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Elastic Net-Based Identification of a Multigene Combination Predicting the Survival of Patients with Cervical Cancer

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The objective of the present study was to identify prognostication biomarkers in patients with cervical cancer.

Material/Methods: Survival related genes were identified in The Cancer Genome Atlas (TCGA) cervical cancer study, and they were included into an elastic net regularized Cox proportional hazards regression model (CoxPH). The genes that their coefficients that were not zero were combined to build a prognostication combination. The prognostication performance of the multigene combination was evaluated and validated using Kaplan-Meier curve and univariate and multivariable CoxPH model. Meanwhile, a nomogram was built to translate the multigene combination into clinical application.

Results: There were 37 survival related genes identified, 9 of which were integrated to build a multigene combination. The area under the curve (AUC) of receiver operating characteristic (ROC) curve at 1-year, 3-year, 5-year, and 7-year in the training set were 0.757, 0.744, 0.799, and 0.854, respectively, and the multigene combination could stratify patients into significantly different prognostic groups (hazard ratio [HR]=0.2223, log-rank $P<0.0001$). Meanwhile, the corresponding AUCs in the test set was 0.767, 0.721, 0.735, and 0.703, respectively, and the multigene combination could classify patients into different risk groups (HR=0.3793, log-rank $P=0.0021$). The multigene combination could stratify patients with early stage and advanced stage into significantly different survival groups in the training set and test set. The prognostication performance of the multigene combination was better compared with 3 existing prognostic signatures. Finally, a multigene containing nomogram was developed.

Conclusions: We developed a multigene combination which could be treated as an independent prognostic factor in cervical cancer and be translated into clinical application.

MeSH Keywords: Biological Markers • Proportional Hazards Models • Survival Analysis • Uterine Cervical Neoplasms

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Background

Cervical cancer, caused by persistent human papilloma virus (HPV) infections [1–3], is one of the most common malignant tumors in the female reproductive system, accounting for third place in female malignant tumors, and its incidence is second only to the incidence of breast cancer [4–6]. In recent years, several studies have shown that the incidence of cervical cancer is increasing year by year, and patients with cervical cancer are gradually becoming younger [7,8]. It has been reported that the increase in incidence of cervical cancer was nearly 40% in young women in recent decades [9,10]. Although conventional treatment strategies including radical surgery, radiotherapy and chemotherapy, and targeted therapy have significantly improved the treatment efficacy of patients with cervical cancer, the clinical outcome of cervical cancer patients remains poor; the median overall survival (OS) for advanced cervical cancer is 16.8 months [11]. Nearly 20% of early stage cervical cancer patients who receive surgical treatment and radiotherapy will suffer cancer recurrence, and the recurrence rate of patients with advanced stage cervical cancer is up to 70% [12].

Meanwhile, due to early detection of cervical cancer and early treatment, the cure rate of the disease is almost 100% [13,14]. However, the prognosis of patients with advanced disease remains poor. Therefore, the development of tumor markers that can be used for early screening and long-term prognosis is of vital importance for improving the diagnosis and treatment status of cervical cancer [15]. In the present study, we introduced a multigene combination for predicting the prognosis of cervical cancer patients using an elastic net regularized Cox proportional model (CoxPH).

Material and Methods

Cervical cancer gene expression studies

Two publicly available cervical cancer gene expression studies were included in the present study. The Cancer Genome Atlas Cervical Cancer (TCGA-CESC), including a total of 290 samples, was measured using the Illumina HiSeq 2000 RNA Sequencing platform by the University of North Carolina TCGA genome characterization center [16]. We downloaded the level 3 data of TCGA-CESC and the associated clinical information (including age at diagnosis, clinical stage, overall survival, survival status, etc.) from UCSC Xena (*https://xenabrowser.net/datapages/*). The expression profile was shown as in $\log_2(x+1)$ transformed RSEM normalized count. Cervical cancer gene expression study GSE44001 [17], measured by Illumina HumanHT-12 WG-DASL V4.0 R2 expression beadchip, included a total of 300 cervical cancer samples and we downloaded the quantile normalized expression profile of GSE44001 and its associated clinical information (including clinical stage, disease-free survival, and survival status, etc.) from gene expression omnibus (GEO) database (*https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE44001*).

