Original Article

A prognostic model for laryngeal squamous cell carcinoma based on the mitochondrial metabolism-related genes

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Background: Mitochondrial metabolism-related genes (MMRGs) have emerged as potential therapeutic targets in cancer. This study aimed to construct a prognosis model based on MMRGs for patients with laryngeal squamous cell carcinoma (LSCC).

Methods: Differentially expressed MMRGs in LSCC were identified from The Cancer Genome Atlas (TCGA) and Molecular Signatures Database (MSigDB). Their functions were characterized by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG). A prognostic model was established using univariate, least absolute shrinkage and selection operator (LASSO), and multivariate Cox regression analyses, and its performance was evaluated using Kaplan-Meier and receiver operating characteristic (ROC) curves. Gene set enrichment analysis (GSEA) was performed to elucidate the biological pathways associated with the hub prognostic MMRGs. Genetic perturbation similarity analysis (GPSA) was used to determine the regulatory network of hub genes. Additionally, the correlation of the hub MMRGs with the immune microenvironment and drug sensitivity was investigated.

Results: We identified 308 differentially expressed MMRGs, enriched in various metabolic processes and pathways. The prognostic model comprising four hub MMRGs (*POLD1*, *PON2*, *SMS*, and *THEM5*) accurately predicted patient outcomes, with the high-risk group exhibiting poorer survival. Additionally, high expression of *POLD1* and *THEM5* while low expression of *PON2* and *SMS* indicated better prognosis for LSCC patients. GSEA revealed pathways correlated with each prognostic MMRG, such as PI3K-AKT-mTOR signaling pathways, while GPSA identified key regulatory genes interacting with four hub MMRGs. Furthermore, differences in the tumor immune microenvironment and somatic mutation profiles were observed between high- and low-risk groups. Finally, the correlation of four hub MMRGs with 30 drug sensitivity was revealed.

Conclusions: This study highlights the prognostic significance of MMRGs in LSCC and underscores their potential as biomarkers for LSCC therapy.

Keywords: Laryngeal squamous cell carcinoma (LSCC); mitochondrial metabolism-related gene (MMRG); prognosis; mutation; immune microenvironment

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Introduction

Laryngeal squamous cell carcinoma (LSCC) is one of the most common malignancies of the head and neck region (1). New cases of laryngeal cancer exceeded 180,000 worldwide in 2020, among which more than 90% of cases were squamous cell carcinoma (2). Due to the subtle nature of early symptoms, approximately 60% of patients are diagnosed at an advanced stage. Advanced LSCC patients typically present with difficulty swallowing and breathing, greatly impacting their quality of life (3). Despite advancements in treatment modalities, including surgery, chemotherapy, radiotherapy, and even immunotherapy, the prognosis for LSCC patients remains variable. The 5-year survival rate of LSCC patients in the advanced stage is below 50% (4). The poor prognosis of LSCC emphasizes the need for novel prognostic markers and therapeutic targets for LSCC.

In recent years, there has been growing recognition of the role of mitochondrial metabolism (MM) in cancer progression and treatment response (5). Maintaining proliferation and evading apoptosis are hallmark characteristics of cancer. Mitochondria regulate extensive energy metabolism-associated signaling networks and serve as crucial organelles in balancing oxidative stress and cell death processes during cellular proliferation (6). Metabolic reprogramming is essential for cancer cells to sustain unlimited proliferative and metastatic potential (7). Initially, the Warburg effect characterized cancer cells by an increased rate of glycolysis, where pyruvate is primarily converted to lactate (8). However, subsequent research has revealed that some cancer cells exhibit metabolic plasticity to adapt to changes in the tumor microenvironment (TME), shifting their metabolism from glycolysis to oxidative phosphorylation (OXPHOS) (9). OXPHOS may be a primary metabolic pathway for cancer stem cells and is often implicated in cancer drug resistance, metastasis, and tumor recurrence (10,11). Targeting MM has emerged as a promising strategy in cancer therapy, such as breast cancer (12), thyroid cancer (13), and colorectal cancer (14). A previous study identified the metabolism-related genes as prognostic biomarkers in head and neck squamous cell carcinoma (15). However, the role of MM-related genes (MMRGs) in the prognosis of LSCC patients has not been explored.

In this study, we constructed a prognostic model integrating MMRGs and evaluated its prognostic performance. Our study aims to advance our understanding of the MMRG's role in LSCC progression and prognosis, thus improving patient management and clinical outcomes in LSCC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1436/rc).

Highlight box

Key findings

- A four-gene prognostic model related to mitochondrial metabolism (MM) was constructed, with promising predictive performance in the prognosis of laryngeal squamous cell carcinoma (LSCC).

What is known, and what is new?

- It is known that MM-related genes (MMRGs) have emerged as potential therapeutic targets in many cancers.
- This study revealed the prognostic significance of MMRGs in LSCC and identified four key MMRGs associated with immune-related signaling pathways.

What is the implication, and what should change now?

- The four hub MMRGs are expected to become biomarkers in LSCC prognosis.

Methods

Data acquisition

RNA-sequencing data and clinical information of LSCC were acquired from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov). MMRGs were screened from the Molecular Signatures Database (MSigDB) database (https://www.gsea-msigdb.org/gsea/msigdb). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Differentially expressed MMRG identification and functional enrichment analysis

The Limma package in R version 4.1.2 was employed to identify differentially expressed genes (DEGs) based on the TCGA dataset, and DEGs were visualized using a volcano plot. The threshold was set as $P<0.05$ and $|\text{fold change}| \geq 1.5$. Following intersecting the DEGs and MMRGs, differentially expressed MMRGs in the LSCC were screened out using the VennDiagram package in R.

Next, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted based on the differentially expressed MMRGs using R package clusterProfiler and org.Hs.eg.db, with

criteria of P<0.05.

