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ORIGINAL ARTICLE

Pan-cancer analysis of TP53 expression: prognostic significance and identification of diagnostic and prognostic biomarkers in hepatocellular carcinoma

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ABSTRACT

Background: Hepatocellular carcinoma (LIHC) is a common and aggressive liver malignancy, often diagnosed at advanced stages. Dysregulation of the TP53 tumor suppressor gene, critical for cell cycle control, apoptosis, and genomic stability, is frequently observed in LIHC; however, its prognostic value remains uncertain.

Objectives: To investigate TP53 expression levels, prognostic relevance, and molecular interactions in LIHC within a broader pan-cancer context.

Methods: Publicly available datasets from The Cancer Genome Atlas and Gene Expression Omnibus were analyzed. TP53 differential expression was evaluated using TIMER 2.0, Gene Expression Profiling Interactive Analysis (GEPIA), and UALCAN Online Cancer Data Analysis Tool (UALCAN). Survival analysis was performed via Kaplan-Meier Plotter, GEPIA, and UALCAN. Genomic alterations were assessed through cBioPortal. Gene expression validation was conducted using GEO2R and ggplot2. Protein–protein interaction networks were constructed using STRING and GeneMANIA.

Results: TP53 Messenger Ribonucleic Acid expression was significantly elevated in LIHC tumor tissues compared to normal liver tissues ($p < 0.05$). Promoter hypo-methylation was noted in tumor samples, potentially contributing to this up-regulation. Survival analysis revealed conflicting findings: Kaplan-Meier Plotter associated high TP53 expression with better prognosis (HR = 0.65, $p = 0.029$), whereas GEPIA and UALCAN linked high expression with poorer outcomes. Furthermore, TP53 expression positively correlated with immune cell infiltration and advanced clinical stage, suggesting a complex role in tumor progression.

Conclusion: TP53 demonstrates a dual, context-dependent role in LIHC, acting as both a tumor suppressor and a potential oncogenic driver. Its variable expression patterns and inconsistent prognostic associations highlight its potential as a diagnostic and prognostic biomarker and support the need for further functional and clinical validation.

Keywords: TP53, hepatocellular carcinoma, prognosis, Gene expression, tumor suppressor, immune microenvironment, bioinformatics.

Introduction

Hepatocellular carcinoma (LIHC) represents a major global health burden, ranking as the fifth most common cancer in men and the seventh in women (1). This life-threatening malignancy, marked by the uncontrolled proliferation of hepatocytes, frequently develops in individuals with chronic liver conditions such as cirrhosis and viral hepatitis. The poor prognosis of LIHC is primarily due to late-stage diagnosis; over 80% of

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cases are inoperable, leaving only 10%-20% of patients eligible for curative treatment (2).

TP53 is a well-established tumor suppressor gene, often referred to as the "guardian of the genome," due to its essential roles in preserving genomic stability, regulating cell cycle progression, and initiating apoptosis in response to cellular stress. Mutations in TP53 are a hallmark of numerous human cancers, including LIHC (3). These alterations disrupt its tumor-suppressive functions, contributing to unchecked cellular proliferation, resistance to apoptosis, and therapeutic failure (4). In addition to mutations, TP53 function can be modulated by mechanisms such as altered Messenger Ribonucleic Acid (mRNA) expression and changes in protein stability, further complicating its role in oncogenesis.

The high frequency of TP53 alterations in LIHC underscores the need for improved molecular diagnostic and prognostic tools (5). This study aimed to comprehensively examine TP53 gene expression and its prognostic relevance in LIHC, alongside a broader pan-cancer analysis to contextualize TP53 dysregulation in other malignancies such as lung and breast cancer. We utilized publicly available datasets from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO), leveraging their large sample sizes and comprehensive genomic profiles. Furthermore, the STRING database (6) was employed to explore protein–protein interaction (PPI) networks, offering insights into the functional context of TP53 in cancer.

Specifically, we hypothesized that: (i) TP53 expression is significantly dysregulated in LIHC compared to normal liver tissue; (ii) TP53 expression correlates with clinic-pathological features of LIHC; and (iii) TP53 expression is associated with patient survival outcomes. These findings are anticipated to support the development of improved prognostic strategies and potential therapeutic targets for LIHC and related cancers.

Materials and Methods

Transcriptional expression analysis of the TP53 Gene using databases

This study employed a multi-platform bioinformatics approach to investigate the expression and prognostic significance of the TP53 gene in LIHC. The study aims to use the TP53 as a potential diagnostic and prognostic biomarker.

Data sources and analysis

TP53 is a tumor suppressor gene frequently mutated in various cancers, including LIHC. This study aims to investigate the role of TP53 in LIHC by analyzing its differential expression, prognostic significance, and interaction networks. The general workflow was to first analyze differential expression and immune infiltration using TIMER 2.0, then validate the expression and survival using Gene Expression Profiling Interactive Analysis (GEPIA) and UALCAN Online Cancer Data Analysis Tool (UALCAN). The Kaplan-Meier plotter was then used for further survival analysis. cbioportal was used to examine genetic alterations. GEO2R and ggplot2 were used to validate expression changes. Finally, Gene MANIA and STRING were used to examine PPI networks.

1. Tumor immune estimation resource (TIMER 2.0)

The TIMER 2.0 platform was utilized to analyze the differential expression of the TP53 gene between the tumor and adjacent normal tissues across all TCGA cancer types. Furthermore, TIMER 2.0 was employed to estimate the infiltration levels of six key immune cell types (B cells, CD4+ T cells, CD8+T cells, neutrophils, macrophages, and dendritic cells) within the LIHC tumor microenvironment (3).

2. Gene expression profiling interactive analysis (GEPIA)

The GEPIA database was used to analyze the RNA-seq expression data of the TP53 gene in LIHC from the TCGA-LIHC and GTEx datasets. GEPIA was employed to assess differential TP53 gene expression, generate overall survival (OS) curves, and explore correlations between TP53 expression and clinical parameters. OS data was obtained, and hazard ratios were compared using the log-rank test. A p-value < 0.05 was considered (7)**.**

3. University of Alabama at Birmingham Cancer Data Analysis Portal UALCAN

UALCAN was used to explore OS, promoter TP53 DNA methylation levels, and analyze TP53 gene expression in relation to various clinicopathological parameters, including age, race, gender, cancer stages, and mutation status. A p-value < 0.05 was considered statistically significant (8).

4. Kaplan-meier plotter

The Kaplan-Meier plotter was used to generate survival curves for LIHC patients based on high and low TP53 gene expression levels. The cut-off values for high and low expression were determined using the default median cut-off method provided by the Kaplan-Meier plotter. Specific gene probe information was also obtained from the website (9)**.**

5. cBioPortal for cancer genomics

The cBioPortal for Cancer Genomics was used to explore genetic alterations of the TP53 gene across diverse cancer types within the TCGA datasets (10).