Elastic net regularized Cox proportional hazards regression model

We use TCGA-CESC as a discovery set. In the discovery set, we performed a univariate CoxPH model to identify genes that was related with the OS of patients with cervical patients. *P* values less than 0.05 were subjected to subsequent Bonferroni correction. Thus, genes with a family-wise error rate less than 0.05 were considered as candidates to build an elastic net regularized CoxPH. Before building such a model, we randomly divided the discovery set into a training set and a test set according to a 1: 1 ratio (*http://topepo.github.io/caret/index.html*). The elastic net regularized CoxPH model was trained in the training set and was applied to the test set. As previously suggested, the elastic net applied a combination of the L1-and L2-penalty [18]. Similar to least absolute shrinkage and selection operator (LASSO) [19], the elastic net performed automatic feature selection by setting some coefficient estimates to zero. The R package "c060" was used to identify the optimal 2 hyperparameters (α, λ) in the elastic net, for which the 10-fold cross-validated penalized (partial) log-likelihood deviance of the model is minimal [20]. Subsequently, genes with non-zero coefficients in this CoxPH model was applied to build a multigene combination.

Characterization of the prognostication performance of the multigene signature

Firstly, we calculated the risk score for each cervical cancer patient based on the coefficients of each gene in the elastic regularized CoxPH model, and the prognostication performance of the multigene combination was assessed using time-dependent receiver operating characteristic curve (ROC) analysis at specific time points (1-year, 3-year, 5-year and 7-year) [21] in the R package "survivalROC". Meanwhile, cervical cancer patients were classified into the multigene combination low-risk group and the multigene combination high-risk group based on the optimal cutoff from the time-dependent ROC analysis. Then, we evaluated the OS and the disease-free survival (DFS) of patients in these 2 groups in the training set, test set, and an independent validation set (GSE44001) using Kaplan-Meier curve. Meanwhile, univariate and multivariable CoxPH models were applied to test whether the multigene combination was an independent prognostic factor in cervical cancer. The survival analysis was performed using R packages "survival" and "survminer".

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Comparison of the prognostication performance between the multigene signature and established prognostic signature

Several prognostic signatures aiming at predicting the survival of patients with cervical cancer had been published. Fernandez-Retana et al. [22], Huang et al. [23], and Shen et al. [24] respectively introduced an 8-gene, 7-gene, and 2-gene based prognostic signature, which had been widely accepted. Therefore, we compared the prognostication performance of the multigene combination (9-gene) with theirs using concordance index (C-index).

Construction of the multigene based nomogram and its clinical use

To investigate the clinical use of the multigene signature, we built a multigene based nomogram which included the age, clinical stage, and the risk score of each cervical cancer the training set. To build such patients in a nomogram, the aforementioned variables were included into a multivariable survival model, and bootstraps with 1000 resamples were used to validate the performance of the nomogram internally and externally. The nomogram was drawn using R package "rms". Next, we performed decision curve analysis (DCA) to render the clinical validity to the nomograms [25].

Results

Characteristics of patients with cervical cancer in the training set, test set and validation set

As shown in Supplementary Table 1, a total of 145, 145, and 300 cervical cancer patients were included into the training set, test set, and validation set, respectively. The median age of patients were 47 years and 46 years in the training set and test set, respectively. Meanwhile, there were 83 patients with stage I cervical cancer, 26 patients with stage II cervical cancer, 26 patients with stage III cervical cancer, and 7 patients with stage IV cervical cancer in the training set, and the corresponding numbers in the test set were 78, 38, 15, and 13, respectively. The validation set consisted of 258 patients with stage I cervical cancer and 42 patients with stage II cervical cancer.

Development of a multigene combination predicting the survival patients with cervical cancer

A total of 37 genes with family-wise error rate less than 0.05 were identified and were included into the elastic net regularized CoxPH model. After performing a 10-fold cross validation, an optimal set of hyperparameters (α=0.0247, and λ=1.4674) were identified and were used to fit the final elastic net regularized CoxPH model (Figure 1). As a result, 9 genes (ITGA5, EREG, SYCE2, SLN, MEI1, RIBC2, PEAR1, GATS and ESM1, Supplementary Table 2) with non-zero coefficients in the model were found. Thus, we build a multigene combination by combining the coefficient and the expression levels of the aforementioned genes in order to predict the survival of patients with cervical cancer.