Construction and validation of the prognostic model

Univariate Cox regression analysis was initially conducted on the differentially expressed MMRGs to identify genes associated with the prognosis of LSCC patients. Subsequently, least absolute shrinkage and selection operator (LASSO) regression was applied using the "glmnet" package in R. The LASSO method could reduce the number of genes in the model and mitigate the issue of overfitting, thereby reducing redundancy in the predictive framework. Following this, hub prognostic genes were determined through multivariate Cox regression. These genes were then utilized to construct a prognostic model for LSCC. The risk scores for each LSCC patient in TCGA were calculated as follows:

$$Risk\ score = \sum_{1}^{i} \exp_{RNAi} \times coef_{RNAi} \quad [1]$$

Based on the optimal truncation value of the risk score, the patients in the TCGA dataset were divided into two different risk groups. Kaplan-Meier curves were used to compare the overall survival time in low- and high-risk groups. A receiver operating characteristic (ROC) curve was constructed to evaluate prognostic performance at 1-, 3-, and 5-year using the survival package, and the area under the curve (AUC) value was calculated.

Evaluation of the hub prognostic MMRGs

The expression levels of hub prognostic MMRGs were compared between the low- and high-risk groups. Kaplan-Meier curves were constructed to determine the predictive performance of the four hub MMRGs.

Single-sample gene set enrichment analysis (ssGSEA) and protein-protein interaction (PPI) network construction

To further explore the underlying mechanism of hub genes in LSCC, ssGSEA analysis was performed to find out the hub prognostic MMRGs-related pathways using the GSVA package. Genes that modulate the hub prognostic genes were then searched from the genetic perturbation similarity analysis (GPSA) database (https://www.gpsadb.com/). Then, a Venn diagram was used to screen the overlapping genes that regulate all of the hub prognostic genes. Finally, a PPI network showing the interaction of overlapping genes with hub genes was generated in the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (http://stringdb.org). The network was visualized using Cytohubba in Cytoscape 3.7.0.

Immune infiltration analysis

To reveal the difference in immune cell infiltration between two different risk groups, the xCell algorithm was used based on the TCGA dataset. The expression levels of immune checkpoint regulators in the high- and low-risk groups were further compared using the Wilcoxon. Finally, the Pearson method was used to reveal the correlation among immune cells, immune factors, and hub prognostic genes.

Mutation analysis

After obtaining mutation files of LSCC from the TCGA database, the gene mutation landscape of LSCC between the different risk groups was evaluated using the Maftools package.

Drug-sensitive analysis

After the hub genes were determined based on the above analysis, drug sensitivity analysis of hub genes was performed in the Gene Set Cancer Analysis (GSCA) database (https://guolab.wchscu.cn/GSCA/#/). The correlation of hub prognostic genes with potential drugs was determined through the Pearson method. P<0.05 was considered statistical significance.

Statistical analysis

Statistical analyses were performed using R version 4.1.2. A comparison between the two groups was conducted using the *t*-test. Statistical significance was set as P<0.05.

Results

Identification and functional analysis of MMRGs in LSCC

There were 4,639 DEGs in the LSCC RNA-sequencing data from the TCGA (*Figure 1A*). Subsequently, 308 overlapping genes between these DEGs and 1,234 MMRGs were obtained through a Venn diagram (*Figure 1B*). GO enrichment analysis showed that the biological processes of

