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ILLUMINATING THE ROLE OF TP53 IN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) USING INTEGRATED BIOINFORMATICS METHODOLOGY

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Abstract

In this study, we investigated the expression pattern, promoter methylation pattern, and diagnostic significance of TP53 in acute lymphoblastic leukemia (ALL) through a multi-faceted bioinformatics approach. Utilizing the GSE48558 dataset from the GEO database, we observed a significant down-regulation of TP53 mRNA expression in ALL samples compared to normal controls (P value < 0.05). ROC curve analysis further demonstrated TP53's robust discriminatory power, highlighting its promise as a diagnostic marker for ALL. Subsequent investigation using the UALCAN database revealed consistent TP53 expression patterns across different races and genders of ALL patients, with no significant differences observed (P values > 0.05). Additionally, promoter methylation analysis indicated a slight elevation in TP53 promoter methylation levels in African-American and Asian ALL patients compared to Caucasians, although these differences were not significant (P value > 0.05). Survival analysis using the KM plotter tool revealed that low TP53 expression correlated with poorer overall survival (OS) among ALL patients (P value < 0.05), suggesting its potential as a prognostic biomarker. Our findings underscore the diagnostic and prognostic significance of TP53 in ALL, providing valuable insights for future research and clinical interventions. These results emphasize the importance of TP53 in guiding therapeutic strategies and improving outcomes for ALL patients.

Keywords: TP53: ALL: Cancer: Biomarker: Treatment

Introduction

Comprising a cluster of aggressive aberrant hematopoietic malignancies such as acute/chronic lymphoblastic leukemia (ALL/CLL) and lymphoma, acute lymphoblastic leukemia (ALL) poses significant challenges in treatment (1-3). Despite advancements in therapeutic approaches leading to improved clinical outcomes for many patients, a subset still experiences resistance to single or multiple chemotherapeutic agents, often resulting in relapse or refractory disease with a grim prognosis (4-6). Additionally, the overall survival rates for ALL patients remain notably low. Given these clinical realities, there exists a pressing need to delve into the underlying mechanisms of ALL pathogenesis. Doing so holds the promise of elucidating novel insights that could inform more effective strategies for disease management, thereby enhancing patient outcomes.

Tumor Protein 53 (TP53), a tumor suppressor gene located on chromosome 17, is well recognized for its crucial role in maintaining genomic stability and regulating cell cycle progression (7, 8). In ALL, TP53 alterations have emerged as significant determinants of disease progression and treatment outcome (9, 10). TP53 dysregulation and mutations are frequently observed in ALL patients, particularly in those with high-risk disease subtypes or relapsed/refractory cases. These genetic aberrations in TP53 disrupt its tumor suppressor function, leading to the dysregulation of critical cellular processes such as cell cycle arrest, apoptosis, and DNA repair (11). Consequently, leukemic cells harboring TP53 abnormalities acquire a proliferative advantage, evade apoptosis, and exhibit enhanced resistance to chemotherapy, contributing to disease aggressiveness and treatment failure (12). Moreover, TP53 alterations have been associated with adverse clinical features, including increased relapse rates, poorer response to therapy, and inferior overall survival outcomes in ALL patients. Therefore, understanding the role of TP53 in ALL pathogenesis is paramount for the development of novel therapeutic strategies aimed at targeting this molecular aberration and improving clinical outcomes for patients with this aggressive hematologic malignancy.

In recent years, the advent of high-throughput sequencing and microarray technologies has led to the generation of vast amounts of bioinformatics data from human disease samples. This wealth of data has significantly advanced our understanding of the molecular mechanisms underlying various biological processes. In our study, we capitalized on this wealth of information by integrating datasets from the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) to investigate multi-omics level variations in the TP53 gene. Moreover, our findings hold the potential to uncover novel treatment opportunities and therapeutic targets for ALL, offering hope for improved clinical outcomes in patients affected by this challenging disease.

