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RESEARCH

An integrated prognosis prediction model based on real-word clinical characteristics for immunotherapy in advanced esophageal squamous cell carcinoma

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Abstract

Introduction Immune checkpoint inhibitors (ICIs) benefit only a subset of patients in advanced esophageal squamous cell carcinoma (ESCC). Our study aims to develop and validate a clinically accessible model to better identify those who may respond to ICIs.

Methods This study enrolled advanced ESCC patients treated with ICIs at Peking University Cancer Hospital from January 14, 2016, to January 26, 2024 for the training cohort and at Harbin Medical University Cancer Hospital between January 10, 2019, and July 6, 2022 for the validation cohort. Combined positive score (CPS) was recorded to assess the predictive value of programmed cell death ligand-1 (PD-L1). Baseline clinical and laboratory characteristics were identified as predictors through Akaike information criterion (AIC) and Cox proportional hazards regression. The prediction model underwent internal validation through bootstrapping and was externally validated in the validation cohort.

Results The training cohort consisted of 430 patients, while the validation cohort included 184 patients. PD-L1 expression failed to discriminate survival outcomes. The prediction model incorporates 10 variables: stage, bone metastasis, line of therapy, treatment, lactate dehydrogenase, carcinoembryonic antigen, carbohydrate antigen 199, systemic immune-inflammation index, lymphocyte count and prognostic nutritional index. The model achieved a C-index of 0.725 in the training cohort, 0.722 following bootstrapping, and 0.691 in the external validation cohort. An interactive online prediction tool (https://escc-survival.shinyapps.io/shiny_app/) was subsequently developed.

Conclusions This is the first large-scale, real-world model for individualized survival prediction for advanced ESCC patients treated with ICIs, offering a practical tool for optimizing clinical decisions.

Keywords ICIs · Prediction model · Advanced ESCC · Real-world data

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Introduction

China accounts for more than half of the global esophageal cancer cases [1], with over 90% being esophageal squamous cell carcinoma (ESCC) [2] and a five-year survival rate below 5% [3]. Immune checkpoint inhibitors (ICIs) has transformed the therapeutic approach [4–6] and become the standard therapy for advanced ESCC [7], yet benefit only a small subset of patients. Even when combined with chemotherapy, the five-year survival rate remains below 13% [8], underscoring the critical need for reliable predictors to better identify populations that may potentially benefit from ICIs.

Traditional biomarkers including programmed cell death ligand-1 (PD-L1) expression [9] and tumor mutational load (TMB) [10] have been extensively studied. However, their predictive utility in ESCC remains suboptimal, particularly as PD-L1 expression's role in ICI efficacy is riddled with inconsistencies across clinical trials [11, 12]. Recently, several multigene signatures, such as fibroblast-associated signature [13], immunogenic cell death (ICD)-associated gene panel [14] and angiogenesis-associated risk score [15] have been developed as predictive models and have demonstrated some promise. Nevertheless, these predictors either rely on tumor tissue and complex molecular analyses, or have not been trained and validated in large-scale and real-world datasets, leading to considerable limitations in effectiveness, clinical accessibility and reliability. Therefore, there is an urgent need to construct an integrated model that incorporates the most direct, accessible and noninvasive clinical biomarkers, enhancing efficiency and cost-effectiveness while enabling rapid and precise prognostic predictions for patients treated with ICIs.

Our study seeks to establish and validate a multivariable model which better predict survival outcomes for advanced ESCC patients receiving ICIs based on extensive and long-term follow-up real-world data. Furthermore, we aim to provide actionable insights that guide clinicians and patients in making informed decisions about optimal ICIs strategies for advanced ESCC.

Methods

Study population and follow-up

The training cohort included advanced ESCC patients treated at Peking University Cancer Hospital from January 14, 2016, and January 26, 2024. The external validation cohort consisted of patients in Harbin Medical University Cancer Hospital from January 10, 2019, and July 6, 2022. Inclusion criteria: (1) pathologically confirmed ESCC; (2) unresectable advanced, recurrent cases (including postoperative recurrence), or metastatic ESCC without prior systemic therapy; (3) treated with mono-ICIs, ICIs in combination with chemotherapy or targeted therapy; (4) at least one measurable lesion based on RECIST 1.1 criteria [16]; and (5) availability of comprehensive clinical and follow-up data. Exclusion criteria were: (1) lost to follow-up after only one cycle of ICIs; (2) absence of regular imaging evaluations (at least once every two cycles); and (3) severe organ dysfunction, significant blood count abnormalities, or autoimmune diseases affecting liver or kidney function.