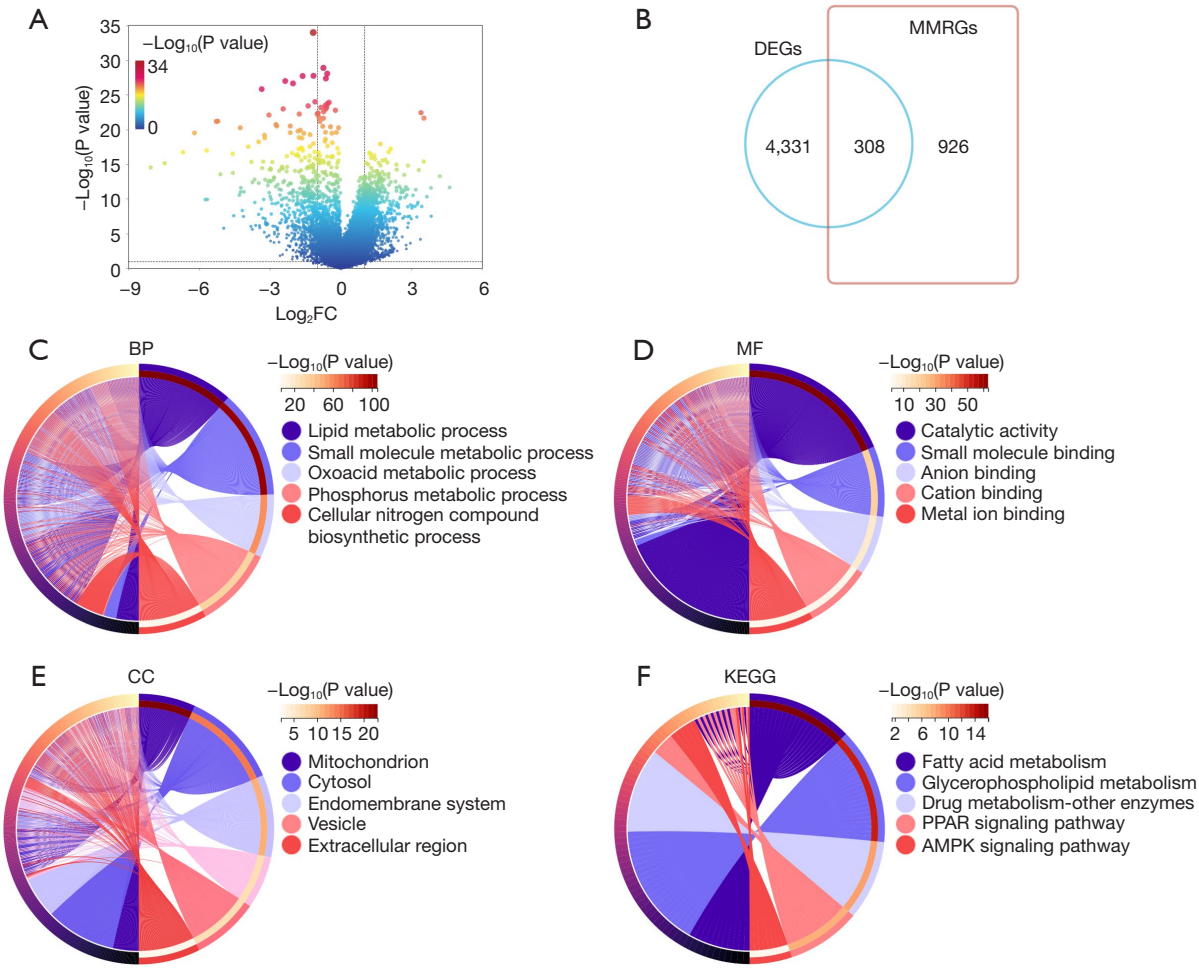

Figure 1 Identification and functional analysis of MMRGs in LSCC. (A) Volcano plot of DEGs in normal and tumor samples within LSCC patients. (B) Identification of overlapping genes between DEGs and MMRGs. (C-F) GO and KEGG enrichment analyses based on the overlapping genes: (C) BP terms of GO, (D) MF terms of GO, (E) CC terms of GO, (F) KEGG pathways. FC, fold change; DEGs, differentially expressed genes; MMRGs, mitochondrial metabolism-related genes; BP, biological process; MF, molecular function; CC, cellular components; KEGG, Kyoto Encyclopedia of Genes and Genomes; LSCC, laryngeal squamous cell carcinoma; GO, Gene Ontology.

the 308 DEGs were major associated with lipid metabolic process, small molecule metabolic process, oxoacid metabolic process, phosphorus metabolic process, and cellular nitrogen compound biosynthetic process (*Figure 1C*). Molecular functions were related to catalytic activity, small molecule binding, anion binding, cation binding, and metal ion binding (*Figure 1D*). Cellular compounds were mainly correlated with mitochondrion, cytosol, endomembrane system, extracellular region, and vesicle (*Figure 1E*). Additionally, KEGG pathways of the 308 genes were prominently enriched in fatty acid metabolism, glycerophospholipid metabolism, drug metabolism-other enzymes, PPAR signaling pathway, and AMPK signaling (*Figure 1F*).

Construction and assessment of the prognostic model

Based on the 308 differentially expressed MMRGs, univariate Cox regression analysis was performed to identify 25 MMRGs that were significantly related to the prognosis of LSCC patients (*Figure 2A*). Next, using the LASSO regression analysis, 13 MMRGs were screened out, with a λ value of 0.11. The correlation coefficient change curve and cross-validation curve are presented in *Figure 2B*. Multivariate Cox regression analysis further identified four hub prognostic MMRGs (P<0.05; *Figure 2C*), including *POLD1* [hazard ratio (HR) =0.384; 95% confidence interval (CI): 0.192–0.769], *PON2* (HR =1.628; 95% CI:

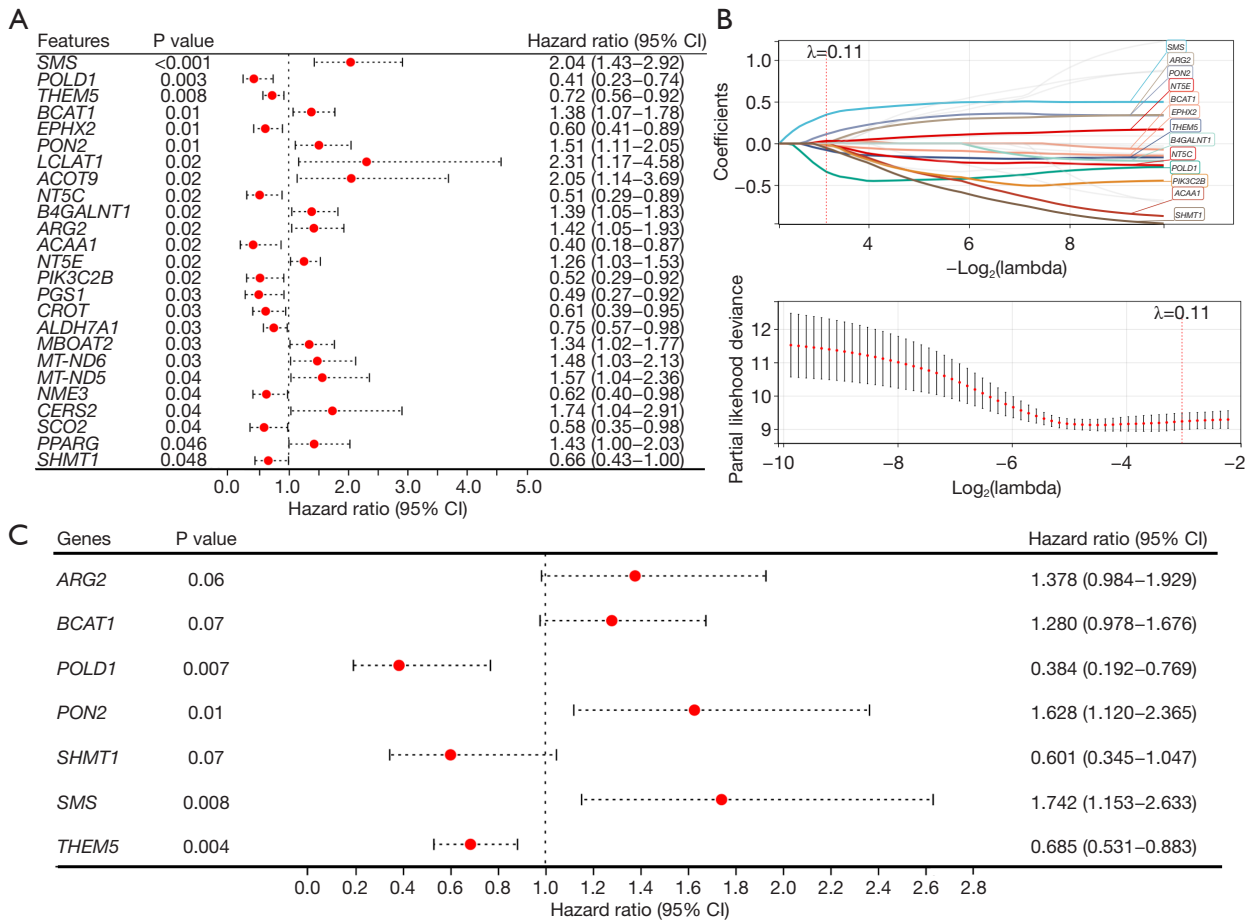

Figure 2 Construction of the prognostic model. (A) Univariate Cox regression analysis based on the differentially expressed MMRGs. (B) Correlation coefficient change curve and cross-validation curve. (C) Multivariate Cox regression analysis identified four hub MMRG-related prognostic genes. CI, confidence interval; MMRGs, mitochondrial metabolism-related genes.

