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Machine Learning–based Identification of Prognostic Factors for Surgical Management in Patients With NOS Sarcoma

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Background: Non-otherwise specified (NOS) sarcomas, a diverse and diagnostically challenging group of mesenchymal malignancies, pose significant clinical dilemmas due to their variable clinical trajectories and therapeutic responses. This study utilizes advanced machine learning techniques, namely classification and regression trees and Shapley additive explanation (SHAP) values, to identify predictors of survival, metastatic progression, and recurrence within a well-defined patient cohort, aiming to improve risk stratification and individualized care strategies.

Methods: Through the application of classification and regression trees and SHAP values to a cohort of 122 patients with NOS sarcoma, we identified critical factors impacting disease outcomes.

Results: The study findings revealed that age and tumor diameter significantly influenced the development of metastasis, whereas body mass index and tumor grading were key predictors for relapse. Additionally, tumor size, location, and age were identified as influential factors for overall survival in patients with NOS sarcoma. These results have direct clinical relevance and can aid in risk stratification and surgical planning in this challenging patient population.

Conclusions: Considering the comparatively small cohort with which the machine learning algorithm was trained, this study underscores the importance of considering age, tumor size, location, body mass index, and tumor grading in the management of NOS sarcomas, shedding light on factors that may impact clinical outcomes and guide personalized treatment strategies. *(Plast Reconstr Surg Glob Open 2025;13:e6653; doi: 10.1097/GOX.0000000000006653; Published online 2 April 2025.)*

INTRODUCTION

Non-otherwise specified (NOS) sarcomas, a diverse group of mesenchymal malignancies with elusive histological characteristics, present significant clinical challenges due to their variable clinical course and response to treatment.[1] The complexity of NOS sarcomas necessitates innovative approaches to stratify patient outcomes and enhance therapeutic decision-making. This study aimed to address this need by leveraging advanced machine learning (ML) techniques, namely classification and regression trees (CARTs) and Shapley additive explanation (SHAP) values, to identify robust predictors of survival, metastatic progression, and recurrence within a well-defined patient cohort.

NOS sarcomas, as a diagnostic category, encompass a multitude of subtypes and exhibit substantial heterogeneity in clinical behavior. The heterogeneity of NOS sarcomas can be attributed to various factors, including genetic alterations, histological differences, and the presence of different cellular components. This makes it extremely challenging to make accurate predictions about the disease course for individual patients. Conventional prognostic models often rely on general clinical parameters, which may not be sufficient to consider the individual variances

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among patients. These models often struggle to provide accurate individualized risk assessments for patients, given the wide variation in disease progression.[2,3] In this context, ML models offer a promising avenue for discriminating between distinct patient outcomes and optimizing personalized care strategies.[4] By considering a multitude of factors, these models can make more precise predictions for individual patients. This can aid in developing personalized treatment strategies tailored to each patient's specific needs and risks.

ML models can also assist in identifying the most appropriate treatment options for each patient.[5] By analyzing data from thousands of patients, they can detect trends and patterns that support healthcare professionals in decision-making. This can help avoid unnecessary treatments and maximize the effectiveness of therapy.[6] So far, there is no ML-based model to identify prognostic factors for surgical management of NOS sarcomas. These models can therefore be of particular benefit to plastic surgeons, who not only perform the actual surgery but also work with other specialties to determine the course of treatment.

Overall, ML models offer a promising way to address the challenges associated with the heterogeneity of NOS sarcomas and improve the clinical care of patients. They enable more accurate risk assessment and personalized treatment approaches that can ultimately enhance patients' quality of life and survival.

The primary objective of this investigation is to develop initial predictive models capable of discerning patient subgroups within the NOS sarcoma population, effectively identifying those at higher risk of mortality, metastasis, or recurrence, and how we can cope with an operational intervention. To achieve this, we use CARTs, a powerful decision tree-based ML algorithm known for its interpretability and ability to discern complex data relationships. Additionally, we leverage SHAP values, an advanced technique that provides insights into feature importance, thereby shedding light on the influence of various clinical and biological variables on the predicted outcomes.