6. Validation of TP53 expression using ggplot2

Public gene expression datasets GSE101685 and GSE138178 from the National Center for Biotechnology Information GEO were analyzed using the GEO2R tool (https://www.ncbi.nlm.nih.gov/geo/geo2r). Differential gene expression analysis was performed to identify genes significantly altered in LIHC. The criteria for differential expression were a log2 fold change |Log2FC| > 1 and an adjusted p-value < 0.05. Volcano plots were generated using the ggplot2 R package (version 3.3.6) in R (version 4.3.2) to visualize the results (11).

7. Gene MANIA analysis

Gene MANIA (http://genemania.org/) was used to analyze the PPI network of TP53, exploring physical gene interactions, prediction, gene co-expression, co-

localization, genetic interactions, pathways, and shared protein domains. The term "TP53" was entered, and the top 20 gene networks were visualized (12). The biological significance of the genes found within this network will be discussed in the results section.

8. STRING analysis

The STRING database was used to analyze the PPI network of TP53. The analysis parameters were set to: network type (full STRING network), meaning of the network edges (evidence), active interactors sources (all), minimum required interaction score (low confidence, 0.150), and maximum number of interactors for display (no more than 10 interactors). The use of low confidence was used to capture a wider range of potential interactions. Further discussion of the confidence score will be addressed in the discussion section (6).

Potential biases and limitations

It is important to acknowledge that TCGA data, while comprehensive, may exhibit biases related to patient selection and data collection. The GEO datasets used can also introduce biases, related to the specific parameters of the original experiments.

Results

Pan-cancer analysis of differential TP53 expression

The differential expression of TP53 across various cancer types was examined using the TIMER, GEPIA, and UALCAN databases. *TP53* expression varied significantly across cancer types (Figure 1, TIMER, $p < 0.001$). Specifically, TP53 was found to be up-regulated in several cancer types, including Bladder Urothelial Carcinoma, Cholangiocarcinoma, Colon Adenocarcinoma, Esophageal Carcinoma, Head and Neck Squamous Cell Carcinoma, HNSC-HPVpos, HNSC-HPVneg, Kidney Renal Clear Cell Carcinoma, LIHC, Lung Adenocarcinoma, Lung Squamous Cell Carcinoma, Prostate Adenocarcinoma, Rectum Adenocarcinoma, Skin Cutaneous Melanoma, Stomach Adenocarcinoma, Thyroid Carcinoma, and Uterine Corpus Endometrial Carcinoma. In contrast, *TP53* expression was significantly down-regulated in Kidney Chromophobe.

p-value Significant Codes: $0 \leq$ *** $< 0.001 \leq$ ** $< 0.01 \leq$ * $< 0.05 \leq$. < 0.1.

TP53 expression in liver hepatocellular carcinoma (LIHC)

The expression of *TP53* in LIHC was further analyzed using GEPIA and UALCAN. GEPIA analysis (Figure 2) revealed a significant increase in *TP53* expression in tumor tissues ($n = 369$) compared to normal tissues ($n = 160$) ($p < 0.05$). This finding was corroborated by UALCAN analysis (Figure 3), which also showed significantly higher *TP53* expression in primary tumor samples ($n = 371$) compared to normal samples ($n = 50$) ($p < 0.05$). These results strongly suggest that TP53 plays a role in LIHC.

Tumor samples (T) are represented in red ($n = 369$), and normal samples (N) are represented in gray ($n = 160$).

Statistical significance is denoted as follows: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

Correlation with clinical parameters

The relationship between *TP53* expression and various clinic-pathological parameters in LIHC was explored using UALCAN. Analysis of patient age groups (Figure 4) showed a significant up-regulation of *TP53* expression in the 41-60 years age group compared to normal controls ($p < 0.001$). While *TP53* was also up-regulated in other age groups, these differences were not statistically significant ($p > 0.001$). *TP53* expression also increased progressively with cancer stage (Figure 5), suggesting its potential as a diagnostic biomarker and its involvement in LIHC progression ($p = 0.024$). There was a statistically significant difference in the expression of TP53 across gender (Figure 6) ($p = 0.0126,847$).

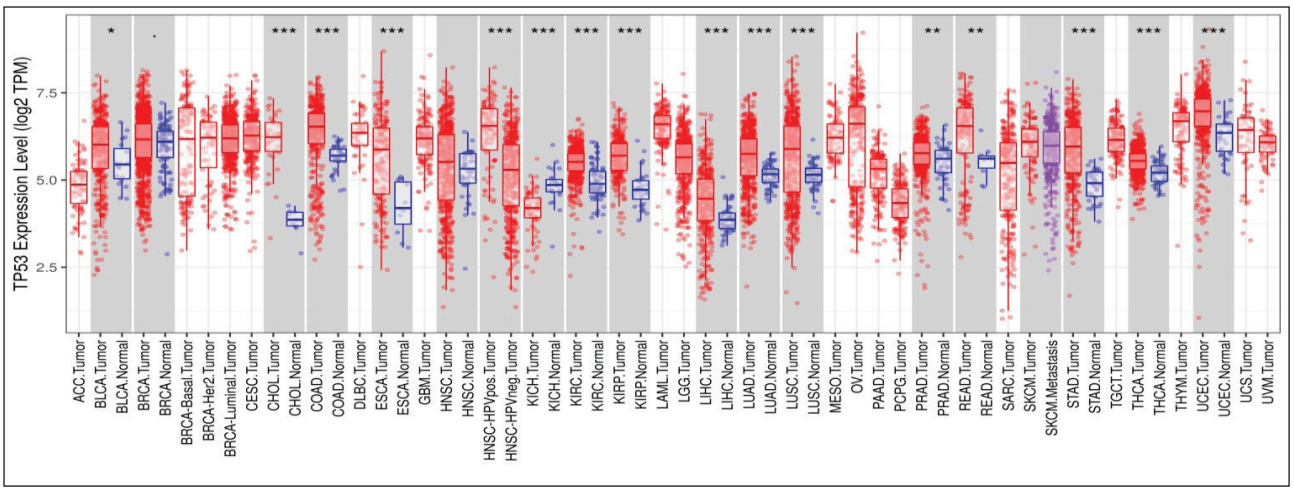

Fig. 1. *The general patterns of TP53 expression levels across various tissue and tumor types in tumors versus normal tissues.*

