



# Constructing a Novel Signature Based on Immune-Related lncRNA to Improve Prognosis Prediction of Cervical Squamous Cell Carcinoma Patients

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## Abstract

We downloaded gene expression data, clinical data, and somatic mutation data of cervical squamous cell carcinoma (CSCC) patients from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases. Predictive lncRNAs were screened using univariate analysis and least absolute shrinkage and selection operator (LASSO) regression, and risk scores were calculated for each patient according to the expression levels of lncRNAs and regression coefficients to establish a risk model that could be a novel signature. We assessed the correlation between immune infiltration status, chemotherapeutics sensitivity, immune checkpoint proteins (ICP), and the signature. Therefore, we selected 11 immune-related lncRNAs (WWC2,AS2, STXBP5.AS1, ERICH6.AS1, USP30.AS1, LINC02073, RBAKDN, IL21R.AS1, LINC02078, DLEU1, LINC00426, BOLA3.AS1) to construct the risk model. Patients who were in the high-risk group had a shorter survival time than those in the low-risk group ( $p < 0.001$ ). Risk scores in the signature were negatively correlated with macrophage M1, macrophage M2, and T cell CD8 +; what's more, T cell CD8 + was higher in the low-risk group. The expression levels of ICP such as PD-L1, PD-1, CTLA-4, TIGIT, LAG-3, and TIM-3 were substantially higher in the low-risk group. For chemotherapeutic agents, high-risk scores were associated with higher half-inhibitory concentrations (IC50) of cisplatin. These findings suggested that the risk model can be a novel signature for predicting CSCC patients' prognosis, and it also can be used to formulate clinical treatment plans for CSCC patients.

**Keywords** Cervical squamous cell carcinoma · lncRNA · Prognosis · Immune infiltration · Immune checkpoint proteins · Chemotherapeutics

## Introduction

Cervical squamous cell carcinoma (CSCC) is the fourth dominant cause of cancer-related deaths in women worldwide, accounting for 80–85% of all cervical cancer diagnoses [1, 2]. With human papillomavirus (HPV) vaccination and early-stage screening, the incidence rate of CSCC has decreased significantly. Surgery, radiotherapy, and chemotherapy have been commonly used for cervical cancer patients, but the 5-year survival rate is still not satisfactory because of advanced stage, relapse, metastasis, and drug resistance [3–5]. Although the use of immunotherapy checkpoint inhibitors (ICIs) has been successful in the treatment of various cancers [6], the development and application of immunotherapy for CSCC patients are restricted because the positive response remains low [7]. Thus, it is crucial to provide CSCC with new therapeutic targets and to find novel biomarkers for its early diagnosis and prognosis.

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Long non-coding RNAs (lncRNAs) are a class of non-coding transcripts with sequences longer than 200 nucleotides that can mediate post-transcriptional modifications [8, 9]. They play a key role in immune activation, cancer immunity, antigen presentation, and immune cell infiltration [10, 11]. For example, lncRNA CamK-A was found to be highly expressed in various human cancers and could regulate Ca<sup>2+</sup>-signaling-mediated tumor micro-environment remodeling [12]. Also, in colorectal cancer cells, overexpression of HLA-F-AS1 could repress miR-375 and promote the expression of PFN1, further parting macrophages toward M2 phenotype and exacerbating tumorigenesis [13]. EGFR promoted immune escape of hepatocellular carcinoma cells and Treg cell differentiation through specific binding to EGFR protein [14]. In addition to participating in the tumor microenvironment, lncRNAs can also affect the response to immunotherapy [15], which is rarely reported in CSCC patients.

In this study, we used the RNA sequencing data of CSCC patients in the Cancer Genome Atlas (TCGA)

and Genotype-Tissue Expression (GTEx) database to identify immune-related lncRNA (irlncRNA) and established an 11-irlncRNA signature based on LASSO regression analysis. Subsequently, we explored the company between the signature of 11-irlncRNA and several disease characteristics in CSCC patients. Drug sensitivity analysis also was performed to improve drug therapy. Collectively, the present study may provide a strategy to predict prognosis and immune-related therapeutic targets in CSCC patients.

## Materials and Methods

### Processing Data and Obtaining Immune-Related lncRNAs

The gene expression data, clinical data, and somatic mutation data of CSCC patients were acquired from the TCGA index. The gene expression profiles of 10 normal

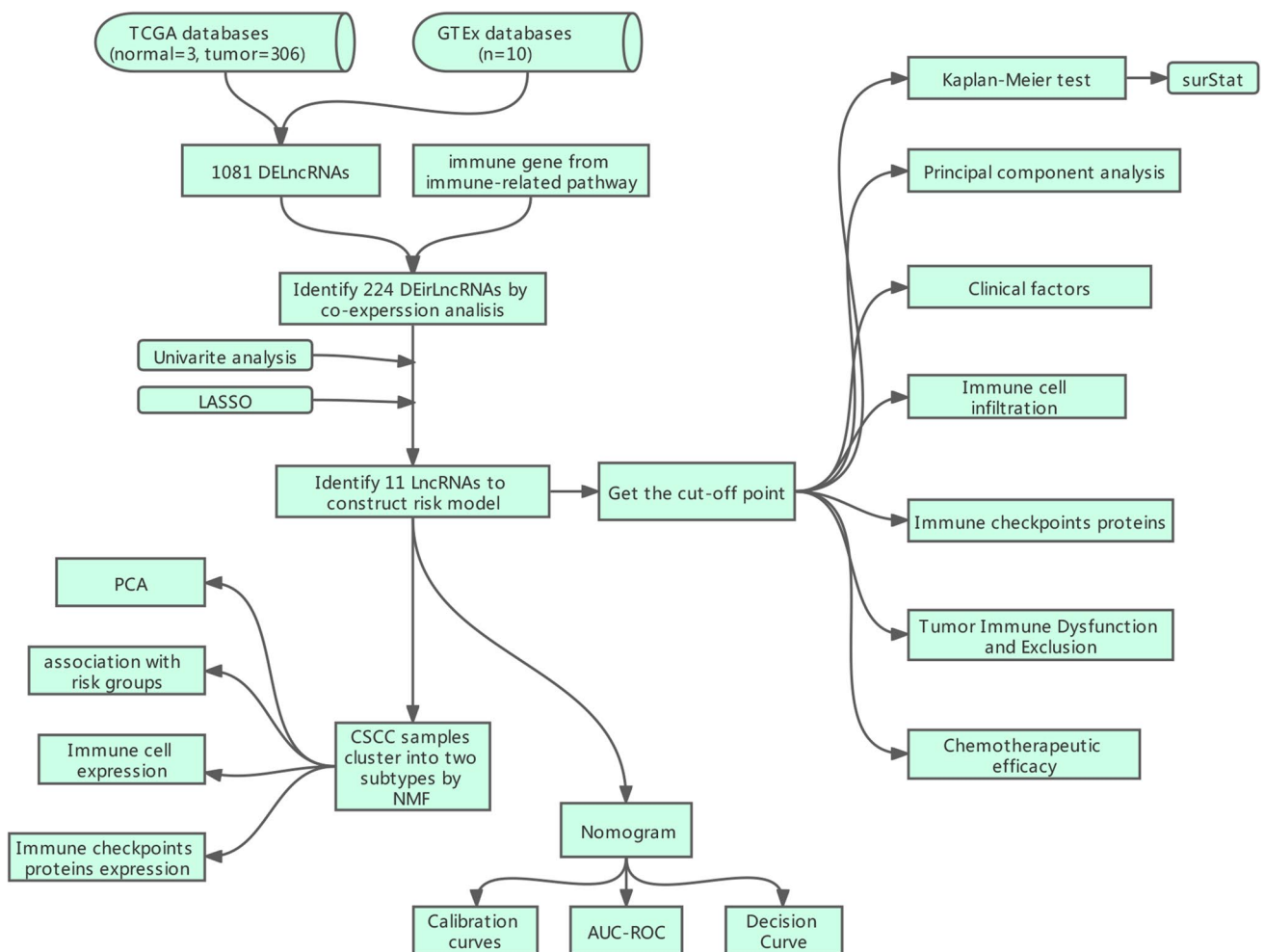
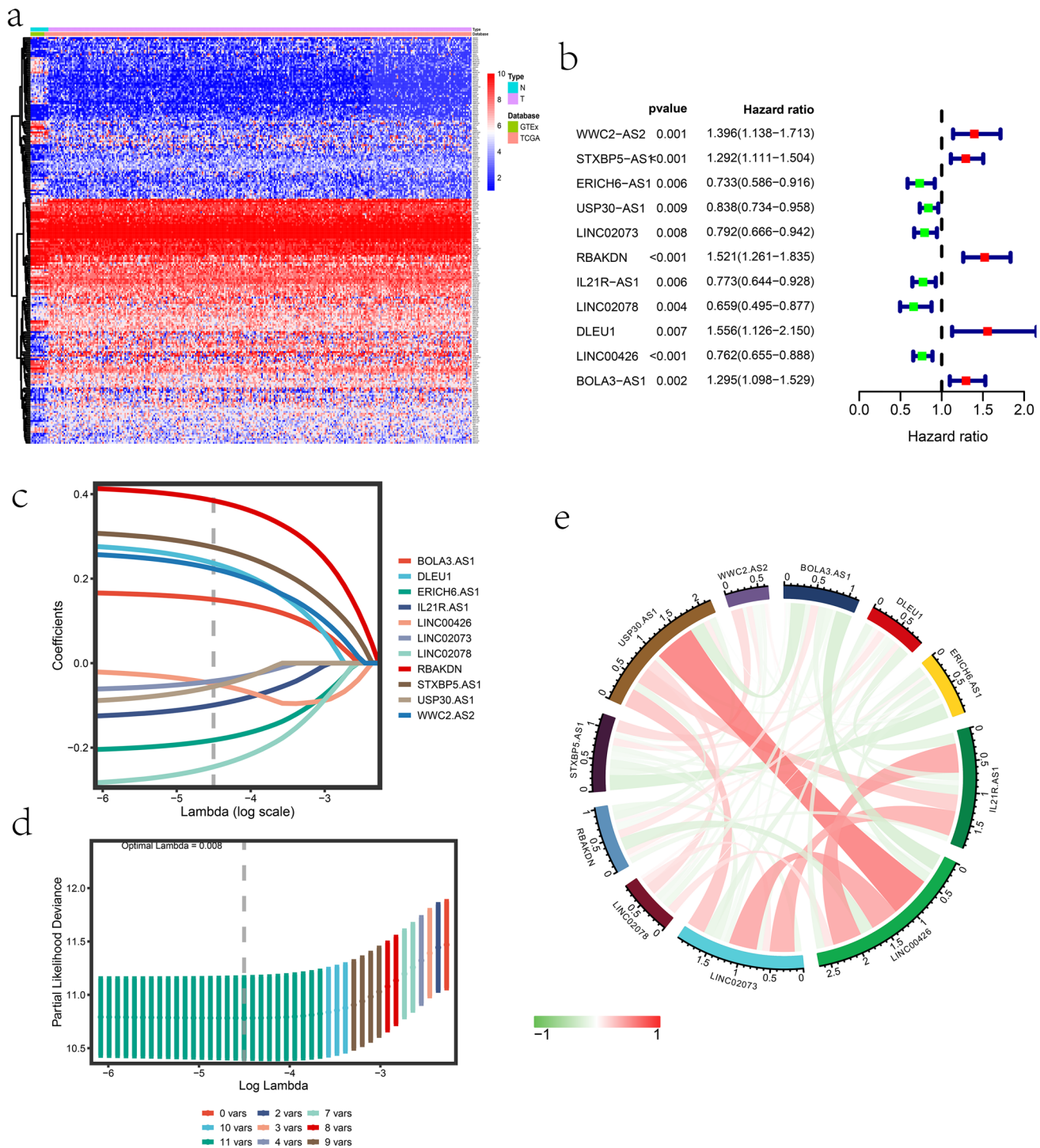


