Risk factors for bone metastasis in lung cancer and the efficacy of palliative radiotherapy and opioid analgesics in alleviating bone metastasis pain

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Abstract. Bone metastasis is a severe complication in advanced lung cancer, which notably affects the quality of life and prognosis in patients. The present study investigated risk factors for bone metastasis and evaluated the effects of radiotherapy and opioids on bone metastasis-related pain. Clinical data from 200 patients with lung cancer (100 with and 100 without bone metastasis) were retrospectively analyzed. Risk factors were identified using logistic regression analyses and a predictive model was validated with receiver operating characteristic curve and decision curve analyses. Pain relief from radiotherapy, opioids and combined therapy was assessed using visual analog scale (VAS) and Pittsburgh Sleep Quality Index (PSQI) scores. Larger tumor diameter, respiratory symptoms, EGFR mutations (85 vs. 35%; P<0.001) and elevated serum markers (including carcinoembryonic antigen, neuron-specific enolase and alkaline phosphatase, all P<0.001; and CA199, P=0.043) were significant risk factors for bone metastasis. The predictive model achieved an area under the curve value of 0.996, which demonstrated enhanced accuracy and clinical utility. Combined therapy provided improved pain relief, and markedly improved VAS and PSQI scores compared with monotherapy. Key risk factors for bone metastasis were identified and a robust predictive model was established. Combined radiotherapy and opioids effectively manage bone metastasis pain and potentially offer novel insights for early detection and treatment strategies in the future.

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Introduction

Lung cancer is the most common malignancy worldwide. According to the 2022 International Agency for Research on Cancer report, there were an estimated 2.5 million novel cases globally. The incidence rate is as high as 74.31% in men and 39.08% in women (1). Advanced-stage lung cancer accounts for a notable proportion of cases, highlighting the importance of effective treatment strategies, particularly the need for individualized approaches based on different metastatic sites.

Among the various complications associated with lung cancer, bone metastasis occurs in 10-15% of cases (2,3). Particularly in patients with lung adenocarcinoma, the incidence of bone metastasis can reach 30-40% (4). Bone-related events (such as pathological fractures, spinal cord compression and hypercalcemia) are common and further worsen the prognosis and quality of life for patients with lung cancer. Bone metastasis can lead to intense bone pain, fractures and other complications, which impose substantial physical and psychological burdens on patients (5-7). Following bone metastasis, survival rates drop sharply, with a 1-year survival rate of 5.3%, a 2-year survival rate of 2.1% and a median survival time of 6-10 months (8,9). The occurrence of bone-related events not only markedly increases mortality risk but also exacerbates physical pain, functional limitations and emotional distress (10). Therefore, the early identification of bone metastasis in lung cancer is key for the improvement of patient outcomes.

Currently, bone metastasis in patients with cancer is mainly detected through local computed tomography (CT), radionuclide bone scans and positron emission tomography (PET)-CT (11,12). While these methods are widely used, they are costly, involve high radiation exposure and have limited specificity. Previous studies have increasingly focused on identifying non-invasive methods for the detection of bone metastases in patients with lung cancer. However, non-invasive approaches remain in the exploratory stage and face challenges such as inconsistent sensitivity, lack of standardization and limited clinical validation. Although various treatment options, such as bisphosphonates, denosumab, radiotherapy and surgery, are available to manage bone metastasis, the effectiveness varies among individuals. However, these

treatments primarily focus on symptom relief rather than prolonging survival and their efficacy may be influenced by patient-specific factors (13). These limitations highlight the need for further investigation to optimize treatment strategies and improve outcomes for patients with bone metastasis.

Given the high incidence and notable impact of bone metastasis on the prognosis of patients with lung cancer, there is an urgent need to identify early diagnostic markers and optimize treatment strategies. The present study aims to identify key risk factors for bone metastasis based on clinical data and to develop an effective predictive model for early screening. Additionally, it systematically evaluates the pain management outcomes of radiotherapy, opioid therapy and their combination in patients with bone metastasis. Through this research, clinical risk assessment could be enhanced, individualized treatment approaches could be improved, and valuable insights for early detection and comprehensive management of lung cancer bone metastasis could be provided.

Materials and methods

Study participants. The present retrospective study included 100 patients with lung cancer with bone metastasis and 100 without metastasis, who were treated at The First Affiliated Hospital, Qiqihar Medical University Hospital (Qiqihar, China) between January 2019 and December 2023. The selection of 100 patients in each group was based on a consecutive sampling method, where eligible patients who met the inclusion criteria were recruited until the predetermined sample size was reached. The exact number of patients in each group was determined by available clinical data during the study period, which ensured balanced representation for comparison. The inclusion criteria were as follows: i) Newly diagnosed primary lung cancer, confirmed pathologically; ii) single-photon emission CT bone scintigraphy, bone magnetic resonance imaging or PET-CT performed to assess the presence of bone metastasis; iii) complete clinical data; and iv) expected survival time ≥3 months. Exclusion criteria were as follows: i) Presence of any other primary tumors; ii) concurrent diseases that affect bone metabolism, traumatic fractures and severe liver or kidney dysfunction; iii) incomplete clinical data; and iv) expected survival time <3 months. Due to this heterogeneity in chemotherapy types, doses and durations, chemotherapy was not included as a uniform variable in the comparative pain analysis. The expected survival time was evaluated by the attending physicians, who considered factors such as the general health status of the patient, the type and pathological staging of the primary tumor, and any comorbidities. The present study adhered to ethical principles and informed consent was obtained from all participants. The present study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Qiqihar Medical University (approval no. 2023-008-01).

Data collection. Clinical data on age, sex, occupation, family history, smoking status, initial symptoms, primary tumor location, primary tumor diameter, pathology type, EGFR status and tumor markers [such as carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), CA199, cancer antigen 153 (CA153), neuron-specific enolase (NSE) and alkaline phosphatase (ALP)] were retrospectively collected for the present study. For patients with lung cancer with bone metastasis, data on pain treatment (radiotherapy, opioid therapy or combination therapy) were collected, along with the visual analog scale (VAS) and Pittsburgh Sleep Quality Index (PSQI) scores before and after treatment (14,15). The VAS is a tool used to assess pain intensity, ranging from 0 (no pain) to 10 (worst imaginable pain). The PSQI is a questionnaire designed to evaluate sleep quality, with total scores ranging from 0 to 21; higher scores indicate poorer sleep quality.

