REVIEW ARTICLE

Is Ambulatory Status a Prognostic Factor of Survival in Patients with Spinal Metastases? An Exploratory Meta-analysis

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This study was conducted to identify the influence of ambulatory status prior to treatment on survival of patients with spinal metastases. Two investigators independently retrieved relevant electronic literature in PubMed, Embase, and Cochrane Library databases, to identify eligible studies. Effect estimates for hazard risk (*HR*) were extracted and synthesized through fixed-effects or random-effects models as appropriate. A total of 17 eligible studies were identified, with an accumulated number of 3962 participants. *HR* from 14 studies regarding comparison between ambulatory versus non-ambulatory groups were pooled using a random-effects model, and statistical significance was presented for the pooled *HR* (*HR* = 1.96; 95% confidence interval [*CI*], 1.65–2.34). In subgroups of mixed primary tumor and lung cancer, ambulatory status was considered to be a significant prognostic factor ($P < 0.05$), while in the subgroup of prostate cancer it was not (*HR* = 1.72; 95% *CI*, 0.79–3.74). HR from 4 studies related to comparison between Frankel E versus Frankel C–D were pooled using a fixed-effects model, which revealed statistical significance (*HR* = 1.73; 95% *CI*, 1.27–2.36). Ambulatory status is a significant prognostic factor in patients with spinal metastases. However, in patients with primary prostate cancer, the prognostic effect of ambulatory status has not yet been confirmed to be significant.

Key words: Ambulatory status; Overall survival; Prognostic factor; Spinal metastasis

Introduction

With notable improvements in systemic treatment options and diagnostic techniques, cancer patients' overall survival has increased obviously over the past three decades. The likelihood of spinal metastasis, however, has grown, impacting patients' quality of life and treatment outcomes. As many as 70% of advanced cancer patients develop spinal metastases and approximately 10% of all malignant tumor cancer patients are treated for metastatic spinal cord compression (MSCC)[1,2]. In general, 20% of the patients with spinal metastases suffer from neurological deficits[3–5]. These patients are more likely to benefit from aggressive surgical intervention.

However, patients with a limited life expectancy sometimes benefit little from surgery. For instance, Rades *et al.* report that elderly patients with MSCC did not benefit from surgery in addition to radiotherapy in terms of functional outcome, local control of MSCC, or survival[6]. In addition, complications and death can follow surgical treatment. Hence, to select the optimal therapeutic modality for patients with spinal metastases, prognostic factors associated with the postoperation life expectancy should be taken into consideration. Many studies have attempted to identify the prognostic factors for predicting survival of patients with MSCC, such as ambulatory status, presence of visceral or extraspinal bone metastases, and number of spinal metastases involved.

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The ambulatory status before treatment, as one of the prognostic factors, has commonly been cited in many previous studies. However, these studies report conflicting results for the prognostic effect on patients' survival after treatment. We also know that Tokuhashi *et al.* and Sioutos *et al.* included the grade of neurological deficits in their prognostic scores, whereas Tomita *et al.*, Bauer and Wedin, North *et al.*, and Van der Linden *et al.* did not[7–13]. However, there have been very few conclusive studies to resolve this controversy. Thus, the current exploratory meta-analysis is performed with the goal of identifying and quantifying the role of ambulatory status before treatment in predicting survival of patients with spinal metastases and the difference in the prognostic effect of ambulatory status among each subgroup of primary tumor types, to give some guidance in selecting a treatment.

Methods

Data Sources and Searches

Two individual researchers (XG Yang and DX Lun) conducted database searches in the PubMed, Embase, and Cochrane Library using the following keywords: "spinal metastasis, overall survival, prognostic factor". This way, studies published between 1997 and 2017 were retrieved, with the publication language restricted to English. In addition, reference studies involved in retrieved studies were hand-searched.

Inclusion and Exclusion Criteria for Studies

Complete texts published with a cohort or case-control study design that examine the survival and prognostic effects of ambulatory status before treatment in patients with spinal metastases from various primary tumors were included in the current study.

