Research Article

Lung Adenocarcinoma With Bone Metastases: Clinicogenomic Profiling and Insights Into Prognostic Factors

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Abstract

Introduction: Lung adenocarcinoma is the leading cause of cancer-related mortality worldwide. Understanding the clinicopathological profiles and genomic drivers of its metastatic patterns is a crucial step for risk stratification. Herein, we investigated the clinicogenomic features of bone metastases in lung adenocarcinoma and their prognostic value.

Methods: A retrospective cohort study with a total of 4064 patients with various metastatic patterns of lung adenocarcinoma were included, obtaining relevant clinical data and genomic profiles. Patients were categorized based on the presence or absence of bone metastases. A comparative analysis of both groups in terms of demographics, disease status, somatic mutations, and microsatellite instability was carried out. Significantly different variables were tested for their association with bone metastases. Cox regression analyses were utilized to identify independent survival prognostic variables in the bone metastases sub-cohort.

Results: Gender, concomitant metastases (to adrenal gland, nervous system, lymph nodes, liver, lung, mediastinum, pleura, and skin), and aberrations in *TP53*, *EGFR*, *KEAP1*, and *MYC* were associated with bone metastases in lung adenocarcinoma. Survival analyses within the bone metastases sub-cohort have illustrated the following variables to possess poor prognostic signature including age > 75, female gender, White ethnicity, distant metastases (adrenal gland, central nervous system, intra-abdominal, and liver), *EGFR* (wild type), *KEAP1* (mutant), *MYC* (mutant), *KRAS* (mutant), and *SMARCA4* (mutant).

Conclusion: Key clinical and genomic factors associated with lung adenocarcinoma bone metastases have been highlighted, providing exploratory insights into high-risk individuals. Future studies should be directed to validate these prognostic variables in larger, more diverse cohorts to enhance generalizability.

Keywords

non-small-cell lung cancer, lung adenocarcinoma, bone metastases, clinicopathological predictors, MSK-MET cohort, prognostic factors

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Introduction

Lung cancer remains the leading cause of cancer-related mortality globally, characterized by diverse clinical presentations and poor outcomes. Overall, the incidence within 2024 has declined at a rate of 2.5% in men and 1% in women. According to the American Cancer Society (ACS), an estimated 234 580 new lung cancer cases are expected to be diagnosed in the United States, with approximately 80% classified as non-small cell lung cancer (NSCLC) and 14% as small cell lung cancer (SCLC). The reduction in lung cancer mortality, 59% in men and 36% in women compared to rates from the late 1990s and early 2000s can be largely attributed to decreased smoking prevalence and advances in early detection through improved diagnostic techniques.[1]

NSCLC is categorized based on histological features into three main subtypes: lung adenocarcinoma (LUAD), squamous cell carcinoma (LUSC), and large cell carcinoma (LCC).[2] LUAD is the most prevalent subtype of NSCLC, accounting for approximately 50% of cases. LUAD typically presents at an advanced stage, often exhibiting both local and distant metastasis, with a 5-year mortality rate ranging from 51% to 99%.[3,4] It is particularly common among non-smokers, females, and individuals of Asian descent, with a propensity to originate in the distal airways.[5,6] Histologically, LUAD is distinguished by glandular differentiation or mucin production within the airways. According to the 2021 World Health Organization (WHO) classification, LUAD is further categorized based on the predominant histological pattern into lepidic, acinar, papillary, micropapillary, solid, invasive mucinous, minimally invasive, and adenocarcinoma in situ.[7]

Bone metastases, manifesting as skeletal-related events (SREs), represent a frequent manifestation of hematogenous metastases and are indicative of disease progression across various cancer types. The advancement in oncologic therapy has increased overall survival (OS) in cancer patients, increasing the likelihood of SREs.[8] Approximately 20-30% of NSCLC patients develop bone metastases at diagnosis, and 35-60% will develop them during the disease.[9] The most commonly involved locations are the thoracic, lumbar, and cervical/sacral vertebrae. Clinically, bone involvement may manifest as pain, pathological fractures, spinal cord compression, and hypercalcemia.[10,11] Regarding the burden of bone metastases; it carries a significant risk for morbidity and mortality. The median survival of lung cancer patients with bone metastases has been reported to be around 6 to 7 months.[12,13]

The predominant mechanism of tumor invasion in bone involves osteolytic destruction, a process driven primarily by osteoclast differentiation rather than direct destruction by tumor cells. It is mediated by complex interactions within the bone microenvironment, involving tumor-derived factors such as PTHrP, TNF, TGF-β, and IL-8. Bone resorption further amplifies this process by releasing bone-derived growth factors, perpetuating a vicious cycle of tumor progression.[14] PTHrP works through the activation of the RANKL/RANK pathway; which is crucial for osteoclast differentiation and maturation. Osteoclasts are activated in advanced lung cancer by circulating miR-21, a microRNA overexpressed in various malignancies, promoting the differentiation of monocytes into osteoclasts.[15] Moreover, inflammatory mediators like IL-7, which are produced by lung cancer cells, can stimulate T-cell mediated cytokines, including the RANKL and TNF-α to further promote osteoclastogenesis.[16] Other mechanisms involving immune cells include the role of enzymes such as tryptase, which facilitates tumor invasion, and the activation of SFK by CDCP1.[17,18] Chemokines such as CX3CL1 and CCL12 are prominently involved in the development of spinal metastases as well.[19,20] Other mediators include PDGFR-β, MMPs, and VEGF.[9]

Lung cancer is also known as a "disease of the genome", which underscores the importance of understanding its genetic profiles to tailor individual therapeutic regimens. This is however a developing field, and not enough information is known regarding the genetic characteristics of various primary and metastatic lung cancers. In our study, we further investigate the crucial role of clinical and genomic prognostic factors in LUAD bone metastases as a step forward in identifying high-risk patients.

Materials and Methods

This is a retrospective observational study aimed to identify clinical and genomic variables associated with bone metastases in LUAD and to assess their value as prognostic markers. The manuscript was prepared in concordance with the Equator guidelines (STROBE guidelines).[21]

Data Acquisition and Processing

The MSK MetTropism cohort was accessed on the 9th of August, 2024 through cBioPortal; a web-based bioinformatics tool designed to retrieve and visualize large-scale genomic and transcriptomic data.[22] The MSK MetTropism cohort was assembled using clinical and genomic data from over 25 000 patients with metastatic diseases.[23] The LUAD MSK MetTropism cohort (n = 4064) was downloaded. Cohort demographics (age, gender, and ethnicity), metastatic patterns (adrenal gland, biliary tract, urinary tract, bone, bowel, breast, central nervous system, peripheral nervous system, male genital, female genital, distant lymph nodes, head and neck, intra-abdominal, kidney, liver, lung, mediastinal, ovary, pleura, and skin), microsatellite instability type, and somatic mutation profiles were included in the analysis. The OS data defined as the length of time from either the date of diagnosis or the start of treatment until the loss of follow-up or death of any cause were obtained as well. Manual inspection and curation of the data were performed to ensure data quality before statistical analysis. The LUAD MSK MetTropism cohort was subdivided based on the presence (n = 1591) or

absence (n = 2473) of bone metastasis. The no lung metastases group contained patients with non- metastatic LUAD and metastatic LUAD with various metastases patterns.