Fig. 1 Flow chart of this study

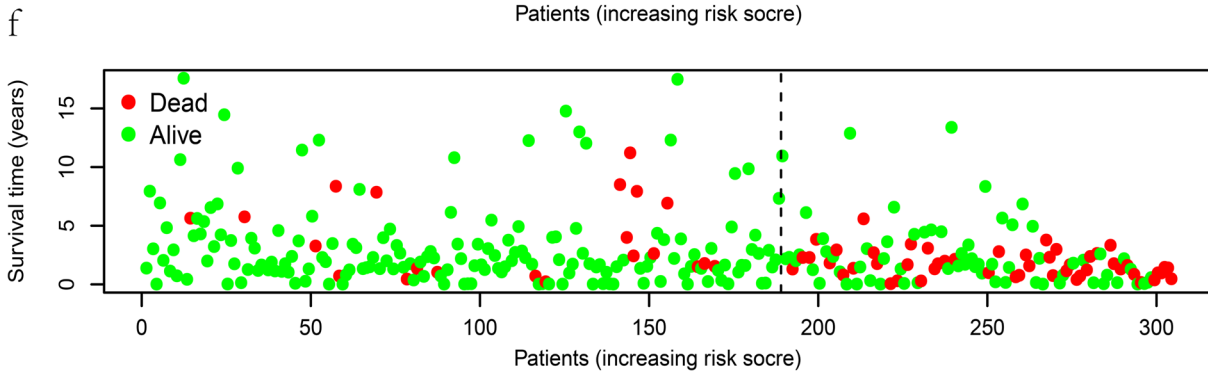
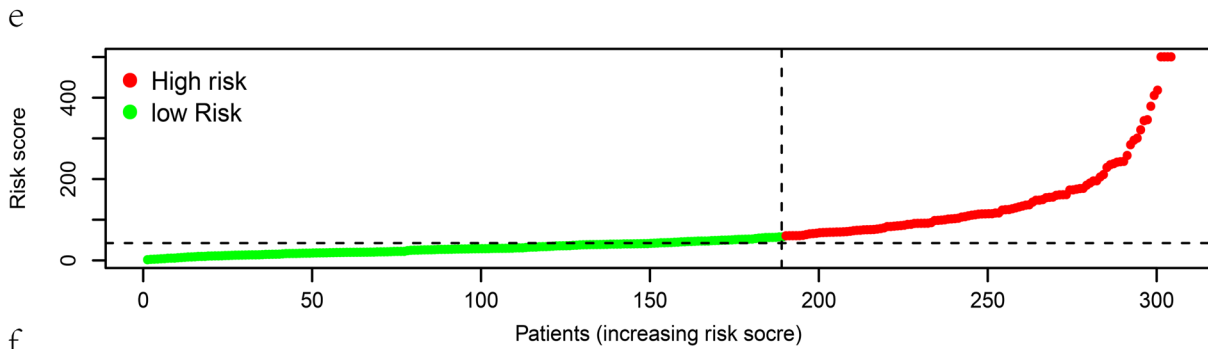
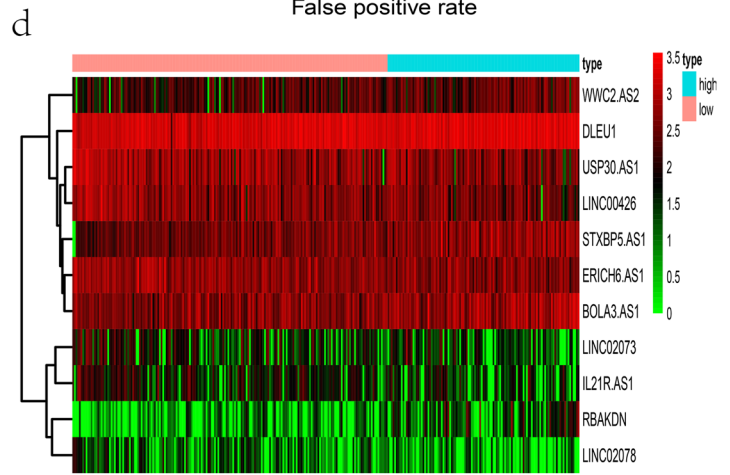
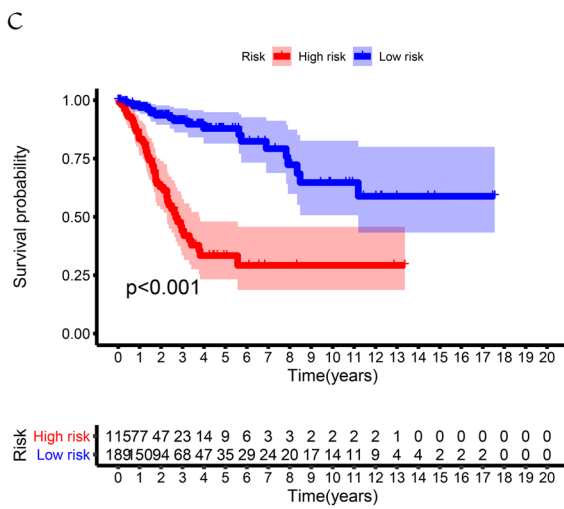
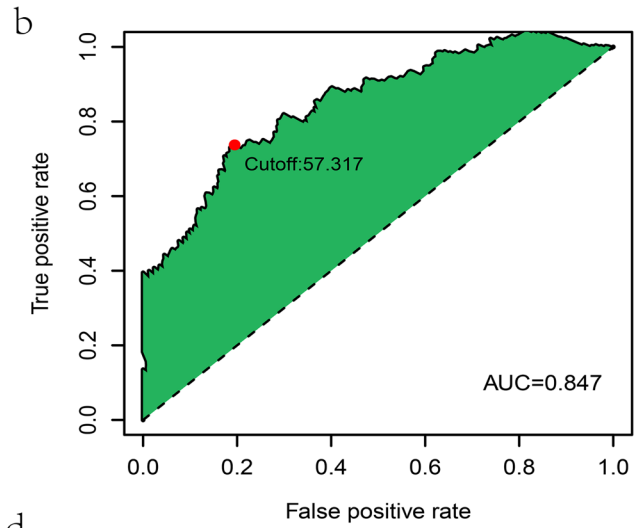
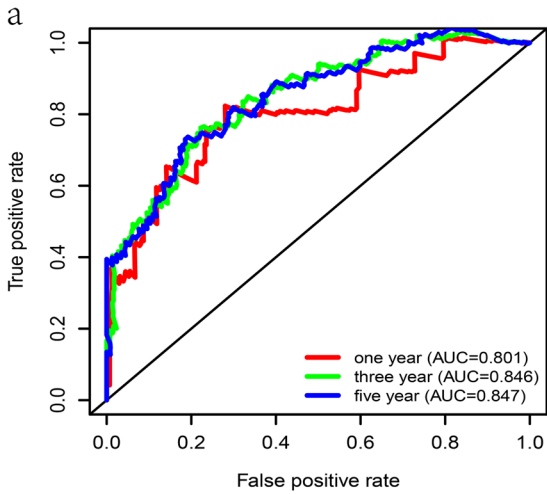
cervical tissues were obtained from the GTEx database. The GTF file from Ensembl was used to annotate and distinguish mRNAs and lncRNAs. Gene set enrichment analysis (GSEA) was applied to screen immune-related