Methodology

Dataset retrieval and expression analysis of TP53 using Bioinformatics tools

The GEO database serves as a vital repository for high-throughput gene expression data, encompassing a wide array of biological samples across various species (13). It provides researchers with access to a wealth of publicly available datasets generated from microarray and next-generation sequencing experiments. By enabling the storage, sharing, and analysis of these datasets, GEO facilitates collaborative research efforts and fosters the discovery of new insights into gene expression patterns, regulatory networks, and disease mechanisms.

In this study, for the mRNA gene expression, we selected the GSE48558 dataset from GEO database, containing 13 ALL patient samples and 17 normal samples. GEO2R (14) was used to compare the gene expressions of TP53 between ALL sample group and control sample group. Benjamini & Hochberg method was used to adjust the p-value. A p-value < 0.05 was considered significant.

Receiver Operating Characteristic (ROC) curve analysis

To evaluate the diagnostic significance of TP53, ROC curve analysis was employed. The Area Under Curve (AUC) values were interpreted to assess the efficacy of TP53 as a diagnostic biomarker. AUC values ranging between 0.7 and 0.8 were considered reasonable, indicating

moderate diagnostic accuracy. AUC values falling within the range of 0.8–0.9 were deemed good, suggesting TP53's potential as a robust biomarker. Furthermore, AUC values exceeding 0.9 indicated TP53's exceptional diagnostic utility, highlighting its unique role as a biomarker. Statistical significance was determined by a p-value less than 0.05, ensuring the reliability of the analysis results.

UALCAN database analysis

UALCAN is a widely utilized and user-friendly online platform designed for cancer research. It offers comprehensive analysis tools to explore cancer-related data from The Cancer Genome Atlas (TCGA) database (15). Researchers can conveniently access and analyze gene expression, DNA methylation, protein expression, and patient survival data across various cancer types. UALCAN enables users to compare gene expression profiles between tumor and normal tissues, as well as stratify data based on clinical parameters such as patient demographics and cancer stages. Its intuitive interface and extensive data visualization features make it an invaluable resource for cancer biologists and clinicians alike. In the present study, UALCAN was used analyze the expression and promoter methylation pattern of TP53 in ALL patients of different clinical variables.

Survival analysis

The KM plotter tool is a web-based platform widely utilized in cancer research for survival analysis. It integrates gene expression data with clinical information from a multitude of cancer patients to generate Kaplan-Meier survival plots (16). Researchers can input their gene of interest and specify parameters such as cancer type, patient cohort, and clinical characteristics to explore the association between gene expression levels and patient survival outcomes. In the present study, KM plotter was used to perform the survival analysis of TP53.

Statistical analysis

Statistical comparisons between different groups were made using t-test. A p-value < 0.05 was referenced as statistically significant.

Results

Datasets retrieval and expression analysis of TP53 using Bioinformatics tools

In the initial phase of our investigation, we obtained the GSE48558 dataset from GEO database to delve into the expression patterns of TP53 using bioinformatics tools. This dataset comprised a total of 13 samples from patients diagnosed with ALL and 17 samples from individuals without the condition, serving as normal controls. Through comprehensive analysis facilitated by GEO2R, we observed a statistically significant (P value < 0.05) down-regulation of TP53 mRNA expression in the ALL samples compared to the normal controls (Figure 1).

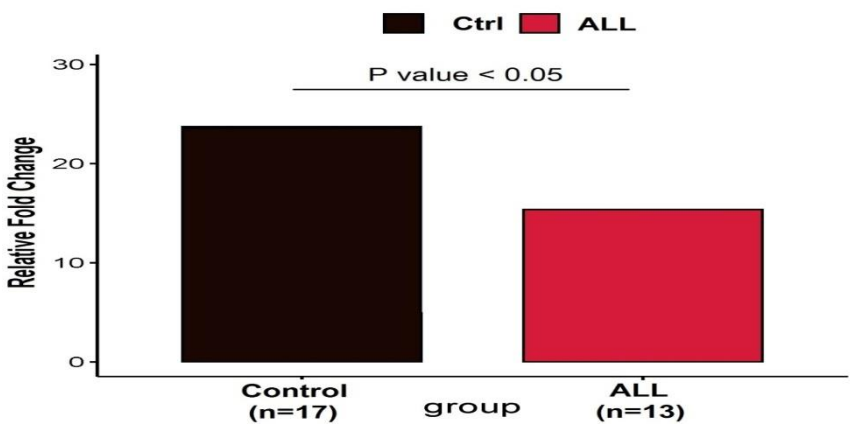

Figure 1: Expression pattern of TP53 across control and ALL samples in GSE48558 dataset. P value < 0.05.