Efficacy assessment

Patients were evaluated for efficacy by imaging scans after every two cycles of treatment. Follow-up were conducted to assessed survival status (alive or deceased). The endpoint, overall survival (OS), was defined as the time from the initial ICIs administration to death from any cause.

Variable selection and model construction

Potential variables were divided into four categories: demographic characteristics (e.g., sex, age, smoking and drinking), tumor characteristics (e.g., staging, metastases to lymph nodes, liver, lung, or bone), treatment-related data (e.g., line of therapy, treatment options), and baseline laboratory test results obtained within seven days prior to ICIs [e.g., lactate dehydrogenase (LDH), hemoglobin (Hb), lymphocytes count (ALC)]. A total of 26 variables were initially considered as potential predictors. Variables with over 10% missing data were excluded. Missing rates for carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199) in the validation cohort were 4.3% and 5.4%, respectively, and missing data were handled using multiple imputation. All remaining variables had complete datasets. Optimal cutoff values were established using clinical reference ranges or calculated via the "surv_cutpoint" algorithm (Supplementary Table 1). Univariate Cox regression analyses evaluated the prognostic relevance of all 26 variables. Variables ultimately enrolled in the multivariable Cox regression model were chosen by clinical relevance and selection through Akaike information criterion (AIC) [17]. Then a nomogram was constructed for individual 1-, 2-, and 3-year OS probabilities.

Model evaluation and validation

Harrell's concordance index (C-index) was used to access the discriminatory performance of the prognostic model [18]. Calibration curves was plotted to compare the survival between model-predicted and Kaplan–Meier

observed [19]. Time-dependent ROC curves were generated using "timeROC" R package to evaluate predictive accuracy at 1-, 2-, and 3-year intervals [20]. Area under the curve (AUC) was determined along with its 95% confidence intervals.

To assess accuracy and generalizability of the model, internal validation was conducted using bootstrapping with 1000 resamples [21], while external validation was carried out in the validation cohort.

Risk stratification

Risk scores for individual patients were derived from the nomogram using the "predict" algorithm. Patients were categorized into three risk groups of low-, moderate-, and high- by tertile cutoff values. Kaplan–Meier survival curves for these three risk groups were plotted and compared using the logrank test [22].

Data analysis

R 4.3.0 and SPSS 26.0 were used to analyze statistics and generate figures, with two-sided P-value < 0.05 considering statistical significance.

Results

Baseline characteristics

A total of 513 advanced ESCC patients treated with ICIs from Peking University Cancer Hospital (January 14, 2016–January 26, 2024) and 213 patients from Harbin Cancer Hospital (January 10, 2019–July 6, 2022) were screened. Following the inclusion and exclusion criteria, 430 patients were ultimately enrolled in the training cohort, while 184 patients constituted the validation cohort (Fig. 1). For the training cohort, the median follow-up time was 29.7 months (95% CI 28.1–31.3 months), with 282 (65.5%) deaths occurred. For the validation cohort, the median follow-up was 43.2 months (95% CI 39.9–46.6 months), with 152 (82.6%) deaths recorded.

The enrollment process for patients in both two cohorts strictly followed the inclusion and exclusion criteria. '*': ICIs used in these cohorts include camrelizumab, sintilimab, pembrolizumab, toripalimab, atezolizumab and tislelizumab. '#': Some patients participated in clinical trials, including NCT03189719, NCT03748134 and NCT03430843.

Table 1 provides a summary of the baseline characteristics. The patients' median age of the two cohorts was 61.0 years, with a higher proportion of females in the training cohort. No significant differences was observed between two cohorts in terms of disease stage or metastatic sites (liver,

