

Prognostic factors affecting overall survival in patients with spinal metastasis due to lung cancer: a systematic review and meta-analysis

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Abstract. – **OBJECTIVE:** Metastatic lung cancer often spreads to the musculoskeletal structures and spinal column. Patients suffering from spinal metastasis due to lung cancer present poorer prognostic outcomes in terms of overall survival compared to spinal metastases from other origins. To date, no meta-analysis has attempted to evaluate the prognostic impact of various predictive factors that may influence the overall survival of patients with spinal metastasis due to metastatic lung cancer. The aim of the study was to evaluate the prognostic impact of different predictive factors that might influence the overall survival of patients with spinal metastasis due to metastatic lung cancer.

MATERIALS AND METHODS: Five electronic databases (Web of Science, EMBASE, CENTRAL, Scopus, and MEDLINE) were screened for eligible studies according to PRISMA guidelines. We conducted a random-effects meta-analysis to evaluate the prognostic impact of aging, pre-ambulatory status, radiotherapy, adenocarcinoma, performance status, visceral metastasis, and number of affected vertebrae on the overall survival of patients with spinal metastasis due to lung cancer.

RESULTS: From 963 studies, we found 13 eligible studies with data on 1144 patients. Our meta-analysis revealed that pre-treatment ambulatory status (2.08), Eastern cooperative oncology group score (1.78), and aging (1.68) had significant impacts on overall survival.

CONCLUSIONS: We provide preliminary evidence highlighting three factors potentially predictive of overall survival for patients suffering from spinal metastasis due to metastatic lung cancer. These findings may help clinicians stratify and manage patients more effectively.

Key Words:

Spinal metastasis, Lung cancer, Meta-analysis, Overall survival.

Introduction

Metastatic lung cancer is a commonly occurring terminal malignancy¹⁻³ with extremely poor prognostic outcomes⁴, complicated by the fact that 30% to 40% of metastatic lung cancer cases feature musculoskeletal tumor metastasis⁵⁻⁷. Interestingly, patients with spinal metastases arising due to malignant lung disease exhibit worse morbidity and mortality compared with spinal metastases from other origins^{8,9}, exhibiting shorter life spans^{10,11} as well as paralysis, loss of bowel/bladder control, and severe pain¹².

Selecting a treatment approach for managing spinal metastasis depends on prognostic outlook¹³. Patients with poorer prognoses typically receive non-operative care or undergo careful posterior instrumentation with/without laminectomy, while patients with good prognostic outlooks are recommended for radical procedures, including bloc resection or even radical curettage^{14,15}. Personalized treatment interventions have therefore been widely recommended for managing spinal metastases due to metastatic lung cancer^{6,16,17}. However, developing these approaches is also problematic due to a lack of robust scoring systems capable of precisely estimating prognosis^{13,18}. Existing prospective scoring systems by Van der Linden et al¹⁹ (2005), Tomita et al²⁰ (2001), Sioutos et al²¹ (1995), and Tokuhashi et al¹⁵ (1990) show limited consistency and reliability as they analyze different predictive factors. Additionally, these scoring systems were devised based on small, heterogeneous patient cohorts featuring different tumor origins, weakening their specific applicability for spinal metastases arising due to malignant lung disease.

Several individual cohort studies^{8,22-25} have attempted to evaluate the prognostic impact of factors, such as aging, the presence/absence of visceral metastases, pre-treatment ambulatory status, pre-treatment performance status, and the number of affected vertebrae for overall survival in patients with metastatic lung cancer-related spinal metastases. However, these studies did not obtain consensus. As one example, some studies^{22,24} reported that higher Frankel Scale scores influenced patient survival while others^{8,25,26} found lower scores to be more predictive.

To the best of our knowledge, no systematic review or meta-analysis to date has attempted to evaluate the comparative impact of factors, such as aging, the presence/absence of visceral metastases, number of affected vertebrae, presence of radiotherapy, presence of adenocarcinoma, and pre-treatment ambulatory status on overall survival in patients suffering from spinal metastasis due to malignant lung cancer. We, therefore, attempt to bridge this gap through the present study. The findings from this study will help deduce best practice guidelines for more effective reductions in morbidity and mortality-related outcomes for patients with spinal metastasis due to metastatic lung cancer.

Materials and Methods

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines²⁷ were followed for this meta-analysis.

Search Strategy

Five scientific databases (Web of Science, MEDLINE, CENTRAL, EMBASE, and Scopus) were systematically searched for relevant studies published prior to April 2021. The search was performed across a combination of MeSH keywords, including “spinal metastasis”, “lung cancer”, “pulmonary cancer”, “overall survival”, and “prognostic factors”. Works cited by included studies were manually examined to identify further relevant studies.

Inclusion criteria were as follows:

- Studies reporting data on patients diagnosed with spinal metastases due to lung cancer;
- Studies evaluating the prognostic impact of various predictive factors on the overall survival;
- Studies on human participants;
- Case-control studies, prospective cohort trials, or retrospective cohort trials;

- Studies published in peer-reviewed scientific journals;
- Studies published in English;
- Study screening was performed by two reviewers, with disagreements resolved through discussion with a third independent reviewer.

Study Quality Assessment

Bias risk within individual included studies was appraised using the Newcastle Ottawa scale²⁸, which evaluates studies for selective reporting, confounding bias, outcome measurements, and incomplete data availability. Methodological quality was appraised independently by two reviewers. In case of disagreements, a third reviewer intervened to arbitrate.

