A machine learning model for three years survival state prediction of HPSCC patients via multi parameters

Zufei Li
Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Key Laboratory of Otolaryngology Head and Neck Surgery (Capital Medical University), Mini

Shuo Ding
Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Key Laboratory of Otolaryngology Head and Neck Surgery (Capital Medical University), Mini

Qi Zhong
Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Key Laboratory of Otolaryngology Head and Neck Surgery (Capital Medical University), Mini

Jugao Fang
Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Key Laboratory of Otolaryngology Head and Neck Surgery (Capital Medical University), Mini

Xiaohong Chen
Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Key Laboratory of Otolaryngology Head and Neck Surgery (Capital Medical University), Mini

Junwei Huang
Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Key Laboratory of Otolaryngology Head and Neck Surgery (Capital Medical University), Mini

Yang Zhang (zhangyangent@163.com)
Capital Medical University

Zhigang Huang
Capital Medical University

Research Article

Keywords: survival, prediction model, XGBoost, hypopharyngeal squamous cell carcinoma, machine learning

Posted Date: May 20th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1671233/v1

Abstract

Background and Objective: The survival rate of patients with hypopharyngeal squamous cell carcinoma (HPSCC) was poor. The aim of this study was to establish a prediction model to predict the 3-year survival state of HPSCC patients by using artificial intelligence (AI) algorithms.

Methods: The survival and clinical-pathological data of 295 patients with HPSCC in our hospital were analyzed retrospectively. 70% of the data were set as training sets and the other 30% were set as test sets. Total 22 clinical parameters which may correlated to the survival states of HPSCC patients were included as the training features. Total 12 kinds of different machine learning (ML) algorithms were used for model construction and were evaluated to find the model with the best model performance. The accuracy, sensitivity, specificity, area under the receiver operating characteristic curve (ROC), as well as Cohen's kappa coefficient were used to evaluated the model performance.

Results: We successfully conducted a 3-year survival prediction model of HPSCC patients based on the above clinical features by using XGBoost algorithm, which is the algorithm with the best model performance among all the 12 ML algorithms. The accuracy, sensitivity, specificity, area under ROC (AUC), and kappa value of the model were 80.9%, 92.6%, 62.9%, 77.7%, 58.1%, respectively.

Conclusion: The XGBoost algorithm can construct a relatively reliable prediction model of 3-year survival state of HPSCC patients. The proposed model can offer a new prognostic evaluation method for clinical treatment of HPSCC.

Introduction

Hypopharyngeal carcinoma is relatively rare, accounting for about 3% of all head and neck tumors and 7% of upper respiratory tract tumors[1–2]. The onset site of hypopharyngeal cancer is hidden, and the early symptoms are not typical. Most patients have been in advanced stage (stage III-IV) at the time of diagnosis. More than 90% of hypopharyngeal cancer is squamous cell carcinoma (HPSCC), and the vast majority of patients are male[3]. These patients usually have a long-term history of smoking and drinking. In terms of treatment, early HPSCC (stage I-II, with a small proportion) can be treated mainly by surgery, whether endoscopic transoral laser microsurgery (TLM), open partial hypopharyngectomy or partial laryngectomy, supplemented by radiotherapy or chemotherapy[4]. For advanced HPSCC, comprehensive treatment can be selected, including surgery, preoperative and postoperative chemotherapy and/or radiotherapy.

The prognosis of HPSCC is poor, with a 5-year survival rate of 30–35% and a 3-year survival rate of 43–57%[1,5]. Without any treatment, usually less than 20% of patients with HPSCC can survive for more than 12 months, and only a few patients can survive for more than 2 years. Despite advances in medicine and oncology in the treatment of other kinds of head and neck cancers, the prognosis of HPSCC is still relatively poor, especially for the patients with advanced HPSCC (stage III-IV), the overall survival rate has only improved slightly in the past few years[6]. Some researchers have pointed out that it is not perfect to formulate treatment methods and predict the prognosis of patients only by the TNM stage, which should be comprehensively evaluated in combination with specific variables related to the survival of patients[7].