Furthermore, to assess the diagnostic utility of TP53 in distinguishing ALL patients from healthy individuals, we conducted ROC curve analysis. The results of this analysis revealed that the down-regulated expression of TP53 exhibited robust discriminatory power, further highlighting its potential as a promising diagnostic marker for ALL (Figure 2).

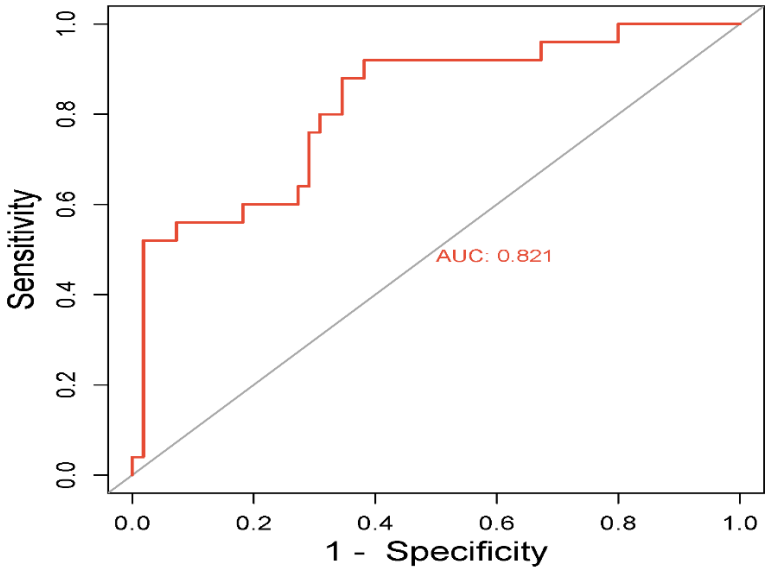

Figure 2: ROC of TP53 expression based on the data taken from the GSE48558 dataset. P value < 0.05.

Correlation of TP53 gene expression with clinical variables of ALL

Next, we investigated the expression of TP53 among ALL patients categorized by various races (Caucasian, African-American, and Asian) and genders (Male and female) using the UALCAN database. The analysis revealed consistent TP53 expression patterns across different clinical variables, with no significant differences (p-values > 0.05) observed (refer to Figure 4 and Figure5).

