



A new prognostic model of esophageal squamous cell carcinoma based on Cloud-least squares support vector machine

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Background: In view of the low accuracy of the prognosis model of esophageal squamous cell carcinoma (ESCC), this study aimed to optimize the least squares support vector machine (LSSVM) algorithm to determine the uncertain prognostic factors using a Cloud model, and consequently, to establish a new high-precision prognosis model of ESCC.

Methods: We studied 4,771 ESCC patients(training samples) from the Surveillance, Epidemiology, and End Results (SEER) database and 635 ESCC patients(validation samples) from the Henan Provincial Center for Disease Control and Prevention (HCDC) database, with the same exclusion criteria and inclusion criteria for both databases, and obtained permission to obtain a research data file in the SEER database from the National Cancer Institute. The independent risk factors were analyzed using the log-rank method, survival curves, univariate and multivariate Cox analysis. Finally, the independent prognostic factors were used to construct the nomogram, random forest and Cloud-LSSVM prognostic models were utilized for validation.

Results: The overall median survival time of the SEER database was 14 months (HCDC samples was 46 months), the mean survival time was 26.5 months (HCDC samples was 36.8 months), and the 3-year survival rate was 65.8%. This is because most of the patients with Henan samples are early ESCC, and most of the Seer patients are T3 and T4 people. The multivariate Cox analysis showed that age at diagnosis ($P<0.001$), sex ($P=0.001$), race ($P=0.002$), differentiation grade ($P<0.001$), pathologic T category ($P<0.001$), and pathologic M category ($P<0.001$) were the factors affecting the prognosis of ESCC patients. The SEER data and HCDC database results showed that the accuracy of the Cloud-LSSVM (C-index =0.71, 0.689) model is higher than the differentiation grade (C-index =0.548, 0.506), random forest (C-index =0.649, 0.498), and nomogram (C-index =0.659, 0.563). This new model can realize the unity of the randomness and fuzziness of the Cloud model and utilize the powerful learning and non-linear mapping abilities of LSSVM.

Conclusions: Due to the difference of clans between training samples and test samples, the accuracy of prediction is generally not high, but the accuracy of Cloud-LSSVM model is much higher than other models. The new model provides a clear prognostic superiority over the random forest, nomogram, and other models.

Keywords: Esophageal squamous cell carcinoma (ESCC); Cloud-least squares support vector machine (Cloud-LSSVM); Surveillance, Epidemiology, and End Results (SEER); prognostic; machine learning

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Introduction

Esophageal cancer is the eighth most common cancer in the world and ranks seventh in terms of mortality, and its histological types are mainly divided into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) (1-3). More than 80% of the world's new cases and deaths occur in less developed regions. Histologically, approximately 90% of ESCC cases occur in high-incidence areas, with 60% of cases occurring in China. ESCC is characterized by high aggressiveness and poor prognosis. Despite treatment with a combination of surgery, radiotherapy, and chemotherapy, the 5-year survival rate is still less than 22% (4,5). The significant geographical variation in the incidence of esophageal cancer suggests that environmental and genetic factors may play an important role in the occurrence and development of esophageal cancer (6). The known risk factors for esophageal cancer include smoking and alcohol consumption, whereas fruit and vegetable intake has a high likelihood of preventing

esophageal cancer (7-9). Currently, the tumor-node-metastasis (TNM) staging system is used to predict the prognosis of ESCC patients, but its clinical value is limited. Given that the clinical course of ESCC patients with the same clinical stage often varies greatly, a new ESCC prognosis system is needed for more accurate prognostic prediction, so as to achieve more targeted treatment and improve the prognosis of the disease (10,11).