pathways; genes in these pathways were identified as immune genes. We used R software packages “limma” and “edgeR” to filter differentially expressed lncRNAs (DELncRNAs), with  $|\log_2FC| > 2$  and FDR  $q$  value  $< 0.05$ .



**Fig. 2** Screen immune-related lncRNA to construct a risk model. **a** Heat map showing the expression of 224 DELncRNAs in CSCC tissues ( $n=306$ ) and normal cervical tissues ( $n=13$ ). **b** Forest map of univariate Cox analysis, green indicates protection factor, and red

indicates risk factor. **c** Distribution of the LASSO coefficients for 11 lncRNAs. **d** Partial likelihood deviation of the LASSO coefficient distribution. Vertical dashed lines indicate lambda. **e** Correlation chord diagram between 11 lncRNAs



**Fig. 3** Validation of the risk model. **a** The 1-, 3-, and 5-year ROC of the risk model. **b** The maximum inflection point is the cut-off point obtained by the AIC. **c** Survival analysis of high- and low-risk patients in CSCC. Patients with CSCC were divided into a low-risk group ( $n=189$ ) and a high-risk group ( $n=115$ ) according to their AIC values. **d** Expression profile of 11 lncRNAs in the CSCC patients ( $n=306$ ). **e** Risk score distribution of CSCC patients ( $n=306$ ). **f** Survival status and survival time of CSCC patients ( $n=306$ )

DElncRNAs with immune gene correlation coefficients greater than 0.5 and  $p$  value  $< 0.001$  were selected as irlncRNAs.

### Construction of Risk Model

We first used univariate Cox analysis to identify irlncRNAs that were significantly associated with overall survival of CSCC patients ( $p < 0.05$ ). Immediately after, we used LASSO regression analysis to further screen the irlncRNAs with prognostic value [16]. The features were chosen based on the best penalty parameter  $\lambda$ . We used the coefficients obtained from LASSO to calculate the risk scores:

$$\text{riskScore} = \sum_{i=1}^n \text{Coef}_i * x_i$$

where Coef<sub>*i*</sub> is the coefficients and  $x_i$  is the fragments per kilobase million (FPKM) value of each irlncRNA. We can calculate the risk scores of each patient according to this equation.

### Validation of the Risk Model

The receiver operating characteristics (ROC) for 1, 3, and 5 years of the model were calculated. The Akaike information criterion (AIC) value of the ROC curve was evaluated to select the maximum inflection point, which was considered to be the key point for distinguishing high-risk and low-risk groups. We used Kaplan–Meier analysis to explore the prognostic value based on the patient survival time; the survival curves were used for visualization of the model. The specific risk scores value of each sample in the model were visualized with R software. We performed principal component analysis (PCA) on all samples based on irlncRNAs, 224 DElncRNAs, immune genes, and whole gene expression profiles in the risk model, respectively. The PCA results were compared to observe the differences in the distribution of risk scores.

### Pathways in Two Risk Groups

To figure out the significantly changed immunological pathways, we did a gene set enrichment analysis (GSEA)

[17] for two risk groups. We selected significantly enriched pathways according to  $p$  value and FDR  $q$  value; they were less than 0.05 and 0.25, respectively.

### Correlation Analysis of Risk Model with Clinicopathological Features

The relationship between the model and clinicopathological features of CSCC patients was evaluated with a Chi-square test. These features included age, grade, clinical stage, and TNM stage. Tumor mutational burden (TMB) and microsatellite instability (MSI) were also analyzed. The risk score difference between the groups corresponding to these clinicopathological characteristics was calculated with the Wilcoxon rank-sum test.

### Immune Cell Infiltration Analysis

For the connection between risk and immune cell characteristics, we calculated the amount of immune cell infiltration in TCGA cervical cancer samples. The immune cell data were mainly obtained from XCELL, TIMER, QUANTISEQ, MCPOUNTER, EPIC, CIBERSORT, and CIBERSORT-ABS. We used Spearman correlation analysis to evaluate the association between the risk scores and immune infiltrating cells. According to the immune cell infiltration data in CIBERSORT, we assessed the interaction among these immune cells and also the correlation between 11 irlncRNA and immune cells.

### Exploring the Immunotherapeutic Treatment of the Risk Model

The Wilcoxon's test was used to explore the differential expression of ICP (PD-L1, PD-1, CTLA-4, TIGIT, LAG-3, and TIM-3) between two risk groups. Then we used the tumor immune dysfunction and exclusion algorithm (TIDE) to predict the possibility of immunotherapy response, which is a computational framework expanded for immunotherapy forecast, and its predictive function has been successfully verified [18].