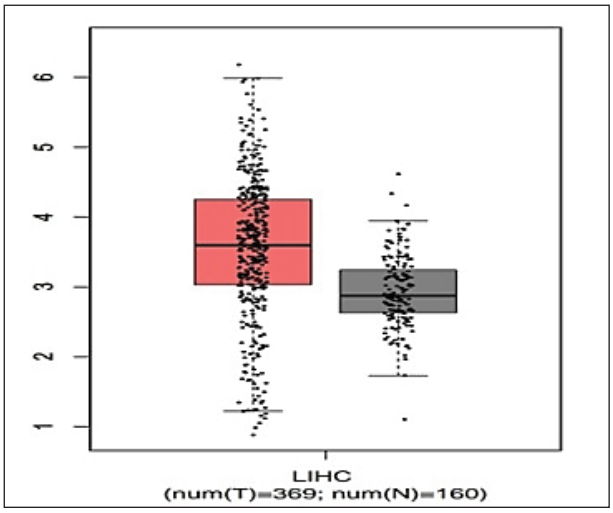

Fig. 2. *Expression of TP53 in LIHC using GEPPIA database.*

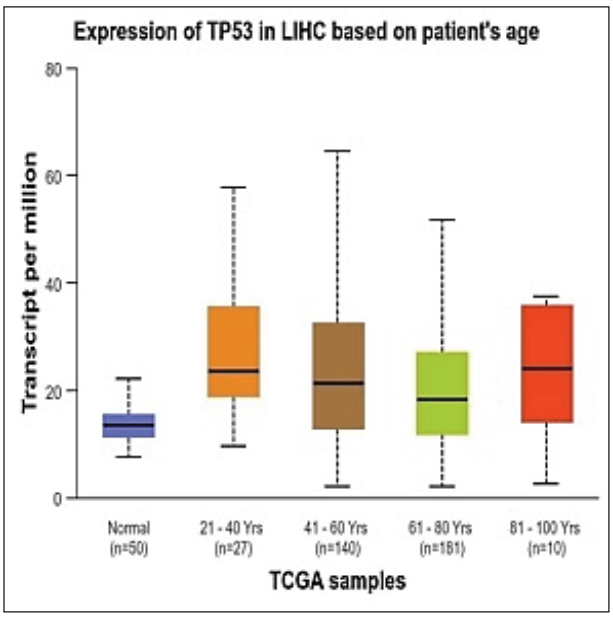

Fig. 4. *Distribution of TP53 expression across different patient age groups. Statistical significance is indicated as follows: p < 0.05, p < 0.01, *p < 0.001.*

The boxplot shows elevated TP53 expression in liver hepatocellular carcinoma (LIHC) compared to normal tissues, with levels increasing progressively across cancer stages (Stages 1-4). This highlights TP53's potential as a diagnostic biomarker and its utility in cancer staging and prognosis.

TP53 promoter methylation

The promoter methylation levels of *TP53* in LIHC samples were analyzed using TCGA data (Figure 7). Beta values, representing the degree of DNA methylation, ranged from 0.12 to 0.17. Normal samples (n = 50) exhibited Beta values tightly clustered around ~0.15, whereas primary tumor samples (n = 377) showed slightly lower and more variable Beta values (p = 0.048), indicating a trend towards TP53 promoter hypo-methylation in LIHC tumors.

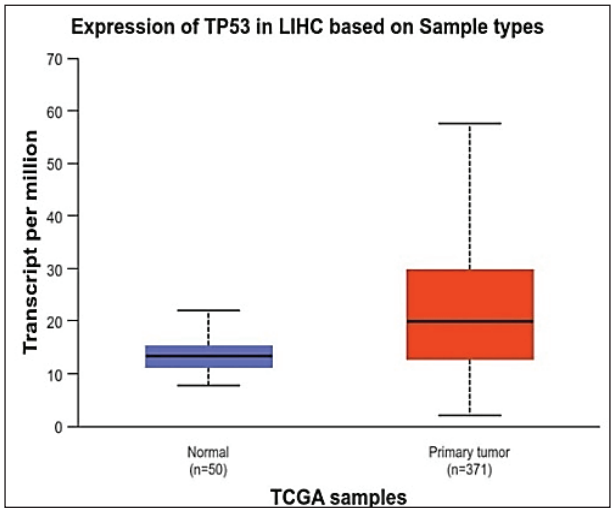

Fig. 3. *Boxplot depicts the expression levels of the TP53 gene in liver hepatocellular carcinoma (LIHC): Normal (n = 50) and Primary Tumor (n = 371) using the UALCAN database.*

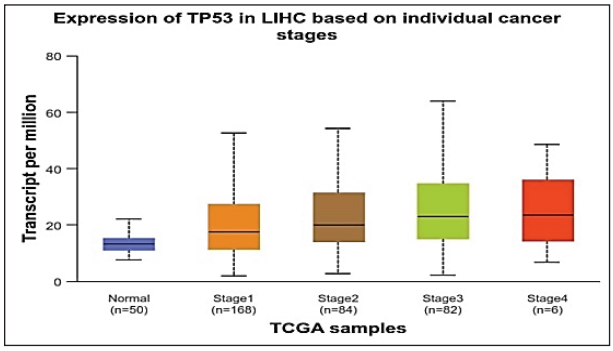

Fig. 5. *Distribution of TP53 expression across different patient cancer stages. Statistical significance is indicated as follows: p < 0.05, p < 0.01, *p < 0.001. (p = 0.024178).*

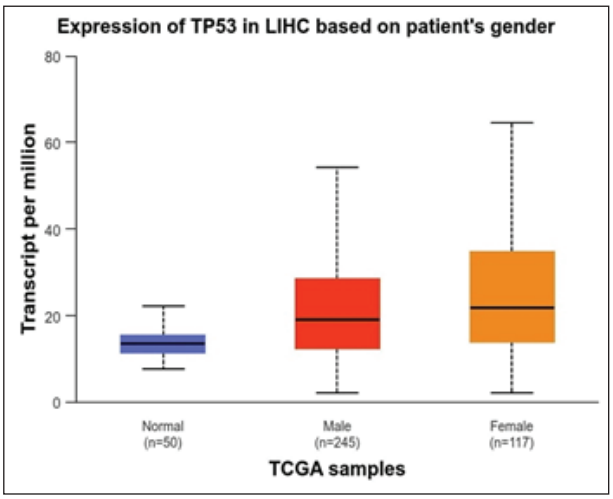

Fig. 6. *Distribution of TP53 expression across the patient gender. Statistical significance is indicated as follows: p < 0.05, p < 0.01, *p < 0.001. (p = 0.0126847).*

Validation of survival of TP53 in LIHC

The survival analysis results demonstrate that individuals with high TP53 expression (represented by the red curve)