Data Analysis

A within-group meta-analysis was performed using Comprehensive Meta-analysis (CMA) version 2.0²⁹. The meta-analysis was conducted using a random effects model³⁰. We calculated hazard ratios to evaluate the prognostic impact of patient age, visceral metastases, number of affected vertebrae, Frankel score, Eastern cooperative oncology group score, and pretreatment ambulatory status on overall survival in patients with spinal metastases due to lung cancer. I^2 statistics were used to assess heterogeneity, with a value between 0-25% considered indicative of negligible heterogeneity, a value between 25%-75% indicative of moderate heterogeneity, and a value $\geq 75\%$ of substantial heterogeneity³⁰. For studies that provided descriptive statistics as medians and ranges, we used the method of Hozo et al³¹ (2005) to convert these values into means and standard deviations. Publication bias was evaluated using Duval and Tweedy's trim and fill procedure³², which imputes studies on either side of the plotted graph to identify any unbiased effects. The significance level for this study was set at 5%.

Results

The literature search across five academic databases provided a total of 950 candidate studies, while screening of works cited sections revealed an additional 13 studies (Figure 1). After applying inclusion criteria, 13 studies remained for inclusion. Twelve of these were retrospective cohort studies^{8,23-26,33-39}, while the one remaining was a prospective cohort study²². Relevant study data has been summarized in Table I.

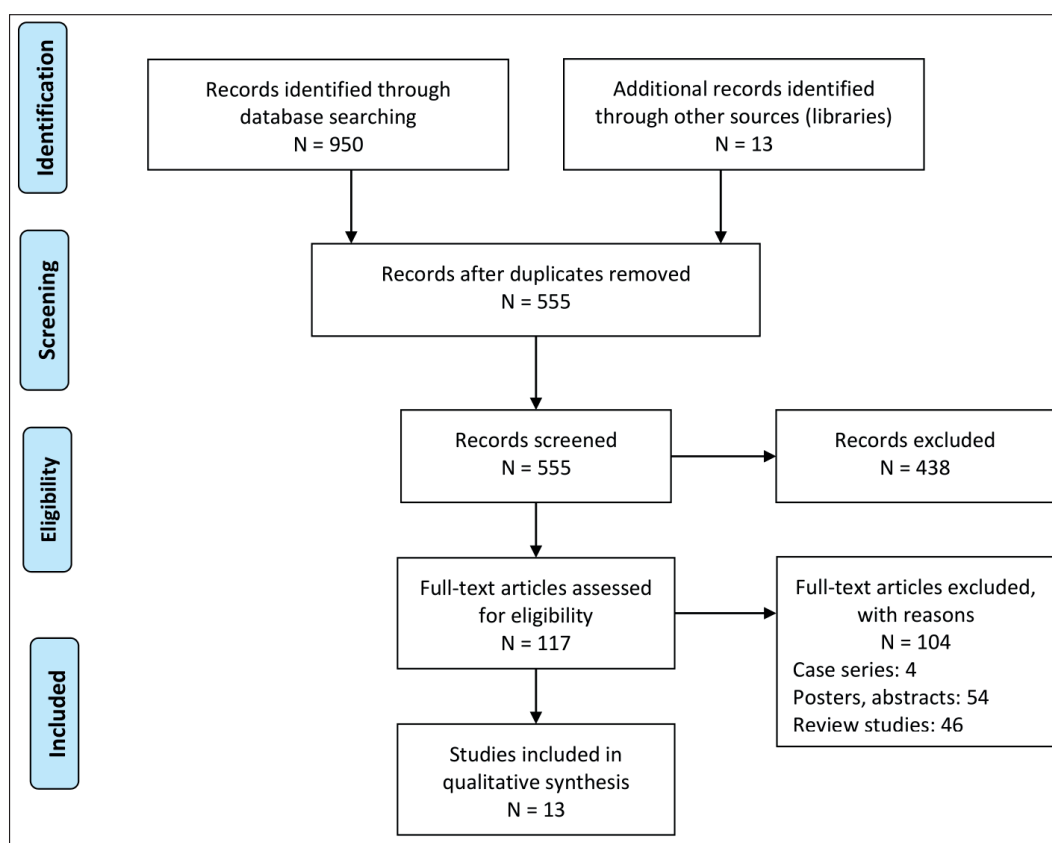


Figure 1. PRISMA flowchart for study identification and screening.

Participant Information

Pooled data from eleven of the included studies contained data on a total of 1,902 (560M, 947F) patients with spinal metastasis due to metastatic lung cancer. One study failed to provide the gender distribution of their cohort²⁵. Average patient age was 56.9 ± 8.8 years, with three studies not reporting patient data^{8,23,24}.

Cohort Study Quality Assessment

Newcastle Ottawa scale analysis found low overall risk of bias (Table II, Figure 2).

Publication Bias

Duval and Tweedy's trim and fill method found that two studies were missing on the left side of the mean effect. The overall random effect models determined the point estimates and the 95% confidence intervals for all the combined studies as 1.32 (1.17 to 1.50). After using the trim and fill method, the imputed points were estimated as 1.29 (1.14 to 1.46) (Figure 3).

Meta-Analysis Report

Age

Six studies^{18,26,33-36} investigated the relationship between aging and overall survival. We observed an increased hazard ratio, suggesting that aging had a significant influence on overall survival in patients with spinal metastasis (Figure 4) (Hazard ratio: 1.68, 95% CI: 1.16 to 2.45, $p < 0.01$, I^2 : 56.9%).