In recent years, artificial intelligence (AI), including machine learning (ML) and deep learning (DL), have played an important role in the diagnosis, treatment and prognosis of various kinds of tumors, including the application in head and neck tumors[8–10]. The commonly used ML algorithms include[11]: K-nearest neighbor (KNN), support vector machine (SVM), decision tree (DT), random forest (RF), linear discriminant analysis (LDA), AdaBoost, XGBoost, CATBoost, etc., different algorithms have different model performance in different data sets.

The main purpose of this study is to establish a multi-parameter AI model for predicting the 3-year survival state of patients with HPSCC by using ML algorithms and 22 parameters, so as to provide a reference for the prediction of clinical treatment prognosis of HPSCC.

Methods

Data acquisition

This is a retrospective study and was approved by the institutional review board of Beijing Tongren Hospital (TRECKY2016-025). The clinical data of 295 patients with HPSCC who underwent surgery in our Hospital from December 2004 to December 2015 were collected, including the basic clinical information and treatment at the time of diagnosis. The follow-up date was December 31, 2018. Inclusion criteria: 1) squamous cell carcinoma (SCC) confirmed by pathology, 2) primary case. Exclusion criteria: non-SCC, 2) patients with secondary HPSCC, 3) recurrent disease, 4) palliative treatment only.

Smoking history was defined as smoking more than 10 cigarettes per day for more than 10 years, and drinking history was defined as at least 1 time/week for more than 10 years. Among all the data, 70% are set as training sets and the other 30% are set as test sets. The division method between training sets and test sets is to apply the Sklearn Library based on Python programming language, The train_test_split module is assigned, and the random seed is set to 0.

Feature selection

This study is a multi-parameter AI model constructed study. We conduct the feature selection of this study from a clinical perspective. All clinical data that may be related to the prognosis of HPSCC patients are chosen as the input features of the model. Including the patient's age, gender, smoking history, drinking history, whether there is a basic disease, TNM stage and clinical stage at the time of diagnosis, whether there is radiotherapy or chemotherapy before and after the operation, pathological differentiation, whether transoral laser microsurgery (TLM), partial laryngectomy, partial hypopharyngeal resection, total laryngectomy, total hypopharyngeal resection, and skin flap repair were performed. Because our hospital routinely makes immunohistochemical analyses of p53 and Ki67 protein in the pathological sections of patients with head and neck tumors, the expression levels of p53 and Ki67 protein are also included in the model training. To sum up, we included 22 clinical parameters for model training and compared the model performance with/without p53 or Ki67 protein.

Model establishment

We use the XGBoost algorithm for the model establishment, the fine-tuning detail of the parameters of XGBoost were shown in the supplementary material. XGBost classifier is a machine learning method newly defined by

Chen et al., which is characterized by combining several weak learning algorithms into a single strong learning algorithm to obtain high-performance results[12].

In addition, to obtain the best model performance, other common machine learning algorithms are also established. The differences between the model results of the XGBoost algorithm and those of other machine learning algorithms are compared and recorded. These algorithms include SVM, RF, Logistic Regression, KNN, LDA, multinomial Naive Bayes, Decision Tree, AdaBoost, multi-layer perceptron (MLP), Light GBM and CATBoost.

Model evaluation and statistical analysis

Common parameters such as accuracy, specificity, sensitivity, Receptor operation characteristic (ROC) curve and kappa value were used for model evaluation. The area under the ROC curve (AUC) value was calculated. Spss22.0 was used for the statistical analysis. The difference in the 3-year survival status of HPSCC under different characteristics was analyzed by the chi-square test.

Results

Demographic data of enrolled patients

The data of 295 patients with HPSCC were included in this study. The age was 33–86 years (59.7 ± 10.1 years), and the follow-up time was 6-126 months (median follow-up time was 52 months). The comparison of demographic data and 3-year survival status of HPSCC patients under different clinical characteristics is shown in Table 1.

