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Original Article

Development and validation of a machine learning-based model to predict postoperative overall survival in patients with soft tissue sarcoma: a retrospective cohort study

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Abstract: Background: The aim of this study is to develop a machine learning-based model to predict postoperative overall survival (OS) in patients with soft tissue sarcoma (STS) that demonstrates superior comprehensive performance. Methods: This analysis leveraged data from the SEER database spanning 2010-2020, alongside a STS cohort from the National Cancer Center. Machine learning methods were applied for predictor selection by wrapper methods and the development of the predictive model. The optimal model was determined using the concordance index (C-index), time-dependent calibration curves, time dependent receiver operating characteristic (ROC) curves, and decision curve analysis (DCA). Results: Six machine learning learners identified six feature subsets. Subsequently, six feature subsets and six machine learning learners were combined, resulting in the development of 36 prognostic models. The CAM model, exhibiting the highest prediction performance, was selected. The CAM model achieved a C-index of 0.849 (95% CI 0.837-0.859) in the training cohort and 0.837 (95% CI 0.809-0.871) in the validation cohort. Furthermore, time-dependent calibration curves, time-dependent ROC curves, and DCA indicate that the PAM demonstrates excellent calibration, predictive accuracy, and clinical net benefit. A publicly accessible web tool was developed for the CAM. Notably, CAM's performance exceeds that of all existing STS prognostic nomograms and prediction models. Conclusions: The CAM has the potential to identify postoperative OS in STS patients. This can assist clinicians in assessing the severity of the disease, facilitating patient follow-up, and aiding in the formulation of adjuvant treatment strategies.

Keywords: Soft tissue sarcoma, machine learning, prognostic model, surgery, web calculator

Introduction

Soft tissue sarcoma (STS), constituting only 1% of adult malignancies, is a rare and heterogeneous group of tumors [1]. Originating from mesenchymal tissues, STS displays a range of clinical behaviors [2]. STS predominantly occurs in subcutaneous soft tissues of extremities and the trunk, comprising about 40%-50% and 13% of cases, respectively [3, 4]. Surgical intervention remains the mainstay treatment for the majority of STS cases [5]. In elderly patients, STS is associated with a 5-year relative survival rate below 50%, posing substantial risks [6]. Consequently, identifying prognostic risk factors for extremity and trunk STS and developing a precise prognostic prediction system is essential.

The eighth edition of the American Joint Committee on Cancer (AJCC) staging system is commonly applied in the clinical staging of STS. However, studies suggest that AJCC system does not sufficiently capture the heterogeneity of soft tissue sarcomas, leading to suboptimal predictive accuracy [7, 8].

Previous studies have identified prognostic factors for STS and integrated them into various models [9]. Notably, the MSKCC and Sarculator models stand out in this context [10, 11]. These models incorporate clinical characteristics, us-

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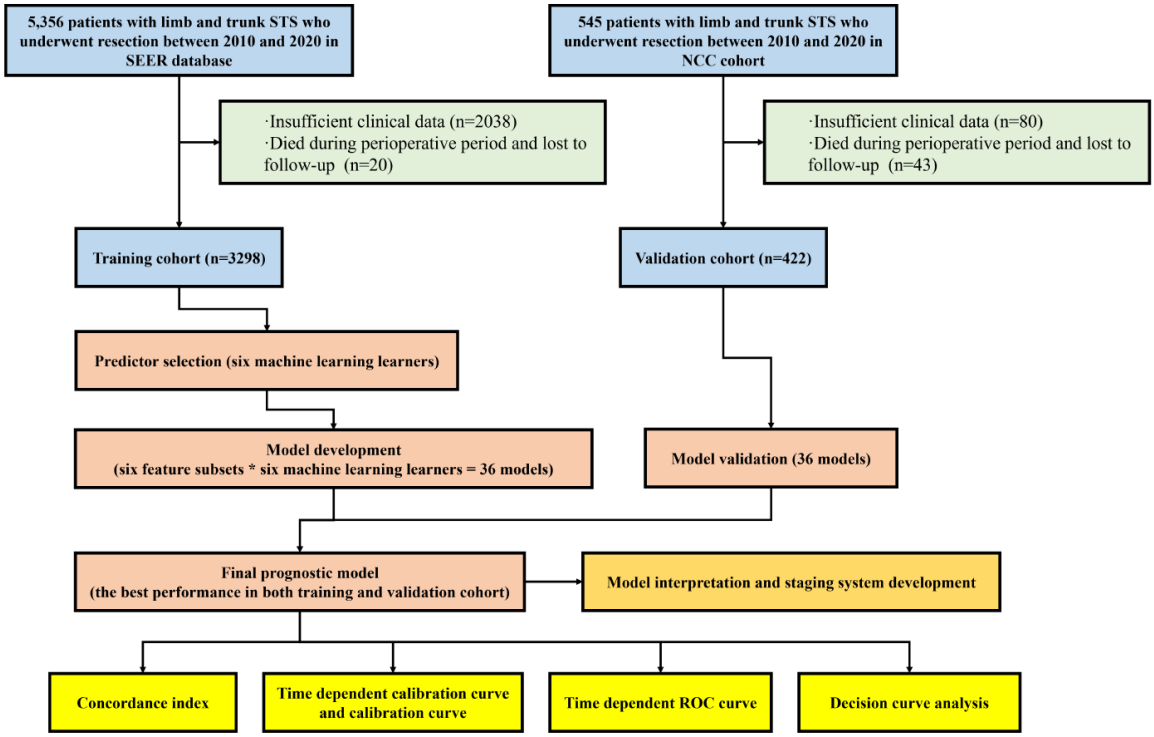

Figure 1. Overall workflow.

ing the Cox proportional hazards model to create nomograms with robust predictive capabilities. Recently, machine learning has emerged as a new methodology for investigating STS prognostic factors. Machine learning is significant, offering advanced tools for analyzing complex biological data [12, 13]. Theoretically, machine learning potentially surpasses traditional Cox regression in predictive accuracy. It is increasingly used in predicting survival rates in cancers such as glioblastoma, breast, colorectal, and STS [14-19]. However, these studies have limitations. For instance, Yeramosu's study approached 5-year survival as a binary classification, not a survival analysis [18]. Additionally, Yang's study on STS imaging developed a complex, less generalizable deep learning model [17].