The random forest algorithm and nomogram have not only been frequently used to predict the survival of patients with all types of cancer but also to successfully quantify risk prediction by illustrating important factors for tumor prognosis (12-14). Machine learning is widely used in cancer research, mainly in cancer diagnosis, image recognition, prognosis prediction and so on. While the results are encouraging, machine learning has its limitations, such as being less sensitive to missing data and simpler algorithms, which are usually used for text classification (15). The amount of data that neural networks need to process is too large to handle multi-dimensional data. Although the nomogram is simple and easy to use, it has defects in processing continuous variables (16-18). They cannot deal with uncertainty, and their accuracy needs to be improved. The characteristics of LSSVM in solving nonlinear and high-dimensional pattern recognition make us choose this method

Therefore, this study used the SEER and HCDC databases as the basis to explore the risk factors for patient prognosis and further establish and verify the Cloud-LSSVM prognostic model to assist clinical practice. We present this article in accordance with the TRIPOD reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1058/rc>).

Methods

Patient population

We extracted the ESCC cases from the SEER database (available at <https://seer.cancer.gov/>), and had obtained

Highlight box

Key findings

- The Cloud-least squares support vector machine (LSSVM) model provides a clear prognostic superiority over the random forest, nomogram, and other models. This model is more advantageous in dealing with uncertain problems.

What is known and what is new?

- We know that entropy can be a measure of both the randomness of qualitative concepts as well as the value range of Cloud droplets allowed by qualitative concepts in the domain space of the Cloud model.
- The new model used the powerful learning and non-linear mapping abilities of the LSSVM. The penalty parameter C (Ex) and kernel function parameter (Entropy) were obtained by inverse normalization calculation of the Cloud parameters.

What is the implication, and what should change now?

- The popularization of the new model can improve the accuracy of esophageal squamous cell carcinoma prognosis, which is conducive to the choice of treatment for clinicians.

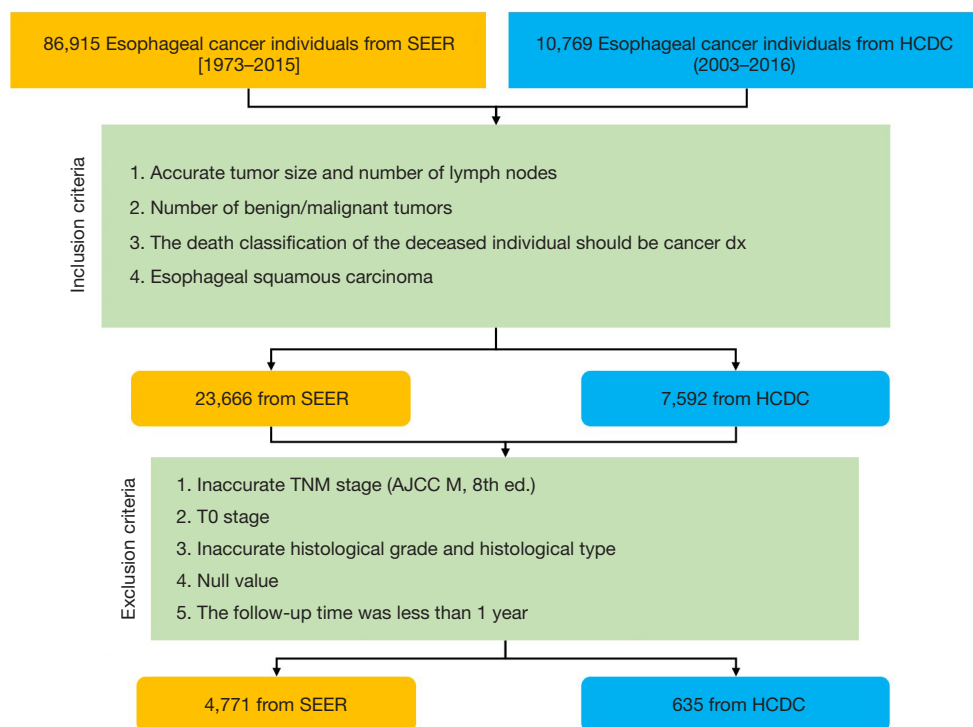


Figure 1 Patient exclusion criteria and inclusion criteria. SEER, Surveillance, Epidemiology, and End Results; HCDC, Henan Provincial Center for Disease Control and Prevention; TNM, tumor-node-metastasis; AJCC, The American Joint Committee on Cancer.

