Cancer Management and Research

Open Access Full Text Article

ORIGINAL RESEARCH

Development and Validation of an Interpretable ML Model for Survival Prediction in Unresectable ESCC with Immunochemotherapy

Yaru Wang, Qibing Wu

Department of Radiation Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China

Correspondence: Qibing Wu, Email Wqb71vip@163.com

Background: To address the heterogeneity in treatment responses and the lack of robust prognostic tools for unresectable esophageal squamous cell carcinoma (ESCC) patients undergoing immunochemotherapy, this study aimed to develop and validate an interpretable machine learning (ML) model for survival prediction and risk stratification.

Methods: A retrospective cohort of 323 unresectable ESCC patients treated with immunochemotherapy (2019–2025) was analyzed. Using the XGBoost algorithm, we integrated baseline clinical features (age, tumor location, TNM stage) and laboratory parameters (albumin, globulin, blood glucose) to construct a prognostic model. SHapley Additive exPlanations (SHAP) values were employed to quantify feature contributions, and external validation (n=48) was performed to assess generalizability. SHAP (SHapley Additive exPlanations) is a game theory-based framework that enables model interpretability by quantifying the contribution of each feature to predictions. The primary endpoint was overall survival (OS).

Results: The model achieved AUC values of 0.794 (internal test) and 0.689 (external test), with calibration curves demonstrating strong concordance between predicted and observed survival rates. Key prognostic factors included tumor response, age, hypoalbuminemia, hyperglobulinemia and hyperglycemia. Risk stratification using a nomogram-derived cutoff (total score ≥50) revealed significantly inferior 2-year OS in high-risk versus low-risk patients (21.3% vs 58.6%, P<0.001).

Conclusion: This interpretable ML model effectively predicts survival outcomes in unresectable ESCC patients receiving immunochemotherapy, offering a data-driven tool for personalized therapeutic decision-making. Multicenter prospective trials are warranted to validate its clinical utility.

Keywords: esophageal squamous cell carcinoma, immunochemotherapy, machine learning, prognostic model, SHAP

Introduction

Esophageal carcinoma persists as a globally significant malignancy, occupying the seventh position in cancer-related mortality worldwide.[1] Regional histopathological variations are prominent, with esophageal squamous cell carcinoma (ESCC) constituting the primary histological subtype across Asian populations, reflecting distinct etiological and environmental influences.[2] While surgical resection remains a cornerstone of localized disease management, a substantial proportion of patients exhibit contraindications for operative intervention. The characteristically indolent symptomatic presentation of esophageal malignancies frequently delays diagnosis, resulting in advanced locoregional or metastatic disease at initial clinical evaluation.[3,4] Consequently, curative surgical approaches become unfeasible for these advanced-stage patients, necessitating reliance on systemic therapeutic strategies.

For unresectable ESCC cases, platinum-based dual-agent chemotherapy has historically served as the first-line therapeutic standard.[5] However, clinical outcomes associated with conventional chemotherapeutic regimens remain unsatisfactory, evidenced by persistently suboptimal overall survival (OS) rates in treated cohorts.[6] This therapeutic limitation has catalyzed the integration of immune checkpoint inhibitors into treatment paradigms. Mechanistic studies reveal that targeted blockade of programmed death receptor 1 and its ligand disrupts tumor-mediated immune suppression, reinstating anti-neoplastic T-cell activity across diverse malignancies.[7,8] The synergistic potential of combining immunotherapeutic agents with cytotoxic chemotherapy has demonstrated enhanced antitumor efficacy in multiple solid

Received: 7 April 2025
Accepted: 15 September 2025
Published: 4 November 2025

tumors, attributable to chemotherapy-induced immunogenic cell death and subsequent antigen exposure.[9] Current clinical guidelines now endorse immunochemotherapy combinations as first-line interventions for advanced ESCC.[10,11]

Despite these therapeutic advances, significant interpatient heterogeneity persists in clinical responses. While subsets of patients achieve marked improvements in objective response rates (ORR) and OS, others exhibit minimal therapeutic benefit.[12] This variability, compounded by the substantial financial burden of immunotherapy, potential immune-related adverse events,[13,14] and the absence of reliable predictive biomarkers, underscores the critical need for robust prognostic stratification tools. Effective risk stratification could optimize therapeutic selection, mitigate unnecessary toxicity exposure, and facilitate personalized treatment strategies tailored to individual biological profiles.

Prognostic evaluation in ESCC patients undergoing immunochemotherapy presents inherent challenges due to the multi-dimensional nature of clinical, laboratory, and therapeutic interaction data. Conventional prognostic models for advanced ESCC predominantly utilize expert-curated feature selection paired with linear statistical methodologies,[15] approaches inherently limited in addressing data noise and modeling complex nonlinear relationships among prognostic variables. Contemporary advancements in computational analytics have positioned machine learning (ML) as a transformative modality in oncological research, particularly in prognostic modeling.[16,17] ML algorithms excel at identifying latent patterns within high-dimensional datasets through automated feature engineering and nonlinear relationship modeling. Despite increasing adoption in medical research, translational gaps persist in clinical validation, interpretability, and evidence-based implementation of ML-driven prognostic systems. Recent methodological innovations have prioritized interpretable ML frameworks to bridge this translational divide,[18,19] enabling clinically actionable insights while maintaining predictive performance.

This investigation developed and validated an interpretable ML-based prognostic model for unresectable ESCC patients receiving immunochemotherapy. The analytical pipeline incorporated SHAP[20] (SHapley Additive exPlanations) values to quantify feature importance and elucidate prediction mechanisms, thereby enhancing clinical interpretability. SHAP was chosen for its ability to provide both global and local interpretability, offering quantitative feature importance scores that align with clinical needs. Unlike black-box models, SHAP ensures transparency by decomposing predictions into contributions from individual features, facilitating clinician trust and adoption. This dual-focused approach—combining predictive accuracy with explanatory transparency—aims to empower clinicians in identifying critical prognostic determinants, optimizing survival outcomes through data-driven decision support, and advancing personalized therapeutic strategies in advanced ESCC management.