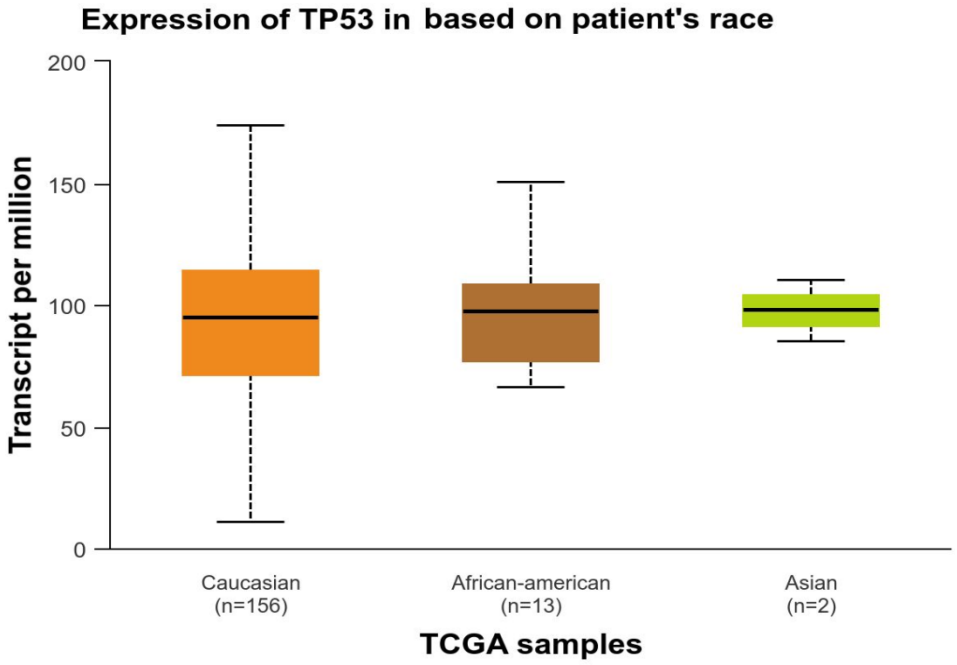

Figure 4: Expression pattern of TP53 in ALL patients based on different races. P value < 0.05.

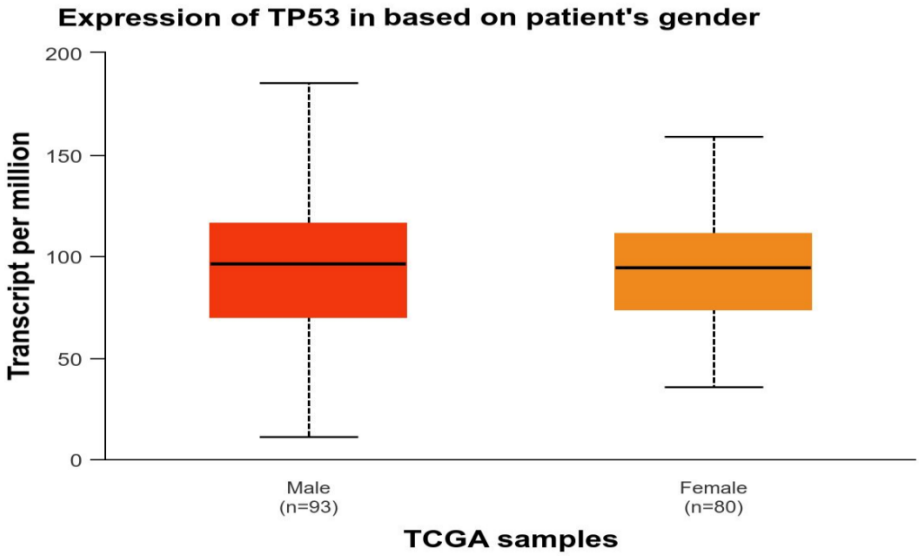

Figure 5: Expression pattern of TP53 in ALL patients based on different genders. P value < 0.05.

Promoter methylation analysis of TP53 in ALL patients

Promoter methylation plays a pivotal role in gene expression dysregulation. Consequently, we proceeded to assess the expression of TP53 in ALL patients from diverse racial backgrounds using the UALCAN database. Our findings revealed that the promoter methylation level of TP53 exhibited a slight elevation in African-American and Asian ALL patients compared to Caucasian patients. However, statistical analysis indicated that these differences were not significant (p-value > 0.05) (refer to Figure 6).