### Non-negative Matrix Factorization

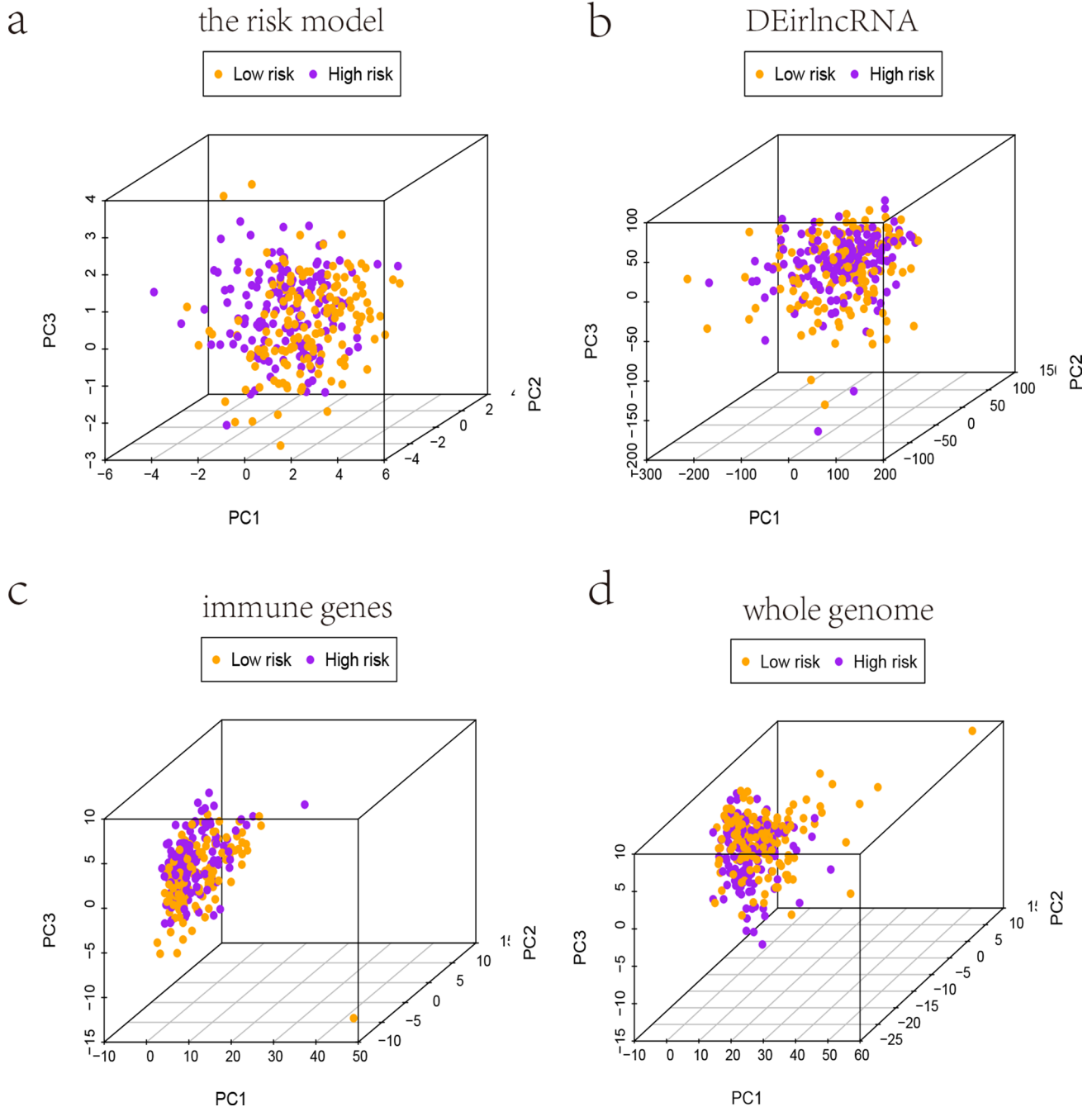
To assess if any clusters were present in the CSCC cohorts, molecular subtyping was used to perform non-negative matrix factorization (NMF). The best  $r$  value was chosen according to quality factors. These factors were the first  $r$  value at which the concord coefficient began to decline and the first value at which the residual sum of squares curve appeared to have an inflection point, as well as a direct visual inspection of the consensus matrix. The association

of two subtypes and risk groups was showed in Sankey diagram. We also explored the expression of immune cells and immune checkpoints proteins in two subtypes. PCA was performed with the R package ggplot2.

**Exploration of Drug Therapy Targeting Risk Model**

To determine if the models we constructed could be used for drug therapy in CSCC patients, we

calculated the half-maximal inhibitory concentration (IC50) of common chemotherapy drugs in the CSCC dataset. Anti-tumor drugs such as cisplatin, paclitaxel, docetaxel, gemcitabine, and vinorelbine were advocated for the treatment of CSCC patients. The IC50 difference between the two risk groups was compared by Wilcoxon’s test. Results were plotted with R packages “pRRophetic” and “ggplot2.”



**Fig. 4** Principal component analysis between the high- and low-risk groups. Principal component analysis based on **a** lncRNAs in risk model, **b** 224 DElncRNA, **c** immune genes, and **d** whole gene expression profiles

## Establishing a Predictive Nomogram

A nomogram combined various factors, and a calibration curve evaluated whether the predicted survival was consistent with certain survival in the nomogram. Calibration curves and AUC-ROC were also used to appraise the predictive ability of the prognostic model, and the clinical efficacy of the nomogram was evaluated with the decision curve analysis (DCA) (Fig. 1).

## Result

### Construction and Validation of the Risk Assessment Model

Data analysis of TCGA and GTEx databases produced 1,081 DElncRNAs, of which 224 were DEirIncRNAs (Fig. 2a), and 11 of those were related to prognosis in

CSCC samples. These 11 DEirIncRNAs were subjected to univariate analysis (Fig. 2b) and LASSO regression analysis (Fig. 2c, d), and a risk signature including these 11 DEirIncRNAs was constructed. Eleven DEirIncRNAs were dominated by moderate or weak correlations, suggesting that they might play a role in similar biological processes (Fig. 2e). The risk scores for each patient were computed using the following:

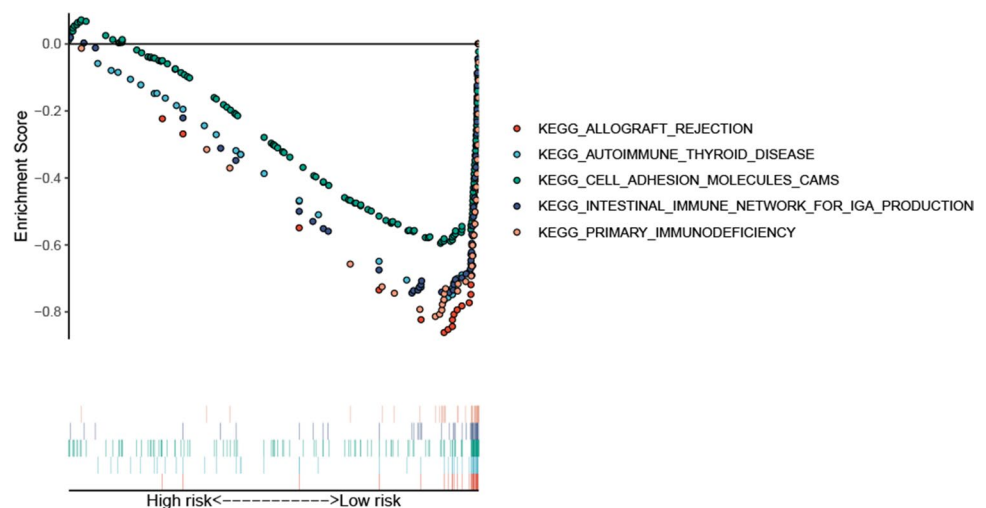
$$\begin{aligned} \text{Risk scores} = & WWC2.AS2 * 0.223 + STXBP5.AS1 * 0.274 + ERICH6.AS1 * \\ & - 0.182 + USP30.AS1 * (-0.055) + LINC02073 * (-0.043) \\ & + RBAKDN * 0.385 + I L21R.AS1 * (-0.099) \\ & + LINC02078 * (-0.245) + DLEU1 * 0.236 \\ & + LINC00426 * (-0.049) + BOLA3.AS1 * 0.150. \end{aligned}$$