However, studies would be excluded for the following reasons: (i) duplicated studies; (ii) systematic reviews, literature reviews, basic research, letters to the editor, and or diagnostic studies; (iii) studies that involved fewer than 10 participants; and (iv) studies using the same patient cohorts as any other study. When several cohorts used the same population as each other, only the most recent (or thorough) study was used. There were no limitations on the participants' nationalities and study designs applied to the search.

Data Extraction and Quality Assessment

For studies meeting the inclusion criteria, data that referred to prognostic factors of ambulatory status before treatment were extracted by the two individual reviewers independently and entered into a pre-built Microsoft Excel spreadsheet. Collected data included general information (title, author, year of publication, country, period of the study, and study design), participants' characteristics (age, percentage of males, number of involved patients, number of patients with MSCC, ambulatory status of patients before treatment, and primary tumor histology), therapeutic modality provided for patients, follow-up information and patients' overall survival time, effect sizes of hazard ratio (*HR*) or risk ratio (*RR*) combined with their 95% confidence interval (95%*CI*), and also associated raw data which involved some further calculations, such as survival rates at certain points in time, or diagrams, such as Kaplan–Meier survival curves to gain relevant data using the software Get Data Graph Digitizer (version 2.25, getdata-graph-digitizer.com). The calculations spreadsheet was also used to assist us in carrying out the calculations. We determined the causes of diversity in the obtained information and resolved disagreements with face-to-face discussion[14].

The Newcastle–Ottawa Scale was used for assessment of eligible studies' methodological quality and risk of bias by the previously mentioned two researchers independently[15]. This scale employs a 9-star system that assesses three domains: patient selection, comparability of the study groups, and the ascertainment of study outcome. Studies with a score of 9 stars have a low risk of bias, whereas scores of 7–8 mean there is a medium bias risk; a score of 6 or less than 6 indicates a high chance of bias.

Data Synthesis and Analysis

Data extracted into a Microsoft Excel spreadsheet were pooled using an exploratory time-to-event meta-analysis. All recorded *HR* combined with 95%*CI* (including statistically significant or non-significant) from eligible literature, incorporating *HR* re-calculated from raw data or Kaplan–Meier curves obtained from primary studies, were synthesized narratively. The pooled estimates for *HR* and 95%*CI* of ambulatory status before treatment were determined using a random-effects or fixed-ffects model, and heterogeneity among each involved study was tested by estimating I^2 and using the Cochrane *Q*-test (significance level at $P < 0.1$). In case of significant heterogeneity, irrespective of the I^2 estimation, random effects models were used to allow for it. Subgroup analyses were performed according to the participants' primary tumor histology in each study. A test for the overall effect of pooled *HR* by *Z*-test was performed and statistical significance was defined as a two-sided *P*-value of less than 0.05. Data synthesis and analysis was carried out using Stata's metan command. Publication bias was assessed using a funnel plot and Egger's regression asymmetry test ($P < 0.10$ represented statistically significant publication bias)[16]. A sensitivity analysis was also performed when significant heterogeneity existing by omitting each individual study to check the stability of the result. The meta-analysis, testing for publication bias, and the sensitivity analysis were performed using Stata software (version 13.0, StataCorp LLC, College Station, Texas, USA).

Results

Search Result and Study Selection

The process of eligible literature selection is presented in Fig. 1. The initial electronic literature search conducted by the two individual researchers yielded a total of 1065 studies published from 1997 to 2017. After 147 duplicates were excluded, 918 articles remained. Then, after skimming over titles and abstracts and further perusing full texts, 816 of the titles and abstracts and 79 of the full-texts were excluded, respectively. In addition, there were 3 studies by Lei that used the same patient cohort, and only the study that identified primary tumor histology as non-small cell lung cancer (NSCLC) was included[17–19]. Another 4 studies by Rades were also excluded that used the same patient cohorts as other studies[6,20–22]. Finally, 17 studies containing 3962 participants met the inclusion criteria, of which 14 studies involved comparison between ambulatory and non-ambulatory groups of patients on the influence of overall survival after treatment and 4 studies reported comparison between Frankel grade C–D and Frankel grade E[12,19,23–37].

