

Machine Learning to Predict the Occurrence of Distant Organ Involvement in Primary Lymphoma of Bone: A Population-Based Study Using the SEER Database

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Abstract: Primary lymphoma of bone (PLB) has a substantially poorer prognosis when distant organ involvement is present, making early risk identification clinically important. We used SEER data to develop and validate machine-learning models for predicting distant organ involvement in PLB and applied SHAP to interpret key predictors. A web-based calculator was built from the best-performing model. Among 690 analyzed patients, the Random Forest (RF) model showed the best performance, with an internal-validation accuracy of 0.852 and AUC of 0.907. This RF-based model may support individualized risk assessment and clinical decision-making in PLB.

Keywords: primary lymphoma of bone, metastasis, SEER, machine learning, prediction model

1. Introduction

Primary lymphoma of bone (PLB) is a rare malignancy, accounting for approximately 3-7% of primary bone tumors and 5% of extranodal lymphomas, and most often involves the axial skeleton and long bones[1-3]. Five-year survival is approximately 40-70%, but varies with stage and treatment response[4]. PLB comprises several non-Hodgkin lymphoma (NHL) subtypes, and accurate histological classification is important for treatment and prognosis[5,6].

Distant organ involvement markedly worsens PLB outcomes, with reported 5-year survival falling to approximately 20-30% in metastatic disease[5,6]. Because PLB is rare, evidence on metastatic patterns and risk factors remains limited, largely to small cohorts and case reports. Early identification of patients at high risk of distant spread could therefore improve risk stratification and treatment planning.

This study aimed to develop a machine-learning model for predicting distant organ involvement in PLB, identify influential risk factors using SHAP (Shapley Additive Explanations), and construct a web-based calculator for individualized risk estimation.

2. Methods and Materials

2.1 Data Source & Study Design

This retrospective study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guideline[7]. Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database[8]. SEER provides de-identified demographic, tumor, treatment, and follow-up information; therefore, additional informed consent or institutional review board approval was not required.

Patients with histologically confirmed PLB were identified in SEER using primary bone site codes 40.0-41.9 in ICD-O-3. Patients with multiple primary cancers, unclear clinicopathological diagnoses, unknown distant organ involvement, or incomplete records were excluded. A total of 690 eligible patients were included and randomly divided into training (n=482) and internal validation (n=208) cohorts at a 7:3 ratio.

2.2 Study Population

Demographic, pathological, and treatment variables were extracted from SEER. Seventeen variables were analyzed: age, race, sex, median household income, laterality, histology, year of diagnosis, PRCDA 2020, marital status, primary site, surgery, radiation, chemotherapy, treatment modality, time from diagnosis to treatment, first malignant primary indicator, and metastasis. Histology was grouped by ICD-O-3 codes as malignant lymphoma NOS/diffuse (9590-9599), mature B-cell NHL (9670-9699), mature T/NK-cell NHL (9700-9719), and plasma cell tumors (9730-9739).

2.3 Statistical Analysis & Risk Factor Screening

Statistical analyses were performed using SPSS 22.0 and R. Continuous variables were assessed for normality by the

Kolmogorov-Smirnov test and reported as mean $\pm$ SD or median (IQR), as appropriate; groups were compared using the t test or Wilcoxon rank-sum test. Categorical variables were reported as counts and percentages and compared using the chi-square or Fisher exact test.

Because distant organ involvement was infrequent in the original SEER dataset (583 without and 107 with distant involvement), Synthetic Minority Over-sampling Technique (SMOTE) was applied to the training data to address class imbalance[9-12]. LASSO regression was then used for feature selection[13,14]. Ten-fold cross-validation determined the optimal penalty parameter, with lambda.1se used to select a parsimonious predictor set and reduce overfitting.

All tests were two-sided, and $P < 0.05$ was considered statistically significant.

2.4 Model Establishment & Evaluation

Features selected by LASSO were entered into eight machine-learning algorithms. Models were trained in the training cohort and evaluated in the internal validation cohort. Discrimination was assessed by ROC curves and AUC[15], calibration by calibration plots and the Hosmer-Lemeshow test[16], and clinical utility by decision curve analysis (DCA). Accuracy, precision, recall, PPV, NPV, sensitivity, specificity, and F1-score were also calculated.

The best-performing model was interpreted using SHAP to quantify the direction and relative contribution of each predictor[17-20]. Two representative patients were selected to illustrate individual-level predictions.

2.5 Online Web Calculator

An interactive web calculator was developed from the optimal model to provide real-time individualized estimates of distant organ involvement risk in PLB.

3. Results

3.1 Patient Characteristics

The final cohort was divided into a training cohort ($n=482$) and an internal validation cohort ($n=208$). No significant differences were observed between the two cohorts in baseline demographic, clinical, or treatment characteristics ($P > 0.05$).