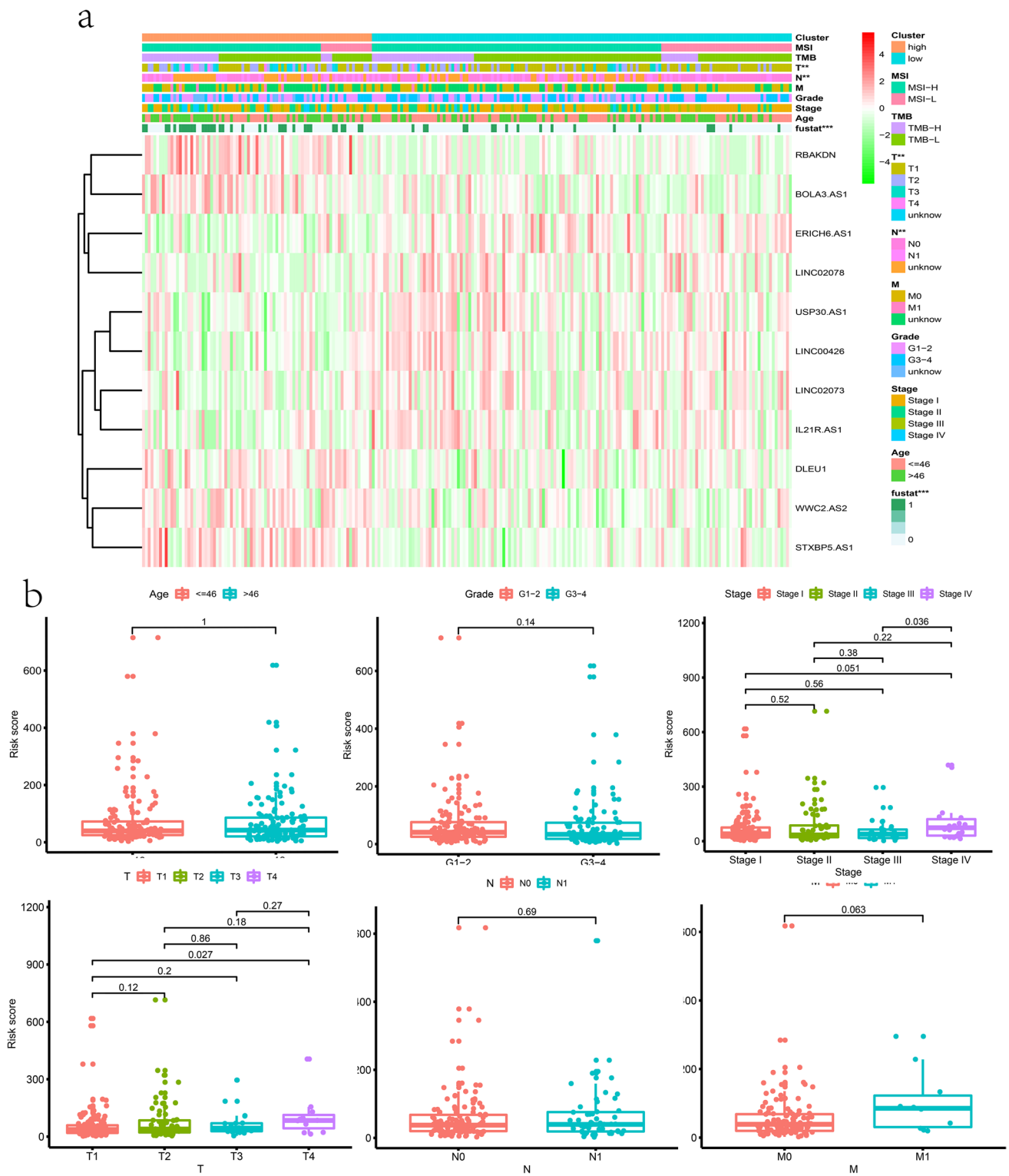
The AUC-ROC of the risk model for OS was 0.801, 0.846, and 0.847 at 1, 3, and 5 years (Fig. 3a), respectively. Using the AIC value (Fig. 3b), we selected the maximum inflection point as the demarcation cut-off

**Table 1** Top 10 pathway enriched in the low-risk group

Name	ES	NES	NOM <i>p</i> value	FDR <i>q</i> value
KEGG_AUTOIMMUNE_THYROID_DISEASE	-0.78236496	-2.1533732	0	0
KEGG_PRIMARY_IMMUNODEFICIENCY	-0.82993656	-2.0816772	0	3.00E-04
KEGG_CELL_ADHESION_MOLECULES_CAMS	-0.6021577	-2.0348785	0	0.001877939
KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	-0.75884634	-2.038879	0	0.001890281
KEGG_ALLOGRAFT_REJECTION	-0.8792095	-2.0443735	0	0.002214069
KEGG_TYPE_I_DIABETES_MELLITUS	-0.78216136	-2.002412	0	0.003311558
KEGG_ASTHMA	-0.76662517	-1.9769996	0.001908397	0.005337439
KEGG_HEMATOPOIETIC_CELL_LINEAGE	-0.6412886	-1.9576701	0.002024292	0.005633736
KEGG_VIRAL_MYOCARDITIS	-0.63541704	-1.9355513	0.002024292	0.006129693

**Fig. 5** Gene set enrichment analysis. GSEA showed a significant enrichment of immune-related pathways in the low-risk group





**Fig. 6** Correlation analyses of risk scores with clinicopathological characteristics of CSCC patients. **a** Heatmap and clinicopathologic features of high- and low-risk groups ( $<0.001=***$ ,  $<0.01=**$ , and  $<0.05=*$ ). Chi-square test acted as the statistical significance

test. **b** Relationship between the risk scores and clinical parameters. Wilcoxon rank-sum or Kruskal–Wallis rank-sum test acted as the statistical significance test



point of the 5-year ROC curve. Using this cut-off point, we obtained a high-risk group of 115 patients and a low-risk group of 189 patients. As shown by Kaplan–Meier analysis, patients in the high-risk group lived for a shorter period of time than those in the low-risk group (Fig. 3c). Figure 3d depicted the distribution of risk levels between the low-risk group and the high-risk group. Figure 3e showed the survival time of patients and the survival status in two risk groups, and Fig. 3f displayed the corresponding expression standards of the 11 lincRNAs for each patient. This implied that the risk model had a high accuracy in predicting the prognosis of CSCC patients.

### PCA Further Verifies the Grouping Ability of the Risk Model

Based on the expression profiles of 11 lincRNAs in the risk model, 224 lincRNA, immune genes, and whole genes, we used PCA to research the distribution patterns of the high-risk and low-risk groups in the CSCC patients (Fig. 4a–d). While based on the 11 lincRNA, these two groups were significantly different, indicating that the risk model was best for CSCC patients.

### Immune-Related Pathways of the Two Risk Groups

The results of GSEA (Table 1) suggested that three of the TOP 5 pathways enriched in the low-risk group were related to immunity, including autoimmune thyroiditis, primary immunodeficiency, and intestinal immune network (Fig. 5). This indicated that patients in the low-risk group had a better immune status.

### Clinical Evaluation by the Risk Model

We investigated the relationship among risk signature, clinicopathological characteristics, and 11 DElincRNAs. T stage, N stage, and just were related to the risk group (Fig. 6a). Further, patients at T4 had higher risk scores than at T1 (Fig. 6e), whereas patients at stage IV had higher risk scores than at stage III (Fig. 6f). These results suggested that risk scores can be used to assess the degree of progression of CSCC, and that the higher the risk score, the more malignant the tumor.

### Immune Landscape in CSCC Patients

The risk scores were negatively associated with macrophages M1, macrophages M2, myeloid dendritic cell, and CD8 + T cells, whereas it was positively associated with macrophages M0 (Fig. 7a). Meanwhile, the

difference analysis also showed CD8 + T cells were significantly higher in the group of low-risk, and macrophages M0 were significantly higher in the group of high-risk (Fig. 7c). The proportion and infiltrating level of immune cells in 309 CSCC samples is shown in Fig. 7b, and CD4 + T cells made up the highest percentage (Fig. 7d). There was a weak or moderate correlation between 22 tumor immune cells (Fig. 7e). Two lincRNAs among the risk signature had better relationship with immune cells; they were LINC00426 and USP30. AS1(|correlation coefficients| > 0.4) (Fig. 7f).

Six immune checkpoint proteins PD-L1, PD-1, CTLA-4, LAG-3, TIGIT, and TIM-3 were expressed highly in the low-risk group (Fig. 7g), suggesting that the immunosuppressive microenvironment led to a poor prognosis for low-risk patients. The prediction results of the TIDE algorithm showed that low-risk patients score higher than high-risk patients, which indicated that low-risk patients responded better to immunotherapy (Fig. 7h).