Table 1
Demographic data of the study and their relationship with the 3-years survival state

Clinical data	Survival	Dead	χ^2	P	Clinical data	Survival	Dead	χ^2	P
Sex					Ki67				
Male	114	170	0.733	0.392	Positive	77	138	4.903	0.019
Female	3	8			Negative	40	70		
Age					P53				
≥ 60 years	50	96	3.541	0.039	Positive	42	84	3.680	0.036
< 60 years	67	82			Negative	75	94		
T stage					Chemo-pre				
T1−2	27	68	7.397	0.004	Yes	51	57	4.070	0.029
T3−4	90	110			No	66	121		
LNM					Radio-pre				
Yes	74	96	2.519	0.071	Yes	13	25	4.168	0.030
No	43	82			No	104	153		
M					CO2 laser				
Yes	0	4	2.665	0.131	Yes	15	54	9.646	0.002
No	117	174			NO	102	124		
Pathological grading					Total Larynx Cut				
Non-poorly differentiate	105	101	36.497	0.000	Yes	42	143	12.088	0.000
poorly differentiate	12	77			No	75	35		
Clinical stage					Partial Larynx Cut				
I-II	16	56	12.1	0.000	Yes	28	34	0.992	0.197
III-IV	101	122			No	89	144		
Basic disease					Partial hypopharynx				
Yes	30	57	1.384	0.148	Yes	50	61	2.156	0.089
No	87	121			No	67	117		

Chemo-pre: chemotherapy before surgery; Radio-pre: radiotherapy before surgery.

Clinical data	Survival	Dead	χ^2	P	Clinical data	Survival	Dead	χ^2	P
Smoking					Total hypopharynx				
Yes	85	126	0.120	0.416	Yes	16	11	4.770	0.025
No	32	52			No	101	167		
Alcohol					Chemo-post				
Yes	68	118	2.024	0.097	Yes	29	88	20.853	0.000
No	49	60			No	167	11		
Radio-post					Flap				
Yes	46	36	12.821	0.000	Yes	36	43	1.574	0.132
No	71	142			No	81	135		
Chemo-pre: chemotherapy before surgery; Radio-pre: radiotherapy before surgery.									

Among all the 22 clinical features, 9 had no significant correlation with the 3-year survival status of HPSCC: gender, LNM, distant metastasis, basic disease, smoking history, drinking history, partial laryngectomy, partial hypopharyngeal resection and flap repair. Considering that these characteristics are also important clinical parameters, even if they are not statistically different from the 3-year survival status of HPSCC patients, we still use them as the input characteristics of the model.

The other 13 characteristics were significantly related to the 3-year survival status of HPSCC. Patients with the following conditions were more likely to die after 3 years: age ≥ 60 years, T3-4, pathology was poorly differentiated, P53 and Ki67 protein expression were positive, advanced HPSCC (stage III-IV), and no radiotherapy or chemotherapy was performed before or after operation; patients who never undertaken TLM / total laryngectomy / total hypopharyngeal resection.

Model performance of XGBoost and other ML algorithms

The model performance of each algorithms were shown in Table 2. Among which, model that constructed by XGBoost algorithm were the best, the accuracy, sensitivity, specificity, AUC and kappa value were: 80.9%, 92.6%, 62.9%, 77.7%, 58.1%, respectively. The confusion matrix and the ROC curve were shown in Fig. 1 and Fig. 2, respectively, the feature importance of the XGBoost model was shown in Fig. 3, it should be noticed that, because the number of HPSCC patients with distant metastasis were too small, its role in the model was not significant, so it was not shown in the feature importance diagram. However, because it is a very important clinical data, we still retain it as the input feature of the model.

Table 2
The model performance of XGBoost and compare of other machine learning algorithms

Algorithms	Accuracy	Sensitivity	Specificity	AUC	Kappa value
Support vector machine	75.3%	88.9%	54.3%	71.6%	45.5%
Random forest	75.3%	87.0%	57.1%	72.1%	46.0%
Logistic Regression	73.0%	87.0%	51.4%	69.2%	40.5%
K-nearest neighbor	61.8%	70.3%	48.6%	59.4%	19.1%
Linear discriminant analysis	73.0%	85.2%	54.3%	69.7%	41.1%
Multinomial Naive Bayes	73.0%	88.9%	48.5%	68.7%	39.9%
Decision Tree	62.9%	72.2%	48.6%	60.4%	21.1%
AdaBoost	77.5%	88.9%	60.0%	74.4%	50.9%
Multi layer perceptron	70.8%	90.7%	40.0%	65.4%	33.4%
Light GBM	73.0%	87.0%	51.4%	69.2%	40.5%
CATBoost	74.2%	83.3%	60.0%	72.0%	44.4%
XGBoost	**80.9%**	**92.6%**	**62.9%**	**77.7%**	**58.1%**