permission to obtain a research data file in the SEER database from the National Cancer Institute (reference number: 14574-Nov2019) (19,20). We used SEER*Stat Version 8.3.6 (Information Management Services, Inc., Calverton, MD, USA) to download all primary ESCC patient data from the SEER Database from 1973 to 2016 (21,22). The inclusion and exclusion criteria were as follows: (I) patients' basic personal information is missing, such as age at diagnosis, Sex, race, etc.; (II) TNM stage, tumor size, and number of lymph nodes are unknown; and (III) pathological type was not adenocarcinoma or squamous cell carcinoma. Variables such as race, age, sex, city, tumor location, degree of differentiation, TNM, differentiation grade (well differentiated as differentiation grade I, moderately differentiated as differentiation grade II, poorly differentiated as differentiation grade III, and undifferentiated anaplastic as differentiation grade IV), histological type, tumor size, number of lymph nodes, and survival status and time were extracted and analyzed.

The overall survival estimate registered in the SEER database is the "cause-specific classification of death", and stratified "dead (attributable to this cancer dx)" or "alive or dead of other cause". Survival time was calculated from the

diagnosis date to the date of death or last contact. The last contact, or the cut-off date of the study, was December 31, 2019, which was the last date of update on the follow-up time. The T, N, and M of all patients were staged according to the eighth edition of The American Joint Committee on Cancer (AJCC) esophageal cancer staging protocol. The patient exclusion and inclusion criteria are shown in *Figure 1*. The validation data were ESCC patients from 2003 to 2016 in China, Henan Provincial Center for Disease Control and Prevention, and the exclusion and inclusion criteria were the same as those applied for the SEER data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Firstly, we calculated the correlations and P values of each clinical characteristic. Next, the risk factors were analyzed by the log-rank method, and survival curves were drawn using the Kaplan-Meier method (23). Then, the significant risk factors in the univariate Cox analysis were introduced into the Cox proportional risk model for multivariate analysis, and the independent prognostic factors of

esophageal cancer were obtained (21,24). The test standard was defined as $P < 0.01$, which was considered statistically significant. Finally, the independent prognostic factors were used to construct the nomogram, random forest, and Cloud-LSSVM prognostic model of esophageal cancer (25-27). The C-index between the predicted probability and the actual outcome was calculated to judge the prognostic accuracy of the model. In this paper, C-index less than 0.65 was considered as low accuracy, and C-index more than 0.65 was considered as high accuracy. The Hmisc, Survival, RMS, Complex Heatmap, and other software packages of RStudio Version 1.1.463 (RStudio, Inc., Boston, MA, USA) were mainly utilized for the above calculation (28,29). The Cloud-LSSVM model employed libsvm and other software packages of MATLAB R2016a Version 9.2.341360 (MathWorks, Inc., Natick, MA, USA).

Establishment of the Cloud-LSSVM prognosis model

The factors affecting prognosis are generally uncertain, and the probability theory and fuzzy mathematics are insufficient to deal with this problem. We hypothesized that the Cloud theory could solve this issue. Cloud is the model of the uncertain transition between the qualitative and quantitative concept that is described by language; it completely collects fuzziness and randomness together. The Cloud model can be reflected by its three characteristics: Expected value (*Ex*), Entropy (*En*), and Hyper-Entropy (*He*) (30). Two parameters, namely kernel function parameter σ and penalty parameter *C*, are required to determine the radial basis kernel function LSSVM that is commonly used in prediction. These two parameters have a considerable influence on LSSVM's learning and generalization ability. The traditional parameter optimization method is not good at dealing with the uncertainty problem, but the optimization of the Cloud model least squares support vector machine (Cloud-LSSVM) solves this problem.

In this study, data distribution curves and the normal Cloud were obtained by Cloud transformation for factors affecting prognosis. Then, according to the reverse Cloud generator algorithm, the digital features of the Cloud (*Ex*, *En* and *He*) were obtained. In the Cloud model combined with LSSVM, the penalty parameter *C* is replaced by the Cloud model *Ex*, and the kernel parameter σ is replaced by entropy *En*. In this way, the new model can realize the unity of the randomness and fuzziness of the Cloud model and make use of the powerful learning and non-linear mapping abilities of LSSVM.

