

Clinical prediction models for malignant bone tumors

A comprehensive review of development and applications

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Abstract: Malignant bone tumors, consisting of primary and secondary types, present significant clinical challenges due to high morbidity and mortality rates, where prognosis is closely tied to recurrence and metastasis. Current diagnostic processes for bone malignancies face difficulties, including high rates of misdiagnosis and significant delays, particularly for conditions like osteosarcoma and Ewing's sarcoma. Clinical prediction models (CPMs) serve as essential mathematical tools that integrate multiple risk factors to provide individualized estimates for outcomes such as recurrence, treatment efficacy, or prognosis. These models are typically implemented as scoring scales, nomograms, or web applications to enhance clinical utility. In spinal oncology, CPMs have been developed for rare primary tumors using machine learning and inflammatory markers, as well as for more common spinal metastases. Established systems, including the Tokuhashi, Tomita, and Bauer scores, along with the recent Skeletal Oncology Research Group (SORG) nomogram, are utilized to predict survival and guide treatment strategies. Furthermore, models such as SPRING, OPTIModel, PATHfx, and the Istituto Ortopedico Rizzoli (IOR) score have demonstrated clinical utility in prognosticating extra-spinal bone tumors. Although CPMs show promise as routine auxiliary tools in bone oncology, most current models are limited by retrospective designs and small sample sizes, requiring extensive multicenter validation to ensure accuracy and reliability before widespread clinical implementation.

Abbreviations AJCC = American Joint Committee on Cancer, AUC = Area under the curve, CSS = Cancer-specific survival, CPM = Clinical prediction model, OS = Overall survival, PET-CT = Positron emission tomography-computed tomography, SORG = Skeletal Oncology Research Group, SRE = Skeletal-related event

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1. Introduction to malignant bone tumors

Malignant bone tumors are categorized into primary bone tumors and secondary bone tumors. Primary bone tumors mainly consist of three types: osteosarcoma, Ewing's sarcoma, and chondrosarcoma. Among

these, osteosarcoma is the most prevalent, accounting for nearly two-thirds of all cases.^[1] Osteosarcoma predominantly affects adolescents and children, ranking as the third most common childhood malignancy.^[2] Ewing's sarcoma also frequently occurs in adolescents and children; statistics indicate an incidence of 1 in 100,000 among individuals aged 10 to 19 years.^[3] The cellular origin of Ewing's sarcoma remains unclear. It is hypothesized that these tumors arise from undifferentiated primitive neuroectodermal or neural crest cells. Some researchers suggest that Ewing's sarcoma originates from primitive stem cells, with the degree of malignancy depending on the stage at which the stem cells are arrested during differentiation.^[4] Chondrosarcoma, conversely, is a malignant bone tumor originating from cartilage. Unlike osteosarcoma and Ewing's sarcoma, chondrosarcoma occurs primarily in adults aged 40 to 75 years.^[5,6] It is more frequently found in the axial skeleton or proximal bones, typically originating from the pelvic girdle, vertebrae, and proximal long bones. Although primary malignant bone tumors account for less than 1% of all confirmed cancer cases annually, they carry high morbidity and mortality rates. Furthermore, the prognosis is usually closely associated with recurrence and metastasis.^[7]

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Secondary bone tumors result from the metastasis of malignancies from other organs. It is reported that bone is one of the organs most frequently affected by metastatic cancer.^[8,9] Although the exact mechanism of bone metastasis has not been fully elucidated, the bidirectional interaction between tumor cells and the bone microenvironment, along with genetic alterations in primary tumor cells, is considered a critical factor in the occurrence and progression of bone metastasis.^[10–13] It is well established that bone metastasis is associated with various skeletal-related events, such as spinal cord compression, pathological fractures, or hypercalcemia, which lead to a decline in quality of life and increased mortality.^[12,14]

2. Introduction to clinical prediction models (CPMs)

In current clinical practice, pathology, immunohistochemistry, and imaging hold vital positions in the diagnosis and differential diagnosis of bone-related malignancies; however, many difficulties still persist in the diagnostic process. Research indicates that, to date, the rates of misdiagnosis and missed diagnosis for osteosarcoma based on imaging and medical history are high, particularly in elderly patients, with an incidence of approximately 23% to 43%.^[15–17] Wurtz et al.^[18] reported that the average diagnostic delay for Ewing's sarcoma patients is about 10 months, while another study found a misdiagnosis rate of 80.77%.^[19] The diagnosis of bone metastases with an unknown primary site is also typically challenging, and confirming the diagnosis for such patients usually requires a combination of positron emission tomography-computed tomography (PET-CT) and other auxiliary examinations.^[20]