1.12–2.365), *SMS* (HR =1.742; 95% CI: 1.153–2.633), and *THEM5* (HR =0.685; 95% CI: 0.531–0.883). A prognostic risk model was constructed according to the regression coefficients and expression levels of the identified four hub MMRGs. The risk score was calculated as:

$$Risk\ score = -0.956 \times POLD1 + 0.487 \times PON2 + 0.555 \times SMS - 0.379 \times THEM5 \quad [2]$$

Furthermore, to evaluate the prognostic performance of this risk model, LSCC patients in the TCGA dataset were divided into high- and low-risk groups based on the optimal truncation value of their risk scores. Low-risk group exhibited longer survival time than the high-risk group (*Figure 3A*). In addition, the AUC values at 1-, 3-, and 5-year were 0.67, 0.79, and 0.81, respectively (*Figure 3B*). These results revealed that the risk model accurately predicted the prognosis of LSCC patients.

Validation of four hub MMRGs as the potential prognostic biomarkers in LSCC

To further investigate the prognostic value of four hub MMRGs in LSCC, their expression between different risk groups and the correlation with survival time were analyzed. Higher expression of *POLD1* and *THEM5* were observed in the low-risk group compared with the high-risk group (P<0.001; *Figure 4A*), and high expression of *POLD1* and *THEM5* indicated a better prognosis (*Figure 4B*). In contrast, expression levels of *PON2* and *SMS* were higher in the high-risk group than those in the low-risk group (P<0.01; *Figure 4A*), and their high expression indicated a poor prognosis (*Figure 4B*).

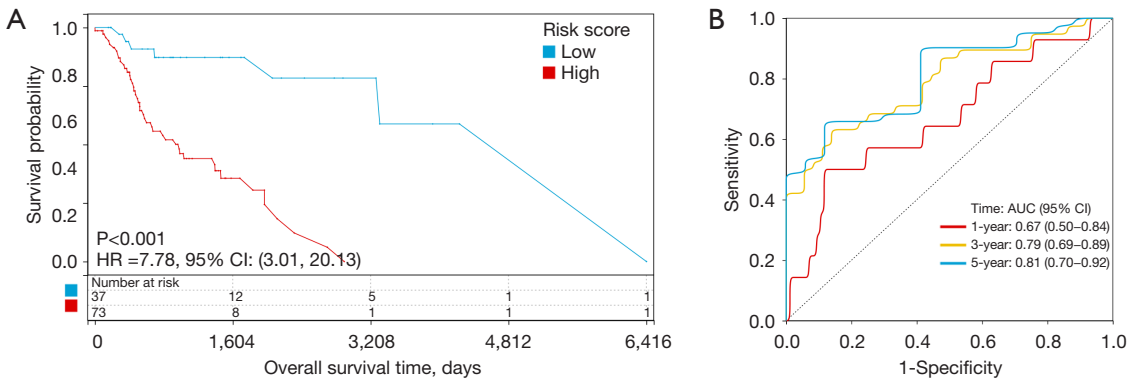

Figure 3 Assessment of the prognostic model. (A) Kaplan-Meier curve of LSCC patients in the low- and high-risk group. (B) ROC curve at 1-, 3-, and 5-year. HR, hazard ratio; CI, confidence interval; AUC, area under the curve; LSCC, laryngeal squamous cell carcinoma; ROC, receiver operating characteristic.