Treatment ambulatory status

Three studies^{23,37,38} reported on the relationship between pre-treatment ambulatory status and overall survival. We observed an increased odds ratio, suggesting increased risk associated with a lack of pre-treatment ambulation on overall survival in patients with spinal metastasis (Figure 5) (Hazard ratio: 2.08, 95% CI: 1.64 to 2.63, $p < 0.001$, I^2 : 0%).

Eastern cooperative oncology group score

Five studies^{19,26,35,37,38} investigated the relationship between Eastern cooperative oncology

Table I. Extracted data and summarized details for included studies.

Study	Country	Type of study	Sample size	Age	Period	Ambulatory status	Frankel score	Visceral metastases	Number of affected vertebrae	Overall survival (months)	Predictive factors of overall survival
da Silva et al ³⁵ (2021)	Brazil	Retrospective cohort study	64 (29F, 35M)	60.6 ± 9.5	2008-2017	-	-	Yes: 17 No: 47	≤3: 39 ≥3: 25	2.5 (1.6-3.5)	Visceral metastases: 1.18 (0.5 to 2.80) Age: 1.66 (0.97 to 2.84) ECOG: 1.76 (1.03 to 2.99)
Amelot et al ²² (2020)	France	Prospective cohort study	210 (69F, 141M)	33.1 (33 to 87)	2014-2017	-	A: 13 B: 22 C: 23 D: 21 E: 131	-	-	5.9 ± 0.6	Frankel: 0.42 (0.20 to 0.86)
Gao et al ¹⁸ (2020a)	China	Retrospective cohort study	146 (60F, 86M)	-	2009-2019	-	A to C: 28 D: 82 E: 36	Yes: 24 No: 122	<3: 38 ≥3: 108	5.5 (5-6)	Age: 10.98 (2.60 to 46.21) Visceral metastases: 2.15 (0.39 to 11.62) No. of involved vertebrae: 0.85 (0.15 to 4.75) Frankel: 4.42 (0.32 to 58.8)
M. Yang et al ²⁵ (2019)	China	Retrospective cohort study	376	56.9 ± 10.96	2010-2016	Yes: 200 No: 176	A: 37 B: 47 C: 102 D/E: 190	Yes: 98 No: 278	<3: 227 ≥3: 149	-	Frankel: 1.26 (1.10 to 1.43) No. of involved vertebrae: 1.42 (1.08 to 1.86) Visceral metastases: 1.51 (1.11 to 2.05)
Rades et al ²³ (2019)	Germany	Retrospective cohort study	120 (32F, 88M)	-	1996-2016	Yes: 67 No: 53	-	Yes: 77 No: 43	<3: 49 ≥3: 70	-	Visceral metastases: 2.46 (1.61 to 3.83) Ambulatory status: 1.99 (1.30 to 3.04) ECOG: 2.02 (1.31 to 3.17) Radiotherapy: 1.21 (0.94 to 1.56)
Cai et al ³³ (2019)	China	Retrospective cohort study	120 (49F, 71M)	62 (27-88)	2010-2017	-	A-B: 5 C-D: 83 E: 32	Ye: 23 No: 97	<3: 57 ≥3: 63	11.8 (0.3 to 66)	Age: 1.22 (0.82 to 1.81) Adenocarcinoma: 1.16 (0.72 to 1.87) Radiotherapy: 1.23 (0.84 to 1.80)
Kumar et al ³⁶ (2018)	Singapore	Retrospective cohort study	180 (74F, 106M)	62.6 ± 11.6	2001-2012	-	-	Yes: 86 No: 94	-	4.7 (3.45 to 6.08)	Age: 1.01 (1 to 1.03) Adenocarcinoma: 0.57 (0.28 to 1.17) Radiotherapy: 0.86 (0.64 to 1.16)
Uei and Tokuhashi ²⁴ (2018)	Japan	Retrospective cohort study	207 (71F, 136M)	-	-	-	-	-	<3: 121 ≥3: 86	5.2 ± 3.3	Adenocarcinoma: 0.93 (0.66 to 1.30) Frankel: 0.73 (0.55 to 0.97)
Tan et al ³⁹ (2016)	Singapore	Retrospective cohort study	180 (74F, 106M)	63 (33-93)	2001-2012	-	-	Yes: 86 No: 94	<3: 57 ≥3: 88	4.8 (0.1 to 111.1)	Visceral metastases: 0.56 (0.33 to 0.97) Frankel: 0.17 (0.06 to 0.53)
Park et al ³⁸ (2016)	S o u t h Korea	Retrospective cohort study	50 (23F, 27M)	58.0 ± 11.3	2010-2014	Yes: 35 No: 15	-	-	-	5.2 (2.3 to 5.8)	ECOG: 2.73 (1.05 to 7.13) Ambulatory: 2.08 (0.94 to 4.61)
Chen et al ³⁴ (2015)	China	Retrospective cohort study	50 (16F, 34M)	61.6 (20-87)	2000-2010	Yes; 34 No: 16	-	Yes: 10 No: 40	<3: 24 ≥3: 26	-	Visceral metastases: 1.08 (0.52 to 2.23) No. of involved vertebrae: 0.7 (0.39 to 1.25) Adenocarcinoma: 0.38 (0.2 to 0.71) Age: 3.28 (1.37 to 7.82)
Lei et al ³⁷ (2015)	China	Retrospective cohort study	64 (22F, 42M)	57	2005-2015	-	-	Yes: 31 No: 33	<3: 28 ≥3: 36	-	ECOG: 2.78 (1.54 to 5.02) Ambulatory: 2.24 (1.30 to 3.86) Visceral metastases: 2.29 (1.33 to 3.94) No. of involved vertebrae: 2.46 (1.39 to 4.35)
Tang et al ²⁶ (2015)	China	Retrospective cohort study	135 (41F, 75M)	55 (26-79)	2002-2013	-	-	-	-	-	Age: 1.30 (0.82 to 2.08) Frankel: 3.89 (2.14 to 7.06) No. of involved vertebrae: 1.25 (0.79 to 1.98) ECOG: 0.74 (0.42 to 1.31) Radiotherapy: 2.7 (1.69 to 4.32)