Given the aforementioned issues, it is clinically crucial to combine multiple types of useful information to achieve a more precise estimation method. A CPM is a mathematical tool used to predict a specific future event. In disease research, CPMs can integrate multiple risk factors into a unified calculation tool through various statistical methods, thereby enabling individualized prediction and evaluation for each specific patient. The construction of any model follows a similar basic principle: identifying factors that may cause or influence a specific outcome (such as recurrence, metastasis, treatment efficacy, or prognosis), and then utilizing this information to predict the probability of that outcome occurring in an individual in the future. Depending on the clinical outcome under study, CPMs are categorized into two types: diagnostic models and prognostic models. Diagnostic models are used to estimate the probability of a specific individual having a certain disease, whereas prognostic models primarily evaluate the probability of a certain outcome occurring within a specific future timeframe.^[21]

The primary expression formats of CPMs include the following three:

- **Scoring scales:** A traditional prediction model presented in the form of text and options, frequently seen in clinical guidelines for various diseases.^[22]
- **Nomograms:** A graphical format primarily composed of several lines marked proportionally. By reading the scores for each factor line, the probability of the outcome can be predicted on the outcome line. Nomograms have been widely studied in recent years and are the most utilized clinical models in bone tumor modeling.^[23,24]
- **Web applications:** A relatively new model format, usually based on nomograms, which further visualizes calculation formulas using programming languages (such as R, Python, and C++).^[25,26] Compared with traditional nomograms, web applications offer more intuitive and effective outcome predictions. Since results are calculated by computer algorithms, manual calculation errors are minimized by automating the complex mathematics involved in nomogram interpretation, although the accuracy of the prediction still depends on the user for correct data entry. While web applications minimize calculation errors, their deployment requires robust data encryption and privacy protocols to protect sensitive patient information in accordance with medical data regulations.

In addition to the three common types above, CPMs also have some less common expression formats, such as tables, other graphical formats, and mobile software.

3. Development and application of CPMs in spinal tumors

3.1. Primary spinal tumors

Primary spinal tumors are relatively rare, accounting for only about 10% of all spinal tumors.^[27,28] Due to their low incidence, the development of CPMs for primary spinal tumors is relatively limited and is mainly based on multicenter collaborations or public databases. A summary of representative CPMs for primary spinal tumors, including their target populations and key predictors, is presented in Table 1.

A retrospective study evaluated the prognostic value of inflammatory markers and preoperative D-dimer levels in the Ewing's sarcoma family of tumors. The results showed that preoperative D-dimer levels and the C-reactive protein/albumin ratio are independent prognostic factors for overall survival (OS).^[29] By combining age, surgical approach, and metastasis information, the authors successfully constructed a CPM for the Ewing's sarcoma tumor family. Based on four machine learning algorithms—Cox, Random Survival Forest, CoxBoost, and DeepCox—Fan et al. developed a survival prediction model for spinal and pelvic Ewing's sarcoma. This model outperformed the traditional American Joint Committee on Cancer (AJCC) staging system in predicting OS and cancer-specific survival (CSS).^[30] Huang et al.^[31] established a specific prediction model for the survival of primary spinal osteosarcoma patients, utilizing age, tumor grade, surgical status, and tumor size to determine 1-, 3-, and 5-year OS. Research on chordoma found that age, disease progression, tumor size, and surgical treatment are independent risk factors for the prognosis of classic spinal chordoma patients; the

Table 1
Summary of CPMs for primary spinal tumors.

Author and year	Target population	Key predictors	Outcomes
Xu et al. (2019) ^[29]	Spinal Ewing's sarcoma family of tumors	Age, resection mode, D-dimer level, metastasis, and C-reactive protein/albumin ratio	Successfully constructed a prognostic nomogram for OS
Fan et al. (2022) ^[30]	Spinal and pelvic Ewing's sarcoma	ML algorithms (Cox, Random Survival Forest, CoxBoost, DeepCox)	Outperformed traditional AJCC staging in predicting OS and CSS
Huang et al. (2022) ^[31]	Primary spinal osteosarcoma	Age, tumor grade, tumor stage, surgical status, and tumor size	Predicted 1-, 3-, and 5-year OS with high specificity
Lin et al. (2020) ^[32]	Spinal conventional chordoma	Age, extent of disease, tumor size, and surgical treatment	Developed a nomogram incorporating four independent risk factors
Huang et al. (2022) ^[31]	Elderly primary spinal tumor (nonsurgical)	Age, histological type, and tumor stage	Effectively identified high-risk individuals within the elderly population

AJCC = American Joint Committee on Cancer, CSS = cancer-specific survival, ML = machine learning, OS = overall survival.

researchers subsequently constructed a nomogram incorporating these four characteristics.^[32]

To date, surgery remains the optimal treatment for primary spinal tumors; however, the prognosis for elderly patients who cannot undergo surgery is often difficult to assess.^[33] To address this, Huang et al.^[34] developed a prognostic nomogram for elderly primary spinal tumor patients who are unable to tolerate or refuse surgery. The model consists of age, histological type, and tumor stage. Validation results indicated that the model effectively identifies individuals at high risk for survival within the elderly population.