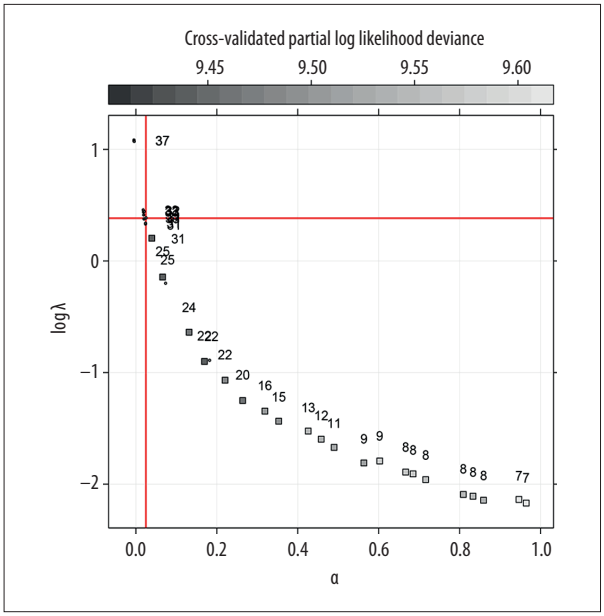

Figure 1. Optimal α and log λ for the elastic net derived using 10-fold cross validation.

The prognostication value of the multigene combination in cervical cancer

We analyzed the prognostication performance of the multigene combination in the training set and test set. Patients in the training set and test set were classified into the multigene signature high risk group and the multigene combination low risk group according to the result of time-dependent ROC analysis (Figure 2). As shown in Figure 2A, the area under the curve (AUC) of ROC at 1-year, 3-year, 5-year, and 7-year were 0.757, 0.744, 0.799, and 0.854, respectively, and the multigene combination could stratify patients in the training set into significantly different prognostic groups (HR=0.2223, 95% confidence interval [CI]: 0.105–0.4707, log-rank *P*<0.0001, Figure 2B and Supplementary Table 3). Meanwhile, the 1-year, 3-year, 5-year, and 7-year AUC of the ROC in the test set were 0.767, 0.721, 0.735, and 0.703, respectively (Figure 2C), and the multigene combination could also classified patients into different risk groups (HR=0.3793, 95% CI: 0.1995–0.721, log-rank *P*=0.0021, Figure 2D, Supplementary Table 4). Moreover, we performed Kaplan-Meier curve analysis for patients with early stage (pathological stage I and II) and advanced stage (pathological stage III and IV) in the training set and test set, and the associated results suggested that the

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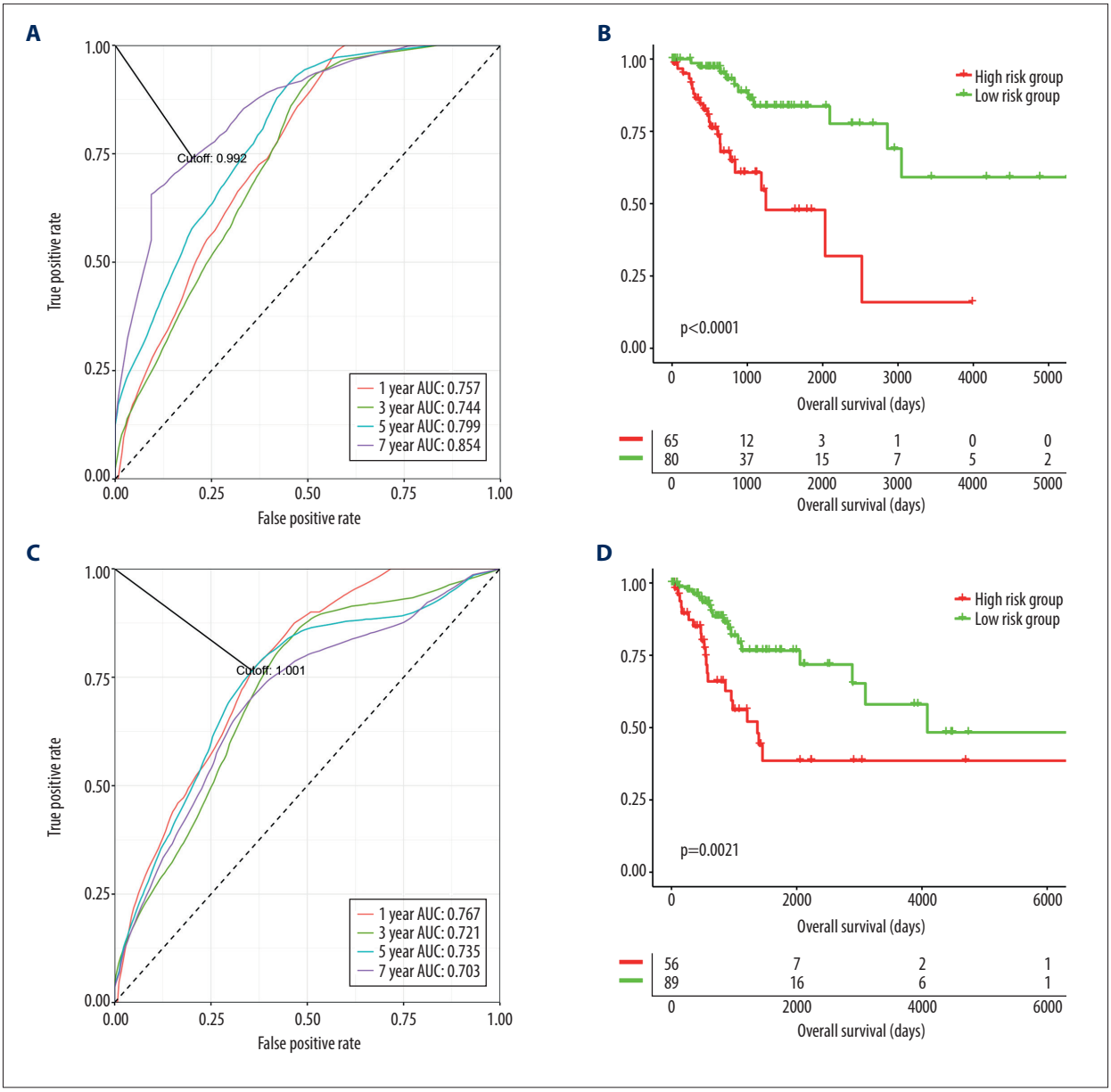