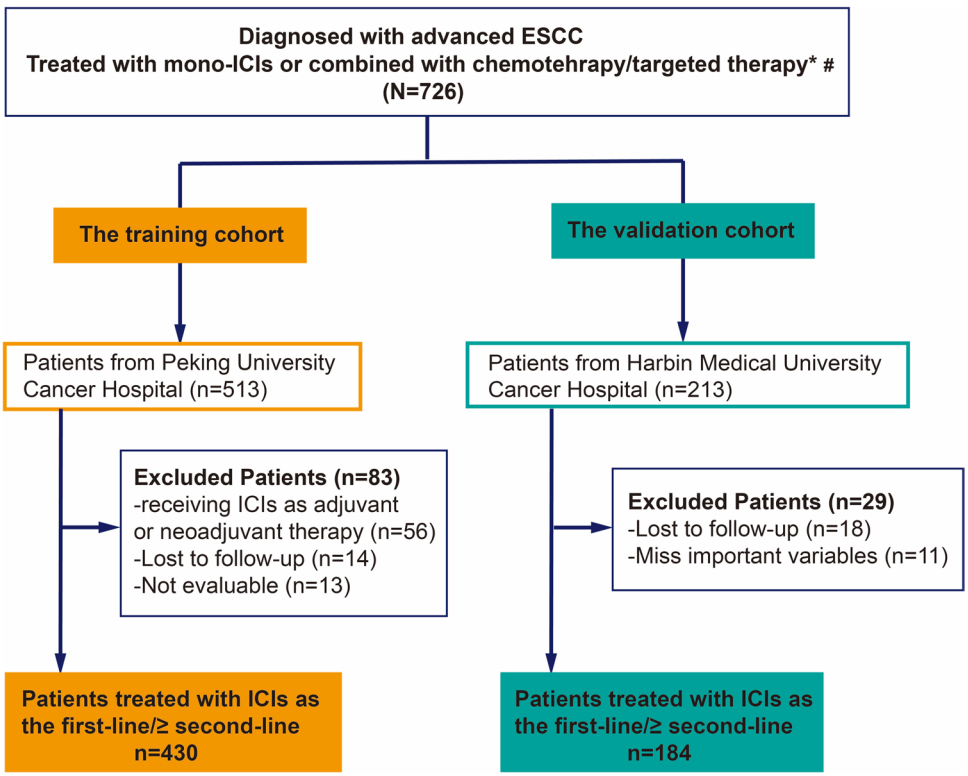

Fig. 1 Patient Enrollment Flowchart

Table 1 Baseline Characteristics in Two Cohorts

Characteristics	Patients, no. (%)		*P* value
	Training cohort (n = 430)	Validation cohort (n = 200)	
Age			
Median (IQR)	61 (56.0–66.0)	61 (56.0–66.8)	0.812
Sex			
Male	383 (89.1)	180 (97.8)	
Female	47 (10.9)	4 (2.2)	< 0.001
Smoke			
No	106 (24.7)	66 (35.9)	
Yes	324 (75.3)	118 (64.1)	0.005
Alcohol			
No	148 (34.4)	61 (33.2)	
Yes	282 (65.6)	123 (66.8)	0.762
Stage			
III	24 (5.6)	10 (5.4)	
IV	406 (94.4)	174 (94.6)	0.942
Liver metastasis			
No	344 (80.0)	156 (84.8)	
Yes	86 (20.0)	28 (15.2)	0.163
Lung metastasis			
No	328 (76.3)	147 (79.9)	
Yes	102 (23.7)	37 (20.1)	0.327
Bone metastasis			
No	382 (88.8)	171 (92.9)	
Yes	48 (11.2)	13 (7.1)	0.120
Line of therapy			
First-line	290 (67.4)	150 (81.5)	
≥ Second-line	140 (32.6)	34 (18.5)	< 0.001
Treatment			
Mono-ICIs/ ICIs + targeted therapy	157 (36.5)	15 (8.2)	
ICIs + chemotherapy	273 (63.5)	169 (91.8)	< 0.001
CEA			
≤ 5	330 (76.7)	146 (79.3)	
> 5	100 (23.3)	38 (20.7)	0.479
CA199			
≤ 37	389 (90.5)	167 (90.8)	
> 37	41 (9.5)	17 (9.2)	0.909
LDH			
≤ 240	341 (79.3)	163 (88.6)	
> 240	89 (20.7)	21 (11.4)	0.006
ALC			
≤ 1.7	309 (71.9)	110 (59.8)	
> 1.7	121 (28.1)	74 (40.2)	0.003
PNI			
≤ 49.50	196 (45.6)	115 (62.5)	
> 49.50	234 (54.4)	69 (37.5)	< 0.001
SII			
≤ 589.41	149 (34.7)	73 (39.7)	
> 589.41	281 (65.3)	111 (60.3)	0.235

lung, or bone). In the training cohort, 140 (32.6%) patients received second-line or later treatment, significantly more than 34 (18.5%) patients in the validation cohort. Additionally, 95 (22.1%) patients in the training cohort received mono-ICIs, 273 (63.5%) received ICIs combined with chemotherapy and 62 (14.4%) received ICIs combined with targeted therapy. In contrast, most patients (91.8%) in the validation cohort were treated with ICIs combined with chemotherapy (Table 1).

The proportion of patients across subgroups is presented. Chi-square tests were used to analyze categorical variables, and t-tests were applied for continuous variables.