Statistical Analysis

Statistical analysis using IBM SPSS statistical package for Windows v.26 (Armonk, New York, USA) and GraphPad Prism v.9.3.1 (San Diego, California, USA) was performed as previously described with slight modifications.[24,25] The cohort's demographics and clinical characteristics were analyzed. Nominal data were presented as counts (n) and percentages (%). On the other hand, continuous normally distributed variables were presented as mean ± standard error of the mean (SEM) while continuous non-normally distributed variables were presented as median (interquartile range (IQR)). Kolmogorov-Smirnov test, Shapiro-Wilk test, and quantile-quantile (Q-Q) plots were used to assess data normality. Comparison between bone metastases and no bone metastases groups in terms of clinical and somatic mutations were performed as follows: statistical analysis of categorical variables was conducted using the *Chi*-square test or Fisher's exact test. Significance across continuous variables was identified using paired and unpaired *t*-test, Welch's corrected unpaired *t*-test, Wilcoxon matched pairs test, Mann-Whitney U-test, one-way ANOVA, and Kruskal-Wallis based on the number of groups, data normality, and equality of variance.

Significantly associated variables with bone metastases were evaluated using univariate and multivariate binary logistic regression after variables dichotomization. Survival analysis of the Kaplan-Meier (KM) curves was performed using the log-rank test reporting the hazard ratio (HR), 95% confidence interval (95% CI), and a *P*-value. Univariate and multivariate Cox logistic regression analysis was used to identify the independent prognostic significance of the test variables. All statistical tests conducted were two-sided, and a *P*-value ≤ .05 was considered to indicate statistical significance.

Results

Demographics and Clinical Characteristics of the MSK-MET LAUD Cohort

Table 1 represents the demographics and clinical characteristics of the MSK MetTropism LAUD cohort. This cohort consisted of 4064 patients. The median age at first metastases was 66.25 years (IQR: 14.59), with median ages at sequencing and surgical procedures of 67.23 years (IQR: 14.55) and 66.87 years (IQR: 14.60), respectively. The cohort was predominantly female (61.70%, n = 2506), with (38.30%, n = 1557) being male. The majority of patients identified as White (82.20%, n = 3188), followed by Asian/Indian (10.80%, n = 420), and African-American (4.90%, n = 190).

Metastatic sites varied significantly, with the lung being the most common site (40.90%, n = 1664), followed by bone (39.10%, n = 1591), pleura (35.50%, n = 1441), central nervous system (28.10%, n = 1142), liver (18.40%, n = 747), and distant lymph nodes (16.70%, n = 678). Other metastatic sites included the adrenal gland (12.60%, n = 514), peripheral nervous system (12.10%, n = 490), mediastinal (8.20%, n = 332), intra-abdominal regions (6.50%, n = 265), biliary tract (4.90%, n = 200), kidney (2.80%, n = 112), skin (2.20%, n = 90), bowel (1.60%, n = 67), head and neck (1.40%, n = 56), urinary tract (0.90%, n = 35), female genital (0.80%, n = 32), breast (0.60%, n = 24), male genital (0.30%, n = 12) and ovary (0.30%, n = 11). A significant proportion of patients (50.00%, n = 2034) had metastases at an unspecified "other" site.

Microsatellite instability type was predominantly stable (97.30%, n = 3480), with (2.50%, n = 89) showing intermediate instability and (0.20%, n = 7) being unstable. Overall survival revealed that (58.10%, n = 2360) of patients were alive at the time of database construction, while (41.90%, n = 1704) were deceased.

Demographics and Clinical Characteristics Differences Between Bone Metastases and No Bone Metastases Groups

Table 2 represents the demographics and clinical characteristics differences between bone metastases and no bone metastases groups. The bone metastases group showed a slightly lower median age at first metastases compared to the no bone metastases group (65.30 years (IQR: 14.83) vs 67.16 years (IQR: 14.62); $P < .001$). Similar patterns were observed for age at sequencing (66.20 years (IQR: 14.34) vs 68.18 years (IQR: 14.28); $P < .001$) and age at surgical procedure (65.93 years (IQR: 14.40) vs 67.87 years (IQR: 14.42); $P < .001$). While both groups were predominantly female (57.70% vs 64.20%, respectively), the difference was statistically significant ($P < .001$). The ethnic distribution was statistically significant between the two groups ($P = .034$), with white being the most predominant in the bone metastases group 83.20% (n = 1233), followed by Asian/Indian 10.90% (n = 166), and African-American 6.00% (n = 92). Regarding the no bone metastases group, white was the most predominant 83.20% (n = 1955), followed by Asian/Indian 10.80% (n = 254), and African-American 4.20% (n = 98).

Various metastatic sites were significantly different between the bone metastases group and no bone metastases group including adrenal glands (23.80% (n = 379) vs 5.50% (n = 135); $P < .001$), biliary tract (9.30% (n = 148) vs 2.10% (n = 52); $P < .001$), urinary tract (1.50% (n = 24) vs 0.40% (n= 11); $P < .001$), bowel (2.50% (n = 40) vs 1.10% (n = 27); $P < .001$), breast (1.00 % (n = 16) vs 0.30% (n = 8); $P = .006$), central nervous system (49.00% (n = 779) vs 14.7% (n = 363); $P < .001$), peripheral nervous system (27.70% (n = 441) vs 2.00% (n = 49); $P < .001$), female genital (1.10% (n = 18) vs

Table 1. MSK MetTropism LAUD Cohort Demographics and Clinical Characteristics.