### CSCC Sample Cluster into Two Subtypes

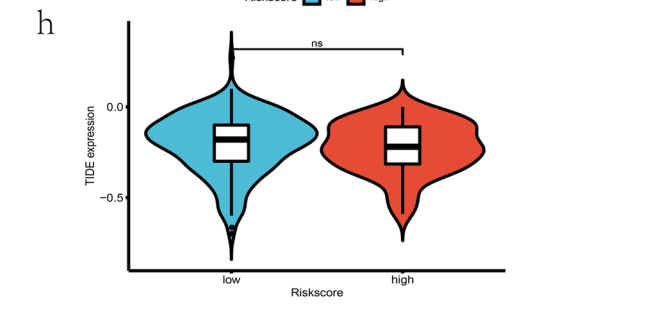
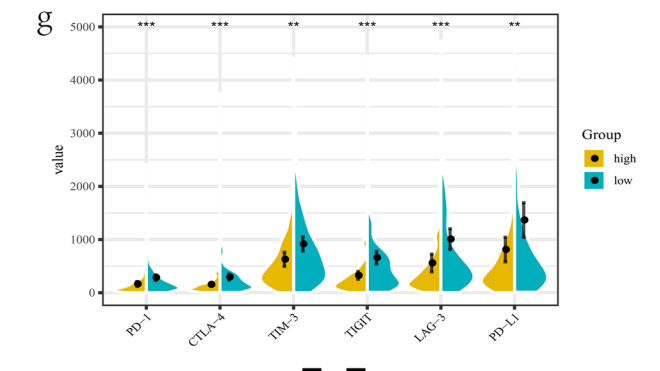
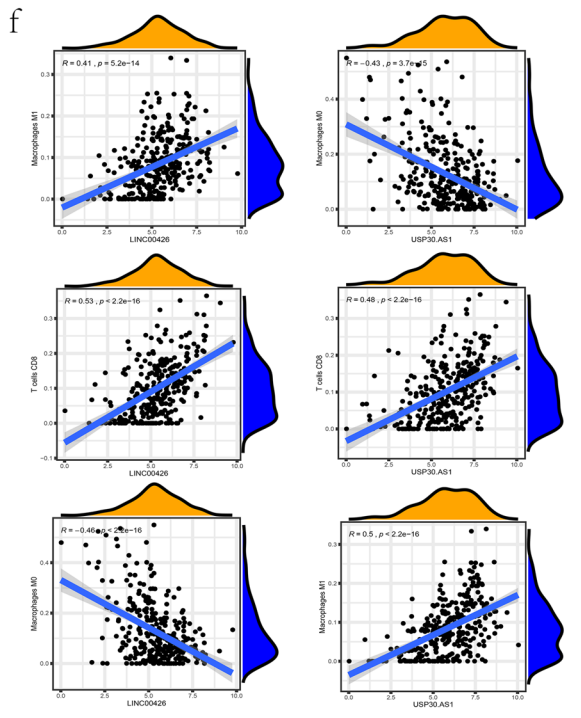
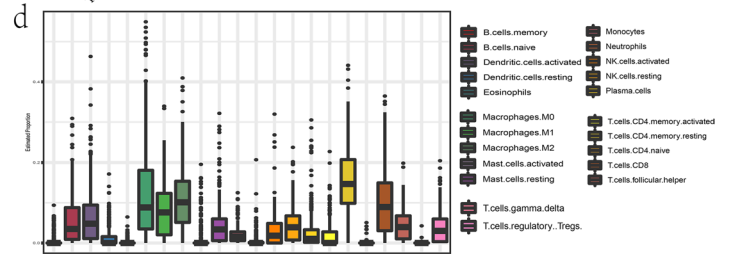
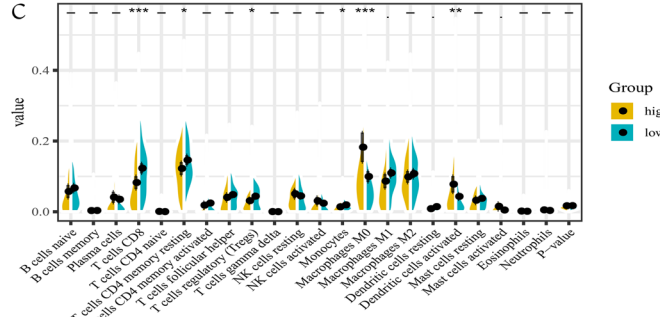
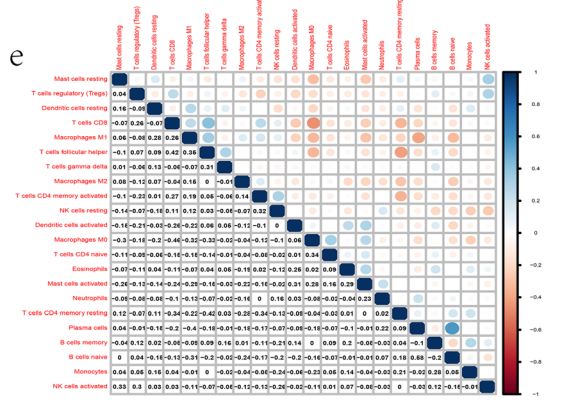
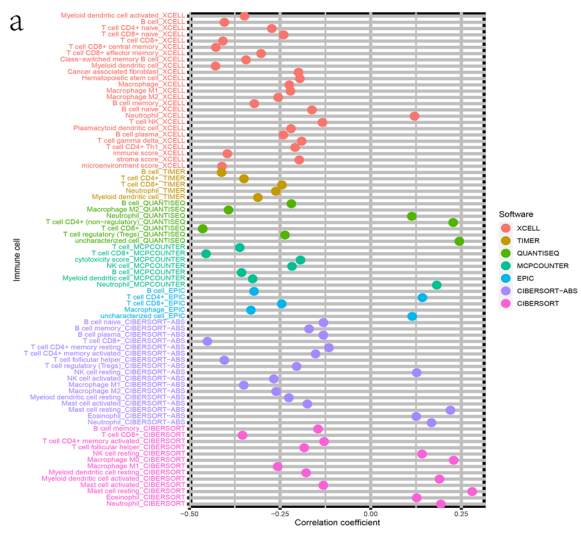
CSCC tumors were classified into two clusters containing 64 and 242 members. (Fig. 8a). The two subtypes identified by the NMF algorithm were confirmed by PCA (Fig. 8b). Cluster 1 mainly contained patients with low-risk scores, while the high-risk and low-risk patients in cluster2 were basically the same (Fig. 8c). This showed a good agreement in CSCC subtypes and risk groupings. PD-L1, PD-1, CTLA-4, LAG-3, TIGIT, and TIM-3 in cluster 1 had significantly higher expression than in cluster 2 (Fig. 8d). Expression of immune cells like CD8 + T cells, macrophages M1, T cells follicular helper, T cells regulatory (Tregs), and Mast cells activated expressed was higher in cluster 2, whereas that of macrophages M0 was higher in cluster 1 (Fig. 8e).

### The Significance of the Model in Clinical Treatment

Our study demonstrated that the low-risk group had a lower IC50 of cisplatin ( $p < 0.05$ ) (Fig. 9), also implying that low-risk patients were more sensitive to cisplatin. This suggested that the low-risk patients might be better suited for chemotherapy.

### Construction and Assessment of Predictive Nomograms

A nomogram was constructed to predict the 1-, 3-, and 5-year OS incidences (Fig. 10a). Calibration curves and ROC analyses showed good predictive performance of the



**Fig. 7** Immune infiltrate landscape in CSCC patients and estimation of immunosuppressed molecules by the risk model. **a** Correlation between immune cells and risk scores, **b** relative proportion of immune cell infiltrates in CSCC patients, **c** content of 22 immune cells, **d** correlation matrix of immune cells, **e** comparison of the expression of immune infiltrating cells in low- and high-risk patients, **f** correlation of lncRNAs in risk model with immune cells, **g** differential expression of immune checkpoint proteins in the high- and low-risk patients, **h** TIDE prediction difference in the high- and low-risk patients

nomogram in predicting patient survival (Fig. 10b, c). The decision curve showed that the nomogram has good clinical efficacy (Fig. 10d–f), suggesting that it can predict the survival of CSCC patients.

