

Machine Learning Model for Predicting Regional Lymph Node Metastasis in Acral Melanoma

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Abstract

Background

Acral melanoma (AM) is an aggressive subtype characterized by delayed diagnosis and poor prognosis. Accurately and non-invasively assessing regional lymph node metastasis (RLNM) remains a significant clinical challenge. This study aimed to develop an interpretable machine learning (ML) model to preoperatively predict RLNM in AM patients.

Method

Retrospective analysis was conducted on 189 patients with histologically confirmed AM. These patients were randomly assigned to a training cohort and a validation cohort. Boruta algorithm and least absolute shrinkage and selection operator (LASSO) regression were employed to select features. Seven ML models were developed, and the optimal model was selected based on the area under the curve (AUC) value. Shapley Additive Explanations (SHAP) analysis was used to interpret and visualize the contribution of each feature. Model performance was evaluated using calibration curves and decision curve analysis (DCA) curves.

Result

Five key predictors were identified: Breslow thickness, lymph node short-axis diameter, contrast-enhanced ultrasound (CEU) finding, vascular invasion, and Positron Emission Tomography/Computed Tomography (PET-CT) finding. The GradientBoost model demonstrating optimal performance, achieving an AUC of 0.87 in the validation cohort. Calibration and DCA curves indicate that the model exhibits excellent fit and demonstrates significant net clinical benefit.

Conclusion

This study developed a machine learning-based non-invasive diagnostic model that effectively assesses the risk of regional lymph node metastasis in patients with AM.

Introduction

Acral melanoma is a distinct and aggressive subtype of cutaneous melanoma that arises on glabrous skin of the palms, soles, and nail apparatus [1]. Unlike other cutaneous melanomas, its pathogenesis is not primarily driven by ultraviolet radiation but is often associated with mechanical stress, and it exhibits a unique molecular profile with frequent mutations in genes such as *KIT*, *NF1*, and *TERT* [1][2]. This subtype, particularly the acral lentiginous melanoma histological variant, disproportionately affects individuals with darker skin phototypes and is frequently diagnosed at advanced stages, contributing to

its notoriously poor prognosis compared to other melanoma subtypes [3][4]. The presence of regional lymph node metastasis (RLNM) is a critical determinant of staging and survival, yet a significant proportion of patients present with occult nodal disease not detectable by physical examination alone [5]. Accurate pre-operative identification of RLNM is therefore paramount for guiding surgical management, such as the decision to perform sentinel lymph node biopsy or complete lymph node dissection, and for informing neoadjuvant therapy strategies.

Current clinical practice for assessing RLNM risk in AM relies on a combination of clinical examination, histopathological evaluation of the primary tumor, and imaging modalities. Established histopathological risk factors, most notably Breslow thickness, along with ulceration and lymphovascular invasion, form the cornerstone of risk stratification [6]. Imaging techniques, including PET-CT, and CEU, provide additional morphological and functional data on lymph nodes [7][8]. However, each of these approaches has inherent limitations. Clinical examination is insensitive for non-palpable nodes, histopathological assessment is invasive and available only after excision, and the interpretation of imaging findings can be subjective with variable diagnostic accuracy. Consequently, there is a pressing need for more objective, accurate, and integrated tools to predict RLNM pre-operatively, which could help avoid unnecessary invasive procedures in low-risk patients while ensuring aggressive management for those at high risk.

Despite the recognized importance of factors like Breslow thickness and imaging characteristics, research specifically focusing on their combined predictive value for RLNM in the distinct context of AM remains limited. Most prognostic models and guidelines are derived from studies of cutaneous melanoma in general, which may not fully capture the unique biological behavior and clinical presentation of AM [9]. Furthermore, while individual studies have explored the role of PET-CT standardized uptake value (SUVmax) or specific CEU features, a comprehensive model that synergistically integrates multi-dimensional data—spanning clinical demographics, detailed pathological features, and multi-parametric imaging parameters—specifically for AM patients is lacking.

To address this gap, advanced analytical methodologies such as machine learning offer a powerful solution. ML algorithms, particularly ensemble methods like Gradient Boosting, are adept at identifying complex, non-linear interactions within high-dimensional datasets that may elude traditional statistical approaches [10]. These techniques have shown promise in various oncological predictive tasks but have not been extensively applied to the specific challenge of RLNM prediction in AM [11]. Therefore, the primary objective of this study was to develop an interpretable machine learning-based diagnostic model to pre-operatively predict RLNM in patients with AM. We aim to achieve this by conducting a retrospective analysis of a comprehensive set of variables and building multiple machine learning models to identify top performers. The ultimate goal is to provide clinicians with a reliable, non-invasive risk stratification tool, thereby facilitating more personalized and effective management strategies for this challenging disease.