ECOG: Eastern cooperative oncology group, M: Male, F: Female

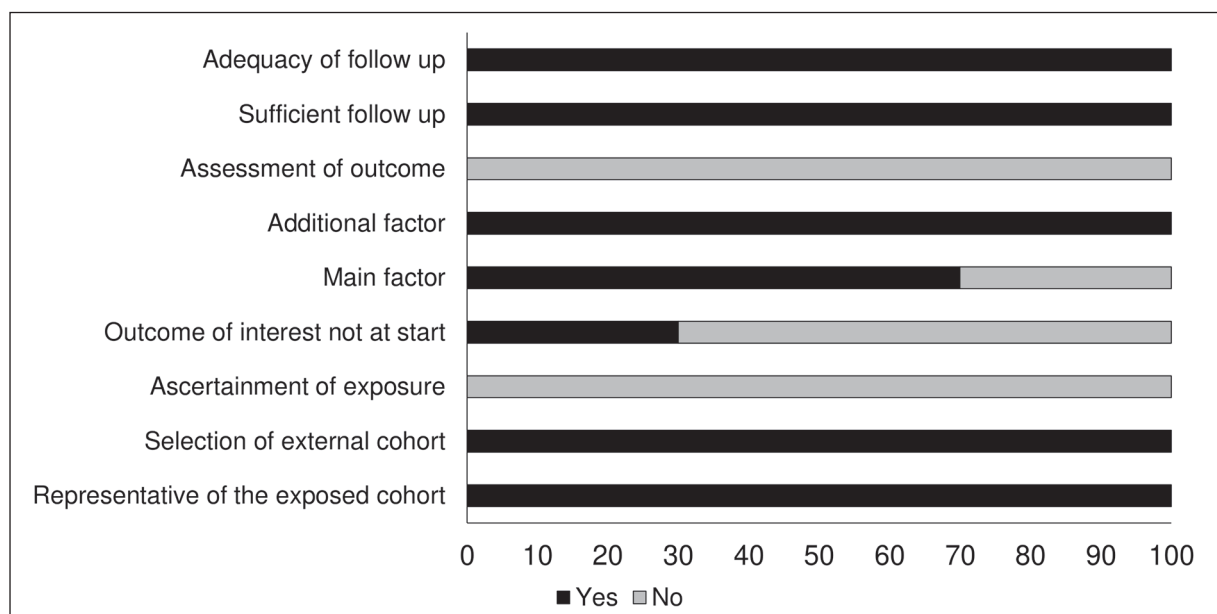


Figure 2. Bias risk for cohort studies as assessed via the Newcastle Ottawa scale.

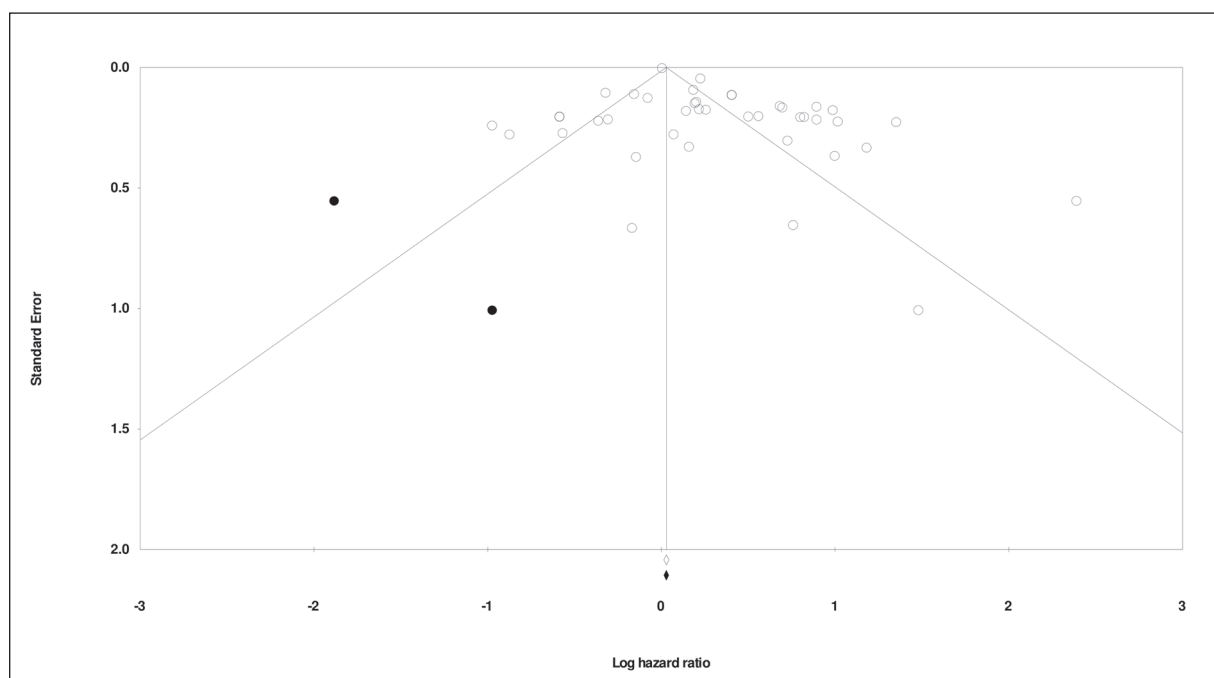


Figure 3. Publication bias as assessed by Duval & Tweedy's trim and fill method.

group score and overall survival. We observed an increased hazard ratio, suggesting increased risk associated with Eastern cooperative oncology group scores of 3-4 on overall survival in patients with spinal metastasis (Figure 6) (Hazard ratio: 1.78, 95% CI: 1.12 to 2.82, $p=0.01$, $I^2: 4.75\%$).