## Discussion

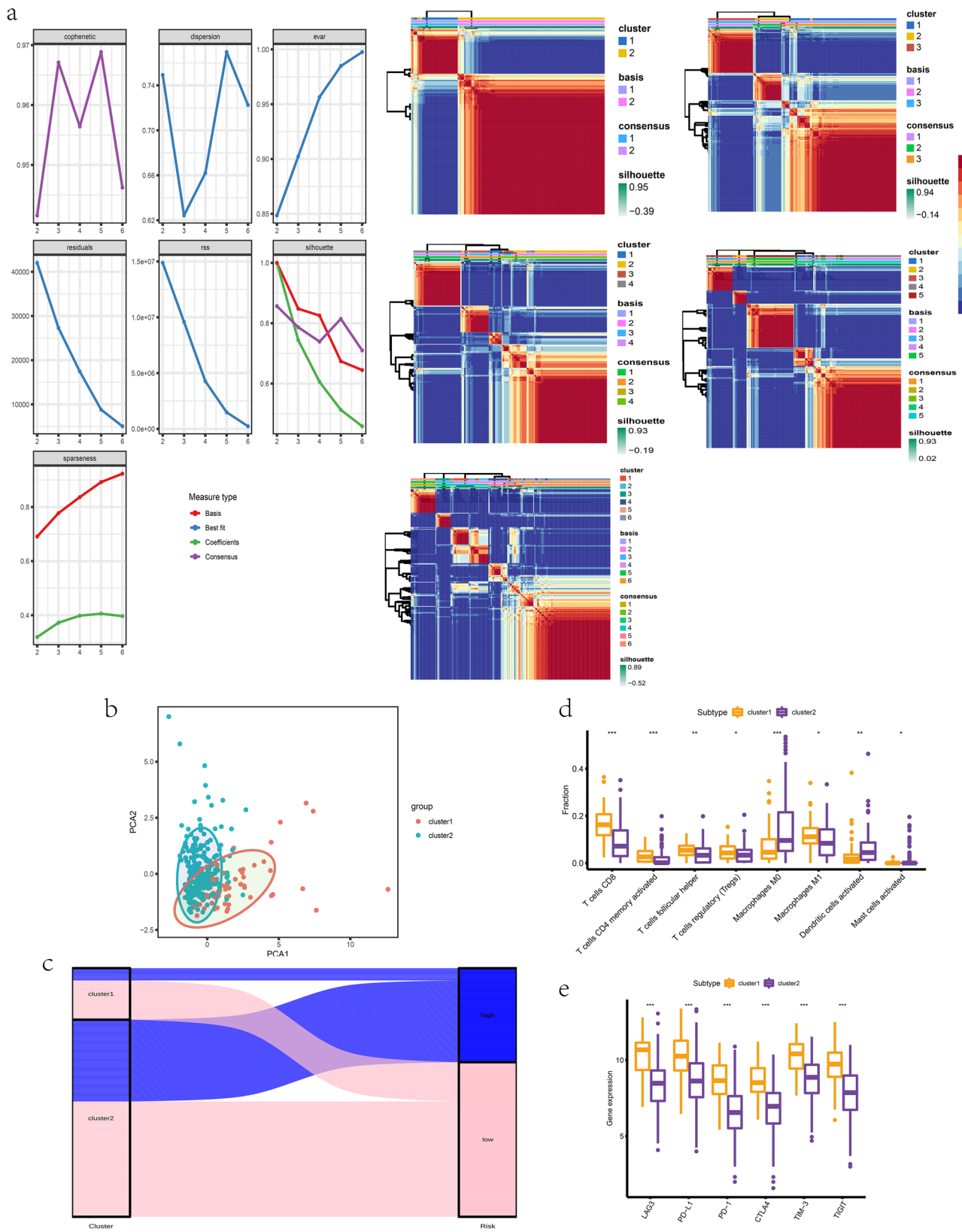
It has been suggested that lncRNAs play a key role in the adjustment of the immune system and the tumor microenvironment [10]. Immune-related lncRNAs are prognostic markers of various types of cancer [18] linked to immune cell infiltration and are a potential target for cancer treatment [19]. lncRNA SNHG14 has been shown to be involved in the activation of the JAK-STAT pathway in cervical tumor cells [20]. In cervical cancer HeLa cells, the STAT3 binding sequence in the enhanced region of lncRNA MALAT1 proved to be the key to the activation of the MALAT1 promoter induced by IL-6 or STAT3 [21]. In the eleven immune-related lncRNAs of the risk model, STXBP5-AS1 targets miR-96-5p/PTEN axis to drive cervical cancer cell proliferation and invasion [22], and DLEU1 promotes cervical cancer cell proliferation and invasion via the miR-381/HOXA13 axis [23].

We used the AIC value to get the best cut-off point for the model fitting. The prognostic model performed better in distinguishing between risk groups of high and low. Patients with low-risk showed a favorable prognosis, which suggested that our model may be able to stratify risk. GSEA revealed that immune-related pathways were significantly enriched in the low-risk group. We also analyzed the tumor immune infiltration and efficacy of chemotherapy drugs in the treatment of CSCC, which determined that this model worked well. In this study, consensus clustering based on NMF was used to define CSCC subtypes. The CSCC sample could be separated into two subtypes with distinct molecular profiles with differences in immune cell infiltration and checkpoint-related biomarkers. A nomogram was established to show the exact agreement between the observation rate and the predicted rate of 1-year, 3-year, and 5-year OS. The nomogram had better prediction accuracy and higher clinical efficacy, which passed calibration curve and DCA verification.

The ability of immunotherapy depends on the immunogenicity of the tumor microenvironment, so the understanding of the tumor microenvironment is the key to assessing the possibility of immunotherapy [24]. Immune cell infiltration can be a predictive biomarker of cancer immunotherapy [25]. Patients with more CD8 + T cell infiltration get a better response from pembrolizumab than those with less infiltration [26]. Macrophages suppressed T cell recruitment and regulated other aspects of tumor immunity; they can be regulators of tumor immunity and immunotherapy [27]. We used seven accepted methods to estimate the correlation between risk scores and immune cells; the methods include XCELL [28], QUANTISEQ [29], MCPcounter [30], EPIC [31], TIMER [32, 33], CIBERSORT [34], and CIBERSORT-ABS [35]. By integrating analysis, our results revealed that the risk model was negatively associated with macrophages M1, macrophages M2, and CD8 + T cells, meanwhile CD8 + T cells were significantly higher in the low-risk group. We can support that patients in the low-risk group may be more suitable for immunotherapy.

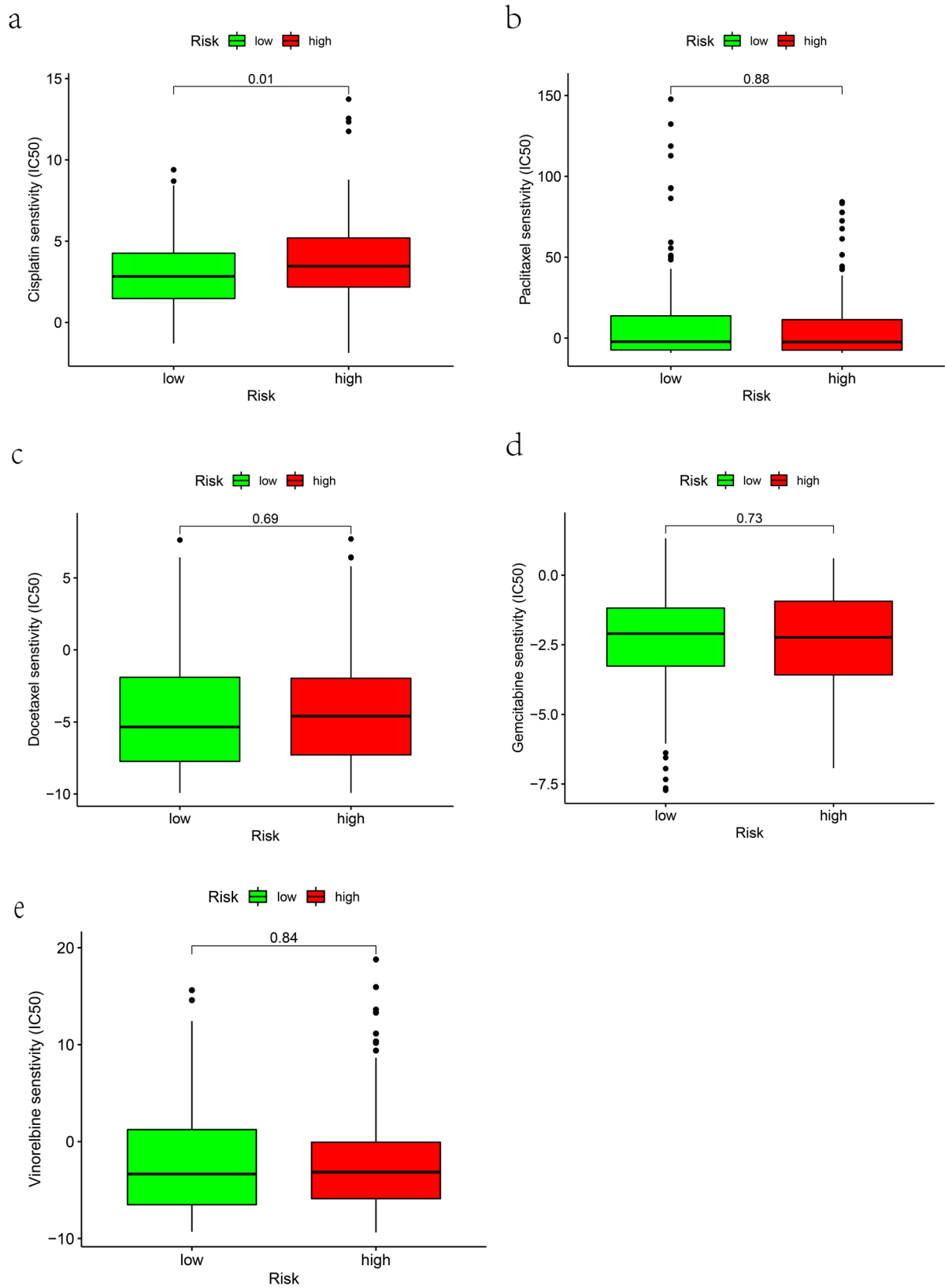
Cancer cells activate inhibitory immune checkpoint pathways to prevent the occurrence of autoimmunity [36]; therefore, suppression of the immune checkpoint approach is a promising treatment. Evidence suggests that immunotherapy is a novel therapeutic strategy for the treatment of cervical cancer [37]. Anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapies are possible treatment options for cervical cancer, studies show [38–40]. Furthermore, in a well-defined clinical study of 115 cervical cancer patients, PD-L1 was expressed in 19% of cervical tumors, and more than 50% of tumor-infiltrating CD8 + T cells were expressed PD-1 [41]. We explored the relationship between several common immune checkpoint proteins in the treatment of cervical cancer and risk models, showing that all six immune checkpoints were higher in the group of low-risk. Thus, under this model, it suggested that patients with low-risk may benefit more from immunotherapy. The predictions of the TIDE algorithm indicated that patients with low-risk subtypes had a better response to immunotherapy, which was consistent with the above-mentioned studies. Our risk model also showed that low-risk patients were more sensitive to cisplatin, a small-molecule platinum compound that treat recurrent cervical cancer effectively [42], so we can formulate chemotherapy regimens for low-risk patients.