Methods

Patient Cohort

This retrospective study adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Medical Ethics Committee of the First Affiliated Hospital of Anhui Medical University. Due to the retrospective nature of the study, the requirement for informed consent was waived.

A total of 388 patients with unresectable ESCC who underwent immunochemotherapy between January 2019 and January 2025 at the authors' institution were retrospectively reviewed. The inclusion criteria were as follows: (1) age ≥18 years; (2) histopathologically confirmed ESCC; (3) clinical stage II–IV; (4) ECOG (Eastern Cooperative Oncology Group) performance status score: a scale from 0 (fully active) to 4 (completely bedridden), with ≤2 indicating acceptable functional status for treatment; (5) no history of other malignancies; and (6) absence of severe chronic comorbidities. Exclusion criteria included: (1) age <18 years; (2) non-squamous cell carcinoma confirmed by histopathology; (3) ECOG score >2; (4) concurrent malignancies; or (5) severe chronic comorbidities. Concurrent malignancies were excluded to minimize confounding effects of comorbid cancer therapies on survival outcomes. The ECOG ≤2 criterion was applied to ensure patients had sufficient functional status to tolerate immunochemotherapy, as poorer performance is associated with worse prognosis. Among the initially identified 388 patients, 65 were excluded due to incomplete survival data (eg, loss to follow-up). Consequently, 323 patients from two institutions were included in the final analysis (Institution 1: n=275; Institution 2: n=48). All participants underwent baseline assessments before treatment initiation, including physical and laboratory examinations. Data collection was censored in January 2025. The patient enrollment flowchart is illustrated in Figure 1.

 https://doi.org/10.2147/CMAR.S532944

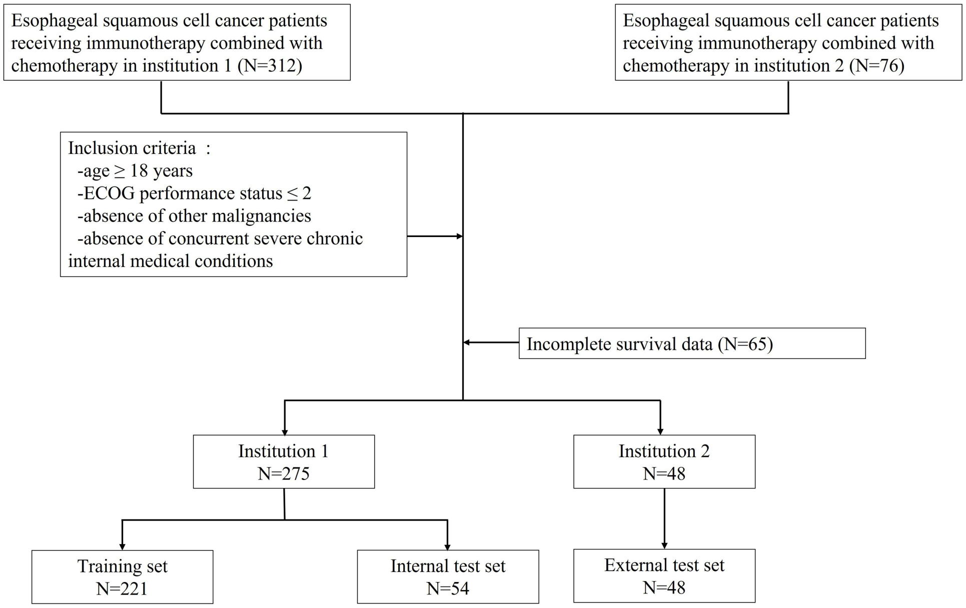

Figure 1 Screening of enrolled cases based on inclusion and exclusion criteria.

Follow-Up and Study Endpoints

In this retrospective study, 323 patients received immunochemotherapy between 2019 and 2025. Baseline data, including sex, age, tumor location, differentiation grade, TNM stage, T stage, and N stage, were recorded. Follow-up evaluations (physical and laboratory examinations) were conducted within two months post-treatment. Tumor response was assessed according to RECIST[21] (Response Evaluation Criteria In Solid Tumors) v1.1: a standardized method to assess tumor response based on bidimensional lesion measurement, classifying responses as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR and PR were classified as favorable treatment responses, whereas SD and PD were considered unfavorable. After treatment completion, follow-up intervals were every two months in the first year, every three months during years 2–3, and biannually thereafter. The primary endpoint was OS, defined as the time from immunochemotherapy initiation to death from any cause or the last follow-up date.

Data Preprocessing and Model Development

TNM staging: a system defining tumor (T) size, lymph node (N) involvement, and metastasis (M). T stage reflects primary tumor extent (eg, T2: tumor invades muscularis propria), while N stage indicates regional lymph node metastasis (N0: no metastasis, N1: 1–2 lymph nodes involved). Baseline clinical parameters and OS outcomes were systematically collected and subjected to comprehensive preprocessing protocols. This involved categorical data encoding to transform non-numeric variables into machine-readable formats, rigorous data cleaning to address missing values and inconsistencies, and feature standardization to normalize variable scales across the dataset. The cohort from Institution 1 was partitioned into an 8:2 training-internal test set ratio to balance model optimization and validation power. The external test set from Institution 2 (n=48) was reserved to assess generalizability across distinct clinical settings, as multicenter validation is critical for real-world applicability.

