e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2023, Volume 28, Number 5, pages: 646–653
DOI: 10.5603/rpor.97512
Submitted: 24.01.2023
Accepted: 11.09.2023

# Survival prediction nomogram for patients with vertebral bone metastases treated with palliative radiotherapy

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## ABSTRACT

**Background:** In the treatment of vertebral bone metastases, estimating patient prognosis is important to select the optimal treatment strategy. The purpose of this study was to identify prognostic factors for vertebral bone metastases treated with palliative radiotherapy and to establish a nomogram for predicting patient survival.

**Materials and methods:** We analyzed patients who underwent palliative radiotherapy for vertebral bone metastasis between January 2010 and December 2020 at a single institution. Exclusion criteria were as follows: (1) primary bone malignancy, (2) stereotactic body radiotherapy, (3) concurrent radiotherapy to sites other than the vertebral bone, (4) radiotherapy to other sites within 12 weeks before or after the current radiotherapy, and (5) lack of more than half of blood test data before radiotherapy.

**Results:** A total of 487 patients met the inclusion criteria. Clinical and hematologic data were collected from the patient record system. Patients were divided into training and test groups in a 7:3 ratio. Multivariate Cox regression analysis in the training cohort revealed six significant factors, including a history of chemotherapy, primary site (breast cancer, prostate cancer, or hematologic malignancy), use of analgesics, neutrophil-lymphocyte ratio, serum albumin, and lactate dehydrogenase. A prognostic nomogram was developed and validated in the test cohort. The area under the curve (AUC) values in predicting survival at 6, 24, and 60 months were 0.83, 0.88, and 0.88 in the training cohort and 0.85, 0.81, and 0.79 in the test cohort, respectively.

**Conclusions:** This nomogram may help to select the treatment strategy for vertebral bone metastases.

**Key words:** palliative radiotherapy; bone metastasis; survival prediction; nomogram; neutrophil-lymphocyte ratio (NLR)

*Rep Pract Oncol Radiother 2023;28(5):646–653*

## Introduction

Vertebral bone metastases are common in patients with advanced malignant neoplasms. It can cause various symptoms, including bone pain, compression fracture, and spinal cord compression, and affect the patient's quality of life. The role of palliative radiotherapy for bone pain and neurological symptoms in patients without surgical indications is well established. Classically, fractionated radiotherapy, such as 30 Gy in 10 fractions and 20 Gy in five fractions, was indicated for these cases. However, some alternative doses and fractionations have been proposed for these patients. On the one hand, single-fraction radiotherapy with a dose of 8 Gy or 10 Gy has been reported to be

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as effective as multi-fraction radiotherapy for bone pain [1, 2]. Because single-fraction radiotherapy is thought to be associated with more frequent use of re-irradiation, it is used considering the patient's symptoms, prognosis, and treatment accessibility. On the other hand, high-dose stereotactic body radiotherapy (SBRT) for vertebral metastases has been shown to be safe and effective in selected patients [3, 4]. In clinical practice, clinicians determine the treatment dose and fractionation based on each patient's symptoms and prognosis.

Therefore, the prediction of patient prognosis is essential for treatment decision-making. Some studies have predicted the survival time of patients with bone metastases treated with or without radiotherapy [5–8]. However, these existing prediction systems are based on clinical information and only basic hematological parameters. Recently, the usefulness of novel combined hematological indices, such as neutrophil-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), has been proposed in various types of cancer treatment [9]. Using these parameters may contribute to a more accurate prognosis prediction in patients with vertebral bone metastases treated with radiotherapy.

In this study, we retrospectively analyzed patient records to identify prognostic factors in patients with vertebral bone metastases treated with radiotherapy and established a nomogram using novel hematological parameters to estimate patient prognosis for optimal treatment decision-making.

## Materials and methods

We reviewed the treatment records of the Radiation Oncology Department of the Tohoku University Hospital from January 2010 to December 2020. In total, 956 patients received radiotherapy for vertebral bone metastases. The following records were excluded: (1) primary vertebral bone malignancies; (2) stereotactic body radiotherapy; (3) concurrent irradiation for lesions other than vertebral bone; (4) history of vertebral bone radiotherapy or radiotherapy to any site within 12 weeks of the current treatment course; or (5) missing blood test data in more than half of the parameters. A total of 487 patients met the eligibility criteria. Electronic medical records were extracted in March 2022. Age, sex, ECOG performance status (PS), primary site, history of chemotherapy, analgesic prescription within 12 weeks before radiotherapy, details of radiotherapy, blood test parameters at the start of radiotherapy, including hemoglobin concentration, platelet count, neutrophil count, lymphocyte count, calcium concentration, lactate dehydrogenase (LDH) level, serum albumin level, C-reactive protein (CRP), and survival information were collected. NLR and PLR were calculated based on the blood cell count data. Based on previous reports, patients with prostate, breast, or hematologic malignancy were considered the favorable group [5, 6].