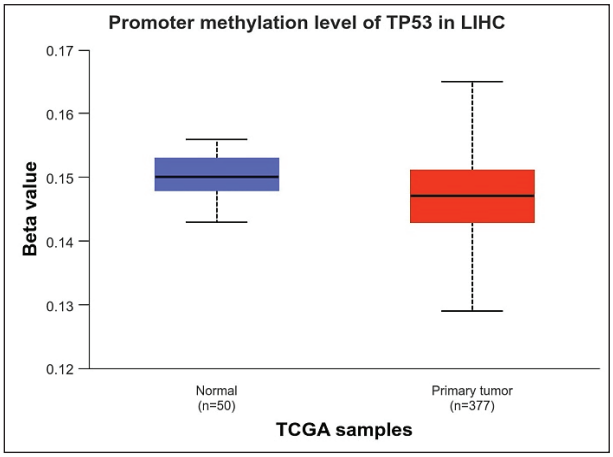

Fig. 7. *The boxplot displays the promoter methylation levels of TP53 in liver hepatocellular carcinoma (LIHC) samples based on TCGA data. The level of DNA methylation at specific CpG sites can be quantified using the Beta value, which ranges from 0 (un methylated) to 1 (fully methylated), Beta values ranging from 0.7 to 0.5 are indicative of hyper-methylation, and Beta values between 0.3 and 0.25 reflect hypo-methylation.*

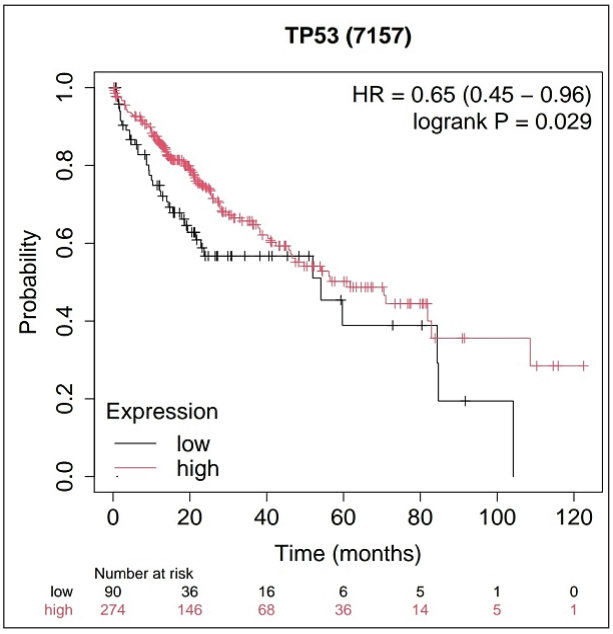

Fig. 8. *Kaplan-Meier survival analysis for patients with LIHC, comparing overall survival probabilities between groups with low and high TP53 expression levels over time (measured in months).*

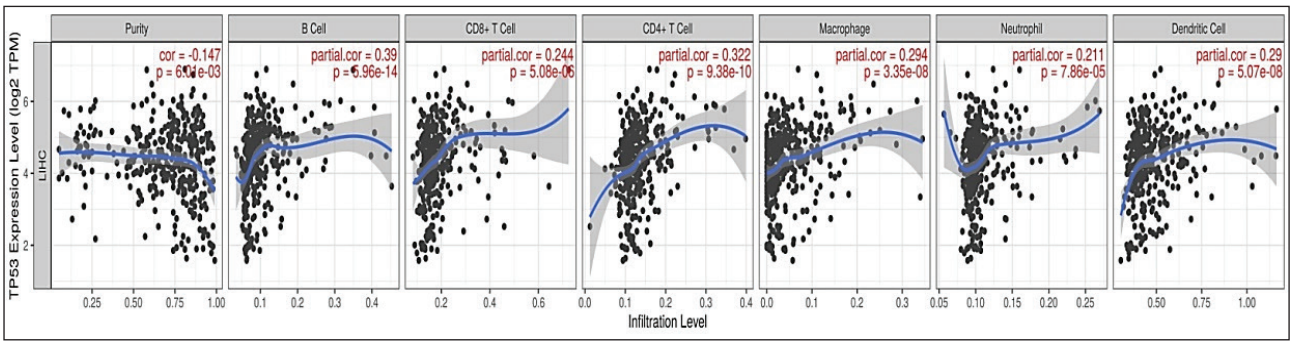

Fig. 9. *Association of TP53 Expression with Immune Cell Infiltration Levels (Macrophages, Neutrophils, Dendritic Cells, B Cells, CD8+ T Cells, and CD4+ T Cells) in LIHC Tumors Using TIMER Database Analysis, Including Correlation Coefficients and p-values.*

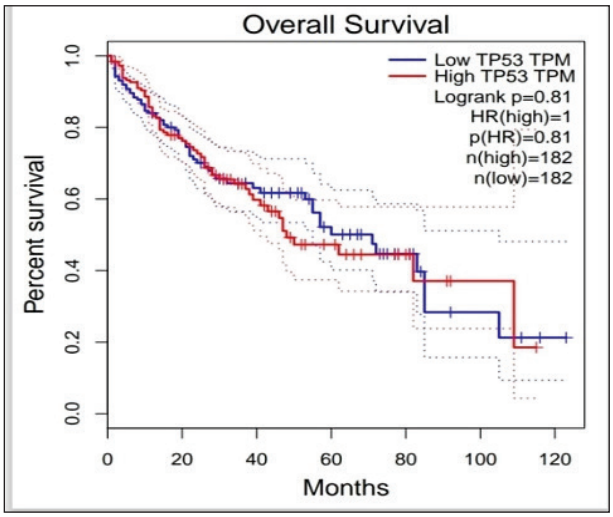

Fig. 10. *Correlation between TP53 expression levels and survival outcomes in LIHC patients based on GEPIA database analysis.*

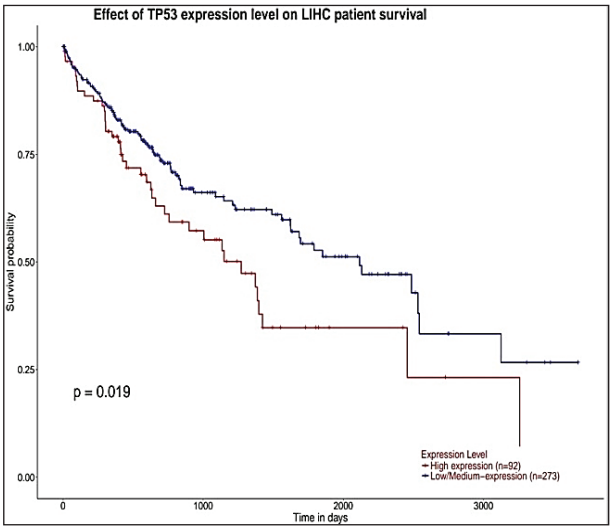

Fig. 11. *Correlation between TP53 expression levels and survival outcomes in LIHC patients using the UACLAN database.*

