

Investigation of CDH3 as a Diagnostic and Prognostic Biomarker in Lung Adenocarcinoma: An Integrative Analysis of Gene Expression, Promoter Methylation, and Clinical Significance

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DOI: <https://doi.org/10.46382/mjb.2026.10309>

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Article Received: 12 July 2026

Article Accepted: 19 September 2026

Article Published: 23 September 2026

ABSTRACT

Background: LUAD constitutes the most prevalent type of lung cancer and one of the major causes of death due to malignancies worldwide. Identification of reliable molecular biomarkers will be crucial to improve diagnosis, prognosis and therapy for this disease.

Objectives: This study will analyze the role of CDH3 gene expression in LUAD as a potentially useful diagnostic and prognostic biomarker using an integrated bioinformatic approach focusing on gene expression, promoter methylation, clinicopathological characteristics, survival outcomes and its correlation with MAP7D1.

Methods: Datasets from publicly available transcriptomic and clinical databases will be employed for the analysis of CDH3 gene expression in different types of cancers and in LUAD in particular. Different expression analyses will compare CDH3 expression levels in tumor vs normal lung tissue samples, whereas subgroup analyses will investigate relationships with demographic and clinicopathological features. Analysis of promoter methylation will address any possible epigenetic regulation of CDH3 expression. Survival analyses will be performed to test the prognostic value of CDH3 expression levels. Finally, correlation analyses will explore the association between CDH3 and MAP7D1 gene expression in LUAD tumors.

Results: Overexpression of CDH3 was found in LUAD in comparison with normal lung tissues. High CDH3 expression levels were associated with several clinicopathological and demographic features, including tumor stage, nodal metastasis, tumor subtype and TP53 mutation status. Analysis of promoter methylation pointed at a possible role of the epigenetic regulation of CDH3 in LUAD. Survival analysis highlighted a negative association between CDH3 expression levels and survival in LUAD patients, which was significantly different across gender, race and smoking status subgroups. Moreover, CDH3 expression in LUAD was positively correlated with MAP7D1 expression.

Conclusion: The integrative analysis suggests that CDH3 is a good biomarker for diagnosis and prognosis of lung adenocarcinoma. The abnormal expression of CDH3, the connection with clinical features, the interaction with methylation of the promoter region and the correlation with MAP7D1 altogether highlight its potential importance. Further researches are needed to confirm CDH3 as a treatment target.

Keywords: Bioinformatics; Biomarker; CDH3; Gene Expression; Lung Adenocarcinoma; MAP7D1; Promoter Methylation; Prognosis; Survival Analysis; TCGA; UALCAN.

1.0. Introduction

Despite recent advances in targeted therapy and immunotherapy, lung cancer continues to be the leading cause of cancer-related mortality around the globe. In 2022, there were around 2.5 million newly diagnosed cases of lung cancer, with 1.8 million people dying from it. Histologically, lung adenocarcinoma (LUAD) accounts for the highest proportion of non-small cell lung cancer (NSCLC), with almost 40% of all lung cancer being diagnosed as LUAD [1]. The survival rate at five years for LUAD with metastasis and/or resistance to therapy is relatively low because of late diagnosis, heterogeneity of tumor cells, metastasis development, and drug-resistance [2]. For this reason, the discovery of efficient biomarkers of LUAD is highly relevant for its treatment.

Cadherins belong to a group of calcium-binding transmembrane proteins responsible for the establishment and maintenance of cell-to-cell junctions and adhesions. The alterations in the functioning of any cadherin can promote epithelial to mesenchymal transition (EMT), invasiveness, metastasis, and acquired resistance to anti-tumor therapy [3]. Among cadherins, Cadherin-3 (CDH3) or P-cadherin has attracted much interest due to its connection

with the progression and metastasis of tumors. In addition to its functional role, CDH3 regulates a number of pro-oncogenic signaling pathways, namely Wnt/ β -catenin, EGFR, PI3K/AKT, and Rho GTPase signaling pathway and promotes the proliferation and metastasis, as well as increases the stemness of cells [4].

It has been demonstrated that the overexpression of CDH3 occurs in many types of cancer such as breast, colorectal, gastric, pancreatic, ovarian, thyroid, and lung cancers. The overexpression of CDH3 is often related to the development of aggressive clinical features and poor prognosis [5]. Current studies showed that CDH3 was highly overexpressed in LUAD tissues when compared with adjacent non-tumor lung tissues and associated with poor overall survival, increased tumorigenesis, inflammation, hypoxia, glycolysis, and immune-cell infiltration. Functional experiments also revealed that depletion of CDH3 inhibited the proliferation, migration, and invasion of LUAD cells, suggesting the involvement of CDH3 in the development of LUAD [6].

It has been also found that CDH3 plays a vital role in the regulation of ferroptosis in LUAD. USP8 facilitates the stabilization of CDH3 and blocks ferroptosis, leading to increased tumor growth and malignant behavior [7]. Thus, it can be assumed that CDH3 can become an attractive therapeutic target in cancer treatment based on the mechanism of ferroptosis. Circulating soluble CDH3 has also been suggested as a new marker of EGFR-TKIs-resistance monitoring in LUAD [8].

