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ORIGINAL RESEARCH

Platelet/Neutrophil Count Ratio (PNR) and Fibrinogen/Lymphocyte Count Ratio (FLR) Can Be Used as Predictive Indicators of Bone Metastasis in Non-Smoking Patients with Lung Cancer, but Not in Smoking Patients

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Objective: The purpose of this study is to evaluate the relationship between some comprehensive indices (platelet-to-neutrophil ratio (PNR), fibrinogen-to-lymphocyte ratio (FLR), albumin-to-monocyte ratio (AMR)) and bone metastasis of lung cancer.

Methods: A total of 1535 patients with lung cancer treated in Meizhou People's Hospital from November 2017 to May 2025 were retrospectively analyzed. Clinical characteristics (age, body mass index (BMI), bone metastasis, and PNR, FLR, and AMR levels) were collected. The optimal cutoff values of PNR, FLR, and AMR were calculated through the receiver operating characteristic (ROC) curve. The relationships between PNR, FLR, AMR and bone metastasis were analyzed.

Results: There were 665 (665/1535, 43.3%) patients had bone metastasis and 870 (870/1535, 56.7%) without. The levels of PNR (54.11 (38.11, 79.59) vs 50.06 (33.55, 72.10), p=0.004), and FLR (3.88 (2.67, 6.03) vs 3.36 (2.26, 5.27), p<0.001) in patients with bone metastasis were higher, and AMR (67.22 (47.55, 97.00) vs 70.45 (50.66, 104.91), p=0.027) was lower than those in patients without bone metastasis. The levels of PNR and FLR in bone metastasis group were higher than those in non-bone metastasis group among non-smoking patients, while AMR in bone metastasis group was lower than those in non-bone metastasis group among smoking patients. ROC analyses revealed that the critical value was 75.40 and area under the ROC curve (AUC) was 0.673 for PNR as an indicator for bone metastasis, while the critical value was 4.515 and AUC was 0.659 for FLR in non-smoking patients.

Conclusion: In conclusion, lung cancer mainly occurs in elderly men, among whom approximately 43% of patients have bone metastases. PNR and FLR have good predictive value in bone metastasis of non-smoking lung cancer patients.

Keywords: lung cancer, bone metastasis, platelet, to, neutrophil count ratio, fibrinogen, to, lymphocyte count ratio

Introduction

Lung cancer is a malignant tumor that originates from the bronchial mucosa or glands of the lung.[1] According to histological characteristics, it can be divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[2] Among them, NSCLC accounts for approximately 80–85% of lung cancer cases, mainly including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[3] SCLC has a high degree of malignancy and rapid proliferation, accounting for approximately 15–20%.[4,5] According to the latest global cancer statistics, lung cancer is one of the malignant tumors with the highest incidence and mortality rates worldwide, and its incidence and mortality rates are still on the rise.[6] In China, lung cancer also ranks first among malignant tumors in terms of incidence and mortality, seriously threatening the health of the nation.[7]

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Bone metastasis of lung cancer refers to the process in which lung cancer cells migrate to the bones through the blood circulation or lymphatic system, grow within the bones and destroy the bone tissue.[8] It is one of the common distant metastasis sites of lung cancer. The incidence rate varies depending on the type and stage of lung cancer. In patients with advanced lung cancer, the incidence of bone metastasis is approximately 30% to 40%.[9] In patients with SCLC, the incidence of bone metastasis is about 20% to 30%.[10] Among NSCLC, adenocarcinoma has a relatively higher proportion of bone metastasis, accounting for about 40%.[9,11] Bone metastasis of lung cancer not only causes serious complications such as severe pain, pathological fractures, and hypercalcemia, but also significantly reduces the quality of life of patients and shortens their survival time.[9,11] Imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and nuclide bone imaging play an important role in the diagnosis of bone metastasis of lung cancer.[12,13] However, imaging methods have some limitations due to issues such as resolution, specificity, and the tolerance of patients.[14] It is of great value to explore the predictive markers of bone metastasis of lung cancer. The detection of hematological markers has great potential in predicting bone metastasis of lung cancer due to its advantages such as convenient specimen collection, simple detection methods, and high compliance.