The purpose of this study is to develop an accurate prognostic model using fundamental clinical characteristics to predict postoperative overall survival (OS) in patients with STS.

Materials and methods

This study strictly adhered to the Prediction model Risk Of Bias Assessment Tool (PROBAST) standards and a checklist for useful clinical prediction tools reported by Florian Markowetz, and followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Checklist for reporting [20-22]. The complete research process of this study is shown in **Figure 1**.

Study population

This retrospective cohort study involved patients with limb and trunk STS who underwent radical surgery between 2010 and 2020 from Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Center (NCC), a specialized secondary care center. Prior to surgery and the subsequent follow-up survey, each patient from NCC provided informed consent. The surgical procedures were expertly conducted by seasoned senior surgeons. Adherence to ethical standards was ensured by conducting the study in compliance with the Declaration of Helsinki (revised in 2013), and ethical approval was secured from the Hospital Ethics Committee of the National Cancer Center (No. NCC2020C-341). The SEER cohort and the NCC cohort were used as the training and validation cohort, respectively.

Inclusion and exclusion criteria

Adult participants with STS (defined as pathologically diagnosed STS) who underwent radical resection were included. The exclusion criteria were as follows: (1) Death during perioperative period; (2) Loss to follow-up; (3) Insufficient clinical data.

Predictor selection

In the training cohort, over 35% of missing parameters were excluded from the analysis. 10 variables of the training cohort, including demographic details (age and sex); pathological information (tumor site, size, pathological diagnosis, lung metastasis, other metastasis); stage parameters (AJCC T, AJCC N, AJCC M, and Grade); and adjuvant treatment status (adjuvant radiotherapy and chemotherapy), were included in six machine learning learners to select predictors.

We chose widely recognized machine learning learners capable of handling continuous, nominal categorical and ordinal categorical variables. These included: Gradient Boosting (GB), Survival Tree (ST), Conditional Inference Tree (CIT), Random Survival Forest (RSF), Conditional Random Forest (CRF), Accelerated Oblique Random Survival Forest (AORSF). These learners were all sourced from the "mlr3proba" R package [23].

The GB is an ensemble learning algorithm that iteratively adds weak learners (typically decision trees) to fit the residuals of the previous step, progressively optimizing the loss function to enhance the overall predictive performance of the model [24]. ST is a decision tree model used in survival analysis that recursively splits data to group individuals based on their survival times and the risks of event occurrence, thereby providing insights into survival probabilities [25]. Besides, ST can also be used to identify cut-off. The CIT is a method for constructing decision trees that uses statistical tests to select splitting variables and points, thereby reducing bias and overfitting in the model during the splitting process in a non-parametric and conditional inference-based manner [26]. RSF is an ensemble learning method used in survival analysis that constructs multiple survival trees and uses the results from these trees to estimate the survival functions and hazard ratios for individuals, thereby offering powerful analysis of survival time data [27]. The CRF is an ensemble learning algorithm that builds multiple decision trees and uses conditional inference tests to select variables and splitting points. This approach enhances the robustness and accuracy of the model while reducing bias in variable selection [28]. The AORSF is a survival analysis model that combines the ensemble learning techniques of random forests with the approach of oblique decision trees. This integration enhances the accuracy and efficiency in handling complex survival data [29].

We use Wrapper methods (WM) for the predictor selection. WM work by fitting models on selected feature subsets and evaluating their performance and ultimately select the feature subset that performs best for that learner. The entire predictor selection process using WM is as follows: (1) The learner selects a feature subset (iteratively adding features to the model in sequential forward selection); (2) A 10-fold cross-validation resampling strategy is used to develop a pre-model and calculate the concordance index (C-index) of the pre-model for that feature subset; (3) Repeat the above process until the C-index for all feature subsets has been calculated; (4) Select and output the feature subset with the highest C-index as the result of the WM for that learner. The predictor selection result for each learner is a feature subset that includes several clinical features.

After separately calculating the above six machine learning learners, we obtained a total of six feature subsets for subsequent model development.

Development and validation of machine learning model

The six machine learning learners, combined with six feature subsets, were used to develop models. These models were trained using the training cohort, culminating in 36 prediction models. These models were subsequently validated within validation cohort.

The C-index was utilized to assess model performance. As a statistical measure for evaluating the predictive capability of survival analysis models, the C-index is widely used in medical research. It gauges the congruence between

model predictions and actual outcomes, with its value ranging from 0 to 1. A higher C-index indicates superior predictive accuracy of the model. The model that achieved the highest average C-index was chosen for further investigation. Calibration curves were generated to evaluate the correspondence between predicted and actual non-incidence rates of all-cause death at 1, 3, and 5 years. Time-dependent calibration curves were used to reflect the degree of calibration over an entire time range. The area under the time-dependent receiver operating characteristic (ROC) curves (AUC) served to compare the predictive accuracy and discriminative power of the model and its components. Decision curve analysis (DCA) was conducted to determine the clinical utility of the model, assessing the clinical benefits for patients at 1, 3, and 5 years. Risk scores were calculated in the training and validation cohorts using the machine learning model.

To examine how different features influence model performance over time, a time-dependent feature importance analysis method was employed. The significance of each predictor was evaluated by computing the model's Brier score loss after permuting feature values, with this process repeated through a 10-fold cross-validation resampling strategy for statistical reliability. This approach enabled identification of which features' importance for model predictions varies over time, providing insights crucial for time-sensitive clinical decision-making.