General Information of Studies

A summary of individual studies is provided in Supplementary Appendix S1. Participants come from different countries: the USA in 5 studies, Germany in 4 studies, China in 2 studies, and 1 each from the UK, the Netherlands, Sweden, Austria, Korea, and Czech Republic. Primary tumor histology was various among the included studies, with six not specified, three non-small cell lung cancer (NSCLC), three prostate cancer, two renal cell cancer, two thyroid cancer and one breast cancer. The percentage of non-ambulatory patients before treatment in cohorts of prostate cancer was the highest, with an average percentage of 64%, while only 44%, 31%, and 21% in cohorts of NSCLC, non-identified cancer, and other kinds of tumors, respectively. In 13 cohorts of studies, patients underwent surgery plus other adjuvant therapy, while patients in the remaining 4 studies received radiotherapy alone. The majority of the studies were of high quality, with an average score of 8.0 stars; only 1 study had a score of 6.0 stars.

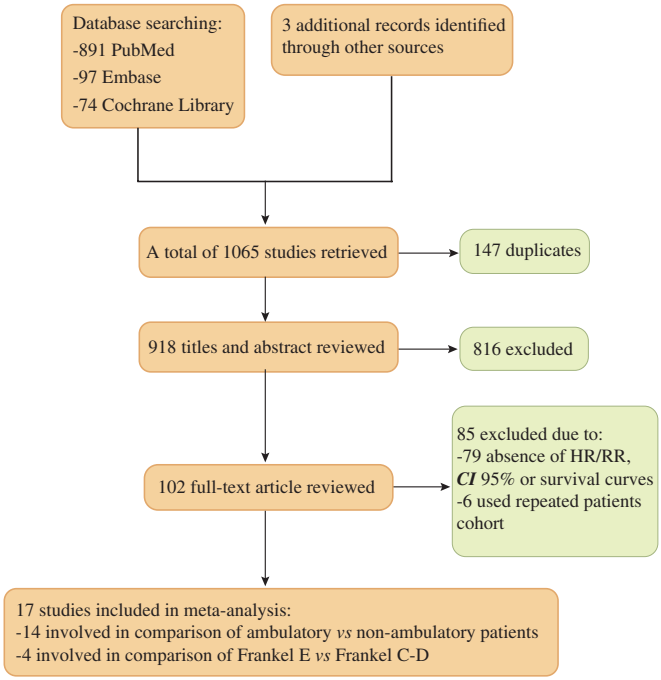

Fig. 1 Flowchart of eligible literature selection.

Qualitative Summary and Data Synthesis

A total of 17 studies were related to influence of ambulatory before treatment on survival in patients with spinal metastases. Fourteen studies reported comparison between ambulatory and non-ambulatory groups directly, with 8 of them having significant results. Four studies reported comparisons between Frankel grades before treatment, which provided information on neurological status as patients with Frankel grade E were neurologically complete while those with Frankel C–D were neurologically defective. Among these 4 studies, 2 had significant results. In addition, 1 study that compared patients with MRC (British Medical Research Council) scores of 0–3, which means that patients are non-ambulatory, and those with MRC scores of 4–5, which means that patients have enough strength to walk before treatment, found no influence on overall survival after treatment.

Data extracted included 14 effect estimates of the hazard ratio (*HR*) for patients who were ambulatory (including Frankel D, E) versus non-ambulatory (including Frankel A-C) before treatment and 4 effect estimates of *HR* for patients without (Frankel E) versus with neurological deficit (Frankel C-D). All these effect estimates of *HR* are presented in two individual forest plots and are pooled together with Stata software (version 13.0, StataCorp LLC, College Station, Texas, USA) (Fig. 2).

According to the histology of primary tumors, the 14 studies related to patients ambulatory versus non-ambulatory before treatment were stratified into subgroups of mixed tumor type, NSCLC, prostate cancer and others, and an exploratory subgroup meta-analysis was carried out in forest plot A using a random-effects model. The overall pooled *HR* was 1.96 (95% *CI*, 1.65–2.34), I^2 = 34.1%. In the test for the overall effect by *Z*-test, the pooled effect estimate of *HR* proved to be statistically significant (Z = 7.57, P < 0.001). In subgroups of no identified tumor type and NSCLC, pooled *HR* were 1.93 (95%*CI*, 1.68–2.22; I^2 = 0.0%) and 2.23 (95%*CI*, 1.33–3.76; I^2 = 60.7%), respectively, and were proved to be significant by *Z*-test (Z = 9.34, P < 0.001 and Z = 3.03, P = 0.002, respectively). While in subgroups of patients with primary tumors of prostate cancer and others (one each for thyroid cancer and breast cancer), pooled *HR* were 1.72 (95%*CI*, 0.79–3.74; I^2 = 76.3%) and 2.40 (95%*CI*, 0.50–11.68; I^2 = 55.9%), respectively, and were considered