Survival outcomes

In the training cohort, the median OS for first-line treatment was 21.3 months (95% CI 17.0–27.1 months), with 2-, 3-, and 5-year OS rates of 47.3%, 29.8%, and 20.2%. For second-line or later treatment, the median OS was 10.2 months (95% CI 8.6–13.4 months), with corresponding OS rates of 16.6%, 8.2%, and 5.4%. (Fig. 2A). In the validation cohort, the median OS for first-line treatment was 15.6 months (95% CI 13.1–18.8 months), with 2-, 3-, and 5-year OS rates of 36.7%, 25.1%, and 12%. For second-line or later treatment, the median OS was 8.5 months (95% CI 6.3–12.5 months), with OS rates of 17.6%, 11.0%, and 0.0%. (Supplementary Fig. 2A).

OS in patient subgroups with (A) first-line versus second-line or later therapy, (B) mono-ICIs versus ICIs + chemotherapy versus ICIs + targeted therapy, and (C) high PD-L1 (CPS ≥ 10) versus low PD-L1 (CPS < 10).

Among different treatment regions in the training cohort, the median OS was significantly higher in patients treated with ICIs combined with chemotherapy (24.6 months, 95% CI 17.6–28.5) compared to targeted therapy (10.3 months, 95% CI 8.4–13.2, $P < 0.001$) and mono-ICIs groups (10.2 months, 95% CI 7.9–14.0, $P < 0.001$). However, no noticeable OS difference was found between ICIs combined with targeted therapy and mono-ICIs (HR = 1.07, 95% CI 0.76–1.50, $P = 0.701$, Fig. 2B). A similar trend was noted in the validation cohort, although where most patients received ICIs combined with chemotherapy (Supplementary Fig. 2B).

Additionally, patients were further stratified into high PD-L1 expression (CPS ≥ 10) and low PD-L1 expression (CPS < 10) groups to assess potential of PD-L1 as a prognostic biomarker. Surprisingly, PD-L1 failed to differentiate survival outcomes between this two groups (HR = 0.94, 95% CI 0.74–1.19, $P = 0.6$, Fig. 2C), indicating that PD-L1 was not a reliable prognostic predictor in the training cohort.

Construction and validation of the prognosis prediction model

Survival and prognosis in ESCC are influenced not only by tumor characteristics (e.g., stage, metastasis) and treatment regimens but also by biomarkers, including tumor markers (CEA and CA199 [23]), inflammatory markers (LDH [24], NLR, PLR [24], SII [25], etc.), and nutritional markers [albumin, PNI [26], etc.]. Despite their significance, these markers are underutilized in predictive models for clinical immunotherapy.

In this study, 26 candidate variables were incorporated into the multivariable Cox regression model (Supplementary Table 1). Stage, bone metastasis, line of therapy, treatment, LDH, CEA, CA199, ALC, PNI, and SII were identified as predictors in the final model after stepwise selection base on the AIC. The model identified stage III, first-line ICIs combined with chemotherapy and elevated levels of PNI (> 49.50) (HR = 0.73, 95%CI 0.56–0.95, $P = 0.019$) as factors associated with improved survival. Conversely, elevated levels of CEA (> 5) (HR = 1.35, 95%CI 1.03–1.79, $P = 0.030$), CA199 (> 37) (HR = 1.75, 95% CI 1.17–2.62, $P = 0.006$), LDH (> 240) (HR 1.45, 95%CI 1.09–1.91, $P = 0.010$) and SII (> 589.41) (HR = 1.63, 95%CI 1.23–2.16, $P < 0.001$) were linked to increased mortality risk (Supplementary Table 2). A risk prediction nomogram was developed (Fig. 3). Stage demonstrated the most significant impact on prognosis, despite only 24 (5.5%) patients being classified as stage III.