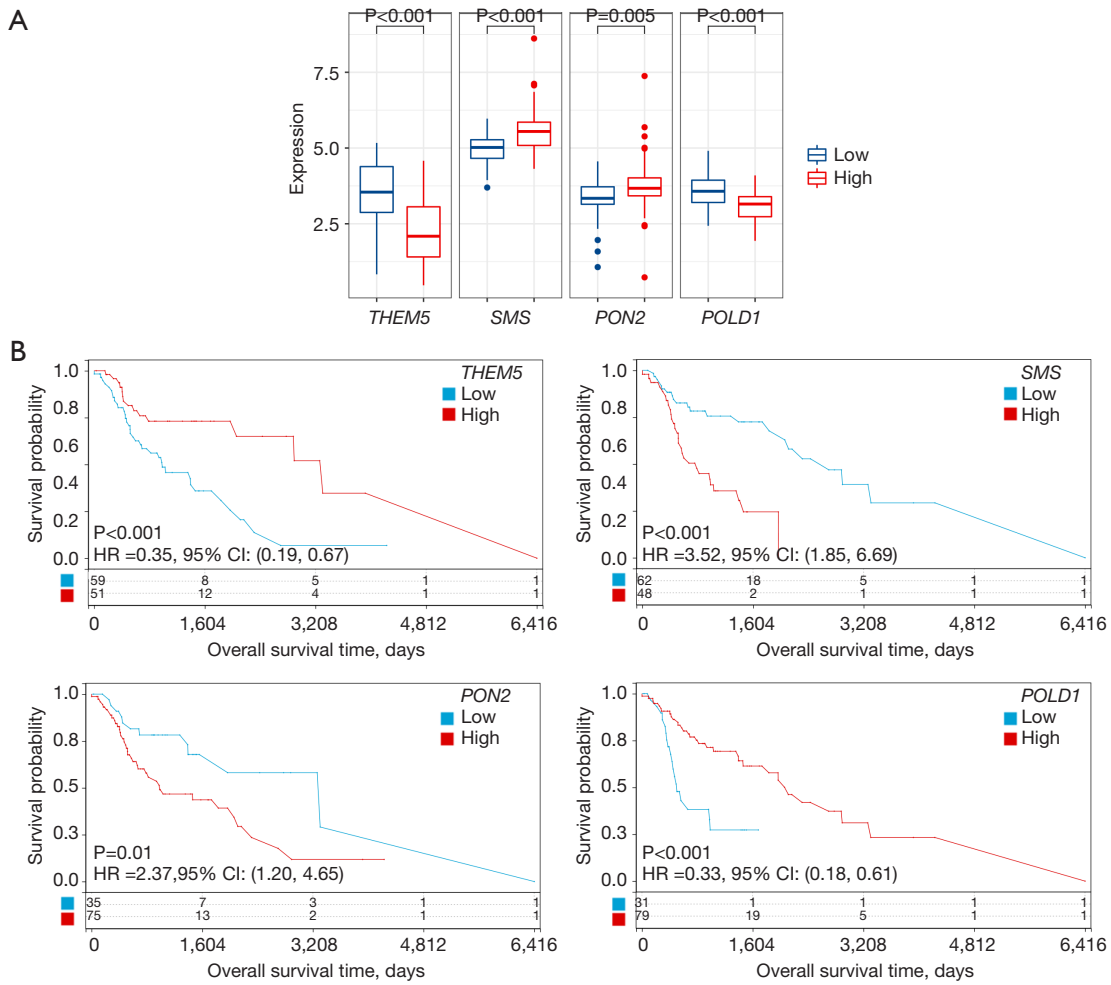

Figure 4 Validation of four MMRGs as the potential prognostic biomarkers. (A) Expression of four MMRGs in the low- and high-risk groups. (B) Kaplan-Meier curve of LSCC patients in the low expression and high expression of *THEM5*, *SMS*, *PON2*, or *POLD1*. HR, hazard ratio; CI, confidence interval; LSCC, laryngeal squamous cell carcinoma; MMRGs, mitochondrial metabolism-related genes.

GSEA was then performed to analyze the enriched pathways of the four prognostic genes. *POLD1* positively correlated with IL6-JAK-STAT3, p53, and PI3K-AKT-mTOR signaling pathways (*Figure 5A*). *PON2* exhibited positive correlations with angiogenesis, epithelial-mesenchymal transition, and TGF-β signaling (*Figure 5B*). *SMS* is positively related to mTORC1 signaling, OXPHOS, and Wnt-β catenin signaling (*Figure 5C*). Besides, *THEM5* was negatively associated with apoptosis, IL2-STAT5 signaling, and TNFA signaling via NFKB (*Figure 5D*).

Furthermore, we explored the gene sets regulating these four hub genes based on the GPSA database. A total of 99 genes, such as STAT3, FOXO1, and KLF4, were found to interact with all four genes, visualized in a Venn diagram (*Figure 6A*). The interaction between these upstream genes and the four prognostic genes was visualized through a PPI network (*Figure 6B*).

Difference of tumor immune microenvironment in different risk groups

The tumor immune microenvironment is essential to cancer progression. we further explored the difference in immune microenvironment between the two different risk groups. Immune infiltration analysis identified five immune cells [$CD4^+$ central memory T cells, $CD8^+$ naive T cells, $CD8^+$ T cells, natural killer (NK) T cells, and Th1 cells], with more number in the low-risk group ($P<0.05$; *Figure 7A*). Further analysis revealed the differential expression of immune checkpoint regulators in different risk groups. Compared to the low-risk group, expression levels of IL6 and VTCN1 were elevated while expression levels of RAET1E and TNFRSF25 were reduced in the high-risk group ($P<0.05$; *Figure 7B*). The correlation among five immune cells, four immune checkpoint regulators, and four hub genes was visualized in *Figure 7C*.

Mutation and drug sensitivity analysis

Cancer cells gather somatic mutations throughout a lifetime, which is important to cancer progression (16). Somatic mutation analysis showed that all LSCC samples in the low-risk group had somatic mutations (*Figure 8A*), and 70 samples (97.22%) of 72 LSCC samples had mutations in the high-risk group (*Figure 8B*). TP53 had the highest mutation frequency, with 88% in the high-risk group and 81% in the low-risk group, followed by TTN and CSMD3 (*Figure 8A,8B*).

Additionally, we screened the potential drugs for LSCC patients from the Genomics of Drug Sensitivity in Cancer (GDSC) database. The correlation between 30 GDSC drug sensitivity and messenger RNA (mRNA) expression of four prognostic genes is shown in *Figure 9*. *PON2* was positively related to almost all drugs except for 17-AGG. In contrast, *POLD1* and *THEM5* were negatively correlated with most of these drugs except for 17-AGG. SMS was only negatively related to PIK-93.

Discussion

Mitochondria influence cancer progression by modulating mitochondrial dynamics and metabolism reprogramming (17). MM is a promising therapeutic target for cancer. However, the role of MM in LSCC is still elusive. This study identified 308 differentially expressed MMRGs in LSCC. Based on these MMRGs, a prognostic model containing four hub MMRGs, namely POLD1, PON2, SMS, and THEM5, was constructed through LASSO Cox regression. Further analyses explored TME-related pathways associated with four hub prognostic MMRGs. Moreover, there were significant differences in the TME between low- and high-risk groups.

Mitochondria are the metabolism hub, and their changes are closely associated with various cellular events such as apoptosis and various pathologies (18). Studies have shown significant changes in cellular metabolism and mitochondria in cancer cells (19,20). The adenosine triphosphate (ATP) generated by MM is crucial for tumor growth. Previous research has reported pathways inducing apoptosis in LSCC cells by targeting mitochondria. For instance, epidermal growth factor receptor monoclonal antibodies induce a decrease in mitochondrial membrane potential in LSCC, ultimately activating the mitochondrial apoptosis pathway (21). Melatonin increases mitochondrial ROS generation in head and neck cancer to drive apoptosis (22). Combination therapy with cetuximab and oridonin enhances the mitochondrial apoptosis pathway within LSCC cells (23). Glutamine metabolism plays a crucial role in MM. Wang *et al.* found that the downregulation of the tumor suppressor gene CECR2 contributes to the proliferative effect of glutamine on LSCC cells (24). These studies reveal the potential of targeting MM for treating LSCC. Therefore, the present study constructed a four MMRGs prognostic model for patients with LSCC. This model indicated good prognostic prediction performance for LSCC patients at 1-, 3-, and 5-year, especially at 5-year.