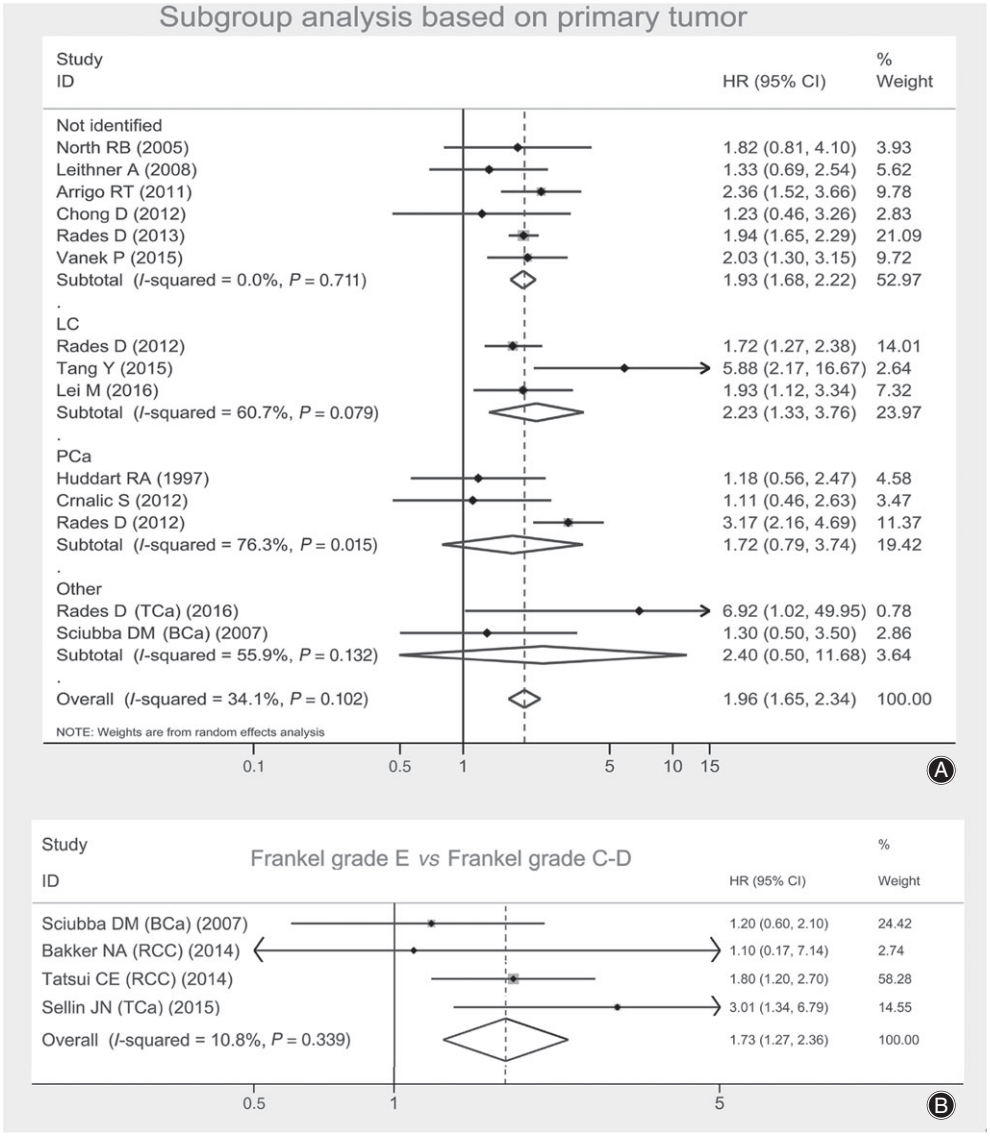

Fig. 2 Forest plots presenting combined effect estimates (hazard ratios [*HR*]) of survival in spinal metastatic patients: (A) ambulatory versus non-ambulatory, a subgroup analysis based on the histology of primary tumor; and (B) Frankel E versus Frankel C&D.

non-significant ($Z = 1.37$, $P = 0.169$ and $Z = 1.09$, $P = 0.277$, respectively).