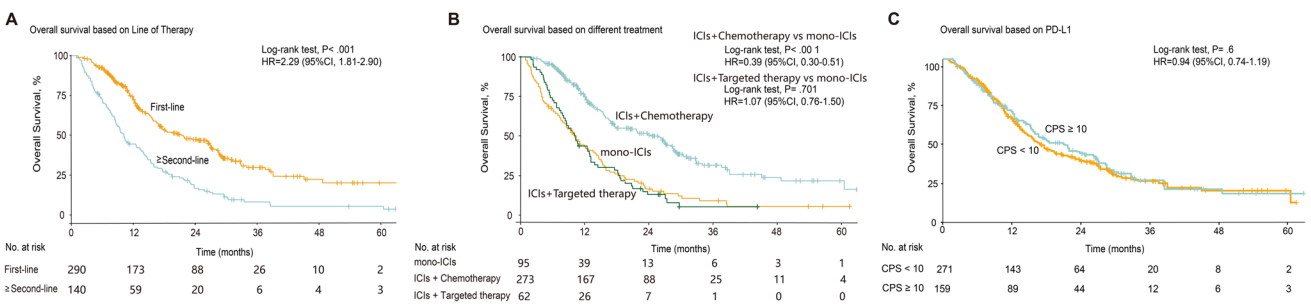

Fig. 2 Clinical survival outcomes in training cohort

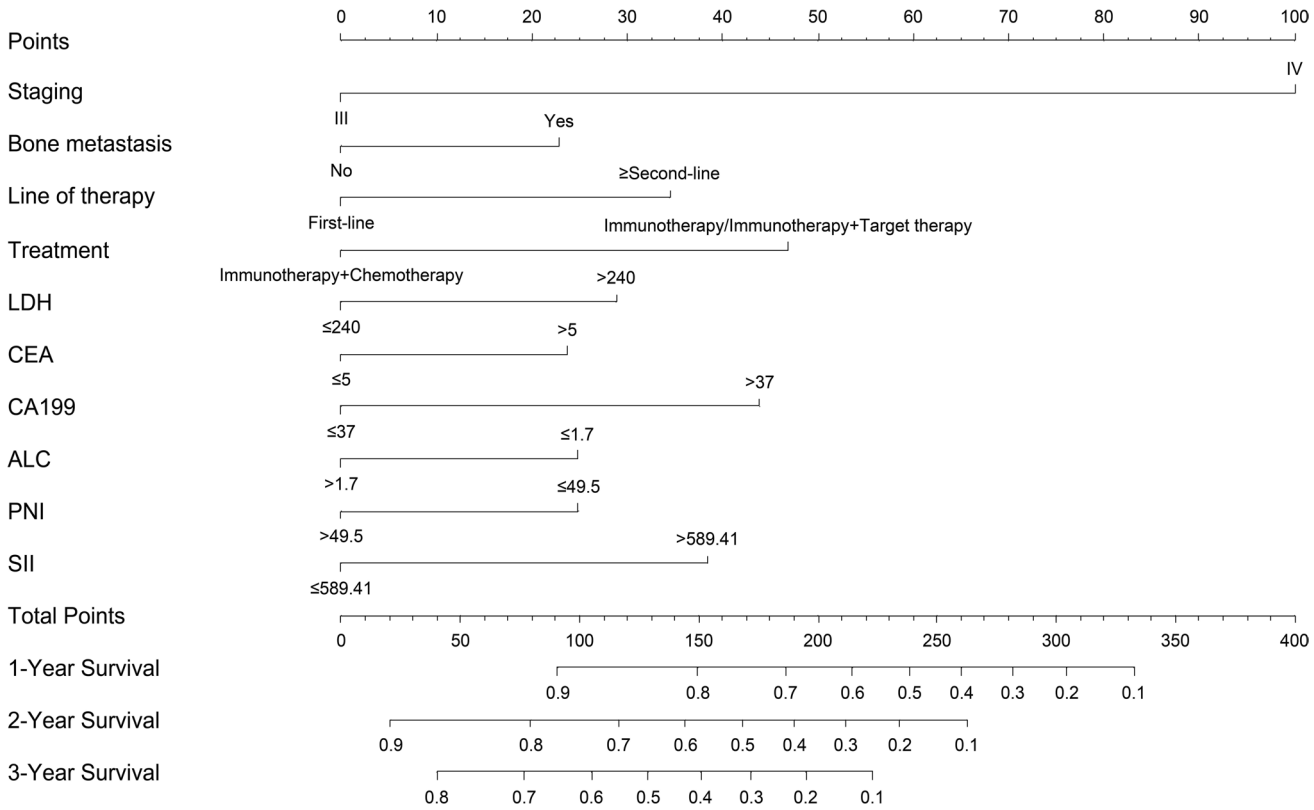

Fig. 3 Postoperative prognostic nomogram for advanced ESCC

To apply the nomogram, locate each predictor on its respective points scale and assign the corresponding value. Calculate the total score by summing these values, then trace a vertical line from the total score to the probability scales to estimate survival outcomes.

The calibration plot showed strong concordance between nomogram predictions and actual outcomes for 2-, and 3-year OS in both the training and validation cohorts, remaining within an acceptable range for survival probability prediction. However, the 1-year OS prediction exhibited moderate discrimination, potentially due to inherent characteristics of the training cohort (Supplementary Fig. 3). Further exploration with larger cohorts are necessary to enhance precision. The model achieved a C-index of 0.725 (95% CI 0.694–0.756) in the training cohort, and the bootstrap-corrected C-index was 0.722 (95% CI 0.688–0.751), demonstrating robust discriminative ability for survival prediction. The time-dependent ROC curve analysis further underscored the model's strong predictive accuracy for 1-, 2-, and 3-year OS, with AUC values reflecting excellent discrimination and confirming the reliability of model for prognostic predictions across these time points (Fig. 4A).