Patients were randomly divided into two groups in an approximate 7:3 ratio: a training cohort of 351 patients and a test cohort of 136 patients. Missing clinical and hematological parameters were filled using the median values in each group. For patients in the training cohort, Cox regression analysis was used as a univariate analysis to extract predictive parameters for overall survival. The multivariate Cox regression analysis included parameters with a p-value less than 0.1. Using parameters with statistical significance based on multivariate Cox regression analysis, a nomogram was created to estimate the overall survival of patients. Patients were divided into four risk groups according to their nomogram scores: group A (estimated overall survival less than 6 months), group B (6–24 months), group C (24–60 months), and group D (60 months or more). The nomogram was evaluated in the training and test cohorts using time-dependent receiver operating characteristic (ROC) analysis.

Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used to evaluate the different groups. In each analysis, a p-value less than 0.05 was considered significant. R software version 4.2.2 (The R Foundation for Statistical Computing) and JMP® Pro 16.2.0 (SAS Institute Inc.) were used for data analysis. The R packages "glmnet", "survival", and "timeROC" were used for nomogram construction and time-dependent ROC analysis [10].

## Results

Patient characteristics are shown in Table 1. The most common dose prescriptions were 30 Gy in 10 fractions (48.4% and 42.7% in the training and test cohorts, respectively), 8Gy in a single fraction (7.4% and 8.1%), and 20 Gy in five fractions

**Table 1.** Patient characteristics

| | Training cohort (n = 351) | Validation cohort (n = 136) | p-value |
|---|---|---|---|
| **Sex** | | | |
| Female | 153 (43.6%) | 60 (44.1%) | 0.92 |
| Male | 198 (56.4%) | 76 (55.9%) | |
| Age [years] | 67.0 (3.0–93.0)* | 66.0 (16.0–89.0)* | 0.60 |
| **Performance status** | | | |
| 0–1 | 95 (27.1%) | 23 (16.9%) | 0.51 |
| 2 | 64 (18.2%) | 29 (21.3%) | |
| 3 | 32 (9.1%) | 9 (6.6%) | |
| 4 | 36 (10.3%) | 20 (14.7%) | |
| Unknown | 154 (43.9%) | 55 (40.4%) | |
| **History of chemotherapy** | | | |
| Yes | 181 (51.6%) | 72 (52.9%) | 0.79 |
| No | 170 (48.4%) | 64 (47.1%) | |
| **Use of analgesics** | | | |
| Yes | 296 (84.3%) | 113 (83.1%) | 0.74 |
| No | 55 (15.7%) | 23 (16.9%) | |
| **Risk of primary site** | | | |
| High-risk | 240 (68.4%) | 106 (77.9%) | 0.03 |
| Low-risk | 111 (31.6%) | 30 (22.1%) | |
| **Primary site** | | | |
| Lung and mediastinum | 69 (19.6%) | 27 (19.8%) | < 0.001 |
| Gastrointestinal tract | 54 (15.3%) | 13 (9.6%) | |
| Breast | 55 (15.6%) | 15 (11.0%) | |
| Liver, bile duct, and pancreas | 36 (10.2%) | 10 (7.4%) | |
| Prostate | 31 (8.8%) | 10 (7.4%) | |
| Head and Neck | 24 (6.8%) | 12 (8.8%) | |
| Bone, skin, and soft tissue | 21 (6.0%) | 15 (11.0%) | |
| Urinary tract | 25 (7.1%) | 12 (8.8%) | |
| Hematological malignancy | 25 (7.1%) | 5 (3.7%) | |
| Gynecologic organ | 3 (0.9%) | 14 (10.2%) | |
| Unknown or others | 8 (2.3%) | 3 (2.2%) | |
| Treatment dose in BED10 [Gy] | 39.0 (4.8–72.0)* | 39.0 (7.8–72.0)* | 0.33 |
| **Pretreatment hematological parameters** | | | |
| Hemoglobin [g/dL] | 11.7 (5.4–17.2)* | 11.6 (6.3–16.2)* | 0.37 |
| Neutrophil [$10^3$/mL] | 4.5 (0.1–49.8)* | 4.2 (0.0–20.7)* | 0.19 |
| Lymphocyte [$10^3$/mL] | 1.2 (0.1–7.0)* | 1.2 (0.1–3.7)* | 0.62 |
| Platelet [$10^3$/mL] | 239 (18–745)* | 242 (18–548)* | 0.23 |
| NLR | 3.9 (0.1–91.4)* | 3.5 (0.0–45.2)* | 0.23 |
| PLR | 200 (11–3538)* | 187 (9–1071)* | 0.28 |
| Calcium [mg/dL] | 8.9 (6.6–12.4)* | 9.0 (7.1–12.4)* | 0.18 |
| Albumin [g/dL] | 3.5 (1.7–5.1)* | 3.6 (1.6–4.9)* | 0.86 |
| Lactate dehydrogenase [U/L] | 225 (103–2504)* | 226 (111–7564)* | 0.85 |
| C-reactive protein [mg/dL] | 0.5 (0.0–28.9)* | 0.7 (0.0–30.0)* | 0.64 |