Figure 2. Prognostication performance of the multigene combination in the training set and test set. (**A**) Area under the curves (AUCs) of receiver operating characteristic (ROC) curve at 1-year, 3-year, 5-year and 7-year in the training set. (**B**) The overall survival of patients in the multigene combination low risk group and multigene combination high risk group in the training set. (**C**) AUCs of ROC at 1-year, 3-year, 5-year and 7-year in the test set. (**D**) The overall survival of patients in the multigene combination low risk group and multigene combination high risk group.

multigene combination could stratify patients with early stage and advanced stage into significantly different survival groups in the training set (Supplementary Figure 1A, 1B) and test set (Supplementary Figure 1C, 1D). Finally, we tried to validate the prognostic performance of the multigene combination in the cervical cancer gene expression study GSE44001, as shown in Figure 3, patients in the multigene low risk group were associated with better DFS compared with those in the multigene high-risk group. Taken together, the prognostic performance of the multigene combination was excellent in the training set, test set, and validation set.

C-index comparison between the multigene combination and previously published multigene combinations in cervical cancer

To further characterize the prognostication performance of the multigene signature, we tried to compare the C-indexes of our

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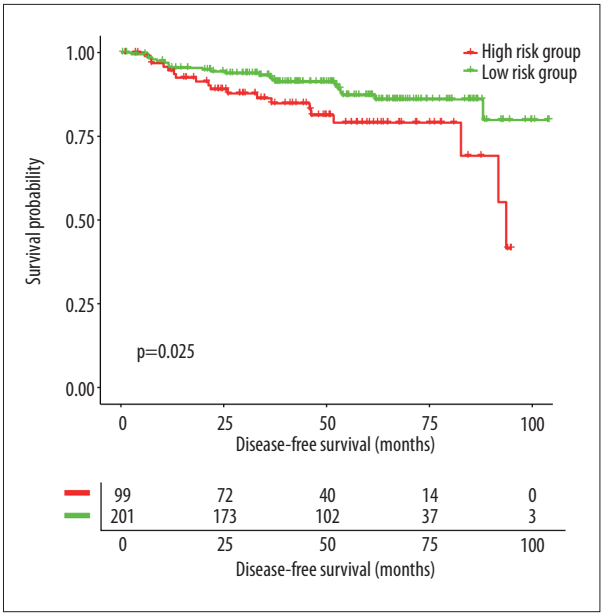

Figure 3. Disease-free survival of patients in the multigene combination low risk group and multigene combination high risk group.