Furthermore, four hub genes *POLD1*, *PON2*, *SMS*,

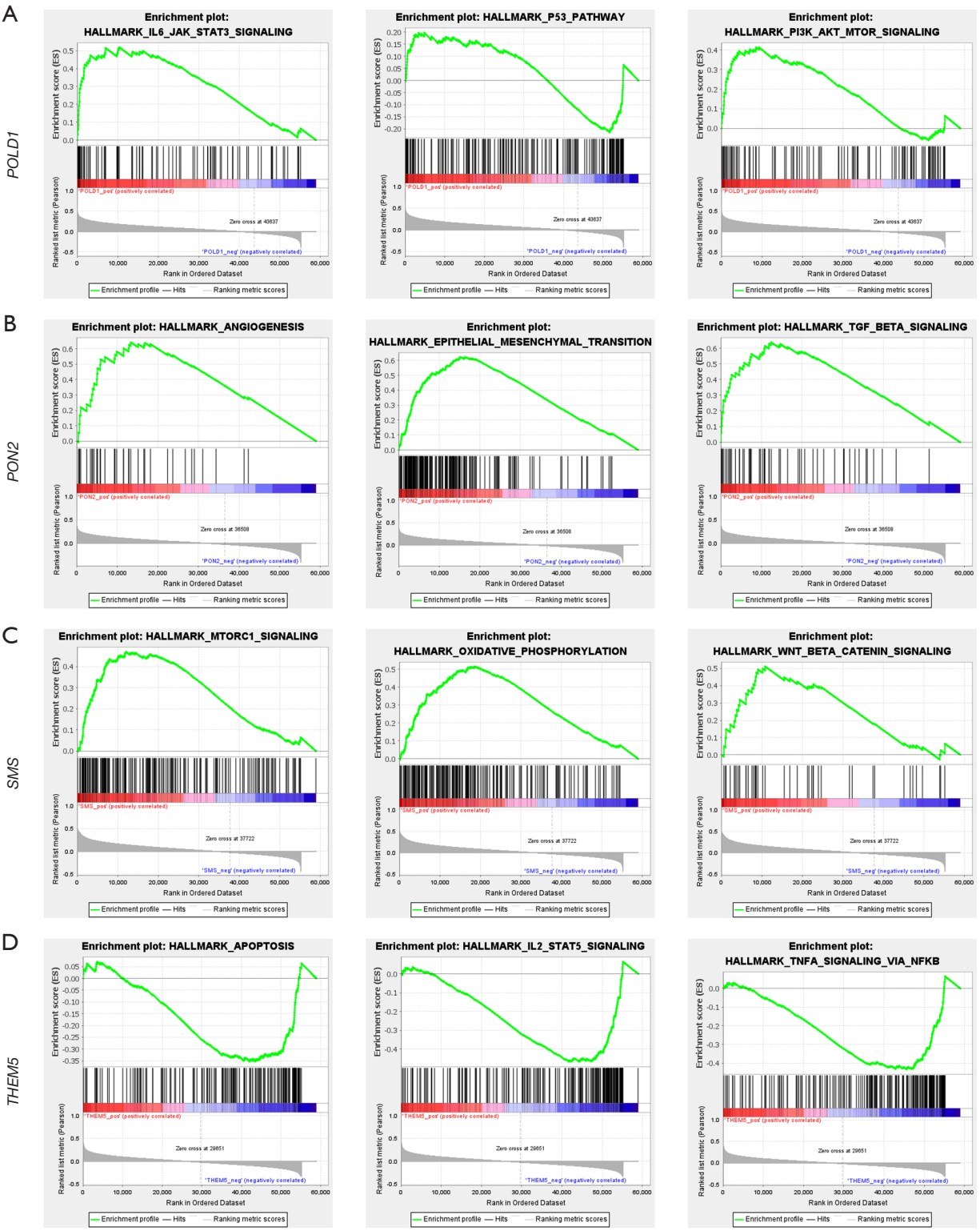

Figure 5 GSEA enrichment analysis. Pathways related to (A) *POLD1*, (B) *PON2*, (C) *SMS*, and (D) *THEM5*. GSEA, gene set enrichment analysis.

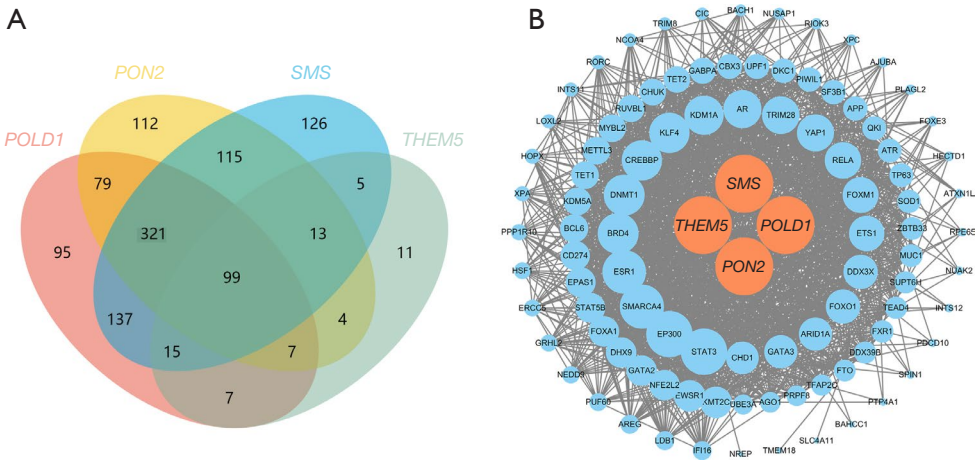

Figure 6 The interacting genes of four prognostic genes. (A) Venn diagram was utilized to intersect interacting genes of *POLD1*, *PON2*, *SMS*, and *THEM5*. (B) PPI network between four prognostic genes and the common interacting genes. PPI, protein-protein interaction.