Materials and Methods

Patients

Clinical, pathological, and imaging data of 189 AM patients diagnosed between February 2019 and March 2023 were retrospectively collected. Inclusion criteria comprised: (a) histologically confirmed acral melanoma with pathologically confirmed regional lymph node status; (b) age ≥ 18 years, < 80 years; and (c) complete clinical, pathological, and imaging data. Exclusion criteria comprised: (a) presence of organ failure or secondary malignancies; (b) combine other conditions that may cause lymph node enlargement; (c) unavailability of key clinical/pathological/imaging documentation. Patients were allocated to the training cohort ($n = 132$) or validation cohort ($n = 57$) via 7:3 randomization(Figure S1).

Clinical features included: gender, age, comorbidities (cardiovascular disease,diabetes mellitus, and hypertension), regional lymph node location(Axillary/Inguinal/Popliteal), primary lesion location(upper extremities/lower extremities), primary lesion diameter,time after local excision,local excision margin, palpable lymph node enlargement, local excision without biopsy, lactate dehydrogenase (LDH).

Pathological features included: Breslow thickness, Clark level, Ki-67, ulceration, vascular invasion, perineural invasion, microsatellite metastasis, lymphocytic infiltrate, and mutational status of *KRAS*, *BRAF*, and *KIT*.

Imaging features selection: according to Cha's study, a standardized uptake value (SUVmax) of 2.4 in lymph nodes was used as the cutoff value for determining a positive PET-CT result. CEU findings were identified to be positive if any of the following signs were present: balloon-like morphology of lymph nodes, peripheral perfusion, loss of central echoes, hump structure, loss of central perfusion, or echo-poor islands.CEU inhomogeneous enhancement were evaluated as presence or absence. Quantification parameters for lymph node diameter obtained from ultrasound examinations were also included as imaging features, including short-axis diameter (SD) and long-axis diameter (LD).

Feature selection

Feature selection was performed on the training dataset using the Boruta algorithm and LASSO regression, respectively; the features selected by these two methods were then combined to form the final set of variables.

Model establishment & validation

Seven ML models were developed within the training cohort based on selected features: Logistic Regression (LR), Random Forest (RF), Support Vector Machine (SVM), Light Gradient Boosting Machine (LightGBM), Extreme Gradient Boosting (XGBoost), Ada Boost Classifier (AdaBoost), and Gradient Boosting Classifier (GradientBoost). The optimal model was selected based on the ROC curve and AUC value. To further elucidate the machine learning-based radiomics models, we visualized the importance

of each radiomics feature using SHAP analysis. Validate the selected ML model in the validation cohort, evaluating model performance through ROC curves, calibration curves, and DCA curves.

Statistical analysis

All statistical analyses were performed with Python (version 3.6; <https://python.org/>) and R software (version 4.5.2; <https://cran.r-project.org>). Two-sided P values less than 0.05 were considered statistically significant. Categorical data were analyzed using the chi-square test. Continuous variables with normal distribution were described using the mean and standard deviation, and an independent samples t-test was used to compare differences between the two groups. Continuous variables with non-normal distributions were described using the median and interquartile range, and the Mann–Whitney U test was used to compare differences between the two groups. The predictive performance of different models was evaluated using receiver operating characteristic (ROC) curves and their areas under the curve (AUC), calibration curves, and decision curve analysis (DCA) curves. SHAP analysis was used for explaining the importance of each feature of the model, quantifying each input feature's contribution to the model's prediction results.

Result

Baseline characteristics

Among all enrolled patients, 89 cases (47%) exhibited RLNM, including 62 cases in the training cohort and 27 cases in the validation cohort. The median age was 61 years (interquartile range: 52–69 years). Female patients constituted a slightly higher proportion (100 patients, 53%). The majority of primary lesions were located in the lower extremities (163 patients, 78%). The primary distribution site for RLNs was the inguinal lymph nodes (80%). The mean diameter of the primary lesions was 21.1 ± 10.0 mm. The median Breslow thickness was 4 mm (interquartile range: 2.3, 6 mm). Ulceration of the primary lesion occurred in 108 patients (57%). Clark level IV was the most common (116 cases, 61%). Ki-67 > 0.2 was observed in 131 patients (70%). Vascular invasion was observed in 27% of enrolled patients. Nerve invasion was only observed in 7% of enrolled patients. Lymphocytic infiltration was observed in 135 patients, with 14 patients classified as active (indicating an active immune response) and 121 patients as inactive. Microsatellite lesions were observed in 35 patients (19%). There were 59 patients with positive PET-CT findings, and 65 patients with positive contrast-enhanced ultrasound (CEU) findings. The mean short axis diameter of lymph nodes was 9.33 ± 6.00 mm, and the mean long axis diameter was 21.48 ± 9.05 mm. Inhomogeneous enhancement of LN was observed in 90 patients (48%). Elevated LDH was identified in 27 patients (14%). Palpable lymph node enlargement was observed in 30 patients (16%) (Table 1).