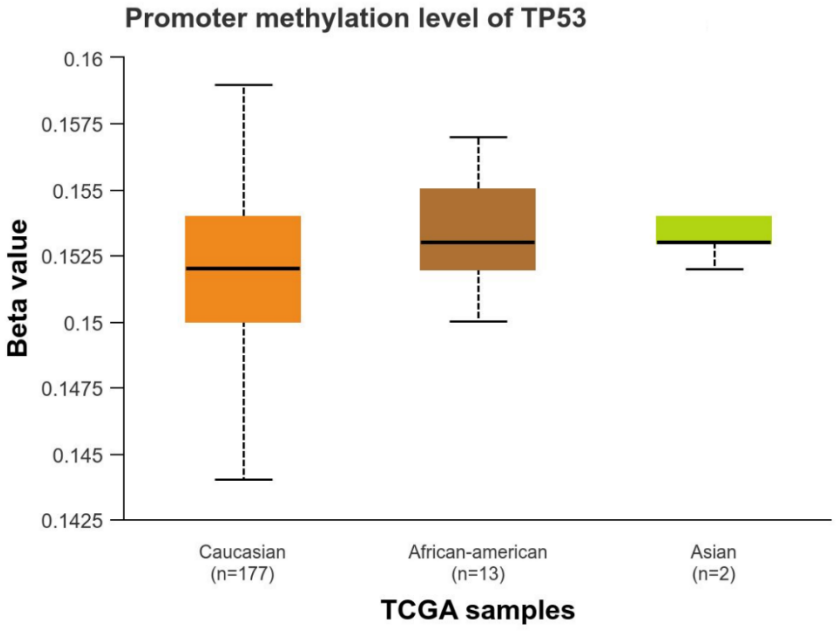

Figure 6: Promoter methylation level of TP53 in ALL patients of different races. P value < 0.05.

Survival analysis of TP53

Subsequently, we conducted survival analysis of TP53 based on gene expression levels using the KM plotter tool to assess its prognostic significance. ALL sample data available on the KM plotter platform was stratified into high and low expression groups based on the median mRNA level of TP53. Our findings revealed that low expression of TP53 correlated with poorer overall survival

(OS) among ALL patients (Figure 7). These results suggest that TP53 may serve as a potential prognostic biomarker for predicting outcomes in ALL patients. This highlights the importance of TP53 in the prognosis and management of ALL, offering valuable insights for future research and clinical interventions.

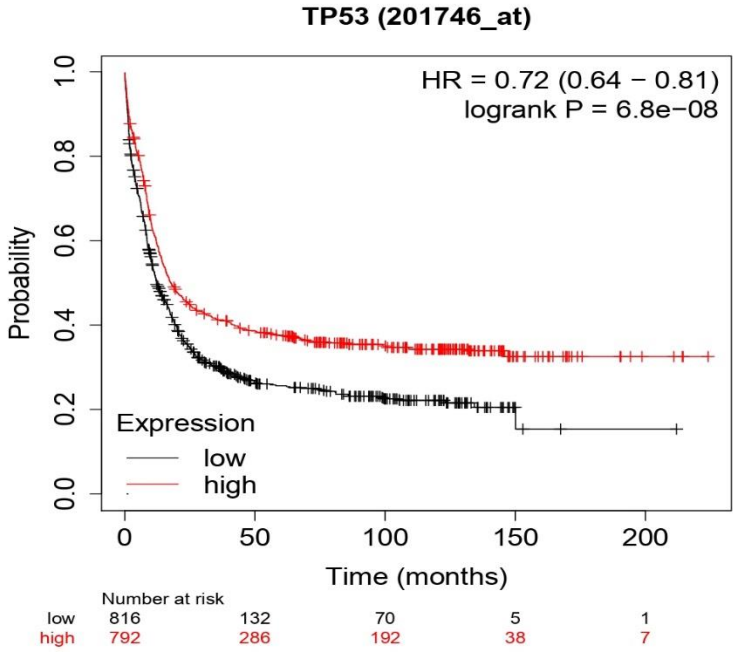

Figure 7: KM survival curve of TP53 in ALL patients. P value < 0.05.

Discussion

Acute lymphoblastic leukemia (ALL) continues to pose significant challenges due to its high recurrence rate and poor prognosis (17-21). Therefore, gaining insights into the regulatory mechanisms underlying ALL could offer valuable perspectives for enhancing both diagnosis and treatment strategies. The present study aimed to investigate the expression patterns and diagnostic significance of TP53 in ALL through a combination of bioinformatics analysis and experimental validation. Our findings underscore the potential role of TP53 as a diagnostic and prognostic marker in ALL, shedding light on its clinical implications and therapeutic relevance.