Development of a web risk calculator and a staging system

The ST was employed to determine the cut-off value for the risk score, thereby classifying patients into high-risk, medium-risk, and low-risk group. Furthermore, a web-based application was developed to make these predictive models accessible online, utilizing the R package "shiny" for its development [30].

Statistical analysis

Kolmogorov-smirnov test was used to assess whether the data followed a normal distribution. For normally-distributed continuous variables, the data were described as mean ± standard deviation and compared using the t-test. If continuous variables did not conform to a normal distribution, the MannWhitney U test was used, and results were presented as median (interquartile range). Categorical data were presented as numbers and frequencies, and either the Chi-square test or Fisher's exact test was used for comparisons. Kaplan-Meier (KM) survival analysis and the log-rank test were utilized to assess differences in OS across the high-risk and low-risk group. All statistical tests were two-sided, with *P*-values <0.05 indicating statistical significance. All figure illustrations and statistical analyses were conducted using R version 4.2.3.

Results

Characteristics of training and validation cohorts

A total of 5,901 patients with limb and trunk STS who underwent radical resection were identified. Among them, 2,181 patients who did not meet the inclusion criteria were excluded. Consequently, 3,720 patients were included in the analysis.

The baseline characteristics of the training cohort (n = 3,298) and validation cohort (n = 422) are presented in **Table 1**. In the training cohort, the median age is 62 and the median follow-up time is 4 years. Among them, 55.3% were male. In the validation cohort, the median age is 51 and the median follow-up time is 4.71 years. Among them, 56.6% were male.

Predictor selection

Ten variables from the training cohort were included for the selection of predictor. Using six machine learning learners and applying the WM, we obtained six feature subsets, the details of which are displayed in **Table 2**.

Model development, validation, and evaluation

For the development of model using the training cohort, six feature subsets were processed through six machine learning learners and subsequently validated internally in the training cohort using the 10-fold cross-validation resampling strategy and externally in the validation cohort. This process resulted in a total of 36 machine learning models specifically designed for predicting OS.

Table 1. Baseline characteristics of the cohort

	Training cohort N = 3,298	Validation cohort N = 422	*P*
Sex			0.650
Female	1473 (44.7%)	183 (43.4%)	
Male	1825 (55.3%)	239 (56.6%)	
Age (years)	62.0 [48.0; 73.0]	51.0 [38.0; 62.0]	<0.001
Site			<0.001
Lower limb	1959 (59.4%)	203 (48.1%)	
Trunk or pelvis	706 (21.4%)	137 (32.5%)	
Upper limb	633 (19.2%)	82 (19.4%)	
Size (cm)	7.60 [4.30; 13.5]	4.50 [3.00; 6.50]	<0.001
AJCC T			<0.001
T1	1055 (32.0%)	247 (58.5%)	
T2	1016 (30.8%)	139 (32.9%)	
T3	600 (18.2%)	28 (6.64%)	
T4	627 (19.0%)	8 (1.90%)	
AJCC N			0.960
N0	3210 (97.3%)	410 (97.2%)	
N1	88 (2.67%)	12 (2.84%)	
AJCC M			<0.001
M0	3099 (94.0%)	304 (72.0%)	
M1	199 (6.03%)	118 (28.0%)	
AJCC stage			<0.001
I	768 (23.3%)	164 (38.9%)	
II	787 (23.9%)	92 (21.8%)	
III	1494 (45.3%)	46 (10.9%)	
IV	249 (7.55%)	120 (28.4%)	
Grade			<0.001
G1	797 (24.2%)	207 (49.1%)	
G2	704 (21.3%)	143 (33.9%)	
G3	1797 (54.5%)	72 (17.1%)	
Adjuvant radiotherapy			0.149
No	1706 (51.7%)	202 (47.9%)	
Yes	1592 (48.3%)	220 (52.1%)	
Adjuvant chemotherapy			<0.001
No	2827 (85.7%)	298 (70.6%)	
Yes	471 (14.3%)	124 (29.4%)	
Follow-up time (years)	4.00 [1.75; 6.67]	4.71 [2.77; 7.00]	<0.001
Survival status			0.292
Alive	2377 (72.1%)	315 (74.6%)	
Dead	921 (27.9%)	107 (25.4%)	

Initial evaluation focused on the C-index, with rankings the average C-indexes of 36 prediction models displayed in **Figure 2**. The CIT + AORSF model (CAM) showcased the highest average C-index of two cohorts at 0.843, making it the most effective model among all. The C-index for CAM was 0.849 (95% CI 0.837-0.859) in the training cohort and 0.837 (95% CI 0.809-0.871) in the validation cohort, marking the highest values compared to other models.

The time-dependent calibration curves, along with the 1, 3, and 5-year calibration curves for CAM, demonstrate that CAM achieved good calibration in the training cohort and the validation cohort (**Figure 3**).

The AUC of the prediction model at 1, 3, 5, and 10 years highlighted predictive accuracy of the CAM. In the training cohort, CAM achieved an AUC of 0.898 (95% CI 0.876-0.917) at 1 year, 0.884 (95% CI 0.869-0.898) at 3 years, and 0.891 (95% CI 0.877-0.904) at 5 years (**Figure 4A**). In the validation cohort, CAM achieved an AUC of 0.876 (95% CI 0.805-0.940) at 1 year, 0.863 (95% CI 0.822-0.902) at 3 years, and 0.883 (95% CI 0.842-0.922) at 5 years (**Figure 4B**).

The DCA for the CAM demonstrated a consistent net benefit in the training cohort and three validation cohorts over a range of threshold probabilities (**Figure 5**). In two cohorts, the CAM outperformed the 'treat none' and 'treat all' strategies, indicating that it had practical utility in decision-making.