Frankel score

Seven studies^{18,22,24-26,35,39} reported on the relationship between Frankel's score and overall survival. We observed an increased hazard ratio, suggesting increased impact of Frankel scores of A-B on overall survival in patients with spinal

Table II. Bias risk for individual studies as assessed via the Newcastle Ottawa scale.

Study	Selection			Comparability			Outcome			Total (9/9)
	Representative of the exposed cohort	Selection of external cohort	Ascertainment of exposure	Outcome of interest does not present at start	Main factor	Additional factor	Assessment of outcome	Sufficient follow up	Adequacy of follow up	
da Silva et al ³⁵ (2021)	+	+	0	+	+	+	0	+	+	7
Amelot et al ²² (2020)	+	+	0	0	0	+	0	+	+	5
Gao et al ¹⁸ (2020a)	+	+	0	+	+	+	0	+	+	7
M. Yang et al ²⁵ (2019)	+	+	0	0	+	+	0	+	+	6
Rades et al ²³ (2019)	+	+	0	+	+	+	0	+	+	7
Cai et al ³³ (2019)	+	+	0	0	0	+	0	+	+	5
Kumar et al ³⁶ (2018)	+	+	0	0	0	+	0	+	+	5
Uei and Tokuhashi ²⁴ (2018)	+	+	0	0	+	+	0	+	+	6
Tan et al ³⁹ (2016)	+	+	0	0	0	+	0	+	+	5
Park et al ³⁸ (2016)	+	+	0	0	0	+	0	+	+	5
Chen et al ³⁴ (2015)	+	+	0	0	+	+	0	+	+	6
Lei et al ³⁷ (2015)	+	+	0	0	+	+	0	+	+	6
Tang et al ²⁶ (2015)	+	+	0	0	0	+	0	+	+	5

metastasis (Figure 7) (Hazard ratio: 1.02, 95% CI: 0.64 to 1.61, $p=0.92$, I^2 : 43.2%).

Number of affected vertebrae

Five studies^{18,25,26,34,37} investigated the impact of the number of affected vertebrae on overall survival. We observed an increased hazard ratio, suggesting increased impact on overall survival when higher numbers of vertebrae were affected (Figure 8) (Hazard ratio: 1.30, 95% CI: 1.93 to 1.34, $p=0.17$, I^2 : 15.07%).

Visceral metastases

Seven studies^{18,23,25,34,35,37,39} reported the relationship between visceral metastases and overall survival. We observed an increased hazard ratio, suggesting that the presence of visceral metastases negatively impacted overall survival in pa-

tients with spinal metastasis (Figure 9) (Hazard ratio: 1.41, 95% CI: 0.93 to 2.13, $p=0.09$, I^2 : 0%).

Adenocarcinoma

Four studies^{24,33,34,36} investigated the relationship between adenocarcinoma and overall survival. We observed an increased hazard ratio, suggesting increased risk to overall survival linked with the presence of adenocarcinoma (Figure 10) (Hazard ratio: 0.71, 95% CI: 0.45 to 1.31, $p=0.15$, I^2 : 13.7%).

Radiotherapy

Four studies^{23,26,33,36} reported on the relationship between radiotherapy on overall survival. We observed an increased hazard ratio, suggesting increased impact when radiotherapy was present on

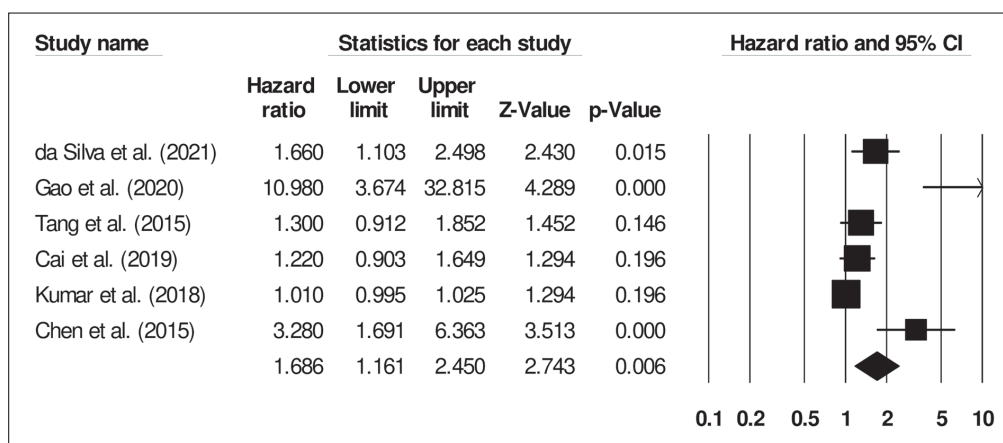


Figure 4. Forest plot for studies evaluating the prognostic impact of age on overall survival. Hazard ratios are presented as black boxes while 95% confidence intervals are presented as whiskers. Higher hazard ratios represent higher impacts of older ages on overall survival while lower hazards ratios represent higher impacts of younger ages on overall survival.