Pain management protocols. For patients in the radiotherapy group, external beam radiotherapy was delivered to symptomatic bone lesions using a linear accelerator. The total dose was 30 Gy in 10 fractions (3 Gy per fraction; five times per week over 2 weeks). Opioid therapy was administered via oral formulations, including oxycodone sustained-release tablets and morphine hydrochloride sustained-release tablets. The specific dosages were individually adjusted according to the pain severity of the patient, in accordance with the World Health Organization three-step analgesic ladder (16). The combined treatment group received both modalities simultaneously and followed the aforementioned protocols.

Statistical analysis. All patients with lung cancer in the present study were classified into two groups: 100 patients without bone metastasis and 100 patients with bone metastasis. Each group was then randomly divided into a training cohort (n=70) and a validation cohort (n=30) in a 7:3 ratio. This approach ensured that the distribution of bone metastasis and non-metastasis cases remained consistent between the training and validation cohorts. The training cohort was used to identify high-risk factors for bone metastasis and to develop a predictive model, while the validation cohort assessed the predictive performance and stability of the model. Continuous variables with a normal distribution are expressed as the mean (standard deviation). Differences between two groups were analyzed by independent sample Student's t-tests and differences between three groups were analyzed by one-way ANOVA. For cases with balanced sample sizes and homogeneity of variances, Tukey's Honestly Significant Difference test was used for pairwise comparisons. For cases with unbalanced sample sizes, Bonferroni correction was applied for post hoc comparisons to ensure robustness and control the type I error rate caused by multiple comparisons. Non-normally distributed variables are presented as the median and interquartile range, and differences between two groups were assessed using the Mann-Whitney U test, while comparisons among multiple groups were performed using the Kruskal-Wallis test. When the Kruskal-Wallis test indicated statistical significance, Dunn's post hoc test with Bonferroni correction was used for pairwise comparisons to control for type I error. Categorical variables are represented as frequency and percentage. Group differences were assessed using the χ^2 test or Fisher's exact test, as appropriate, with the latter applied when expected cell counts were ≤5 in >20% of cells. For paired data (such as VAS and PSQI scores before and after treatment in the same patients) Wilcoxon signed-rank

Table I. Comparison of clinical and demographic characteristics between non-metastasis and metastasis groups.

Patient characteristics	Non-metastasis (n=100)	Metastasis (n=100)	P-value
Age	64.4 (8.68)	64.7 (7.70)	0.803
Sex, n (%)			0.124
Male	83 (83.0)	73 (73.0)	
Female	17 (17.0)	27 (27.0)	
Occupation, n (%)			0.679
No	88 (88.0)	85 (85.0)	
Yes	12 (12.0)	15 (15.0)	
Family history, n (%)			0.308
No	83 (83.0)	89 (89.0)	
Yes	17 (17.0)	11 (11.0)	
Smoking status, n (%)			0.087
No	17 (17.0)	8 (8.00)	
Yes	83 (83.0)	92 (92.0)	
Initial symptoms, n (%)			<0.001
Asymptomatic	62 (62.0)	2 (2.00)	
Respiratory	38 (38.0)	56 (56.0)	
Pain	0 (0.00)	42 (42.0)	
Primary location, n (%)			0.431
Central	69 (69.0)	75 (75.0)	
Peripheral	31 (31.0)	25 (25.0)	
Primary diameter	1.80 [1.30-2.20]	2.80 [2.40-3.40]	<0.001
Pathology type, n (%)			0.928
SCLC	17 (17.0)	15 (15.0)	
SCC	47 (47.0)	48 (48.0)	
Adenocarcinoma	36 (36.0)	37 (37.0)	
EGFR, n (%)			<0.001
Negative	65 (65.0)	15 (15.0)	
Positive	35 (35.0)	85 (85.0)	
CEA, ng/ml	4.26 (1.68)	7.65 (1.97)	<0.001
CA125, U/ml	32.6 (8.55)	31.7 (9.34)	0.492
CA199, U/ml	33.1 (9.49)	36.4 (8.53)	0.011
CA153, U/ml	25.3 (6.85)	25.7 (6.33)	0.650
NSE, ng/ml	25.6 (7.35)	36.2 (8.56)	<0.001
ALP, U/ml	132 [117-158]	169 [154-184]	<0.001

Age, CEA, CA199, CA125, CA153 and NSE are presented as mean (standard deviation) due to their approximate normal distribution. Variables such as primary tumor diameter and ALP are presented as median [interquartile range] due to a non-normal distribution. SCLC, small cell lung cancer; SCC, squamous cell carcinoma; CA, cancer antigen; NSE, neuron-specific enolase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen.

tests were used. The normality of variables was assessed using the Shapiro-Wilk test. Univariate and multivariate logistic regression models were used to analyze risk factors, including age, sex and smoking status. P<0.05 was considered to indicate a statistically significant difference. Significant factors from the univariate analysis were subsequently included in the multivariate analysis. Receiver operating characteristic (ROC) curves, calibration curves, nomograms and decision curve analysis (DCA) were generated using R software (v4.3.2; R Core Team).

Results

Baseline characteristics of patients. A comparative analysis was conducted between 100 patients with lung cancer with bone metastasis and 100 patients with lung cancer without metastasis to investigate their clinical characteristics and demographic factors, as shown in Table I. There were no significant differences between patients with and without bone metastasis in terms of age, sex, occupation, family history, primary tumor location and smoking status (P>0.05). Symptoms were absent

in 62.0% of patients in the non-metastasis group but only in 2.0% of patients in the metastasis group, revealing a significant difference (P<0.001). A post hoc pairwise comparison of initial symptoms using Fisher's exact test with Bonferroni correction (significance threshold set at P<0.0167) revealed significant differences in the proportions of asymptomatic (P<0.001) and pain symptoms (P<0.001) between the metastasis and non-metastasis groups. The difference in respiratory symptoms did not reach statistical significance after correction (P=0.019). The median diameter of primary tumors was significantly lower in the non-metastasis group (1.80 cm) compared with that in the metastasis group (2.80 cm) (P<0.001). There was no significant difference in pathology type between the two groups (P=0.928). However, there was a significant difference in EGFR mutation positivity between the non-metastasis group (35.0%; n=35) and the metastasis group (85.0%; n=85) (P<0.001). Tumor markers CEA and CA199 were significantly higher in the metastasis group compared with those in the non-metastasis group (P<0.001 and P=0.011). NSE and ALP levels were also significantly higher in the metastasis group compared with those in the non-metastasis group (both P<0.001). These results suggested that tumor size, the presence of symptoms, EGFR mutations and elevated tumor markers were strongly associated with the occurrence of bone metastasis in patients with lung cancer.