Model interpretation and development of stage system

The time-dependent feature importance curves show the varying importance of each predictor in CAM over time (**Figure 6**). The results indicate that the age, tumor size, and the tumor grade are the most important factors over the follow-up period. To further enhance the usability of the model, we developed a web-based risk calcula-

Table 2. Feature subsets after WM feature selection

Learner	Feature subset
GB	Age, Size, Lung metastasis, Grade, and Chemotherapy
ST	Age, Size, Lung metastasis, and Grade
CIT	Age, Size, AJCC N, Lung metastasis, Other metastasis, Grade, Chemotherapy, and Radiotherapy
RSF	Age, Size, AJCC N, Lung metastasis, Other metastasis, Grade, and Radiotherapy
CRF	Age, Site, Size, AJCC N, Lung metastasis, Other metastasis, Grade, Chemotherapy, and Radiotherapy
AORSF	AJCC N

WM, Wrapper method; GB, Gradient Boosting; ST, Survival Tree; CIT, Conditional Inference Tree; RSF, Random Survival Forest; CRF, Conditional Random Forest; AORSF, Accelerated Oblique Random Survival Forest Model.

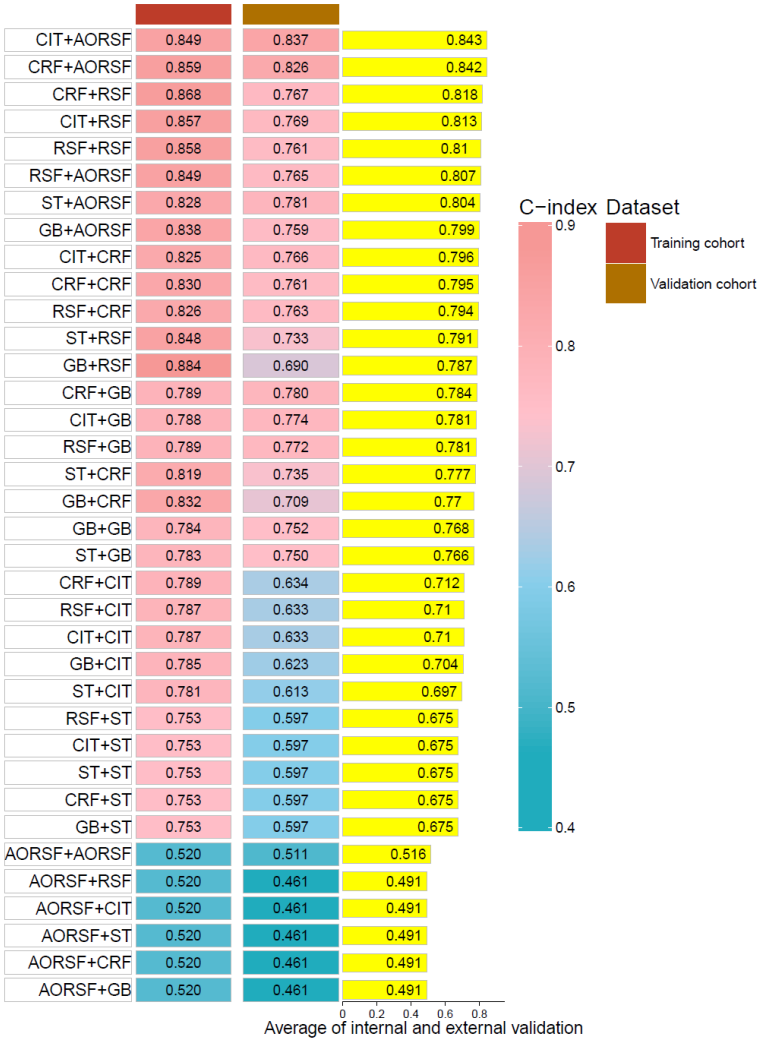

Figure 2. Concordance index of 36 machine learning models. The C-index for the 36 machine learning models was calculated for the training cohort and the validation cohort. Ranking of the models was based on the average C-index two cohorts. GB, Gradient Boosting; ST, Survival Tree; CIT, Conditional Inference Tree; RSF, Random Survival Forest; CRF, Conditional Random Forest; AORSF, Accelerated Oblique Random Survival Forest; C-index, concordance index.

tor (https://zlyygk8778.shinyapps.io/CAMforSTS/). Additionally, we developed a staging system based on CAM, utilizing the ST learner to categorize DA patients into two risk groups according to CAM's risk scores. The KM survival curves indicate that, in both the training cohort and the validation cohort, the OS of the low-risk group (risk score <51.5) is longer than that of the high-risk group (risk score ≥51.5), and the difference is statistically significant (**Figure 7**).

Comparing the performance of CAM with other nomograms and predict models

We compared CAM's performance with 42 established STS nomograms and prognostic models [10, 11, 17, 18, 31-69] (**Table 3**). The results showed that CAM outperformed other nomograms and prediction models, achieving the highest C-index and AUC at 3- and 5-year. Consequently, the comparison of CAM with 42 nomograms and prediction models revealed that the prediction efficiency of CAM was better than them.

Discussion

In this study, we developed and validated a machine learning-based model to predict OS in postoperative STS patients. The prognostic model exhibited accuracy in the training and validation cohorts. In

