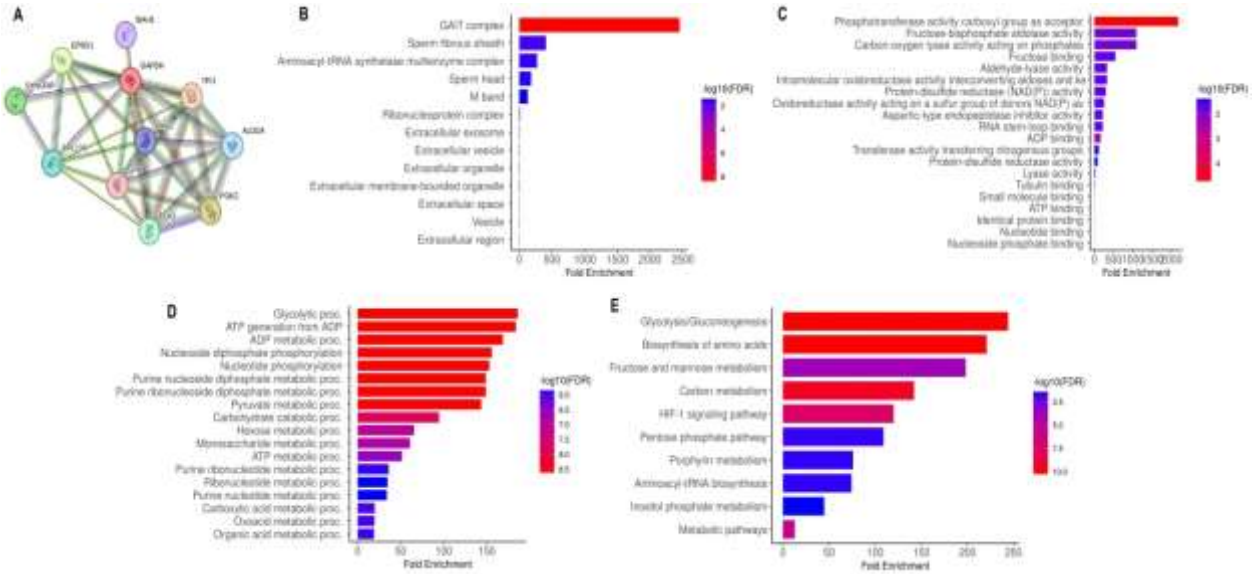

Figure 5: A PPI network construction and gene enrichment analysis. (A) A PPI network of GAPDH enriched genes. (B) Cellular components. (C) Molecular functions. (C) Biological functions. (D) Pathways. P-value < 0.05.

Drug sensitivity analysis of GAPDH

The Figure 6 illustrates the correlation between GAPDH mRNA expression and sensitivity to various drugs from the CTRP (Cancer Therapeutics Response Portal). Each point on the plot represents a different drug, with the size of the point corresponding to the statistical significance (-log10(FDR)) of the correlation, and the color intensity indicating the strength of the correlation. The results show a consistent positive correlation between GAPDH expression and drug sensitivity across multiple compounds, with the correlation values ranging around 0.1 to 0.3 (Figure 6). The size of the circles indicates that many of these correlations are statistically significant, as denoted by the False Discovery Rate (FDR) values being less than or equal to 0.05 (Figure 6). This suggests that higher GAPDH expression might be associated with increased resistance to a variety of drugs. Notable drugs with significant correlations include apicidin, BRD-K94375914, ciclopirox, entinostat, and paclitaxel, among others (Figure 6). These findings indicate that GAPDH expression could potentially be used as a biomarker to predict the sensitivity of cancer cells to these therapeutic agents, thus aiding in personalized treatment strategies.