Variables	MSK MetTropism LAUD (n = 4064)
Age at first metastases (years)	66.25 (14.59)
Age at sequencing (years)	67.23 (14.55)
Age at surgical procedure (years)	66.87 (14.60)
Gender	
Male	1557 (38.30)
Female	2506 (61.70)
Ethnicity	
White	3188 (82.20)
African-American	190 (4.90)
Asian/Indian	420 (10.80)
Other	78 (2.01)
Metastases sites	
Adrenal gland	514 (12.60)
Biliary tract	200 (4.90)
Urinary tract	35 (0.90)
Bone	1591 (39.10)
Bowel	67 (1.60)
Breast	24 (0.60)
Central nervous system	1142 (28.10)
Peripheral nervous system	490 (12.10)
Male genital	12 (0.30)
Female genital	32 (0.80)
Distant Lymph nodes	678 (16.70)
Head and neck	56 (1.40)
Intra-abdominal	265 (6.50)
Kidney	112 (2.80)
Liver	747 (18.40)
Lung	1664 (40.90)
Mediastinal	332 (8.20)
Ovary	11 (0.30)
Pleura	1441 (35.50)
Skin	90 (2.20)
Other	2034 (50.00)
Microsatellite instability type	
Stable	3480 (97.30)
Intermediate	89 (2.50)
Instable	7 (0.20)
Overall survival	
Alive	2360 (58.10)
Deceased	1704 (41.90)

Data are presented as median (IQR) or *n* (%).

0.60% (n = 14); $P = .047$), distant lymph nodes (27.20% (n = 432) vs 9.90% (n = 246); $P < .001$), head and neck (1.90% (n = 30) vs 1.10% (n = 26); $P = .026$), intra-abdominal (11.90% (n = 189) vs 3.10% (n = 76); $P < .001$), kidney (5.40% (n = 86) vs 1.10% (n = 26); $P < .001$), liver (37.00% (n = 588) vs 6.40% (n = 159); $P < .001$), lung (60.00% (n = 954) vs 28.70% (n = 710); $P < .001$), mediastinal (13.00% (n = 207) vs 5.10% (n = 125); $P < .001$), pleura (46.40% (n = 738) vs 28.40% (n = 703); $P < .001$), and skin (4.00% (n = 64) vs 1.10% (n = 26); $P < .001$). No statistical differences between the bone metastases and no bone metastases groups were noted between male genital (0.40% (n = 7) vs 0.20% (n = 5); $P = .173$) and ovaries (0.30% (n = 5) vs 0.20% (n = 6); $P = .668$).

Microsatellite instability type was statistically significant between the bone metastases and no bone metastases groups ($P = .005$), with the stable type being most predominant between them at 96.20% (n = 1355) vs 98.00% (n = 2125), followed by intermediate 3.60% (n = 50) vs 1.80% (n = 39), and instable 0.20% (n = 3) vs 0.20% (n = 4). The overall death

Table 2. Comparison of Patient Characteristics With and Without Bone Metastases Within the MSK MetTropism LAUD Cohort.

Variables	Bone metastases group (n = 1591)	No bone metastases group (n = 2473)	χ^2	*P*-value
Age at first metastases (years)	65.30 (14.83)	67.16 (14.62)		<.001
Age at sequencing (years)	66.20 (14.34)	68.18 (14.28)		<.001
Age at surgical procedure (years)	65.93 (14.40)	67.87 (14.42)		<.001
Gender				
Male	673 (42.30)	884 (35.8)	17.52	<.001
Female	918 (57.70)	1588 (64.20)		
Ethnicity				
White	1233 (83.20)	1955 (83.20)	8.67	.034
African-American	92 (6.00)	98 (4.20)		
Asian/Indian	166 (10.90)	254 (10.80)		
Other	36 (2.40)	42 (1.80)		
Metastases sites				
Adrenal gland	379 (23.80)	135 (5.50)	295.48	<.001
Biliary tract	148 (9.30)	52 (2.10)	107.25	<.001
Urinary tract	24 (1.50)	11 (0.40)	12.83	<.001
Bowel	40 (2.50)	27 (1.10)	12.08	<.001
Breast	16 (1.00)	8 (0.30)	7.67	.006
Central nervous system	779 (49.00)	363 (14.7)	563.24	<.001
Peripheral nervous system	441 (27.70)	49 (2.00)	604.65	<.001
Male genital	7 (0.40)	5 (0.20)		.173
Female genital	18 (1.10)	14 (0.60)	3.96	.047
Distant Lymph nodes	432 (27.20)	246 (9.90)	206.18	<.001
Head and neck	30 (1.90)	26 (1.10)	4.96	.026
Intra-abdominal	189 (11.90)	76 (3.10)	123.17	<.001
Kidney	86 (5.40)	26 (1.10)	68.49	<.001
Liver	588 (37.00)	159 (6.40)	601.44	<.001
Lung	954 (60.00)	710 (28.70)	391.06	<.001
Mediastinal	207 (13.00)	125 (5.10)	81.69	<.001
Ovary	5 (0.30)	6 (0.20)		.668
Pleura	738 (46.40)	703 (28.4)	136.44	<.001
Skin	64 (4.00)	26 (1.10)	39.47	<.001
Other	996 (62.60)	1038 (42.00)	164.80	<.001
Microsatellite instability type				
Stable	1355 (96.20)	2125 (98.00)	10.54	.005
Intermediate	50 (3.60)	39 (1.80)		
Instable	3 (0.20)	4 (0.20)		
Overall survival				
Alive	547 (34.40)	1813 (73.30)	602.64	<.001
Deceased	1044 (65.60)	660 (26.70)		

Data are presented as median (IQR) or *n* (%).

was significant between bone metastases and no bone metastases (65.60% (n = 1044) vs 26.70% (n = 660; $P < .001$).

Somatic Mutation Landscape Differences Between Bone Metastases and No Bone Metastases Groups

A comparative analysis including 932 mutated genes between bone metastases and no bone metastases sub-cohorts was performed (Supporting information, Table S1). A total of 11 genes were significantly different. The most common one was *TP53* (56.32%, n = 896 vs 42.82%, n = 1059, *Q*-value < .0001). Other genes include *CDKN2B* (14.77%, n = 235 vs 7.80%, n = 193, *Q*-value < .0001), *CDKN2A* (21.18%, n = 337 vs 13.75%, n = 340, *Q*-value < .0001), *FOXA1* (7.98%, n = 127 vs 4.00%, n = 99, *Q*-value < .0001), *RAC1* (2.45%, n = 39 vs 0.61%, n = 15, *Q*-value < .001), *EGFR* (34.51%, n = 549 vs 27.66%, n = 684, *Q*-value < .001), *KEAP1* (17.54%, n = 279 vs 12.41%, n = 307, *Q*-value < .001), *MYC* (7.92%, n = 126 vs 4.49%, n = 111, *Q*-value < .001), *NFKBIA* (7.87%, n = 113 vs 4.71%, n = 111, *Q*-value < .01), and *SMARCA4* (11.00%, n = 175 vs 7.40%, n = 183,

Q-value < .01). All the aforementioned genes were enriched in patients with bone metastasis. On the other hand, *KRAS* mutations were enriched within the no-bone metastases cohort (30.55%, n = 486 vs 36.60%, n = 905, *Q*-value < .01).