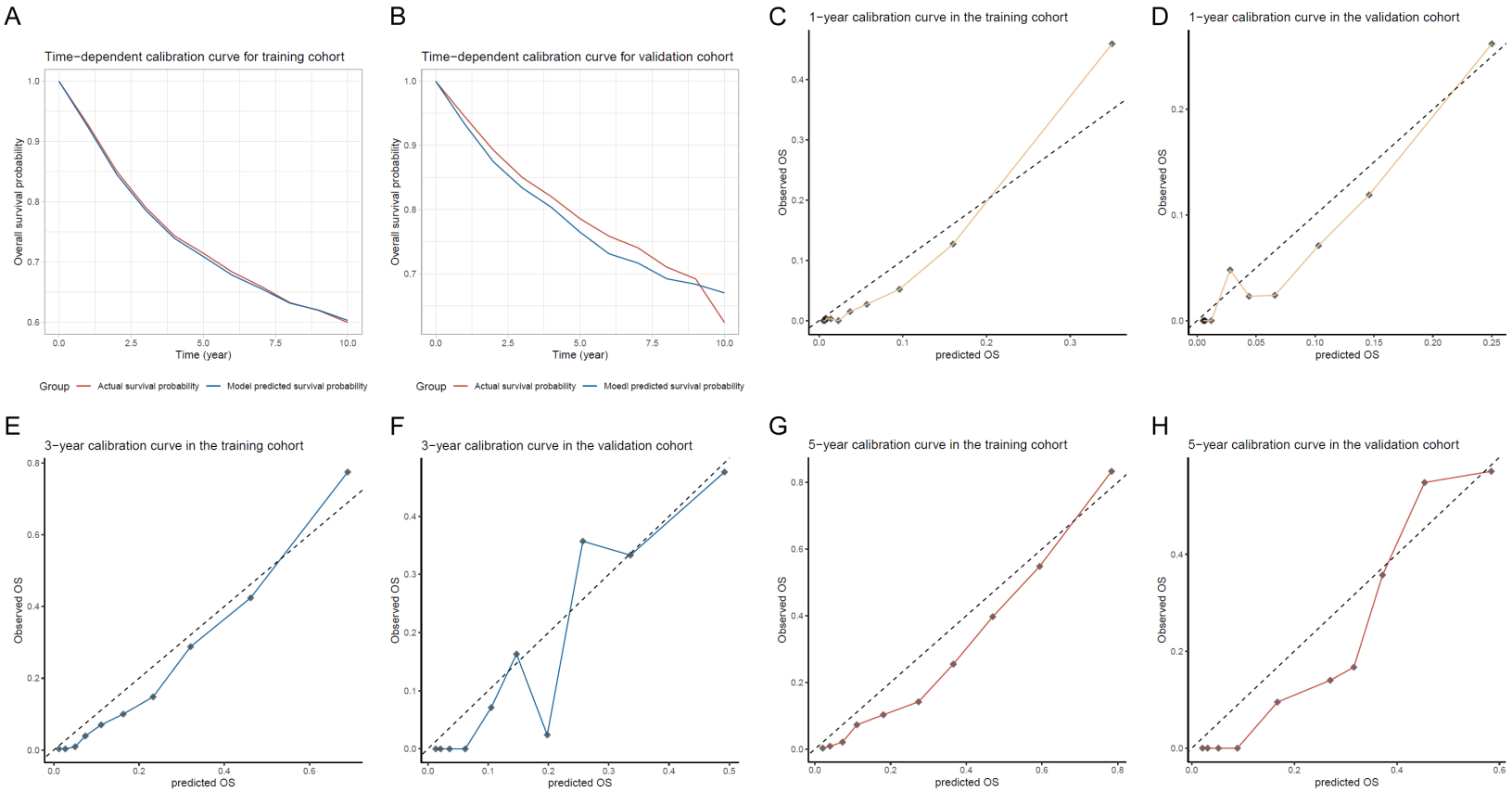

Figure 3. Evaluating the calibration of CAM by time-dependent calibration curves. A. Time-dependent calibration curve of training cohort; B. Time-dependent calibration curve of validation cohort; C. 1-year calibration curve for training cohort; D. 1-year calibration curve for validation cohort; E. 3-year calibration curve for training cohort; F. 3-year calibration curve for validation cohort; G. 5-year calibration curve for training cohort; H. 5-year calibration curve for validation cohort. CAM, Conditional Inference Tree + Accelerated Oblique Random Survival Forest Model.

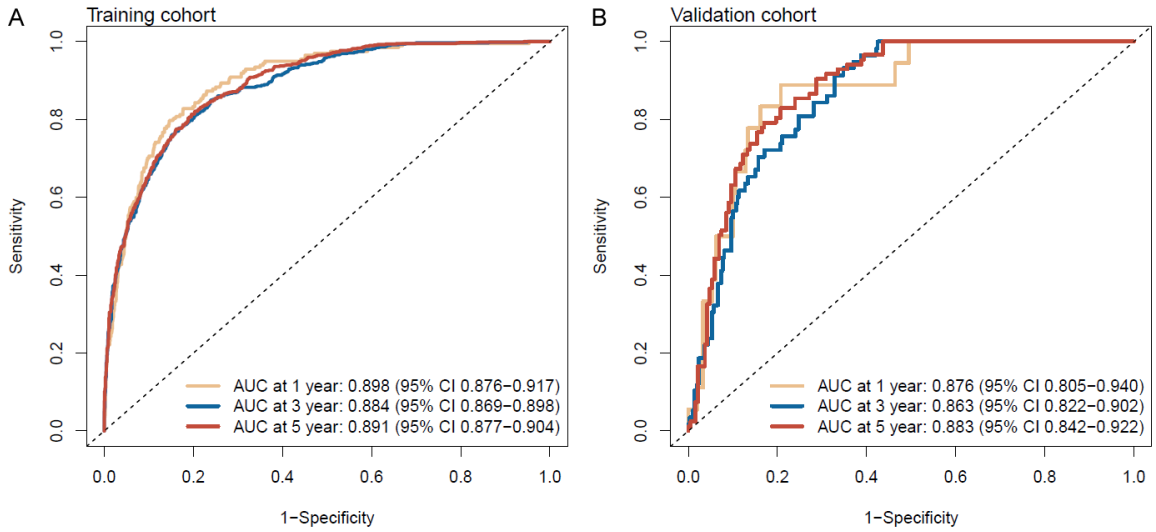

Figure 4. Evaluating the predictive accuracy of CAM by time-dependent ROC curves. A. Time-dependent ROC curves training cohort; B. Time-dependent ROC curves validation cohort. CAM, Conditional Inference Tree + Accelerated Oblique Random Survival Forest Model.

terms of predictive values, CAM generally exhibits a high C-index and AUC, indicating the model's accuracy and stability in predicting OS. Additionally, the time-dependent calibration curves and DCA demonstrate the excellent calibration and clinical net benefit of PAM. Our study indicates that CAM has the potential to identify postoperative OS in STS patients. This can assist clinicians in assessing the severity of the disease, facilitating patient follow-up, and aiding in the formulation of adjuvant treatment strategies.