Identification of potential variables for predictive model construction. To construct a predictive model, all 200 patients were randomly divided into a training cohort (n=140) and a validation cohort (n=60) (Table II). In the training cohort, univariate logistic regression analysis identified several significant factors (Table III). Initial symptoms (OR, 71.067; 95% CI, 15.669-1,257.246; P<0.001), primary tumor diameter (OR, 18.021; 95% CI, 7.680-51.901; P<0.001), CEA (OR, 2.952; 95% CI, 2.172-4.308; P<0.001), CA199 (OR, 1.042; 95% CI, 1.002-1.086; P=0.043), NSE (OR, 1.176; 95% CI, 1.115-1.253; P<0.001), ALP (OR, 1.043; 95% CI, 1.027-1.060; P<0.001) and EGFR status (OR, 13.141; 95% CI, 5.888-31.792; P<0.001) were significantly associated with bone metastasis. In multivariate logistic regression, primary tumor diameter (OR, 151.425; 95% CI, 3.084-7,435.895; P=0.012), CEA (OR, 3.048; 95% CI, 1.229-7.557, P=0.016), initial symptoms (OR, 183.618, 95% CI, 2.299-14,667.163, P=0.020) and EGFR status (OR, 49.892; 95% CI, 1.264-1,969.338; P=0.037) remained statistically significant. CA199, NSE and ALP were not significantly associated with bone metastasis (P>0.05) (Table IV). These findings indicated that initial symptoms, primary tumor diameter, CEA levels and EGFR mutations were the most reliable predictors of bone metastasis and formed a solid foundation for model construction.

Model construction. Based on the aforementioned analysis, four high-risk factors, namely primary diameter, CEA, initial symptoms and EGFR mutation, were selected to construct a predictive model for bone metastasis. The ROC curve demonstrated high predictive performance, with an AUC of 0.996, which indicated an outstanding diagnostic performance (Fig. 1A). The optimal cut-off value was 0.5, with a sensitivity of 0.99 and specificity of 1.00, which indicated enhanced diagnostic performance. In the validation cohort, the discriminatory performance of the model was further validated, wherein results demonstrated an AUC of 0.983 (Fig. 1B). The calibration curve demonstrated a high level of agreement between predicted probabilities and actual results, with a mean absolute error of 0.009, which indicated strong calibration and low predictive error (Fig. 2). Overall, the model demonstrated notable predictive power and reliability in both internal and external validations.

Nomogram construction. A nomogram was developed based on the four aforementioned risk indicators to provide a visual high-risk scoring system for bone metastasis in patients with lung cancer (Fig. 3). Each variable corresponded to a specific score and the total score indicated the predicted probability of metastasis. This approach provided clinicians with a rapid and practical risk assessment tool. The nomogram allowed for intuitive interpretation of model predictions and facilitated personalized clinical decision-making.

Clinical utility assessment. DCA was conducted to evaluate the clinical utility of the predictive model. The DCA curve (Fig. 4) demonstrated a higher net benefit across various risk thresholds in both the training and validation cohorts, which suggested greater net benefit in clinical decision-making across different high-risk thresholds. These results highlighted the practical value of the model for the identification of high-risk patients and supporting early intervention strategies.

Baseline and efficacy analysis of different treatment methods. The present study conducted a comparative analysis of baseline characteristics across three pain management approaches (radiotherapy, opioid therapy and combined therapy) for patients with tumors and bone metastasis, as shown in Table V. No significant differences were observed among the three groups regarding age, sex, occupation, or family history. However, smoking status varied significantly between patients in the radiotherapy group (81.8%; n=27), the opioid therapy group (97.0%; n=32) and the combined therapy group (97.1%; n=33) (overall P=0.031). There were no significant differences among the groups in terms of initial symptoms, primary tumor location, primary tumor diameter, pathological type, metastatic site or EGFR mutation status. Similarly, comparisons of tumor markers (CEA, CA125, CA199, CA153, NSE and ALP) indicated no significant differences between the radiotherapy, opioid therapy and combined therapy groups.

Before treatment, there were no significant differences in VAS scores among the three groups: Radiotherapy, opioid treatment, and combined treatment (P>0.05; Table VI). Post-treatment, the VAS scores ranked from highest to lowest were as follows: i) Radiotherapy group; ii) opioid therapy group; and iii) combined treatment group (wherein lower VAS scores indicated reduced levels of pain). Similarly, there was no significant difference in PSQI scores in the three groups when comparing before treatment and after treatment scores (P>0.05; Fig. 5). After treatment, the PSQI scores ranked from lowest to highest were as follows: i) Combined treatment group; ii) radiotherapy group; and iii) opioid therapy group (wherein higher PSQI scores indicated improved sleep quality) (17). These findings demonstrated that combined therapy provided

Table II. Baseline characteristics of the training and validation cohorts.

Patient characteristics	Training cohort (n=140)	Validation cohort (n=60)	Overall P-value
Age, years	64.5 (8.68)	64.6 (6.97)	0.923
Sex, n (%)			0.034
Male	103 (73.6)	53 (88.3)	
Female	37 (26.4)	7 (11.7)	
Occupation, n (%)			0.786
No	120 (85.7)	53 (88.3)	
Yes	20 (14.3)	7 (11.7)	
Family history, n (%)			0.689
No	119 (85.0)	53 (88.3)	
Yes	21 (15.0)	7 (11.7)	
Smoking status, n (%)			0.351
No	20 (14.3)	5 (8.33)	
Yes	120 (85.7)	55 (91.7)	
Initial symptoms, n (%)			0.158
Asymptomatic	39 (27.9)	25 (41.7)	
Respiratory	70 (50.0)	24 (40.0)	
Pain	31 (22.1)	11 (18.3)	
Primary location, n (%)			0.810
Central	102 (72.9)	42 (70.0)	
Peripheral	38 (27.1)	18 (30.0)	
Primary diameter (29)	2.30 [1.70-2.80]	2.25 [1.78-2.90]	0.970
Pathology type, n (%)			0.710
SCLC	21 (15.0)	11 (18.3)	
SCC	69 (49.3)	26 (43.3)	
Adenocarcinoma	50 (35.7)	23 (38.3)	
EGFR, n (%)			0.431
Negative	59 (42.1)	21 (35.0)	
Positive	81 (57.9)	39 (65.0)	
CEA, ng/ml	5.91 (2.47)	6.07 (2.58)	0.701
CA125, U/ml	32.1 (8.72)	32.4 (9.53)	0.823
CA199, U/ml	34.1 (8.67)	36.4 (10.1)	0.131
CA153, U/ml	25.4 (6.73)	25.6 (6.28)	0.880
NSE, ng/ml	30.9 (9.71)	31.0 (9.28)	0.928
ALP, U/ml	152 (29.5)	152 (33.7)	0.901

