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ATM is a Prognostic Biomarker of Survival in Head and Neck Squamous Cell Carcinoma Patients

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Abstract: This review examines the role of *ATM* expression in head and neck squamous cell carcinoma (HNSCC). Analysis revealed significant overexpression of *ATM* in HNSCC cells compared to normal control samples, suggesting its involvement in cancer proliferation. *ATM* expression was notably upregulated across various clinical parameters, including different stages of cancer, racial groups, genders, and age groups, highlighting its role in cancer progression. Validation using the GEPIA2 tool confirmed strong *ATM* expression throughout all four stages of HNSCC, with the highest levels in stage II and the lowest in stage I. Promoter methylation analysis of ATM showed distinct patterns across different demographics and cancer stages, reinforcing its significance. The study also explored the relationship between *ATM* expression and patient outcomes using the KM plotter tool, finding that high *ATM* expression was associated with better overall survival (OS), while low ATM expression correlated with better disease-free survival (DFS). Genetic mutation analysis via cBioPortal identified minimal *ATM* mutations in HNSCC, including in-frame, splice, truncating, and missense mutations, suggesting their role in *ATM* dysregulation. The STRING tool was used to construct a protein-protein interaction (PPI) network, revealing that the *ATM* gene interacts with ten key genes (*NBN*, *ATR*, *CHEK2*, *MDC1*, *MSH2*, *MSH6*, *MRE11*, *TP53*, *TP53BP1*, *BRCA1*), indicating its involvement in various biological functions. Functional annotation of differentially expressed genes (DEGs) through the DAVID web server revealed their participation in critical biological processes, including double-strand break repair, cellular response to DNA damage, and DNA damage checkpoints. KEGG pathway analysis further linked DEGs to cellular senescence, platinum drug resistance, homologous recombination, p53 signaling, and the cell cycle, underscoring *ATM*'s multifaceted role in HNSCC.

Keywords: Head and neck squamous cell carcinoma; Diagnosis; Treatment; Biomarker

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1. Introduction

Head and neck squamous cell carcinoma (HNSCC) poses a significant global health challenge, ranking as the sixth most common cancer worldwide [1]. Projections suggest a 30% increase in HNSCC cases by 2030, with an estimated 1.08 million new diagnoses annually [2]. HNSCC develops from the mucosal epithelium of the oral cavity, pharynx, and larynx and remains the most common cancer in these regions. Despite substantial efforts, survival rates for HNSCC patients only improved marginally from 55% to 66% between 1992–1996

and 2002–2006 [3]. Notably, HNSCC survivors have the second-highest suicide risk among cancer survivors, often due to psychological distress and reduced quality of life [4]. In 2020 alone, approximately 0.88 million new cases and 0.44 million deaths were reported globally, making HNSCC the eighth most prevalent cancer [5]. Despite comprehensive treatment strategies, including chemotherapy and surgery, the median overall survival (OS) of HNSCC patients remains less than one year, highlighting the urgent need for reliable biomarkers for diagnosis, prognosis, and treatment [6]. Previous studies have identified several genes and pathways associated with HNSCC mutation rates, which play critical roles in the disease's pathogenesis, progression, metastasis, and outcomes [7]. These statistics underscore the urgent need to identify biomarkers that can improve patient outcomes in HNSCC [8]. Biomarkers can guide personalized treatment approaches, such as targeted therapies, enhancing treatment efficacy while minimizing toxicity. Therefore, future research must prioritize the identification and validation of biomarkers to improve HNSCC patient outcomes.

Over the past thirty years, *ATM* (ataxia telangiectasia mutated) has played a central role in advancing our understanding of the mammalian DNA damage response, cancer initiation and progression, and redox signaling pathways. Recent publications have highlighted ATM's diverse roles in cellular processes such as growth, metabolism, energy production, oxidative homeostasis, chromatin remodeling, and genomic integrity, all of which are crucial in cancer development and progression. The *ATM* gene, an onco-suppressor located on chromosome 11q23, encodes a 350-KDa protein composed of 3056 amino acids [9]. It belongs to the phosphatidylinositol 3-kinase-related protein kinase (PIKK) superfamily, which includes six serine/threonine kinases with sequence similarities to phosphatidylinositol 3-kinases (PI3Ks), such as ATR (ATM-and RAD3-related), DNA-PKcs (DNA-dependent protein kinase catalytic subunit), and mTOR (mammalian target of rapamycin). ATM is involved in DNA repair and activates DNA damage response pathways [10]. HEAT motifs are crucial for ATM's interaction with and recruitment of various proteins to DNA damage sites for repair [11-14]. ATM is a key initiator of the DNA damage response in mammalian cells through the Mre11/Rad50/Nbs1 (MRN) complex at DNA lesion sites [15-18]. Mutations in the *ATM* gene result in deficiencies in the DNA damage response, leading to ataxia telangiectasia, a rare autosomal recessive disorder with a frequency of 1 in 40,000 to 300,000 in Caucasians [19]. ATM's primary cancer-suppressing mechanisms include inducing apoptosis and cell cycle arrest by activating p53, SIRT1, CHK1, CHK2, DBC1, RAIDD, and other downstream targets [20]. Consequently, cancer cells can employ various mechanisms to downregulate ATM. For example, in breast cancer cells, miRNA-18a can reduce ATM expression [21]. Enhancing ATM signaling and expression may enable cancer cells to resist chemotherapy and radiation, metastasize, and survive [22]. Epidemiological studies of families affected by both AT and BC suggest that heterozygous ATM mutation carriers have a two- to thirteen-fold increased risk of developing breast cancer, with a higher relative risk under 50 years of age [23-26].