In our research, a total of 36 models were developed, utilizing 6 distinct machine learning learners for both feature selection and model development. This approach mirrors the methodology of Liu et al., who employed a similar strategy to develop an immune long non-coding RNA (lncRNA)-based prognostic model for overall survival in colorectal cancer [16]. Unlike many studies that rely solely on traditional Cox regression and least absolute shrinkage and selection operator (LASSO) for model development, our method incorporated a broader range of techniques. This diversification allowed for the creation of a predictive model with enhanced performance, marking a significant bedside innovation within this study [10, 11].

Recently, the development of predictive models has gained significant attention among clinical scientists. Therefore, the standardized development and validation of predictive models are crucial, and our study adhered rigorously to these standards. Finhn et al. noted that the proliferation of predictive models has been accompanied by an increasing awareness of the need for standards to ensure their accuracy. A significant milestone was the publication of the TRIPOD guidelines nearly a decade ago [22, 70]. Wolff et al. developed a tool to assess the risk of bias and the applicability of prediction model studies [20]. This tool includes 20 signal questions designed to enable researchers to self-assess their studies. Florian Markowetz proposed a checklist for useful clinical prediction tools aimed at making clinical prediction models impactful for patients [21]. The aforementioned checklist and tools were used to standardize our research.

CAM incorporates clinical characteristics like age, size, N stage, lung metastasis, other metastasis, Grade, adjuvant chemotherapy and adjuvant radiotherapy. These clinical characteristics are notably easily obtainable. Parameters like age, adjuvant chemotherapy and adjuvant radiotherapy information can be sourced from patients' histories and medical records. Information on regional lymph node involvement and distant metastasis can be determined via imaging assessments. Tumor size is ascertainable through physical examination, imaging,

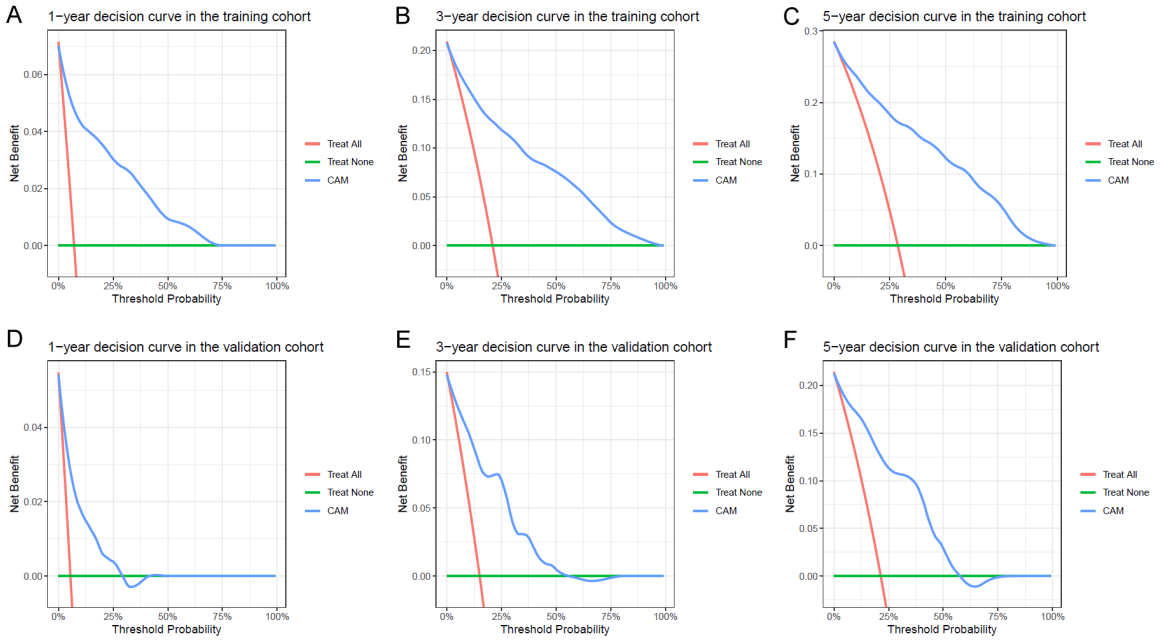

Figure 5. Evaluating the net benefit of CAM by DCA. A. 1-year DCA for training cohort; B. 3-year DCA for training cohort; C. 5-year DCA for training cohort; D. 1-year DCA for validation cohort; E. 3-year DCA for validation cohort; F. 5-year DCA for validation cohort. CAM, Conditional Inference Tree + Accelerated Oblique Random Survival Forest Model; DCA, Decision curve analysis.

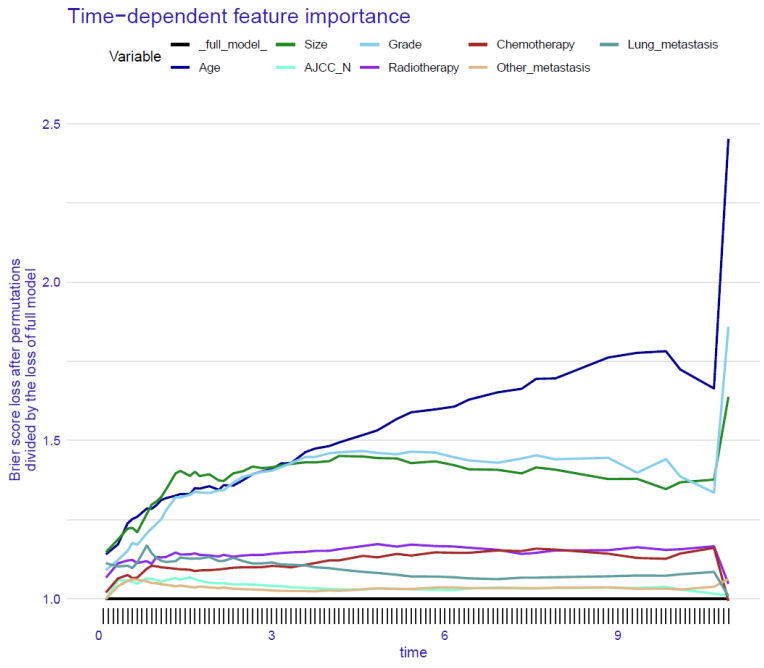

Figure 6. Interpretation the CAM by time-dependent feature importance curves. CAM, Conditional Inference Tree + Accelerated Oblique Random Survival Forest Model.