Time-dependent ROC analysis illustrates the model's robust performance in stratifying patient outcomes at 1-, 2-, 3-year intervals.

To evaluate generalizability, the model was tested using the external validation cohort, achieving a C-index of 0.691 (95% CI 0.650–0.733). AUC values were consistent with those from the training cohort, further supporting the model's predictive value in real-world settings (Fig. 4B). These internal and external validation results highlight the robustness and reliability of this model, demonstrating consistent performance across various follow-up intervals.

Risk stratification for advanced ESCC patients

To facilitate the practical application in clinical settings, risk scores for each patient were calculated based on this model. Patients were classified into low-, moderate-, and high-risk groups according to tertile risk scores calculated from the training cohort. For 1-, 2- and 3-year survival probabilities, in the training cohort, the high-risk group exhibited the lowest at 37.5%, 9.8% and 1.9%, compared to 69.2%, 38.1% and 21.4% for the moderate-risk group and 83.6%, 65.0% and 45.8% for low-risk group. Similarly, in the validation cohort, the high-risk group showed survival probabilities of 29.2%, 8.3% and 0%, while 55.7%, 22.8% and 13.9% in the moderate-risk group and 77.8%, 50.6% and 36.7% in the low-risk group (Supplementary Table 3). Survival curves for

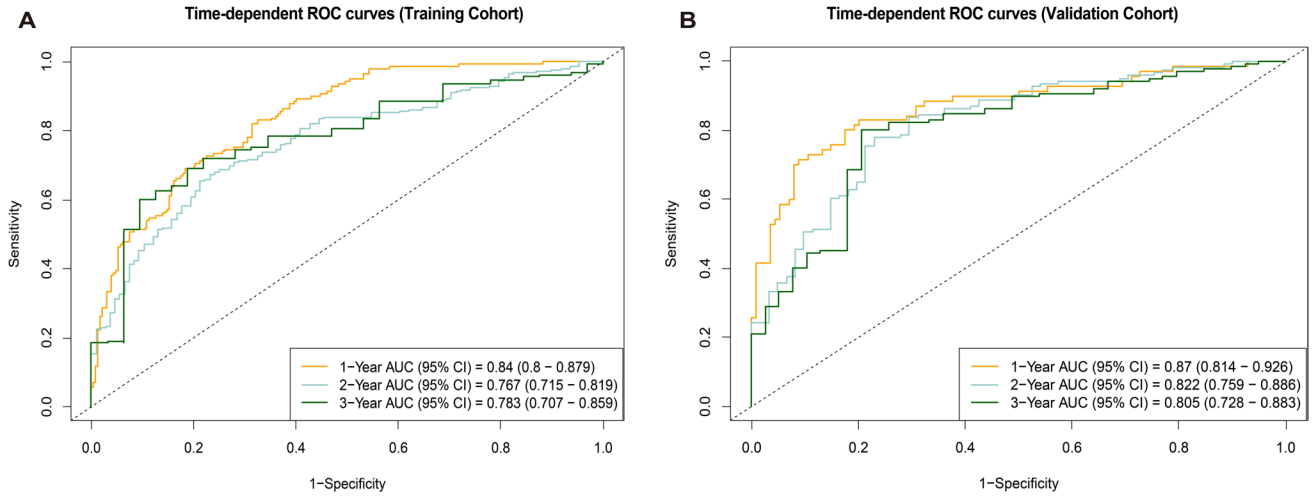

Fig. 4 Time-dependent ROC curves

the three risk groups in both cohorts revealed statistically differentiation (logrank $P < 0.001$) (Fig. 5).

Patients were categorized into low-, moderate- and high-risk groups, with cutoff values determined by tertiles of the risk scores.

Discussion

We analyzed 430 advanced ESCC patients treated with ICIs and described their survival outcomes. We subsequently developed and validated an integrated model incorporating 10 clinical variables to predict OS. This model demonstrated robust discrimination ability (C-index = 0.725), providing real-world evidence that patients receiving first-line ICIs in combination with chemotherapy, along with favorable clinical indicators such as high PNI (> 49.5), low LDH (≤ 240), CEA (≤ 5), CA199 (≤ 37) and SII levels (≤ 589.41), were more likely to achieve survival benefits. To facilitate clinical use, this model was integrated into an interactive online prediction tool (Supplementary Fig. 5, https://escc-survival.shinyapps.io/shiny_app/), enabling parameter input and graphical visualization.

