

IDENTIFICATION OF KEY HUB GENES AND PROGNOSTIC BIOMARKERS IN HEAD AND NECK CANCER THROUGH INTEGRATED TRANSCRIPTOMIC AND NETWORK ANALYSIS

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ABSTRACT

Head and neck cancer (HNC) is a heterogeneous malignancy with limited reliable prognostic biomarkers. This study aimed to identify molecular signatures associated with HNC progression using integrative transcriptomic and network analyses. In this study, a total of 896 differentially expressed genes (DEGs) were identified, including 412 up-regulated and 484 down-regulated genes. Up-regulated DEGs were enriched in extracellular matrix (ECM) organization, immune and inflammatory responses, and oncogenic signaling pathways, whereas down-regulated genes were associated with epithelial differentiation and metabolic processes. Protein-protein interaction (PPI) network analysis identified key clusters and 46 hub genes. Among these, a combined four-gene signature (MMP1, SPP1, SERPINE1, and SERPINH1) was consistently up-regulated and centrally connected within the network. Validation confirmed that the combined four-gene signature was significantly overexpressed in HNC and associated with poor overall survival. These findings suggest that coordinated ECM remodeling and tumor microenvironment regulation drive HNC progression. The identified signature represents a potential diagnostic and prognostic biomarker with relevance for clinical application.

Keywords: Transcriptomic Analysis, Head and Neck Cancer, Prognostic Biomarkers, Gene Signature, Network Analysis

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INTRODUCTION

Head and neck cancer (HNC) is a significant global health burden, accounting for over 930,000 new cases and approximately 460,000 deaths annually (Sung et al., 2021). HNC ranks as the seventh most common cancer worldwide and contributes to approximately 3% of all cancer-related mortality. It arises from epithelial cells lining the oral cavity, pharynx, and larynx, and is strongly associated with environmental and behavioral risk factors, including tobacco use, alcohol consumption, and oncogenic viral infections, particularly Epstein-Barr virus (EBV) and human papillomavirus (HPV) (Blanco et al., 2021).

Currently, advance in transcriptomic technologies have enabled comprehensive characterization of gene expression alterations in HNC, providing insights into tumorigenic mechanisms, including virus-host interactions in virus-associated cancers and dysregulated signaling pathways in non-viral cases (Farah, 2021). Importantly, these approaches facilitate the identification of multi-gene signatures that may provide improved diagnostic accuracy and prognostic performance compared to single marker. In parallel, considerable efforts have focused on identifying diagnostic and prognostic biomarkers for HNC. Several molecular markers, including p16, TP53, and EGFR, have been widely investigated for their roles in early detection, tumor classification, and prediction of clinical outcomes (Gupta et al., 2024). Notably, p16 overexpression is commonly used as a surrogate marker for HPV-associated HNC and is associated with better prognosis, while TP53 mutations and EGFR overexpression are often linked to poor survival and treatment resistance (Wang et al., 2024). Despite these advances, the clinical utility of individual biomarkers remains limited due to tumor heterogeneity and interpatient variability, highlighting the need for more robust and integrative biomarker strategies for early detection, risk stratification, and outcome prediction.

However, most existing multi-gene signatures are primarily based on statistical associations and often lack functional coherence, limiting their biological interpretability and translational relevance. In contrast, extracellular matrix (ECM)-related genes represent a biologically interconnected network that directly regulates tumor invasion, metastasis, and tumor-microenvironment interactions, suggesting that ECM-focused signatures may provide more mechanistically meaningful and clinically robust biomarkers.

Therefore, this study aims to apply integrative transcriptomic analyses to identify key gene signatures and molecular pathways involved in HNC tumorigenesis. By specifically prioritizing ECM-related hub genes and their network interactions, we seek to identify reliable prognostic biomarkers to improve risk stratification, early diagnosis, and clinical management of HNC patients.