Values are shown as numbers and percentages, and values with an asterisk (*) are shown as medians and ranges. p-values were calculated by likelihood ratio test or t-test, as appropriate. BED10 — biologically effective dose at $\alpha/\beta = 10$; NLR — neutrophil-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio

**Table 2.** Univariate and multivariate analyses for overall survival

| | Univariate analysis | p-value | Multivariate analysis | p-value |
|---|---|---|---|---|
| | HR (95% CI) | | HR (95% CI) | |
| **Sex** Female/male | 0.84 (0.63–1.11) | 0.22 | | |
| **Age [year]** | 1.00 (0.99–1.01) | 0.93 | | |
| **Performance status** | | | | |
| 2/0–1 | 1.32 (0.83–2.12) | 0.24 | 1.17 (0.79–1.74) | 0.42 |
| 3/0–1 | 1.99 (1.10–3.62) | 0.02 | 1.31 (0.67–2.56) | 0.43 |
| 4/0–1 | 1.99 (1.12–3.54) | 0.02 | 1.61 (0.81–3.22) | 0.18 |
| **Chemotherapy history** Yes/no | 2.48 (1.83–3.36) | < 0.001 | 2.30 (1.59–3.31) | < 0.001 |
| **Use of analgesics** Yes/no | 3.41 (1.98–5.87) | < 0.001 | 2.46 (1.31–4.65) | 0.01 |
| **Risk of primary site*** High/low | 2.58 (1.84–3.61) | < 0.001 | 1.94 (1.26–2.97) | 0.003 |
| **Hemoglobin [g/dL]** | 0.84 (0.78–0.91) | < 0.001 | 1.01 (0.91–1.11) | 0.86 |
| **Neutrophil [$10^3$/mL]** | 1.08 (1.05–1.11) | < 0.001 | 1.03 (0.97–1.08) | 0.38 |
| **Lymphocyte [$10^3$/mL]** | 0.55 (0.42–0.72) | < 0.001 | 0.86 (0.59–1.18) | 0.37 |
| **Platelet [$10^3$/mL]** | 1.00 (1.00–1.00) | 0.47 | | |
| **NLR** | 1.03 (1.02–1.04) | < 0.001 | 1.03 (1.00–1.06) | 0.04 |
| **PLR** | 1.00 (1.00–1.00) | 0.003 | 1.00 (1.00–1.00) | 0.12 |
| **Calcium [mg/dL]** | 0.71 (0.57–0.88) | 0.002 | 1.19 (0.90–1.56) | 0.21 |
| **Albumin [g/dL]** | 0.39 (0.31–0.49) | < 0.001 | 0.50 (0.33–0.75) | < 0.001 |
| **Lactate dehydrogenase [U/L]** | 1.00 (1.00–1.00) | < 0.001 | 1.00 (1.00–1.00) | < 0.001 |
| **C-reactive protein [mg/dL]** | 1.14 (1.11–1.17) | < 0.001 | 1.02 (0.98–1.07) | 0.32 |

*primary tumors other than low-risk (prostate, breast, and hematologic neoplasms) were defined as a high-risk group. HR — hazard ratio; CI — confidence interval; NLR — neutrophil-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio

(5.1% and 9.6%). Median follow-up of all and alive patients were 4.4 and 8.0 months in the training cohort and 7.4 and 14.5 months in the test cohort, respectively. In the Kaplan-Meier analysis, median survival was 12.4 months in the training cohort and 14.9 months in the validation cohort, without statistical significance (p = 0.53). Table 2 shows the results of univariate and multivariate Cox regression analyses in the training cohort to identify the predictive factors for overall survival. Six factors, including prior chemotherapy, primary tumor site, analgesic use, NLR, albumin, and LDH, were identified as significant predictive factors for overall survival. Figure 1 shows a nomogram created based on these six factors to estimate the overall survival of patients.