PD-L1 has been investigated as a potential predictive biomarker for the efficacy of ICIs in advanced ESCC [27]. However, its predictive value remains controversial due to conflicting evidence. For instance, CheckMate-648 [28] indicated ICIs provided OS benefits only in patients exhibiting elevated PD-L1 expression [tumor cell proportion score (TPS) > 1%], while RATIONALE-302 [29], ORIENT-15 [7] and two meta-analyses [11, 12] suggested that patients with low PD-L1 expression (TPS < 1% or CPS < 10) could also experience OS benefits. In this study, we evaluated various ICIs including sintilimab, pembrolizumab, nivolumab, and

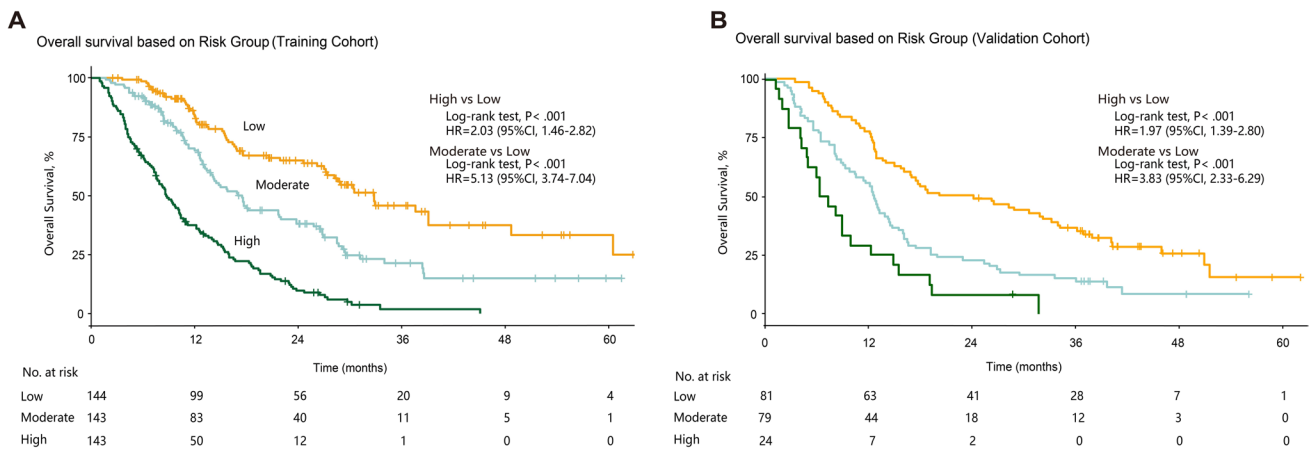

Fig. 5 Survival curves of three risk groups

camrelizumab. Overall, PD-L1 failed to demonstrate predictive accuracy (Fig. 2C, Supplementary Fig. 4), suggesting its limitations in reliably predicting prognosis for ICIs and underscoring the need for further research to establish its clinical utility as a biomarker.

Conversely, our prediction model exhibited superior prognostic accuracy for both mono-ICIs and combined with chemotherapy, significantly outperforming PD-L1. This model integrates comprehensive array of factors across four categories, encompassing fundamental tumor characteristics, treatment strategies, and biological predictors such as LDH, CEA, CA199, ALC, PNI and SII. To our knowledge, it is the first model designed for individualized survival prediction in advanced ESCC patients treated with ICIs, utilizing large-scale, high-quality real-world data. These predictors, derived from routine tumor assessments and laboratory tests, ensure practicality, cost-effectiveness, and clinical accessibility. Moreover, this study represents a broad patient population and facilitates a thorough exploration of the interactions between clinical characteristics and survival outcomes for immunotherapy, ultimately informing personalized therapeutic decision-making.

Tumor characteristics, such as stage and metastasis, are critical in predicting prognosis for ESCC. In our training cohort, stage IV disease with concurrent bone metastases was associated with poorer outcomes, while the line of therapy also significantly influenced survival. The median OS for first-line treatment in the training cohort reached 21.3 months, with 2-, 3-, and 5-year survival probabilities of 47.3%, 29.8%, and 20.2%, exceeding the average level. In contrast, the validation cohort exhibited slightly lower median OS, reflecting regional variations in clinical practice, therapeutic approaches and treatment experience across the two study centers. Regarding treatment regimens, ICIs combined with chemotherapy [7, 8, 12, 30, 31] or targeted inhibitors such as tyrosine kinase inhibitors (TKIs) and epidermal growth factor receptor (EGFR) inhibitors [32, 33], are widely recognized options. However, few studies have compared these therapies simultaneously. Our findings revealed that ICIs combined with chemotherapy provided the best survival benefits, while no significant difference was observed between ICIs combined with targeted therapy and mono-ICIs, underscoring the need for further clinical trials to validate these targets.