Takeaways

Question: Can machine learning models identify key prognostic factors for predicting survival, metastasis, and relapse in patients with NOS sarcomas, thus enabling improved surgical management?

Findings: In this study, we analyzed a cohort of 122 patients with NOS sarcoma using machine learning techniques to identify that age, tumor size, location, body mass index, and tumor grading are the most significant prognostic factors for predicting metastasis, relapse, and overall survival.

Meaning: Machine learning algorithms prove effective in identifying key prognostic factors, provided that there are sufficient and high-quality data. As these algorithms have the potential to enhance patient outcomes, ensuring consistent and robust datasets is critical for generating reliable results.

MATERIALS AND METHODS

Patient Acquisition

The present study was a retrospective, single-center cohort study that was conducted in compliance with the Declaration of Helsinki and was approved by the responsible ethics committee. Patients with a history of an NOS sarcoma between January 2000 and July 2019 were included from a single sarcoma center within a university hospital in Germany. All of them were histologically declared as NOS sarcoma according to current guidelines based on histological, morphological, and immunochemical patterns.[7–9] The patients were monitored in accordance with established guidelines during the initial 2 years, with quarterly assessments, followed by biannual evaluations for the subsequent three years, and subsequently, annual follow-ups.[10–12] This included a contrast-enhanced magnetic resonance imaging of the region of interest and x-rays or computed tomography scans of the chest. The relevant data were extracted from the hospital information system and collected in an Excel database. This report follows the "Strengthening the Reporting of Observational Studies in Epidemiology" guidelines for cohort studies.

Profiling of the NOS Sarcoma

The NOS sarcomas were diagnosed based upon the current WHO guidelines.[13] The diagnosis was based on the histological morphology within the absence of a specific line of differentiation after careful histologic examination. Markers and patterns for the differential diagnosis are shown in Table 1.[7–9]

ML Methods

Classification and Regression Tree

CART analysis was used for binary recursive partitioning in Python (version: 3.11.5). Pandas (version: 2.1) and NumPy (version: 1.25.0) were implemented for data handling. To evaluate feature importance correlation, attribute evaluation was utilized. For the decision tree classifier (version: 1.2.2, scikit-learn) a maximal depth of 2 was chosen with a train size of 0.9 and test size of 0.1.

Table 1. Patterns of Differential Diagnosis for NOS Sarcoma

Differential Diagnosis	Pattern
Dedifferentiated carcinoma	Expression of p63, p40, Keratins, MNF116
Dedifferentiated liposarcoma	MDM2, CDK4
Malignant melanoma	S100
Pleomorphic rhabdyomyosarcoma	Desmin, actin, myogenin
Myxofibrosarcoma	Multinodular growth pattern, myxoid stroma
Pleomorphic leiomyosarcoma	Desmin
Synovial sarcoma	c-KIT, bcl2
Kaposi sarcoma	CD34

1. Splitting: Begin with a dataset D containing observations and features. A feature j and a threshold s is selected to split the data into subsets D_{left} and D_{right}.
2. Criterion for splitting: j and s based on a criterion like entropy are chosen.
3. Recursion: The splitting for subsets D_{left} and D_{right} is repeated until a depth limit is reached or a termination condition is met.
4. Leaf node formation: Leaf nodes with predicted values are created when termination conditions are satisfied.

This process optimizes the split and criteria selection by minimizing the chosen criterion. Implementation-wise, we iterate through possible splits and thresholds for each feature.

Shapley Additive Explanation

SHAP values were computed to understand the impact of individual features on the output of an ML model. This analysis was performed using Python. The SHAP values were calculated with the SHAP library (version 0.42.1), and specifically, the TreeExplainer class was utilized to explain the predictions of the decision tree classifier. We used the method for medical research as described before.[14,15]

1. Baseline value: The model's prediction for a baseline or reference instance is calculated. This is denoted as f(baseline).
2. Subset combinations: For each feature x_i, the difference in predictions when x_i is added to all possible subsets of features excluding x_i is calculated.
3. Weighted summation: The SHAP values formula to get the contribution of each feature, considering all possible subset combinations, is applied.