A structured analytical framework was implemented to evaluate OS outcomes and identify clinically significant prognostic markers in unresectable ESCC patients receiving immunochemotherapy. The XGBoost algorithm,[22] a gradient-boosted decision tree ensemble method, was selected for its demonstrated efficacy in handling nonlinear relationships and heterogeneous clinical data. Model construction was conducted exclusively on the training set, with hyperparameter optimization performed through iterative cross-validation to balance predictive accuracy and generalization capability. Feature importance analysis was integrated into the modeling pipeline, enabling simultaneous survival prediction and identification of variables most strongly associated with OS outcomes. This dual-focused approach facilitated the development of a prognostic tool that not only predicted survival probabilities but also elucidated critical risk factors influencing clinical trajectories in this patient population.

 https://doi.org/10.2147/CMAR.S532944

Statistical Analysis

Receiver operating characteristic (ROC) curves and area under the curve (AUC) values were used to evaluate model performance. Calibration curves assessed the concordance between predicted and observed outcomes. Independent risk factors were integrated into a nomogram, where each factor was weighted based on its contribution to OS, and total risk scores were calculated. Patients were stratified into high- and low-risk groups using a nomogram-derived cutoff, and Kaplan-Meier curves compared survival between groups. SHAP[23] was applied to interpret model predictions. Continuous variables were analyzed using t-tests, and categorical variables using χ^2 or Fisher's exact tests. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

Results

Patient Baseline Characteristics

Among the initially identified 388 patients with unresectable ESCC treated with immunochemotherapy, 65 were excluded due to incomplete survival data. Consequently, 323 patients from the aforementioned institutions were included in the final analysis. A comparison of baseline characteristics between the training set (N=221), internal test set (N=54), and external test set (N=48) revealed no statistically significant differences (Table 1).

Table 1 Comparison of Baseline Characteristics in Training, Internal and External Test Sets

Variable	Training Set (N=221)	Internal Test Set (N=54)	External Test Set (N=48)	P
Age				0.97
≤65 years	77 (34.8)	18 (33.3)	17 (35.4)	
>65 years	144 (65.2)	36 (66.7)	31 (64.6)	
Sex				0.40
Male	188 (85.0)	42 (77.8)	39 (81.2)	
Female	33 (15.0)	12 (22.2)	9 (18.8)	
ECOG				0.57
0	182 (82.4)	41 (75.9)	36 (75.0)	
1	33 (14.9)	12 (22.2)	11 (22.9)	
2	6 (2.7)	1 (1.9)	1 (2.1)	
Tumor location				0.46
Upper	14 (6.3)	3 (5.6)	2 (4.2)	
Middle	186 (84.2)	42 (77.8)	38 (79.2)	
Distal	21 (9.5)	9 (16.7)	8 (16.7)	
Histologic grade				0.54
Well differentiated	2 (0.9)	1 (1.9)	1 (2.1)	
Moderately differentiated	23 (10.4)	8 (14.8)	7 (14.6)	
Poorly differentiated	31 (14.0)	9 (16.7)	11 (22.9)	
Unknown	165 (74.7)	36 (66.7)	29 (40.4)	
T stage				0.83
T2	9 (4.1)	3 (5.6)	2 (4.2)	
T3	179 (81.0)	40 (74.1)	37 (77.1)	
T4	33 (14.9)	11 (20.4)	9 (18.8)	
N stage				0.30
N0	22 (10.0)	6 (11.1)	4 (8.3)	
N1	158 (71.5)	31 (57.4)	33 (68.8)	
N2	41 (18.6)	17 (31.5)	11 (22.9)	
TNM stage				0.87
Stage II	11 (5.0)	3 (5.6)	3 (6.3)	
Stage III	58 (26.2)	14 (25.9)	9 (18.8)	
Stage IV	152 (68.8)	37 (68.5)	36 (75.0)	

 https://doi.org/10.2147/CMAR.S532944

Model Performance

An XGBoost ML model was developed to predict OS, and its effectiveness was evaluated using ROC curves and AUCs. As shown in Figure 2, the XGBoost model achieved an AUC of 0.794 in the internal test set and 0.689 in the external validation set for OS prediction. Calibration curves were also used to assess model performance. Figure 3 illustrates that the predicted and observed outcomes in both internal and external test sets exhibited close alignment with the diagonal reference line.

Survival Analysis

Tumor response, age, serum albumin (ALB), globulin (GLO), and blood glucose (GLU) were identified as independent prognostic predictors for OS in ESCC patients receiving immunochemotherapy. A nomogram incorporating these

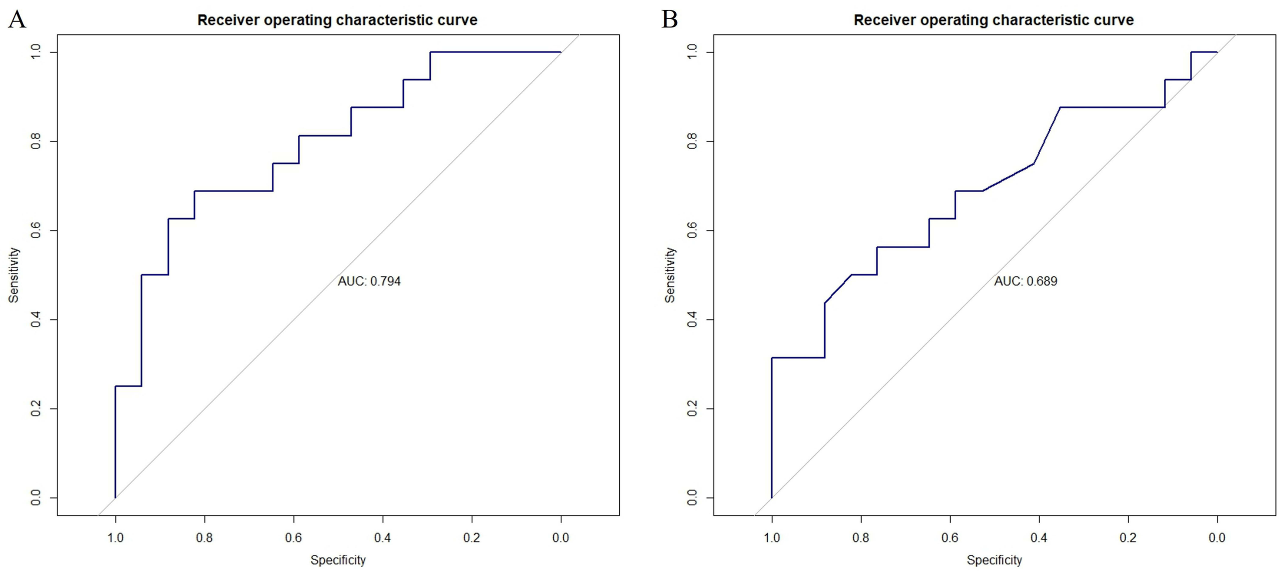

Figure 2 ROC curves of prediction model in internal and external test sets (**A**) ROC curve in internal test set; (**B**) ROC curve in external test set.