Table 1
Clinicopathological variables and imaging characteristics of patients enrolled

Variables	Total (n = 189)	Training cohort (n = 132)	Validation cohort (n = 57)	p
RLN metastasis, n (%)				1
NO	100	70	30	
YES	89	62	27	
Gender, n (%)				0.598
Male	89	60	29	
Female	100	72	28	
Age, Median (Q1,Q3)	61 (52, 69)	61.5 (52.75, 68.25)	61 (51, 69)	0.781
Primary site, n (%)				0.762
Upper extremities	26	17	9	
Lower extremities	163	115	48	
RLN location, n (%)				1
Axillary	26	18	8	
Inguinal	156	109	47	
Popliteal	7	5	2	
Palpable LN enlargement, n (%)				0.529
NO	159	113	46	
YES	30	19	11	
Cardiopathy, n (%)				0.639
NO	184	129	55	
YES	5	3	2	
Diabetes, n (%)				0.728
NO	172	119	53	
YES	17	13	4	
Hypertension, n (%)				0.472
<i>RLN</i> regional lymph node, <i>LN</i> lymph node, <i>LE</i> local excision, <i>LDH</i> lactate dehydrogenase, <i>CEU</i> contrast-enhanced ultrasound, <i>PET-CT</i> positive positron emission tomography				

Variables	Total (n = 189)	Trainng cohort (n = 132)	Validation cohort (n = 57)	p
NO	141	96	45	
YES	48	36	12	
RLN_Number, Mean ± SD	4.94 ± 5.16	4.36 ± 4.17	6.28 ± 6.81	0.052
Primary lesion diameter, Mean ± SD	21.12 ± 9.99	20.48 ± 9.54	22.61 ± 10.9	0.203
LE without biopsy, n (%)				0.023
NO	104	65	39	
YES	85	67	18	
LE margin, n (%)				0.059
Negative	164	110	54	
Positive	25	22	3	
Time after LE, Mean ± SD	25.01 ± 51.69	25.5 ± 54.79	23.88 ± 44.14	0.83
LDH, n (%)				1
Normal	162	113	49	
Elevated	27	19	8	
Positive PET-CT finding, n (%)				0.92
NO	130	90	40	
YES	59	42	17	
LN SD, Mean ± SD	9.33 ± 6	9.38 ± 5.98	9.23 ± 6.09	0.875
LN LD, Mean ± SD	21.48 ± 9.05	21.72 ± 9.27	20.91 ± 8.56	0.563
CEU Positive, n (%)				0.194
NO	124	91	33	
YES	65	41	24	
Inhomogeneous enhancement of LN, n (%)				0.393
NO	86	64	22	
RLN regional lymph node, LN lymph node, LE local excision, LDH lactate dehydrogenase, CEU contrast-enhanced ultrasound, PET-CT positive positron emission tomography				

Variables	Total (n = 189)	Trainng cohort (n = 132)	Validation cohort (n = 57)	p
YES	90	60	30	
Unknown	13	8	5	
Breslow thickness, Median (Q1,Q3)	4 (2.3, 6)	3.65 (2, 6)	5 (3, 7)	0.004
Ulceration, n (%)				0.036
NO	80	63	17	
YES	108	68	40	
Unknown	1	1	0	
Clark level, n (%)				0.205
I	3	3	0	
II	16	13	3	
III	16	11	5	
IV	116	84	32	
V	38	21	17	
Ki67 raito, n (%)				0.494
≤ 0.2	58	43	15	
>0.2	131	89	42	
Vascular invasion, n (%)				0.753
NO	138	95	43	
YES	51	37	14	
Perineural invasion, n (%)				0.35
NO	176	121	55	
YES	13	11	2	
Microsatellite metastasis, n (%)				0.213
NO	154	104	50	
YES	35	28	7	
RLN regional lymph node, LN lymph node, LE local excision, LDH lactate dehydrogenase, CEU contrast-enhanced ultrasound, PET-CT positive positron emission tomography				

Variables	Total (n = 189)	Training cohort (n = 132)	Validation cohort (n = 57)	<i>p</i>
Lymphocytic infiltrate, n (%)				0.232
NO	54	34	20	
Active	14	12	2	
Inactive	121	86	35	
BRAF mutation, n (%)				0.473
NO	63	41	22	
YES	19	15	4	
Unknown	107	76	31	
RAS mutation, n (%)				0.333
NO	47	29	18	
YES	22	15	7	
Unknown	120	88	32	
KIT mutation, n (%)				< 0.001
NO	36	30	6	
YES	11	2	9	
Unknown	142	100	42	
<i>RLN</i> regional lymph node, <i>LN</i> lymph node, <i>LE</i> local excision, <i>LDH</i> lactate dehydrogenase, <i>CEU</i> contrast-enhanced ultrasound, <i>PET-CT</i> positive positron emission tomography				

Feature selection

Features were selected using Boruta analysis and LASSO regression, independently. After taking the intersection of the variables identified by the two screening methods, five variables were ultimately selected: Breslow thickness, short-axis diameter of lymph nodes, positive CEU finding, vascular invasion, and positive PET-CT finding (Fig. 1).