Age, CEA, CA199, CA125, CA153, NSE and ALP are presented as mean (standard deviation) due to their approximate normal distribution. Primary tumor diameter is presented as median [interquartile range] due to non-normal distribution. SCLC, small cell lung cancer; SCC, squamous cell carcinoma; CA125, cancer antigen 125; CA199, cancer antigen 199; CA153, cancer antigen 153; NSE, neuron-specific enolase; ALP, alkaline phosphatase.

superior efficacy in the management of bone metastasis-related pain symptoms compared with monotherapy.

Discussion

The present study focused on the identification of high-risk factors associated with bone metastasis in lung cancer and evaluating the efficacy of palliative radiotherapy and opioid treatments for bone metastasis-related pain. Results from the present study indicated that initial symptoms, primary tumor diameter, CEA levels and EGFR mutations were significant independent risk factors for bone metastasis in lung cancer. Furthermore, the combination of palliative radiotherapy and opioid treatment proved more effective in managing pain compared with either radiotherapy or opioid treatment alone.

Although the relationship between lung cancer and bone metastasis has been widely studied, the present study aimed to fill a gap in the literature by constructing a predictive model specifically based on clinical characteristics, tumor markers and EGFR mutation status. These factors were most

Table III. Univariate logistic regression analysis of risk factors for bone metastasis.

Risk factors	OR	Lower CI	Upper CI	P-value
Age, years	1.014	0.976	1.054	0.489
Primary diameter (29)	18.021	7.680	51.901	<0.001
CEA, ng/ml	2.952	2.172	4.308	<0.001
CA125, U/ml	1.002	0.965	1.042	0.905
CA199, U/ml	1.042	1.002	1.086	0.043
CA153, U/ml	1.009	0.960	1.061	0.726
NSE, ng/ml	1.176	1.115	1.253	<0.001
ALP, U/ml	1.043	1.027	1.060	<0.001
Sex	1.748	0.821	3.801	0.151
Occupation	1.658	0.640	4.506	0.304
Family history	0.924	0.360	2.353	0.868
Smoking status	2.579	0.965	7.697	0.069
Initial symptoms	71.067	15.669	1,257.246	<0.001
Primary location	0.498	0.227	1.060	0.075
Pathology type	1.111	0.682	1.816	0.672
EGFR	13.141	5.888	31.792	<0.001

OR, odds ratio; CA, cancer antigen; NSE, neuron-specific enolase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen.

Table IV. Multivariate logistic regression analysis of risk factors for bone metastasis.

Risk factors	OR	Lower CI	Upper CI	P-value
Primary diameter	151.425	3.084	7,435.895	0.012
CEA, ng/ml	3.048	1.229	7.557	0.016
CA199, U/ml	1.011	0.864	1.182	0.894
NSE, ng/ml	1.087	0.879	1.344	0.443
ALP, U/ml	0.996	0.931	1.066	0.909
Initial symptoms	183.618	2.299	14,667.163	0.020
EGFR	49.892	1.264	1,969.338	0.037

OR, odds ratio; NSE, neuron-specific enolase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; CA, cancer antigen.

significant in the prediction of bone metastasis risk, which made the model particularly valuable for early screening and prognostic assessment in patients with lung cancer. The novelty of the current study arose in the use of clinical data to create a practical tool for clinical decision-making.

Firstly, initial symptoms, especially respiratory symptoms and pain, are closely associated to the occurrence of bone metastasis (18). The present study demonstrated that the proportion of patients with pain was significantly higher in the bone metastasis group, which suggested that early symptoms might reflect a more aggressive tumor. Pain in bone metastasis may arise from bone destruction, changes in the bone marrow microenvironment, and the release of exosomes and inflammatory factors by tumor cells (19,20). Previous studies have also reported that pain is common in patients with bone metastasis and is closely associated with disease progression (6,21). Thus, pain should be considered as a clinical indicator for bone metastasis while screening high-risk patients.

Secondly, primary tumor diameter and bone metastasis are significantly associated. The present study reported that patients in the bone metastasis group had significantly larger median tumor diameters compared with patients without metastasis. Larger median tumor diameters may be correlated with increased tumor burden, higher cell proliferation and potential enhancement in invasiveness. Larger tumor sizes can facilitate the ability of the tumor to breach the tissue barriers of the primary site and spread to distant tissues via blood or lymphatic systems (22). This finding aligned with the present study results, which demonstrated that larger primary tumor diameters were associated with a higher risk of bone metastasis, which underscored the importance of tumor size as a predictive factor for bone metastasis, particularly in the guidance of non-invasive imaging evaluations and follow-up strategies.

Elevated CEA levels are a significant high-risk factor for lung cancer bone metastasis. In the multivariate logistic regression analysis of the present study, CEA demonstrated strong