In this review, we explore *ATM* mutations, expression levels, prognostic outcomes on survival, and functional perspectives within the context of HNSC through bioinformatics analysis. We also examine the relationship between *ATM* expression and promoter methylation levels. To achieve this, we utilized various databases, including The Cancer Genome Atlas (TCGA) dataset, the UALCAN portal, the Kaplan-Meier tool, Gene Expression Profiling Interactive Analysis (GEPIA2), cBioPortal, STRING for predicting protein-protein interactions (PPI), and the Database for Annotation, Visualization, and Integrated Discovery (DAVID). DAVID provides a comprehensive set of functional annotation tools to understand the biological significance of large gene lists. The primary aim of this study was to assess the *ATM* expression pattern in HNSC and determine its potential importance in cancer development, treatment, and prognosis.

2. Materials and methods

2.1. Expression and promoter methylation analysis of ATM

To investigate *ATM* expression, we utilized the UALCAN online database. UALCAN is a comprehensive, user-friendly, and visually appealing web resource for analyzing cancer genomics data [27]. It draws on extensive data from The Cancer Genome Atlas (TCGA) to facilitate in-depth analyses of gene expression, protein abundance, and patient survival across various cancer types. UALCAN's intuitive interface allows researchers to explore and visualize gene expression patterns across different cancer stages, molecular subtypes, and patient demographics. In this study, the UALCAN dataset was used to assess *ATM* expression across different stages of cancer development, where this gene shows significant dysregulation and a strong correlation with poorer overall survival (OS). For the assessment of *ATM* promoter methylation levels in HNSC, we also used the UALCAN dataset. Additionally, promoter methylation data were analyzed across various clinical parameters, including patient age, gender, and race.

2.2. Validation analysis of ATM

GEPIA2 is a widely used online tool for the analysis of gene expression and survival in genomic data [28]. With 198,619 isoforms and 84 cancer subtypes, GEPIA2 has extended gene expression quantification from the gene level to the transcript level and supports the examination of specific cancer subtypes and comparisons between them. Since cancers often consist of heterogeneous subtypes with distinct prognoses, GEPIA2 allows users to tailor their investigations to focus on all 84 cancer subtypes and to compare across different subtypes. Moreover, as single-cell sequencing becomes more prevalent, new standards of analysis have emerged. The differences in *ATM* expression and prognosis (OS and DFS) in HNSCC patients were obtained from the GEPIA2 dataset. In this study, GEPIA2 was employed to explore the association between *ATM* expression and prognosis (OS and DFS) in HNSCC patients.

2.3. Survival analysis of ATM

The Kaplan-Meier (KM) plotter is an essential online tool for survival analysis [29]. This platform leverages extensive clinical data to examine the impact of specific genes on patient survival across various cancer types. Researchers can easily explore the prognostic value of gene expressions, identifying potential prognostic biomarkers. KM Plotter's user-friendly interface offers Kaplan-Meier survival curves, providing insights into how gene expression correlates with patient outcomes. In this study, the KM plotter tool was used to assess the impact of *ATM* dysregulation on the overall survival (OS) of HNSCC patients.

2.4. Mutational analysis of ATM

cBioPortal is a crucial online platform for cancer genomics analysis [30]. It provides an intuitive platform for exploring large-scale cancer genomic datasets, enabling researchers to delve into genetic alterations, pathways, and clinical significance across various cancer types. With user-friendly visualization tools, it simplifies the analysis of complex genomic data, making it accessible to a wide range of researchers. This database was utilized in the present study to perform a mutational analysis of *ATM* in HNSCC.

2.5. PPI development and gene enrichment analysis of ATM

The STRING database is an essential resource for elucidating protein-protein interactions (PPIs) [31]. It aggregates a wealth of information to help researchers unravel complex networks of protein interactions. In this study, we used STRING to construct the ATM protein interaction network. Among all databases, STRING is well-known for its comprehensive coverage, data abundance, and high-quality control of PPI information [32-34].

STRING contains PPIs from both experimental and computational methods and provides a combined quality score for each interaction by integrating data from various sources such as literature and gene expression profiles. For functional annotation of Gene Ontology (GO) terms and analysis of KEGG pathway enrichment, we utilized the online DAVID tool [35]. DAVID is a significant resource for the functional evaluation of high-throughput gene expression profiles.

3. Results

3.1. Expression analysis of ATM in HNSCC

To examine *ATM* expression in HNSCC and typical control samples, we used the UALCAN dataset (**Figure 1**). Upon analysis, we found a significant upregulation of *ATM* expression in HNSCC cancer cells compared to normal control samples. This overexpression indicated a strong association between *ATM* expression and the proliferation of HNSCC cancerous cells. This observation suggests that *ATM* may play a crucial role as a regulator of proliferation in HNSCC, highlighting its potential as a therapeutic target or diagnostic marker in this cancer type.