Establishment of machine learning model

Using the five selected variables, seven machine learning models were built. The top three models ranked by AUC in the training cohort were: GradientBoost (AUC 0.95, 95% CI 0.91–0.98), Random Forest

(AUC 0.93, 95% CI 0.88–0.97), and XGBoost (AUC 0.92, 95% CI 0.87–0.96). In the validation cohort, the top three models by AUC were GradientBoost (AUC 0.87, 95% CI 0.77–0.96), Random Forest (AUC 0.87, 95% CI 0.77–0.96), and XGBoost (AUC 0.85 95% CI 0.74–0.95). Therefore, the GradientBoost model was identified as the optimal model, as it achieved the highest AUC values in both cohorts (Table 2, Fig. 2).

Interpretation of feature importance in the GradientBoost model using Shapley analysis. Breslow thickness, short-axis diameter of the lymph node, and positive CEU finding are the three features that contribute most significantly to the model's predictive value (Fig. 3A). The beeswarm plot shows the distribution of Shap values across all samples. The vertical axis represents feature names, while the horizontal axis shows SHAP values. Point colors indicate feature value magnitude (blue for low values, red for high values). Point distribution reflects the direction and strength of a feature's influence on model output. Points clustered on the right indicate a positive impact on prediction, while those clustered on the left indicate a negative impact. The larger the absolute value of a feature's SHAP, the greater its implied influence on the prediction model (Fig. 3B). The decision plot is used to track the prediction paths of multiple samples; each line represents the decision path of a single sample from ϕ_0 to the final prediction, and turning points indicate the direction (left/right) in which features influence the prediction (Fig. 3C). The waterfall plot (Fig. 3D) and force plot (Fig. 3E) illustrate the prediction results for individual samples, visually presenting the cumulative contribution paths of each feature from the baseline value (the model's average prediction) to the final prediction. Red bars indicate positive contributions, blue bars indicate negative contributions, and arrow length reflects the magnitude of the contribution. The sum of Shapley values for this sample is -3.06, which is lower than the baseline value of -0.15, indicating that the model predicts a low probability of RLNM. The overall influence plot is a summary of the SHAP values for all samples, the x-axis represents individual samples, and the y-axis represents the sum of the SHAP values for each feature (Fig. 3F).

Table 2
Predictive performances of different ML models

Cohort	Model Name	Accuracy	AUC	AUC 95% CI Lower Limit	AUC 95% CI Upper Limit	Sensitivity	Specificity
Training Cohort	Logistic Regression	0.7879	0.8631	0.7955	0.9245	0.6774	0.9286
	Random Forest	0.8485	0.9295	0.8829	0.9658	0.8548	0.8714
	SVM	0.803	0.8894	0.8247	0.9441	0.8387	0.8143
	LightGBM	0.8182	0.9084	0.8511	0.9549	0.8226	0.8571
	XGBoost	0.8561	0.9218	0.8712	0.964	0.8387	0.8857
	AdaBoost	0.8258	0.9109	0.8614	0.9506	0.6935	0.9429
	GradientBoost	0.8485	0.95	0.9122	0.9785	0.7742	0.9714
Validation Cohort	Logistic Regression	0.7018	0.771	0.63	0.8889	0.6296	0.9
	Random Forest	0.7895	0.871	0.7654	0.9585	0.9259	0.7
	SVM	0.7193	0.8228	0.7058	0.9225	0.7037	0.8333
	LightGBM	0.7368	0.8605	0.7574	0.9458	0.8148	0.8
	XGBoost	0.807	0.8537	0.741	0.9463	0.8889	0.7667
	AdaBoost	0.7895	0.8463	0.7346	0.9399	0.7407	0.8667
	GradientBoost	0.7895	0.8735	0.7653	0.9594	0.7407	0.9333

Evaluation of Model Performance

The calibration curve indicates that the model demonstrates well-fitting performance in both the training and validation sets. DCA analysis shows that the model exhibits a significant increase in net benefit(Fig. 4).

Discussion

This study developed and validated a machine learning-based diagnostic model specifically for predicting regional lymph node metastasis in acral melanoma, a rare and aggressive subtype with distinct clinicopathological and genetic features [1]. While established risk factors like Breslow thickness and ulceration are recognized prognostic markers in cutaneous melanoma, their specific predictive value for RLNM in the unique context of AM, particularly when integrated with multi-parametric imaging

features, has been underexplored[12]. Prior studies that often examined variables in isolation or within heterogeneous melanoma populations, our model synthesizes a concise panel of five readily available predictors—Breslow thickness, lymph node short-axis diameter, positive contrast-enhanced ultrasound (CEU) findings, vascular invasion, and positive PET-CT findings—leveraging their combined power through ML. This integrative, data-driven approach represents a novel strategy for pre-operative risk stratification in AM. The selection of both structural (lymph node size) and functional (CEU, PET-CT) imaging parameters underscores the complementary value of multi-modal assessment, a concept less emphasized in previous AM-specific predictive studies. Furthermore, while the prognostic importance of Breslow thickness in AM is acknowledged [13], our SHAP analysis quantitatively confirms it as the foremost contributor to the model's predictive output, alongside novel imaging-derived features like CEU positivity, providing a new, interpretable hierarchy of risk factors tailored for this disease.