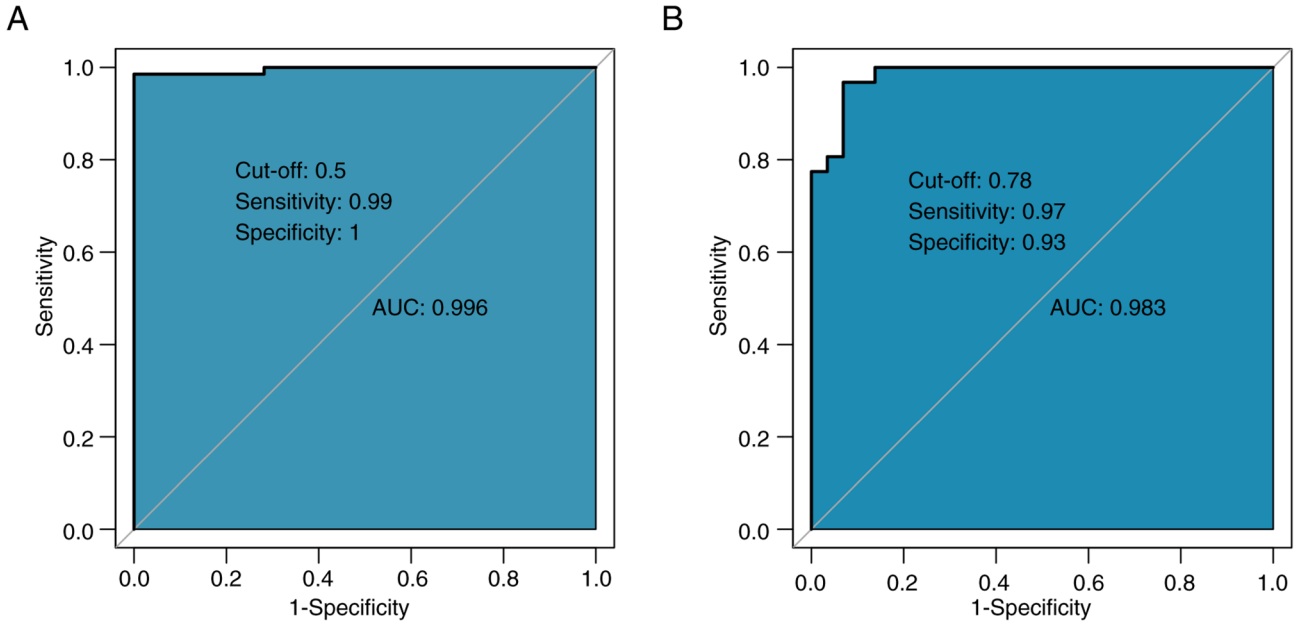

Figure 1. Receiver operating characteristic curve illustrating the ability to predict bone metastasis in lung cancer using a multivariate logistic regression model. (A) Training cohort. The AUC of 0.996 demonstrated excellent discriminative power. An optimal cut-off value of 0.5 was identified, which achieved a sensitivity of 0.99 and a specificity of 1.00. (B) Validation cohort. The model was validated in a validation cohort, where it achieved an AUC of 0.983, which further confirmed its predictive accuracy. AUC, area under curve.

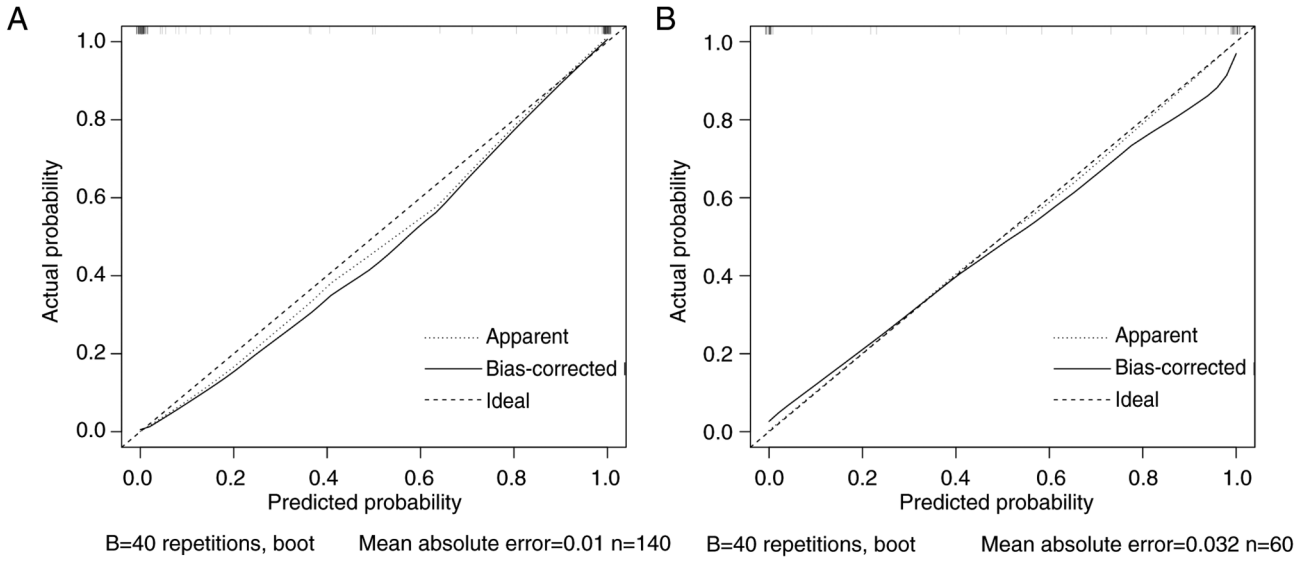

Figure 2. Calibration curve for the predictive model distinguishing lung cancer with bone metastasis from lung cancer without bone metastasis. (A) Training cohort. (B) Validation cohort. Calibration curve of the predictive model, which compared the predicted probabilities to the actual outcomes. The bias-corrected curve closely approximated the ideal curve, which demonstrated excellent alignment and confirmed the precision of the model in distinguishing between lung cancer with and without bone metastasis. The mean absolute error of the model was 0.01 in the training cohort and 0.032 in the validation cohort. 'Apparent' indicates the calibration curve was based on apparent probabilities, 'Bias-corrected' indicates the curve was adjusted for bias using bootstrapping and 'Ideal' indicates the curve where predicted probabilities perfectly matched actual outcomes.

predictive efficacy for bone metastasis. As a traditional tumor marker in lung cancer, CEA levels are generally positively associated with tumor burden, differentiation and disease progression, and previous studies have reported that elevated CEA is associated with an increased risk of lymph node and brain metastases (23,24). Potential mechanisms include the increased adhesion of high CEA-expressing tumor cells to vascular walls or bone tissues, which promote the formation of metastatic foci via interactions with platelets or endothelial cells (25,26). Therefore, close monitoring and timely intervention for bone metastasis should be considered for patients with elevated CEA levels.