LITERATURE REVIEWS

Head and neck cancer

Head and neck cancer (HNC) is the seventh most common cancer worldwide, accounting for approximately 5% of all malignancies. Over 90% of cases are squamous cell carcinomas (SCC) arising from the epithelial lining of the oral cavity, oropharynx, and larynx, while smaller proportion (5%) originates from salivary glands and sinonasal tissues (Chow, 2020). Globally, HNC represents a major health burden, with approximately 930,000 new cases and 467,000 deaths annually (Sung et al., 2021). The incidence varies geographically, with higher rates observed in South and Southeast Asia due to prevalent risk factors such as tobacco use and betel quid chewing (Chen et al., 2025).

In Thailand, HNC remains a major public health concern, with age-standardized rate (ASR) of approximately 15.7 per 100,000 in males and 10.7 per 100,000 in females (Tangjaturonrasme et al., 2018). Despite advances in treatment, prognosis remains poor, largely due to late-stage diagnosis. Globally, the 5-year overall survival rate for HNC ranges from 40 % to 60 %, while

in Thailand it is approximately 30-35%, with more than 60% of patients presenting at advanced stages (Ngamphaiboon et al., 2025).

The development of HNC is multifactorial, involving environmental, viral, genetic, and epigenetic factors. Tobacco smoking and alcohol consumption are the primary risk factors, contributing to approximately 75% of cases, often acting synergistically to induce DNA damage and carcinogenesis (Hecht & Hatsukami, 2022). Additional risk factors include betel quid chewing and oncogenic viral infections, particularly EBV and HPV. These factors collectively contribute to the complex molecular pathogenesis of HNC, although the precise mechanisms underlying early tumorigenesis remain incompletely understood. (Senevirathna et al., 2023).

Diagnosis and treatment for HNC

HNC is a heterogeneous disease requiring comprehensive diagnostic and therapeutic approaches. Diagnosis relies on clinical examination, imaging, and histopathological confirmation, with biopsy remaining the gold standard. (Zhang et al., 2025). Imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are essential for staging and treatment planning (Yu et al., 2023). However, many patients present with nonspecific symptoms and are diagnosed at advanced stages, limiting treatment success.

Recent studies have emphasized the importance of molecular biomarkers and gene signatures in improving prognostic stratification and guiding therapy. For example, Tang et al. (2022) developed a 14-gene involved in drug absorption, distribution, metabolism, and excretion (ADME)-related signature that stratifies HNC patients into high- and low-risk groups with distinct survival outcomes (Tang et al., 2022). Similarly, Cai et al. (2022) identified a nine-gene mast cell signature (MCS) through single-cell RNA sequencing that was associated with immune infiltration and immunotherapy response (Cai et al., 2022). In another study, Schinke et al. (2022) reported a five-gene EGFR-mediated EMT signature (DDIT4, FADD, ITGB4, NCEH1, and TIMP1) predictive of survival and cetuximab response (Schinke et al., 2022). Ribeiro et al. (2022) integrated three types of omics data including copy number alterations (CNAs), DNA methylation, and mRNA expression profiles to construct a nine-gene signature that effectively predicted patient survival independently of relapse or metastasis (Ribeiro et al., 2022). Despite these notable advances, overall survival rates remain suboptimal, highlighting the need for improved early detection strategies and the identification of robust molecular biomarkers to guide precision medicine in HNC.

Hypothesis

During the carcinogenesis of HNC, multiple genes are dysregulated and act synergistically, particularly those involved in extracellular matrix (ECM) remodeling to drive tumor development and progression. Therefore, identification of these genes through transcriptomic analysis provides insights into HNC pathogenesis and may serve as potential diagnostic and prognostic biomarkers.