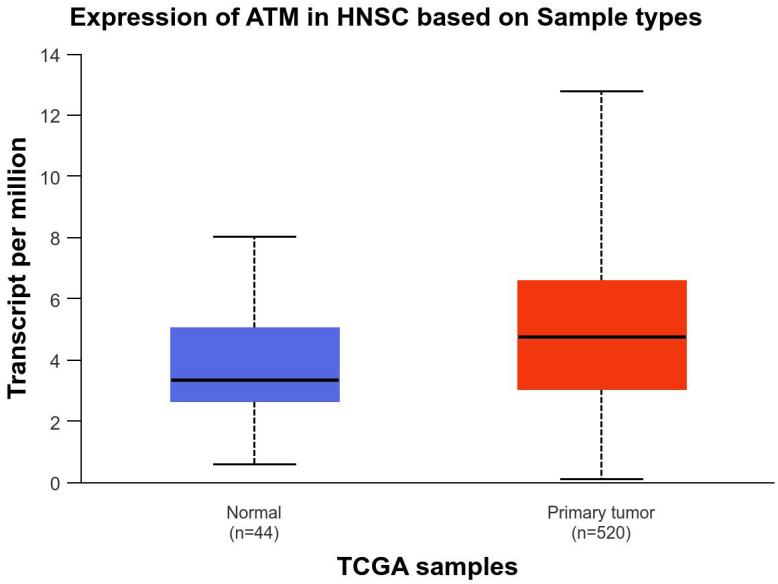

Figure 1. Expression profiling of *ATM* in HNSCC and normal tissue samples

3.2. Expression analysis of ATM in HNSCC stratified by clinical parameters

We further evaluated *ATM* expression in HNSCC samples across various clinical parameters, including individual cancer stages, patient race, gender, and age (**Figure 2**). Initially, we analyzed *ATM* expression across different tumor stages and observed significant overexpression of *ATM* in HNSCC at all stages compared to normal control samples (**Figure 2A**). Next, we investigated *ATM* expression in HNSCC patients across racial groups, revealing significant upregulation of *ATM* expression in Caucasian, African-American, and Asian patients compared to normal control samples (**Figure 2B**). Additionally, we examined *ATM* expression in HNSCC patients stratified by gender, showing notable upregulation of *ATM* in both male and female patients compared to normal controls (**Figure 2C**). Finally, we explored the association between *ATM* expression and patient age in HNSCC, revealing overexpression of *ATM* across different age groups among HNSCC patients (**Figure 2D**). These findings underscore the significance of *ATM* in HNSCC and its potential as a valuable biomarker for diagnosis and therapeutic targeting.

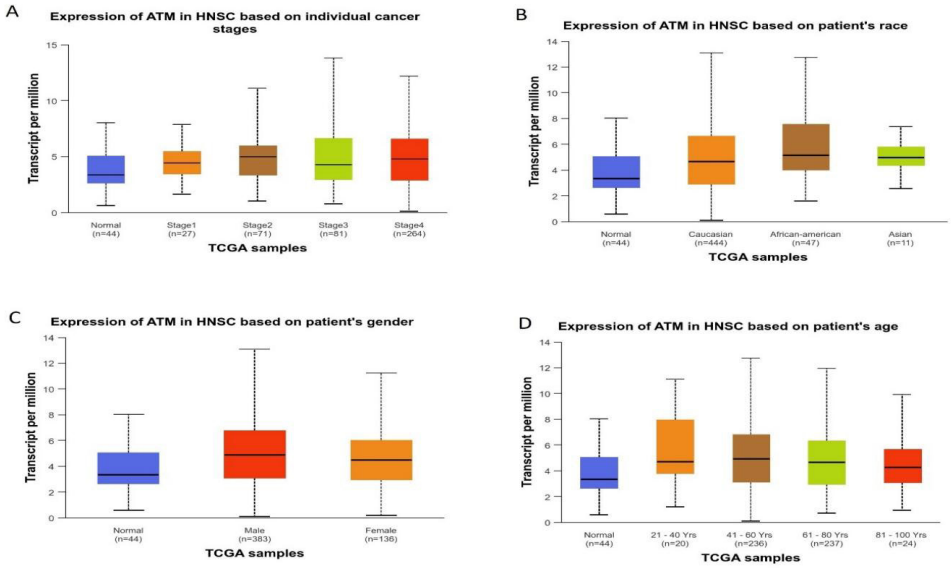

Figure 2. Expression of *ATM* across different clinical parameters

3.3. Prognostic analysis of ATM expression in HNSCC

To investigate *ATM* expression between HNSCC cells and normal control samples, we utilized GEPIA2. The results showed that *ATM* expression was significantly higher in HNSCC compared to normal control samples (**Figure 3A**). We further analyzed the association between *ATM* expression and different cancer stages using the GEPIA2 dataset. The outcomes revealed a strong correlation between *ATM* expression and the stages of HNSCC patients, with the highest expression observed in stage II and the lowest in stage I (**Figure 3B**).