Previous studies have supported the association between EGFR mutations and bone metastasis in NSCLC (27-29). EGFR mutations are commonly observed in patients with bone metastases, and EGFR mutation is associated with increased tumor invasiveness and metastasis (30-32). EGFR activation enhances tumor cell proliferation and migration,

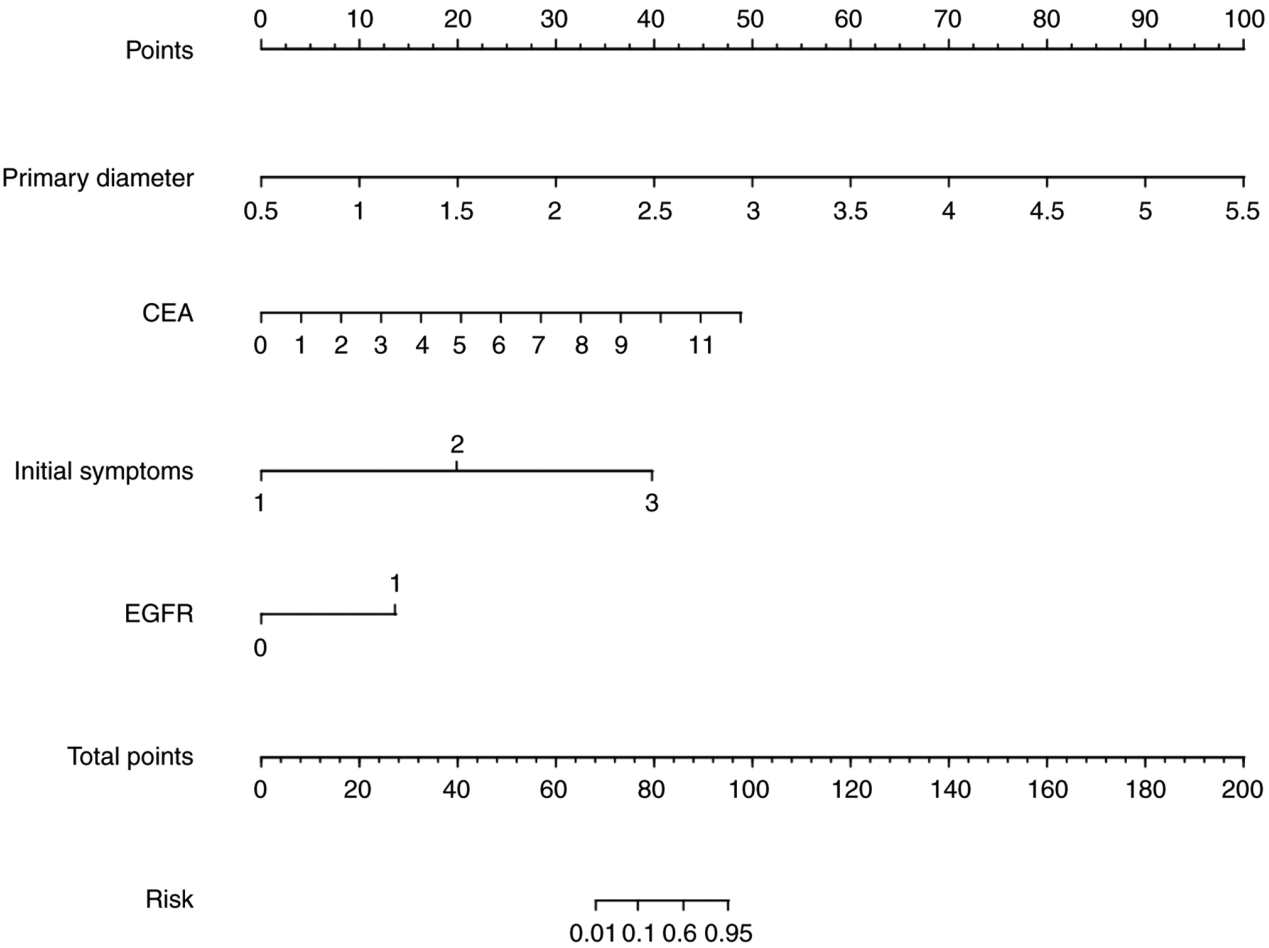

Figure 3. Nomogram for predicting the risk of differentiating lung cancer with bone metastasis from lung cancer without bone metastasis. A nomogram based on the predictive model, which provided a visual representation of the risk scoring system used to differentiate between lung cancer with bone metastasis and without bone metastasis. By converting clinical indicator values into total points, the present nomogram enabled the estimation of the probability of a patient having bone metastasis. CEA, carcinoembryonic antigen.

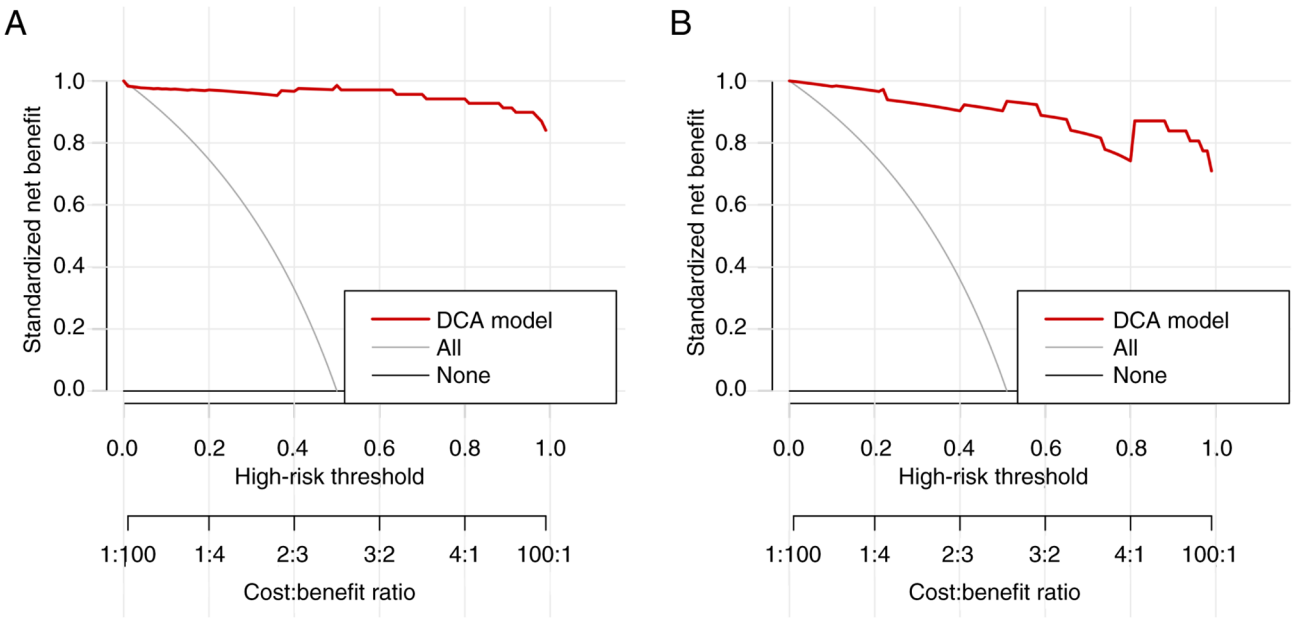

Figure 4. DCA for the predictive model distinguishing lung cancer with bone metastasis from lung cancer without bone metastasis. (A) Training cohort. (B) Validation cohort. A DCA curve, which evaluated the net benefits of the model at varying high-risk thresholds. The model compared these benefits to the scenarios where all patients in the present study were classified as high-risk and where none were classified as high-risk. 'DCA Model' represents the DCA for the predictive model, 'All' indicates the assumption that all patients are at high-risk and 'None' indicates the assumption that no patients are at high-risk. DCA, decision curve analysis.