Conceptual Framework

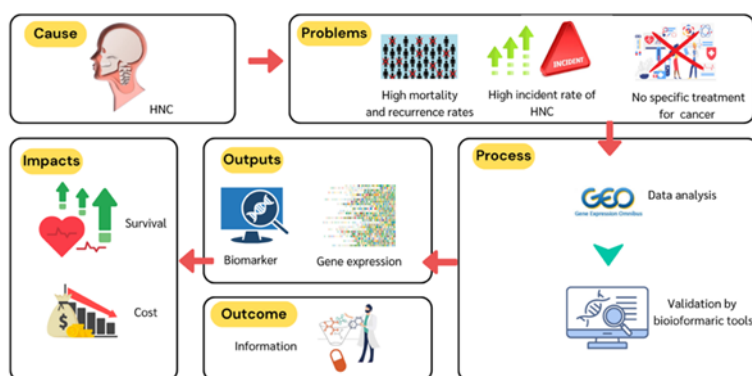


Figure 1 Schematic representation of the conceptual framework of the study

RESEARCH METHODOLOGY

Data retrieval

RNA sequencing (RAN-seq) data for the identification of differentially expressed genes (DEGs) in HNC were obtained from the publicly available dataset GSE227919 in the Gene Expression Omnibus (GEO) database. The GSE227919 dataset was selected based on the following inclusion criteria: (i) availability of both head and neck cancer and corresponding normal tissue samples, (ii) use of primary tumor specimens, (iii) inclusion of treatment-naïve patients, and (iv) generation using RNA-seq technology. However, detailed demographic and clinical characteristics, including smoking status and HPV/EBV infection status, were not available in the dataset.

Data analysis and differential gene expression profiling

Raw RNA sequencing data were first subjected to quality assessment using FastQC. High-quality reads were then aligned to the human reference genome (GRCh38) using HISAT2. Gene-level quantification was performed using HTSeq to generate read count metrics, which were subsequently used for differential expression analysis with the DESeq2 package in RStudio (version 4.4). Differentially expressed genes (DEGs) were defined based on an adjusted p-value < 0.05 and a $\log_2(\text{fold change}) \geq 2$ for up-regulated genes or ≤ -2 for down-regulated genes. Visualization of DEGs was conducted in RStudio using the pheatmap package for heatmap generation and the ggplot2 package for volcano plot construction.

Functional and pathway enrichment analysis

Functional enrichment analyses were performed to investigate the biological relevance of DEGs in HNC. Gene ontology (GO) enrichment analysis was conducted using the database for annotation, visualization, and integrated discovery (DAVID, v2023q4), categorizing genes into biological process (BP). In addition, Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis was performed to identify significantly enriched signaling pathways. The top ten enriched terms were visualized as bubble plots using ggplot2 package in RStudio.

Protein-protein interaction network analysis of DEGs

Protein-protein interaction (PPI) networks of DEGs were constructed using the search tool for the retrieval of interacting genes/proteins (STRING) plugin in Cytoscape software (version 3.10.3). Key network modules were identified using the molecular complex detection (MCODE) plugin (degree cut-off = 2, max depth = 100, and MCODE score > 2), and the top five clusters were selected for further analysis. Hub genes were identified using CytoHubba plugin with three topological algorithms, including maximal clique centrality (MCC), maximum neighborhood component (MNC), and density of maximum neighborhood component (DMNC). The top 20 genes from each method were compared, and genes identified by at least two algorithms were defined as hub genes.

Validation of gene expression and survival analysis

Expression patterns and prognostic significance of candidate hub genes were validated using the gene expression profiling interactive analysis 2 (GEPIA2) web server. Analysis was performed using the default parameters with applying a $\log_2(\text{fold change})$ cutoff of 2 and an adjusted $p\text{-value} < 0.05$. Overall survival (OS) analysis was conducted using the Kaplan-Meier method, patients stratified into high- and low-expression groups based on median gene expression levels. Statistical significance was evaluated using the log-rank test, with $p\text{-value} < 0.05$ considered significant.

RESEARCH RESULTS

Identification of differentially expressed genes (DEGs)

To identify the dysregulated genes during HNC carcinogenesis, differential gene expression analysis was performed. In this study, we detected 26,479 expressed genes. Of these, 412 genes were significantly up-regulated, while 484 genes were down-regulated in HNC compared to normal samples (Figure 2A). As expected, the clear distinct expression patterns were observed among HNC and normal samples, suggesting their roles in HNC carcinogenesis (Figure 2B).