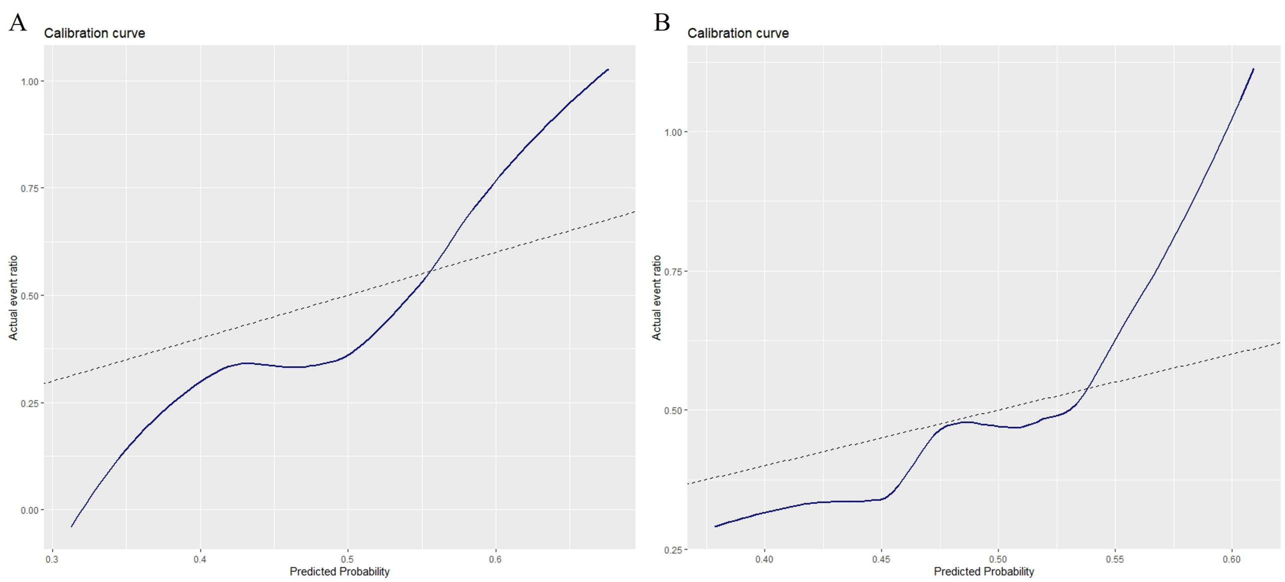

Figure 3 Calibration curves of prediction model in internal and external test sets (**A**) calibration curve in internal test set; (**B**) calibration curve in external test set.

https://doi.org/10.2147/CMAR.S532944

predictors was constructed to estimate 1- and 2-year OS probabilities (Figure 4). Patients were stratified into low-risk (total score <50) and high-risk (total score ≥50) groups based on their nomogram-derived scores. Kaplan-Meier survival curves (Figure 5) demonstrated significant differences in survival probabilities between the two groups in both the internal and external test sets (P <0.05). A comparison of clinical characteristics between high- and low-risk groups is summarized in Table 2, which showed no significant differences in baseline characteristics (P >0.05) across either set.

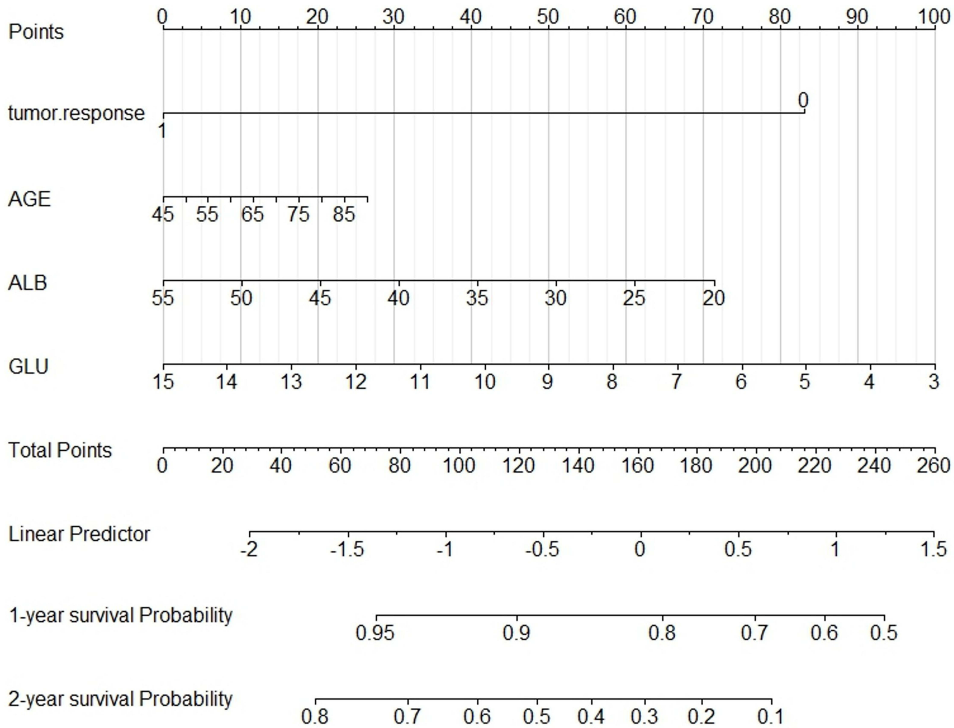

Figure 4 Nomogram for 1- and 2-year OS.