In the complex pathological process of tumor metastasis, some cells and molecules cannot be ignored. Platelets can promote tumor angiogenesis by releasing cytokines such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), and form platelet-tumor cell aggregates, enhancing the survival ability and invasiveness of tumor cells and helping tumor cells evade the surveillance of the immune system.[15] Tumor-associated neutrophils (TANs) can release reactive oxygen species (ROS) and matrix metalloproteinases (MMPs), destroy the extracellular matrix and promote the migration of tumor cells. Lymphocytes are the core force of the body's anti-tumor immunity.[16,17] Cytotoxic T lymphocytes (CTL)[18] and natural killer (NK) cells[19] can directly kill tumor cells, while regulatory T cells (Treg)[20] assist tumor cells in escaping by suppressing the immune response. When the number of lymphocytes decreases or their functions are defective, the risk of tumor metastasis increases significantly. Monocytes can differentiate into tumor-associated macrophages (TAMs). TAMs regulate the tumor microenvironment by secreting cytokines and chemokines, and promote tumor angiogenesis, invasion and metastasis.[21,22] Fibrinogen, as a key protein in the coagulation coupling reaction, an increase in its level can activate the coagulation system, form a microenvironment conducive to the adhesion and migration of tumor cells, and at the same time, fibrin clots can also provide mechanical support for tumor cells.[22] Albumin not only maintains the colloid osmotic pressure of plasma, but also can combine with fatty acids, and hormones to exert biological functions. Albumin may indirectly promote tumor metastasis by influencing the metabolism of tumor cells and the nutritional status of the body.[23,24]

Some comprehensive indices reflecting the levels of platelet count, neutrophil count, fibrinogen, lymphocyte count, albumin and monocyte count (such as platelet-to-neutrophil ratio (PNR),[25] fibrinogen-to-lymphocyte ratio (FLR)[26] were related to metastasis in some cancers, and albumin-to-monocyte ratio (AMR)) was related to the progression of NSCLC.[27] However, it is still unclear whether PNR, FLR, and AMR are related to bone metastasis of lung cancer. Diabetes mellitus may have a potential impact on lung function. Is diabetes mellitus a risk factor for bone metastasis of lung cancer?[28,29] In addition, smoking is recognized worldwide as the primary risk factor for lung cancer, and there is a relationship between smoking and the occurrence of bone metastasis in lung cancer.[30] The difference in the risk of bone metastasis in lung cancer between smokers and non-smokers stems from the multiple effects of smoking on the biological behavior of tumor cells,[31,32] the tumor microenvironment,[33] and the balance of bone metabolism.[34,35] Does the relationship between PNR, FLR and AMR and bone metastasis in lung cancer differ between smoking patients and non-smoking patients? To date, no studies have evaluated the predictive value of PNR, FLR, and AMR for bone metastasis in lung cancer stratified by smoking status. So it is also a question that needs to be studied and answered. The purpose of this study is to evaluate the relationship between these comprehensive indices and bone metastasis of lung cancer, and to determine whether there are any differences in this relationship between smoking patients and non-smoking patients.

Materials and Methods

Subjects

The lung cancer patients who were hospitalized in Meizhou People's Hospital from November 2017 to May 2025, were included in this study. Inclusion criteria: (1) diagnosed as primary lung cancer by histopathology or cytology; (2) bone metastasis of the tumor is determined based on the results of whole-body bone scans conducted by emission computed tomography (ECT), CT, MRI, or nuclide bone imaging; (3) platelet count, neutrophil count, fibrinogen, lymphocyte count, albumin, and monocyte count were tested before the treatment; and (4) age ≥18 years old. Exclusion criteria: (1) combined with other histories of malignant tumors; (2) have hematological diseases or are currently undergoing clinical treatment that affects hematological indicators; and (3) clinical data are missing. This study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

Data Collection and Calculation of PNR, FLR, and AMR

Clinical characteristics of the patients were collected from the medical records system of our hospital, including age, gender, body mass index (BMI), and bone metastasis. The results of platelet count, neutrophil count, lymphocyte count, monocyte count, fibrinogen, and albumin were collected during the first hospital examination.

The comprehensive indices (PNR, FLR, and AMR) were calculated according to the following formula:

PNR=platelet count/neutrophil count

FLR=fibrinogen/lymphocyte count

AMR=albumin/monocyte count

Statistical Analysis

SPSS statistical software version 26.0 (IBM Inc., USA) and GraphPad Prism 8.0 were used for data analysis and mapping. Perform normality tests for all continuous variables. Comparisons among variables that follow a normal distribution were analyzed using independent sample *t*-test or one-way analysis of variance (ANOVA). Comparisons among variables that do not follow a normal distribution are conducted using Mann–Whitney *U*-test for groups comparisons or correlation analysis. The categorical variables were compared using by *Chi*-square test. The specificity and sensitivity of the indicators were described using the receiver operating characteristic (ROC) curve analysis. The accuracy of PNR, FLR, and AMR in differentiating bone metastases was evaluated by calculating the area under the ROC curve (AUC), and the optimal cut-off values of PNR, FLR, and AMR were determined using the Youden index. Logistic regression analysis was used to reveal the relationship of PNR, FLR and bone metastasis in non-smoking patients with lung cancer adjusting for other major influencing factors, such as age, gender, BMI, history of alcohol drinking, hypertension, and diabetes mellitus. $p<0.05$.