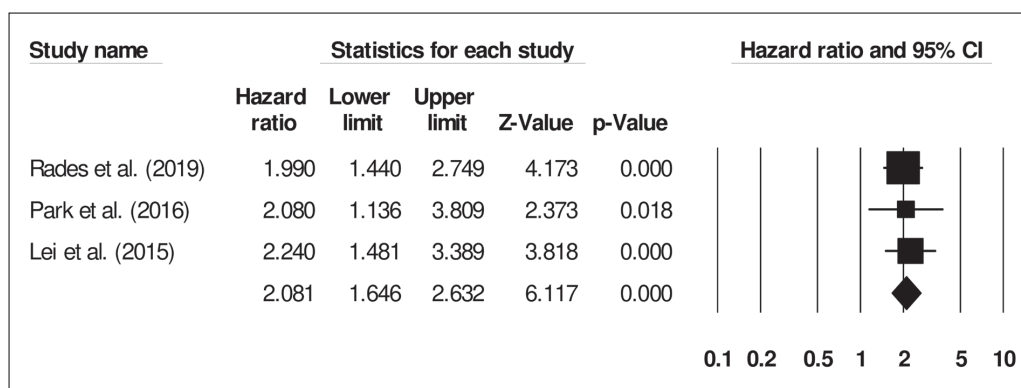


Figure 5. Forest plot for studies evaluating the prognostic impact on pre-treatment ambulation status (yes or no) on overall survival. Hazard ratios are presented as black boxes while 95% confidence intervals are presented as whiskers. Higher hazard ratios represent higher impacts of non-ambulatory status on overall survival while lower hazards ratios represent higher impacts of ambulatory status on overall survival.

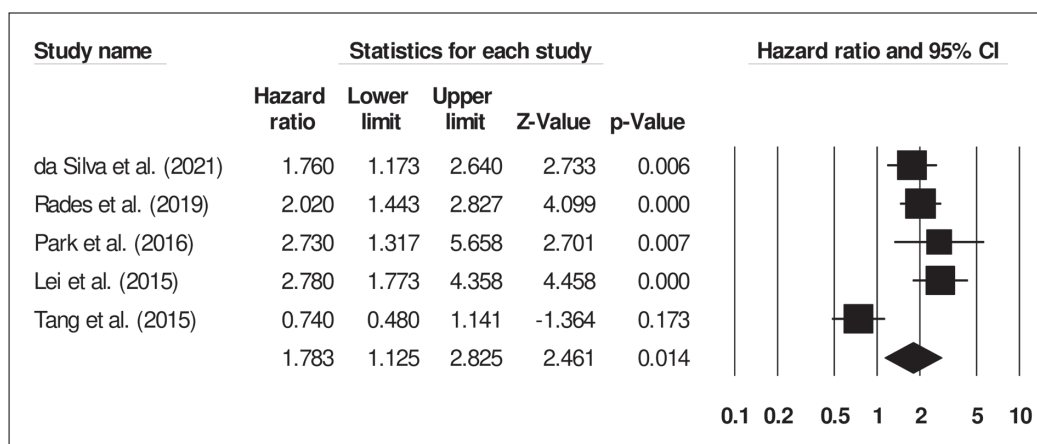


Figure 6. Forest plot for studies evaluating the prognostic impact of Eastern cooperative oncology group score (3-4 vs. 1-2) on overall survival. Hazard ratios are presented as black boxes while 95% confidence intervals are presented as whiskers. Higher hazard ratios represent higher impacts of scores of 3-4 on overall survival while lower hazards ratios represent higher impacts of scores of 1-2 on overall survival.

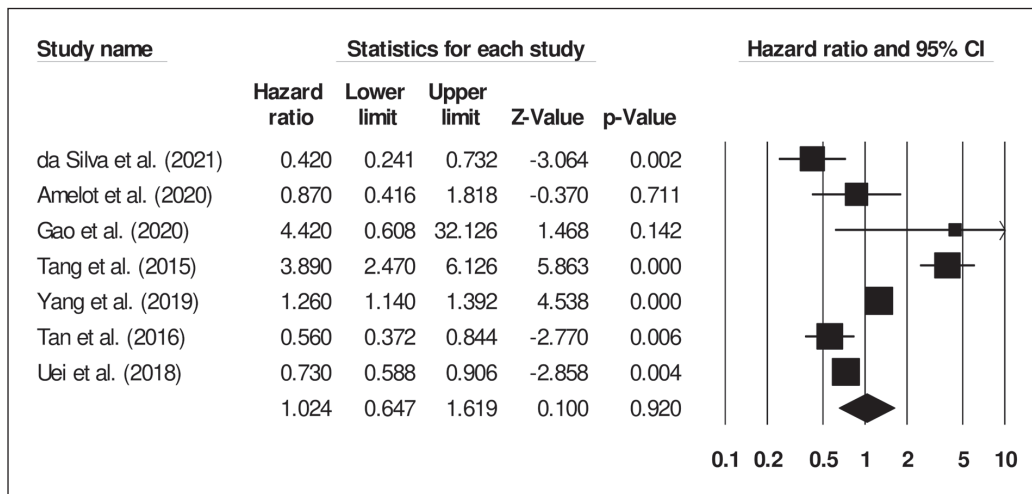


Figure 7. Forest plot for studies evaluating the prognostic impact of Frankel score (A-B vs. C-E) on overall survival. Hazard ratios are presented as black boxes while 95% confidence intervals are presented as whiskers. Higher hazard ratios represent higher impacts of scores of A-B on overall survival while lower hazards ratios represent higher impacts of scores of C-E on overall survival.