3.2. Spinal metastases

Spinal metastases are more common than primary spinal tumors. Statistics show that approximately 20% to 40% of cancer patients will develop spinal metastases, with up to 20% of these patients experiencing symptoms due to spinal cord compression.^[35] The treatment goal for spinal metastasis patients is palliative, focusing on maintaining or restoring neurological function, controlling pain, improving quality of life, and maintaining spinal stability. The development and application of CPMs in spinal metastatic disease primarily focus on predicting patient survival rates.

Tokuhashi et al.^[36,37] introduced the first preoperative prognostic scoring system for spinal metastases in 1990, which was later modified and released as the Revised Tokuhashi Score in 2005. This system provides a comprehensive evaluation based on general condition, primary site, metastasis status (spinal, extra-spinal bone, and major visceral metastases), and the degree of spinal cord-derived paralysis, serving as a reliable basis for determining survival and treatment options.^[35]

The Tomita Score, developed by Professor Tomita's team at Kanazawa University in 2001, is another widely used prognostic model for spinal metastases. Prognostic factors in this model include the biological behavior of the primary cancer (growth rate), visceral metastasis status (treatability), and bone metastasis status (isolated, single, or multiple).^[38] Summing these three factors yields a prognostic score, which determines the treatment strategy: a score of 2 to 3 suggests wide or marginal resection for long-term

control; 4 to 5 suggests marginal or intralesional resection; 6 to 7 suggests palliative surgery for short-term relief; and 8 to 10 suggests nonsurgical treatment.^[38]

Bauer and Wedin^[39] evaluated the postoperative survival of 153 extremity bone metastasis patients and 88 spinal metastasis patients, identifying pathological fractures, visceral metastases, brain metastases, and bronchial lung cancer as risk factors, while isolated bone metastasis, breast cancer, renal cancer, myeloma, and lymphoma were protective factors. Based on these variables, the Bauer prediction model was developed to categorize patients into prognostic groups. Because pathological fracture was never proven to be a prognostic factor for spinal metastasis, the Medical University of Graz modified the Bauer score for spinal applications. The Revised Bauer Scoring System includes four factors: visceral metastasis, isolated bone metastasis, primary lung cancer, and primary breast/renal cancer, lymphoma, or myeloma. Studies show this system effectively assists in determining treatment strategies for spinal metastasis patients.^[40]

Notably, the Skeletal Oncology Research Group (SORG) recently developed a prognostic algorithm and nomogram for 30-day, 90-day, and 365-day survival rates in spinal metastatic disease.^[41,42] The SORG algorithm indicates that advanced age, poor performance status, primary tumor type, multiple spinal metastases, lung/liver metastasis, brain metastasis, any preoperative systemic therapy (chemotherapy, immunotherapy, hormone therapy, etc), higher white blood cell counts, and lower hemoglobin levels are significantly associated with decreased survival. The SORG nomogram is shown in Figure 1.

To validate the clinical efficacy of spinal metastasis models, a US-based study compared the value of multiple models, finding that the SORG nomogram had the highest accuracy in predicting postoperative survival.^[43] Similarly, Li et al.^[44] applied these models to a cohort of 268 Chinese patients, where the SORG model demonstrated superior predictive performance compared with other scoring systems. The success of these site-specific models in spinal oncology underscores the necessity of having similarly tailored prognostic tools for malignant involvement in other skeletal regions.