Results

Clinical Characteristics of Lung Cancer Patients and Comparison of Lung Cancer Patients with and Without Bone Metastasis

A total of 1535 patients with lung cancer, including 1105 (72.0%) elderly (≥60 years old) patients, 1096 (71.4%) male patients. There were 248 (16.2%) cases with underweight, 884 (57.6%) cases with normal weight, and 403 (26.3%) cases with overweight. There were 650 (42.3%), 213 (13.9%), 458 (29.8%), and 198 (12.9%) cases had history of cigarette smoking, alcoholism, hypertension, and diabetes mellitus (Table 1).

There were 665 (665/1535, 43.3%) patients had bone metastasis and 870 (870/1535, 56.7%) without. The platelet count, neutrophil count, monocyte count, and fibrinogen level in patients with bone metastasis were higher than those in patients without bone metastasis (all $p<0.05$). The differences of levels of lymphocyte count, and serum albumin level were not statistically significant (Table 1).

Comparison of PNR, FLR, and AMR in Lung Cancer Patients with or Without Bone Metastasis

The levels of PNR (54.11 (38.11, 79.59) vs 50.06 (33.55, 72.10), $p=0.004$), and FLR (3.88 (2.67, 6.03) vs 3.36 (2.26, 5.27), $p<0.001$) in patients with bone metastasis were higher, and AMR (67.22 (47.55, 97.00) vs 70.45 (50.66, 104.91), $p=0.027$) was lower than those in patients without bone metastasis (Figure 1A).

Table 1 Clinical Characteristics of Lung Cancer Patients and Comparison of Lung Cancer Patients with and Without Bone Metastasis

Clinical Characteristics	Lung Cancer Patients (n=1535)	Non-Bone Metastasis Group (n=870)	Bone Metastasis group (n=665)	χ^2/Z	*p* Values
Age (Years)					
<60, n (%)	430 (28.0%)	232 (26.7%)	198 (29.8%)	χ^2=1.805	0.187
≥60, n (%)	1105 (72.0%)	638 (73.3%)	467 (70.2%)		
Gender					
Male, n(%)	1096 (71.4%)	608 (69.9%)	488 (73.4%)	χ^2=2.259	0.133
Female, n(%)	439 (28.6%)	262 (30.1%)	177 (26.6%)		
BMI (kg/m^2)					
Underweight, n (%)	248 (16.2%)	138 (15.9%)	110 (16.5%)	χ^2=3.346	0.187
Normal weight, n (%)	884 (57.6%)	488 (56.1%)	396 (59.5%)		
Overweight, n (%)	403 (26.3%)	244 (28.0%)	159 (23.9%)		
Cigarette smoking					
No, n(%)	885 (57.7%)	611 (70.2%)	274 (41.2%)	χ^2=130.075	<0.001
Yes, n(%)	650 (42.3%)	259 (29.8%)	391 (58.8%)		
Alcoholism					
No, n(%)	1322 (86.1%)	761 (87.5%)	561 (84.4%)	χ^2=3.051	0.087
Yes, n(%)	213 (13.9%)	109 (12.5%)	104 (15.6%)		
Hypertension					
No, n(%)	1077 (70.2%)	593 (68.2%)	484 (72.8%)	χ^2=3.845	0.056
Yes, n(%)	458 (29.8%)	277 (31.8%)	181 (27.2%)		
Diabetes mellitus					
No, n(%)	1337 (87.1%)	738 (84.8%)	599 (90.1%)	χ^2=9.238	0.003
Yes, n(%)	198 (12.9%)	132 (15.2%)	66 (9.9%)		
Laboratory parameters					
Platelet count (×10^9/L), median (IQR)	245.0 (186.0, 317.0)	226.0 (167.0, 287.25)	276.0 (207.0, 346.5)	Z=−9.608	<0.001
Neutrophil count (×10^9/L), median (IQR)	4.80 (3.06, 7.01)	4.48 (2.80, 6.65)	5.32 (3.42, 7.24)	Z=−4.707	<0.001
Fibrinogen, median (IQR)	4.40 (3.50, 5.62)	4.14 (3.33, 5.35)	4.79 (3.76, 5.92)	Z=−5.994	<0.001
Lymphocyte count (×10^9/L), median (IQR)	1.26 (0.87, 1.69)	1.30 (0.89, 1.70)	1.20 (0.87, 1.65)	Z=−1.821	0.069
Serum albumin (g/L), median (IQR)	36.8 (33.2, 40.0)	36.95 (33.10, 40.00)	36.60 (33.20, 39.90)	Z=−0.243	0.808
Monocyte count (×10^9/L), median (IQR)	0.53 (0.38, 0.71)	0.50 (0.38, 0.70)	0.55 (0.39, 0.73)	Z=−2.163	0.031

Abbreviations: BMI, body mass index; IQR, interquartile range.