Besides genetic changes, epigenetic modifications like promoter DNA methylation have vital functions in the regulation of gene expression in carcinogenesis. Altered promoter methylation can either activate oncogenes or inhibit tumor suppressors, thus affecting tumor initiation, progression, metastasis, and patient prognosis [9]. Despite the existing information about altered promoter methylation of CDH3 in many cancers, the impact of CDH3 promoter methylation on the levels of CDH3 expression and prognosis in LUAD is poorly understood. Likewise, there is insufficient research on the interaction of CDH3 and other genes, which may participate in the progression of LUAD, namely, MAP7D1 [10].

Therefore, this study employed an integrated bioinformatics analysis approach to elucidate the diagnostic and prognostic importance of CDH3 in LUAD. CDH3 expression was estimated in cancers and normal vs. tumor tissues, CDH3 expression correlations with clinicodemographic and clinicopathological variables were analyzed, CDH3 promoter methylation was examined, overall survival was analyzed, and a correlation between CDH3 and MAP7D1 gene expression was found. In sum, the results of these analyses provide valuable insights regarding the clinical and biological importance of CDH3 and indicate its applicability for LUAD diagnosis and therapy.

1.1. Study Objectives

In this study, the diagnostic and prognostic implications of CDH3 in LUAD were comprehensively evaluated using a comprehensive bioinformatics approach. The objectives of this study were as follows:

- To determine the expression pattern of CDH3 in different types of human cancers and to compare the expression level of CDH3 in normal lung and LUAD samples.
- To study the correlation between CDH3 expression and the clinicodemographic characteristics of LUAD, such as sex, age, race, and smoking.

- To investigate the correlation between CDH3 expression and the clinicopathological factors, which include pathological tumor stage, nodal metastasis, LUAD subtype, and TP53 mutation.
- To evaluate the promoter methylation status of CDH3 and to explore the regulation of CDH3 expression via methylation.
- To determine the prognostic implication of CDH3 expression using overall survival analysis and subgroup survival analysis according to sex, race, and smoking.
- To study the correlation between CDH3 and MAP7D1 gene expression in LUAD.
- To understand the clinical value of CDH3 in LUAD as a diagnostic marker, prognostic factor, and therapeutic target.

2.0. Literature Review

CDH3, also called P-cadherin, is a calcium-binding transmembrane glycoprotein that belongs to the classic cadherin family. Its primary role is to help maintain cell adhesion, tissue integrity, and cell polarity. Additionally, CDH3 regulates several intracellular signaling pathways involved in the control of proliferation, migration, invasion, and epithelial-to-mesenchymal transition (EMT) by initiating signaling pathways such as Wnt/ β -catenin, EGFR, PI3K/AKT, and Rho GTPase, hence stimulating cell survival and promoting metastatic ability in cancer cells [5].

Transcriptomic analysis recently revealed that CDH3 expression is remarkably high in LUAD compared to normal lung tissues. Increased levels of CDH3 expression were found to be associated with enhanced tumor proliferation, invasion, migration, and worse prognosis in patients. Functionally, silencing CDH3 expression reduces tumor growth and metastasis in LUAD cells. Taken together, the above evidence suggests that CDH3 might be a promising biomarker of aggressive LUAD and prognosis [11].

Several reports have associated the up-regulation of CDH3 with unfavorable clinicopathological parameters like advanced stage of tumor, metastasis to lymph nodes, low differentiation grade, and TP53 mutation [12]. Additionally, higher CDH3 expression has been correlated with poor overall survival and disease-free survival in multiple malignancies, including LUAD. Therefore, there has been considerable interest in CDH3 as a prognostic biomarker that could help in stratification of patients [13].

Abnormal DNA promoter methylation is an essential epigenetic regulation that controls gene expression in the carcinogenic process. It causes cancer either by silencing tumor-suppressor genes or by activating oncogenes [14]. Past research has shown that changes in CDH3 promoter methylation are correlated with the gene expression in various cancers. However, the connection between the methylation of CDH3 promoter and its gene expression in LUAD remains unknown, which requires further study through integrated genomics database analysis [15].

Recent studies show that CDH3 is responsible for regulating the tumor microenvironment by affecting immune cell infiltration, inflammatory signaling, hypoxia, glycolysis, and epithelial-mesenchymal transition [16]. Higher

levels of CDH3 expression correlate with the presence of increased numbers of macrophage tumor-infiltration and decreased antitumor immunity, suggesting its involvement in immune escape mechanisms. Therefore, CDH3 is a good candidate for combination treatment involving immunotherapy and targeted therapy [17].

Current mechanistic research has shown that CDH3 functions as a mediator of ferroptosis, which is a type of iron-dependent programmed cell death that contributes to cancer progression. The stabilizing function of USP8 on CDH3 inhibits ferroptosis and facilitates the progression of LUAD, indicating that inhibition of the USP8-CDH3 pathway represents a promising therapeutic approach. Moreover, serum soluble CDH3 can be used as a possible biomarker in monitoring EGFR-TKIs resistance, which makes it valuable from the point of view of precision medicine [18].