Table V. Baseline characteristics of patients undergoing different pain treatments.

Patient characteristics	Radiotherapy (n=33)	Opioid treatment (n=33)	Combined treatment (n=34)	P-value
Age, years	64.8 (8.21)	63.6 (7.56)	65.5 (7.43)	0.607
Sex, n (%)				0.307
Male	22 (66.7)	23 (69.7)	28 (82.4)	
Female	11 (33.3)	10 (30.3)	6 (17.6)	
Occupation, n (%)				0.818
No	28 (84.8)	29 (87.9)	28 (82.4)	
Yes	5 (15.2)	4 (12.1)	6 (17.6)	
Family history, n (%)				0.648
No	28 (84.8)	30 (90.9)	31 (91.2)	
Yes	5 (15.2)	3 (9.09)	3 (8.82)	
Smoking status, n (%)				0.031
No	6 (18.2)	1 (3.03)	1 (2.94)	
Yes	27 (81.8)	32 (97.0)	33 (97.1)	
Initial symptoms, n (%)				0.518
Asymptomatic	1 (3.03)	0 (0.00)	1 (2.94)	
Respiratory	16 (48.5)	22 (66.7)	18 (52.9)	
Pain	16 (48.5)	11 (33.3)	15 (44.1)	
Primary location, n (%)				0.675
Central	23 (69.7)	26 (78.8)	26 (76.5)	
Peripheral	10 (30.3)	7 (21.2)	8 (23.5)	
Primary diameter (29)	2.87 (0.77)	2.84 (0.76)	2.83 (0.61)	0.975
Pathology type, n (%)				0.106
SCLC	9 (27.3)	2 (6.06)	4 (11.8)	
SCC	12 (36.4)	20 (60.6)	16 (47.1)	
Adenocarcinoma	12 (36.4)	11 (33.3)	14 (41.2)	
Metastasis location, n (%)				0.503
Spine	20 (60.6)	16 (48.5)	20 (58.8)	
Femur	6 (18.2)	7 (21.2)	5 (14.7)	
Rib	4 (12.1)	3 (9.09)	4 (11.8)	
Sternum	1 (3.03)	4 (12.1)	4 (11.8)	
Other	2 (6.06)	3 (9.09)	1 (2.94)	
EGFR, n (%)				0.818
Negative	5 (15.2)	4 (12.1)	6 (17.6)	
Positive	28 (84.8)	29 (87.9)	28 (82.4)	
CEA, ng/ml	7.47 (2.17)	7.85 (1.97)	7.64 (1.81)	0.740
CA125, U/ml	32.9 (10.7)	30.2 (7.14)	32.0 (9.85)	0.492
CA199, U/ml	36.3 (9.18)	35.6 (8.88)	37.3 (7.67)	0.724
CA153, U/ml	25.2 (7.12)	25.3 (6.31)	26.5 (5.61)	0.670
NSE, ng/ml	37.3 (8.01)	35.7 (9.50)	35.6 (8.24)	0.666
ALP, U/ml	165 (22.1)	171 (31.6)	168 (28.9)	0.746

Age, primary tumor diameter, CEA, CA199, CA125, CA153, NSE and ALP are presented as mean (standard deviation) due to their approximate normal distribution. SCLC, small cell lung cancer; SCC, squamous cell carcinoma; CA, cancer antigen; NSE, neuron-specific enolase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen.

while PI3K/AKT and MAPK/ERK pathways further amplify signaling, which accelerate cell proliferation and promote metastasis (33,34). In the formation of bone metastasis, enhanced EGFR signaling may assist tumor cells in bone growth and in modifying the bone remodeling environment to create metastatic foci (35). This finding further supports the need to monitor bone metastasis in EGFR mutation-positive patients and suggests that EGFR inhibitors may serve a more

Table VI. Comparison of VAS and PSQI before and after treatment for different therapeutic modalities.

Scoring system	Radiotherapy (n=33)	Opioid treatment (n=33)	Combined treatment (n=34)	P-value
VAS before	9.00 [9.00-10.0]	9.00 [8.00-9.00]	9.00 [8.00-9.00]	0.349
VAS after	8.00 [7.00-8.00]	5.00 [5.00-6.00]	3.00 [3.00-3.00]	<0.001
PSQI before	21.0 [15.0-21.0]	17.0 [13.0-21.0]	20.5 [15.0-21.0]	0.134
PSQI after	11.0 [10.0-11.0]	15.0 [14.0-17.0]	6.00 [5.00-6.00]	<0.001

Data are presented as median [interquartile range]. VAS, visual analog scale; PSQI, Pittsburgh Sleep Quality Index; IQR, interquartile range.