Comparison of PNR, FLR, and AMR in Lung Cancer with and Without Bone Metastasis Among Non-Smoking Patients and Smoking Patients, Respectively

In non-smoking patients with lung cancer (n=885), there were 274 patients had bone metastasis and 611 without. The levels of PNR (76.33 (48.92, 102.18) vs 49.38 (32.48, 74.19), p<0.001), and FLR (5.62 (3.21, 7.58) vs 3.38 (2.28, 5.53), p<0.001) in patients with bone metastasis were higher than those in patients without bone metastasis (Table 2 and Figure 1B).

In smoking patients with lung cancer (n=650), there were 391 patients with bone metastasis and 259 without. The level of AMR (62.20 (44.72, 83.62) vs 65.00 (49.86, 92.20), p=0.017) in patients with bone metastasis was lower than those in patients without. There was no statistically significant difference in the levels of PNR and FLR between the two groups of patients (Table 3 and Figure 1C).

Evaluation of the Diagnostic Performance of PNR, FLR and AMR in Bone Metastasis of Lung Cancer Based on ROC Analysis

ROC analyses revealed that the critical value was 75.40 and area under the ROC curve (AUC) was 0.673 for PNR (sensitivity=52.9%, specificity=76.4%, 95% confidence interval (CI)=0.637–0.710), and critical value was 4.515 and AUC was 0.659 for FLR (sensitivity=59.9%, specificity=67.3%, 95% CI=0.621–0.698) as indicators for bone metastasis in non-smoking patients with lung cancer (Figure 2A). The critical value of AMR was 53.705 (sensitivity=41.2%, specificity=71.8%, AUC=0.555) (95% CI=0.510–0.600) in smoking patients with lung cancer (Figure 2B).