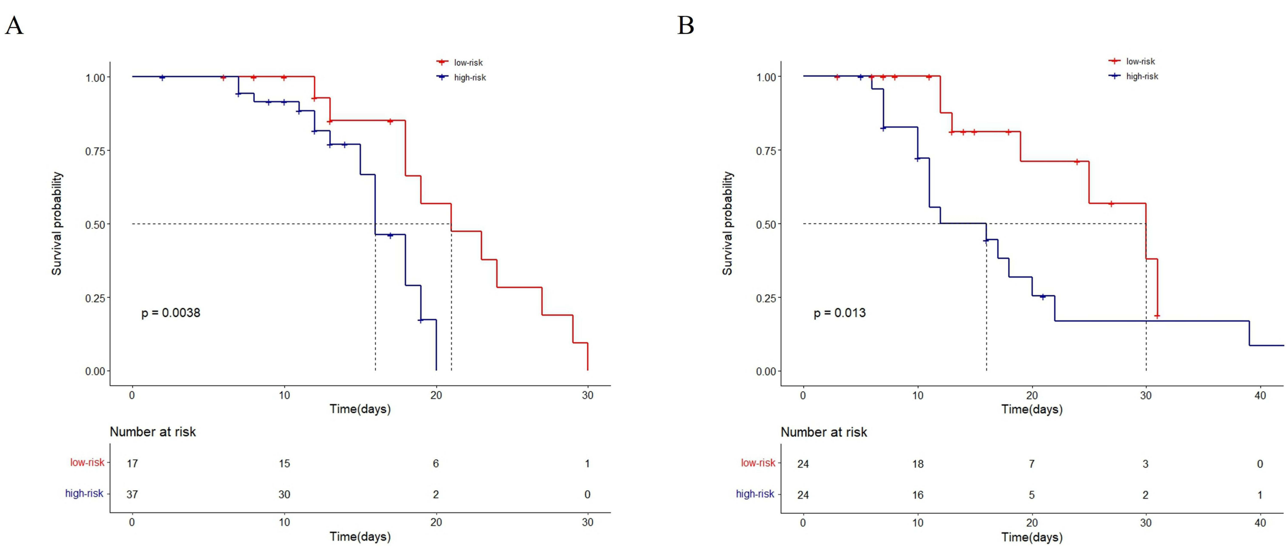

Figure 5 Kaplan-Meier curves for predicting OS of patients in low- and high-risk groups. (**A**) in the internal test set; (**B**) in the external test set.

Table 2 Characteristics of Patients in Low and High Risk in Training, Internal and External Test Sets

Variable	Training Set		P	Internal Test Set		P	External Test Set		P
	Low Risk (N=111)	High Risk (N=110)		Low Risk (N=17)	High Risk (N=37)		Low Risk (N=24)	High Risk (N=24)	
Age			0.22			0.14			0.76
≤65 years	43 (38.7)	34 (30.9)		8 (47.1)	10 (27.0)		9 (37.5)	8 (33.3)	
>65 years	68 (61.3)	76 (69.1)		9 (52.9)	27 (73.0)		15 (62.5)	16 (66.7)	
Sex			0.17			0.39			0.26
Male	98 (88.3)	90 (81.8)		12 (70.6)	30 (81.1)		21 (87.5)	18 (75.0)	
Female	13 (11.7)	20 (18.2)		5 (29.4)	7 (18.9)		3 (12.5)	6 (25.0)	
ECOG			0.08			0.66			0.99
0	96 (86.5)	86 (78.2)		14 (82.4)	27 (73.0)		18 (75.0)	18 (75.0)	
1	11 (9.9)	22 (20.0)		3 (17.6)	9 (24.3)		5 (20.8)	6 (25.0)	
2	4 (3.6)	2 (1.8)		0 (0.0)	1 (2.7)		1 (4.2)	0 (0.0)	
Tumor location			0.70			0.80			0.74
Upper	6 (5.4)	8 (6.3)		1 (5.9)	2 (5.4)		1 (4.2)	1 (4.2)	
Middle	93 (83.8)	93 (84.5)		14 (82.4)	28 (75.7)		20 (83.3)	18 (75.0)	
Distal	12 (10.8)	9 (8.2)		2 (11.8)	7 (18.9)		3 (12.5)	5 (20.8)	
Histologic grade			0.99			0.87			0.99
Well differentiated	1 (0.9)	1 (0.9)		0 (0.0)	1 (2.7)		1 (4.2)	0 (0.0)	
Moderately differentiated	11 (9.9)	12 (10.9)		3 (17.6)	5 (13.5)		4 (16.7)	3 (12.5)	
Poorly differentiated	16 (14.4)	15 (13.6)		2 (11.8)	7 (18.9)		5 (20.8)	6 (25.0)	
Unknown	83 (74.8)	82 (74.5)		12 (70.6)	24 (64.9)		14 (58.3)	15 (62.5)	
T stage			0.60			0.99			0.34
T2	5 (4.5)	4 (3.6)		1 (5.9)	2 (5.4)		0 (0.0)	2 (8.3)	
T3	92 (82.9)	87 (79.1)		13 (76.5)	27 (73.0)		19 (79.2)	18 (75.0)	
T4	14 (12.6)	19 (17.3)		3 (17.6)	8 (21.6)		5 (20.8)	4 (16.7)	
N stage			0.26			0.83			0.53
N0	9 (8.1)	13 (11.8)		1 (5.9)	5 (13.5)		3 (12.5)	1 (4.2)	
N1	77 (69.4)	81 (73.6)		10 (58.8)	21 (56.8)		15 (62.5)	18 (75.0)	
N2	25 (22.5)	16 (14.5)		6 (35.3)	11 (29.7)		6 (25.0)	5 (20.8)	
TNM stage			0.58			0.54			0.99
Stage II	4 (3.6)	7 (6.4)		0 (0.0)	3 (8.1)		1 (4.2)	2 (8.3)	
Stage III	31 (27.9)	27 (24.5)		4 (23.5)	10 (27.0)		5 (20.8)	4 (16.7)	
Stage IV	76 (68.5)	76 (69.1)		13 (76.5)	24 (64.9)		18 (75.0)	18 (75.0)	