Table 3
The model performance of XGBoost with or without P53/Ki67

Algorithms	Accuracy	Sensitivity	Specificity	AUC	Kappa value
Without Ki67	75.3%	87.0%	57.1%	72.1%	46.0%
Without P53	79.8%	88.9%	65.7%	77.3%	56.3%
Without P53 and Ki67	77.5%	83.3%	68.6%	76.0%	52.4%
With P53 and Ki67	**80.9%**	**92.6%**	**62.9%**	**77.7%**	**58.1%**

Model performance of XGBoost with or without P53/Ki67

We also compared the model performance of the model established by XGBoost algorithm with or without P53/Ki67 protein expressed in the HPSCC tissue, to further explore the role of the two protein in the model. We found that, if P53 were not included, the accuracy fall into 79.8%; if Ki67 were not included, the accuracy fall into 75.3%; if the P53 and Ki67 were both not included, the accuracy fall into 77.5%. Thus, to ensure the good model performance which can predicted the 3 years survival states for HPSCC patients, the expression of P53 and Ki67 should be included as the features.

Discussion

The establishment of 3-year or 5-year survival prediction model for different tumors can provide some reference for clinicians to predict the prognosis of patients during tumor treatment. Delen et al. used three different ML algorithms to establish a survival state prediction model for breast cancer[13]. Gong et al. also used a variety of

ML algorithms to establish a 5-year survival state model for esophageal cancer, providing a reference for the prognosis prediction of esophageal cancer[14]. However, for the survival state of HPSCC patients, AI prognosis prediction model has not been reported. We are the first to build a model for the three years survival state prediction for HPSCC patients. This model was constructed based on 22 clinical parameters, using 12 kinds of different ML algorithms and finally choose the best algorithm (XGBoost) for model construction. The performance of the model is relatively good and has certain practicability.

The clinical features of this study can mainly divided into three group, the first group was the basic information group, including age, gender, smoking, alcohol taking, basic disease at diagnosis. According to the feature importance analysis for the prediction model, we found that age was one the most important features, this was in agreement with the finding of Gong et al. in esophageal cancer[14]. In fact, we found that, compared with HPSCC patients who were older than 60 years, HPSCC patients who were young than 60 years have lower probability of death 3 years after diagnosis. The remain 4 features of the first group have lower feature importance, especially the gender, which had not been ranked in the feature importance diagram.

The second group was the diagnosis-related group, including the TNM and clinical stage, the pathological information, as well as the expression of P53 and Ti67 protein. The T stage and clinical stage were well known factors for survival predicting[1], and was also important features for the survival state prediction model in our study. Advanced HPSCC patients were more likely have lower probability of survival than those in early stage[1]. Although we did not find any significant statistical difference in the survival status of patients with / without cervical lymph node metastasis after 3 years, it can be seen from the importance of characteristics that this parameter is still an important feature for predicting the survival status of HPSCC patients after 3 years (ranking sixth). The reason may be that for ML algorithms, the importance of characteristics cannot be completely determined by statistical differences. Different ML algorithms may have their own unique models for evaluating the importance of features. Due to the types of cases included in this study, there are too few patients with distant metastasis at the time of diagnosis, only 4 of 295 cases. Therefore, this feature is not shown in the feature importance diagram, but considering it is a very important clinical parameter, we still retain it as one of the prediction features.

We found that patients with poorly differentiate pathological state, or have P53 and Ti67 expressed in the cancer tissues have significant lower survival probability. The situation that poor differentiated HPSCC patients have poor survival outcome has been well studied[1,4]. P53 was a well studied gene which plays important role in variety of tumor, the positive rate of P53 in our study was 42.7%, which was in accordance with the results of other study (34%-81%)[15–16]. Ki67 is a tumor proliferating marker, and was also be found upregulated in HOSCC, Ki67 levels are significantly associated with the survival outcome in HPSCC[17]. We also found that, if the model was constructed without P53 or Ki67, the model performance would decline, thus, both of P53 and Ki67 are important feature for the prediction of survival states for HPSCC patients 3 years after diagnosis.