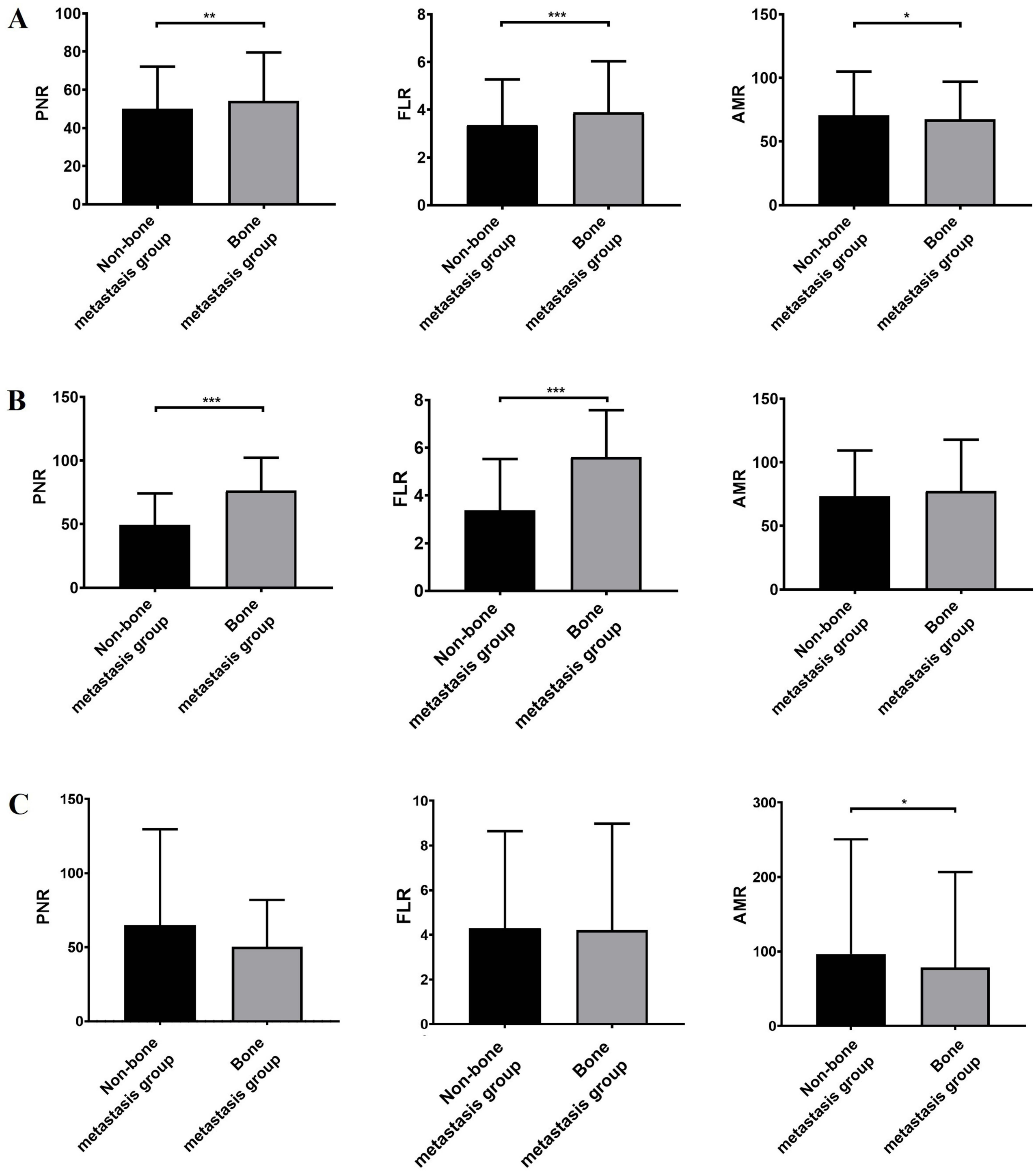

Figure 1 Comparison of PNR, FLR, AMR in lung cancer patients (**A**), non-smoking patients (**B**), and smoking patients (**C**) with and without bone metastasis.
Notes: *, *p*<0.05; **, *p*<0.01; ***, *p*<0.001.
Abbreviations: PNR, platelet-to-neutrophil ratio; FLR, fibrinogen-to-lymphocyte ratio; AMR, albumin-to-monocyte ratio.

Logistic Regression Analysis of the Relationship of PNR, FLR, AMR and Bone Metastasis in Non-Smoking Patients with Lung Cancer

Univariate analysis showed that age <60 years (odds ratio (OR): 1.443, 95% confidence interval (CI): 1.067–1.953, $p=0.017$), female (OR: 2.431, 95% CI: 1.810–3.264, $p<0.001$), high PNR (OR: 3.645, 95% CI: 2.695–4.930, $p<0.001$)

Table 2 Characteristics and Laboratory Parameters of Lung Cancer with and Without Bone Metastasis in Non-Smoking Patients

Clinical Characteristics	Non-smoking Patients with Lung Cancer (n=885)	Non-Bone Metastasis Group (n=611)	Bone Metastasis Group (n=274)	χ^2/Z	*p* Values
Age (Years)					
<60, n (%)	274 (31.0%)	174 (28.5%)	100 (36.5%)	χ^2=5.690	0.018
≥60, n (%)	611 (69.0%)	437 (71.5%)	174 (63.5%)		
Gender					
Male, n(%)	446 (50.4%)	349 (57.1%)	97 (35.4%)	χ^2=35.692	<0.001
Female, n(%)	439 (49.6%)	262 (42.9%)	177 (64.6%)		
BMI (kg/m^2)					
Underweight, n (%)	140 (15.8%)	92 (15.1%)	48 (17.5%)	χ^2=1.786	0.413
Normal weight, n (%)	492 (55.6%)	337 (55.2%)	155 (56.6%)		
Overweight, n (%)	253 (28.6%)	182 (29.8%)	71 (25.9%)		
Alcoholism					
No, n(%)	875 (98.9%)	602 (98.5%)	273 (99.6%)	χ^2=2.079	0.187
Yes, n(%)	10 (1.1%)	9 (1.5%)	1 (0.4%)		
Hypertension					
No, n(%)	598 (67.6%)	406 (66.4%)	192 (70.1%)	χ^2=1.134	0.313
Yes, n(%)	287 (32.4%)	205 (33.6%)	82 (29.9%)		
Diabetes mellitus					
No, n(%)	758 (85.6%)	509 (83.3%)	249 (90.9%)	χ^2=8.819	0.004
Yes, n(%)	127 (14.4%)	102 (16.7%)	25 (9.1%)		
PNR, median (IQR)	55.03 (37.25, 85.26)	49.38 (32.48, 74.19)	76.33 (48.92, 102.18)	Z=−8.261	<0.001
FLR, median (IQR)	3.90 (2.48, 6.26)	3.38 (2.28, 5.53)	5.62 (3.21, 7.58)	Z=−7.594	<0.001
AMR, median (IQR)	75.00 (52.85, 113.75)	73.40 (51.29, 109.25)	77.40 (54.65, 117.77)	Z=−1.668	0.095

Abbreviations: BMI, body mass index; PNR, platelet-to-neutrophil ratio; FLR, fibrinogen-to-lymphocyte ratio; AMR, albumin-to-monocyte ratio; IQR, interquartile range.