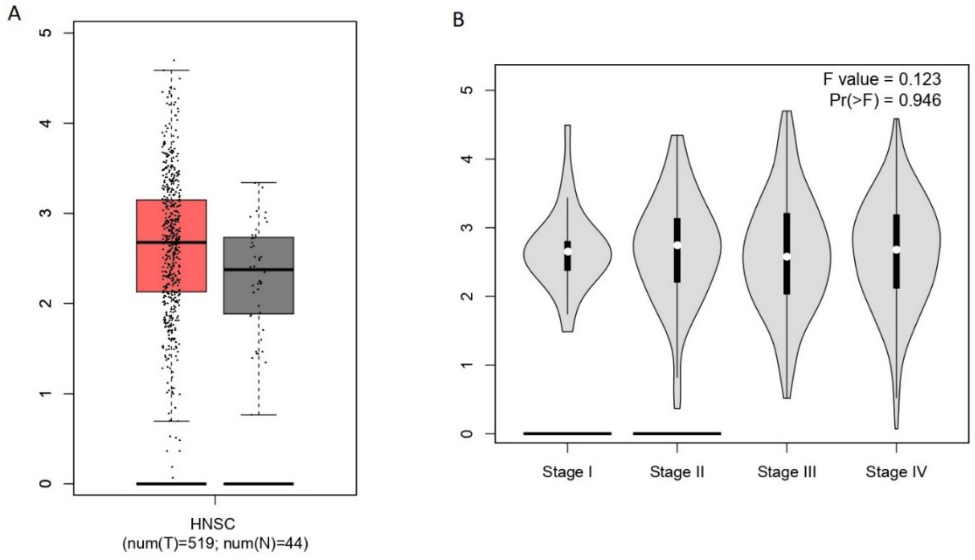

Figure 3. Validation of *ATM* expression across different stages of HNSCC

3.4. Promoter methylation of ATM in HNSCC and normal control samples

We conducted an analysis of the promoter methylation levels of *ATM* in HNSCC and normal control samples using the UALCAN online database. Our findings revealed that ATM was hypomethylated in HNSCC samples compared to normal control samples (**Figure 4**). This observation suggests a negative correlation between *ATM*

expression and promoter methylation in HNSCC. Such a correlation highlights the therapeutic potential of *ATM* in the pathogenesis of HNSCC, suggesting its role as a potential target for therapeutic interventions in this cancer type.

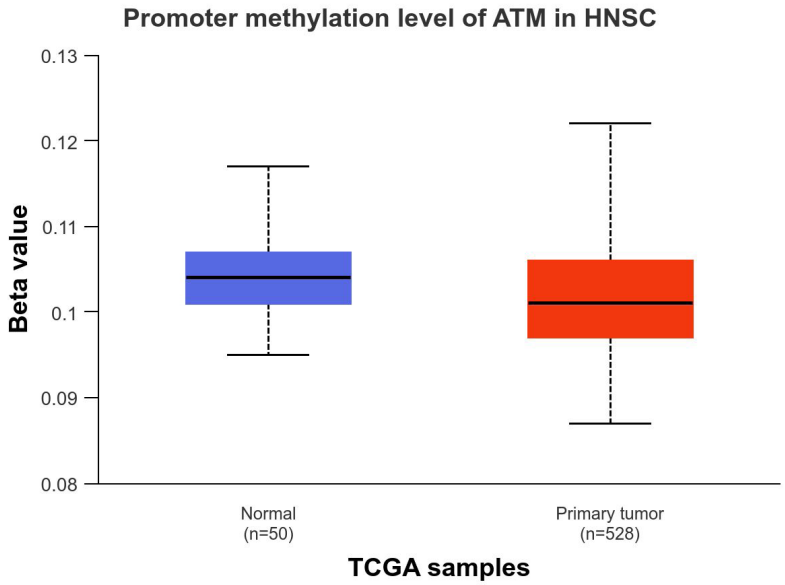

Figure 4. Promoter methylation pattern of *ATM* in HNSCC and normal control samples

3.5. Promoter methylation of ATM in HNSCC stratified by clinical parameters

To further elucidate the promoter methylation of *ATM* in HNSCC, we explored different clinical parameters (**Figure 5**). We examined *ATM* promoter methylation across different HNSCC cancer stages compared to normal control samples, revealing significant variations among stages, with all four stages showing prominent hypomethylation compared to normal controls (**Figure 5A**). We also examined *ATM* promoter methylation in HNSCC patients stratified by race, finding hypomethylation in the *ATM* promoter region across all three racial groups—Caucasian, African-American, and Asian—compared to normal controls (**Figure 5B**). Additionally, the assessment of *ATM* promoter methylation by gender revealed hypomethylation in both male and female patients (**Figure 5C**). Finally, we explored *ATM* promoter methylation concerning patient age, revealing varying methylation levels across different age groups (**Figure 5D**). These comprehensive assessments highlight the strong association between *ATM* promoter methylation and various clinical parameters in HNSCC, consistently showing a pattern of hypomethylation in ATM, emphasizing its potential significance in the pathogenesis of HNSCC.

3.6. Survival analysis of ATM

To further investigate the role of *ATM* gene expression in HNSCC, we conducted an evaluation of overall survival (OS) and disease-free survival (DFS) using the KM plotter tool. The analysis revealed a significant association between *ATM* gene expression and patient survival outcomes in the current study. Specifically, HNSCC patients with high *ATM* expression exhibited favorable OS compared to those with low *ATM* expression levels (**Figure 6A**). Additionally, in DFS analysis, HNSCC patients with low *ATM* expression experienced better DFS compared to those with high *ATM* expression. These findings underscore the critical role of *ATM* in influencing survival outcomes in HNSCC patients, highlighting its potential clinical significance as a prognostic marker in HNSCC management and suggesting its involvement in the progression and development of HNSCC.