Our findings both align with and extend the current understanding of AM biology and metastasis. The high RLNM rate (47%) and the prevalence of poor prognostic factors (e.g., median Breslow thickness of 4 mm, 57% ulceration) in our cohort are consistent with the aggressive nature of AM reported in the literature, which often presents at an advanced stage [3][5]. The identification of vascular invasion as a key predictor aligns with its biological role in facilitating hematogenous and lymphatic spread. However, our model's selection of specific imaging features over some traditional clinical factors (e.g., Clark level was not among the top five predictors) offers new insights. This suggests that in the specific task of predicting nodal involvement in AM, quantitative and functional imaging characteristics may capture metastatic potential more directly than some histological grading systems. Compared to a study by Mejbelt et al., which focused on anatomic site (subungual vs. non-subungual) as a prognostic factor [14], our model shifts the paradigm towards a multi-parameter, continuous risk assessment. Importantly, the superior performance of the GradientBoost model (AUC 0.87 in validation) over traditional logistic regression highlights the advantage of ML in modeling complex, non-linear interactions between these multimodal variables, a methodological advancement for AM research. This contrasts with simpler, single-modality assessments and demonstrates how leveraging existing clinical data with sophisticated analytics can yield more accurate tools.

The model provides a non-invasive, pre-operative tool to quantify the risk of RLNM, addressing a critical need in AM management where physical examination is notoriously insensitive, as evidenced by only 16% of our RLNM-positive patients presenting with palpable lymphadenopathy. This can directly inform surgical planning. For patients predicted to be at high risk, clinicians may be more inclined to perform or extend lymph node dissection, potentially improving regional disease control. Conversely, for those at low risk, the model could help reduce the morbidity associated with unnecessary lymphadenectomies, aligning with the goals of personalized surgery. The Decision Curve Analysis confirms the model's clinical net benefit across a range of probability thresholds, supporting its potential utility in real-world decision-making. Second, by highlighting the paramount importance of Breslow thickness and specific imaging signs, the model reinforces the need for precise pathological measurement and the adoption of standardized imaging protocols, such as CEU, in the workup of AM patients [15]. Finally, this study lays a foundation for future research. The model's framework can be adapted to incorporate emerging

molecular biomarkers (e.g., TERT promoter mutations, which are prevalent in AM [16][17]), potentially further enhancing its predictive accuracy. Successful external validation and prospective implementation could establish this ML model as a valuable decision-support tool, ultimately aiming to improve the staging accuracy, tailor treatments, and hopefully enhance the outcomes for patients with this challenging melanoma subtype.

This study has several limitations. First, the retrospective, single-center design inherently introduces selection bias. Second, while the sample size of 189 patients is moderate for machine learning applications, the relatively small validation cohort (n = 57) following a 7:3 split could impact the stability of performance metrics.

Conclusion

This study successfully developed and validated an interpretable GradientBoost machine learning model that integrates multimodal predictors to accurately predict regional lymph node metastasis in acral melanoma. The model potentially guiding personalized surgical planning and reducing unnecessary invasive procedures.

Abbreviations

AM Acral melanoma, **RLNM** regional lymph node metastasis, **ML** machine learning, **LASSO** least absolute shrinkage and selection operator, **AUC** area under the curve, **SHAP** Shapley Additive Explanations, **DCA** decision curve analysis, **CEU** contrast-enhanced ultrasound, **PET-CT** Positron Emission Tomography/Computed Tomography, **SD** short-axis diameter, **LD** long-axis diameter, **LE** local excision, **LDH** lactate dehydrogenase.

Declarations

Ethics approval and consent to participate:

This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the institutional ethics committee of Fujian cancer hospital.

Consent for publication:

Since this study is a retrospective analysis without any intervention, the requirement for individual informed consent has been waived.

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

YZ analyzed and interpreted the patient data, was a major contributor in writing the manuscript. DL reviewed PET-CT images and calculate the corresponding parameters. XD review contrast-enhanced ultrasound images and measure lymph node dimensions. JL reviewed the literature and contributing to the writing of the manuscript. XW designed the research and oversee project review and supervision. All authors read and approved the final manuscript.