In our risk model, the risk scores are related to the clinical stage, and the risk scores of early cervical cancer are lower than that of the advanced stage. In summary, our findings support that early-stage patients may be better suited for immunotherapy and appropriate chemotherapy.

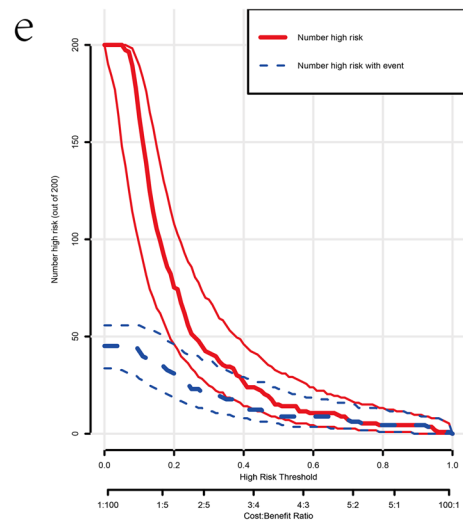
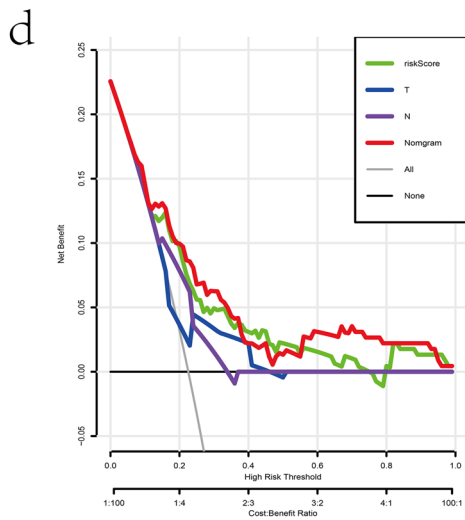
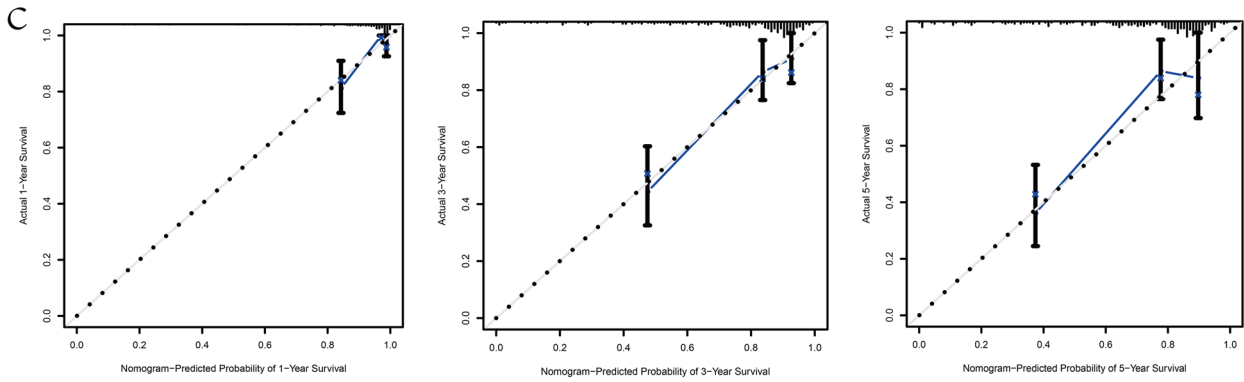
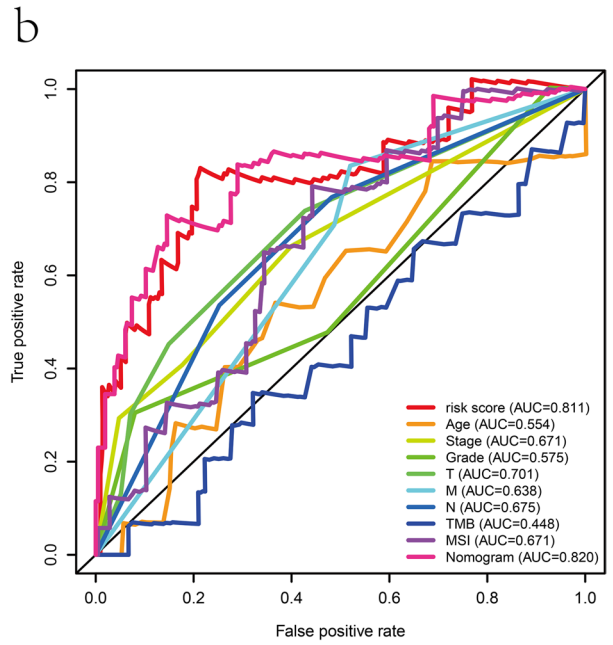
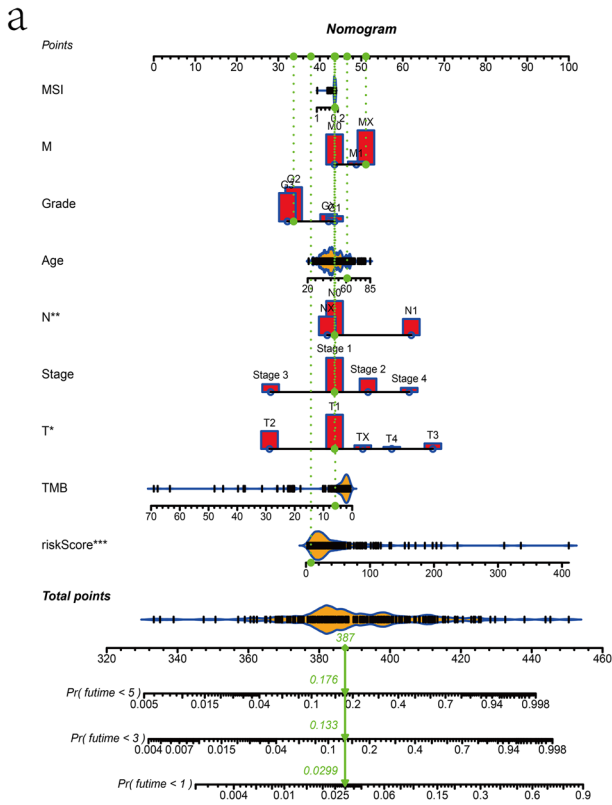


**Fig. 8** CSCC patients clustered into two subtypes based on risk mode. **a** Consensus clustering of CSCC samples by NMF. Correlation matrix heatmap subtypes and risk groups, **d** differential expression of

immune checkpoint proteins in cluster1 and cluster2, **e** differences in the expression of immune cells between the two subtypes



**Fig. 9** Sensitivity of chemotherapy drugs in high- and low-risk groups. **a** cisplatin, **b** paclitaxel, **c** docetaxel, **d** gemcitabine, and **e** vinorelbine



**Fig. 10** Construction and evaluation of a prognostic nomogram. **a** The nomogram predicts the probability of the 1-, 3-, and 5-year OS, **b** the AUC of risk scores and clinical factors, **c** the calibration plot of the nomogram predicts the probability of the 1-, 3-, and 5-year OS, **d** the decision curve of nomogram, and **e** clinical impact curve

## Conclusion

We identified 11 immune-related lncRNAs in cervical squamous cell carcinoma that were used to construct a prognostic signature. Then we compared the differences in immune checkpoints, clinicopathological characteristics, and drug treatments between the high-risk and low-risk groups. The results provide suggestions for the clinical treatment of cervical cancer, but the application of these results must be verified by a multicenter, large-sample clinical study.

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**Data Availability** The datasets supporting the conclusions of this article are available in the Genotype-Tissue Expression (GTEx) database and the cancer genome atlas (TCGA) database.

## Declarations

**Conflict of Interest** The authors declare no competing interests.

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