Though the oncogenic role of CDH3 in lung adenocarcinoma has already been well described, there are still certain issues that need to be addressed. There are no detailed pan-cancer expression analysis, comprehensive analyses combining clinicodemographic parameters, clinicopathological characteristics, promoter methylation, survival analysis, and gene-gene correlations performed. In addition, the link between CDH3 and MAP7D1 in LUAD needs to be further examined. Thus, a bioinformatics analysis should be done to better understand the diagnostic and prognostic value of CDH3 as well as its molecular mechanisms. The current literature review provides the background for the analyses conducted within the study.

3.0. Materials and Methods

Study Design

The current research is based on an integrated bioinformatics approach to evaluate the potential value of Cadherin-3 (CDH3) in the diagnosis and prognosis of lung adenocarcinoma (LUAD). Publicly available transcriptome, epigenome, and clinical databases were explored to investigate CDH3 expression profile, promoter methylation, clinical-pathological relevance, survival outcomes, and co-expression network [2]. The research design is comprised of pan-cancer expression profiling, differential expression analysis, subgroup analysis, promoter methylation analysis, Kaplan-Meier survival analysis, and correlation analysis of CDH3 with MAP7D1.

Pan-Cancer Gene Expression Analysis

Gene expression and related clinical-pathological details of CDH3 in various types of cancers in humans were examined through RNA sequencing data obtained from The Cancer Genome Atlas (TCGA) by the UALCAN website. The relative expression of the gene in tumor tissues was compared to the expression in normal tissues to determine the expression profile of the gene. The main gene expression comparison involved 515 LUAD primary tumor tissues and 59 normal lung tissues. This study utilized online cancer genomic databases based on TCGA data, and all datasets were downloaded on 15 August 2026 [19].

Differential Expression Analysis in LUAD

The expression values for the CDH3 gene were extracted from RNA-seq data that was normalized through the UALCAN platform, which makes use of transcriptomic TCGA datasets using TCGA standard pipelines for

processing. Expression levels in LUAD and normal tissues were compared in order to find different expression of this gene. The expression values were presented in TPM (Transcripts per Million), or in any other exact measurement unit used on the website (normalized counts, $\log_2(\text{TPM}+1)$). The values from UALCAN were taken as they were, without additional normalization. Statistical analysis was performed through default analysis options in the database (significance $P < 0.05$) [19].

Clinicodemographic Analysis

To explore the clinical importance of CDH3 expression, subgroup analysis was performed based on demographic factors like gender, race, age, and smoking status. The differences in CDH3 expression among different groups were analyzed using statistical techniques offered through the online portal. Differences in CDH3 expression based on demographic and clinicopathologic subgroups were analyzed using the statistical techniques available in the UALCAN portal. The Student's t-test was used in case of two groups while one-way analysis of variance (ANOVA) was used in case of more than two groups. P value of less than 0.05 was taken to be statistically significant [19].

Clinicopathological Analysis

For the understanding of the clinicopathological implication of CDH3, correlations with clinical-pathological parameters were explored. The parameters investigated included as pathological stage of tumor, metastatic nodes presence, histological subtype, and status of TP53 mutation. Comparative analyses were done to determine whether the expression levels of CDH3 gene differed significantly among the different pathologies [19].

Promoter Methylation Analysis

Methylation analysis of the CDH3 promoter region was done using the methylation datasets from The Cancer Genome Atlas (TCGA) database through publicly available methylation analysis portals. Promoter methylation levels in LUAD tissues were examined to understand the mechanisms regulating the CDH3 expression. Comparative promoter methylation levels in different clinical classes were examined using the statistical algorithms available in the chosen database [19].

Survival Analysis

The prognostic significance of CDH3 expression was determined through Kaplan-Meier survival analysis. Patients were automatically divided into high- and low-expression groups using the auto-selected best cutoff determined by the Kaplan-Meier Plotter algorithm. The OS was examined in all LUAD patients, males and females categories, racial categories, and smokers and non-smokers categories. Hazard ratio (HR), 95% CI, and log-rank P value were used to describe the relationship between the expression of CDH3 and OS in these patient groups [19].

Gene Correlation Analysis

Correlation analysis was done to determine the relationship between CDH3 and MAP7D1 expression in LUAD tissues. Pearson's correlation coefficient was determined using the normalized RNA-seq data from TCGA. Apart

from the overall LUAD dataset, correlation analyses were also done based on racial classification to identify any disparities among the ethnic groups [19].

Statistical Analysis

Statistical analysis was done using the built-in statistical tools of the relevant online bioinformatics databases. Comparisons of continuous variables were done using the default algorithms of each database, while the differences in survival rates were tested using Kaplan-Meier method and log-rank test. Correlation analysis was done using Pearson's correlation coefficient. A two-tailed P value of less than 0.05 was considered statistically significant. In order to minimize chances of obtaining false positive outcomes due to multiple subgroup analyses, P values were corrected using the Benjamini-Hochberg FDR approach. Adjusted P values of less than 0.05 were considered statistically significant [19].