The third group was the treatment-related group. The treatment of HPSCC mainly include surgery, chemotherapy and radiotherapy. In this study, 10 treatment-related parameters were included as training features. We found that patients who have received preoperative or postoperative radiotherapy / chemotherapy have better survival probability than those haven't. Researches have confirmed the positive value of both chemotherapy and radiotherapy on the prognostic of HPSCC patients[4,18–19]. We also found that, patients ever undergo TLM, total

laryngectomy or total hypopharyngeal resection surgery have better survival outcome than those don't, there were no significant survival difference between HPSCC patients with or without performing of the parameters of partial laryngectomy, partial hypopharyngeal resection or flap reconstruction surgery. The reason may be that, the total resection of larynx and hypopharyngeal may make the tumor cut more thoroughly. The reason why patients undergo TLM surgery have better outcome may be that, most of these patients were usually in the early stage.

These study has the following limitations: 1) the sample size is relatively small, and the data was obtained from single medical center, the generalization ability of the model should be further tested; 2) This model is only applicable to the prediction of the 3-year survival status of patients with HPSCC, and does not predict the 5-year survival status of patients, because the proportion of patients who still survive after 5 years is much lower than after 3 years, so the data distribution will be too unbalanced during training. Therefore, we only predict the 3-year survival status of patients with HPSCC.

In summary, we use the XGBoost algorithm, using 22 clinical parameters to establish a model for the 3-years survival state prediction of HPSCC patients, as well as the analysis the role of each parameters in the model construction. The model performance was relatively satisfied, and can offer the clinicians a new option for the prognostic prediction of HPSCC patients.

Declarations

Acknowledgments

The authors wish to thank the numerous individuals who participated in this study.

Supported by the National Natural Science Foundation of China (82072997).

Conflict of Interest: The authors declare that they have no conflict of interest.

Corresponding author:

Zhigang Huang, MD, Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, 1, DongJiaoMinXiang Street, DongCheng District, Beijing, P.R.China.100730. E-mail: enthzg@trhos.com. Tel: +86-13701208337. Fax: +86-10-5826 9558

Yang Zhang, MD, Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, 1, DongJiaoMinXiang Street, DongCheng District, Beijing, P.R.China.100730. E-mail: zhangyangent@163.com. Tel: +86-13311365369. Fax: +86-10-5826 9558

Authors' contributions

Drafting the manuscript: Zufei Li

Acquisition of data: Zufei Li, Shuo Ding

Analysis of data: Junwei Huang, Zufei Li, Yang Zhang

Revising the manuscript for important intellectual content: Yang Zhang, Zhigang Huang, Qi Zhong, Jugao Fang, Xiaohong Chen

Conception and design of the study: Junwei Huang, Yang Zhang, Zhigang Huang, Zufei Li