Model Interpretability

Leveraging the intrinsic properties of the ML algorithm, importance scores (SHAP values) were calculated using the SHAP framework. SHAP values quantified the contribution of each predictive feature to OS outcomes, providing an intuitive explanation for model predictions. Figure 6 displays the top 20 variables ranked by descending SHAP value importance. The five most influential features were tumor response, age, ALB, GLO, and GLU.

Discussion

ESCC remains a significant oncological challenge across Asian populations, maintaining persistently elevated incidence and mortality rates despite advancements in therapeutic approaches. While contemporary clinical trials have established immunochemotherapy as a treatment modality capable of enhancing ORR and extending OS in esophageal cancer patients,[24] substantial heterogeneity persists in therapeutic outcomes across patient subgroups. This interindividual

https://doi.org/10.2147/CMAR.S532944

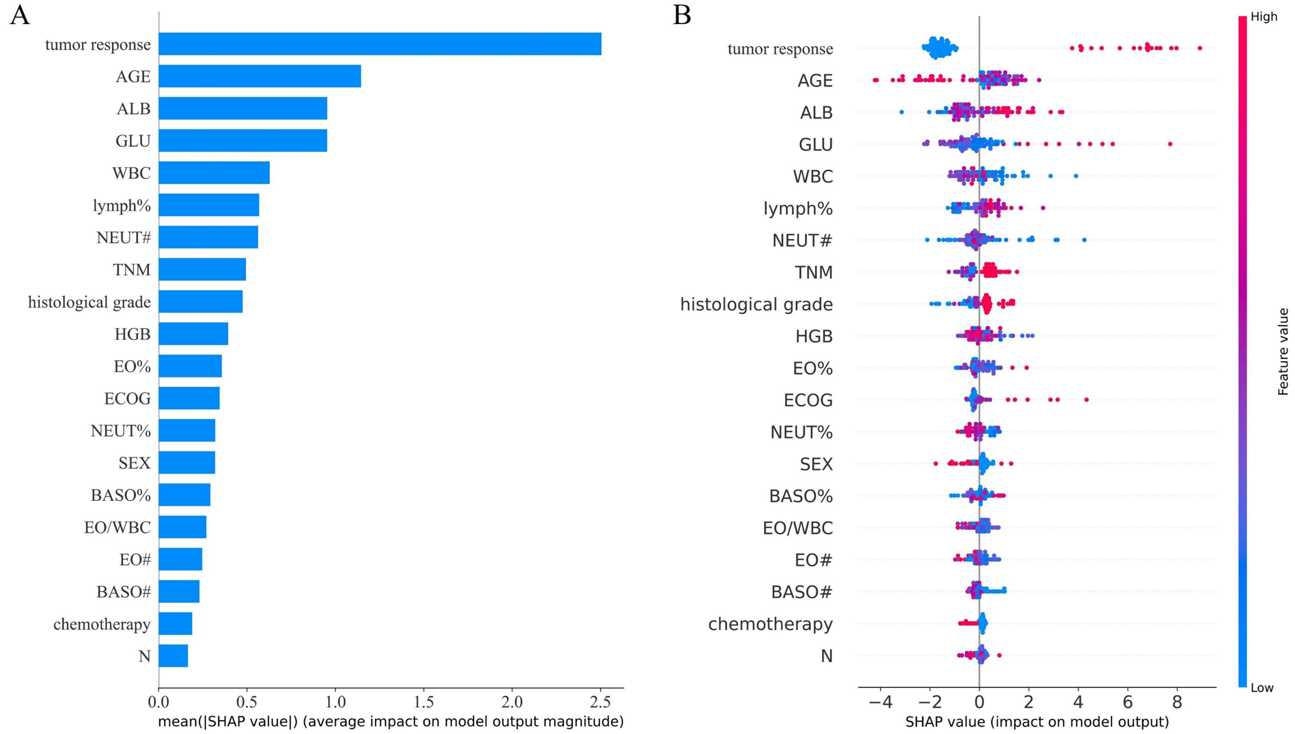

Figure 6 SHAP interpretation of prediction model (**A**) The importance ranking of the model prediction features. The horizontal coordinate represents the SHAP values, the larger SHAP value indicates that the variable is more important, (**B**) Each point represents a feature value, and different colors represent the final influence of the feature on the model output results, where red represents a larger value and blue represents a smaller value.).

variability underscores the critical need for personalized prognostic tools to optimize treatment selection. To address this clinical imperative, our retrospective investigation developed an XGBoost-based ML model leveraging pretreatment clinical parameters and routine laboratory indices for survival prediction in ESCC patients undergoing immunochemotherapy.

ML, operating at the intersection of statistical modeling, computational algorithms, and predictive analytics, has emerged as a transformative force in biomedical research. By processing complex multidimensional datasets through automated pattern recognition, ML techniques enable extraction of clinically relevant predictors from heterogeneous patient data. In oncology practice, such methodologies support risk stratification, therapeutic response prediction, and survival outcome modeling – particularly valuable in malignancies like ESCC where traditional staging systems demonstrate limited prognostic precision. Crucially, ML applications in clinical decision support maintain a complementary role, requiring synergistic integration with clinician expertise rather than autonomous implementation. As emphasized in current medical AI guidelines,[25] model outputs demand rigorous clinical interpretation and context-specific validation prior to influencing therapeutic decisions.