4.0. Results and Discussion

The present research presents a detailed analysis of CDH3 expression profiling, epigenetic control, significance in the clinical setting, prognostic significance, and gene interactions in LUAD through using publicly available cancer genomics data sets. The findings show that there is an extensive dysregulation of CDH3 in LUAD, implying that it can be used as a diagnostic and prognostic biomarker. Moreover, the correlation between CDH3 and MAP7D1 genes indicates their involvement in the common molecular mechanisms related to the development of LUAD. The further discussion summarizes the outcomes illustrated in Figures 1-8.

4.1. Differentially Expressed CDH3 Across Human Cancers

Analysis of the expression of CDH3 across different cancers shows the considerable heterogeneity in expression among different tumor types, thereby suggesting a particular biological function in the tumors (Figure 1). This differential pattern is consistent with the previous information stating that CDH3 acts both as an oncogene and tumor suppressor, depending on the cellular context. High expression of CDH3 in LUAD indicates that this molecule is involved in the development of this cancer via stimulation of epithelial proliferation, migration, and invasion.

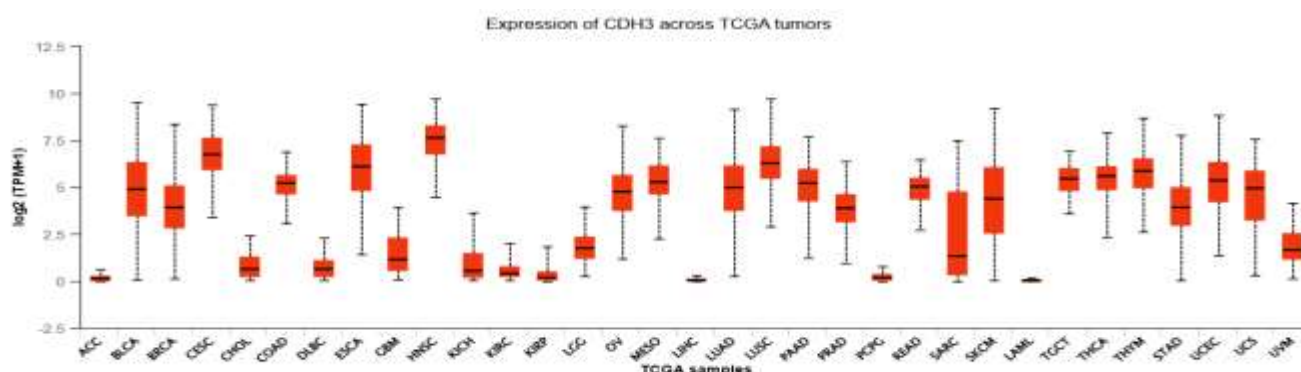


Figure 1. Pan-Cancer Expression Profile of CDH3 based on TCGA datasets.

4.2. Significantly Overexpressed CDH3 in Lung Adenocarcinoma

Similarly to the pan-cancer findings, tumor samples have considerably higher levels of CDH3 than the samples of normal lung tissues (Figure 2). The high level of CDH3 in LUAD suggests its involvement in tumorigenesis and the use of this molecule as a potential diagnostic biomarker for differentiating tumor from normal lung tissues. Enhanced cell-cell adhesion remodeling, epithelial plasticity, and activation of the oncogenic signaling pathways are some of the mechanisms by which increased CDH3 expression can lead to tumor progression.

The gene expression data highlighted the substantial overexpression of CDH3 in LUAD tissues as compared to that in normal lung tissues (Figure 2). As shown in panel (a), the analysis of the TCGA database indicated the presence of significantly higher CDH3 expression in tumors (n = 515) compared to that in normal samples (n = 59), although there was a significant variation of gene expression among tumors. It appeared that CDH3 overexpression in tumor tissues was common.

As evidenced in panel (b), there was a clear distinction in CDH3 expression between the tumor and normal tissues with a significantly higher level of CDH3 expression in the former. This indicated a substantial difference between the two sample groups. Thus, both sets of data supported the hypothesis that CDH3 was overexpressed in LUAD. Since CDH3 encodes P-cadherin – a protein involved in the regulation of cell-cell adhesion, the overexpression of CDH3 may indicate some abnormalities in such mechanisms.

Overall, the findings support the idea that CDH3 overexpression is a typical molecular alteration associated with LUAD. It remains unknown, however, whether CDH3 may be used as a diagnostic and/or prognostic marker of LUAD and what role it plays in its pathogenesis.