and postoperative pathology. Likewise, tumor grade can be ascertained from postoperative pathological analysis. The advantage of such easily obtainable characteristics is that, even in areas with limited medical resources, if these features are accessible, the CAM can accurately predict patient prognosis.

Age and Grade feature in numerous nomograms, underscoring their clear prognostic significance [48, 49, 71, 72]. In this study, there was a significant difference in the overall age of patients between the training cohort and the validation cohort. However, the CAM still demonstrated excellent validation performance, highlighting its generalizability and applicability across different patient populations. Tumor size, a major prognostic factor, is included in many nomograms [23, 58, 60]. Unlike T staging, using tumor size as a continuous variable allows for more personalized and accurate prognostication in STS patients. The N stage indicates lymph node metastasis in STS

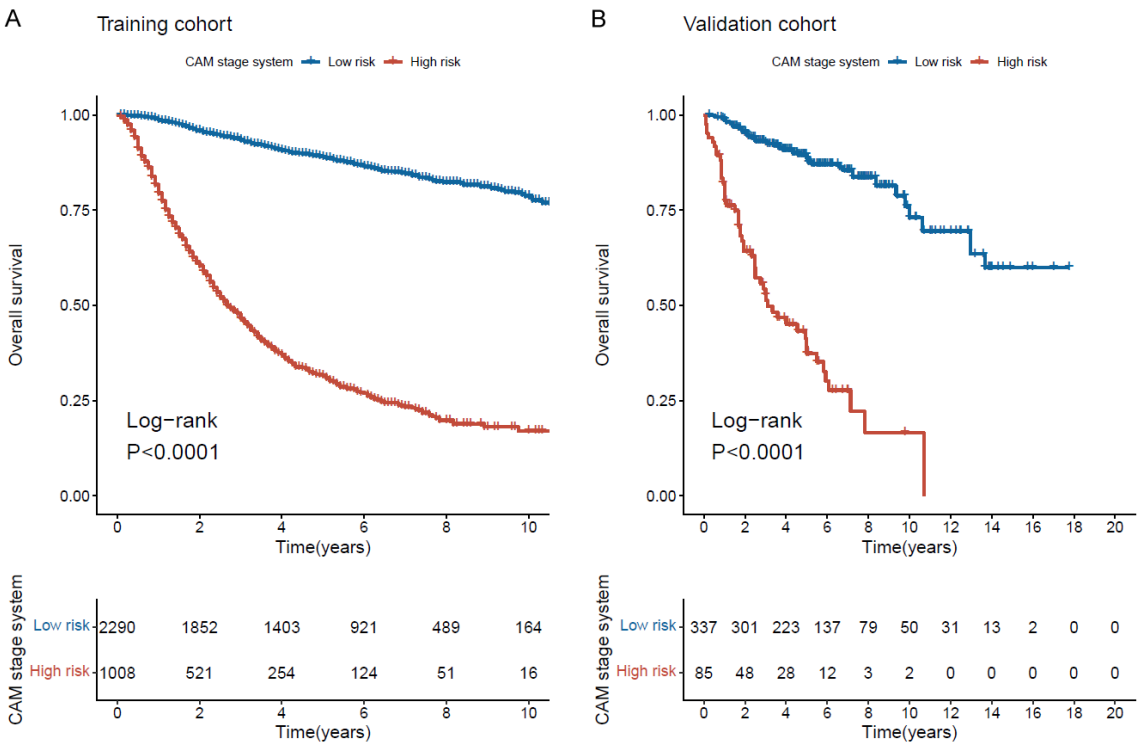

Figure 7. Performance of the CAM staging system in the training cohort and validation cohort. A. Training cohort; B. Validation cohort.

patients, with studies showing that patients with lymph node metastasis generally have poorer prognoses [73-78]. Distant metastasis is an important reason for the poor prognosis of soft tissue sarcoma. Overall survival is generally lower in patients with soft tissue sarcomas who have distant metastases compared with those who do not. The five-year survival rate for patients with soft tissue sarcoma can range from a high of 80% to 90% (early-stage disease) to a low of 15% to 30% (late-stage disease with distant metastases) [79]. Even if distant metastases are controlled, patients are at higher risk for recurrence than those without distant metastases [1].

In terms of treatment, Radiotherapy's role in improving local control of STS in the extremities and trunk was established by two early randomized controlled trials, and it is a vital auxiliary treatment for STS [80, 81]. Regarding the efficacy of adjuvant chemotherapy post-surgery, research results are inconsistent. Some studies suggest that for certain types of high-risk soft tissue sarcomas, an appropriate chemotherapy regimen may improve disease-free survival and overall survival rates [82-84].

Despite survival prediction challenges, research indicates that quantifying prognosis benefits most cancer patients by facilitating end-of-life discussions and minimizing aggressive care. CAM plays a crucial role in this context. Oncologists can utilize CAM to assess patient risk and survival probability during follow-up, guiding treatment decisions effectively. Additionally, inputting non-treatment data into CAM to compare risk scores and survival probability with or without adjuvant treatment can inform the potential benefit of adjuvant treatment, thereby guiding its use. This strategy significantly benefits the personalized treatment of STS.