According to the Cloud transformation calculation method, the diagnostic age data was taken as an example. First, the data were normalized to [0,1] to obtain the data distribution curve of the diagnostic age, and then the maximum method Cloud transformation was carried out for the diagnostic age to obtain a normal Cloud, as shown in *Figure 2A,2B*. At the same time, according to the Cloud transformation calculation method, the Sex data showed two peaks in the distribution curve, so it had two Clouds (*Figure 2C,2D*).

The penalty parameter *C* (*Ex*) and kernel function parameter (Entropy) were obtained by inverse normalization calculation of the Cloud parameters. Entropy can be a measure of both the randomness of qualitative concepts as well as the value range of Cloud droplets allowed by qualitative concepts in the domain space of the Cloud model. In this way, the new model can realize the unity of the randomness and fuzziness of the Cloud model. The new model used the powerful learning and non-linear mapping abilities of the LSSVM. In general, the higher the entropy, fuzziness, and randomness, the harder to quantify determinism.

Results

Univariate Cox analysis

According to the SEER database, which included 86,915 patients with esophageal cancer from 1973 to 2015, 14,708 patients with esophageal cancer were selected in strict accordance with the inclusion criteria. There were 9,550 cases of adenocarcinoma and 4,771 cases of squamous cell carcinoma. The overall median survival time was 14 months, the mean survival time was 26.5 months, and the 3-year survival rate was 65.8%. Univariate Cox analysis of the clinical factors showed that age at diagnosis ($P < 0.001$), sex ($P < 0.001$), race ($P = 0.001$), differentiation grade ($P < 0.001$), pathologic T category ($P < 0.001$), regional lymph node ($P < 0.001$), and pathologic M category ($P < 0.001$) were associated with patient survival. The numbers of malignant tumors ($P = 0.078$) and benign tumors ($P = 0.459$) were not correlated with prognosis.

Meanwhile, according to the HCDC database, which included 10,769 patients with ESCC from 2003 to 2016, 635 patients were selected in strict accordance with the inclusion criteria. Univariate Cox analysis of clinical factors showed that age at diagnosis ($P < 0.001$), differentiation grade ($P < 0.001$), pathologic T category