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Figures

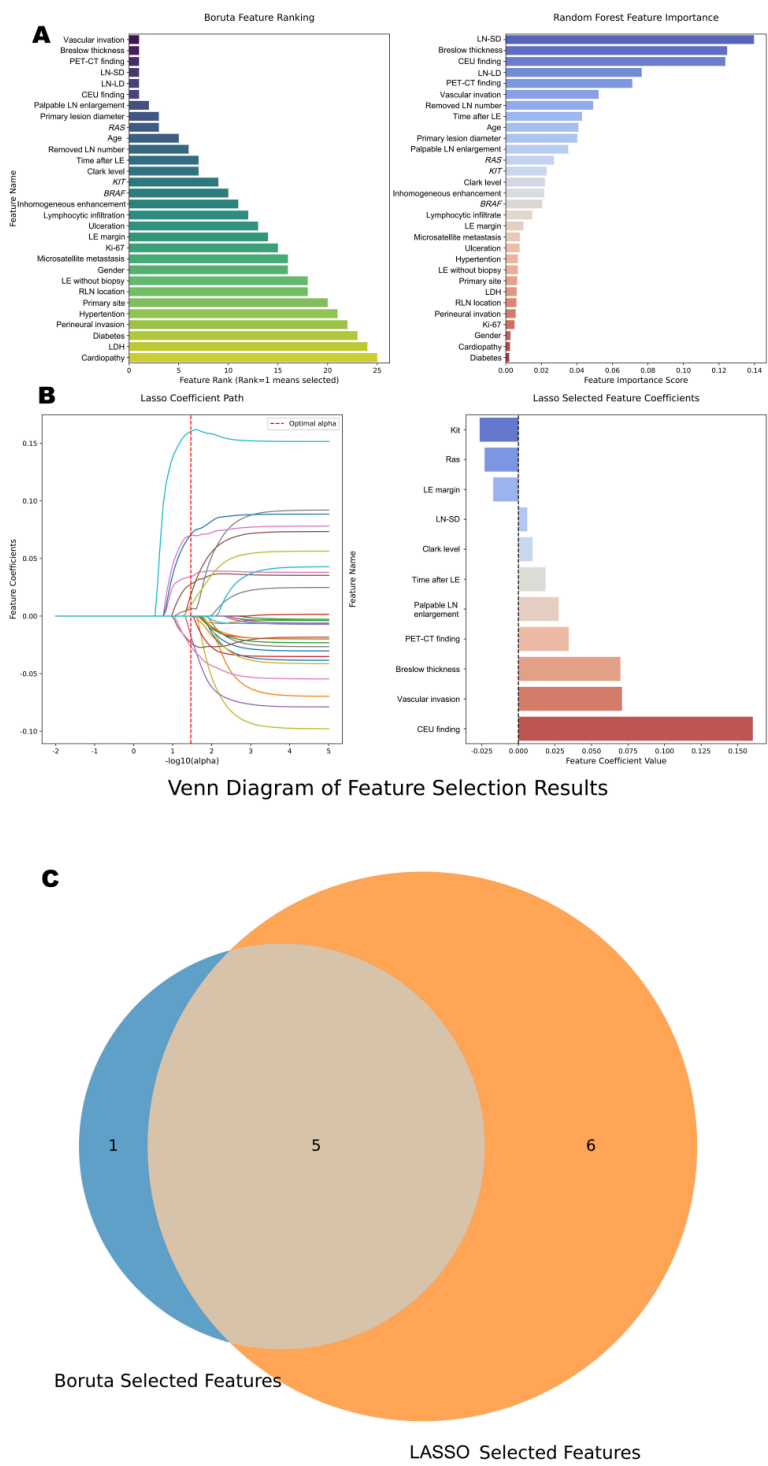


Figure 1

Six features were selected using the Boruta algorithm, and 11 features were selected using LASSO regression. The features intersecting between the two methods are: Breslow thickness, short-axis diameter of lymph nodes, positive CEU finding, vascular invasion, and positive PET-CT finding.