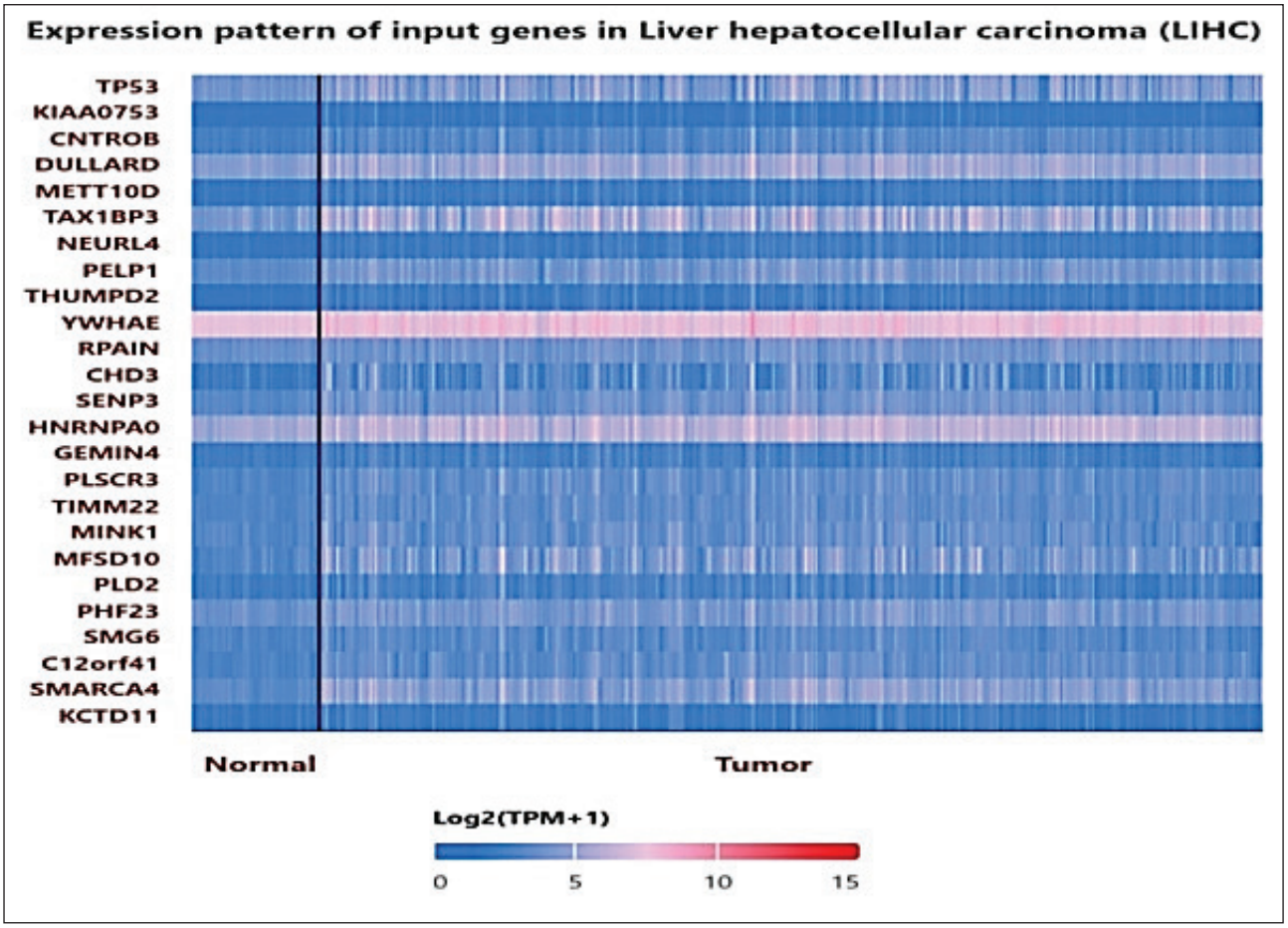

Fig. 12. *The expression patterns of specific genes positively correlated with TP53 in LIHC in Liver Hepatocellular Carcinoma (LIHC), comparing Normal tissues to Tumor tissues. The color scale represents the expression level of each gene. Using the UACLAN Database.*

generally have better survival outcomes compared to those with low TP53 expression (blue curve). This conclusion is supported by a HR of 0.65, indicating that high TP53 expression is associated with a 35% reduction in the risk of mortality. Furthermore, the statistically significant *p*-value of 0.029 underscores the reliability of this survival difference. The data suggest that TP53 expression levels are likely an important prognostic factor in this cohort, with high TP53 expression linked to improved patient survival (Figure 8).

TP53 correlation with immune cell abundance

The correlation between TP53 gene expression and immune cell infiltration in LIHC was examined using the TIMER database. The analysis included B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, dendritic cells, and tumor purity. The results showed statistically significant positive correlations between TP53 expression and infiltration of B cells (Cor. = 0.390, p = 0.0000000000000596), CD8+ T cells (Cor. = 0.243, p = 0.00000508), CD4+ T cells (Cor. = 0.322280493, p = 0.000000000938), macrophages (Cor. = 0.293, p = 0.0000000335), neutrophils (Cor. = 0.210, p = 0.0000786), and dendritic cells (Cor. = 0.290, p = 0.0000000507). In contrast, tumor purity showed a statistically significant negative correlation with TP53 expression (Cor. = -0.147, p = 0.006) (Figure 9).

Overall survival based on TP53 Gene expression levels

The association between TP53 expression and overall survival in LIHC patients was assessed using GEPIA and UALCAN databases. The analysis revealed that up-regulation of TP53 expression was significantly correlated with poorer prognosis in LIHC patients. GEPIA analysis showed a hazard ratio (HR) of 1, with a p HR of 0.81 (Figure 10), including 182 patients with high TP53 expression and 182 with low expression. UALCAN analysis supported this, with a significant p-value of 0.019, indicating that 92 patients with high TP53 expression had worse survival outcomes compared to 273 patients with low/medium expression (Figure 11).

Genes positively correlated and interacting with TP53 in LIHC

The heat map shows TP53 expression is relatively consistent but slightly higher in tumor tissues compared to normal tissues (Figure 12). TP53 is a known tumor suppressor gene, and its expression levels may correlate with tumor behavior or patient outcomes. The gene-