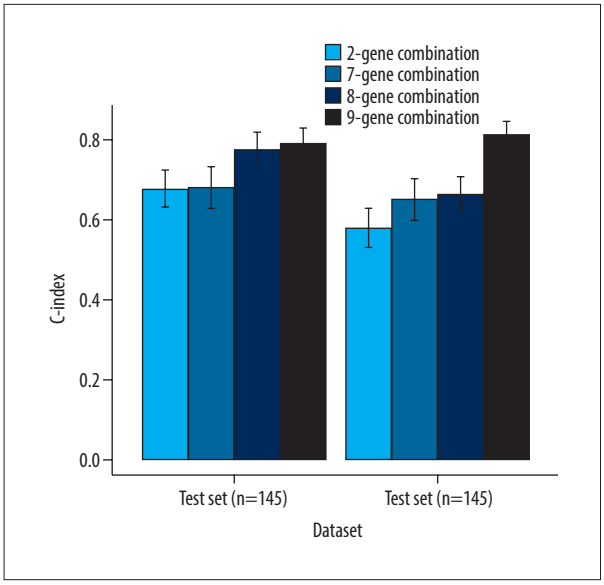

Figure 4. C-index comparison of our multigene combination and 3 existing prognostic signatures.

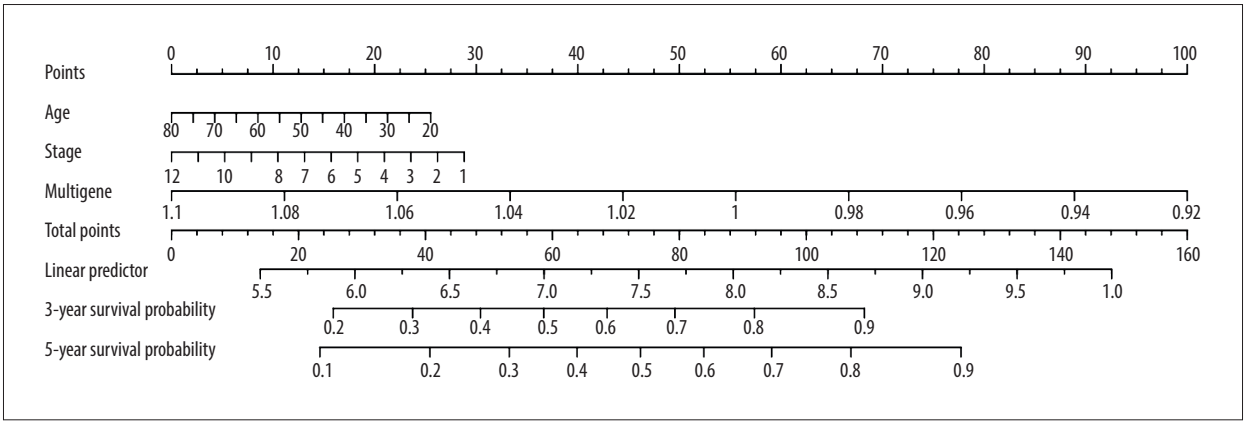

Figure 5. The multigene combination containing signature. To interpreter this nomogram, one should locate the value of each variable at each axis, then a vertical line should be drawn to the "Point" line to determine the points each variable gets. Next, the sum of points of each variable should be located on the "Total points" line, then the probabilities of 3- and 5-year overall survival can be calculated by drawing a vertical line from the total points of one patient to the 3-year survival probability axis and the 5-year survival probability axis.

multigene combination and the existing signatures mentioned. As shown in Figure 4, in the training set, the C-index of our multigene combination (0.8131) was significantly higher compared with that of the 8-gene combination (0.6648), the 7-gene combination (0.6502), and the 2-gene combination (0.5789) in the training set. Meanwhile, the C-index of our multigene combination (0.7921) was significantly higher compared with that the 8-gene combination (0.7772), the 7-gene combination (0.6803), and the 2-gene combination (0.6779) in the test set.