RESULTS

Patient Data

A total of 122 patients who underwent a histological verified NOS-sarcoma resection from a single center were included in this study between January 2000 and July 2019. Seventy-five (61%) patients were men. In the clinical follow-up period (mean: 6.2 y; SD 4.8), 41 patients died (34%), and 32 patients had a recurrent disease (26%), whereas 31 patients had experienced metastasis (25%). The mean age of the patient at first operation was 61.8 years (SD 14.3). The mean body mass index (BMI) was 27.1 kg/cm² (SD 5.3). All the included datasets were complete.

The following attributes were recorded and included in the analysis: primary operation, gender, survival, tumor size, tumor location regarding the fascia, resection status, (neo-)adjuvant radiotherapy, (neo-)adjuvant chemotherapy, relapse, metastasis, secondary resetion, localiztation, age, number of relapses, tumor sizes (breadth, width, diameter, volume, weight), weight of the patient, BMI, American Society of Anesthesiologists classification, arterial hypertension, diabetes, history of smoking, grading of the tumor, and surgical complications. The basic data of the cohort are shown in Table 2.

Patient Age and Tumor Diameter Are Most Predictive for the Development of Metastasis

CART and SHAP values showed a correlation between age and tumor width for the development of metastasis within the follow-up period. Younger age was a negative predictive factor as well as tumor width (Fig. 1). It was observed that all patients younger than 34.5 years included in our training data developed metastasis within the follow-up period (3 [100%] of 3 versus 2 [25%] of 105). A size smaller than 3.25 cm was linked to a significantly lower occurrence of metastasis (1 [4%] of 28 versus 25 [32%] of 77).

Patient BMI and Grading of the Tumor Are Crucial for the Development of a Relapse

Next, factors for the development of a relapse were identified. The CART identified the BMI as the most important predictive feature. None of the patients with a BMI of 21.28 kg/m² or less developed a relapse in the training data (90% of the data classified as training data). None of the patients below a BMI of 21.28 kg/m² developed a relapse (0 [0%] of 10 versus 30 [31%] of 98). A slight increase of the BMI threshold to 21.875 kg/m² changed this observation. Between a BMI of 21.28 and 21.875 kg/m², all patients (3 [100%] of 3) developed a relapse within the follow-up, versus 27 (28%) of 95. However, SHAP values showed a higher importance of the tumors grading over the patients BMI (Fig. 2).

Tumor Diameter, Depth, and Localization as Key Predictors of Overall Survival

The overall survival after NOS sarcoma disease in this cohort is influenced by tumor diameter, tumor depth, and localization at the extremities as shown in the CART. A diameter of 1.5 cm was crucial for the survival rate as displayed in the CART. In patients with smaller tumors (<1.5 cm), 3 (9%) of 32 died within the patients-specific follow-up period, whereas 33 (45%) of 73 died with a tumor size greater than 1.5 cm. The depth of the tumor was a predicting factor with a threshold at

Table 2. Characteristics of the Patient Cohort

Age at operation, y	61.8 (SD 14.3
Follow-up period, y	6.2 (SD 4.8)
BMI, kg/cm²	27.1 (SD 5.3)
Sex, n (%)	
Male	75 (61)
Female	47 (39)
Tumor grade, n (%)	
1	5 (4)
2	36 (30)
3	80 (66)
Location, n (%)	
Trunk	38 (31)
Extremity	84 (69)