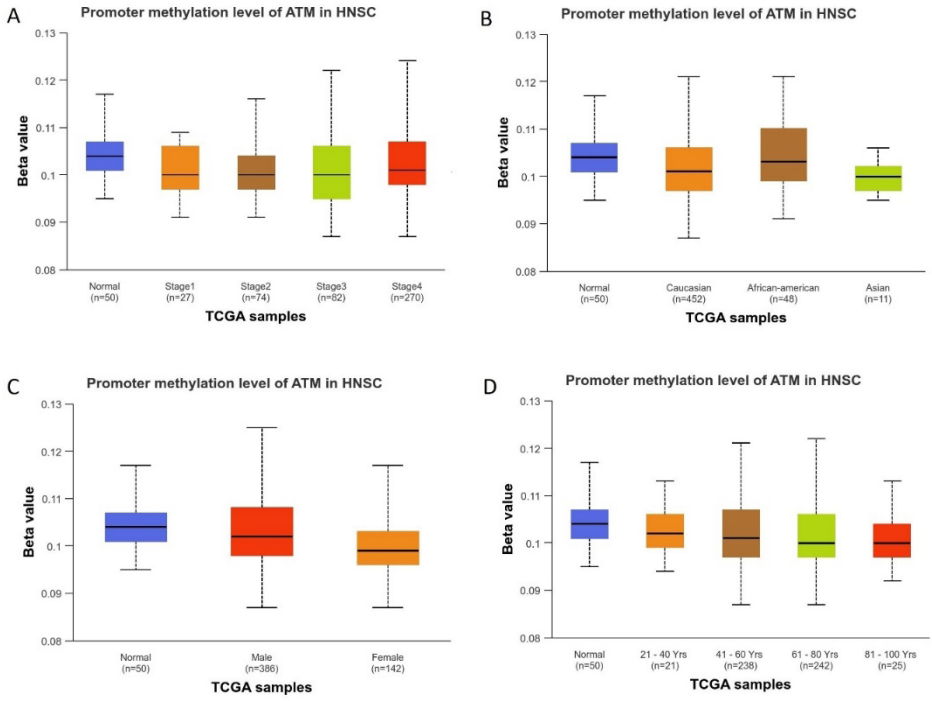

Figure 5. *ATM* promoter methylation pattern across different clinical parameters

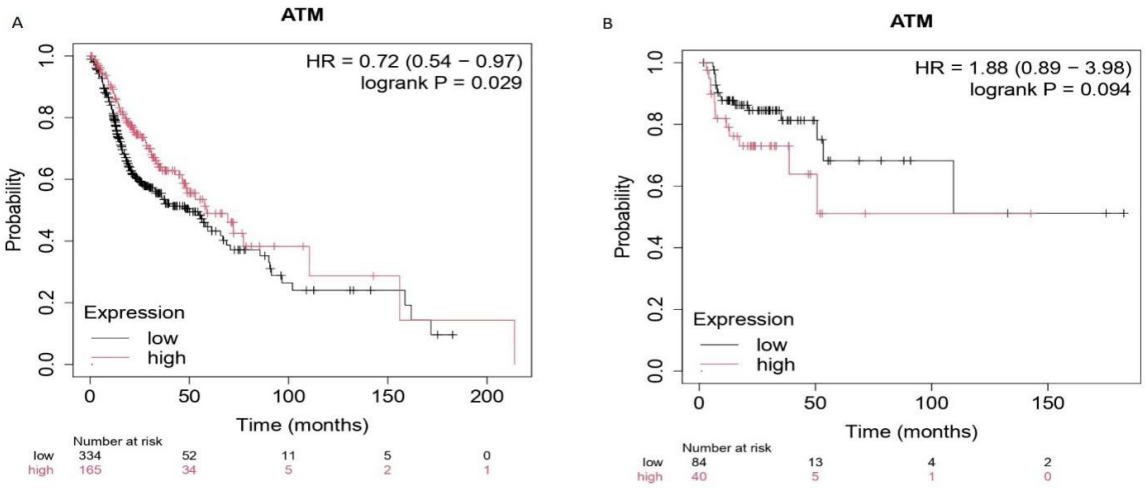

Figure 6. KM survival curve (OS, DFS) of *ATM* in HNSCC patients

3.7. Prognostic analysis of ATM in HNSCC

The GEPIA2 dataset was used to explore the prognostic value of *ATM* expression in HNSCC tumor progression. We stratified HNSCC patients into low and high-expression groups based on *ATM* expression levels. In HNSCC, high *ATM* expression was associated with favorable OS compared to low *ATM* expression (**Figure 7A**). Furthermore, low *ATM* expression was linked to better DFS in HNSCC compared to the high *ATM* expression group (**Figure 7B**). These findings suggest the vital role of the *ATM* gene in the progression and development of HNSCC cancer.