Clinical application of the multigene combination

As shown in Figure 5, we built a prognostic nomogram which included age, stage, and the multigene combination to predict the 3- and 5-year OS of patients with cervical cancer. The internally validated C-index and externally validated C-index were 0.7694 and 0.751, respectively, indicating that the multigene-containing nomogram showed excellent performance in clinical settings. To use this nomogram, one should locate the value of each variable at each axis, then a vertical line should be drawn to the "Point" line to determine the points

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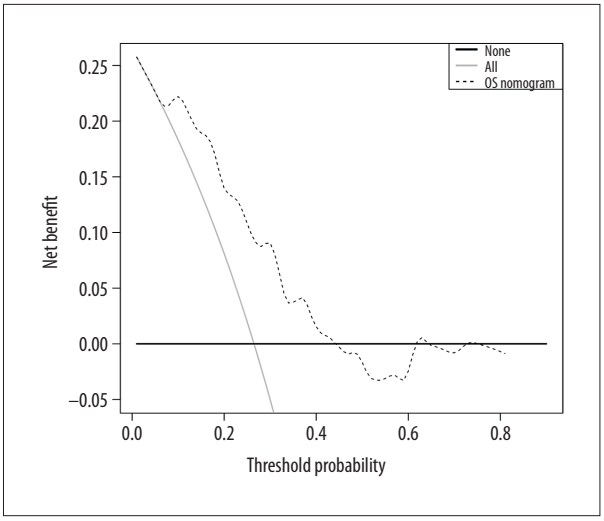

Figure 6. The decision curve analysis evaluating the clinical benefit of the multigene containing nomogram.

each variable gets. Next, the sum of points of each variable should be located on the "Total points" line, then the probabilities of 3- and 5- year OS can be calculated by drawing a vertical line from the total points of one patient to the 3-year survival probability axis and the 5-year survival probability axis. Meanwhile, we evaluated the clinical applicability of the multigene combination containing nomogram. As shown in Figure 6, the multigene combination containing nomogram is superior to the default strategies of treating all or no patient, across the threshold probabilities ranging from 0% to 44%.

Discussion

As mentioned, cervical cancer is a malignant tumor that is second only to breast cancer in female patients. At the same time, due to changes in sexual attitudes, environmental pollution, and poor health habits, the age of patients diagnosed with cervical cancer patients is getting younger and younger [26,27]. Cervical cancer usually progresses from precancerous lesions to carcinoma in situ to early invasive carcinoma, and finally to the continuous process of invasive cancer for about 5 to 10 years [28,29]. During this period, if cervical lesions are intervened, cervical cancer can be prevented and cured early. The cure rate of cervical carcinoma in situ is close to 100%. For invasive cervical cancer, the 5-year survival rate of stage I patients can reach more than 90%, phase II is 60% to 70%, and stage III can still have 40% to 50%, but stage IV is only about 10% [30]. Therefore, early diagnosis and treatment are extremely important. In the present study, we tried to identify biomarkers that could help early diagnosis and risk stratification of cervical cancer.

We first identified a total of 37 survival related genes and included these genes into an elastic net regularized CoxPH model, and finally 9 genes were obtained with non-zero coefficient in the CoxPH model. We combined these 9 genes to build a prognostic signature, and we demonstrated that the multigene combination could classify patients into significantly different survival groups in the training set, test set, and validation set. Moreover, results of multivariable CoxPH model suggested the multigene combination was an independent factor for predicting the survival of cervical cancer patients.

In fact, some of the 9 genes included in the multigene combination had previously been reported to be involved in cervical cancer. Zhu et al. suggested that ITGA5 was involved in the invasion of cervical cancer [31]. Zong et al. suggested that EREG was related with the development of cervical cancer [32]. Zhang et al. demonstrated that MEI1 was associated with the clinical outcome of cervical patients [33]. Meanwhile, we compared the prognostic performance of the multigene combination with 3 existing multigene signatures in cervical cancer, and the results suggested that our multigene combination outperformed other prognostic signatures. Therefore, these studies further verified the performance of the multigene combination.

Several prognostic signatures aiming at predicting the survival of patients with cervical cancer had been published. Fernandez-Retana et al. [22], Huang et al. [23], and Shen et al. [24] respectively introduced an 8-gene, 7-gene, and 2-gene based prognostic signature, which had been widely accepted. Therefore, we tried to compare the prognostication performance of the multigene combination (9-gene) with theirs using concordance index (C-index). In the training set, the C-index of our multigene combination (0.8131) was significantly higher compared with that of the 8-gene combination (0.6648), the 7-gene combination (0.6502), and the 2-gene combination (0.5789) in the training set. Meanwhile, the C-index of our multigene combination (0.7921) was significantly higher compared with that the 8-gene combination (0.7772), the 7-gene combination (0.6803), and the 2-gene combination (0.6779) in the test set (Figure 4).