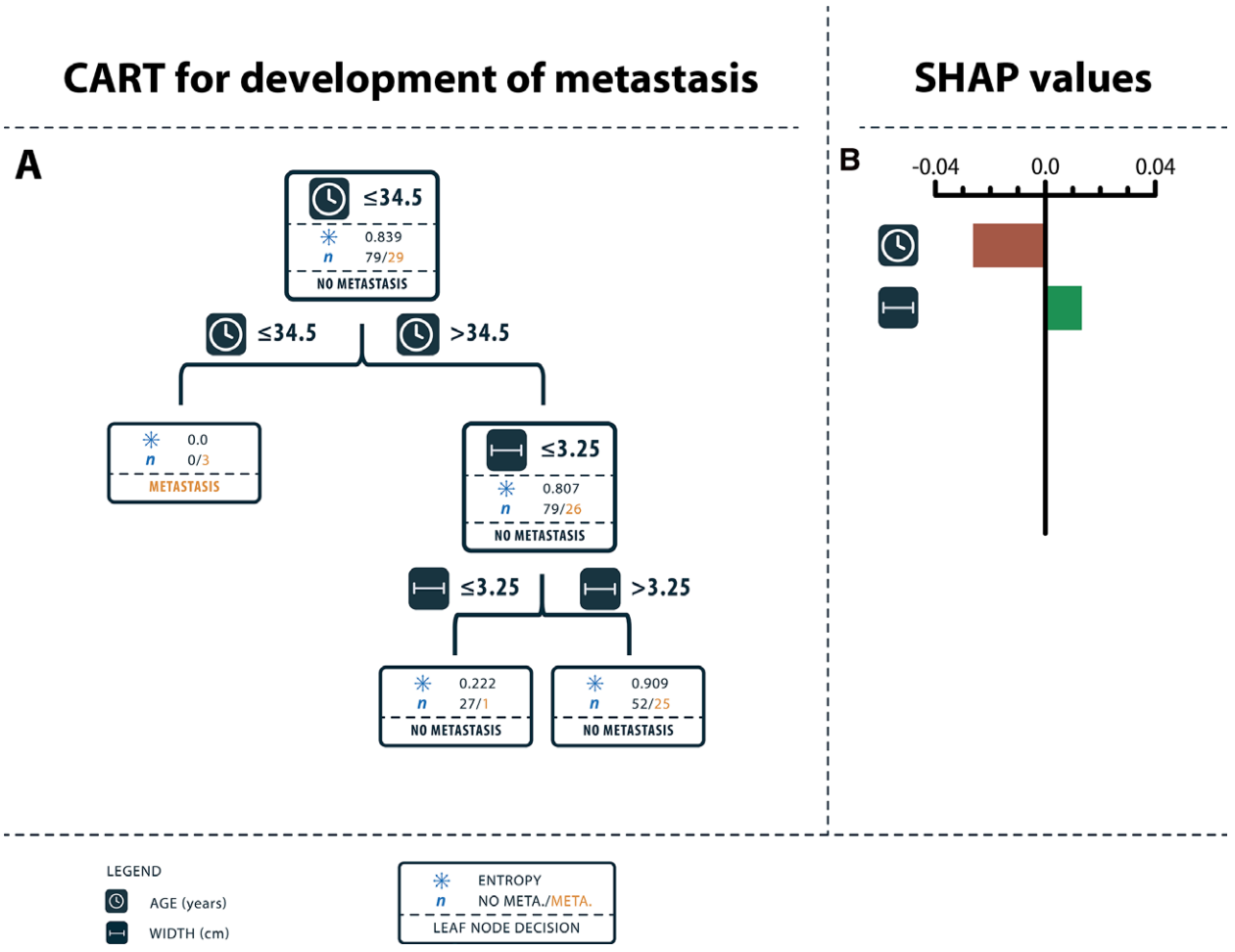

Fig. 1. Predictive factors for the development of metastasis. A, The decision tree (CART) lists the most important dichotomic features for the occurrence of metastasis in the cohort. The root node on the top presents the most important dichotomic feature. All patients 34.5 years or younger developed metastasis in this cohort. Training accuracy is 0.76, and testing accuracy is 0.77. B, The SHAP value quantifies the impact of a specific feature value on a model prediction by measuring the expected difference in prediction compared with a baseline value. Age and tumor width were ranked important.