Comparisons between patients with and without distant organ involvement showed significant differences in sex, race, PRCD 2020, median household income, laterality, primary site, histological type, and chemotherapy status ($P < 0.05$).

In the training cohort, LASSO with 10-fold cross-validation selected age, sex, race, median household income, primary site, laterality, histological type, treatment modality, and first malignant primary indicator as predictors.

3.2 Model Establishment & Evaluation

Eight machine-learning models were built using the selected predictors. In the training cohort, all models achieved AUCs > 0.700 , and RF showed the highest discrimination (AUC=0.982, 95% CI: 0.973-0.992). For RF, accuracy, sensitivity, specificity, F1-score, PPV, and NPV were 0.943, 0.949, 0.939, 0.933, 0.918, and 0.962, respectively.

In internal validation, RF remained the best-performing model (AUC=0.907, 95% CI: 0.872-0.942). Its accuracy, sensitivity, specificity, F1-score, PPV, and NPV were 0.852, 0.862, 0.843, 0.833, 0.807, and 0.890, respectively. Calibration analysis showed satisfactory agreement between predicted and observed risks, and decision curve analysis indicated potential clinical utility.

3.3 SHAP Method

SHAP ranked predictor importance in the RF model. Histological type was the strongest predictor, followed by treatment modality, laterality, sex, median household income, age, race, primary site, and first malignant primary status. Positive SHAP values indicated increased predicted risk, whereas negative values indicated lower risk.

Representative low- and high-risk cases were examined using individual SHAP explanations. In the low-risk example, chemotherapy alone increased predicted risk, whereas malignant lymphoma NOS/diffuse, higher household income, and male sex reduced risk. In the high-risk example, lower household income, chemotherapy alone, and unilateral tumors increased predicted risk, while mature B-cell lymphoma and several demographic or tumor-location features reduced it.

3.4 Web Calculator

The RF model was implemented as an interactive web calculator for individualized risk estimation. Users can enter clinical variables to obtain the predicted probability of distant organ involvement (https://czyyrtj.shinyapps.io/PLB_RF/).

4. Discussion

PLB is rare, accounting for approximately 3-7% of primary bone tumors and 5% of extranodal lymphomas[21-23].

Although overall survival is relatively favorable[24], distant organ involvement markedly worsens prognosis[25]. Because evidence on metastatic PLB is still limited[26], reliable risk stratification remains clinically relevant.

Using SEER data, we developed eight machine-learning models based on routinely available clinical and treatment variables. RF showed the best overall performance, and SHAP provided both global and individual interpretation of model predictions. This population-based approach may help identify patients at higher risk of distant organ involvement.

LASSO selected age, sex, race, median household income, primary site, laterality, histological subtype, treatment modality, and first malignant primary status as predictors.

Age, sex, and household income contributed to risk prediction. Previous studies have identified age and sex as clinically relevant factors in PLB[27-34]. Their associations in our model may reflect differences in disease biology, comorbidity, treatment tolerance, and access to care; however, causal relationships cannot be inferred from SEER data.

Primary site and laterality were also retained as predictors. Axial PLB has been associated with more complex presentations and poorer outcomes[35]. Although anatomical and lymphatic factors may contribute[36,37], the relationship between tumor location and distant organ involvement requires independent validation.

Histological subtype was the most influential SHAP feature. Mature B-cell lymphoma was the predominant subtype, consistent with previous reports. Distinct lymphoma subtypes have different biological and molecular characteristics[38,39], which may partly explain their different predicted risks. PLB-specific molecular studies are needed to clarify these associations.

Treatment modality was another major predictor. Chemotherapy, radiotherapy, and selected surgery remain key components of PLB management, and combined-modality treatment has shown favorable outcomes in previous series[40-48]. In our model, treatment combinations produced different predicted risks, but these associations should not be interpreted as causal because treatment allocation in SEER is non-randomized.

This study has several limitations. SEER lacks detailed biomarkers, imaging features, laboratory data, and specific systemic treatment regimens. Treatment information is retrospective and subject to selection bias. In addition, the model was validated only in a randomly partitioned SEER cohort and lacks independent external validation. Multicenter cohorts are needed to confirm its generalizability and clinical utility.

5. Conclusion

We developed machine-learning models to predict distant organ involvement in PLB using routinely available clinical variables. RF showed the best overall performance, and SHAP identified histological type, treatment modality, and laterality as the most influential predictors. An online calculator was developed to support individualized risk estimation (https://czyyrjj.shinyapps.io/PLB_RF/). The model may assist clinical risk stratification and treatment planning, but external validation is required before broader use.

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