Our GEO expression dataset GSE48558 based findings revealed a significant down-regulation of TP53 mRNA expression in ALL samples compared to normal controls. This observation is consistent with previous studies implicating TP53 dysregulation in various cancers, including breast and colorectal cancers (22-25). The down-regulation of TP53 can significantly contribute to cancer development through various mechanisms. TP53 plays a crucial role in maintaining genomic stability by regulating cell cycle progression, DNA repair, apoptosis, and senescence (26). When TP53 expression is reduced or lost, cells may become more prone to genetic mutations and genomic instability, increasing the risk of malignant transformation (27, 28). Additionally, TP53 down-regulation can lead to the evasion of apoptosis, allowing cancer cells to survive and proliferate uncontrollably. Moreover, TP53 deficiency may impair DNA damage response pathways, rendering cells less capable of repairing DNA lesions induced by carcinogenic insults (29, 30). This can further exacerbate genomic instability and contribute to tumor progression. Furthermore, TP53 down-regulation has been associated with increased resistance to chemotherapy and radiation therapy, leading to treatment failure and disease recurrence in cancer patients (31). Overall, the loss or down-regulation of TP53 function represents a critical event in cancer development and progression, highlighting its significance as a potential therapeutic target and prognostic marker in various malignancies.

The correlation between TP53 gene expression and clinical variables in ALL was further investigated in this study. Analysis of TP53 expression across different races and genders of ALL patients using the UALCAN database revealed consistent expression patterns with no significant differences observed. Despite variations in racial backgrounds and genders, TP53 expression remained stable across these clinical variables, suggesting that race and gender may not significantly influence TP53 expression levels in ALL. Furthermore, promoter methylation analysis showed a slight elevation in TP53 promoter methylation levels in African-American and Asian ALL patients compared to Caucasians, although these differences were not statistically significant. These findings suggest uniformity in TP53 expression across diverse patient demographics in ALL, emphasizing its potential as a consistent biomarker regardless of race or gender.

Further analysis using ROC curve analysis demonstrated that the down-regulated expression of TP53 exhibited robust discriminatory power, suggesting its potential as a diagnostic marker for ALL. Early and accurate diagnosis of ALL is crucial for timely intervention and improved patient outcomes. The identification of reliable diagnostic biomarkers can aid in distinguishing ALL patients from healthy individuals, facilitating prompt treatment initiation and disease management. Our findings suggest that TP53 may serve as a promising diagnostic tool for identifying ALL patients, providing valuable insights for clinical practice.

Survival analysis based on gene expression levels using the KM plotter tool revealed that low expression of TP53 correlated with poorer overall survival among ALL patients. This finding highlights the potential prognostic significance of TP53 in predicting outcomes and guiding treatment decisions in ALL. Patients with low TP53 expression may have a worse prognosis and may require more aggressive therapeutic interventions. The identification of prognostic biomarkers can help stratify patients based on risk profiles, enabling personalized treatment approaches and improved patient management. Our findings are also consistent with previous studies, highlighting prognostic role of TP53 in ALL (32-37).

Overall, our study highlights the diagnostic and prognostic significance of TP53 in ALL and offers valuable insights for its clinical application. TP53 may serve as a promising biomarker for identifying ALL patients and predicting outcomes, facilitating early detection and personalized treatment strategies. Future research efforts should focus on elucidating the underlying molecular mechanisms governing TP53 dysregulation in ALL and exploring its therapeutic potential in preclinical and clinical settings. Additionally, large-scale prospective studies are warranted to validate the clinical utility of TP53 as a diagnostic and prognostic marker in ALL, paving the way for improved patient care and management strategies.

Conclusion

In conclusion, our study comprehensively investigated the expression patterns and prognostic significance of TP53 ALL. Through bioinformatics analysis of publicly available datasets analysis, we demonstrated a significant down-regulation of TP53 mRNA expression in ALL compared to normal controls. Furthermore, our findings highlighted the diagnostic potential of TP53, as evidenced by robust discriminatory power in distinguishing ALL patients from healthy individuals. Additionally, survival analysis revealed that low expression of TP53 was associated with poorer overall survival among ALL patients, suggesting its potential as a prognostic biomarker in this malignancy. Overall, our study provides valuable insights into the role of TP53 in ALL, offering potential avenues for further research and clinical interventions aimed at improving diagnosis, prognosis, and treatment outcomes in patients with this aggressive hematologic malignancy.

Conflict of interest

None

Acknowledgement

None

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