1.1 cm. Below 1.1 cm, none died within the follow-up period (0 of 20 [0%]), whereas 3 of 32 patients with a depth over 1.1 died (9%). On the other hand, SHAP values identified a negative correlation of tumor width, BMI, and age with rate of survival (Fig. 3). Remarkably, there was an elevated mortality rate when the tumor appeared in the proximal extremity (0) compared with the distal (1, 2) or the trunk (3). Of 27 patients, 19 (70%) with a localization at the proximal extremity died versus 14 (29%) of 49 with localization at the trunk or distal extremity.

DISCUSSION

NOS is a diverse group of mesenchymal malignancies with challenging histological traits, presenting significant clinical difficulties due to their unpredictable behavior and varied response to treatment. Because of their heterogeneity, there are fewer approaches concerning the development of predictive AI-driven models. Currently, there is a lack of ML-based models to identify prognostic factors specifically for management of NOS sarcomas. Given the need for better predictive tools in this field, we generated an initial AI-driven model.

In this study, we have demonstrated the existence of certain predictive factors associated with the development of metastases, recurrences, and survival in NOS sarcomas. Specifically, BMI emerged as a clinically unfavorable factor for recurrence and overall survival. A cohort study in the United States comprising 397 patients who underwent sarcoma resection found no correlation between BMI and survival or recurrence.[16] However, the study by Alamanda et al[16] established a distinct threshold at a BMI of 30 kg/m^2. In the present investigation, this threshold is dynamically defined according to CART or SHAP values, making direct comparisons between the study results limited. Instead, BMI should be discussed in the context of increased wound complications, resulting in a higher recurrence rate, and the development of larger tumors due to obesity.[16–20] In summary, the literature suggests a higher likelihood of complications, and our study