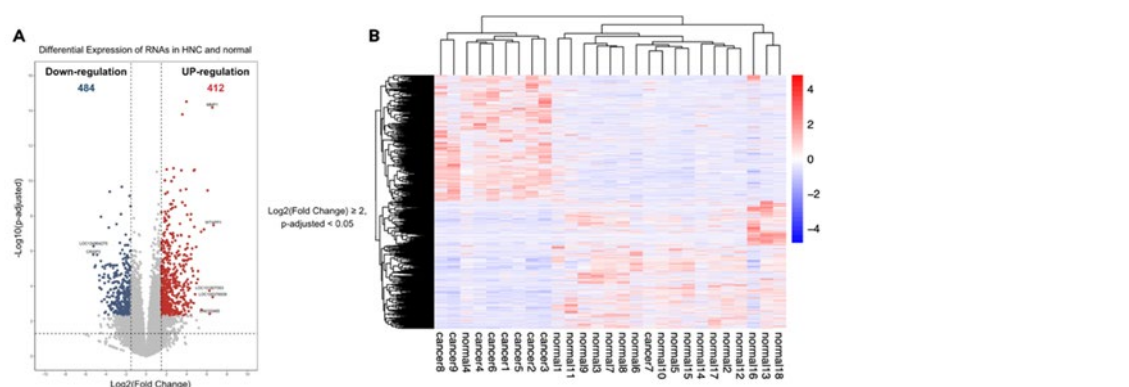


Figure 2 Differential gene expression analysis in HNC. (A) Volcano plot showing upregulated (red) and downregulated (blue) genes between HNC and normal tissues ($\log_2(\text{fold change}) \leq -2$ or ≥ 2 , adjusted $p\text{-value} < 0.05$). (B) Heatmap of DEGs illustrating expression patterns and hierarchical clustering across samples.

Gene ontology (GO) and KEGG pathway enrichment analysis

To determine the biological relevance of the DEGs, functional and pathway enrichment analyses were performed. As shown in Figure 3, in terms of BP, the up-regulated DEGs were significantly enriched in ECM organization, immune and inflammatory responses, cell adhesion, and angiogenesis (Figure 3A), while down-regulated DEGs were associated with epithelial differentiation, lipid metabolism, and intracellular homeostasis (Figure 3B). In addition, KEGG pathway analysis showed that up-regulated DEGs were mainly associated with ECM-receptor interaction, focal adhesion, PI3K-Akt, TNF, and JAK-STAT signaling pathways (Figure 3C), whereas down-regulated DEGs were involved in drug metabolism, xenobiotic metabolism, and glutathione metabolism (Figure 3D). Thus, these results suggest the potential roles of DEGs in contribution to HNC carcinogenesis through the modulation of cellular processes and signaling pathways.