The other four effect size of *HR* for comparison between patients with (Frankel C-D) and without neurological deficit were pooled in forest plot B with a fixed-effect model. The pooled *HR* was 1.73 (95%*CI*, 1.27–2.36; I^2 = 10.8%), which was considered to be statistically significant, with a *Z*-value of 3.48 and a *P*-value of less than 0.001 by *Z*-test.

Heterogeneity and Publication Bias

In subgroups of primary lung cancer, primary prostate cancer and others (one each for thyroid cancer and breast cancer), which are presented in Fig. 2A; I^2 are greater than 50% (60.7%, 76.3% and 55.9%, respectively), which indicates obvious heterogeneity. Hence, sensitivity analyses were performed for all the studies included in Fig. 2A and subgroups of primary lung cancer and prostate cancer but not for the subgroup which included only two studies (one each for thyroid and breast cancer). The sensitivity analysis plots are presented in Fig. 3, which all demonstrated stability when omitting each individual study.

Publication bias was assessed using a funnel plot and Egger's regression asymmetry test. The funnel plot in Fig. 4A presents the publication bias of the 14 studies included in Fig. 2A and shows good symmetry, with most studies converging at the top of the funnel. Hence, based on the funnel plot, there was no obvious publication bias. Egger's publication bias plot in Fig. 4B presents the risk of bias across 14 studies included in forest plot A, with a *P*-value of 0.952, which refutes the existence of obvious publication bias. The funnel plot and Egger's publication bias plot in Fig. 4C,D present the risk of bias across 4 studies related to patients without neurological defects (Frankel grade E) versus with