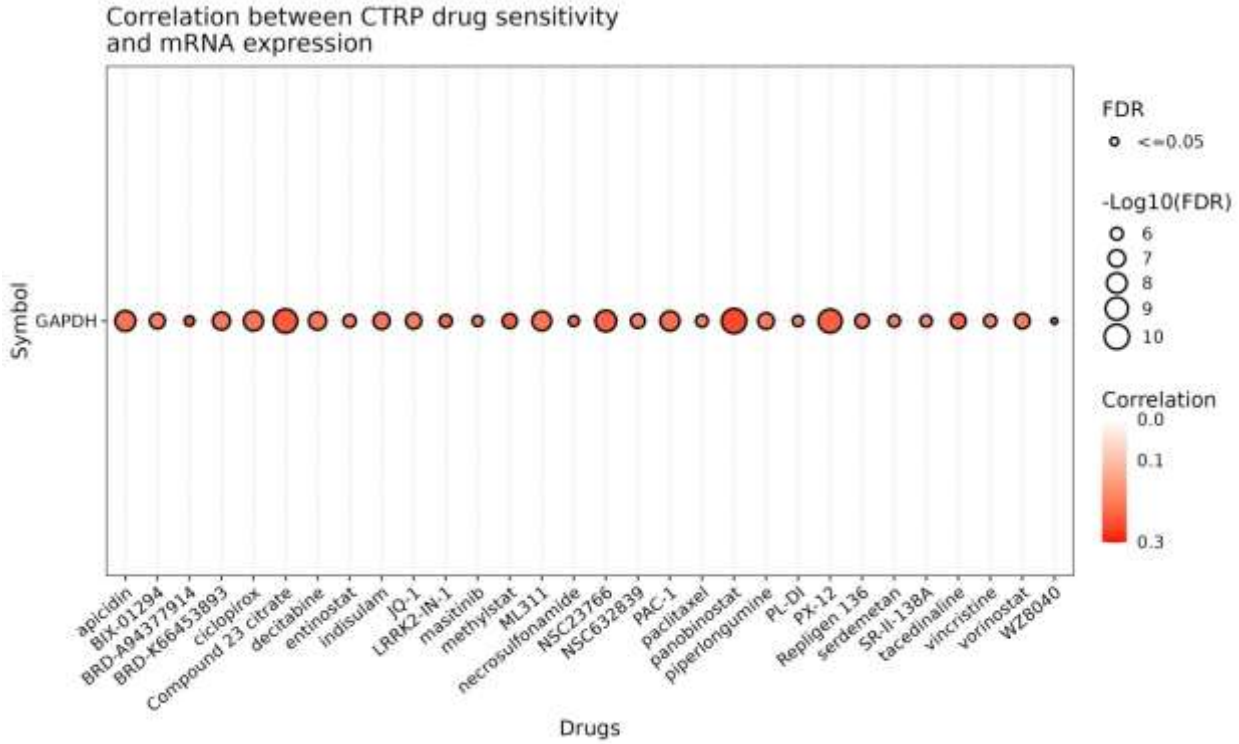

Figure 6: Drug sensitivity analysis of GAPDH using GSCA database. P-value < 0.05.

Discussion

The present study comprehensively examines the role of GAPDH expression and promoter methylation in LIHC and HNSC, exploring its potential as a diagnostic and prognostic biomarker, as well as its interaction with drug sensitivity. The

findings underscore the significant upregulation of GAPDH in both LIHC and HNSC tissues compared to normal tissues, as validated by multiple datasets, and highlight its potential involvement in cancer progression and treatment response.

Our analysis reveals that GAPDH expression is significantly elevated in primary tumor samples of both LIHC and HNSC, with a more pronounced increase observed in LIHC. This upregulation is accompanied by reduced promoter methylation levels in tumor tissues, suggesting that hypomethylation may be a mechanism driving GAPDH overexpression. These observations are consistent with previous studies, which have reported similar patterns of GAPDH expression and promoter methylation in various cancers [25, 26]. For instance, Hoque et al. (2018) noted hypomethylation-induced upregulation of GAPDH in breast cancer, highlighting its role in tumorigenesis .

Further validation across different cancer stages using the GEPIA2 database confirms that GAPDH expression remains consistently higher in tumor tissues compared to normal tissues. Additionally, the stage-wise analysis reveals that GAPDH expression correlates with cancer progression, showing significant variability across different stages in both LIHC and HNSC (Figure 2B). These findings align with the previous works, which demonstrated that increased GAPDH expression is associated with advanced tumor stages and poorer prognosis in colorectal cancer [27, 28].

Mutational analysis via the cBioPortal database indicates that GAPDH genetic alterations are more frequent in HNSC than in LIHC, though they do not significantly impact overall survival in HNSC patients. This suggests that while genetic alterations in GAPDH may contribute to its dysregulation in HNSC, they do not serve as strong prognostic markers. Previous research has also shown mixed results regarding the impact of GAPDH mutations on cancer prognosis, indicating the need for further investigation [29, 30].

Kaplan-Meier survival analyses reveal that high GAPDH expression is associated with significantly worse overall survival (OS) and relapse-free survival (RFS) in LIHC. In HNSC, high GAPDH expression predicts poorer OS but does not significantly affect RFS. These results corroborate previous studies that have identified GAPDH as a negative prognostic marker in various cancers. For example, Jiang et al. (2019) reported that high GAPDH expression correlates with poor survival outcomes in pancreatic cancer patients [31].

The PPI network and gene enrichment analyses highlight GAPDH's extensive interactions with various proteins involved in key cellular processes, including metabolism, protein synthesis, and extracellular interactions. The enrichment analyses reveal significant associations with metabolic processes and pathways, such as glycolysis/gluconeogenesis, biosynthesis of amino acids, and the HIF-1 signaling pathway. These findings are in line with previous studies that have demonstrated GAPDH's multifaceted role in cellular physiology and cancer metabolism [16, 32].

Drug sensitivity analysis reveals a consistent positive correlation between GAPDH expression and sensitivity to multiple drugs, suggesting that high GAPDH expression might be associated with increased resistance to these therapeutic agents. Notable drugs with significant correlations include apicidin, ciclopirox, and paclitaxel, among others. These results indicate that GAPDH expression could potentially serve as a biomarker for predicting drug sensitivity, aiding in personalized treatment strategies. This is supported by prior research, such as the study by Chen et al. (2017), which found that GAPDH expression modulates sensitivity to chemotherapy in ovarian cancer [33].

Conclusion

This study highlights GAPDH's role in LIHC and HNSC, showing its upregulation and reduced promoter methylation, which correlate with poor overall survival and higher relapse rates in LIHC. GAPDH's involvement in metabolic processes and its predictive value for drug sensitivity suggest its potential as a biomarker for diagnosis, prognosis, and personalized treatment. Our findings emphasize GAPDH's significance in cancer progression and therapy, providing a foundation for future research on its regulatory mechanisms and therapeutic targeting in LIHC and HNSC.

Conflict of interest

None

Acknowledgement

None

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