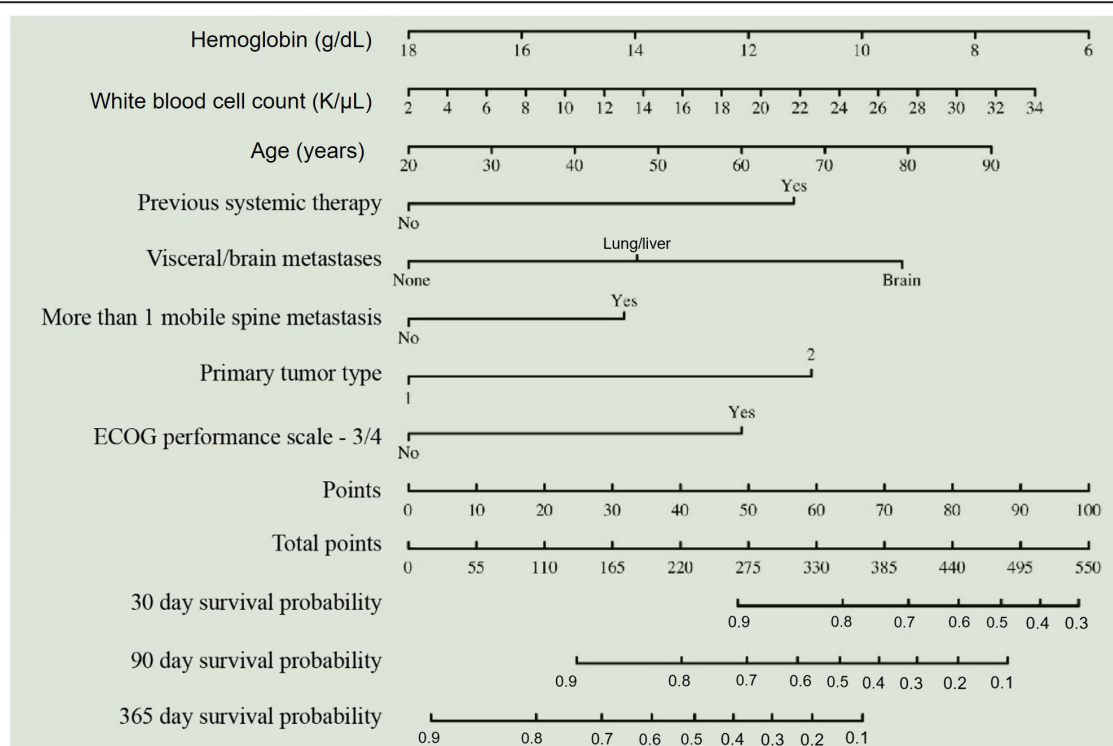


Figure 1. SORG prognostic nomogram for survival probability in patients with spinal metastases. ECOG = Eastern Cooperative Oncology Group, SORG = Skeletal Oncology Research Group.

4. Development and application of CPMs in extra-spinal bone tumors

Expanding beyond the axial skeleton, research on CPMs for extra-spinal bone tumors has primarily focused on the prognosis of extremity bone metastases. In 2016, Sørensen et al.^[45] published the 2008-SPRING model, a survival prediction nomogram for patients undergoing bone resection and reconstruction for extremity metastases. The authors utilized seven variables: hemoglobin, visceral metastasis, multiple bone metastases, fracture status (impending/actual), Karnofsky score, American Society of Anaesthesiologist's score (ASA), and primary cancer group, selecting 3, 6, and 12 months as survival milestones. In 2018, this was updated to the 2013-SPRING model. Comparisons of area under the curve and Brier scores showed that the 2013-SPRING model performed better, with strong calibration and discrimination for 3-, 6-, and 12-month OS.

Leiden University developed the OptiModel score to predict survival in patients with symptomatic long bone metastases by analyzing 1,520 patients across 6 Dutch hospitals.^[46] This model includes only three variables: clinical condition classification (based on Bollen et al.),^[47] Karnofsky score, and the presence of visceral/brain metastasis. External validation in 250 surgical patients showed high similarity between actual and expected survival. The model was subsequently launched as a web application.^[46] In 2019, Meares et al.^[48] found OptiModel to be the most accurate for 12- and 24-month survival predictions in femoral metastasis patients.

The PATHfx model, based on a Bayesian network, was introduced by Forsberg et al.^[49] in 2011 to estimate 3- and 12-month survival in systemic bone metastasis patients. It originally used 10 factors: age, sex, surgical indication, number of metastases, surgeon's estimate, visceral metastasis, lymph node metastasis, hemoglobin, lymphocyte count, and Katagiri score.^[50] Validation in Scandinavian, Italian, and Japanese cohorts confirmed its accuracy and clinical utility.^[51,52]

Errani et al.^[53] published the IOR scoring system in 2021 based on a prospective cohort of patients with symptomatic long bone metastases treated with minor or major surgery. The IOR score showed good discrimination for 12-month survival. Alfaro et al.^[54] compared multiple models (Revised Katagiri, PATHfx, OptiModel, and IOR) in a Chilean population, concluding that the IOR score was the most accurate for predicting 12-month OS.

5. Summary

Numerous prediction models have been successfully developed and applied in bone tumor research, with the potential to become routine auxiliary tools. However, these models are not perfect. Most current constructions are limited by retrospective, single-center designs and small sample sizes. Furthermore, while advanced machine learning algorithms offer enhanced predictive power, their "black box" nature often lacks the transparency and interpretability essential for clinical trust and decision-making. Therefore, extensive multicenter validation and a greater emphasis on model explainability are

required before clinical implementation to ensure reliability, accuracy, and practical utility.

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Ethical statement

Not applicable.

Conflicts of interest

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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