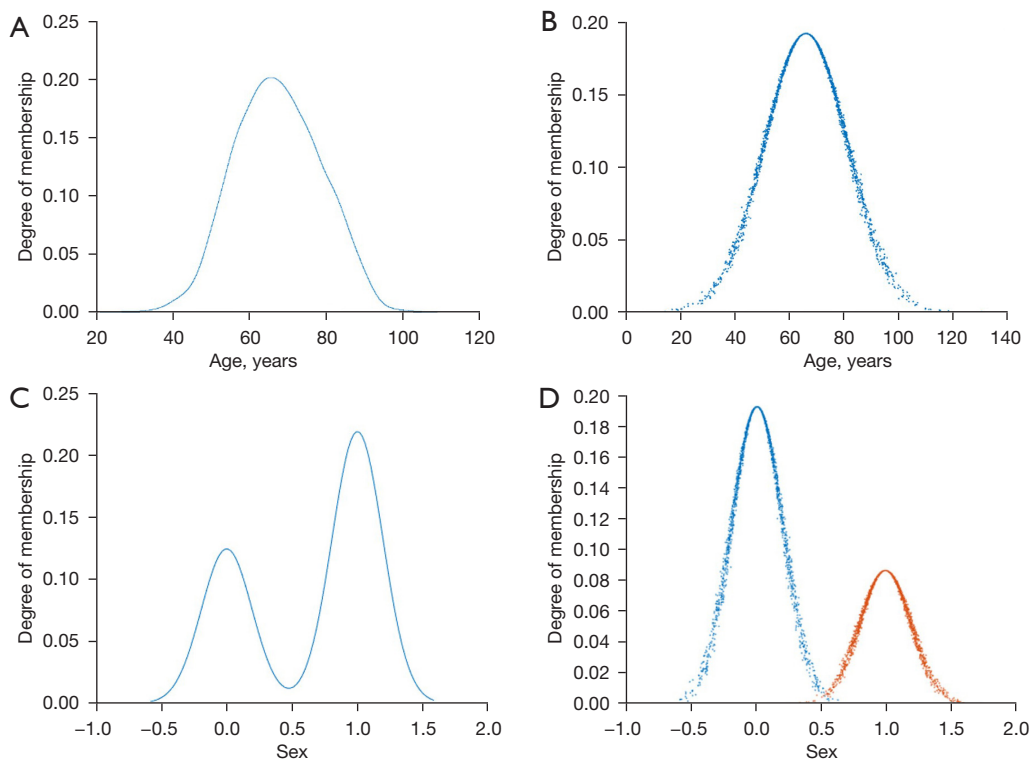


Figure 2 Data distribution and combined Cloud of age at diagnosis (A,B) and sex (C,D); the blue line represents Cloud 1 and the red line represents Cloud 2.

($P < 0.001$), regional lymph node ($P < 0.001$), and sex ($P = 0.049$) were associated with patient survival. The pathologic M category ($P = 0.093$) and race were not correlated with prognosis (Table 1).

Multivariate Cox analysis

Multivariate Cox analysis was performed for factors with statistically significant values according to the SEER database. The results showed that age at diagnosis ($P < 0.001$), sex ($P = 0.001$), race ($P = 0.002$), differentiation grade ($P < 0.001$), pathologic T category ($P < 0.001$), and pathologic M category ($P < 0.001$) were the factors affecting the prognosis of patients with ESCC. Pathologic N category ($P = 0.543$) were not associated with prognosis. Meanwhile, multivariate Cox analysis was performed for factors with $P < 0.05$ according to the HCDC database. The results showed that age at diagnosis ($P = 0.03$), differentiation grade ($P < 0.001$), and pathologic N category ($P < 0.001$) were the factors affecting the prognosis of patients with ESCC. Sex ($P = 0.056$) was not associated with prognosis (Table 1).

Further analysis was performed on the six significant

factors obtained from the multivariate Cox analysis of the SEER database, and the survival curve and correlation coefficient graph were drawn, as shown in Figure 3. The results showed that the prognosis of the low-diagnostic age group was significantly better than that of the high-diagnostic age group (Figure 3A); the prognosis of differentiation grade I was better than that of grades II, III and IV, and the prognosis of grades II was better than that of grade III and IV (Figure 3B); and the prognosis of the pathologic T category was that T2 was better than T3, T3 was better than T1, and T1 was better than T4 (Figure 3C); the prognosis of females was better than that of males (Figure 3D). The prognosis of White people was better than that of Black people (Figure 3E); the prognosis of ESCC patients without the pathologic M category was better than that of ESCC patients with the pathologic M category (Figure 3F). Correlation analysis showed that age at diagnosis was associated with the pathologic T category, race was associated with the pathologic T category and pathologic M category, differentiation grade was not associated with the pathologic M category and sex, the other features were related (Figure 3G).

Table 1 Univariate and multivariate Cox analyses of the clinical characteristics of ESCC patients