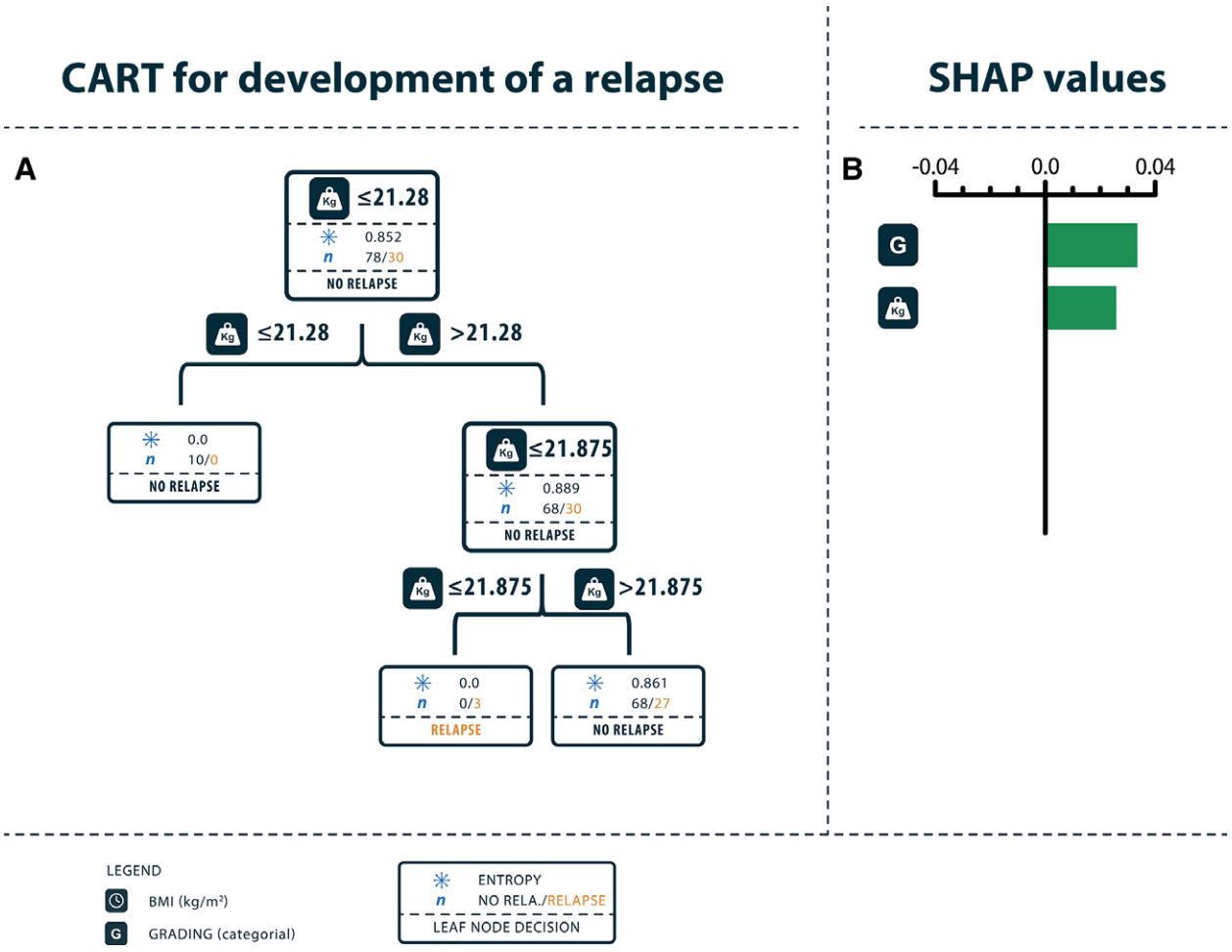

Fig. 2. Predictive factors for the development of a relapse. A, The decision tree (CART) lists the most important dichotomic features for the development of a relapse in the cohort. The root node on the top presents the most important dichotomic feature. No patient with a BMI less than or equal to 21. 28 kg/m^2 developed a relapse in this cohort. Training accuracy is 0.75, and testing accuracy is 0.77. B, The SHAP value quantifies the impact of a specific feature value on a model prediction by measuring the expected difference in prediction compared with a baseline value. Tumor grading and BMI were ranked important.

additionally supports the hypothesis of poorer oncological outcomes with higher BMI.

The disparities in the importance assigned to variables between CART and SHAP values in this study, as seen in overall survival and recurrence of sarcoma, can be attributed to their distinct methodologies for feature selection and interpretation. CARTs rely on recursive partitioning to create decision trees, where variables are selected in a way that maximizes the separation of the dataset based on impurity measures.[21,22] On the other hand, SHAP values are rooted in game theory and provide a holistic approach by evaluating the contribution of each feature to model predictions across all possible combinations.[14,23] This leads to differences in feature importance assessments, as CARTs prioritize variables that yield optimal splits within the dataset, whereas SHAP values offer a more comprehensive view of how each feature impacts predictions under various scenarios. Consequently, the divergent importance rankings are a result of these methodological disparities and the ways in which they capture variable interactions and contributions within the given context.

In the study, we were also able to demonstrate that size and location play a paramount role in sarcomas. When contextualizing this with respect to BMI, operability can be subsumed therein. Small, superficial tumors in individuals with a lower BMI exhibit enhanced operability. The surgical approach, involving an oncologically appropriate resection, coupled with the heightened potential for metastasis and the recurrence of a larger tumor, seems to provide explanations for the inferior oncological outcomes associated with large, challenging-to-access tumors.[24,25] Other studies suggest a lower survival of the patients with localization at the trunk and chest instead of the proximal extremity.[26] This can be due to the heterogeneity of the sarcoma in the other described and this finding of our study specific for NOS sarcoma. Extensive resection of sarcomas of various entities often necessitates plastic reconstruction. Different reconstructive approaches can be considered in such cases. However, the