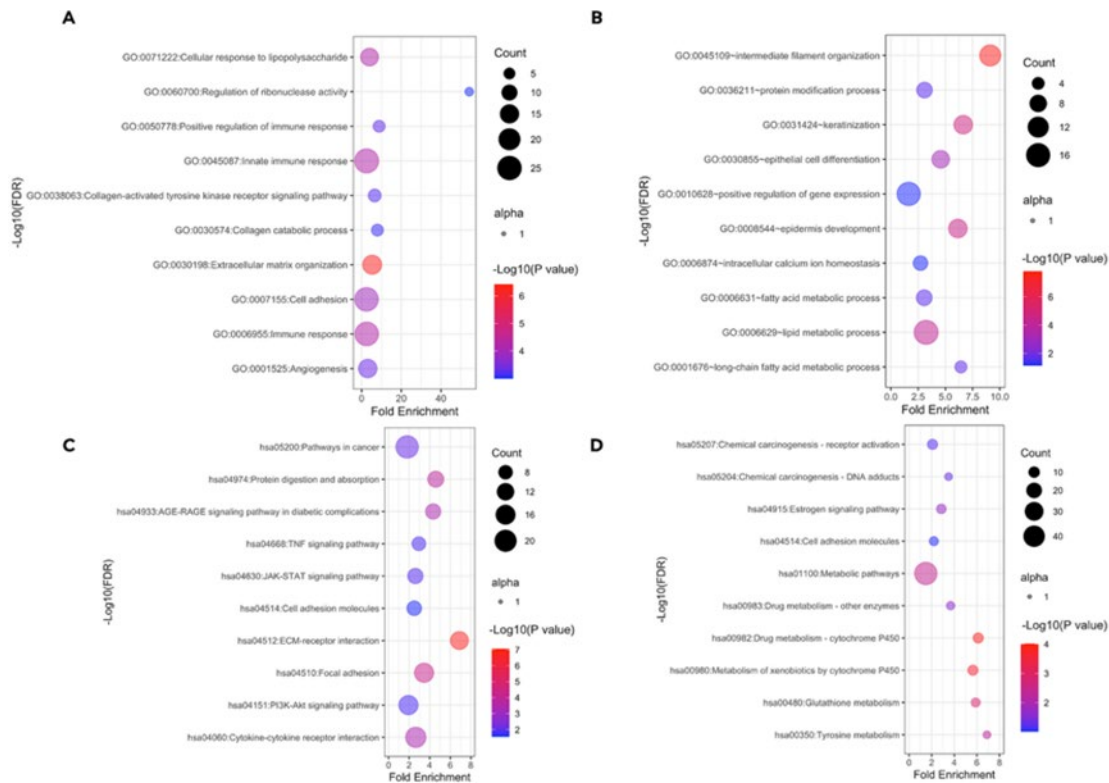


Figure 3 GO and KEGG enrichment analysis of DEGs. Bubble plots illustrating the top enriched GO biological process (BP) terms for up-regulated (A) and downregulated (B) genes, and KEGG pathways for up-regulated (C) and down-regulated (D) genes. Bubble size represents gene count, while color intensity reflects statistical significance ($-\log_{10}$ p-value).

PPI network construction and hub module identification

To identify key regulatory genes involved HNC carcinogenesis, PPI networks were constructed from DEGs. A total of 11 clusters were identified for up-regulated DEGs, with top three clusters primarily associated with cytokine signaling, immune response, extracellular matrix (ECM) organization, and cell proliferation (Figure 4A). In contrast, 9 clusters were constructed from down-regulated DEGs, with top three clusters mainly enriched in epidermal differentiation, keratinization, metabolic processes, and muscle-related functions (Figure 4B). Hub genes were subsequently identified from upregulated DEGs using the CytoHubba plugin, resulting in the identification of 46 hub genes across all clusters. Thus, these hub genes may represent key regulatory elements driving HNC progression and may serve as prognostic biomarkers.