Moreover, we tried to translate the multigene combination into clinical settings by constructing a multigene combination containing nomogram, which would help clinicians to estimate the 3-year and 5-year survival probability of cervical cancer patients and to determine the risk stratification of cervical cancer patients.

In October 2018, the International Federation of Obstetrics and Gynecology (FIGO) updated the latest version of the cervical cancer staging system [34-36]. It first proposed pathological results and imaging findings for staging, which made the clinical stage of cervical cancer close to the surgical pathological stage for the first time. And revolutionize the diagnosis and treatment of cervical cancer

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The FIGO staging system for cervical cancer is mainly based on imaging and pathological findings. Although it guides the treatment options for cervical cancer patients to a certain extent, in the era of individualized treatment, However, in the era of individualized treatment (personalized therapy), the simple use of the FIGO staging system for risk stratification, prognosis assessment, and targeted treatment outcome prediction and evaluation can no longer meet clinical needs. Our multigene panel is based on the molecular level and has unique advantages in patient-targeted therapeutic efficacy assessment and patient risk stratification.

Therefore, our multigene panel is complementary to the existing FIGO staging system, and the combination of the 2 will play a greater role in the clinical.

The clinical stage of cervical cancer is moving closer to the surgical pathological stage. No matter which staging method is used to improve the diagnosis and treatment level and improve the prognosis of patients with cervical cancer, it should follow the principles of standardization, individualization, and evidence-based medicine. Although the new staging system and diagnosis and treatment guidelines have been adjusted with the results of multi-center, large-scale, prospective studies, more evidence-based medical evidence support will be needed in the future to improve the prognosis of patients with cervical cancer.

Conclusions

We developed a multigene combination which might be used as an independent prognostic factor in cervical cancer, and we introduced a prognostic nomogram that could help clinicians to make a decision in clinical settings.

Conflicts of interest

None.

Supplementary Data

Supplementary Table 1. Characteristics of cervical cancer patients in the training set, test set and validation set.

Variable	Training set	Test set	Validation set
No. of samples	145	145	300
Median age in years (range)	47 (21–88)	46 (20–85)	NA
Stage (NO,%)			
I	83 (57.24)	76 (52.41)	258 (86)
II	26 (17.93)	38 (26.21)	42 (14)
III	26 (17.93)	15 (10.34)	0
IV	7 (4.83)	13 (8.97)	0
NA	3 (2.07)	3 (2.07)	0

Supplementary Table 2. Genes with non-zero coefficient in the elastic net regularized Cox proportional hazards regression model.

Gene symbol	Gene name	Coefficient
ITGA5	Integrin subunit alpha 5	0.022249
EREG	Epiregulin	0.032878
SYCE2	Synaptonemal complex central element protein 2	–0.00522
SLN	Sarcolipin	0.005992
MEI1	Meiotic double-stranded break formation protein 1	–0.02739
RIBC2	RIB43A domain with coiled-coils 2	–0.00311
PEAR1	Platelet endothelial aggregation receptor 1	0.006305
GATS	CASTOR family member 3	–0.00132
ESM1	Endothelial cell specific molecule 1	0.012901