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Figures

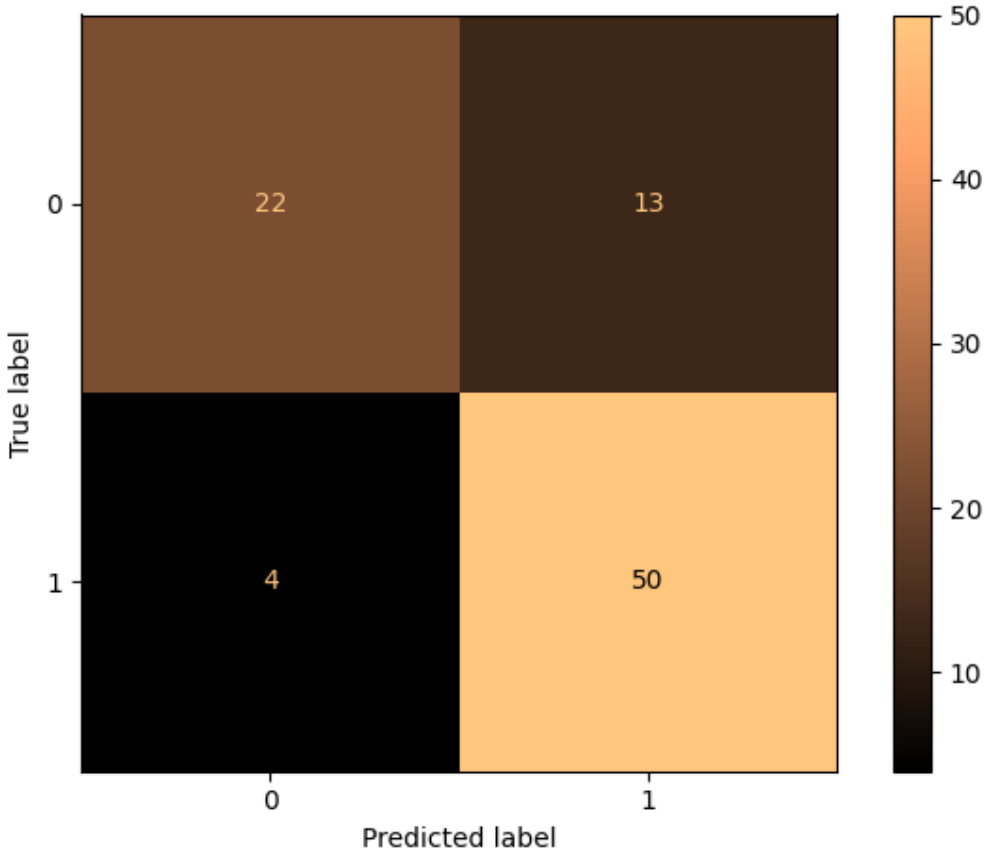

Figure 1

The confusion matrix of the model. “0” represent for “survival” and “1” represent for “death”.