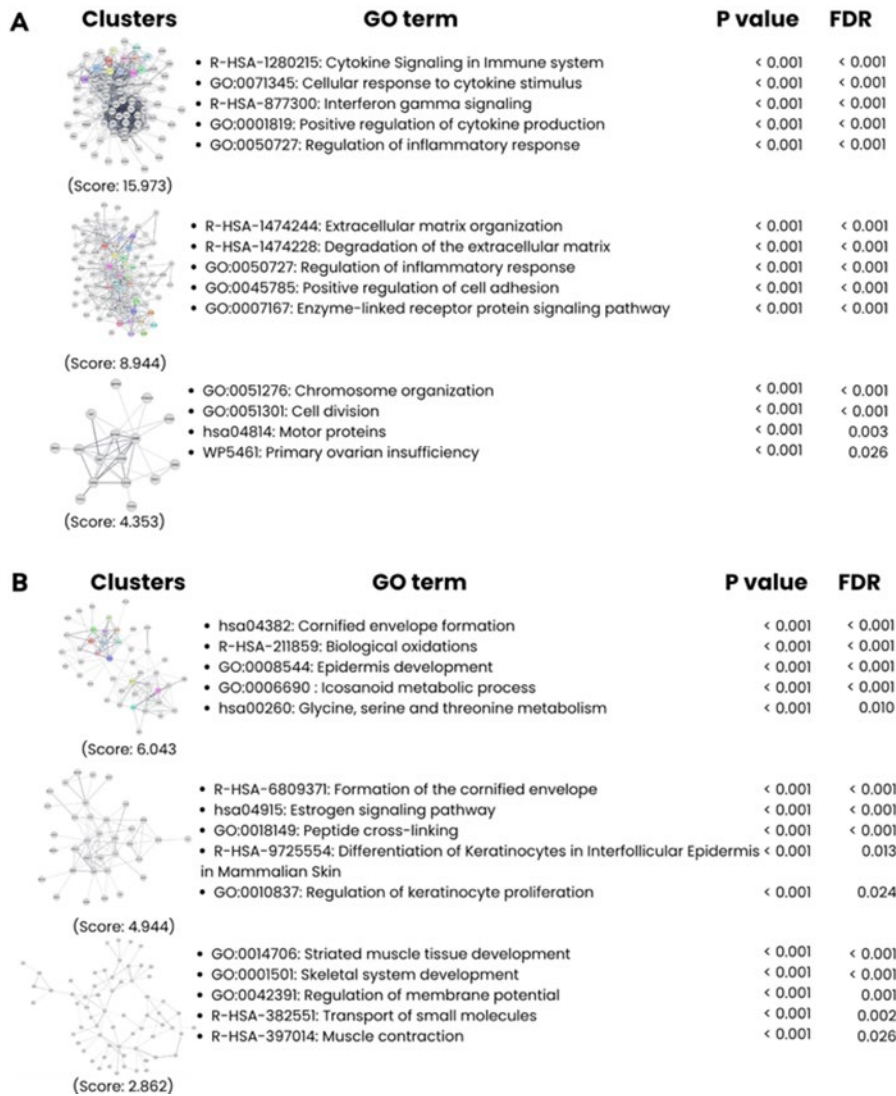


Figure 4 Functional enrichment analysis of PPI network clusters. Top enriched GO terms and pathways for (A) up-regulated and (B) down-regulated DEG clusters identified by Cytoscape.

Validation gene expression and survival analysis

The expression levels of 46 candidate hub genes were validated using the GEPIA2 database, of which 4 genes, including SERPINH1, SPP1, MMP1, and SERPINE1, were significantly associated with OS, with higher expression linked to poorer prognosis (Figure 5). The four-gene signature was significantly associated with OS (log-rank $p = 0.003$; HR = 1.5). Individually, elevated expression of SERPINH1 ($p = 0.022$; HR = 1.4), SPP1 ($p = 0.045$; HR = 1.3), MMP1 ($p = 0.046$; HR = 1.3), and SERPINE1 ($p = 0.00024$; HR = 1.5) was also associated with reduced OS (Figure 5A-E). Subsequent expression analysis confirmed that both the combined four-gene signature and each individual gene were significantly overexpressed in tumor tissues compared with normal samples (Figure 6A-E). Collectively, these findings support the four-gene signature as a potential prognostic biomarker in HNC.

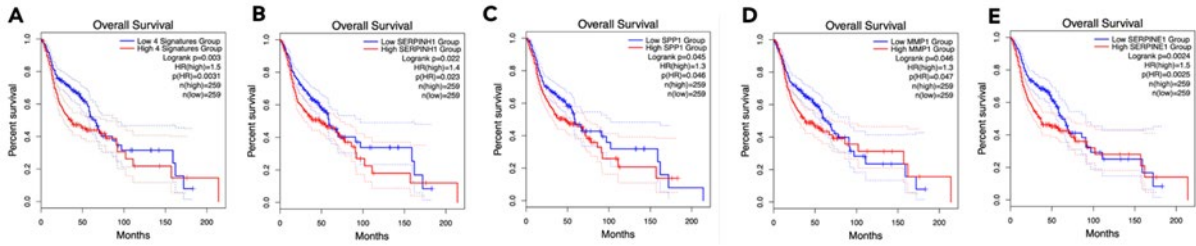


Figure 5 Kaplan-Meier survival analysis of hub genes in HNC. Overall survival curves comparing high- and low-expression groups for (A) four-gene signature, (B) SERPINH1, (C) SPP1, (D) MMP1, and (E) SERPINE1. Red indicates high expression and blue indicates low expression.