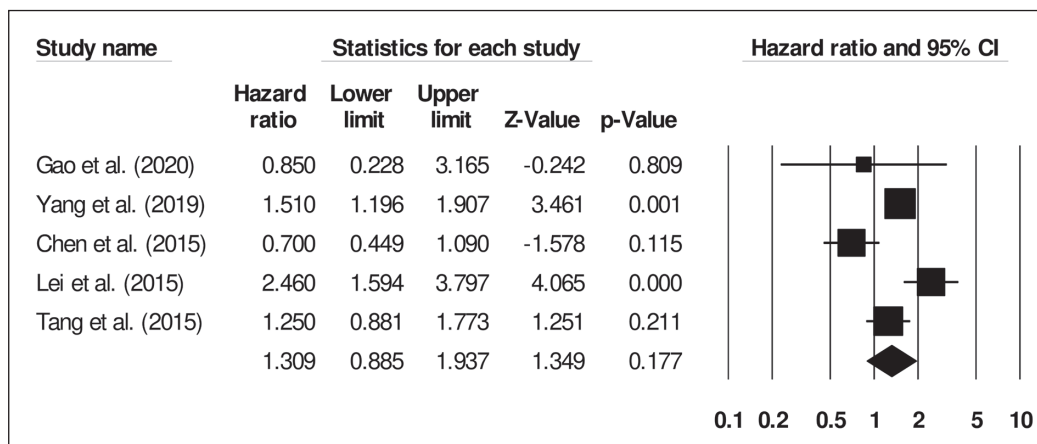


Figure 8. Forest plot for studies evaluating the prognostic impact of number of affected vertebrae (≥ 3 vs. < 3) on overall survival. Hazard ratios are presented as black boxes while 95% confidence intervals are presented as whiskers. Higher hazard ratios represent higher impacts for ≥ 3 vertebrae affected on overall survival while lower hazards ratios represent higher impacts for < 3 vertebrae affected on overall survival.

overall survival in patients with spinal metastasis (Figure 11) (Hazard ratio: 1.33, 95% CI: 0.90 to 1.97, $p=0.14$, $I^2: 28.6\%$).

Discussion

This systematic review and meta-analysis provide a preliminary evidence regarding the prognostic impact of different predictive factors on the overall survival of patients suffering from spinal metastasis due to metastatic lung cancer. We report a substantially elevated negative impact for

pre-treatment non-ambulatory status, higher Eastern cooperative oncology group scores, and older ages on overall survival.

Managing spinal metastasis due to metastatic lung cancer is difficult due to poor prognostic outlook and heterogeneous manifestations^{40,41}. In response, the literature recommends the development of personalized treatment plans that take into account patient prognostic outlook^{16,17}. As such, several scoring systems exist to estimate prognostic outcome in terms of life expectancy^{6,15,20,21,42}. However, these systems bear limitations that complicate their adoption. Leithner et

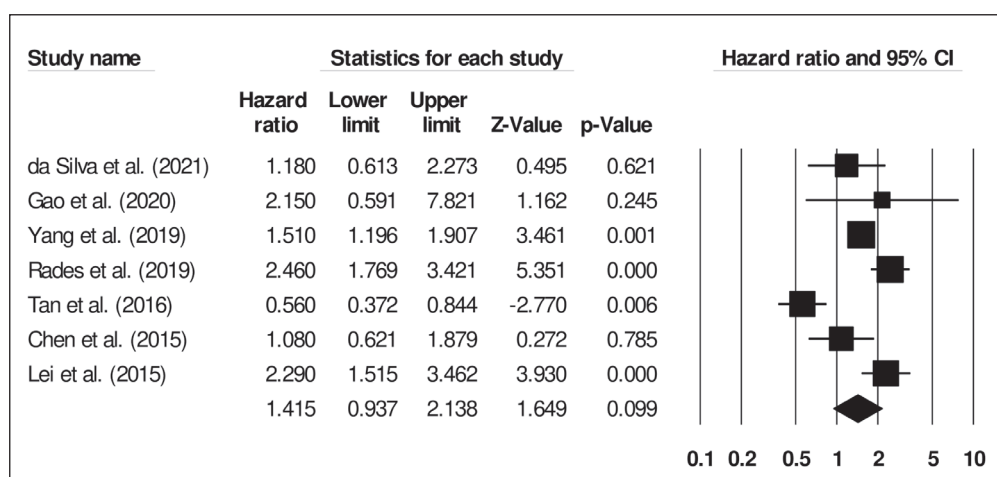


Figure 9. Forest plot for studies evaluating the impact of visceral metastases (present vs. absent) on overall survival. Hazard ratios are presented as black boxes while 95% confidence intervals are presented as whiskers. Higher hazard ratios represent higher impacts for the presence of visceral metastases on overall survival while lower hazards ratios represent higher impacts for the absence of visceral metastases on overall survival.

al¹³ (2008) suggested that different scoring systems can allocate different values to the same patient, as a result of differences in factor weight, cohort heterogeneity, and small sample sizes with varied tumor origins³⁹. It is therefore imperative to better evaluate how different predictive factors influence the overall survival of patients with spinal metastasis due to lung cancer.