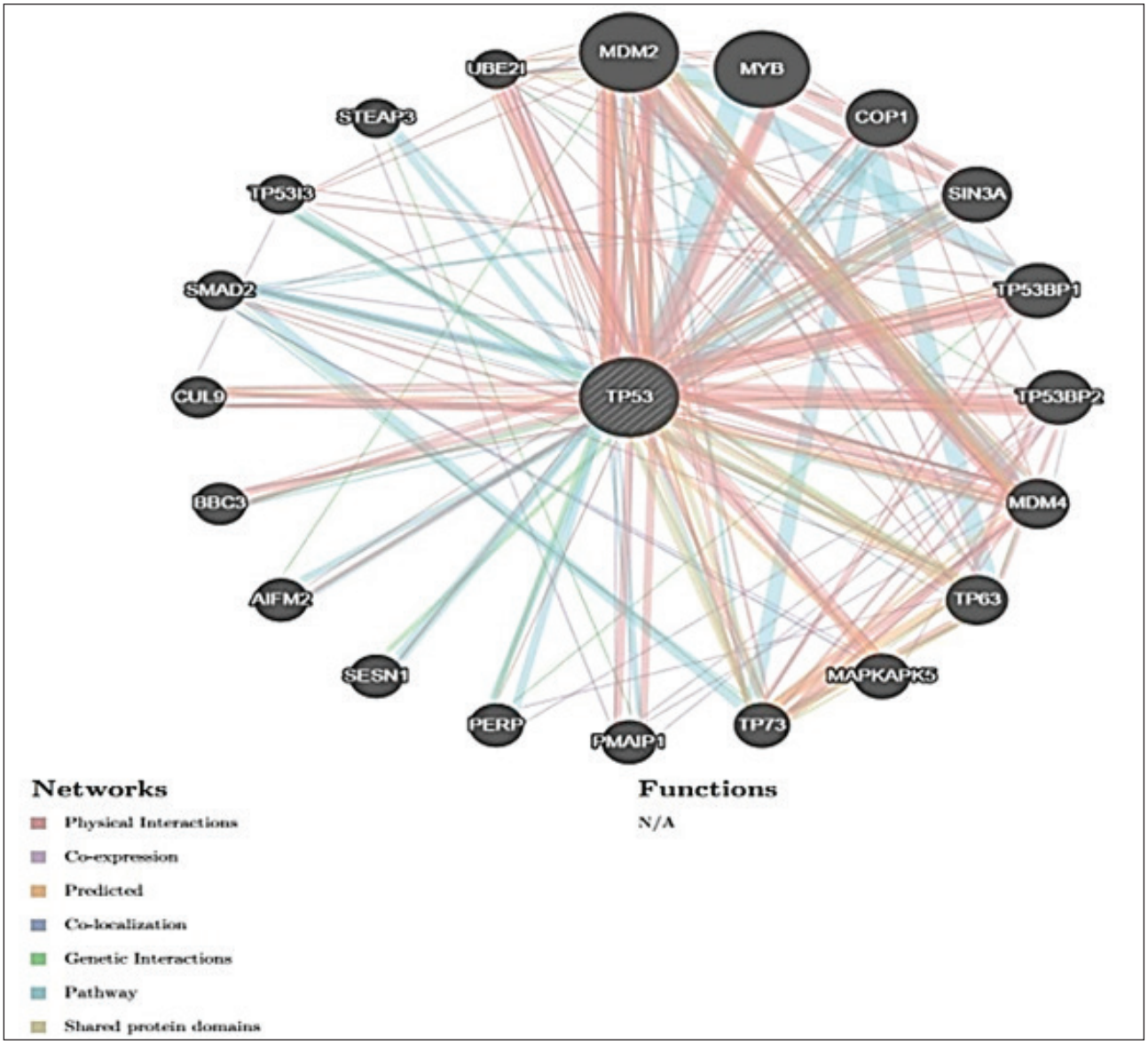

Fig. 13. *TP53 and other genes interaction network in LIHC Co-expression 68.64%, Physical interaction 30.19%, Predicted 1.11%, Shared protein domain0.05%, using the GeneMANIA database.*

gene interaction network focuses on TP53, showing its interactions with other related genes (Figure 13). TP53 is a central regulator of many critical cellular processes, especially in cancer, including apoptosis, DNA repair, and cell cycle arrest. Disruption of this network can promote cancer progression, making TP53 an essential diagnostic and therapeutic target in liver cancer studies.

Blue (0-5): Indicates low gene expression.

Pink/Red (10-15+): Indicates high gene expression.

Protein–protein interaction (PPI): The PPI network explores the functional relationships between proteins and identifies key molecules involved in liver cancer progression. The proteins have more interactions among themselves than expected by chance, suggesting they are biologically connected as a group. The PPI network was derived from the STRING database. The network has 31 nodes and 33 edges, with an average node degree of 2.13, an average local clustering coefficient of 0.388, and a PPI enrichment *p*-value of 1.78e-06.

cBioPortal and cross-validation of TP53 using ggplot

The cBioPortal analysis shows TP53 has both statistically significant and large magnitude of change, indicating its importance in LIHC. The volcano plot visualizes differentially expressed genes based on fold change and *p*-value. TP53 meets one or more significance thresholds and is a well-known tumor suppressor gene. There were 13 up-regulated genes and 5 down-regulated genes, with criteria of logfc > 1 and *p*-value < 0.05 (Figure 16).

Discussion

Our pan-cancer analysis reveals a striking overexpression of TP53 mRNA in LIHC, validated by TCGA, GEPIA, and UALCAN datasets. This raises an important question: does TP53 act as a classical tumor suppressor in LIHC, or might it adopt oncogenic roles, as reported in other cancers? The dual role of TP53 as a tumor suppression