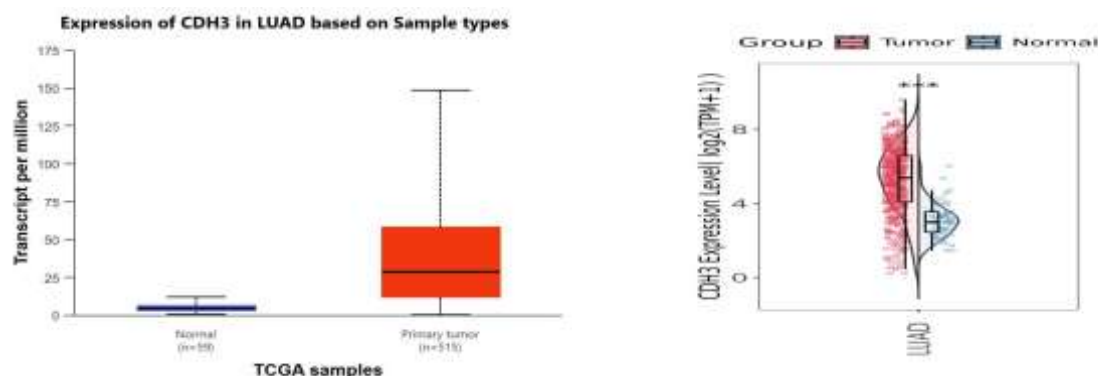


Figure 2. Differential Expression of CDH3 in Normal and Primary Tumor Tissues of Lung Adenocarcinoma (LUAD): (a) Box Plot Showing CDH3 Expression Levels in TCGA Normal and Primary Tumor Samples; and (b) Violin Plot Showing the Distribution of CDH3 Expression Between Tumor and Normal LUAD Samples.

4.3. Clinicodemographic Characteristics Demonstrate Consistent CDH3 Overexpression

Analysis of the clinicodemographic data showed that CDH3 expression was still Elevated for all different patient groups, such as sex, race, age, and smoking status (Figure 3). Thus, these results show that the CDH3 overexpression is a distinctive characteristic of LUAD regardless of particular demographics and not specific for a certain subgroup. The preservation of increased expression in both smokers and non-smokers implies that CDH3 dysregulation can be a common molecular event not associated with any environmental risk's factors.

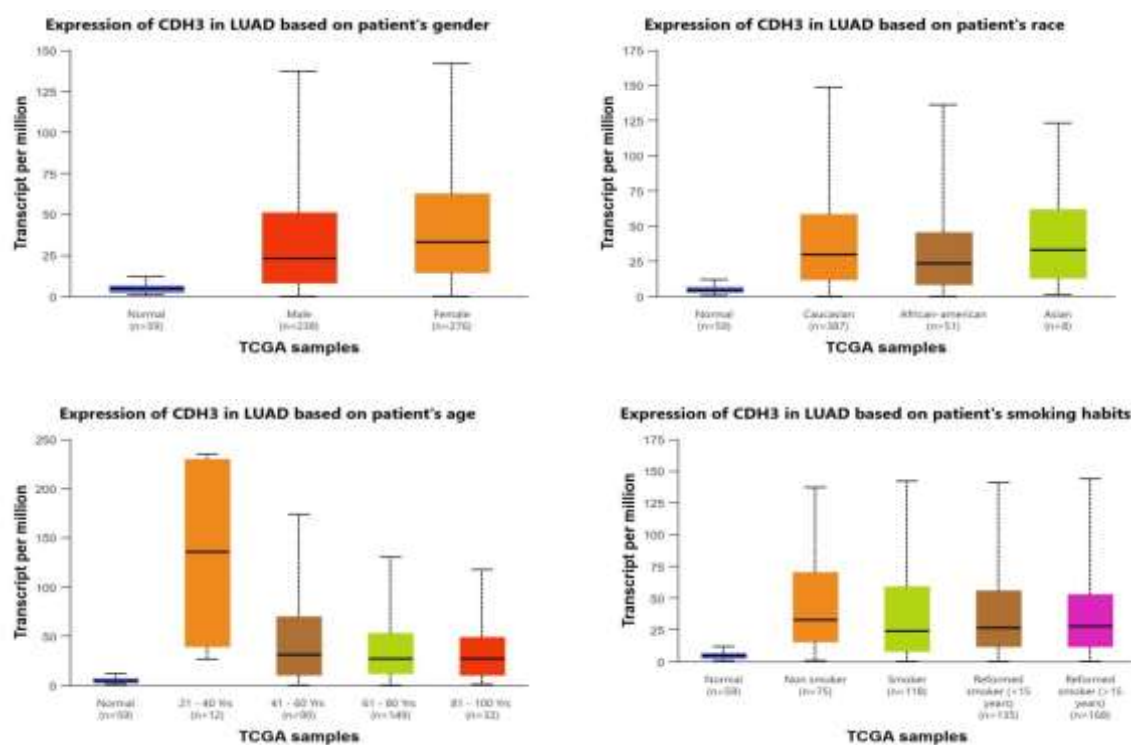


Figure 3. Clinicodemographic Analysis of CDH3 Expression in Lung Adenocarcinoma (LUAD):
(a) Gender, (b) Race, (c) Age, and (d) Smoking Status.

