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**Development and Validation of a Pretreatment Prognostic Index to Predict Death and Lung
Metastases for Extremity Osteosarcoma**

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Abstract

Background: Osteosarcoma is a disease with high heterogeneity, which needs to stratify patients with different prognostic risk at the time of diagnosis. A prognostic index is a valuable tool to make risk stratification in many diseases. However, the application of prognostic index to osteosarcoma patients is unknown now.

Purpose: This study aimed to develop a prognostic index to predict the 5-year overall survival (OS) and 5-year lung metastasis-free survival (LMFS) for patients with extremity osteosarcoma at the time of diagnosis.

Patients and Methods: We retrospectively evaluated 454 patients with extremity osteosarcoma at our center from 2005 to 2013. The cohort was randomly divided into training (340 patients) and validation

(114 patients) sets. Associations of potential risk factors with the 5-year OS and LMFS were assessed by Cox proportional hazards analysis in the training set, and a prognostic index was created according to scores proportional to a regression coefficient for each factor. This prognostic index was assessed in the validation set.

Results: For the 5-year OS, 5 independent prognostic factors were identified: tumor size (1 point), Enneking stage (2 points), pretreatment platelet (1 point), alkaline phosphatase (ALP) (3 points), and neutrophils (1 point). The multivariate Cox model identified tumor size (2 points), pretreatment platelets (1 point), ALP (1 point), and neutrophils (1 point) as associated with the 5-year LMFS. A prognostic index for death and lung metastases was calculated for each patient. Three risk groups were defined for each survival point: low (0-3 points), intermediate (4-6 points), and high (7-10 points) risk for the 5-year OS (Figure 1); low (0-1 points), intermediate (2-3 points), and high (4 points) risk for the 5-year LMFS (Figure 2). The C statistic for the 5-year OS was 0.723 (95% confidence interval, 0.676 to 0.771) in the training set and 0.710 (95% confidence interval, 0.611 to 0.809) in the validation set (Figure 1). The C statistic for the 5-year LMFS was 0.661 (95% confidence interval, 0.612 to 0.710) in the training set and 0.693 (95% confidence interval, 0.592 to 0.795) in the validation set (Figure 2).

Conclusion: This prognostic index is based on routine tests and characteristics of extremity osteosarcoma patients and is useful for predicting overall survival and lung metastases for patients with extremity osteosarcoma. This index could be applied to clinical practice and trials for individualized risk-adapted therapies.

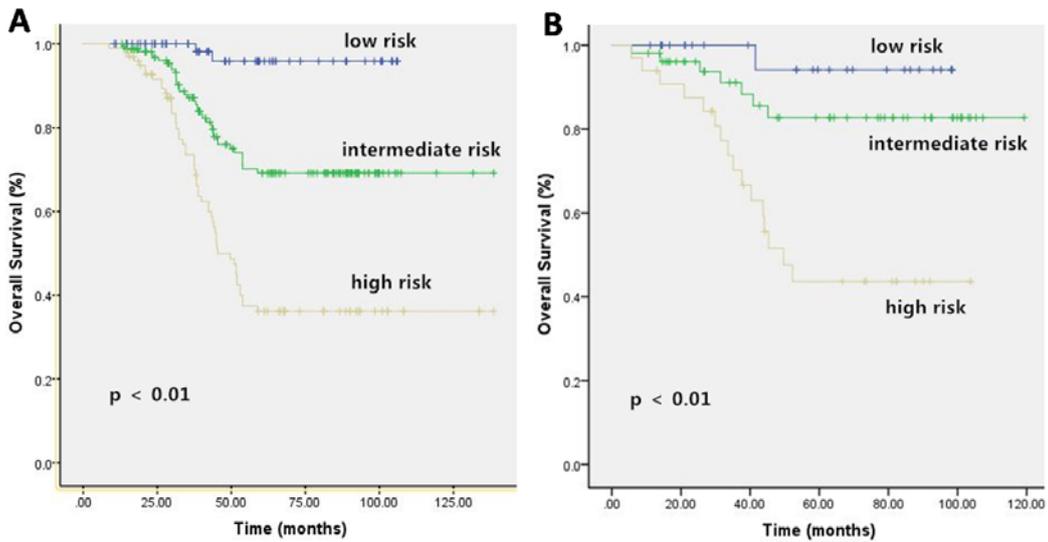


Figure 1. Kaplan-Meier Curves for Overall Survival (OS) in Training Set (A) and Validation Set (B) . (A) Eleven subgroups of development cohort merged to form three categories with significantly different prognoses. (B) There were significant statistical differences on 5 year OS among the three categories of validation cohort, according to our prognostic classification.

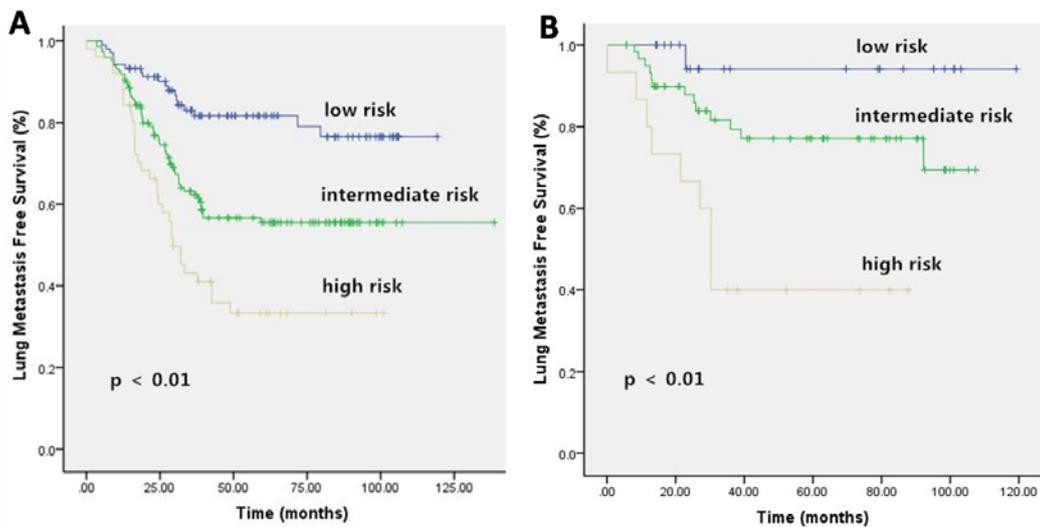


Figure 2. Kaplan-Meier Curves for Lung Metastasis Free Survival (LMFS) in Training Set (A) and Validation Set (B). (A) Five subgroups of development cohort merged to form three categories with significantly different prognoses. (B) There were significant statistical differences on 5 year LMFS among the three categories of validation cohort, according to our prognostic classification.