In this present meta-analysis, we report significantly elevated risk associated with greater age (HR: 1.68), higher Eastern cooperative oncology group scores (1.67), and the absence of pre-treatment ambulation (HR: 2.08) on overall survival. These trends were generally uniform across included studies, with almost all included studies re-

ported aging and non-ambulatory status pre-treatment as significant risks to overall survival. Gao et al⁸ (2020) also reported that in addition to aging, poorer survival outcomes were associated with the presence of visceral metastases, possibly because increased tumor burden decreased patient tolerability for invasive treatments⁴³.

We also attempted to identify a consensus regarding the prognostic influence of pretreatment performance status (i.e., Frankel score), and the number of affected vertebrae on overall survival. Although these observations were not statistically significant, higher numbers of affected vertebrae involved (1.30), presence of radiotherapy (1.33), lower Frankel scale scores (1.15), and the

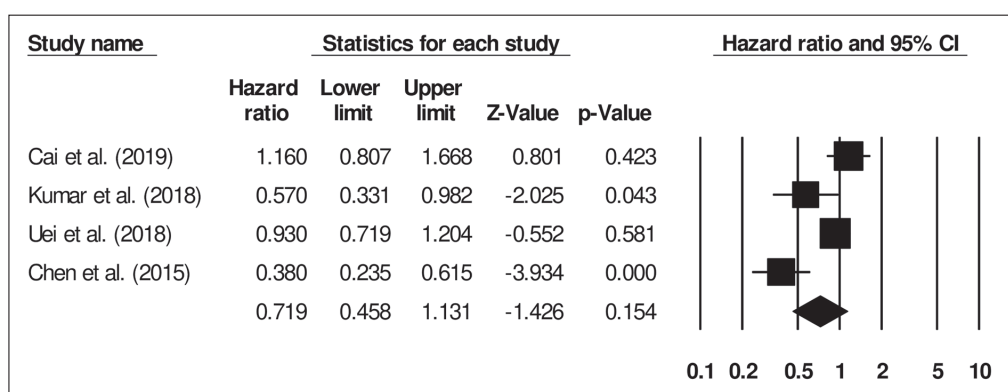


Figure 10. Forest plot for studies evaluating the impact of adenocarcinoma (present vs. absent) on overall survival. Hazard ratios are presented as black boxes while 95% confidence intervals are presented as whiskers. Higher hazard ratios represent higher impacts for the presence of adenocarcinoma on overall survival while lower hazards ratios represent higher impacts for the absence of adenocarcinoma on overall survival.

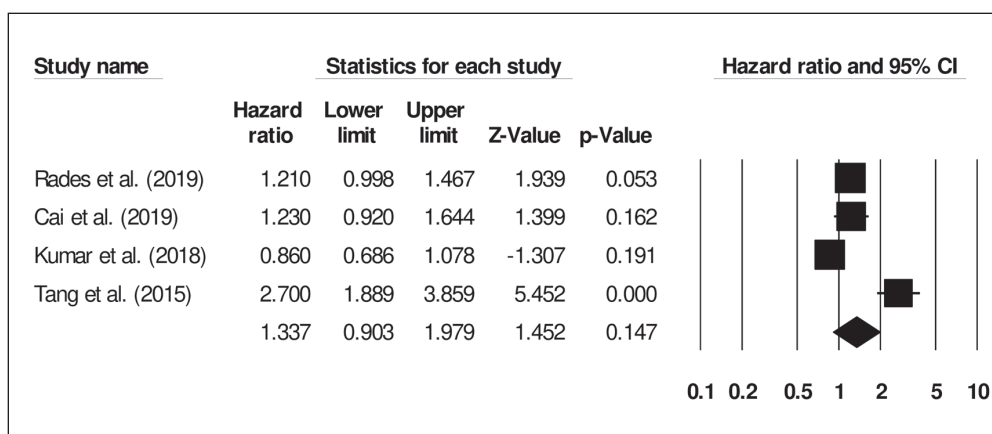


Figure 11. Forest plot for studies evaluating the impact of radiotherapy (present vs. absent) on overall survival. Hazard ratios are presented as black boxes while 95% confidence intervals are presented as whiskers. Higher hazard ratios represent higher impacts for the presence of radiotherapy on overall survival while lower hazards ratios represent higher impacts for the absence of radiotherapy on overall survival.

presence of visceral metastases (1.41) negatively impacted overall survival. We presume that vertebral metastasis affecting greater numbers of vertebrae would result in increased disease severity, possibly contributing to other complications, such as deep vein thrombosis^{8,37} and worsening overall survival. In concert with other reports^{20,22}, we recommend that these parameters be further evaluated.

Despite being a novel study, there were a few limitations in our study. This study was not pre-registered in a systematic review repository, such as PROSPERO York or the Joanna Briggs Institute. We made several attempts, but a registration backlog caused by the current COVID-19 pandemic crisis made timely registration impossible. Additionally, only three studies looking at 234 patients investigated the effect of pre-ambulatory status on overall survival. As such, although we only observed moderate heterogeneity, we cannot rule out the possibility of bias.

Conclusions

We herein provide preliminary evidence that the absence of pre-treatment ambulatory status, higher Eastern cooperative oncology group scores, and greater ages are risk factors for the overall survival of patients suffering from spinal metastases due to metastatic lung cancer. We also found statistically insignificant trends suggesting increased risk associated with lower Frankel scores, the presence of radiotherapy, the presence

of visceral metastases, and greater numbers of affected vertebrae. These findings potentially allow researchers and clinicians to better develop more effective scoring systems for predicting survival outcomes in patients suffering from spinal metastasis due to metastatic lung cancer.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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