Clinical and Genomic Factors Associated With Bone Metastases of LUAD

The association of clinical and genomic variables with bone metastases of LUAD was assessed using univariate binary regression analysis (Table 3). Subsequently, the independent impact of significantly associated variables of the later analysis was confirmed using multivariate binary regression analysis (Table 3). The multivariate model demonstrated independent association of several variables with bone metastases as in gender (OR = 1.34, 95% CI = 1.12-1.603, *P* = .001), adrenal gland metastases (OR = 2.281, 95% CI = 1.734-2.999, *P* < .001), central nervous system metastases (OR = 2.475, 95% CI = 2.03-3.017, *P* < .001), peripheral nervous system metastases (OR = 10.212, 95% CI = 7.026-14.844, *P* < .001), distant lymph nodes metastases (OR = 1.47, 95% CI = 1.148-1.881, *P* = .002), liver (OR = 4.331, 95% CI = 3.397-5.521, *P* < .001), lung (OR = 1.921, 95% CI = 1.6-2.306, *P* < .001), mediastinal metastases (OR = 1.483, 95% CI = 1.088-2.021, *P* = .013), pleura metastases (OR = 1.477, 95% CI = 1.227-1.779, *P* < .001), *TP53* mutation (OR = 1.231, 95% CI = 1.027-1.475, *P* = .024), *EGFR* mutation (OR = 1.358, 95% CI = 1.093-1.686, *P* = .006), *KEAP1* mutation (OR = 1.385, 95% CI = 1.075-1.785, *P* = .012), and *MYC* mutation (OR = 1.455, 95% CI = 1.019-2.079, *P* = .039).

The Survival Prognostic Value of Clinical and Genomic Variables in the Bone Metastases of LUAD

The survival prognostic value of several clinical and genomic variables was tested firstly using KM curves (Figures 1 and 2) and univariate Cox regression analysis (Table 4). Subsequently, the independent impact of significantly associated variables of the later analysis was confirmed using multivariate Cox regression analysis (Table 4). The following variables showed significant association with survival after adjusting for other variables as in age at (HR = 1.179, 95% CI = 1.022-1.361, *P* = .024), gender (HR = 1.305, 95% CI = 1.138-1.497, *P* < .001), and metastases sites, such as Adrenal gland (HR = 1.249, 95% CI = 1.070-1.457, *P* = .005) central nervous system (HR = 1.188, 95% CI = 1.035-1.365, *P* = .014), intra-abdominal metastases (HR = 1.481, 95% CI = 1.219-1.798, *P* < .001), liver metastases (HR = 1.427, 95% CI = 1.240-1.643, *P* < .001). On the other hand, distant lymph node metastases (HR = 1.309, 95% CI = 1.119-1.531, *P* = .001) had a better prognosis. Regarding the genomic alternations, patients with *EGFR* mutations had a better prognosis (HR = 1.234, 95% CI = 1.047-1.455), *P* = .012). While patients with *KEAP1* mutation (HR = 1.594, 95% CI = 1.332-1.908, *P* < .001), *MYC* mutation (HR = 1.353, 95% CI = 1.066-1.716), *P* = .013), *KRAS* mutation (HR = 1.304, 95% CI = 1.110-1.533, *P* = .001), and *SMARCA4* mutation (HR = 1.578, 95% CI = 1.280-1.946, *P* < .001) had worse prognosis.

Discussion

Using the MSK MetTropism LUAD cohort, we analyzed patients' clinical, and genomic data associated with LUAD bone metastases and their prognostic potential. In this cohort, 39.14% of patients had bone metastases at diagnosis. Age was the first variable analyzed, with the median age at presentation being lower in patients with metastases compared to those without (65.30 vs 67.16 years, *P* < .001). However, age was neither associated nor prognostic within the bone metastases sub-cohort, despite several studies presenting age as a prognostic factor in patients with bone metastases.[26-28] Gender was the second variable examined. Cancer epidemiology frequently reports disparities in tumor onset, progression, prognosis, and therapeutic response between males and females, with males generally at higher risk of developing cancer.[29,30] However, in our analysis, the female gender was significantly associated with an increased risk of bone metastases (OR = 1.34, 95% CI = 1.12-1.603, *P* = .001) and worse OS (HR = 1.305, 95% CI = 1.138-1.497, *P* < .001). These results diverge from existing literature, which generally associates the female gender with improved survival and a lower incidence of bone metastases compared to males. Ethnicity was also found to be associated with OS, but it did not demonstrate an association with bone metastases (HR = 1.248, 95% CI = 1.138-1.497, *P* < .001), with white patients exhibiting worse survival outcomes compared to non-whites. Wang et al. reported that ethnicity did not have predictive or prognostic significance in the bone metastases group.[27] In contrast, Xu et al. showed that ethnicity was associated with both prediction and OS, with Asian or Pacific Islanders (API) being more likely to develop bone metastases than white and African American patients. However, the overall prognosis was worse for African-American patients, followed by white patients, with the best outcomes seen in the API group.[31] These findings highlight the potential role of ethnicity in influencing disease progression and OS, emphasizing the need to consider this factor in patient management. We also assessed metastases to other organs, with several sites showing potential correlations with concurrent bone metastasis, including the adrenal glands, liver, lungs, mediastinum, pleura, and central and peripheral nervous systems. However, few of these sites demonstrated an association with OS. Wang et al. identified liver and brain metastases as predictors of bone metastases in lung cancer patients, but only liver metastases impacted overall survival.[27] Zheng et al. similarly found liver metastases to be associated with worse survival outcomes.[28] While Xu et al. showed that lymph node involvement, and metastases to the lungs, liver, and brain, increased the risk of bone metastases.[31]

Table 3. Univariate and Multivariate Binary Logistic Regression Analyses Testing Clinical and Genomic Variables Associated With Bone Metastases Status Within the MSK MetTropism LAUD Cohort.