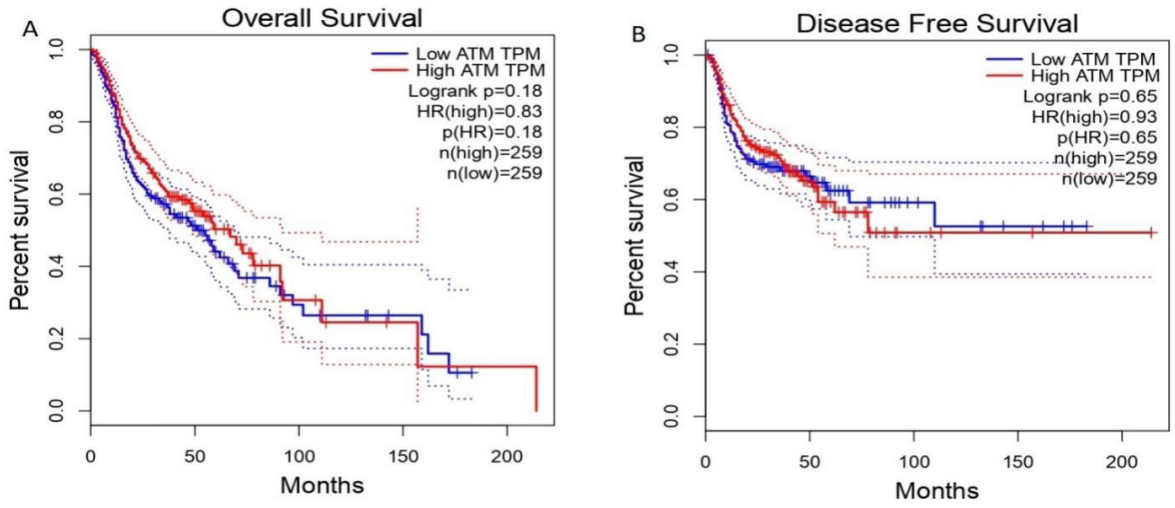

Figure 7. Survival curve (OS, DFS) of *ATM* in HNSCC patients

3.8. Mutational analysis of ATM in HNSCC

We further investigated the genetic mutations of *ATM* in HNSCC patients using cBioPortal. Our findings revealed that only 10% of HNSCC samples exhibited genetic mutations in *ATM*. The mutations identified in HNSCC included in-frame mutations, splice mutations, truncating mutations, and missense mutations (**Figure 8**). These findings suggest that while genetic mutations in *ATM* are relatively rare in HNSCC, the observed mutations may play a crucial role in the dysregulation of *ATM* in this cancer type.

Figure 8. Oncoplot of *ATM* in HNSCC cancer

3.9. Establishment of PPI networks of ATM

The physical and functional relationships among the proteins of differentially expressed genes (DEGs) of ATM were analyzed using the STRING tool. The construction of PPI networks showed that the *ATM* hub gene is interconnected with ten genes: *NBN*, *ATR*, *CHEK2*, *MDC1*, *MSH2*, *MSH6*, *MRE11*, *TP53*, *TP53BP1*, and *BRCA1*, highlighting the versatile nature of the *ATM* gene (**Figure 9**). This suggests that ATM plays a crucial role in various biological functions and strongly interacts with interconnected genes.

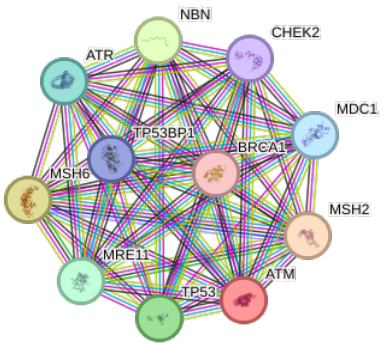

Figure 9. Protein-protein interactions of ATM

3.10. DAVID enrichment analysis

For the functional annotation of DEGs, the DAVID online server was utilized. To identify KEGG pathway-enriched genes and potential Gene Ontology (GO) terms related to biological processes, molecular functions, and cellular components, KEGG pathways were analyzed. By analyzing biological processes (BP), we found that DEGs from the complex PPI network were enriched in double-strand break repair (GO:0006302), cellular response to DNA damage stimulus (GO:0006974), DNA damage checkpoint (GO:0000077), replicative senescence (GO:0090399), and intra-S DNA damage checkpoint (GO:0031573) (**Table 1**). The cellular component (CC) analysis revealed that DEGs from the PPI network were enriched in the chromosome, telomeric region (GO:0000781), chromosome (GO:0005694), nucleoplasm (GO:0005654), site of double-strand break (GO:0035861), and PML body (GO:0016605) (**Table 2**). The molecular function (MF) analysis showed that DEGs were involved in damaged DNA binding (GO:0003684), MutLalpha complex binding (GO:0032405), DNA binding (GO:0003677), p53 binding (GO:0002039), and single thymine insertion binding (GO:0032143) (**Table 3**). Additionally, the KEGG pathway analysis revealed the involvement of DEGs in cellular senescence (hsa04218), platinum drug resistance (hsa01524), homologous recombination (hsa03440), p53 signaling pathway (hsa04115), and the cell cycle (hsa04110). The annotated results were tabulated in **Table 4**.