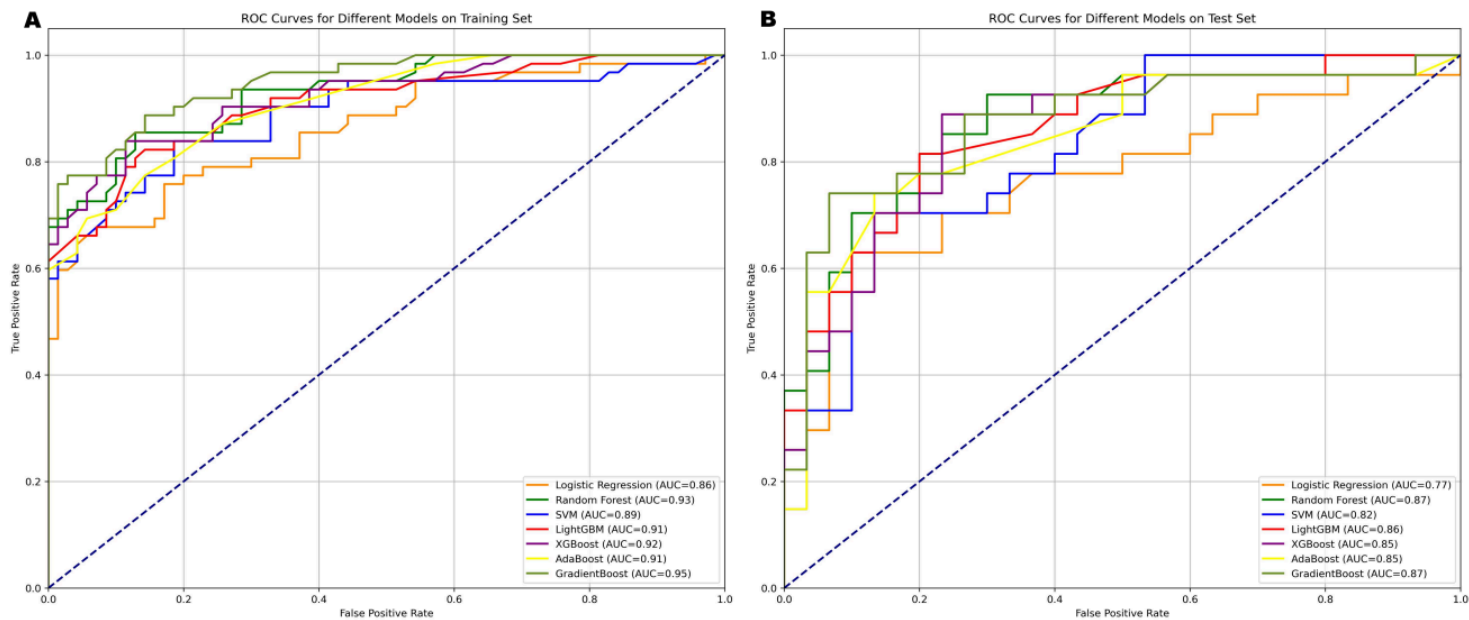


Figure 2

Seven machine learning models were developed based on selected features. GradientBoost model was identified as the optimal model.