	Univariate analyses		Multivariate analyses	
Variables*	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age at sequencing (years)	1.474 (1.293-1.679)	<.001	1.023 (0.854-1.225)	.804
Gender	1.317 (1.157-1.498)	<.001	1.34 (1.12-1.603)	.001
Ethnicity	1.183 (1.001-1.398)	.048	0.847 (0.668-1.073)	.168
Metastases sites				
Adrenal gland	5.416 (4.397-6.670)	<.001	2.281 (1.734-2.999)	<.001
Biliary tract	4.775 (3.458-6.593)	<.001	1.133 (0.74-1.734)	.567
Urinary tract	3.428 (1.675-7.018)	.001	0.797 (0.29-2.189)	.66
Bowel	2.336 (1.428-3.822)	.001	0.776 (0.38-1.585)	.486
Breast	3.130 (1.336-7.331)	.009	1.327 (0.393-4.486)	.649
Central nervous system	5.576 (4.807-6.469)	<.001	2.475 (2.03-3.017)	<.001
Peripheral nervous system	18.970 (14.006-25.694)	<.001	10.212 (7.026-14.844)	<.001
Female genital	2.010 (0.997-4.053)	.051		
Distant Lymph nodes	3.374 (2.841-4.007)	<.001	1.47 (1.148-1.881)	.002
Head and neck	1.809 (1.066-3.070)	.028	0.678 (0.317-1.452)	.317
Intra-abdominal	4.252 (3.232-5.593)	<.001	1.335 (0.91-1.96)	.14
Kidney	5.378 (3.452-8.378)	<.001	1.248 (0.697-2.235)	.456
Liver	8.532 (7.054-10.319)	<.001	4.331 (3.397-5.521)	<.001
Lung	3.719 (3.256-4.247)	<.001	1.921 (1.6-2.306)	<.001
Mediastinal	2.809 (2.228-3.542)	<.001	1.483 (1.088-2.021)	.013
Pleura	2.178 (1.910-2.485)	<.001	1.477 (1.227-1.779)	<.001
Skin	3.945 (2.489-6.250)	<.001	1.895 (1.016-3.534)	.044
Microsatellite instability type	1.933 (1.285-2.907)	.002	0.907 (0.512-1.605)	0.738
Genomic alternations				
TP53	1.721 (1.516-1.955)	<.001	1.231 (1.027-1.475)	.024
CDKN2B	2.047 (1.673-2.505)	<.001	1.522 (0.998-2.321)	.051
CDKN2A	1.686 (1.428-1.990)	<.001	0.898 (0.632-1.275)	.547
FOXA1	2.080 (1.587-2.727)	<.001	1.298 (0.812-2.073)	.276
RAC1	4.118 (2.262-7.495)	<.001	1.664 (0.712-3.89)	.239
EGFR	1.378 (1.203-1.579)	<.001	1.358 (1.093-1.686)	.006
KEAP1	1.500 (1.258-1.789)	<.001	1.385 (1.075-1.785)	.012
MYC	1.830 (1.406-2.382)	<.001	1.455 (1.019-2.079)	.039
K-RAS	1.312 (1.147-1.501)	<.001	1.063 (0.866-1.304)	.559
NFKBIA	1.627 (1.242-2.131)	<.001	1.099 (0.696-1.736)	.685
SMARCA4	1.547 (1.244-1.922)	<.001	1.046 (0.769-1.422)	.776

*Variables were dichotomized as follows (age: >75 or ≤ 75, gender: female or male, ethnicity: white, non-white, metastases sites: Adrenal gland vs no Adrenal gland , Biliary tract vs no Biliary tract, Urinary tract vs no Urinary tract, Bowel vs no Bowel, Breast vs no Breast, Central nervous system vs no Central nervous system, Peripheral nervous system vs no Peripheral nervous system, Female genital vs no Female genital, Distant lymph nodes vs no Distant lymph nodes, Head and neck vs no Head and neck, Intra-abdominal vs no Intra-abdominal, Kidney vs no Kidney, Liver vs no Liver, Lung vs no Lung, Mediastinal vs no Mediastinal, Pleura vs no Pleura, Skin vs no Skin, Microsatellite instability vs no Microsatellite instability, mutated *TP53* vs wild type *TP53*, mutated *CDKN2B* vs wild type *CDKN2B*, mutated *CDKN2A* vs wild type *CDKN2A*, mutated *FOXA1* vs wild type *FOXA1*, mutated *RAC1* vs wild type *RAC1*, mutated *EGFR* vs wild type *EGFR*, mutated *KEAP1* vs wild type *KEAP1*, mutated *MYC* vs wild type *MYC*, mutated *K-RAS* vs wild type *K-RAS*, mutated *NFKBIA* vs wild type *NFKBIA*, mutated *SMARCA4* vs wild type *SMARCA4*).