Characteristics	SEER database				HCDC database					
	N	Univariate Cox analysis		Multivariate Cox analysis		N	Univariate Cox analysis		Multivariate Cox analysis	
		χ^2	P value	χ^2	P value		χ^2	P value	χ^2	P value
Age at diagnosis (years)		40.575	<0.001	90.219	<0.001		21.21	<0.001	14.136	0.03
<60	1,215					238				
60–70	1,556					317				
71–80	1,261					77				
81–85	422					3				
>85	317					0				
Differentiation grade		30.776	<0.001	15.121	<0.001		38.79	<0.001	33.211	<0.001
I	256					109				
II	1,968					308				
III	1,598					78				
IV	26					3				
Other	923					65				
Pathologic T category		42.5	<0.001	30.489	<0.001		49.44	<0.001	21.126	<0.001
T ₁	1,503					125				
T ₂	569					143				
T ₃	1,809					328				
T ₄	890					39				
Pathologic N category		27.798	<0.001	0.37	0.543		37.62	<0.001	31.824	<0.001
N ₀	2,154					384				
N ₁	2,043					222				
N ₂	457					24				
N ₃	117					5				
Pathologic M category		444.688	<0.001	388.414	<0.001		2.81	0.093	–	–
M ₀	3,831					633				
M ₁	940					2				
Race		11.176	0.001	9.727	0.002		–	–	–	–
Black	1,181					0				
White	3,084					0				
Other	506					635				
Sex		53.451	<0.001	36.647	0.001		3.861	0.049	3.662	0.056
Female	1,729					352				
Male	3,042					283				
Malignant tumors	–	3.1	0.078	–	–	–	–	–	–	–
Benign tumors	–	0.548	0.459	–	–	–	–	–	–	–

ESCC, esophageal squamous cell carcinoma; SEER, Surveillance, Epidemiology, and End Results; HCDC Henan Provincial Center for Disease Control and Prevention.

Table 2 The parameters after Cloud transformation

Factors	Cloud	Entropy	The penalty parameter C
Age at diagnosis	1	0.246	1.971
Sex	2	0.245	0.993
Race	2	0.766	3.978
Differentiation grade	4	0.295	1.97
Pathologic T category	4	0.699	3.013
Pathologic M category	2	0.257	0.993

Uncertainty analysis

The multivariate Cox analysis showed that age at diagnosis, sex, race, differentiation grade, pathologic T category, and pathologic M category were the factors affecting the prognosis of patients with ESCC. Uncertainty analysis was performed for factors with multivariate Cox analysis results with $P < 0.01$ according to the SEER database. The parameters after Cloud transformation are shown in *Table 2*, illustrating that there were two Clouds for race (Entropy = 0.766), which also indicates that the fuzziness and randomness of the race data itself were the largest. Sex (Entropy = 0.245) and age at diagnosis (Entropy = 0.246) had the lowest entropy. Pathologic T category (Entropy = 0.699) also showed great fuzziness and randomness. The parameters shown in *Table 2* were substituted into the Cloud-LSSVM model, and the final prognosis result was obtained by weighting calculation.

Comparison of the discriminative ability of the prognostic prediction models containing different artificial intelligence algorithms

To further evaluate the predictive capacity and accuracy of Cloud-LSSVM models, likelihood ratio χ^2 , and Akaike information criterion (AIC) values were then calculated (*Table 3*). Higher C-index and likelihood ratio χ^2 scores denoted better prognostic performance of the system; meanwhile, the lower the AIC value, the better the system (31,32). We also found that the likelihood liner trend χ^2 values of the Cloud-LSSVM (857.43) were higher compared with those of the TNM stage, differentiation grade, random forest, and nomogram (265.8, 52.52, 37.75, and 665.45, respectively) in both cohorts. The AIC values were 52,520.26, 52,733.55, 17,705.76, 25,893,

and 12,952.97 for the TNM stage, differentiation grade, random forest, nomogram, and Cloud-LSSVM in the SEER database, respectively. Regarding the validation cohort, the AIC values were 3,530.48, 3,591.95, 3,593.88, 3,119.95, and 2,981.26 for differentiation grade, random forest, nomogram, and Cloud-LSSVM in the HCDC database, respectively.

Furthermore, the C-index between the predicted probability and actual outcome was calculated. The C-index for predicting overall survival (OS) among the TNM stage, differentiation grade, random forest, nomogram, and Cloud-LSSVM were 0.611, 0.548, 0.649, 0.659, and 0.71 in the SEER database, respectively. As for the validation cohort, the C-index was 0.522 (TNM stage), 0.506 (differentiation grade), 0.498 (random forest), 0.563 (nomogram), and 0.689 (Cloud-LSSVM).