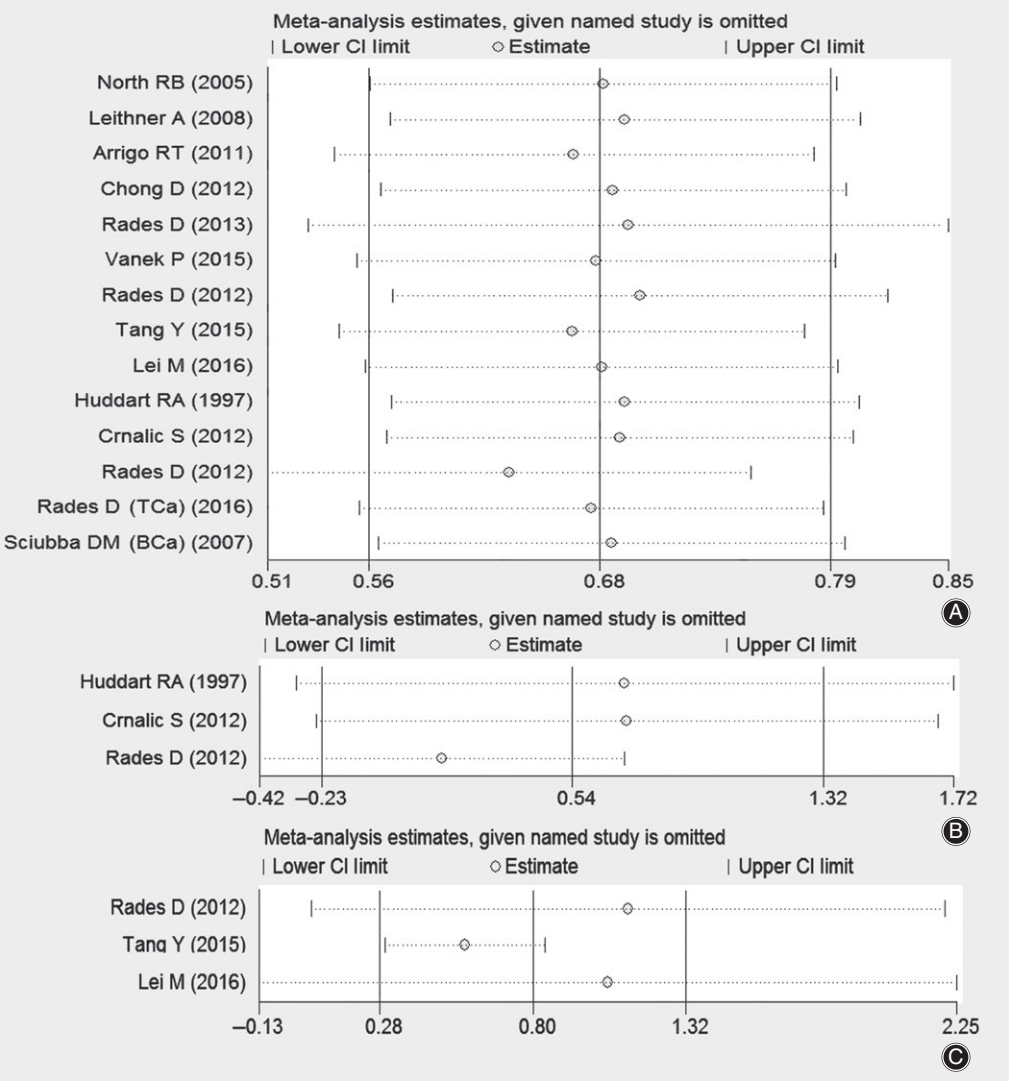

Fig. 3 Plots of sensitivity analysis for 14 studies included in the forest plot A (A) and studies in subgroups of primary prostate cancer (B) and primary lung cancer (C).

neurological defects (including Frankel grade C-D) before treatment. These results are also included in forest plot B, which demonstrates symmetry; the *P*-value of 0.929 also refutes the existence of obvious publication bias.

Discussion

The treatment of spinal metastasis is often focused on optimal relief of symptoms of MSCC, such as severe pain and neurological deficits, to improve the quality of the remaining life span. The various individualized therapeutic options include surgery, radiotherapy, chemotherapy, and targeted therapy. To achieve optimal remission of symptoms, surgeons must consider the patients' life expectancy and clinical outcomes when conducting treatment. The prognostic effect of ambulatory status before treatment has been evaluated in many previous studies. However, conflicting results are reported among these studies[7–13]. In the current study, an exploratory meta-analysis was performed to examine the role of ambulatory status before treatment in predicting the overall survival of patients with spinal metastases. Ambulatory status before treatment has been identified to be a statistically significant prognostic factor for overall survival after treatment. It could provide some answers to the current controversy and make ambulatory status a more remarkable prognostic factor when selecting the treatment modality.

In reviewing the existing literature, it is unclear whether ambulatory status before treatment is a prognostic factor of survival in patients with spinal metastases. We know that Tokuhashi *et al*., Sioutos *et al*., and Enkaoua *et al*. included the grade of neurological deficit in their score systems as one of the prognostic factors[7–9,38]. In the study of Arrigo *et al*., preoperative ambulatory status was considered as one of the most robust predictors of survival[23]. Rades *et al*. also suggested that ambulatory status pre-treatment was significantly associated with survival, and the authors insisted that non-ambulatory patients were more likely to suffer from major complications such as pneumonia, which will cause patients to deteriorate[22]. Tang *et al*. also conclude