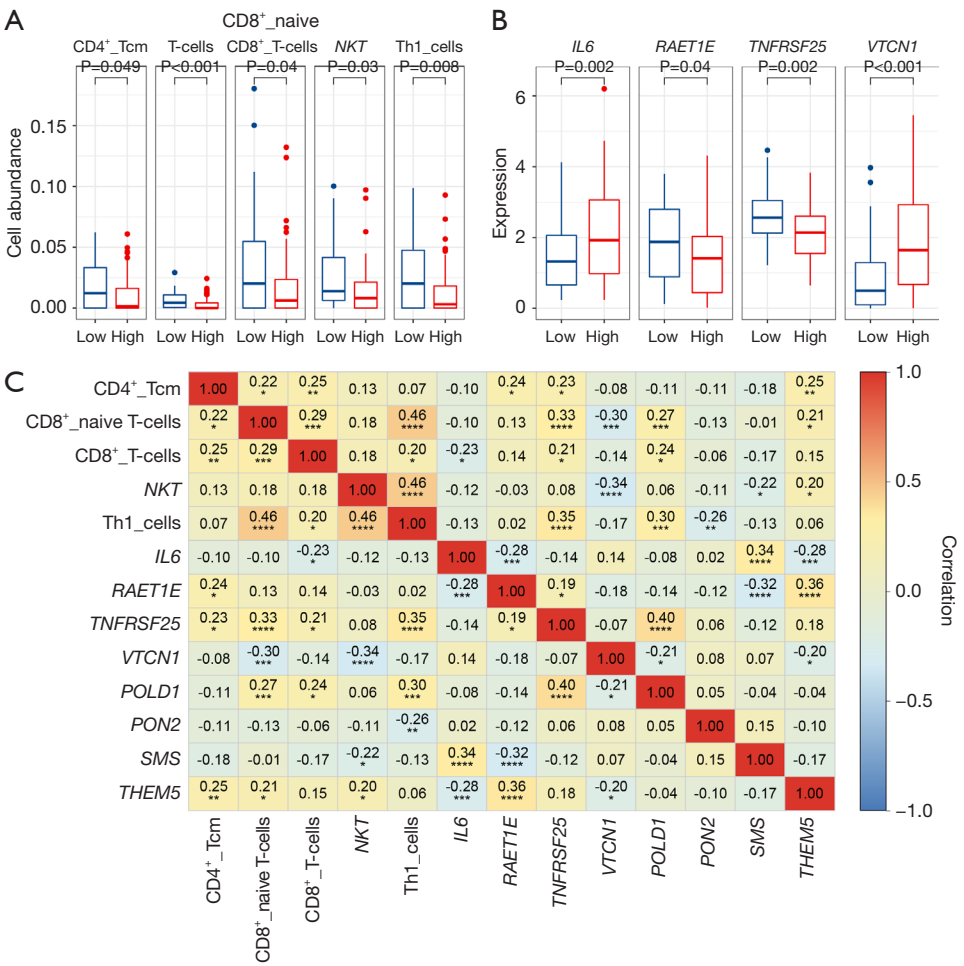

Figure 7 Tumor immune microenvironment analysis. (A) Cell infiltration analysis in the low- and high-risk groups. (B) Expression of immune checkpoint regulators in the low- and high-risk groups. (C) Correlation among immune cells, immune checkpoint regulators, and hub prognostic genes. *, P<0.05; **, P<0.01; ***, P<0.005; ****, P<0.001. NKT, natural killer T cells.

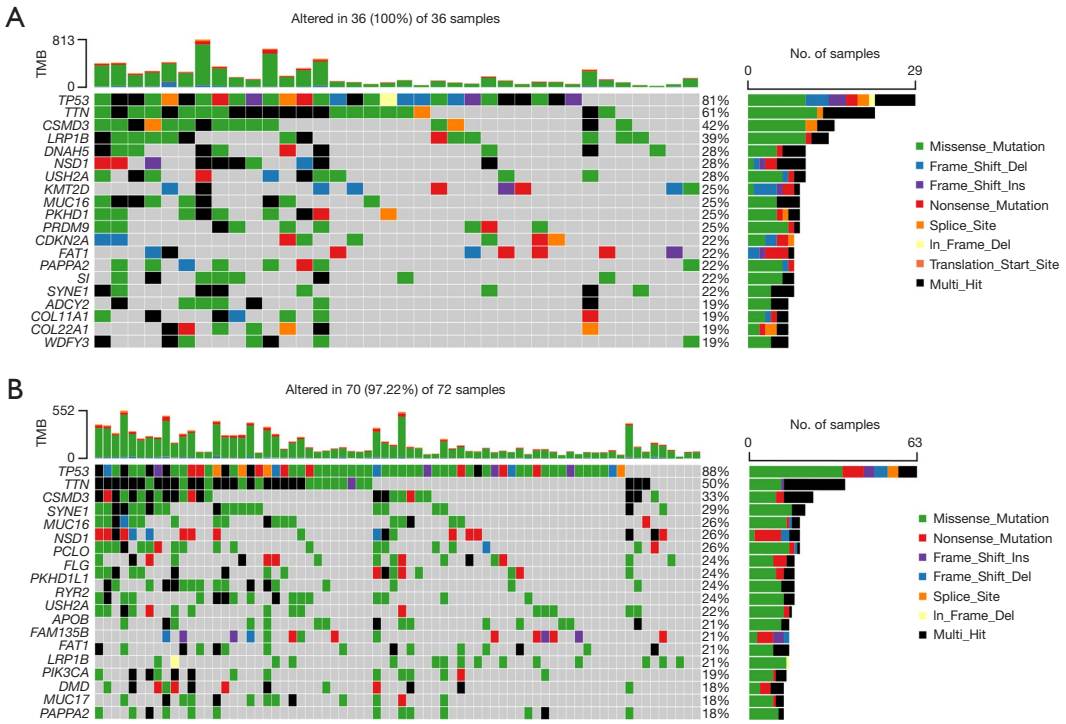

Figure 8 Mutation analysis. (A) Somatic mutations in the low-risk group. (B) Somatic mutations in the high-risk group. TMB, tumor mutational burden.