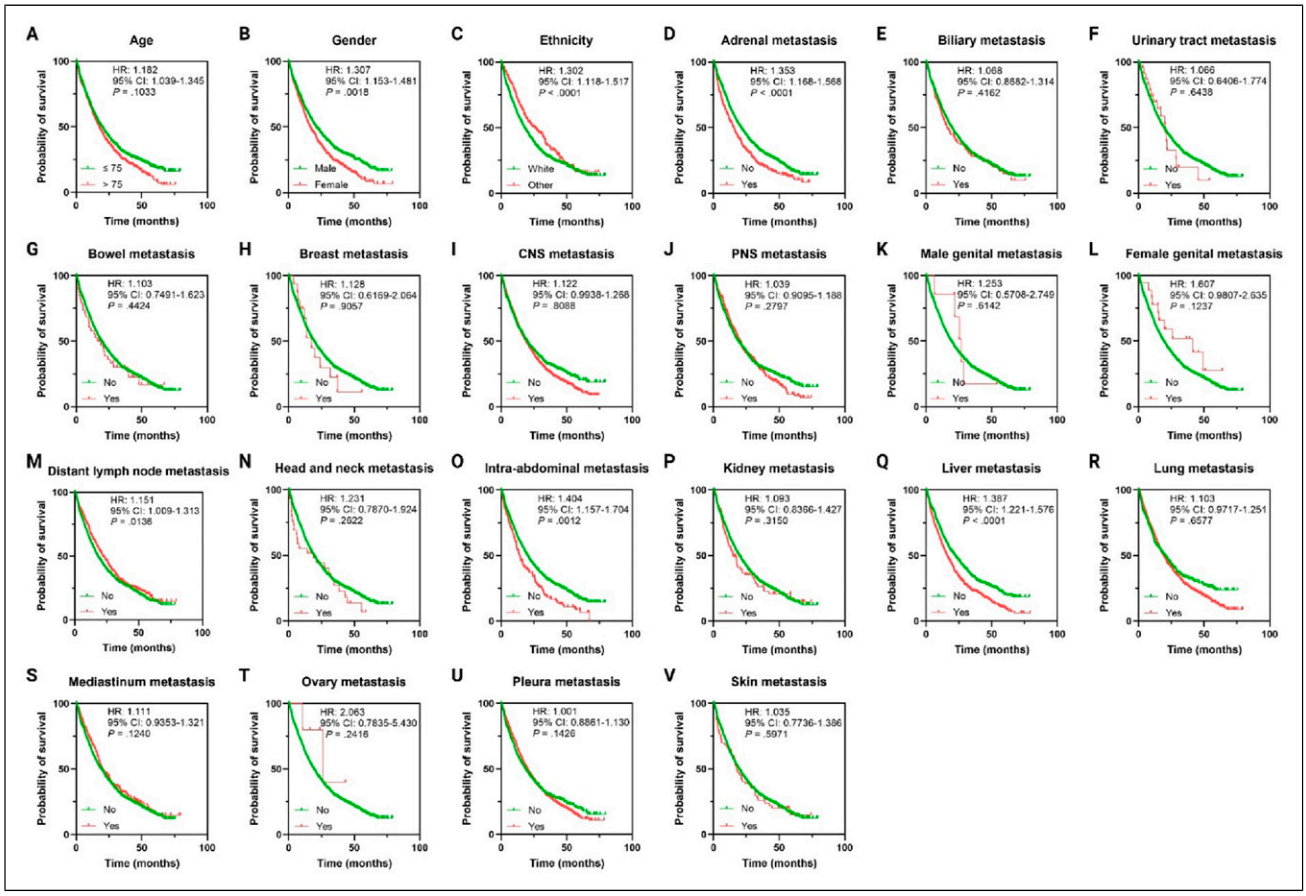

Figure 1. KM curves of clinicopathological variables in the bone metastases MSK-MET LAUD cohort (A-V).

The oncogenic properties of TP53 and its role in distant metastases have been well elucidated in the medical literature.[32] A review of the current data showed that *TP53* mutations were associated with LUAD bone metastases (OR = 1.231, 95% CI: 1.027-1.475, $P = .024$) but did not impact the OS (HR = 1.106, 95% CI: 0.961-1.272, $P = .162$). Numerous reports documented the prevalence of *TP53* mutations in LUAD primary and metastatic tumors specifically bone dissemination.[33] Large-scale clinical sequencing of metastatic LUAD cases demonstrated an enrichment of *TP53* in the bone metastases cohort.[34] Feng et al. showed a significant discrepancy in the genomic landscape of LUAD primary tumors in comparison to bone metastases ones, the later showing a higher mutation burden with more prevalent *TP53* mutations.[35] In regards to its survival impact, Chan et al. investigated the genomic profiles and clinicopathological data of NSCLC patients, a non-significant difference in PFI and OS between those with vs without *TP53* mutations.[36] Analysis of the TCGA LUAD cohort conducted by Zeng et al. depicted a statistically insignificant difference between *TP53*-mutated and wild-type groups in reference to survival curves.[37] Likewise, Van Egeren et al performed genomic analysis of early-stage NSCLC as a part of the AACR Project GENIE Biopharma Collaborative consortium and illustrated that *TP53* mutations are significantly associated with the development of distant liver metastases but not brain or bone metastases. *TP53* mutated group showed a negative association with survival in stages I and III, but detailed survival analysis in the bone metastases cohort was not performed.[38]

In our analysis, *EGFR* mutations were found in 34.51% (n = 549) of LUAD patients with bone metastasis. Harboring EGFR mutations was associated with bone metastases (OR = 1.358, 95% CI: 1.093-1.686, $P = .006$) and its wild type was associated with shorter OS (HR = 1.234, 95% CI: 1.047-1.455, $P = .012$). While numerous prior studies have highlighted the presence and importance of *EGFR* alternations in the development of bone metastases of LUAD,[39-43] Brouns et al. have shown that *EGFR* expression was not associated with bone metastases.[44] In a 3-year retrospective analysis of *EGFR* mutation status in 224 patients with recurrent or metastatic LUAD, Bittner et al. illustrated a non-significant correlation between mutation status and the presence of bone metastases.[45] Previous reports have shown a similar negative predictive impact of EGFR mutations on the OS.[46] An improvement of the OS is expected with the introduction of new EGFR-tyrosine kinase inhibitors (TKIs) into the clinical practice.[2,47] However, *EGFR*-mutated NSCLC populations are prone to high-risk SREs.[48] Noteworthy, bone metastases