The nomogram was applied to training and test cohorts for validation. Figure 2 (A) shows a time-dependent ROC analysis based on the total score of the nomogram. The AUC values in predicting survival at 6, 24, and 60 months were 0.83, 0.88, and 0.88 in the training cohort and 0.85, 0.81, and 0.79 in the test cohort, respectively. Patients were stratified into four risk groups according to estimated survival based on the nomogram: group A (6 months or less), group B (6–24 months), group C (24–60 months), and group D (60 months or more). Figure 2 (B) shows the survival curves for the four groups in the training and test cohorts. The median survival of the four groups in the validation cohort was 71.0, 49.3, 7.8, and 2.5 months, respectively (p < 0.001).

## Discussion

In this study, we retrospectively investigated the predictive factors of overall survival in patients with vertebral bone metastases treated with palli-

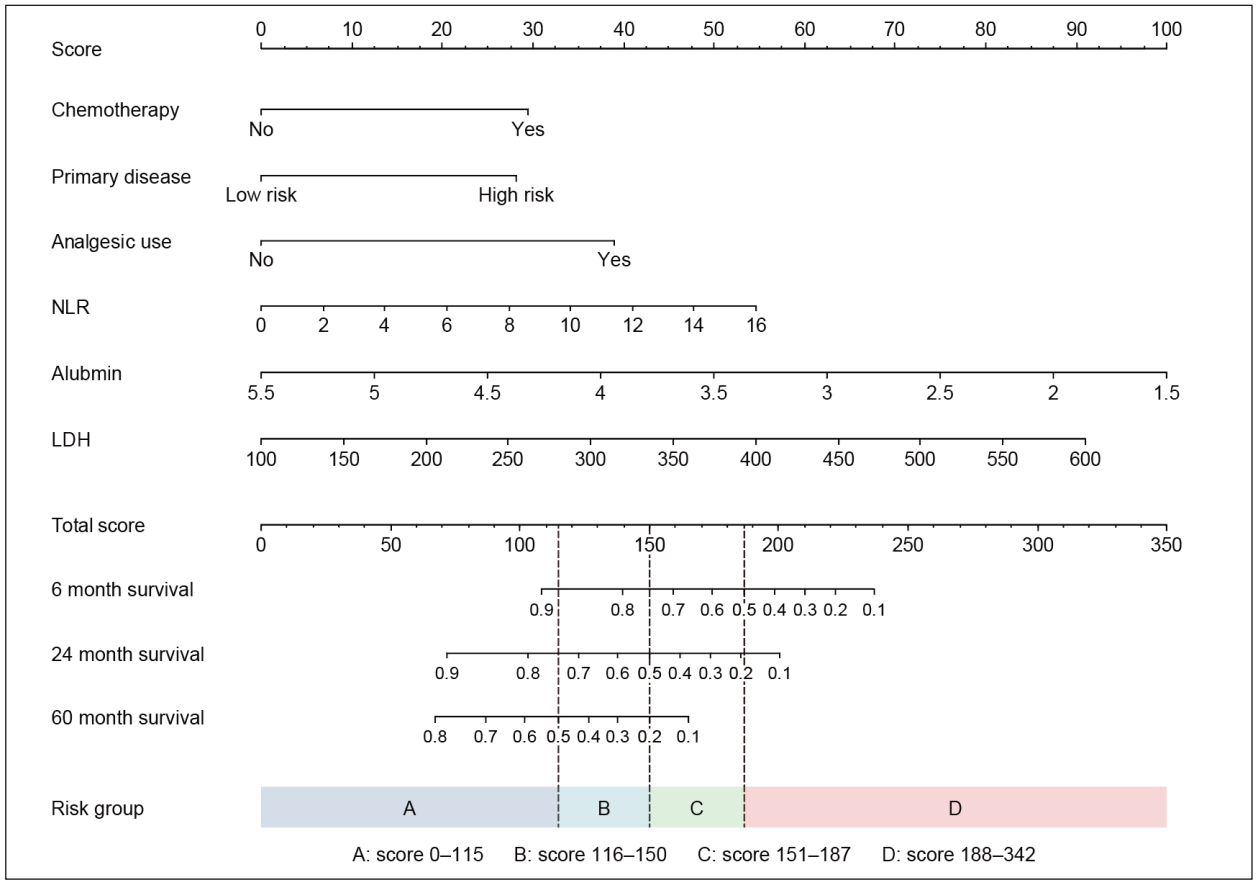


**Figure 1.** Nomogram for predicting the overall survival of patients. Four risk groups were established based on a 50% probability of survival at 6, 24, and 60 months. NLR — neutrophil-lymphocyte ratio; LDH — lactate dehydrogenase

ative radiotherapy. We identified six independent predictive factors: chemotherapy history, primary tumor site, analgesic use, NLR, albumin, and LDH. Using these parameters, we created a new nomogram based on pretreatment clinical and hematological parameters. Compared to existing reports, our predictive model gives more weight to hematological parameters that can be easily and objectively measured. We also performed a validation test using an independent cohort to verify our findings. Based only on patients who had undergone vertebral radiotherapy, this result may be helpful for clinicians in determining the optimal dose and fractionation of radiotherapy.

Among the six significant factors in the multivariate analysis, primary tumor site, albumin, and LDH have been reported as predictive factors in the existing scoring systems [5–8]. The primary tumor site represents the aggressiveness of tumor progression and is used as a predictive factor. In this study, we defined prostate cancer, breast cancer, and hematologic malignancy as the favorable group according to the existing reports. In our cohort, patients with these three tumor types showed longer median overall survival than 36 months, consistent with previous reports. History of chemotherapy, low albumin, and high LDH represent each patient's disease progression, nutritional status, and systemic inflammation and have been identified as prognostic factors in various situations of cancer treatment [6, 11, 12]. Analgesic use is associated with disease extension and aggressiveness of bone lesions. In patients with bone metastases of prostate cancer treated with radionuclides, the presence of pain or analgesic use is known to be associated with poor prognosis [13, 14]. A high NLR represents a systemic inflammatory status and a relatively weakened lymphocyte-mediated immune response to tumors and has recently been identified as a prognostic factor for several types of malignant neoplasms. It is also thought to reflect the immune and nutritional status of the patient [15–18]. Zhang et al. reported that NLR and PLR were significantly increased in prostate cancer pa-