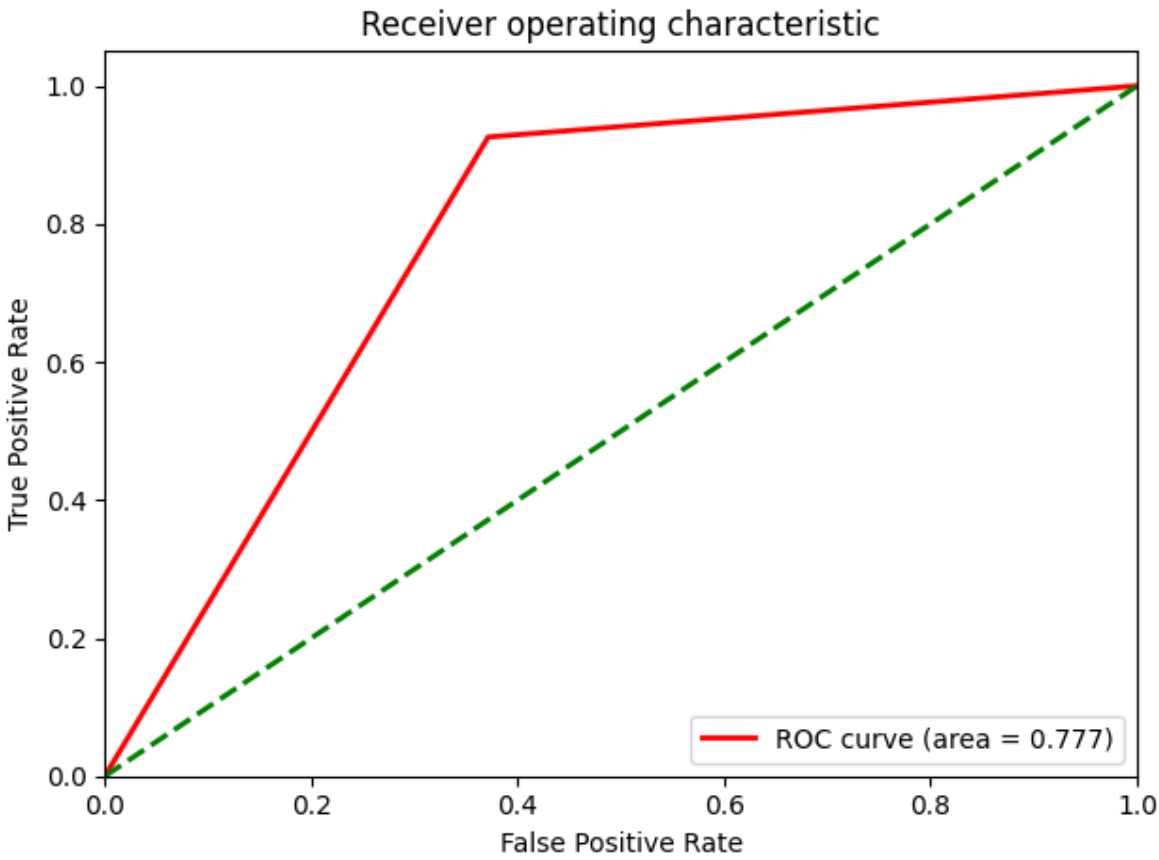

Figure 2

The ROC curve of the model, the AUC value is 77.7%.

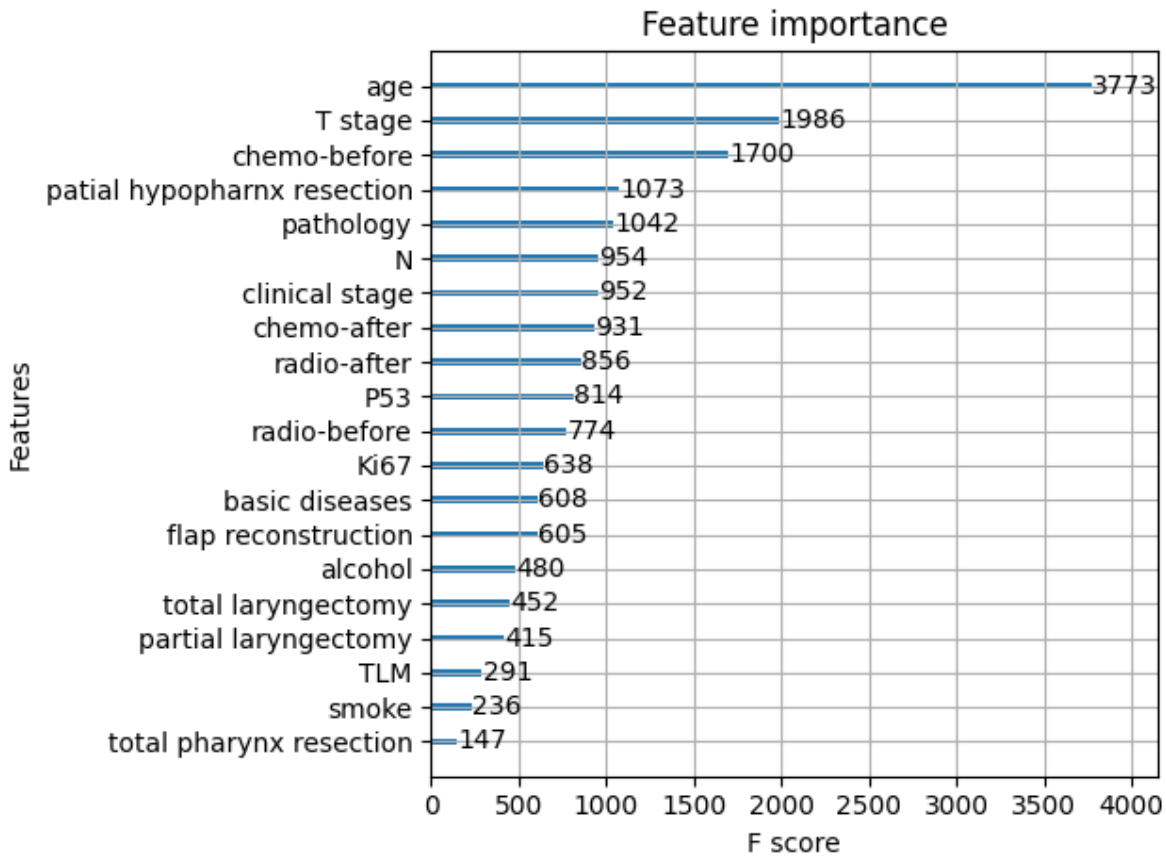

Figure 3

The feature importance of each clinical parameters in the model constructed by XGBoost algorithm.

Supplementary Files

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