Our prognostic model development employed extreme gradient boosting (XGBoost), a ML architecture particularly suited for structured tabular data analysis. The algorithm's predictive performance was quantitatively assessed using ROC curve analysis with corresponding AUC metrics. While an AUC of 1.0 represents perfect discrimination and values ≤0.5 indicate random chance performance, our model achieved clinically meaningful discrimination with AUC values of 0.794 (95% CI: 0.72–0.86) in internal test and 0.689 (95% CI: 0.61–0.76) in external test sets. Model calibration, evaluated through observed vs predicted probability plots, demonstrated satisfactory concordance across both datasets, with minor deviations in high-risk probability ranges suggesting areas for future refinement.

Multivariate analysis identified five independent prognostic determinants incorporated into the final model: tumor treatment response (complete/partial response vs stable/progressive disease), patient age, ALB, GLO and GLU. These parameters were integrated into a clinical nomogram providing individualized 1-year and 2-year survival probability estimates. Risk stratification using a 50-point cutoff (low-risk: <50 points; high-risk: ≥50 points) yielded statistically significant survival differentiation in Kaplan-Meier analyses (log-rank P<0.05) across all validation sets. The significant survival differentiation between high- and low-risk groups (21.3% vs 58.6% 2-year OS) highlights the model's clinical utility in risk stratification. This stratification may guide treatment intensification for high-risk patients, such as prioritizing novel combination therapies, while minimizing overtreatment in low-risk populations. Notably, baseline demographic and clinicopathological characteristics showed no significant intergroup differences, confirming the model's capacity to detect inherent prognostic heterogeneity beyond conventional risk factors.

The model interpretation challenge inherent in "black box" ML systems was addressed through SHAP value analysis. This game theory-derived approach quantifies individual feature contributions to model predictions while maintaining global interpretability. In our XGBoost architecture, tumor response status emerged as the dominant prognostic determinant, aligning with prior studies demonstrating durable survival benefits in immunochemotherapy responders.[26,27] Advanced age exhibited consistent association with reduced survival probability, corroborating epidemiological patterns observed in geriatric oncology cohorts.[28,29] The prognostic relevance of hypoalbuminemia (ALB <3.5 g/dL) reflects its established role as a marker of nutritional status and systemic inflammation in gastrointestinal malignancies.[30–32] GLO and GLU are novel predictors in this context, warranting further validation as potential risk factors for mortality in unresectable ESCC patients.

Several study limitations merit consideration. The retrospective design inherently limits causal inference and introduces potential selection bias, while single-institution data collection may restrict generalizability to diverse ethnic and geographic populations. The absence of molecular biomarkers and detailed treatment toxicity data in the modeling framework represents an opportunity for future model enhancement. External validation across multicenter cohorts and prospective clinical trials remains essential to confirm clinical utility before implementation in routine practice. The single-center design may limit generalizability, though external validation in Institution 2 provided initial evidence of robustness. Prospective multicenter trials are warranted to confirm performance across diverse patient populations and treatment protocols.

Conclusion

In conclusion, we developed and validated an ML model using clinical and laboratory features to stratify prognosis in unresectable ESCC patients undergoing immunochemotherapy. This tool enables clinicians to refine prognostic assessments, optimize survival outcomes, and guide personalized treatment. While the model shows promise, prospective clinical trials are warranted to validate its efficacy and consistency across varied clinical settings. Multicenter prospective trials are essential to validate the model's generalizability and integrate it into routine clinical workflows, ensuring its impact on personalized ESCC management.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. The datasets are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All patient data used in this study were processed in strict compliance with the requirements of the Medical Ethics Committee of the First Affiliated Hospital of Anhui Medical University and relevant data protection regulations. To ensure patient privacy, all personal identifiers (such as name, medical record number, contact information, and other direct identifiers) were permanently removed from the dataset during preprocessing. De-identified data were stored in password-protected secure servers with restricted access limited to members of the research team directly involved in data analysis. No individual patient can be identified through the information presented in this manuscript, and all data usage adheres to the principles of confidentiality and anonymity outlined in the Declaration of Helsinki. The study was in accordance with the national legislation and the institutional requirements.

Acknowledgments

The authors would like to thank all participating patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research received no external funding.