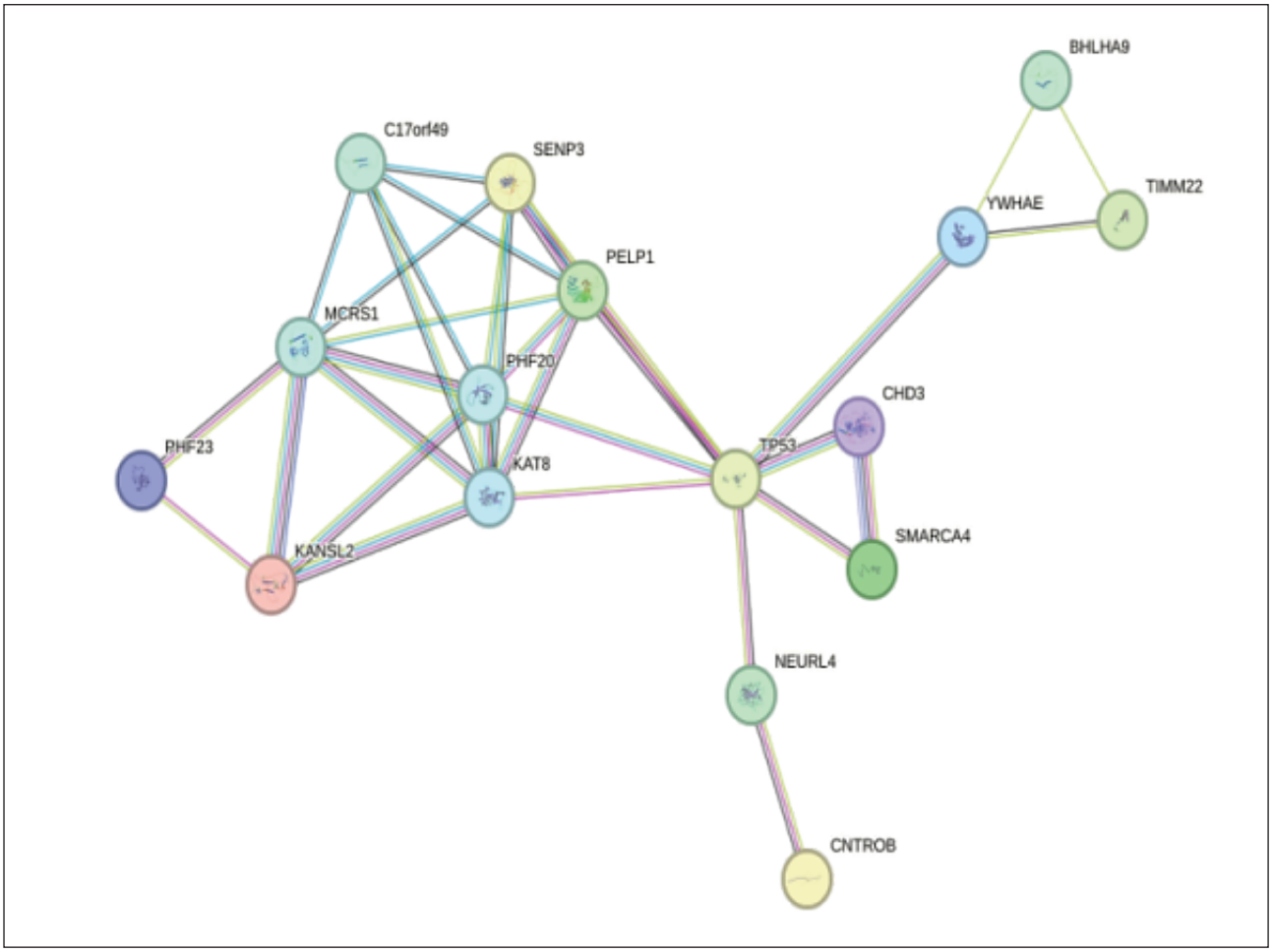

Fig. 14. *The protein–protein interaction (PPI) network, derived from analysis using the STRING database. Number of nodes: 31, number of edges: 33, average node degree: 2.13 avg. Local clustering coefficient: 0.388, expected number of edges: 13, PPI enrichment p-value: 1.78e-06 Using STRING database.*

In its wild-type form versus an oncogenic role when mutated is well-established and may be influenced in the liver by chronic inflammation, viral infections, and metabolic stress.

Notably, TP53 expression increased with advancing LIHC stage, indicating a role in disease progression and potential utility as a biomarker. This may be partially driven by promoter hypo-methylation observed in our analysis, which typically correlates with transcriptional up-regulation. However, the relationship between TP53 expression and methylation status warrants further mechanistic investigation.

The prognostic implications of TP53 in LIHC appear context-dependent and platform-specific. While Kaplan-Meier Plotter linked high TP53 expression to improved survival (HR = 0.65, $p = 0.029$), UALCAN and GEPIA associated it with poorer outcomes. These discrepancies likely arise from differing datasets, normalization methods, and cutoff strategies. Additionally, clinical heterogeneity and varying TP53 mutation statuses complicate interpretation.

Collectively, our findings emphasize the need for integrative multi-omic approaches that account for mutation type, tumor microenvironment, and immune context to clarify TP53's complex, stage-dependent function in LIHC. Its association with immune infiltration further underscores its relevance as both a prognostic marker and potential therapeutic target.

Study Limitations

Acknowledging the inherent challenges of large-scale bioinformatics investigations, this study primarily relies on publicly available TCGA and GEO datasets. While invaluable, these datasets may harbor inherent biases related to their initial collection, processing, and demographic representation, which could influence generalizability. Furthermore, our analysis of protein–protein interactions using STRING included parameters with lower confidence scores, necessitating cautious interpretation of these specific findings, as the underlying interactions may lack robust experimental validation (Figure 14).

A potential methodological limitation lies in the partial overlap of samples across different analytical platforms (e.g., TCGA-derived samples contributing to both GEPIA and UALCAN). While efficient, this overlap could inadvertently inflate perceived consistency or introduce redundancy in certain analytical outputs. More critically, patient cohort heterogeneity - encompassing

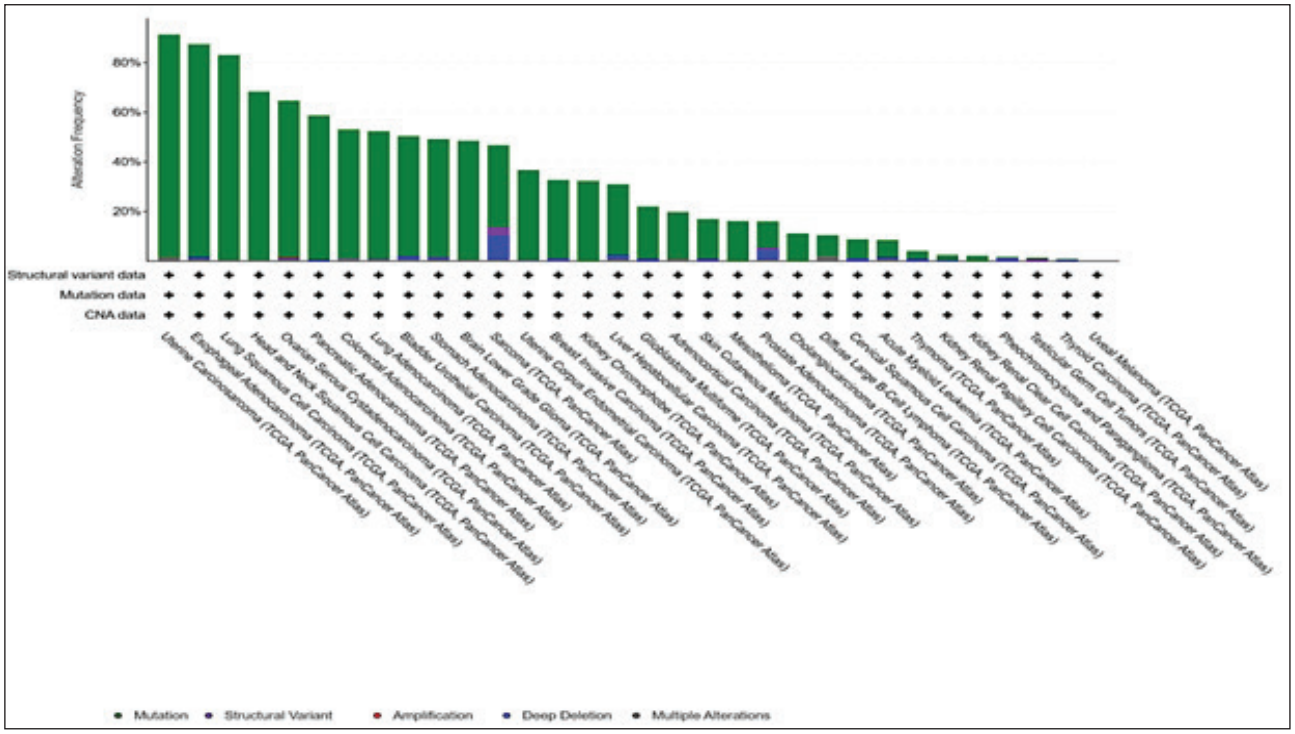

Fig. 15. *The frequency of various TP53 gene alterations across different cancer types.*