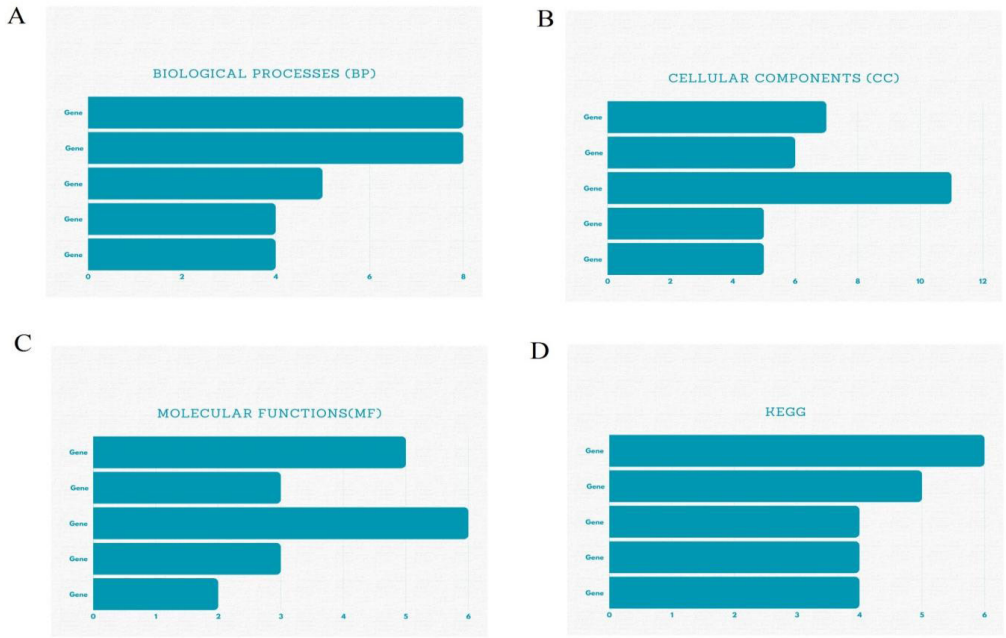

Figure 10. GO and KEGG analysis of ATM by DAVID tool

Table 1. Gene enrichment analysis (BP)

BP			
Gene term	**Gene count**	**Genes**	***P*-value**
GO:0006302~double-strand break repair	08	MRE11, MSH2, CHEK2, ATM, BRCA1, NBN, TP53, ATR	1.4670891505118574E-15
GO:0006974~cellular response to DNA damage stimulus	08	MDC1, MRE11, CHEK2, ATM, BRCA1, TP53BP1, TP53, ATR	2.180060502472521E-11
GO:0000077~DNA damage checkpoint	05	CHEK2, ATM, TP53BP1, NBN, ATR	2.9898564405423035E-9
GO:0090399~replicative senescence	04	CHEK2, ATM, TP53, ATR	5.6279469976638965E-8
GO:0031573~intra-S DNA damage checkpoint	04	CHEK2, ATM, TP53, ATR	6.832071558594709E-8

Table 2. Gene enrichment analysis (CC)

CC			
Gene term	**Gene count**	**Genes**	***P*-value**
GO:0000781~chromosome, telomeric region	07	MRE11, MSH2, CHEK2, ATM, TP53BP1, NBN, ATR	6.720471932650596E-11
GO:0005694~chromosome	06	MRE11, MSH2, CHEK2, ATM, BRCA1, TP53BP1	7.095074850862256E-8
GO:0005654~nucleoplasm	11	MSH6, MDC1, MRE11, MSH2, CHEK2, ATM, BRCA1, TP53BP1, NBN, TP53, ATR	7.313672569344439E-8
GO:0035861~site of double-strand break	05	MDC1, MRE11, TP53BP1, NBN, TP53	8.129255107445212E-8
GO:0016605~PML body	05	MRE11, CHEK2, NBN, TP53, ATR	1.6009955981982125E-7

Table 3. Gene enrichment analysis (MF)

MF			
Gene term	**Gene count**	**Genes**	***P*-value**
GO:0003684~damaged DNA binding	05	MSH6, MSH2, ATR, BRCA1, TP53BP1, TP53	3.371818308101678E-8
GO:0032405~MutLalpha complex binding	03	MSH6, MSH2, ATR	3.7820216211091084E-6
GO:0003677~DNA binding	06	MRE11, MSH2, ATM, BRCA1, TP53, ATR	3.4458833683515824E-4
GO:0002039~p53 binding	03	BRCA1, TP53BP1, TP5	6.151526152403066E-4
GO:0032143~single thymine insertion binding	02	MSH6, MSH2	0.001058901316322019

Table 4. Gene enrichment analysis (KEGG)

KEGG			
Gene term	**Gene count**	**Genes**	***P*-value**
hsa04218:Cellular senescence	06	MRE11, CHEK2, ATM, NBN, TP53, ATR	2.112854669096672E-7
hsa01524:Platinum drug resistance	05	MSH6, MSH2, ATM, BRCA1, TP53	5.666650804938227E-7
hsa03440:Homologous recombination	04	MRE11, ATM, BRCA1, NBN	8.107663061909261E-6
hsa04115:p53 signaling pathway	04	CHEK2, ATM, TP53, ATR	4.846197604830809E-5
hsa04110:Cell cycle	04	MRE11, ATM, TP53, ATR	4.52909326389761E-4

4. Discussion

In this review article, we utilized various online bioinformatics tools to assess *ATM* expression, prognosis, methylation, survival, mutations, and gene enrichment in HNSCC. Furthermore, differentially expressed significant data in HNSCC were validated using OS and DFS. The findings demonstrated the crucial impact of *ATM* expression on the human body and suggested a possible association between *ATM* expression and the development of HNSCC, indicating *ATM* expression as a potential regulator in the pathogenesis of HNSCC.