Table 3 Characteristics and Laboratory Parameters of Lung Cancer with and Without Bone Metastasis in Smoking Patients

Clinical Characteristics	Smoking Patients with Lung Cancer (n=650)	Non-Bone Metastasis Group (n=259)	Bone Metastasis Group (n=391)	χ^2/Z	*p* Values
Age (Years)					
<60, n (%)	156 (24.0%)	58 (22.4%)	98 (25.1%)	χ^2=0.609	0.454
≥60, n (%)	494 (76.0%)	201 (77.6%)	293 (74.9%)		
Gender					
Male, n(%)	650 (100.0%)	259 (100.0%)	391 (100.0%)	-	-
Female, n(%)	-	-	-		
BMI (kg/m^2)					
Underweight, n (%)	108 (16.6%)	46 (17.8%)	62 (15.9%)	χ^2=0.766	0.683
Normal weight, n (%)	392 (60.3%)	151 (58.3%)	241 (61.6%)		
Overweight, n (%)	150 (23.1%)	62 (23.9%)	88 (22.5%)		
Alcoholism					
No, n(%)	447 (68.8%)	159 (61.4%)	288 (73.7%)	χ^2=10.917	0.001
Yes, n(%)	203 (31.2%)	100 (38.6%)	103 (26.3%)		
Hypertension					
No, n(%)	479 (73.7%)	187 (72.2%)	292 (74.7%)	χ^2=0.494	0.524
Yes, n(%)	171 (26.3%)	72 (27.8%)	99 (25.3%)		

(*Continued*)

Table 3 (Continued).

Clinical Characteristics	Smoking Patients with Lung Cancer (n=650)	Non-Bone Metastasis Group (n=259)	Bone Metastasis Group (n=391)	χ^2/Z	*p* Values
Diabetes mellitus					
No, n(%)	579 (89.1%)	229 (88.4%)	350 (89.5%)	χ^2=0.193	0.701
Yes, n(%)	71 (10.9%)	30 (11.6%)	41 (10.5%)		
PNR, median (IQR)	48.60 (33.74, 64.07)	51.71 (34.93, 69.43)	45.59 (33.09, 59.68)	Z=−1.529	0.110
FLR, median (IQR)	3.33 (2.43, 4.75)	3.29 (2.21, 4.73)	3.34 (2.48, 4.77)	Z=−0.849	0.396
AMR, median (IQR)	63.16 (46.31, 85.88)	65.00 (49.86, 92.20)	62.20 (44.72, 83.62)	Z=−2.377	0.017

Abbreviations: BMI, body mass index; PNR, platelet-to-neutrophil ratio; FLR, fibrinogen-to-lymphocyte ratio; AMR, albumin-to-monocyte ratio; IQR, interquartile range.

and FLR (OR: 3.064, 95% CI: 2.282–4.114, p<0.001) were significantly associated with bone metastasis in non-smoking patients with lung cancer. Multivariate logistic regression analysis showed that female (OR: 3.254, 95% CI: 2.303–4.596, p<0.001), high PNR (OR: 5.202, 95% CI: 3.651–7.412, p<0.001) and FLR (OR: 5.709, 95% CI: 3.978–8.192, p<0.001) were independently associated with bone metastasis in non-smoking patients with lung cancer (Table 4).

Discussion

Primary lung cancer is a common tumor in the respiratory system.[36] Bone tissue, as one of the common sites of hematogenous metastasis, has a relatively high incidence rate.[37] Clinically, most patients are found to have bone metastasis at an advanced stage. The occurrence of bone metastasis is one of the signs of deterioration of the disease, which will significantly shorten the survival time of patients and reduce their quality of life.[38] Imaging examination is currently the most commonly used detection method for diagnosing bone metastases in clinical practice, but it has shortcomings such as not being suitable for repeated examinations multiple times in a short period.[14] Therefore, exploring a cheap and convenient detection indicator for predicting bone metastasis is particularly important for the treatment and prognosis of lung cancer patients. In the past, many scholars have explored the risk factors for predicting and diagnosing bone metastasis of primary lung cancer.[39–41] However, there have been few reports on the correlation and predictive value of PNR, FLR, AMR with bone metastasis of primary lung cancer. This study found that PNR and FLR