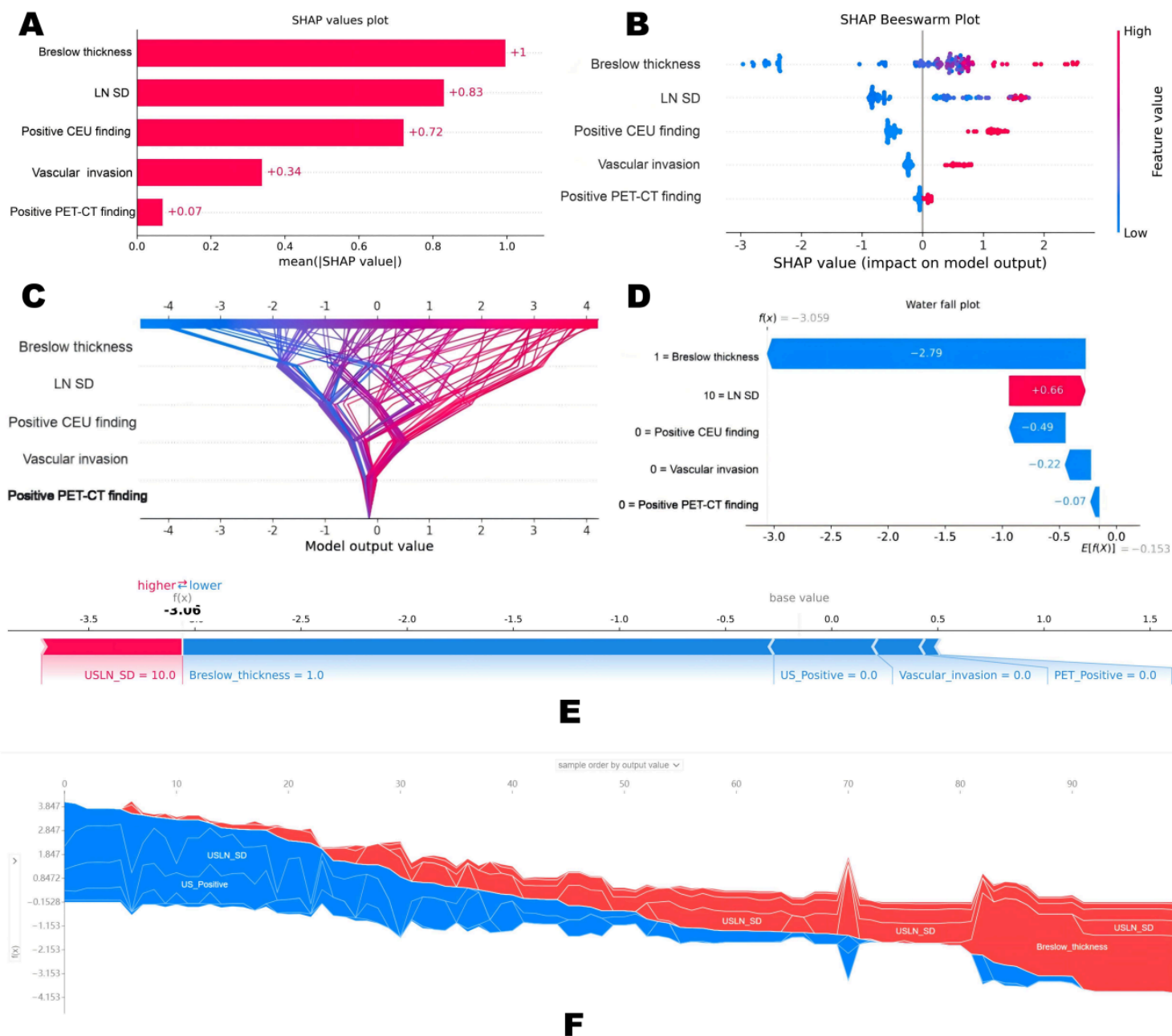


Figure 3

A Features sorted by average contribution to the model, **B** Beeswarm Plot: Visualizes the distribution of SHAP values across all samples, **C** The decision plot is used to track the prediction paths of multiple samples, **D** Waterfall Plot and **E** Force Plot: the prediction results of individual samples, **F** The overall influence plot is a summary of the SHAP values for multiple samples.

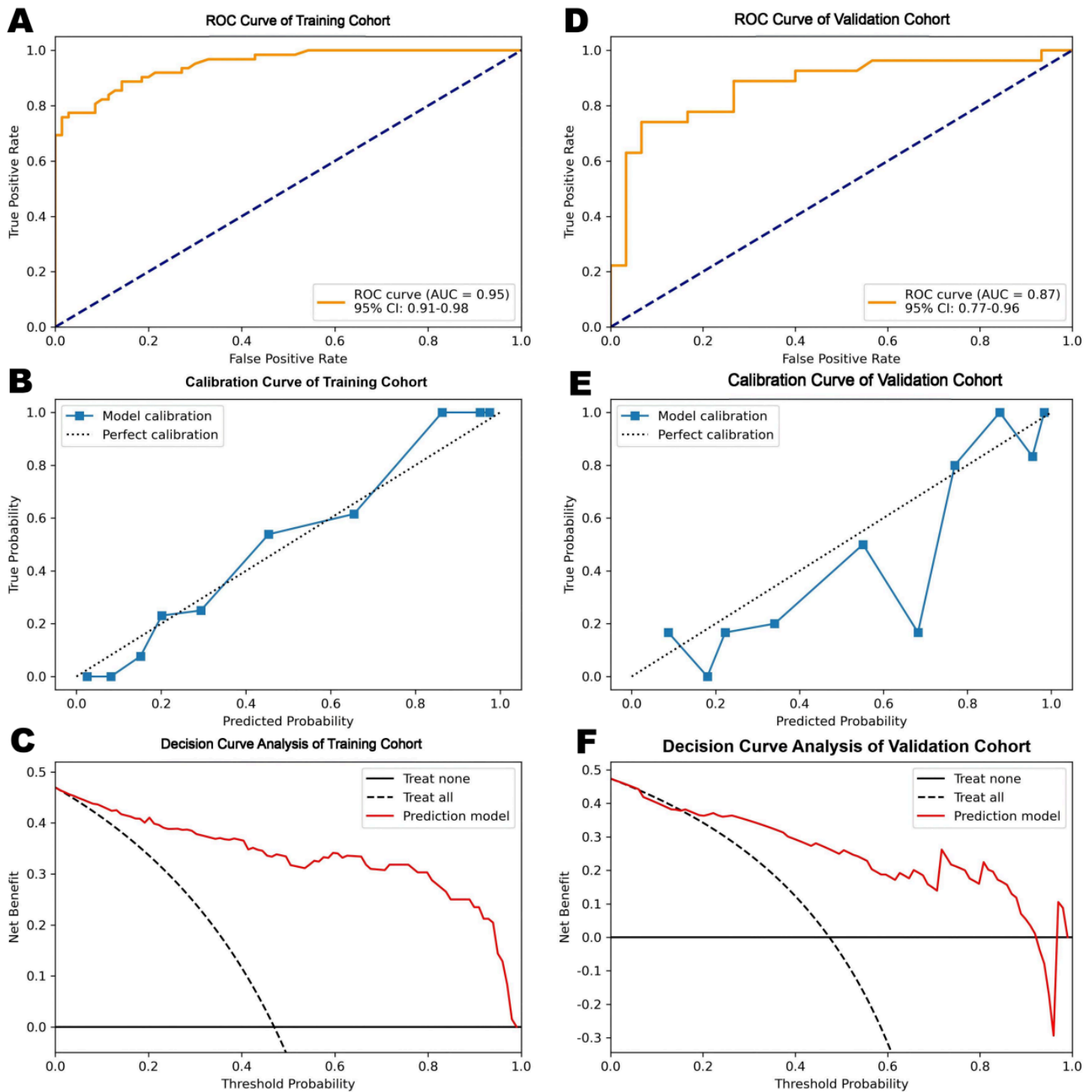


Figure 4

Predictive performance of the model in the training and validation cohorts. **A** ROC of training cohort, **B** Calibration of training cohort, **C** DCA of training cohort. **D** ROC of validation cohort, **E** Calibration of validation cohort, **F** DCA of validation cohort.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [FigureS1.png](#)