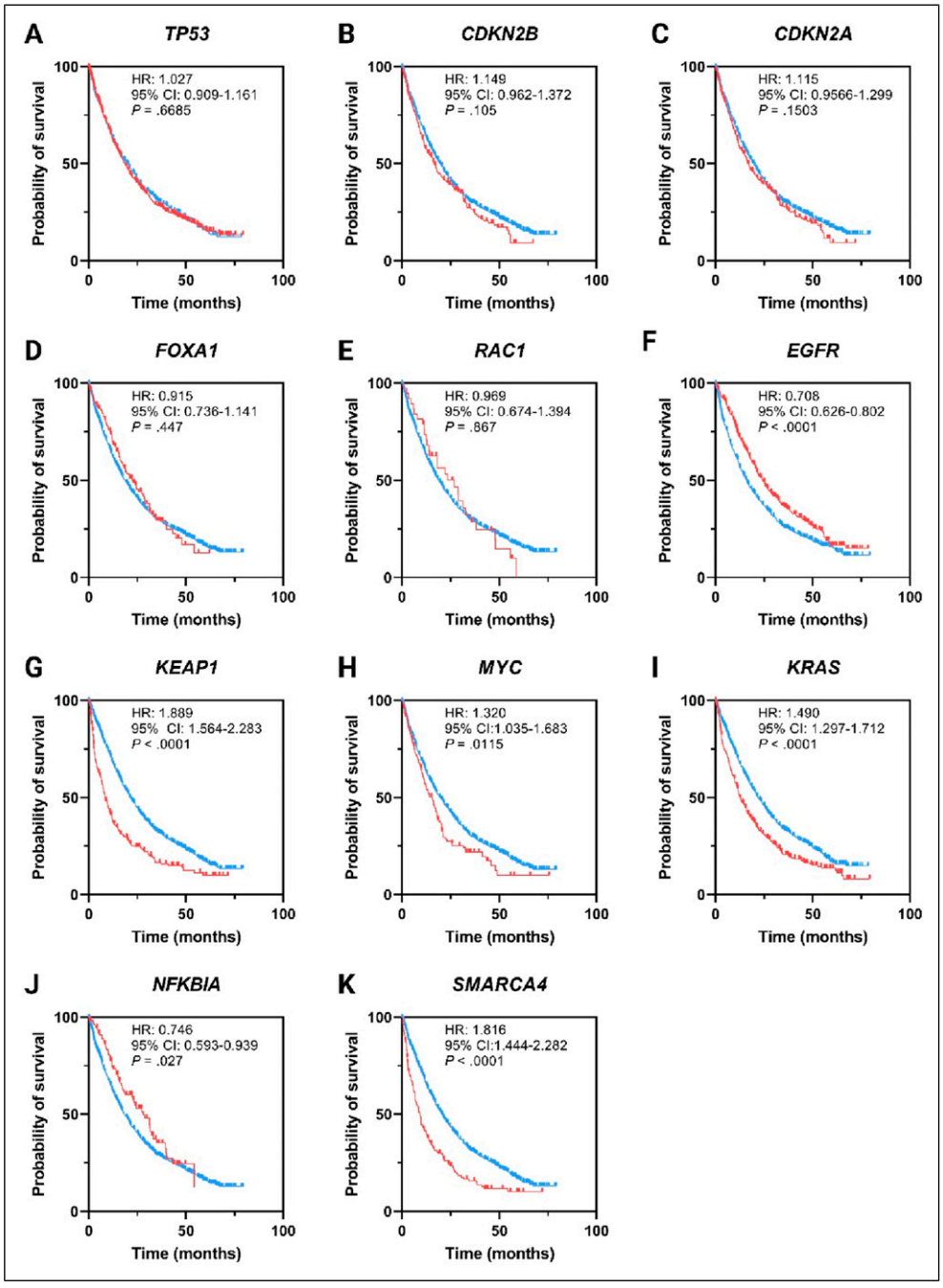

Figure 2. KM curves of genomic variables in the bone metastases MSK-MET LAUD cohort (A-K). Blue line represents wild-type. Red line represents mutated genes.

undermines the efficacy of EGFR-TKIs in individuals with advanced LUAD with EGFR alternations.[49] Many factors impact the prognosis of *EGFR*-mutant LUAD patients with bone metastases as TKI use, *EGFR* exon 19 del, osteogenic bone metastasis, bisphosphonate use, and smocking history.[50] In a retrospective analysis of stage IV LUAD with EGFR mutations, Fujimoto et al demonstrated that *EGFR* mutations were found in 98 out of 246 (39.84%) patients with available sequencing data. *EGFR* mutations were associated with more lung, brain, and bone metastases and its wild-type demonstrated shorter OS and poorer prognosis.[51]

KEAP1 plays a crucial role in cellular homeostasis and its dysfunction is associated with aggressive tumor growth and resistance to chemotherapy, radiotherapy, and targeted agents.[52,53] As the third most commonly mutated gene in LUAD,[54] exploring the predictive and prognostic value of KEAP1 and its associated pathways represents an ongoing field of study.[55] We have observed a poor prognostic signature

Table 4. Univariate and Multivariate Cox Logistic Regression Analyses Testing the Survival Prognostic Value of Clinical and Genomic Variables in the Bone Metastases Cases of MSK-MET LAUD Cohort.

	Univariate analyses		Multivariate analyses	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age at sequencing (years)	1.199 (1.057-1.359)	.005	1.179 (1.022-1.361)	.024
Gender	1.293 (1.144-1.462)	<.001	1.305 (1.138-1.497)	<.001
Ethnicity	1.315 (1.111-1.555)	.001	1.248 (1.033-1.507)	.021
Metastases sites				
Adrenal gland	1.359 (1.186-1.558)	<.001	1.249 (1.070-1.457)	.005
Biliary tract	1.060 (0.865-1.300)	.575		
Urinary tract	1.039 (0.634-1.702)	.881		
Bowel	1.118 (0.773-1.618)	.553		
Breast	1.101 (0.623-1.946)	.739		
Central nervous system	1.147 (1.015-1.296)	.028	1.188 (1.035-1.365)	.014
Peripheral nervous system	1.037 (0.908-1.185)	.593		
Distant Lymph nodes	1.152 (1.005-1.320)	.043	1.309 (1.119-1.531)	.001
Head and neck	1.239 (0.820-1.874)	.309		
Intra-abdominal	1.429 (1.205-1.695)	<.001	1.481 (1.219-1.798)	<.001
Kidney	1.085 (0.839-1.403)	.533		
Liver	1.405 (1.242-1.590)	<.001	1.427 (1.240-1.643)	<.001
Lung	1.114 (0.980-1.267)	.098		
Mediastinal	1.129 (0.980-1.267)	.188		
Pleura	1.022 (0.904-1.154)	.731		
Skin	1.054 (0.789-1.409)	.721		
Microsatellite instability type	1.461 (1.079-1.979)	.014	1.276 (0.921-1.768)	.142
Genomic alternations				
TP53	1.293 (1.144-1.462)	<.001	1.106 (0.961-1.272)	.162
CDKN2B	1.162 (0.981-1.376)	.083		
CDKN2A	1.126 (0.970-1.307)	.119		
FOXA1	1.046 (0.831-1.316)	.702		
RAC1	1.079 (0.746-1.561)	.687		
EGFR	1.420 (1.245-1.619)	<.001	1.234 (1.047-1.455)	.012
KEAP1	1.897 (1.628-2.211)	<.001	1.594 (1.332-1.908)	<.001
MYC	1.363 (1.095-1.696)	.006	1.353 (1.066-1.716)	.013
K-RAS	1.492 (1.312-1.696)	<.001	1.304 (1.110-1.533)	.001
NFKBIA	1.288 (0.992-1.673)	.057		
SMARCA4	1.841 (1.537-2.204)	<.001	1.578 (1.280-1.946)	<.001

*HR references (age ≤ 75, male, non-white, no adrenal metastasis, no biliary tract metastasis, no urinary tract metastasis, no bowel metastasis, no breast metastasis, no central nervous system metastasis, no peripheral nervous system metastasis, distant lymph node metastasis, no head and neck metastasis, no intra-abdominal metastasis, no kidney metastasis, no liver metastasis, no lung metastasis, no mediastinal metastasis, no pleura metastasis, no skin metastasis, no microsatellite instability, wild type *TP53*, wild type *CDKN2B*, wild type *CDKN2A*, wild type *FOXA1*, wild type *RAC1*, mutated *EGFR*, wild type *KEAP1*, wild type *MYC*, wild type *K-RAS*, wild type *NFKBIA*, wild type *SMARCA4*).

of *KEAP1* mutation as it is associated with bone metastases (OR = 1.385, 95% CI: 1.075-1.785, $P = .012$) and poor prognosis in bone metastases sub-cohort of LUAD (HR = 1.594, 95% CI: 1.332-1.908, $P < .001$). Exploring the TCGA database has revealed that *KEAP1*-mutated LUAD exhibits poor prognosis in comparison to non-mutated counterparts.[56,57] Simon et al examined the prognostic impact of KEAP1 mutations in a cohort of 2276 LUAD patients, demonstrating a negative prognostic outcome; however, they did not identify these mutations as predictive biomarkers for immune checkpoint inhibitors.[58] Saleh et al. comprehensively analyzed 6297 patients with localized- and advanced-stage NSCLC reporting that *KEAP1* mutations are associated with a worse prognosis but they did not recommend its utilization in molecular stratification to guide clinical decisions.[59] Multiple reports have consistently reported similar poor clinical impact of *KEAP1* mutations in LUAD.[60,61] Regarding the matter of bone metastases of LUAD, KEAP1 was among the most common oncogenic mutations found.[62] To the best of our knowledge, our study was the first report to demonstrate its predictive and prognostic potential of a bone metastases sub cohort of LUAD.