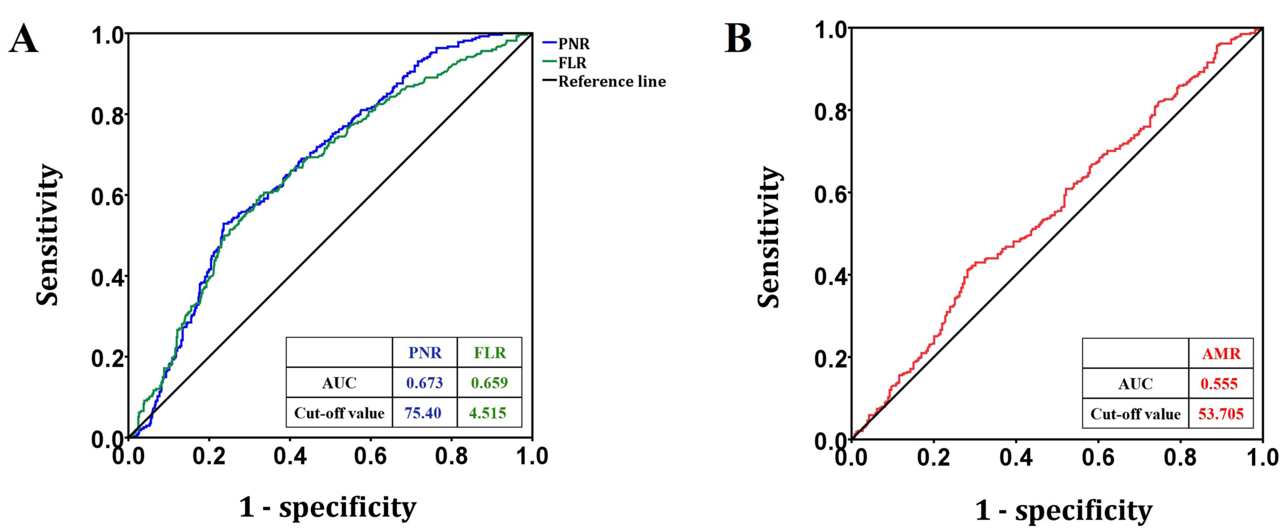

Figure 2 ROC analysis of PNR and FLR used in the prediction of bone metastasis in non-smoking patients with lung cancer (**A**), and AMR used in the prediction of bone metastasis in smoking patients with lung cancer (**B**).
Abbreviations: PNR, platelet-to-neutrophil ratio; FLR, fibrinogen-to-lymphocyte ratio; AMR, albumin-to-monocyte ratio.

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Table 4 Logistic Regression Analysis of Factors Associated with Bone Metastasis in Patients with Lung Cancer

Variables	Unadjusted Values		Adjusted Values	
	OR (95% CI)	*p* Values	Adjusted OR (95% CI)	*p* Values
Age (<60 vs ≥60, years)	1.443(1.067–1.953)	0.017	1.083(0.763–1.539)	0.655
Gender (female vs male)	2.431(1.810–3.264)	<0.001	3.254(2.303–4.596)	<0.001
BMI (kg/m^2)				
Normal weight	1.000 (reference)	–	–	–
Underweight	1.134(0.762–1.688)	0.534	–	–
Overweight	0.848(0.607–1.184)	0.334	–	–
Alcoholism (yes vs no)	0.245(0.031–1.943)	0.183	–	–
Hypertension (yes vs no)	0.846(0.621–1.151)	0.287	–	–
Diabetes mellitus (yes vs no)	0.501(0.315–0.796)	0.003	0.508(0.301–0.857)	0.011
PNR (≥75.40 vs <75.40)	3.645(2.695–4.930)	<0.001	5.202(3.651–7.412)	<0.001
FLR (≥4.515 vs <4.515)	3.064(2.282–4.114)	<0.001	5.709(3.978–8.192)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; PNR, platelet-to-neutrophil ratio; FLR, fibrinogen-to-lymphocyte ratio; AMR, albumin-to-monocyte ratio.

were significantly associated with bone metastasis in non-smoking lung cancer patients and were expected to become novel biomarkers for clinical prediction of bone metastasis.

From the perspective of pathophysiological mechanisms, the abnormal increase of PNR and FLR may reflect the complex inflammation-coagulation cascade reaction in the tumor microenvironment.[42] Platelets play an important role in the migration and adhesion of tumor cells. By releasing cytokines such as vascular endothelial growth factor (VEGF) and transforming growth factor -β (TGF-β), they promote tumor angiogenesis and enhance the invasion ability of tumor cells.[15,43] Neutrophils, as an important component of innate immunity, can be polarized into tumor-associated neutrophils (TANs) in the tumor microenvironment.[44] The matrix metalloproteinases (MMPs) secreted by TANs can degrade the extracellular matrix and create conditions for the metastasis of tumor cells.[45] Furthermore, fibrinogen, as a key factor in the coagulation cascades, not only participates in the formation of thrombi around tumor cells and protects tumor cells from the attack of the immune system,[46] but also enhances the migration ability of tumor cells by binding to integrin receptors.[47,48] Lymphocytes, as the core force of anti-tumor immunity, a decrease in their quantity indicates a decline in the body's anti-tumor immune function,[49,50] which cannot effectively eliminate tumor cells in the circulation, thereby providing an opportunity for distant metastasis of tumors, especially bone metastasis.