4.4. Association of CDH3 Expression with Disease Progression

An analysis of the clinicopathological features showed the difference in CDH3 expression according to the pathological tumor stage and nodal metastasis status (Figure 4). This trend indicates the possible involvement of CDH3 in not only initiation but also progression and dissemination of the disease. Increased CDH3 expression in the advanced stage of the tumor development confirms the assumption that CDH3 increases tumor aggression due to enhanced cellular adhesion dynamics and increased invasion potential.

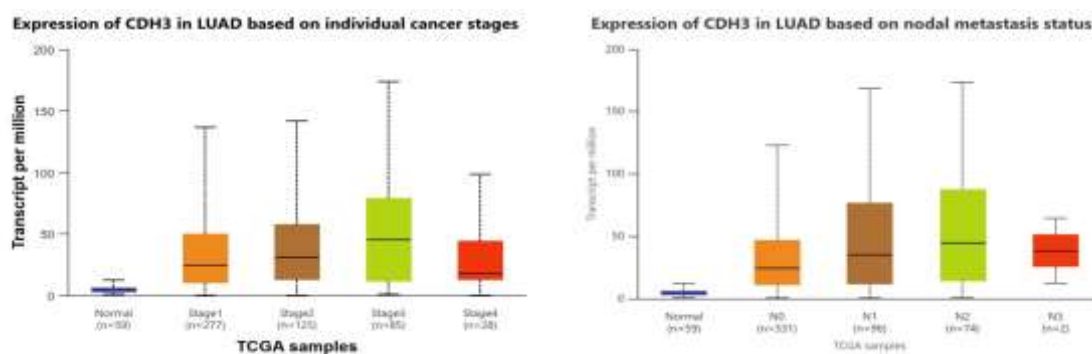


Figure 4. Association of CDH3 Expression with Clinicopathological Characteristics of Patients with Lung Adenocarcinoma (LUAD): (a) Pathological Tumor Stage and (b) Nodal Metastasis Status.

4.5. Relationship Between CDH3 Expression and Molecular Characteristics

A relation between CDH3 expression and histopathological subtype and the TP53 mutation status (Figure 5) highlights the clinical importance of the CDH3 protein. Different expression for histological subtypes indicates

different biological functions of CDH3 for particular subtypes of LUAD. Moreover, the expression differences according to the TP53 mutation status indicate a possibility of CDH3 signaling pathway and TP53-regulated pathway interaction in the cell cycle regulation, apoptosis, and genome stability maintenance.

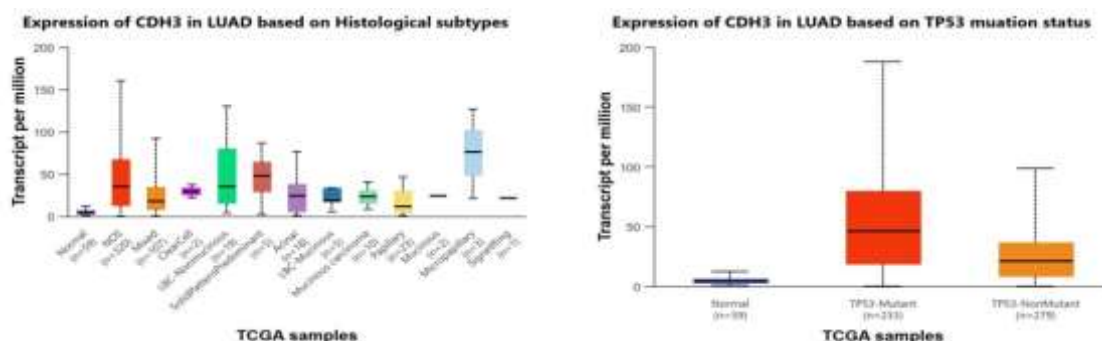


Figure 5. Association of CDH3 Expression with Histopathological and Molecular Characteristics of Patients with Lung Adenocarcinoma: (a) Histological Subtypes and (b) TP53 Mutation Status.

4.6. Promoter Methylation May Regulate CDH3 Expression

Average promoter methylation beta values generated by the UALCAN platform were analyzed. The analysis of the CDH3 promoter methylation status revealed alterations in the CDH3 promoter methylation status in LUAD (Figure 6). Since the promoter methylation is one of the primary epigenetic regulators of transcription, these data suggest the role of the epigenetic modification in CDH3 dysregulation in LUAD. Promoter hypermethylation is the main epigenetic alteration contributing to the activation of the oncogenes and silencing of tumor suppressors.

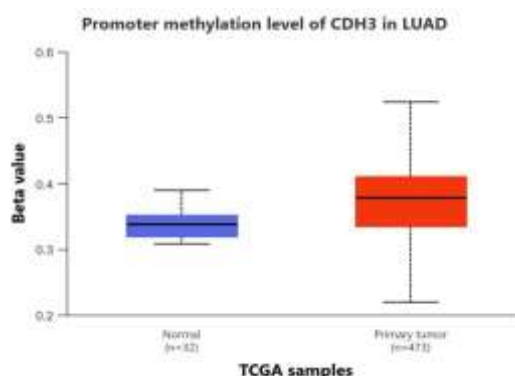


Figure 6. Relationship of CDH3 Expression with Promoter Methylation Status in LUAD.