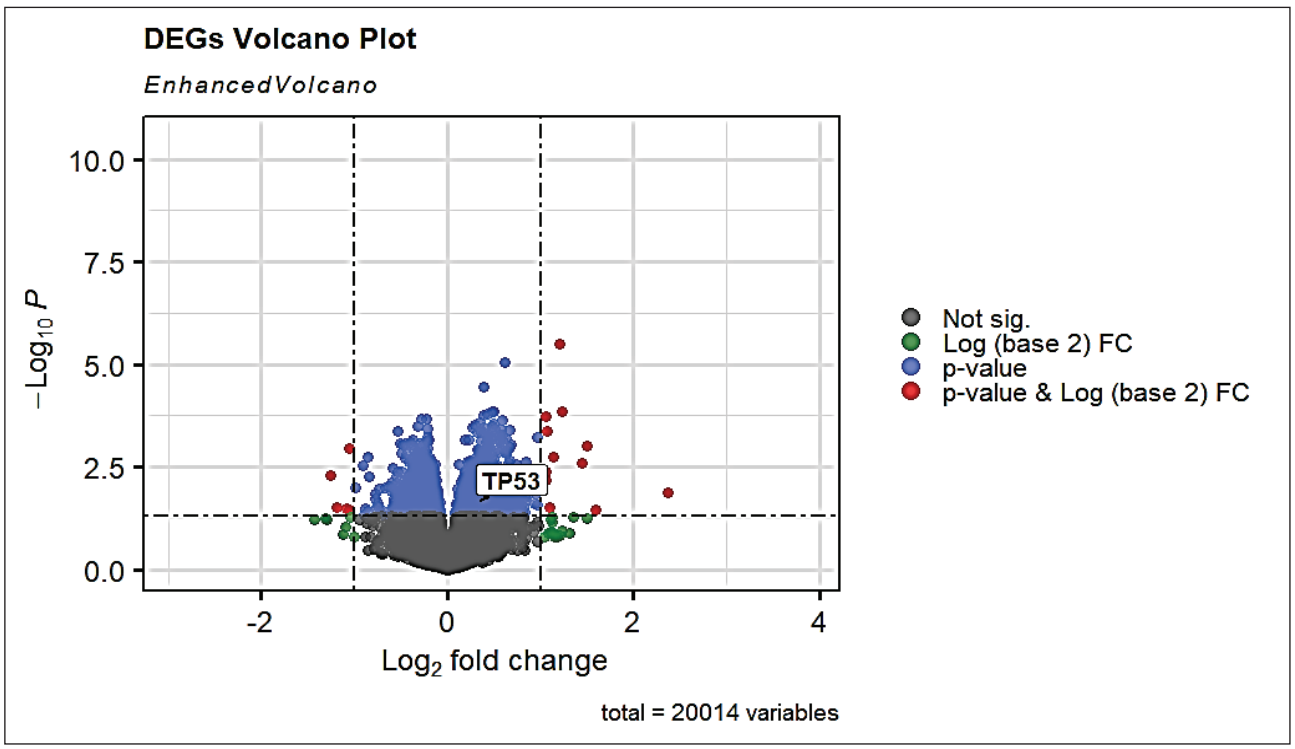

Fig. 16. *A volcano plot that visualizes the results of a differential gene expression analysis Up regulated: 13, down regulated: 5, criteria: logfc > 1 and p value < 0.05.*

variations in ethnicity, prior treatment history, underlying liver disease etiologies (e.g., HBV/HCV status), and the diverse sequencing platforms used - likely contributes significantly to the observed variability in gene expression and survival outcomes. These multifaceted factors are plausible contributors to the discrepancies identified between different analytical platforms and underscore the imperative for rigorous control and careful consideration of these variables in future multi-cohort validation studies (Figure 15).

Conclusion

In conclusion, this pan-cancer analysis highlights TP53 as a context-dependent player in LIHC, with elevated expression linked to disease progression and potentially

modulated by promoter hypo-methylation. Conflicting prognostic associations across platforms underscore the complexity of TP53's role, shaped by mutation status and tumor heterogeneity. These findings reinforce the need for integrative, mutation-aware approaches to define TP53's function and exploit its potential as a biomarker and therapeutic target in liver cancer.

List of Abbreviations

B cells	B lymphocytes
BLCA	Bladder Urothelial Carcinoma
CBioPortal	Cancer Genomics Portal
$CD4^+$	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CHOL	Cholangiocarcinoma
COAD	Colon Adenocarcinoma
DEGs	Differentially Expressed Genes
DNA	Deoxyribonucleic Acid
ESCA	Esophageal Carcinoma
FC	Fold Change
GeneMANIA	Gene Function Prediction Tool
GEO	Gene Expression Omnibus
GEO2R	GEO Online Analysis Tool for Differential Expression
GEPIA	Gene Expression Profiling Interactive Analysis
ggplot	Data Visualization Package in R
GSE101685/ GSE138178	GEO Dataset 101685/ GEO Dataset 138178
GTEx	Genotype-Tissue Expression Project
HNSC	Head and Neck Squamous Cell Carcinoma
HNSC-HPV	HPV-negative Head and Neck Squamous Cell Carcinoma
HR	Hazard Ratio
KICH	Kidney Chromophobe
KIRC	Kidney Renal Clear Cell Carcinoma
LIHC	Liver Hepatocellular Carcinoma
LUAD	Lung Adenocarcinoma
LUSC	Lung Squamous Cell Carcinoma
mRNA	Messenger Ribonucleic Acid
N	Normal Samples
OS	Overall Survival
pG	Cytosine-phosphate-Guanine site
PPI	Protein–Protein Interaction
PRAD	Prostate Adenocarcinoma
READ	Rectum Adenocarcinoma
RNA-seq	RNA Sequencing
SKCM	Skin Cutaneous Melanoma
STAD	Stomach Adenocarcinoma
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
T	Tumor Samples
TCGA	The Cancer Genome Atlas
THCA	Thyroid Carcinoma
TIMER	Tumor Immune Estimation Resource
TP53	Tumor Protein P53
UALCAN	UALCAN Online Cancer Data Analysis Tool
UCEC	Uterine Corpus Endometrial Carcinoma.

Conflict of interest

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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None.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Ethical approval

Given the use of publicly available, de-identified datasets (TCGA and GEO), formal ethical approval was not required.

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