Currently, there is a lack of solid prognostic biomarkers for HNSCC patients' survival. The discovery of these novel biomarkers will be useful for creating innovative, customized therapeutic strategies that meet the emerging needs of precision medicine [36,37]. TCGA HNSCC data have recently been utilized to study patterns

from both progressors and non-progressors from a network perspective. HNSCC presents a significant challenge for humanity. Conventional prognostic models based on single clinical parameters have limited predictive power. Integrating bioinformatics and clinical data offers a promising approach to improving prediction accuracy. Indeed, gene signatures predicting the prognosis of HNSCC have been established in previous studies. For instance, an NK cell-related gene signature has been reported to perform well in assessing the prognosis of HNSCC patients [38]. An oxidative stress-related gene signature could predict prognosis in HNSCC patients [39], and a prognostic signature based on autophagy, apoptosis, and pyroptosis-related genes was constructed [40]. However, these current signatures were developed by analyzing a small number of specific genes. As we are probably aware, genes with particular functions (e.g., angiogenesis [41], metabolism [42], immune escape [43]) have recently been implicated in cancer development, rather than a specific group of genes with explicit functions.

Located on chromosome 11q23, the *ATM* gene is a tumor suppressor that produces a 350-kDa protein with 3,056 amino acids. The *ATM* gene, which is generally involved in telomere maintenance, oxidative stress, gene regulation, cell cycle control, and apoptosis, is dysregulated in many cancers, including breast cancer (BC). Numerous ATM mutations have been identified and linked to a moderate risk of developing BC [44]. Previous research has highlighted the substantial correlation between ATM mutations and the likelihood of developing BC. The D1853V, L546, and S707P isoforms are linked to the lowest chance of developing BC, while the V2424G variant carries the highest risk [45]. Additionally, the COSMIC database indicates that *ATM* is one of the most aberrant genes in sporadic cancer. Moreover, loss of heterozygosity in the *ATM* region has been found in about 40% of human sporadic BC cases, according to next-generation sequencing (NGS) analysis [46,47]. In larger-scale studies including solid cancers, 5% of patients showed ATM aberrations (either mutation or deletion). According to the description, 8% of patients with lung cancer had ATM mutations, which were mainly mutually exclusive with those of TP53. More recently, it has been discovered that patients with colorectal cancer (CRC) who have both stable and unstable microsatellite tumors also have ATM alterations. Targeted next-generation sequencing of prostate cancer has revealed an 8% incidence of ATM mutations. Between 1% and 5% of endometrial, kidney, liver, esophageal, ovarian, salivary gland, gastric, thyroid, and urinary tract tumors were found to have ATM mutations [45]. The ATM protein function is of significant relevance in cancer research because it plays a critical role in DNA repair by activating enzymes that fix broken strands [48]. In ATM, pathogenic mutations are frequent. Specifically, an ATM mutation is present in about 0.35% of the population, and there is a substantial correlation between ATM mutations and cancer. Researchers validated the previously identified two-fold invasive ductal BC in patients with an ATM mutation and found a four-fold increased risk for pancreatic cancer, a three-fold increased risk for stomach cancer, and a two- to three-fold increased risk for prostate cancer. Additionally, they discovered a low to moderate increase in the incidence of melanoma, colorectal cancer, ovarian cancer, and breast cancer in males. *ATM* is a large gene with thousands of potential sites for mutations. Compared to other *ATM* mutations, a frequent variant called c.7271T>G is associated with a notably higher risk of BC (about four times) [49]. Asian patients are more likely than Caucasian patients to have a high association of ATM variants with BC, mostly because of racial disparities in lifestyle and environmental conditions. Recently, 60,466 specimens from BC patients and 53,461 samples were examined using a panel of 34 potential susceptibility genes created by the Breast Cancer Association Consortium. Furthermore, *ATM* proved to be potentially useful for genetic counseling [50]. As was previously indicated, sporadic BC also exhibits *ATM* mutations that result in *ATM* gene inactivation, but the underlying mechanisms are still unknown. Various mutations have been reported, including allelic loss [51].

The UALCAN database was utilized in the current evaluation to determine *ATM* expression in HNSCC. Upregulation of *ATM* expression was observed in various cancer stages, specific cancer development types,

age groups, genders, and racial groupings. Regarding tumor progression, the findings demonstrated that HNSCC tissues had significantly higher *ATM* expression levels than normal control samples. Additionally, our analysis using the KM plotter tool revealed that, compared to low and high *ATM* expression, HNSCC patients with high *ATM* expression had better overall survival, while HNSCC patients with low *ATM* expression had better disease-free survival. Furthermore, STRING and DAVID tool analysis depicted the diverse nature of the *ATM* gene, showing that *ATM* is interconnected with other genes and plays a crucial role in various biological processes and pathways. In our investigation, we found that *ATM* expression level in tissue was an independent poor prognostic factor. Further evaluations should explore the prognostic value of *ATM* expression in cancer development.

5. Conclusion

Our research concludes that promoter methylation, genetic alterations, and poor overall survival are strongly associated with *ATM* overexpression in HNSCC. By effectively utilizing multiple public databases such as UALCAN, TCGA, cBioPortal, STRING, DAVID, and KM plotter, we have highlighted the diagnostic, predictive, and potentially therapeutic roles of *ATM* in HNSCC. To further test and corroborate these results and investigate the underlying mechanisms causing *ATM* dysregulation in HNSCC, more research is necessary. These findings may eventually contribute to the development of better therapeutic approaches and diagnostic tools for HNSCC patients.

Disclosure statement

The author declares no conflict of interest.

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