Disclosure

The authors declare no conflict of interest.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J*. 2022;135(5):584–590. doi:10.1097/CM9.0000000000002108
3. Zhu H, Ma X, Ye T, et al. Esophageal cancer in China: practice and research in the new era. *Int J Cancer*. 2023;152(9):1741–1751. doi:10.1002/ijc.34301
4. Uhlenhopp DJ, Then EO, Sunkara T, Gaduputi V. Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. *Clin J Gastroenterol*. 2020;13(6):1010–1021. doi:10.1007/s12328-020-01237-x
5. Huang FL, Yu SJ. Esophageal cancer: risk factors, genetic association, and treatment. *Asian J Surg*. 2018;41(3):210–215. doi:10.1016/j.asjsur.2016.10.005
6. Rogers JE, Sewastjanow-Silva M, Waters RE, Ajani JA. Esophageal cancer: emerging therapeutics. *Expert Opin Ther Targets*. 2022;26(2):107–117. doi:10.1080/14728222.2022.2036718
7. Annibali O, Crescenzi A, Tomarchio V, et al. PD-1 /PD-L1 checkpoint in hematological malignancies. *Leuk Res*. 2018;67:45–55. doi:10.1016/j.leukres.2018.01.014
8. Huang S, Zheng G, Yang K. Neoadjuvant PD-1/PD-L1 combined with CTLA-4 inhibitors for solid malignancies: a systematic review and meta-analysis. *World J Surg Oncol*. 2023;21(1):349. doi:10.1186/s12957-023-03212-5
9. Wang D, Lin J, Yang X, et al. Combination regimens with PD-1/PD-L1 immune checkpoint inhibitors for gastrointestinal malignancies. *J Hematol Oncol*. 2019;12(1):42. doi:10.1186/s13045-019-0730-9
10. Ji Y, Du X, Zhu W, et al. Efficacy of concurrent chemoradiotherapy with S-1 vs radiotherapy alone for older patients with esophageal cancer: a multicenter randomized phase 3 clinical trial. *JAMA Oncol*. 2021;7(10):1459–1466. doi:10.1001/jamaoncol.2021.2705
11. Kato K, Shah MA, Enzinger P, et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. *Future Oncol*. 2019;15(10):1057–1066. doi:10.2217/fon-2018-0609
12. Liu T, Bai Y, Lin X, et al. First-line nivolumab plus chemotherapy vs chemotherapy in patients with advanced gastric, gastroesophageal junction and esophageal adenocarcinoma: CheckMate 649 Chinese subgroup analysis. *Int J Cancer*. 2023;152(4):749–760. doi:10.1002/ijc.34296
13. Hara Y, Baba Y, Toihata T, et al. Immune-related adverse events and prognosis in patients with upper gastrointestinal cancer treated with nivolumab. *J Gastrointest Oncol*. 2022;13(6):2779–2788. doi:10.21037/jgo-22-281
14. Zheng J, Huang B, Xiao L, Wu M, Li J. Treatment- and immune-related adverse events of immune checkpoint inhibitors in esophageal or gastroesophageal junction cancer: a network meta-analysis of randomized controlled trials. *Front Oncol*. 2022;12:821626. doi:10.3389/fonc.2022.821626
15. Zheng S, Lin N, Wu Q, He H, Yang C. Prognostic model construction and validation of esophageal cancer cellular senescence-related genes and correlation with immune infiltration. *Front Surg*. 2023;10:1090700. doi:10.3389/fsurg.2023.1090700
16. Klein S, Duda DG. Machine learning for future subtyping of the tumor microenvironment of gastro-esophageal adenocarcinomas. *Cancers*. 2021;13(19):4919. doi:10.3390/cancers13194919
17. Li Z, Jiang Y, Li B, et al. Development and validation of a machine learning model for detection and classification of tertiary lymphoid structures in gastrointestinal cancers. *JAMA Network Open*. 2023;6(1):e2252553. doi:10.1001/jamanetworkopen.2022.52553
18. Yu C, Bian Y, Gao Y, et al. Machine learning-based lactate-related genes signature predicts clinical outcomes and unveils novel therapeutic targets in esophageal squamous cell carcinoma. *Cancer Lett*. 2025;613:217458. doi:10.1016/j.canlet.2025.217458
19. Wang JL, Tang LS, Zhong X, et al. A machine learning radiomics based on enhanced computed tomography to predict neoadjuvant immunotherapy for resectable esophageal squamous cell carcinoma. *Front Immunol*. 2024;15:1405146. doi:10.3389/fimmu.2024.1405146
20. Song Y, Zhang D, Wang Q, et al. Prediction models for postoperative delirium in elderly patients with machine-learning algorithms and SHapley additive exPlanations. *Transl Psychiatry*. 2024;14(1):57. doi:10.1038/s41398-024-02762-w
21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. doi:10.1016/j.ejca.2008.10.026
22. Inoue T, Ichikawa D, Ueno T, et al. XGBoost, a machine learning method, predicts neurological recovery in patients with cervical spinal cord injury. *Neurotrauma Rep*. 2020;1(1):8–16. doi:10.1089/neur.2020.0009
23. Chowdhury SU, Sayeed S, Rashid I, et al. Shapley-additive-explanations-based factor analysis for dengue severity prediction using machine learning. *J Imaging*. 2022;8(9):229. doi:10.3390/jimaging8090229

24. Shoji Y, Koyanagi K, Kanamori K, et al. Immunotherapy for esophageal cancer: where are we now and where can we go. *World J Gastroenterol*. 2024;30(19):2496–2501. doi:10.3748/wjg.v30.i19.2496
25. Weidener L, Fischer M. Teaching AI ethics in medical education: a scoping review of current literature and practices. *Perspect Med Educ*. 2023;12 (1):399–410. doi:10.5334/pme.954
26. Kelly RJ, Landon BV, Zaidi AH, et al. Neoadjuvant nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable esophageal/ gastroesophageal junction cancer: a phase Ib trial and ctDNA analyses. *Nat Med*. 2024;30(4):1023–1034. doi:10.1038/s41591-024-02877-z
27. Yan X, Duan H, Ni Y, et al. Tislelizumab combined with chemotherapy as neoadjuvant therapy for surgically resectable esophageal cancer: a prospective, single-arm, Phase II study (TD-NICE). *Int J Surg*. 2022;103:106680. doi:10.1016/j.ijsu.2022.106680
28. Luo H, Lu J, Bai Y, et al. Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: the ESCORT-1st randomized clinical trial. *JAMA*. 2021;326(10):916–925. doi:10.1001/jama.2021.12836
29. Huang X, Huang Y, Li P, Xu K. CT-based deep learning predicts prognosis in esophageal squamous cell cancer patients receiving immunotherapy combined with chemotherapy. *Acad Radiol*. 2025.
30. Song N, Wang Z, Sun Q, et al. Efficacy, safety, and prognostic modeling in neoadjuvant immunotherapy for esophageal squamous cell carcinoma. *Int Immunopharmacol*. 2024;142(Pt A):112845. doi:10.1016/j.intimp.2024.112845
31. Ren J, Wang K, Zhao J, et al. A comparison between single and fractionated doses of albumin-bound paclitaxel in the treatment of advanced esophageal cancer: a multicenter case-control study. *Sci Prog*. 2024;107(4):368504241299016. doi:10.1177/00368504241299016
32. Farag CM, Antar R, Akosman S, Ng M, Whalen MJ. What is hemoglobin, albumin, lymphocyte, platelet (HALP) score? A comprehensive literature review of HALP's prognostic ability in different cancer types. *Oncotarget*. 2023;14:153–172. doi:10.18632/oncotarget.28367