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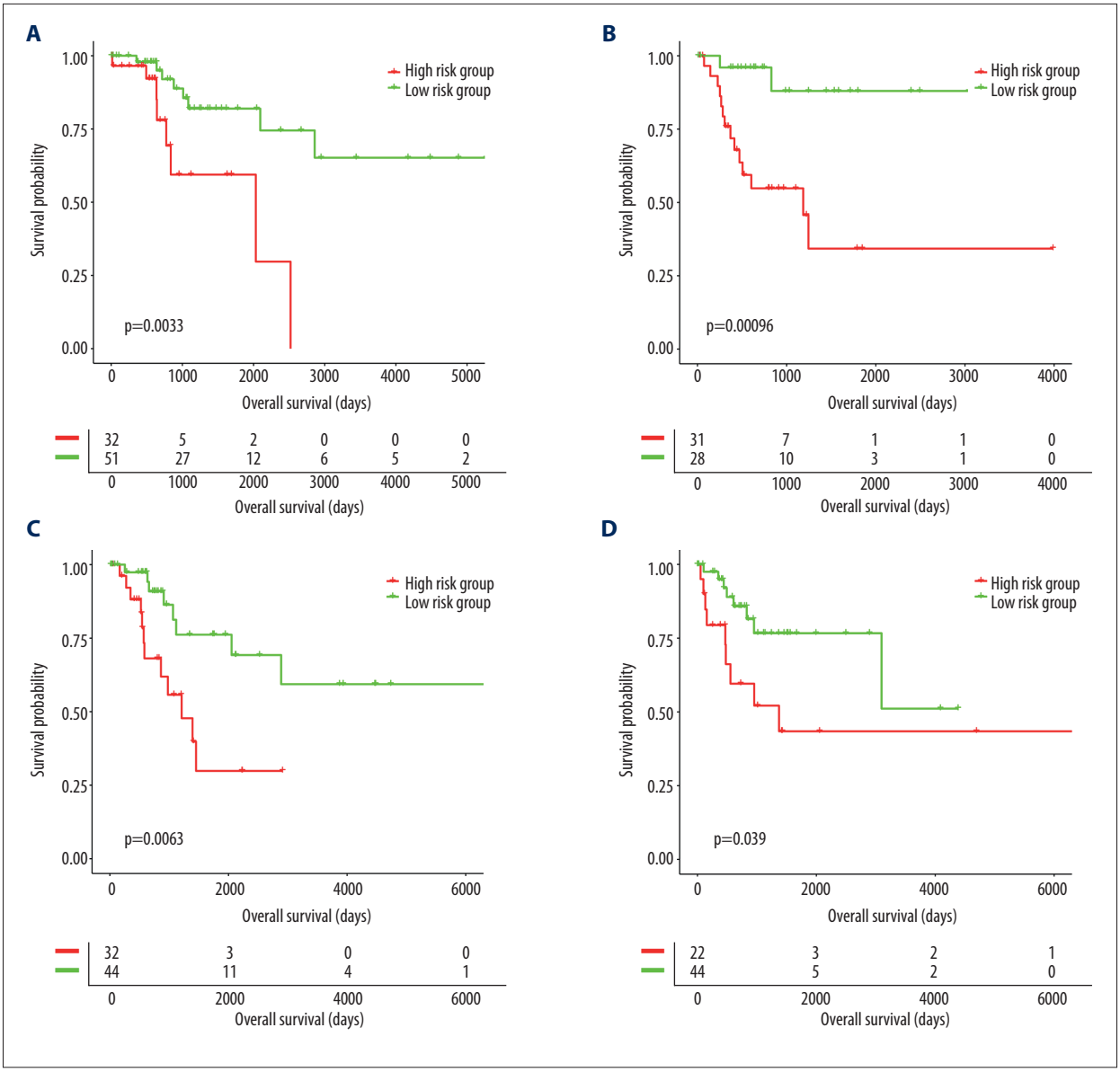

Supplementary Figure 1. The overall of patients with early stage and late stage cervical cancer. (**A**) The overall survival of patients with early stage cervical cancer in the training set. (**B**) The overall survival of patients with late stage cervical cancer in the training set. (**C**) The overall survival of patients with early stage cervical cancer in the test set. (**D**) The overall survival of patients with late stage cervical cancer in the test set.

Supplementary Table 3. Univariate and multivariable Cox proportional hazards regression model on the overall survival of cervical cancer patients in the training set.

Variable	Univariate Cox analysis			Mutivariable Cox analysis		
	HR	95% CI	P value	HR	95% CI	P value
9-gene combination	0.2223	0.105~0.4707	0.0001	0.2687	0.126~0.5729	0.0007
Age	1.0192	0.994~1.045	0.1357	1.0121	0.9866~1.0381	0.3555
Stage	1.1767	1.0587~1.3078	0.0025	1.1211	1.0024~1.2538	0.0453

HR – hazard ration, 95% CI – 95% confidence interval.

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Supplementary Table 4. Univariate and multivariable Cox proportional hazards regression model on the overall survival of cervical cancer patients in the test set.

Variable	HR	95% CI	P value	HR	95% CI	P value
9-gene combination	0.3793	0.1995~0.721	0.0031	0.3521	0.1848~0.6708	0.0015
Age	1.0151	0.9904~1.0404	0.2322	1.0133	0.9885~1.0387	0.2948
Stage	1.1014	0.99~1.2253	0.0758	1.0816	0.968~1.2086	0.166

HR – hazard ration, 95% CI – 95% confidence interval.

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