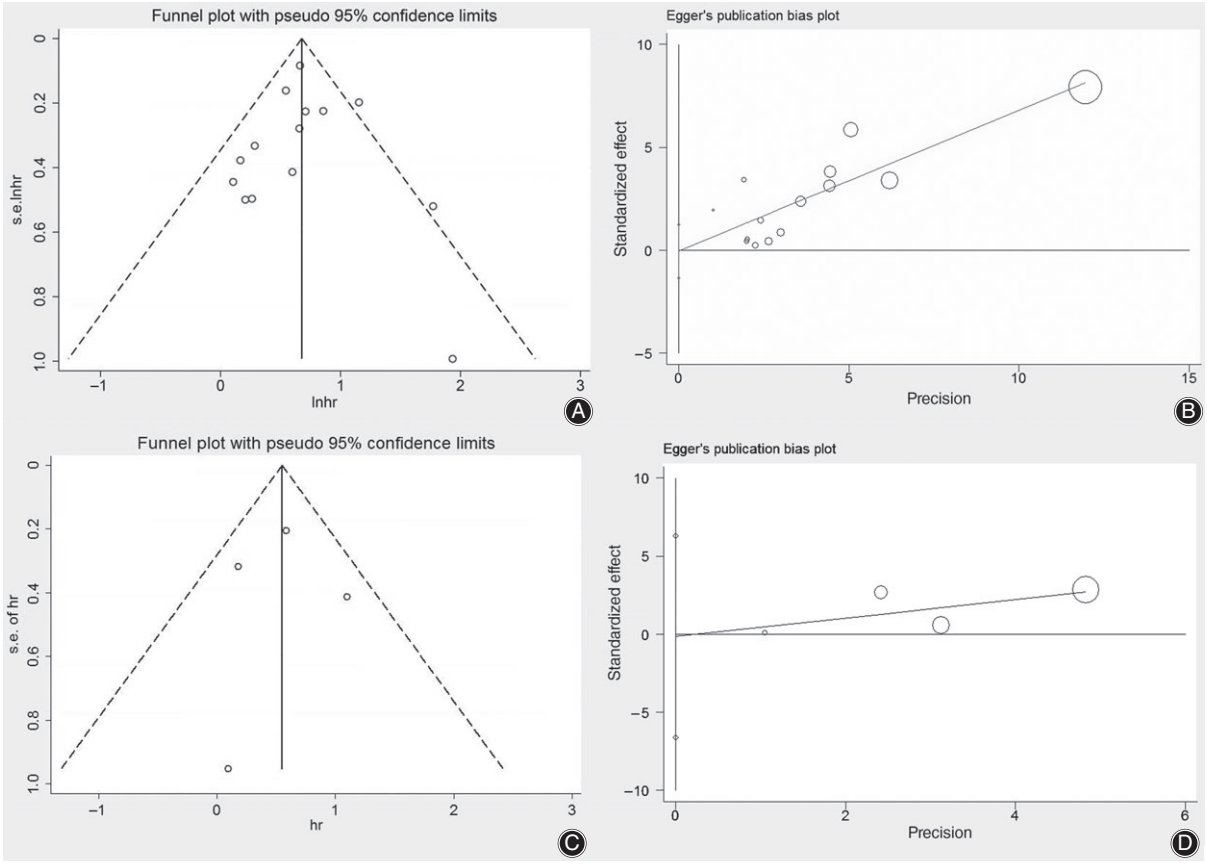

Fig. 4 Funnel plot (A) and Egger's publication bias plot (B) presenting publication condition of 14 studies related to patients ambulatory *versus* non-ambulatory before treatment, which were included in forest plot A; Funnel plot (C) and Egger's publication bias plot (D) presenting the risk of bias across 4 studies related to patients without neurological defect (Frankel grade E) *versus* with neurological defect (including Frankel grade C-D) before treatment which were included in forest plot B.

that preoperation ambulatory status is a significant prognostic factor in patients with spinal metastases from non-small cell lung cancer, that patients with neurological deficit may deteriorate too much to tolerate some more aggressive surgical procedures and adjuvant therapies, and that more severe complications will arise among paraplegic patients[29].

However, there were also numerous studies that were opposed to adopt pre-treatment neurological status as a significant prognostic factor based on their cohorts. In 2001, Tomita *et al.* developed a score system that did not include pre-treatment neurological status as a prognostic factor for survival[10]. The authors insisted that neurological deficit could be improved through appropriate treatment such as spinal cord decompression, which can bring about longer survival, even in patients with severe paraplegia. In the study of Van der Linden *et al.*, a total of 342 patients who were free of neurological deficit with Harrington grade I and II were included, and evaluation of the prognostic effect of neurological status was not conducted[13]. However, the authors refused to accept it as a prognostic factor in their score system, and they speculated that symptoms of myoplegia can just reflect the location and volume of spinal metastasis lesions; this concurred with the opinion of Tomita *et al.*[10]. Yamashita *et al.* used the revised Tokuhashi score system to evaluate the prognostic effect in patients with spinal metastases and found that Frankel grade is not a significant prognostic factor[39]. Chong *et al.* observed that preoperative ambulatory status was a significant factor in predicting postoperative ambulation but not postoperative overall survival[24].