Discussion

Traditionally, clinical cancer prognosis study employed univariate and multivariate Cox analyses or nomograms to predict the survival status of patients. With the rise of artificial intelligence algorithms, random forest, neural networks, and other artificial intelligence algorithms have been introduced into cancer prognostic investigations; however, these algorithms often have limitations and cannot deal with uncertain factors (33). In our previous study, most of the screening of prognostic factors utilized univariate and multivariate Cox analyses. These analyses only study the effect of variables on survival but ignored the effect of the variables themselves, such as uncertainty and randomness (34).

In previous study, it was difficult for researchers to directly explore the effect between the independent and dependent variables due to the existence of many other variables that confound the relationship between them, and selective errors can be controlled and eliminated by propensity score matching (PSM) when dealing with the effects between variables (35). In this study, we found that pathologic T category and race have large fuzziness and randomness. The PSM algorithm cannot solve the errors caused by fuzziness and randomness, while the Cloud-LSSVM model in this study solved this problem.

According to the analysis of the SEER database in *Table 1*, race and pathologic M category were found to be important factors affecting prognosis. However, patients in the validation group from the HCDC data were all Asian people from China, which seriously interfered with the data. In addition, all the data were early-stage cases

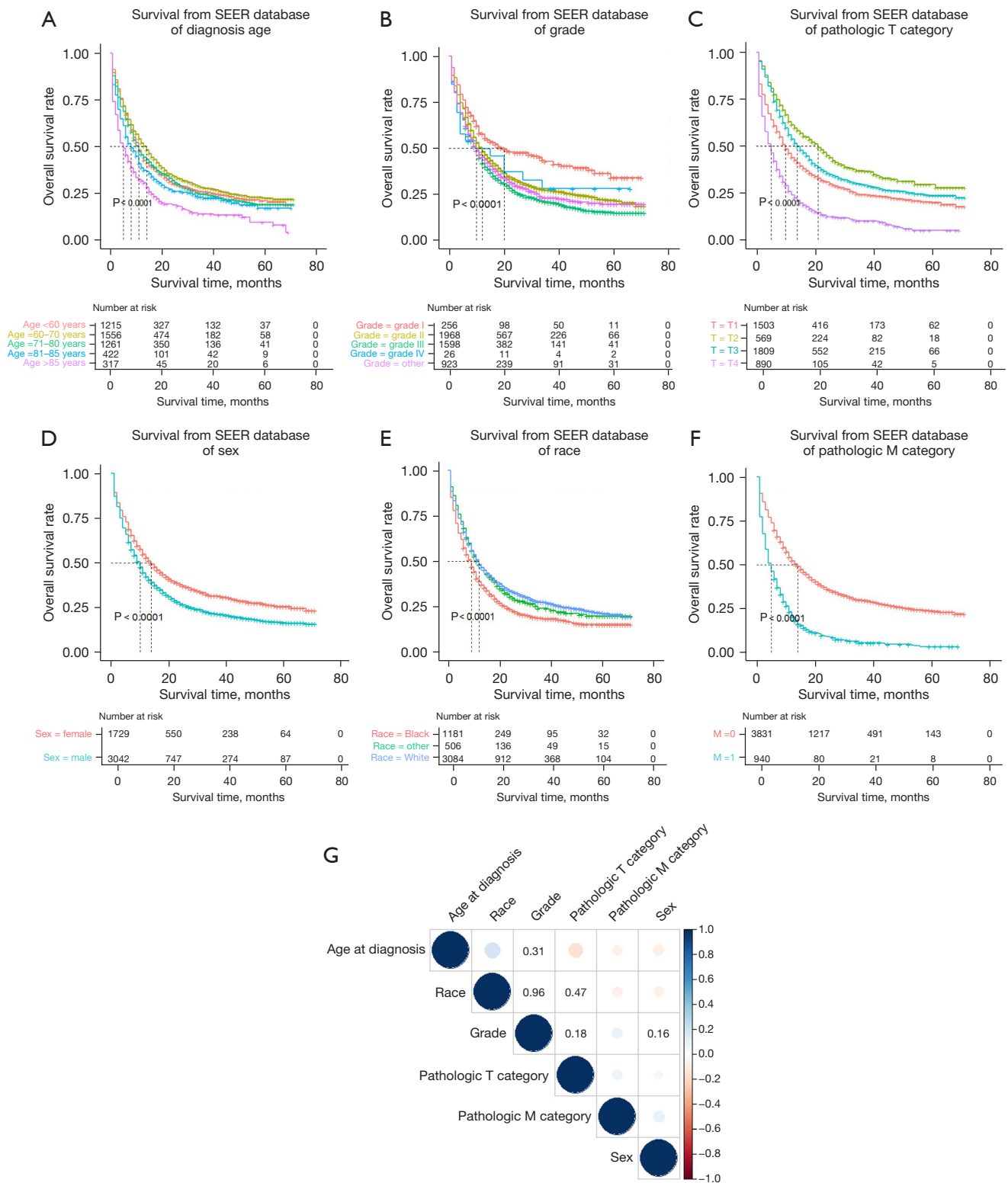


Figure 3 Kaplan-Meier curves for the 6-year overall survival stratified by age at diagnosis (A), differentiation grade (B), pathologic T category (C), sex (D), race (E), and pathologic M category (F) of the SEER database. The correlation and P values of each clinical characteristic (G). SEER, Surveillance, Epidemiology, and End Results.

Table 3 Prognostic ability and accuracy of ESCC based on evaluation by the AIC and C-index

Model	SEER database			HCDC database		
	Likelihood ratio χ^2	AIC	C-index	Likelihood ratio χ^2	AIC	C-index
TNM stage	265.8	52,520.26	0.611	40.47	3,530.48	0.522
Differentiation grade	52.52	52,733.55	0.548	2.3	3,591.95	0.506
Random forest	37.75	17,705.76	0.649	0.37	3,593.88	0.498
Nomogram	665.45	25,893	0.659	68.92	3,119.95	0.563