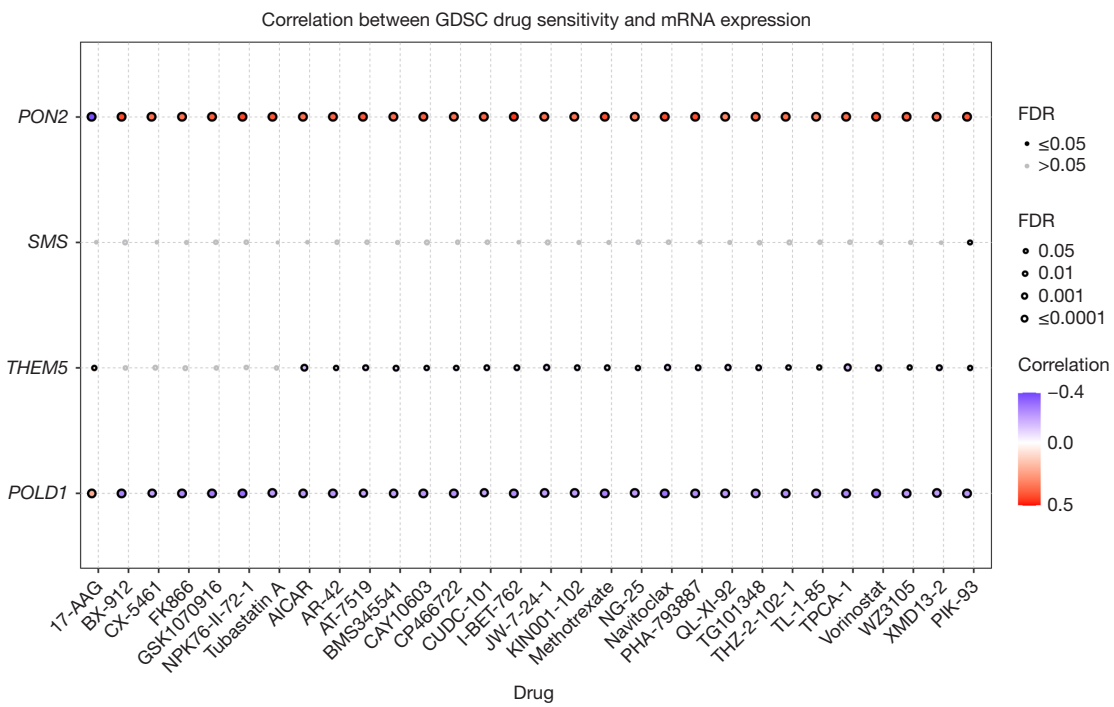

Figure 9 Correlation of four hub prognostic gene expression levels with drug sensitivity. GDSC, Genomics of Drug Sensitivity in Cancer; mRNA, messenger RNA; FDR, false discovery rate.

and *THEM5* were identified as biomarkers in LSCC. Among these four genes, *SMS* has been identified as a prognostic signature in LSCC (25,26). SMS participates in the polyamine metabolic pathway, and its inhibitors suppress tumor cell malignance, indicating that it may be an oncogene (25,27). *PON2* is an intracellular antioxidant enzyme positioned within the inner mitochondrial membrane (28). *PON2* has been found to overexpression in cancer cells, contributing to tumor progression by mitochondrial prevention from oxidative stress and apoptosis (29). Similarly, our study showed that expression of *SMS* and *PON2* was higher in the high-risk group, and LSCC patients with high levels of *SMS* and *PON2* had shorter survival time. *POLD1*, an integral member of the DNA polymerase δ complex, serves as both a catalytic and proofreading subunit, playing a vital role in DNA replication and repair mechanisms (30). Numerous carcinogenic factors stimulate the proliferation of cancer cells by elevating the expression of POLD1 (31,32). Bold *et al.* found that *POLD1* was associated with survival of head and neck cancer (33). *THEM5* is partial to the mitochondrial proteome, and *THEM5* knockout would lead to alterations of mitochondrial morphology and function in mice (34). The role of POLD1 and *THEM5* has rarely been analyzed in LSCC before. Our research revealed that both *POLD1* and *THEM5* expression levels were lower in the high-risk group, and the low levels of *POLD1* and *THEM5* indicated a poor prognosis for LSCC patients. Functionally, these four genes were closely related to signaling pathways that function in tumor initiation and progression, such as PI3K-AKT-mTOR, TGF-β, Wnt-β catenin pathways, and IL2-STAT5 pathways. The PI3K-AKT-mTOR, TGF-β, and Wnt-β catenin signaling plays a crucial role in tumorigenesis. Activation of PI3K-AKT-mTOR and Wnt-β catenin and TGF-β inhibition promote LSCC cell proliferation, migration, and invasion (35-37). Moreover, a large number of studies demonstrated that these signal pathways were all involved in the immune response (38-40). Besides, the function of IL2-STAT5 was also enriched in immune cell proliferation. A further study claimed that IL2-STAT5-mTOR activation could regulate tumor-reactive $CD8^+$ T-cell exhaustion, resulting in the malignant progression of tumors (41). These results indicated that hub genes may promote the development of BC cells by regulating the activation of immune cells.

Considering the importance of the immune microenvironment in tumor progression, we further compared the difference in immune cell infiltration in low- and high-risk groups. Immune cells are important to TME of LSCC (42). NK cells are a key component of the innate immune system, capable of efficiently recognizing and killing undifferentiated tumor cells (43). T cells are a major part of the adaptive immune response in TME, with higher $CD8^+$ T cell infiltration associated with better prognosis (44). In this study, we identified five immune cell populations with significantly different levels of infiltration, including $CD4^+$ central memory T cells, $CD8^+$ naive T cells, $CD8^+$ T cells, NK T cells, and Th1 cells. All of them exhibited higher infiltration levels in the low-risk group, indicating that the immune system in the low-risk group was more effective at recognizing and clearing LSCC cells. In addition, regulatory factors in the TME play key roles in tumor angiogenesis and metastasis. In this study, we found that the immune checkpoint regulators IL6 and VTCN1 were highly expressed in high-risk individuals, while RAET1E and TNFRSF25 were lowly expressed. Production of IL6 in cancers induces tumor immune evasion (45). High expression of VTCN1 is correlated with poor response to immunotherapy (46), while TNFRSF25 promotes $CD8^+$ T cell response and anti-tumor immunity (47). These findings suggest that the poor prognosis of high-risk individuals with LSCC may be caused by immune escape to a certain extent which further results in the lower sensitivity to immunotherapy.

Conclusions

In conclusion, this comprehensive analysis elucidates the significance of MMRGs in LSCC prognosis. The developed prognostic model based on four hub MMRGs provides a reliable tool for predicting patient outcomes. Additionally, the findings shed light on the underlying molecular mechanisms, alteration of tumor immune microenvironment, and mutation, offering potential avenues for targeted therapy and personalized medicine in LSCC management.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1436/rc

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1436/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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