Our exploratory meta-analysis found a significant correlation between pre-treatment neurological status and overall survival, with pooled overall *HR* 1.96 (95%*CI*, 1.65–2.34, $P < 0.001$) in comparison between patients who were ambulatory and non-ambulatory, and 1.73 (95%*CI*, 1.27–2.36; $P < 0.001$) in comparison between patients who were Frankel grade E (without neurological deficit) and C–D (with neurological deficit). This is contrary to the results of Tomita *et al.*, who concluded that pre-treatment neurological status is not an effective prognostic factor as they believed that neurological deficit could be cured following special treatment procedures[10]. Vanek *et al.* report that preoperation neurology is an independent prognostic factor but that improvement in the Frankel scale is

not associated with a longer survival of patients[26]. Moon *et al.* and Quraishi *et al.* report the same result[40,41]. It follows that an improved neurological status after treatment is not a certain factor to influence overall survival through their studies, but ambulatory status pre-treatment is an independent prognostic factor. We found that neurological status could reflect the degree of local compression and progression of local lesion in spinal metastases. Patients who were non-ambulatory pre-treatment usually had a spinal metastasis lesion with a progressive nature. Patients tended to live for a shorter duration after treatment when symptoms of neurological deficit were involved, despite a similar survival span between patients with and without neurological deficit being found in some individual studies with a small sample size after a series of treatment procedures. Based on our meta-analysis, which pooled individual studies together and included 3962 participants, an unfavorable life expectancy was found among patients with neurological deficit prior to treatment, which could lead to the conclusion that although symptoms of neurological deficit can be resolved, the unfavorable nature of local spinal metastases cannot be reversed.

For the subgroup of cohorts with primary prostate cancer, the pooled effect estimate was 1.72 (95%*CI*, 0.79–3.74; $P = 0.169$), which was not statistically significant. This result was in accordance with most of the studies based on a cohort of primary prostate cancer [30,31,42]. Crnalic *et al.* delivered a score system based on 68 patients with spinal metastasis from prostate cancer[30]. In their study, most (87%) of the patients were non-ambulatory before treatment, and the prognostic effect of ambulatory status was non-significant. Meng *et al.* analyzed the prognostic factors based on 31 patients with spinal metastasis from prostate cancer, 59% of whom were non-ambulatory before treatment, and found that neurological status before radiotherapy was not an independent prognostic factor[42]. Among all the included studies, the percentages of non-ambulatory patients before treatment in cohorts of prostate cancer were the highest, with an average percentage of 64%, with only 44%, 31% and 21% in cohorts of NSCLC, non-identified cancer, and other types of tumors, respectively. Thus, it would be speculated that patients were composed of elderly men in prostate cancer mainly and had a poor basic condition probably. These elderly men were more likely to suffer from neurological deficits than relatively younger patients in cohorts with other types of primary tumors. Thus, some patients who had a long life expectancy and favorable biological behaviour of spinal metastases suffered from non-ambulation before treatment, which would mean that ambulatory status does not reflect the real biological behaviour of spinal metastases significantly among this group of patients. Hence, whether ambulatory status is a significant prognostic factor cannot be confirmed yet in spinal metastases from prostate cancer.

Limitations of This Study

Our study has several limitations. Most studies included in the current systematic review and meta-analysis were retrospective cohort studies and not prospective cohort studies. However, most of the studies included here are of relatively high quality according to the Newcastle–Ottawa Scale few prospective cohort studies have been carried out on patients with spinal metastases and. Thus, more observational studies with a prospective design are necessary.

Conclusion

The current study suggests that ambulatory status before treatment is a significant prognostic factor in patients with spinal metastases and should be considered when choosing the treatment modality. We suggested that among patients with neurological deficit or who were non-ambulatory before treatment, the implementation of aggressive surgical procedures should proceed with caution. However, in the subgroup of patients with primary prostate cancer, ambulatory status before treatment cannot yet be confirmed to be a significant prognostic factor of survival, and further study is necessary to give some more constructive guidance.

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Supporting Information

Additional Supporting Information may be found in the online version of this article on the publisher's web-site:

Appendix S1 Summary of included studies.

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