The *KRAS* mutation is one of the most prevalent genetic drivers of LUAD linked to aggressive tumor behavior, widespread metastasis, and poor outcomes.[33,63-65] Even

certain specific *KRAS* mutations exhibit distinct phenotypic features with variable outcomes.[66,67] Analysis of the MSK-MET LAUD cohort illustrated poor prognosis and short OS (HR = 1.304, 95% CI: 1.110-1.533, $P = .001$). Yet, it was not associated with bone metastasis. Conflicting data are available concerning the tumorigenic role of KRAS in driving LUAD bone metastasis. Renaud et al. claimed an association between *KRAS* genomic rearrangements and the development of bone metastases in LUAD patients.[68] While according to the previously described study conducted by Brouns et al, *KRAS* mutations were found to be predictive of treatment efficacy and prognostic for disease progression, but no significant correlation was observed between KRAS mutation status and the presence of bone metastases.[45] Analogously, Dormieux et al. showed no significant difference in metastatic site patterns among the *KRAS* mutated group.[69] Lohinai et al. found that *KRAS* mutation frequency in metastatic LUAD has a site-dependent pattern. Notably, they demonstrated that *KRAS* mutations were associated with significantly poorer OS in patients with bone metastases, underscoring their prognostic relevance in this subgroup.[70]

Another key gene yielded in our analysis was *MYC*. It was liked to borderline association (OR = 1.455, 95% CI: 1.019-2.079, $P = .039$) with LUAD bone metastases with poor prognostic impact (HR = 1.353, 95% CI: 1.066-1.716, $P = .013$). Usually, solid tumors with MYC gain are associated with invasiveness and metastases with their involvement in the pivotal cellular process involved in oncogenesis as a downstream target of the EGFR/RAS/RAF/MEK/ERK signaling pathway.[71-73] Seo et al. screened 255 LUAD patients for *MYC* gains indicating that such gene gain is an independent poor prognostic factor.[74] Whole genome copy number analysis of 254 patients with LUAD demonstrated that *MYC* amplification is a prognostic marker of early disease.[75] Although *MYC* amplification involvement in bone metastases of various malignancies was studied,[76,77] a detailed and comprehensive involvement of bone met metastases of LUAD was first discussed in this report. SMARCA4-deficient NSCLC represents a unique subset of lung cancer with distinctive clinicopathological characteristics.[78] Schoenfeld et al. examined a total of 407 *SMARCA4*-mutant NSCLC cases revealing a worse OS in the mutant group in comparison to the wild-type cohort as the survival indices and response to therapies followed a mutation-specific pattern.[79] Alessi et al. further explored the genomic alternations in advanced NSCLC and their cross-linking to survival and response to chemo-immunotherapy; the *SMARCA4* altered group had a shorter OS and PFI in non-squamous NSCLC.[80] Dagogo-Jack et al. concurred with the previously mentioned findings in a larger cohort of NSCLC cases harboring truncating SMARCA4 mutations.[81] As further support, many reports have emphasized such findings.[82-86] In our analysis, we have concluded that *SMARCA4*-altered sub-cohort held a shorter OS (HR = 1.578, 95% CI: 1.280-1.946, $P < .001$) but was not associated with bone metastasis. SMARCA4-deficient undifferentiated tumors were observed to consistently spread distantly to bones.[57,87] On the contrary, Liang et al. observed a statistically non-significant association between *SMARCA4* loss and bone metastases.[88] Further studies are required to unveil the role of *SMARCA4* in bone metastases of LUAD from a mechanistic and clinical point of view.

This study has several limitations that should be acknowledged. First, the retrospective approach of using publicly available pre-collected data prevented the capturing of all relevant clinical variables. The MSK-MET LAUD cohort represents a group of patients with variable metastatic patterns without the inclusion of non-metastatic cases in which the genomic landscape differences could be further explored and compared to bone metastases cases. The lack of combined survival endpoints and treatment response indices has restricted the depth of our investigation. Lastly, while the study focused on specific genomic alterations (somatic mutations) associated with bone metastasis, further genomic and transcriptomic data could draw more robust conclusions.

Conclusion

In conclusion, bone metastases remain a significant challenge in lung adenocarcinoma, contributing to increased morbidity and complicating disease management. Identifying clinical and genomic predictors of bone metastases offers valuable insight for identifying high-risk patients who may benefit from closer monitoring and early intervention. Nonetheless, further studies are required to validate these predictors and prognostic factors in larger, more diverse cohorts to improve the generalizability of our findings.

Appendix

Abbreviations

AACR	American Association for Cancer Research
ACS	American Cancer Society
API	Asian or Pacific Islanders
CI	Confidence Interval
CX3CL1	Chemokine (C-X3-C motif) ligand 1
CCL12	Chemokine (C-C motif) ligand 12
EGFR	Epidermal Growth Factor Receptor
HR	Hazard Ratio
IQR	Interquartile Range
KEAP1	Kelch-like ECH-associated protein 1
KM	Kaplan-Meier
LUAD	Lung Adenocarcinoma
LUSC	Lung Squamous Cell Carcinoma
LCC	Large Cell Carcinoma
MSK	Memorial Sloan Kettering
MSK-MET	Memorial Sloan Kettering Metastatic
MYC	MYC Proto-Oncogene
NSCLC	Non-Small Cell Lung Cancer
OR	Odds Ratio

OS	Overall Survival
P	*P*-value (significance level)
PFI	Progression-Free Interval
PTHrP	Parathyroid Hormone-related Protein
Q-Q	Quantile-Quantile
RANK	Receptor Activator of Nuclear Factor κ B;
RANKL	Receptor Activator of Nuclear Factor κ B Ligand
SCLC	Small Cell Lung Cancer
SEM	Standard Error of the Mean
SFK	Src Family Kinase
SMARCA4	SWI/SNF-related Matrix-associated Actin-dependent Regulator of Chromatin subfamily A member 4
SREs	Skeletal-Related Events
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCGA	The Cancer Genome Atlas
TGF-β	Transforming Growth Factor Beta
TKI	Tyrosine Kinase Inhibitor
TNF-α	Tumor Necrosis Factor Alpha
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

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Authors 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 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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Ethical Statement

Ethical Approval

This work was conducted utilizing an open-source data. The intuitional review board approval is not needed for such analysis.

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Supplemental Material

Supplemental material for this article is available online.

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