Cloud-LSSVM	857.43	12,952.97	0.71	755.2	2,981.26	0.689

ESCC, esophageal squamous cell carcinoma; AIC, Akaike information criterion; C-index, Concordance index; SEER, Surveillance, Epidemiology, and End Results; HCDC, Henan Provincial Center for Disease Control and Prevention; TNM, tumor-node-metastasis; LSSVM, least squares support vector machine.

of ESCC, and there were only two patients with M_1 and 653 patients with M_0 , so these two important factors could not be predicted by conventional methods. If prognostic algorithms such as nomograms and random forest are used, race and pathologic M category would be missing, thereby making the prediction results extremely inaccurate. There is a great deal of fuzziness and randomness in the race and pathologic T category (Table 2). The Cloud-LSSVM algorithm has a considerable advantage in solving these kinds of issues, and this result was also confirmed in the verification using the SEER and HCDC databases (Table 3). However, this model is limited by the limitations of the LSSVM algorithm itself and is not good at dealing with large samples.

In this study, the SEER data were divided into two parts, and 3,000 cases were randomly selected as the training set and 1,771 cases as the test set. The test results in the SEER database showed that the prognostic ability of Cloud-LSSVM was higher than that of other models. However, in the uncertain HCDC database test, the prognostic ability of Cloud-LSSVM was markedly higher than those of other models. Thus, it is proven that the Cloud-LSSVM model not only has higher prognostic ability than other machine learning models but also has more advantages in dealing with uncertain problems. In previous study, Cloud models have been applied to power system load forecasting and temperature prediction. This is the first time that Cloud models have been applied in the medical field (36). The results of this study indicate that this algorithm has broad development prospects for the prognostic evaluation of patients with ESCC.

Conclusions

In conclusion, we developed and validated a novel Cloud-LSSVM model for predicting survival in ESCC patients. With the advantages of dealing with uncertain problems and ease of use, this Cloud-LSSVM model offers clear prognostic superiority over the random forest, nomogram, and other models.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1058/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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