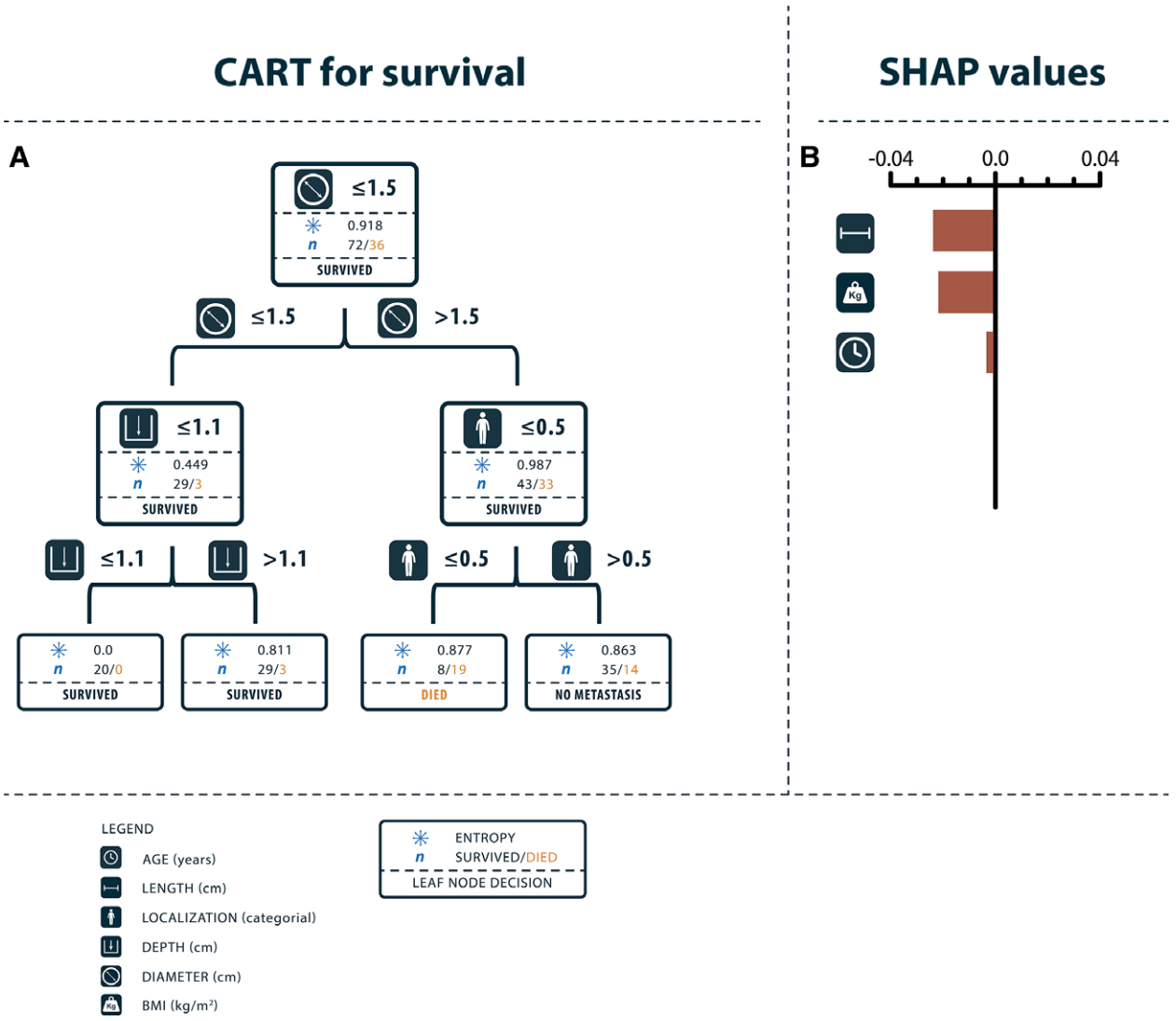

Fig. 3. Predictive factors for survival. A, The decision tree (CART) lists the most important dichotomic features for the development of a relapse in the cohort. The root node on the top presents the most important dichotomic feature. Tumor diameter, tumor depth, and localization at the proximal extremity (0) were the most predictive factors for overall survival. Training accuracy is 0.77, and testing accuracy is 0.54. B, The SHAP value quantifies the impact of a specific feature value on a model prediction by measuring the expected difference in prediction compared with a baseline value. Tumor width, patient age, and BMI were ranked important.

primary goal remains achieving an oncologically sound resection. Factors such as BMI, tumor size, and depth of invasion also have a significant impact on the available reconstruction options.[27]