Our study demonstrates multiple innovations and strengths. First, our study encompassed a considerable total sample size and comprised an external validation cohort from our center. Second, we utilized a wide array of machine learning methods and distinctly separated feature selection from modeling to acquire a broader spectrum of modeling solutions. This approach differs from many studies that merely use machine learning algorithms without implementing such strategies [15, 85, 86]. Third,

Table 3. The C-index and AUC of CAM and 42 existing nomograms or prognostic models

Author or model	C-index in training cohort	C-index in validation cohort	AUC at 3 years in training cohort	AUC at 5 years in training cohort	AUC at 3 years in validation cohort	AUC at 5 years in validation cohort
CAM	0.843	0.837	0.884	0.891	0.863	0.883
Kattan et al. (MSKCC)	0.77	0.76	NA	NA	NA	NA
Callegaro et al. (Sarculator)	0.767	0.698; 0.77; 0.762; 0.726	NA	NA	NA	NA
Zhang-Lyu et al.	0.684	0.74	0.721	0.713	0.721	0.718
Wang-He et al.	0.729	0.735	0.747	0.725	0.736	0.712
Zhou et al.	0.757	0.697	NA	NA	NA	NA
Wu et al.	0.814	0.837	<0.85	<0.85	<0.85	<0.85
Zheng et al.	0.788	0.767	0.803	0.787	0.8	0.74
van Praag et al.		0.677 (CV)	NA	NA	NA	NA
Zhan et al.	0.744	0.803	0.788	0.771	0.734	0.756
Wang-Wang et al.	0.756	0.757	0.785	0.795	0.814	0.812
Liu et al.	0.765	0.721	0.84		0.746	
Zhu et al.	NA	NA	0.751	0.757	0.775	0.829
Shen et al.		0.775	0.935	NA	0.647	NA
Sekimizu et al.		0.75 (CV)	NA	NA	NA	NA
Crombé et al.		0.65	NA	NA	NA	NA
Yang-Ma et al.	0.722	0.676	NA	NA	NA	NA
Zeng et al.	0.78	0.73	NA	0.82	NA	0.77
Ma et al.		0.748			0.746	
Yeramosu et al.	NA	NA	NA	0.891	NA	0.791
Zhang-Li et al.	0.817	0.832	0.809	0.802	0.76	0.771
Shuman et al.		0.78	NA	NA	NA	NA
Gu et al.	NA	NA	0.815	0.823	NA	NA
Le et al.	0.84	0.76	NA	NA	NA	NA
Qi et al.	NA	NA	0.686	0.716	0.636	0.651
Xu et al.	0.759	0.766	0.799	0.8	0.82	0.805
Yang-Ding et al.	0.78-0.86	0.45-0.60	NA	NA	NA	NA
Dai et al.	0.77	0.75	0.82	0.811	0.773	0.764
Szkandera et al.		0.78	NA	NA	NA	NA
Dalal et al.		0.827	NA	NA	NA	NA
Ye et al.	0.79-0.81	0.79-0.81	0.842	0.841	0.862	0.839
Liu et al.	0.666	NA	NA	NA	NA	NA
Huang-Zhou et al.	NA	NA	0.843	0.841	0.835	0.828
Yan et al.	0.686	0.7	NA	NA	NA	NA
Xing et al.	0.733	0.728	0.823	0.829	0.768	0.754
Zhu et al.		0.76	NA	NA	NA	NA
Li-Yin et al.	NA	NA	0.768	0.794	NA	NA
Tong et al.	0.8	0.789	0.86	NA	0.84	NA
Li-Zhang et al.	0.823	0.803; 0.768	0.84	0.83	0.90; 0.75	0.84; 0.80
Huang et al.	NA	NA	0.738	0.762	0.82	0.766
Song et al.	0.819	0.831	NA	NA	NA	NA
Jiang et al.	0.757	0.749	0.733	0.728	0.765	0.772
Yang et al.		0.74 (CV)	NA	NA	NA	NA

CAM, Conditional Inference Tree + Accelerated Oblique Random Survival Forest Model; CV, Cross-validation.

our careful learners selection allowed for computation involving continuous, unordered categorical, and ordered categorical variables. We intentionally excluded learners unable to man-

age categorical variables, like the LASSO, which are suitable solely for continuous variables, minimally applicable to binary categorical variables, and unsuitable for multiple categorical variables. Forth, in terms of model evaluation, we integrated almost all widely recognized prognostic model evaluation methods. Fifth, as mentioned before, the clinical characteristics required for CAM can be easily obtained, which is conducive to the promotion of CAM in various situations. Sixth, we compared CAM with 42 existing nomograms and prognostic models, confirming that CAM stands as the best-performing prognostic model in terms of predictive performance among the existing ones.

Our research presents certain limitations. Most of the machine learning learners we utilized are parametric models, in contrast to non-parametric models like the Cox proportional hazard model. Parametric models lack the ability to create clear and easily understandable nomograms, rendering them less interpretable. Although nomogram cannot be generated, we developed CAM-stage system and a web calculator. Enter the patient's corresponding clinical characteristics into the website to obtain the risk score, CAM stage, and predicted survival probability. In addition, we also use feature importance scores to try our best to explain CAM. In the future, should there be advancements in the interpretability of parametric models, we will pursue further explanation and interpretation of CAM. Finally, although we included the NCC cohort for external validation of the model, further multicentric retrospective or prospective large-scale validation cohorts are required to verify the reliability of the CAM. We plan to conduct a prospective study in the future to further validate and update the CAM.

In summary, our study developed the CAM for accurately predicting OS in STS patients who underwent radical resection. CAM demonstrated stable and excellent predictive performance, calibration, and clinical net benefit in the independent validation cohort. With its outstanding accuracy and reliability, CAM may serve as an effective tool for predicting postoperative OS in STS and guiding adjuvant therapy after surgery.

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Each participant has signed a detailed written consent form.

Disclosure of conflict of interest

None.

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