4.7. Prognostic Value of CDH3 in LUAD

The Kaplan-Meier survival analysis has suggested that there is a significance of CDH3 expression in prognosis of LUAD (Figure 7). The observed distinctions in overall survival of patients depending on whether their CDH3 expression was increased or decreased may suggest that this marker could be utilized for prognosis in LUAD. Furthermore, subgroup analysis based on the characteristics of patients including gender, race, and smoking status showed that the prognostic significance of CDH3 expression could differ across subgroups, which implies that different demographic and clinical features of patients should be taken into account while analyzing its prognostic value.

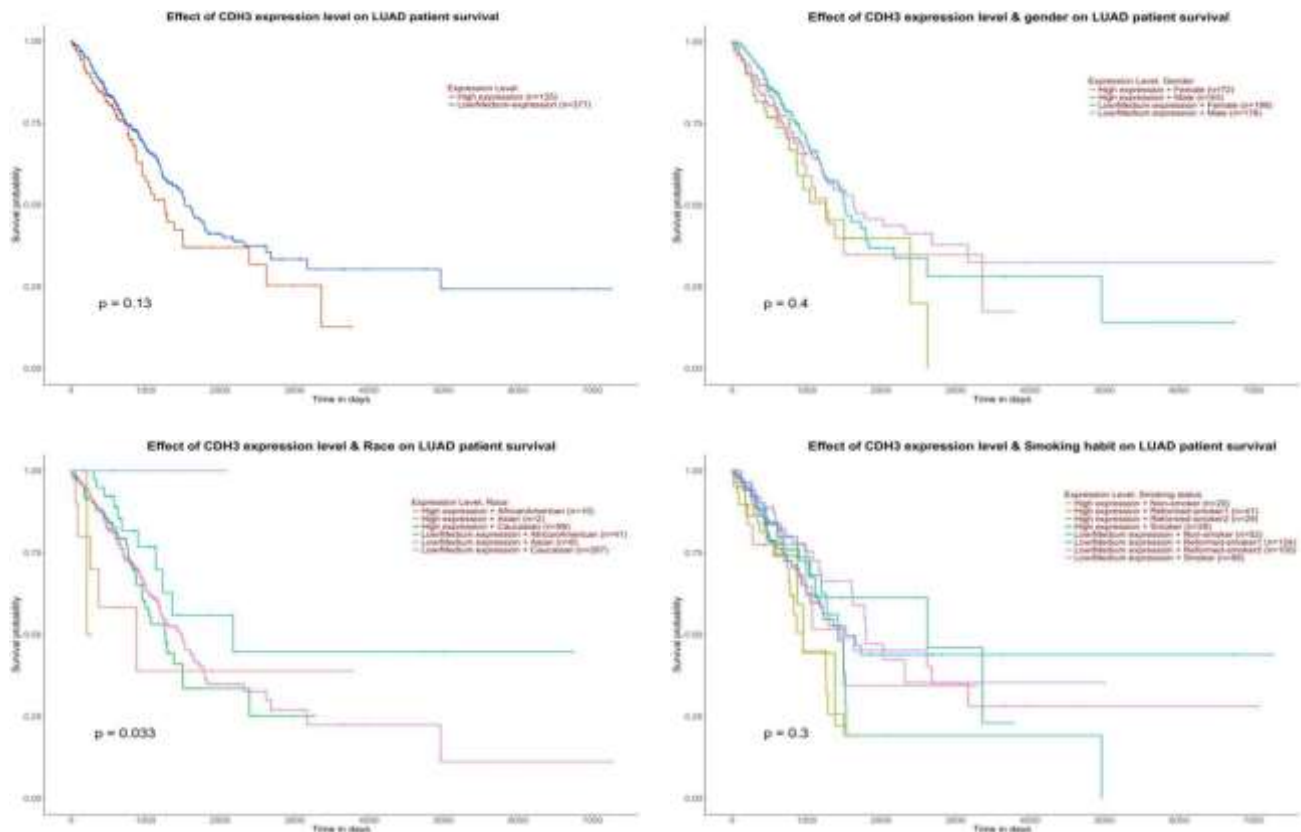


Figure 7. Kaplan–Meier survival analyses of CDH3 expression in lung adenocarcinoma (LUAD): (a) overall survival, (b) gender-specific survival, (c) race-specific survival, and (d) smoking status-specific survival.

4.8. Positive Correlation Between CDH3 and MAP7D1 Expression

The correlation analysis has shown a positive relationship between the expression of CDH3 and MAP7D1 in LUAD (Figure 8a). The persistence of this correlation in various racial groups (Figure 8b) shows that the interaction between these markers is relatively stable regardless of the population. Though no information about the possible mechanisms of this interaction has been provided by the authors, the correlation observed raises the hypothesis that CDH3 and MAP7D1 are involved in some common signaling pathways that control cytoskeleton remodeling, proliferation, and metastasis.