Of particular interest in our study is the observation that both external R1 resection and subsequent R0 resection at our institution, when contrasted with the initial R0 scenario, failed to demonstrate any discernible disadvantage concerning overall survival, metastatic incidence, or recurrence rates. This observation underscores a notable aspect of our findings, emphasizing that the surgical interventions performed at our institution, in cases where margin status was less than optimal, did not yield a statistically significant improvement in the considered clinical parameters. This observation prompts further investigation into the underlying determinants of patient outcomes within the context of surgical resection, raising questions about the precise factors that govern these clinical endpoints. This finding is supported by other studies.[28–30]

Age played a role in both survival and the development of metastases. A younger age increased the likelihood of survival but also elevated the risk of metastasis. In this regard, we encounter a 2-fold limitation in the study. First, although a cohort of 122 patients with this rare tumor entity is relatively substantial, the statistical power is nevertheless constrained. Second, the calculation of survival is challenging to execute. The collective study population exhibited an average age of 61.8, indicating preexisting health conditions and a natural mortality rate. However, independent, and more significant factors, such as BMI and tumor attributes (size, depth, and location), could still be identified.

One notable limitation of this study pertains to the variability in the follow-up period among individual patients, which introduces a degree of uncertainty into our findings. As previously mentioned, the assessment of survival rates is inherently constrained by the high average age of the cohort; however, the substantial SD in the follow-up duration compounds this limitation.[31] The wide variation in the follow-up period further complicates the interpretation of our results, making it challenging to draw definitive conclusions regarding long-term outcomes in the survival prediction. Therefore, it is imperative to acknowledge that the heterogeneity in follow-up duration within the study cohort presents a noteworthy constraint that may impact the generalizability of our findings. Another limitation for the utilization of ML is the relatively small sample size in this rare tumor entity. This study should be considered preliminary, highlighting the need for further multicenter studies to expand the dataset.

It has been stated that the prognosis of soft tissue sarcoma has not improved over the last decades, indicating that current therapy has reached the limits of efficacy.[32] Significantly, due to the current state of clinical-therapeutic interventions in a state of relative stagnation, predictive models grounded in experiential data have the potential to enhance clinical outcomes. ML mechanisms are poised to improve predictive modeling in the field of medicine, particularly with regard to predictors in oncology.[33–35] These advanced techniques harness the power of large datasets and complex algorithms to identify intricate patterns and relationships among diverse clinical variables. As a result, they hold great promise for enhancing our ability to forecast disease outcomes, such as cancer progression, survival rates, and treatment responses. ML can uncover subtle associations that may have eluded traditional statistical approaches, thus offering clinicians and researchers valuable insights for personalized treatment strategies and early intervention.

However, it is essential to acknowledge the limitations of applying ML to medical research. One significant constraint, exemplified in the context of NOS sarcomas, is the cohort size.[36] These rare and heterogeneous tumors often result in relatively small patient populations available for study, which can restrict the generalizability of ML models. Additionally, the high variance within NOS sarcomas, stemming from their diverse genetic and histological characteristics, presents a challenge for building robust predictive models. Despite these limitations, ongoing advancements in ML methodologies and the accumulation of larger, more diverse datasets hold the potential to mitigate these issues, ultimately improving the accuracy and applicability of predictive tools in oncology. Building upon our initial model, we plan to incorporate data from additional sarcoma centers to enhance its accuracy, with the ultimate goal of establishing it as a routine clinical tool for treating NOS sarcoma patients.

CONCLUSIONS

In view of the fact that our model was trained with a relatively small dataset, we conclude that the application of advanced ML techniques, specifically CART and SHAP values, has elucidated critical prognostic factors for NOS sarcomas, offering valuable insights for risk stratification and personalized therapeutic approaches. Although challenges related to limited cohort size and the inherent heterogeneity of NOS sarcomas persist, ongoing advancements in ML methodologies hold promise for enhancing predictive accuracy and optimizing patient care within the field of oncology.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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