From the perspective of biological mechanisms, in non-smoking lung cancer patients, due to the lack of carcinogenic factors related to tobacco exposure, the occurrence and development of tumors may rely more on the body's own inflammation and immune status. PNR and FLR reflect the state of inflammation and immune imbalance in the body. It might explain that PNR and FLR have a predictive effect on the process of bone metastasis in this population. In contrast, smoking behavior may interfere with the correlation between PNR and FLR and bone metastasis through multiple pathways.[51,52] Smoking can cause significant changes in the microenvironment of the lung,[52] and affect tumor biological processes by regulating the methylation of key genes.[53] Harmful substances such as nicotine and tar in the smoke can induce inflammatory responses in the lungs, activate immune cells, and cause changes in the counts of neutrophils, lymphocytes, and so on.[54,55] Such changes may mask the inflammatory and immune signals related to bone metastases. Meanwhile, smoking can also affect the coagulation system and increase the level of fibrinogen.[56] This non-specific increase caused by smoking may weaken the predictive value of FLR for bone metastasis.

In addition, the tumor biological behavior of patients with smoking-related lung cancer differs from that of non-smoking patients.[57] Smoking-related lung cancer patients often have a more complex gene mutation profile (such as a higher rate of *Kirsten rat sarcoma 2 viral oncogene homolog (KRAS)* mutations) and a more aggressive biological phenotype.[58] The metastatic ability of tumor cells may be more dependent on smoking-induced specific molecular pathways (such as abnormal activation of epithelial-mesenchymal transition (EMT))[59] rather than the systemic inflammatory levels reflected by PNR and FLR. Therefore, PNR and FLR are difficult to effectively capture the risk of bone metastasis in smoking patients.

Compared with traditional tumor markers and imaging examinations, PNR and FLR have unique advantages. Blood routine and coagulation function tests, as routine clinical detection items, have the characteristics of simple operation, low cost and strong repeatability, and can be quickly obtained in the early stage of disease diagnosis. Furthermore, these two indicators are not limited by the type and stage of tumor tissue. They can be used as a non-invasive and dynamic tool for monitoring the risk of bone metastasis, which is helpful for clinicians to formulate personalized treatment plans in a timely manner and improve the prognosis of patients.

In addition to this study, several other studies have also reported the relationship between PNR, FLR and tumor metastasis. Wang et al found that elevated PNR is associated with early lymph node metastasis in patients with oral tongue squamous cell carcinoma.[25] Jin et al believed that PNR is a potential biomarker for predicting lymph node metastasis in patients with pT1NxM0 colorectal cancer.[60] Hu et al found that elevated FLR is a risk factor for lymph node metastasis in patients with clinically lymph node negative advanced gastric cancer.[26] Moreover, there have been several reports on the research of PNR and FLR in lung cancer. Cui et al found that PNR has predictive value for the expression level of PD-L1 in lung cancer.[61] Liu et al believed that FLR is related to the stage of non-small cell lung cancer and can be used as an independent prognostic factor for patients with non-small cell lung cancer treated with chemotherapy or chemotherapy combined with surgery.[62]

This study has certain limitations. Firstly, as a single-center retrospective study, the patients in this research were sourced from a single medical institution, which made it difficult to comprehensively reflect the actual distribution of the disease in the general population. The sample representativeness was limited to a certain extent. And the admission selection of patients and the formulation of treatment plans were not based on the randomization principle of the research design, which might lead to potential selection bias. So the universality of the research results needs to be further verified. Secondly, although this study has revealed the relationship between PNR, FLR and bone metastasis in non-smoking lung cancer patients, the results of this study have not been verified externally. Moreover, the specific molecular mechanisms still need to be further explored through basic experiments, such as studying how these indicators affect the interaction between tumor cells and the bone tissue microenvironment through cell experiments and animal models. Thirdly, in this study, PNR and FLR were not combined with other clinical indicators of the patients (such as tumor stage, histological subtype, and treatment history) to construct a more accurate model for predicting bone metastasis. And the AUC of PNR and FLR (0.673 and 0.659, respectively) for predicting bone metastasis of lung cancer are relatively low, suggesting that these two indicators have limited discriminatory power. Furthermore, this study did not conduct long-term follow-up of the patients, and thus the value of PNR and FLR in evaluation of the occurrence time of bone metastasis and the therapeutic effect could not be clarified.

Future research can be carried out in the following directions: First, conduct multi-center and large-sample prospective studies to further verify the clinical value of PNR and FLR in the evaluation of bone metastasis in non-smoking lung cancer patients. Second, by integrating genomics and proteomics techniques, we will deeply explore the molecular mechanisms by which PNR and FLR affect bone metastases and search for potential therapeutic targets. Third, explore the combined application of PNR and FLR with other clinical indicators or molecular markers to construct a more accurate bone metastasis prediction model, providing stronger support for individualized treatment of non-smoking lung cancer patients.

Conclusions

In conclusion, lung cancer mainly occurs in elderly men, among whom approximately 43% of patients have bone metastases. PNR and FLR have good adjunctive diagnostic value in the bone metastasis of non-smoking patients with lung cancer. Of course, larger studies are needed to establish causality and clinical significance. In addition, PNR and FLR need to be combined with other clinical indicators to improve the predictive performance.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital. All participants signed informed consent in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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