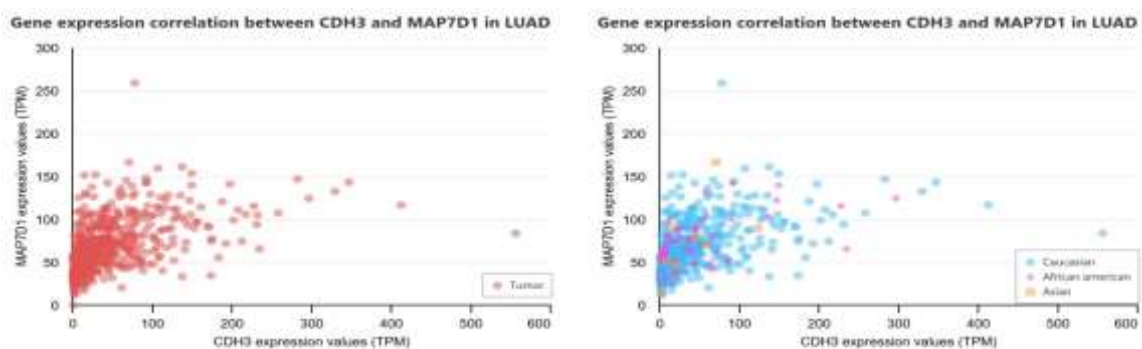


Figure 8. Correlation analysis of CDH3 and MAP7D1 gene expression in lung adenocarcinoma (LUAD): (a) scatter plot showing the correlation in LUAD tumor tissues and (b) race-stratified scatter plot illustrating the correlation between CDH3 and MAP7D1 gene expression.

4.9. Significance of Study Results

As a summary of the entire study, the current results show that CDH3 is highly expressed in LUAD, positively associated with clinicodemographic and clinicopathological features, epigenetically regulated through promoter methylation, prognostically relevant, and positively correlated with MAP7D1 expression. The current results suggest that CDH3 may serve as a useful biomarker in LUAD diagnosis and prognosis, and provide a basis for future studies on its underlying mechanism and therapeutic target.

5.0. Conclusion and Further Studies

5.1. Conclusion

The results of the above integrative bioinformatics analysis reveal a clear overexpression of CDH3 in lung adenocarcinoma (LUAD) when compared to healthy lungs and unique expression profiles of CDH3 in various human malignancies. The correlation of CDH3 with a number of clinico-demographic and clinico-pathological factors (tumor stage, nodal metastasis, histological type, and TP53 mutations), provides evidence for involvement of CDH3 in carcinogenesis and tumor development in LUAD patients. Methylation changes in the CDH3 gene promoter region also suggest that CDH3 may be regulated by epigenetic mechanisms. Kaplan-Meier survival analysis suggests prognostic value of CDH3 expression, thereby confirming its suitability for a prognostic marker. Finally, a positive correlation between CDH3 and MAP7D1 indicates possible connection of these genes that requires more detailed research in the future. Taken together, the current findings support application of CDH3 as a diagnostic and prognostic biomarker in LUAD and pave the way for future experimental investigations of its molecular functions.

5.2. Future Studies

While the present bioinformatics analysis provides significant proof in support of the usefulness of CDH3 as a diagnostic and prognostic marker in lung adenocarcinoma (LUAD), further laboratory and clinical studies are needed to corroborate these findings as well as understand the molecular mechanisms involved.

- Confirm the expression levels of CDH3 in LUAD patient cohorts using qRT-PCR, Western blot, and immunohistochemistry.
- Establish the functional significance of CDH3 through in vitro and in vivo tests.
- Clarify the molecular mechanisms linking CDH3 with methylation and MAP7D1.
- Determine the value of CDH3 as a prognostic indicator in clinical trials conducted in different centers.
- Investigate CDH3 as a potential therapeutic target in LUAD.

Declarations

Source of Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare that they have no competing interests related to this work.

Consent for Publication

The authors declare that they consented to the publication of this study.

Authors' Contributions

Md. Mahbubol Alam took part in literature review, conceptualization, methodology, investigation, analysis, and manuscript writing and editing. Sahariare Nazim, Md. Ishad Rana, Tanjina Tabassom, Hamida Akter Bristi, and Fatema Akhter analyzed data. Md. Mahbubol Alam and Fahamida Binta Anower were involved in the design of the manuscript. Md. Mahbubol Alam reviewed the manuscript. All authors have read and approved the final manuscript.

Availability of Data and Materials

Supplementary information is available from the authors upon reasonable request.

Institutional Review Board Statement

Not applicable.

Ethical Approval

Not applicable for this study.

Informed Consent

Not applicable for this study.

Acknowledgement

Not applicable for this study.

Declaration of Artificial Intelligence

The authors declare that artificial intelligence was not used in the writing, analysis and preparation of this manuscript.

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