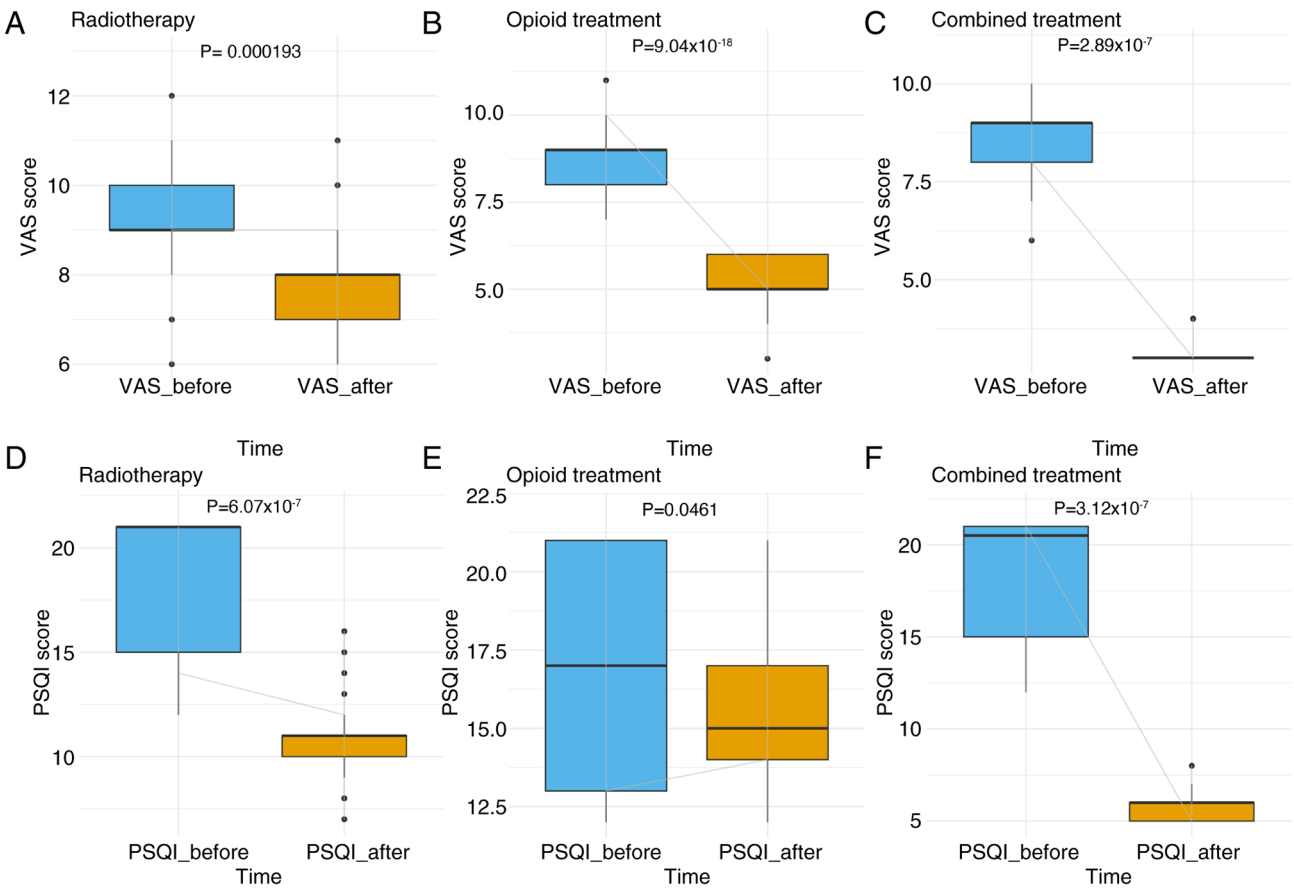

Figure 5. Comparison of VAS and PSQI before and after treatment for different therapeutic modalities. (A) VAS scores of patients before and after radiotherapy. (B) VAS scores before and after opioid treatment. (C) VAS scores before and after combination therapy. (D) PSQI scores of patients before and after radiotherapy. (E) PSQI scores before and after opioid treatment. (F) PSQI scores before and after combination therapy. VAS, visual analog scale; PSQI, Pittsburgh Sleep Quality Index.

active role in the treatment of patients with EGFR mutations. In the present study, the construction of the predictive model for bone metastasis included retrospectively collected data from patients who were newly diagnosed with primary lung adenocarcinoma and had not received any prior treatments, including surgery, chemotherapy or radiotherapy.

In terms of pain relief treatment strategies, the present study indicated that the combined use of palliative radiotherapy and opioid medications was significantly more effective compared with single treatment. Radiotherapy may act directly on bone metastatic sites, which reduces bone destruction and the proliferation of tumor cells within the bone tissue and thereby reduces pain (36). Opioids, on the other hand, directly alleviate pain through neurotransmitter regulation (37). A combined approach not only improves pain management but also enhances the quality of life for patients. In light of the present study findings, clinicians are advised to consider using combined radiotherapy and opioid therapy as a more effective pain management strategy for patients with bone metastasis. Regarding pain management, 87 patients had received chemotherapy either prior to or during the course of treatment as part of a comprehensive therapeutic strategy. However, since the primary aim of this part of the study was to evaluate the efficacy of

palliative radiotherapy, opioid therapy and their combination in managing bone metastasis-related pain, steps were taken to minimize confounding factors. Specifically, only patients who did not receive any new chemotherapy regimens during the pain treatment evaluation period were included in the pain efficacy analysis. Due to this heterogeneity in chemotherapy types, doses and durations, chemotherapy was not included as a uniform variable in the comparative pain analysis. Future prospective studies may further explore the interactions between chemotherapy and pain management efficacy.

The present study has several limitations. First, the risk factors identified in the study were influenced by multiple inclusion variables, including clinical characteristics (such as age, sex and smoking status), tumor markers (ALP, CEA and NSE) and EGFR mutation status. Altering the inclusion or exclusion of any of these variables in the logistic regression models might have led to changes in the final set of risk factors identified. Second, the results were based solely on data from The First Affiliated Hospital, Qiqihar Medical University Hospital, and the findings might differ if applied to patient populations from other centers, which highlights the need for multi-center validation to improve generalizability.

In summary, the present study identified high-risk factors for lung cancer bone metastasis through clinical characteristics, tumor markers and gene mutations, which established an effective prediction model that provides an important reference for early clinical screening, precise diagnosis and treatment. In pain management, the present study demonstrated that combined palliative radiotherapy and opioid therapy can markedly relieve pain and improve the quality of life in patients, which highlighted its value in patients with late-stage lung cancer. Future studies could further optimize the predictive efficacy of the model and verify its applicability with multi-center data. Additionally, with advancements in targeted therapy and immunotherapy, interventions targeting EGFR mutations and other key signaling pathways may offer novel approaches for the prevention and treatment of lung cancer bone metastasis.

The present study elucidated key risk factors for bone metastasis in primary lung cancer, including initial symptoms, tumor diameter, CEA levels and EGFR mutation status. A predictive model was developed to facilitate early screening and targeted interventions. Additionally, the combination of palliative radiotherapy and opioid therapy demonstrated notable efficacy in pain management and thereby improved the quality of life in patients. The present study findings underscored the importance of personalized therapeutic strategies for the management of bone metastasis and highlighted the necessity of integrated approaches for pain alleviation.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QZ and BS designed the manuscript. CC and YG helped with the data analysis. BQ, CL and JF collected the data and participated in data analysis. QZ and BS analyzed the data. QZ and YG confirm the authenticity of all the raw data. All authors contributed to drafting and revising the manuscript and approved the final version for publication.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Qiqihar Medical University (Qiqihar, China; approval no. 2023-008-01). All participants provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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