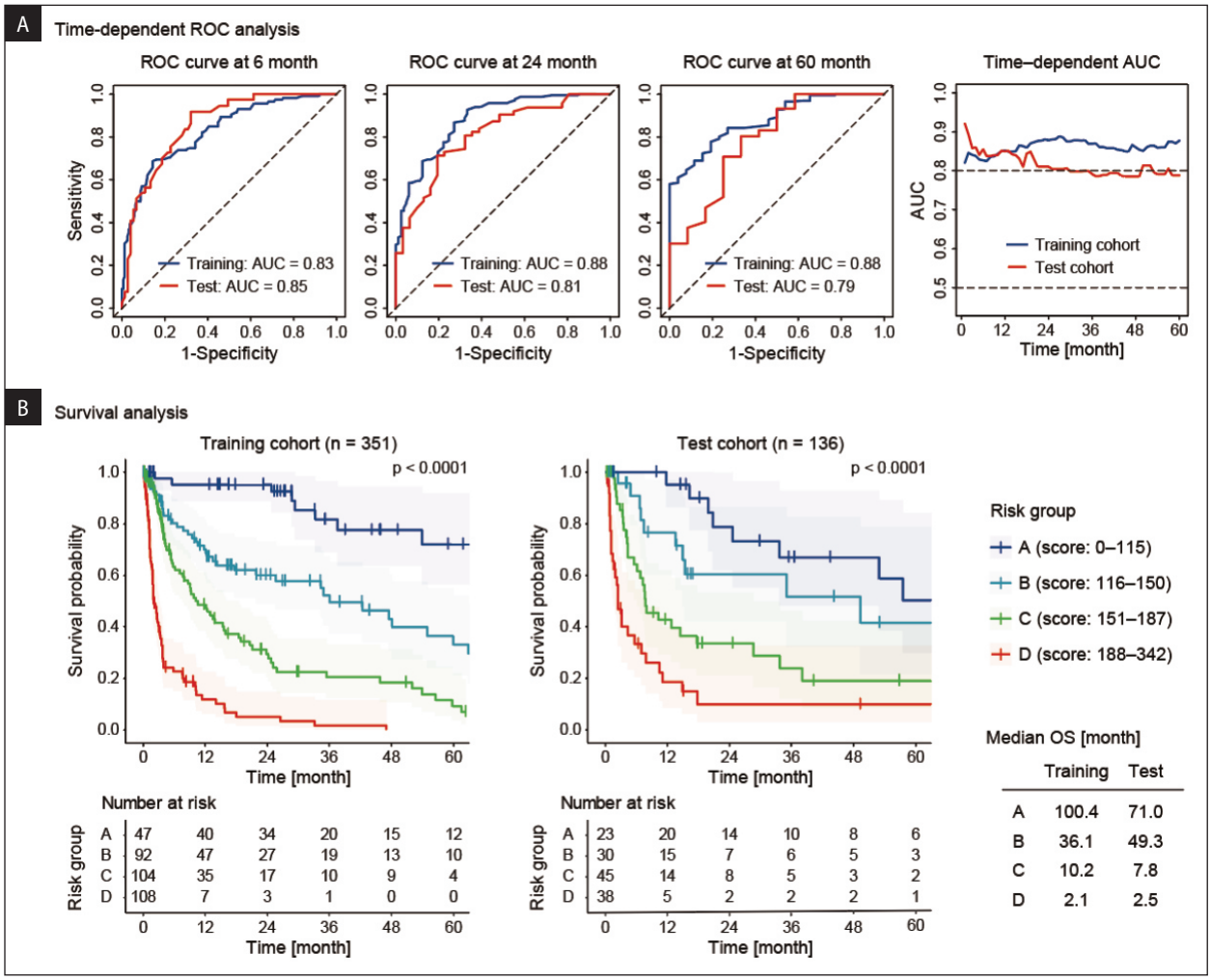


**Figure 2. A.** Time-dependent receiver operating characteristic (ROC) analysis in the training and test cohorts. **B.** Kaplan-Mayer curves of overall survival (OS) of the four risk groups in the training and test cohorts. The number at risk in each group is shown below. The 95% confidence interval is shown as a fill. AUC — area under the curve

tients with bone metastasis [9]. However, to our knowledge, there has been no report on the prognostic effect of high NLR in patients with bone metastases from different types of primary diseases. The current study is the first report to demonstrate the impact of NLR on patient prognosis in this population, with high predictive ability in the independent test cohort by combining multiple parameters.

In the survival analysis, the median survival times of the four risk groups in the test cohort were 71.0, 49.3, 7.8, and 2.5 months, respectively, with statistical significance. The time-ROC analysis also showed an AUC value of around 0.8 for most of the evaluated period, indicating the reliability of the nomogram established in the training cohort. In clinical practice, it might be reasonable to choose 8–10 Gy of single-dose radiotherapy for high-risk patients such as group D (median overall survival = 2.5 months) because there is a low possibility of a pain recurrence requiring re-irradiation in a short prognosis. For low-risk patients such as groups A and B (median overall survival = 71.0 and 49.3 months, respectively), SBRT might be a good treatment option expecting longer symptom control. Sahgal et al. reported that SBRT delivered with 24 Gy in two fractions had a higher pain control rate than standard radiotherapy delivered with 20 Gy in five fractions [19]. However, a recent phase 3 trial showed that SBRT with a single dose of 16–18 Gy was not superior to conventional single-dose irradiation with 8 Gy for pain control [20]. Further studies are needed to determine the optimal patient population and treatment dose.

This retrospective database analysis study had several limitations. First, we could extract information on PS from only 57.1% of all patients due to missing data. Second, pathological details, especially for hematological neoplasms and lung cancer, were not available. These limitations make it difficult to compare the clinical utility of different prediction methods. Further studies are needed to evaluate and compare multiple predictive models.

## Conclusions

We developed and validated a predictive model for overall survival in patients with spinal bone metastases treated with palliative radiotherapy. The combination of clinical and hematologic parameters may help predict patient prognosis and contribute to the optimal treatment strategy for each patient.

### Conflict of interest

None.

### Funding

None received.

### Ethical permission

This study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine (2021-1-1073).

### Acknowledgements

The authors thank Editage (www.editage.com) for English language editing.

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