The role of biological predictors, including serum tumor markers, biochemical markers, inflammatory markers and nutritional markers, cannot be underestimated in assessing prognosis and survival, especially during ICIs therapy. Limited studies have examined the association between tumor markers and therapeutic efficacy in ESCC. Previous small-scale study suggested that CEA and CA199 might predict the effectiveness of postoperative chemotherapy [23]. Our findings further supported their role as prognostic markers for ICIs in advanced ESCC. Elevated LDH, a key enzyme in anaerobic glycolysis, correlate with adverse prognosis [24, 34], consistent with previous research. Additionally, neutrophils, lymphocytes, and platelets reflect immune-inflammatory status [35], linking to tumorigenesis, progression, and metastasis [36]. Inflammatory biomarkers such as PLR, NLR and SII in ESCC remain inconsistent due to sample size constraints [37, 38], our analysis enrolled ALC, PLR, NLR (dNLR), lymphocyte-to-white blood cell ratio (LWR) and SII in multivariable Cox regression, with only ALC and SII retained in the final model, with high SII (>589.61) identified as a poor prognostic indicator for OS. Consistent with prior study [39], we found that PNI (>49.5), reflecting immune and nutritional status [40], was associated with improved survival outcomes, highlighting the importance of timely nutritional and immunological interventions.

The prediction model integrates above variables demonstrates strong performance. There was no deterioration in calibration during internal validation (C-index = 0.722), indicating that the model was likely not overfitted. More importantly, the model also performed well (C-index = 0.691) in the external validation cohort from a geographically distant area in China, despite some expected loss of discriminative performance. Patients were stratified into three risk groups of low-, moderate-, and high- according to risk scores, with OS clearly differentiated among the groups in both two cohorts (Fig. 5 and Supplementary Table 3), highlighting the model's clinical utility, especially in the absence of standardized criteria on patient selection for ICIs. To facilitate clinical use, we developed an interactive online risk calculator (Supplementary Fig. 5, https://escc-survival.shinyapps.io/shiny_app/) for automated prediction of patient outcomes. This tool could serve as a valuable adjunct for treatment decision-making, especially in institutions introducing ICIs as a novel therapeutic option. It can also support patient selection for clinical trials by enabling stratified randomization into risk groups, optimizing trial design, reducing costs and time, and minimizing patient exposure to ineffective treatments.

Several limitations of the present study warrant acknowledgment. Firstly, the single-center design and retrospective nature of the analysis introduce potential selection bias. To address this, larger, multicenter cohorts are needed to validate the prediction model with sufficient statistical power. Secondly, although our findings align with previous studies, the absence of standardized cutoff values limits the generalizability of our conclusions. Consequently, establishing an unified method to confirm appropriate cutoff values is essential.

In summary, we developed the first real-world integrated prognosis prediction model for immunotherapy in advanced ESCC and integrated it into an interactive online tool. This model enables clinicians and patients to generate

individualized survival predictions, facilitating more accurate and efficient decision-making regarding treatment strategies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-025-03963-y.

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Author contributions Author contributions Zhihao Lu: Corresponding author, Conceptualization, Funding acquisition, Writing—review and editing, Final approval of the manuscript. Zhonghu He and Yanqiao Zhang: Corresponding author, Conceptualization, Data curation, Writing-review and editing, Final approval of the manuscript. Liyuan Dong: Investigation, Conceptualization, Data curation, Methodology, Software, Formal analysis, Validation, Visualization, Writing—original draft, Writing—review and editing, Final approval of the manuscript. Yue Ma: Resources, Data curation, Methodology, Validation, Writing—review and editing, Final approval of the manuscript. Guang Cao: Data curation, Writing—review and editing, Final approval of the manuscript. Dongze Chen: Methodology, Writing—review and editing, Final approval of the manuscript. Fengxiao Dong, Xi Jiao, Yanshuo Cao, Chang Liu, Yanni Wang, Na Zhuo, Fengyuan Wang, Yixuan Guo, Tingting Dai, Shuwei Zhang, Hao Jiao, Xingyue Zou, Jian Li and Lin Shen: Data curation, Writing—review and editing, Final approval of the manuscript.

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Data availability Datasets and underlying codes are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval This retrospective study was approved by the Medical Ethics Committee of Peking University Cancer Hospital and Harbin Medical University Cancer Hospital. We confirm that the study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki for medical research involving human subjects.

Consent to participate Written informed consent was obtained from all participants prior to enrollment.

Consent to publish The authors affirm that human research participants provided informed consent for publication of the all the images and tables.

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