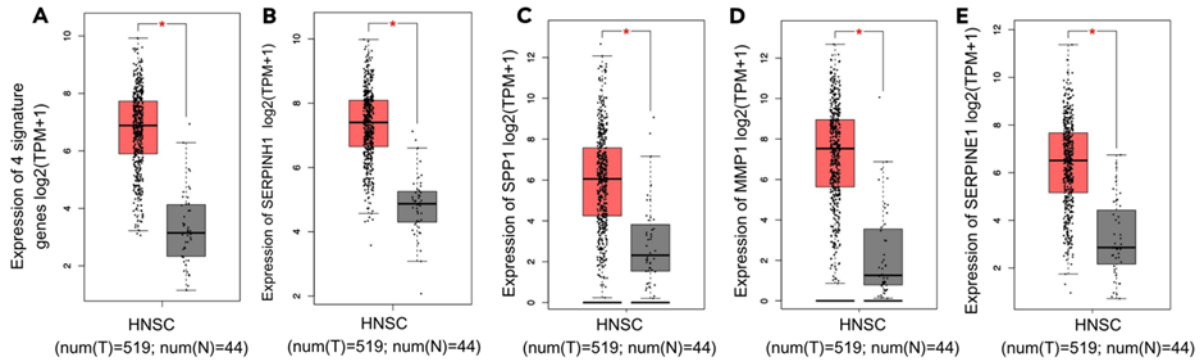


Figure 6 Validation of hub gene expression in HNC. (A) four-gene signature, (B) SERPINH1, (C) SPP1, (D) MMP1, and (E) SERPINE1. Red, tumor; gray, normal. $p < 0.05$.

DISCUSSION & CONCLUSION

HNC is a heterogeneous malignancy with limited robust prognostic biomarkers, underscoring the need for comprehensive molecular characterization approaches to define reproducible molecular signatures driving disease progression. In the present study, integrative transcriptomic analysis identified 896 DEGs, with distinct expression patterns clearly distinguishing tumor from normal tissues. Functional enrichment analyses revealed that upregulated DEGs were predominantly associated with ECM organization, immune and inflammatory responses, and oncogenic signaling pathways, including PI3K-Akt and JAK-STAT, whereas downregulated DEGs were mainly involved in epithelial differentiation, keratinization, and metabolic processes, reflecting loss of epithelial homeostasis during tumorigenesis. Consistently, previous studies have been reported the activation of oncogenic pathways, including EGFR signaling, MAPK/ERK cascade, NF- κ B signaling, Wnt/ β -catenin pathway, and TGF- β signaling in HNC (Li et al., 2023; Molinolo et al., 2009; Pang et al., 2018). Therefore, these findings suggest that disruption of ECM dynamics and epithelial integrity is a central feature of HNC and should be prioritized in future mechanistic studies.

PPI network analysis identified MMP1, SERPINE1, SERPINH1, and SPP1 as centrally connected hub genes enriched in ECM remodeling and tumor-related pathways. Their coordinated upregulation in HNC and association with poor overall survival suggest that they function as a pro-tumorigenic functional module rather than isolated markers. This aligns with the concept that tumor progression is driven by dynamic interactions between cancer cells and the tumor microenvironment (Hynes, 2009; Lu et al., 2012). Within this module, MMP1 acts as a key effector of ECM degradation and invasion by promoting collagen breakdown (Egeblad & Werb, 2002; Kessenbrock et al., 2010), while SERPINH1 (HSP47) supports collagen folding and ECM stabilization, contributing to matrix deposition and structural integrity (Taguchi & Razaque, 2007). The coexistence of ECM-degrading and ECM-stabilizing components

suggests active matrix remodeling and a stiff, invasion-permissive tumor stroma. In addition, SERPINE1 (PAI-1) regulates proteolytic balance and tumor progression, while SPP1 (osteopontin) mediates cell-matrix interactions, immune modulation, and tumor-stroma communication. (Duffy, 2004; Duffy et al., 2014; Liaw et al., 1998; Wai & Kuo, 2008). Collectively, these four genes form an interconnected ECM remodeling and tumor microenvironment regulatory module in which MMP1 drives matrix degradation, SERPINH1 supports collagen maturation, SERPINE1 regulates proteolytic activity, and SPP1 mediates stromal and immune interactions. This coordinated network promotes ECM reorganization, tissue stiffness, tumor invasion, and disease progression, providing a systems-level perspective with greater biological relevance than single-gene biomarkers.

In conclusion, the identified gene signature represents a robust ECM-associated regulatory module in HNC and may serve as a promising tool for risk stratification and outcome prediction. However, further functional validation and large-scale clinical studies are required to confirm its applicability in clinical practice. Future studies should focus on experimental validation, exploration of therapeutic targeting, and integration into clinical decision-making frameworks.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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