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*Original Article*

# Diagnostic value of bone-specific alkaline phosphatase in lung carcinoma patients with bone metastases: a meta-analysis

Qing-Tao Zhao[1], Zhao-Xu Yang[2*], Lei Yang[3*], Dong Xing[2], Jing-Chao Wei[2], Wen-Yi Li[2]

*Departments of [1]Thoracic Surgery, [2]Orthopedics, Hebei General Hospital, Shijiazhuang 050051, Hebei, P. R. China; [3]Department of Pediatrics, Bethune International Peace Hospital of Chinese PLA, Shijiazhuang 050082, Hebei, P. R. China. [*]Co-first authors.*

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**Abstract:** Aim and Backgrounds: The accurate diagnosis of lung carcinoma patients with bone metastases is crucial for therapy and the prevention of complications. We performed a systematic review and meta-analysis to evaluate the diagnostic value of serum bone-specific alkaline phosphatase (BALP) in lung carcinoma patients with bone metastases. Methods: Such databases as PubMed, Embase, Cochrane Library, Web of Science, Ovid, BioMed Central, Biosis previews and four Chinese databases (Chinese Biomedical Literature Database-disc (CBM), Chinese National Knowledge Infrastructure (CNKI), Technology of Chongqing (VIP) and Wan Fang DATA) were retrieved on computer, and the relevant journals were also manually searched to collect the trials on BALP in diagnosis of lung carcinoma patients with bone metastases. The meta-analysis was conducted by using Meta-Disc 1.4 software. Results: A total of 8 studies were included, and there were 848 lung carcinoma patients diagnosed by gold standard, patients were divided into two groups: 419 cases with bone metastases and 429 cases without bone metastases. The meta-analysis showed that, the pooled sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) was 0.48 [95% CI (0.43 to 0.53)], 0.86 [95% CI (0.82 to 0.89)], 3.14 [95% CI (2.47 to 3.99)], 0.62 [95% CI (0.56 to 0.68)], 6.66 [95% CI (4.62 to 9.60)] respectively. And the AUC of SROC was 0.78, ($Q^*$=0.72). Conclusion: BALP has greater diagnostic value in detecting lung carcinoma patients with bone metastases. However, further large scale studies are required to confirm the predictive value.

**Keywords:** Lung carcinoma, bone metastases, BALP, meta-analysis

## Introduction

As the second leading cancer type for the estimated new cancer cases, lung carcinoma represents the major cause of cancer death in both females and males [1]. Bone metastasis can be found frequently in lung carcinoma [1, 2]. It is reported as 24-40% in clinical studies and 36-40% in autopsy series [3, 4]. Lung carcinoma frequently develops bone metastases in advanced stages of disease [5]. The main symptoms of bone metastasis include severe pain, pathological fractures, spinal cord compression, hypercalcemia, anemia and so on [6, 7]. But up to 20-25% of patients are asymptomatic [7]. These skeletal-related events have been associated with reduced quality of life and reduced overall and median survival, so the early diagnose of bone metastasis and effective therapy could be initiated timely and improvement of life quality and treatment to the patients may be achieved [8, 9].

Diagnosis of bone metastasis is usually performed initially with plain radiography or computed tomography (CT) or magnetic resonance imaging (MRI) or bone scintigraphy screening and confirmed by whole body bone scan by single-photon emission computed tomography (SPECT) [10-12]. However, they have very low sensitivity in detecting bone micro metastasis [12]. Bone scan is excellent for whole-body screening and can detect micro metastasis of bone metastasis [13, 14]. However, it can give false-negative results in lytic bone lesions and the risk of radioisotope exposure. Due to SPECT have high price and radioactivity, it is not a necessary recommendation for newly diagnosed patients [14].

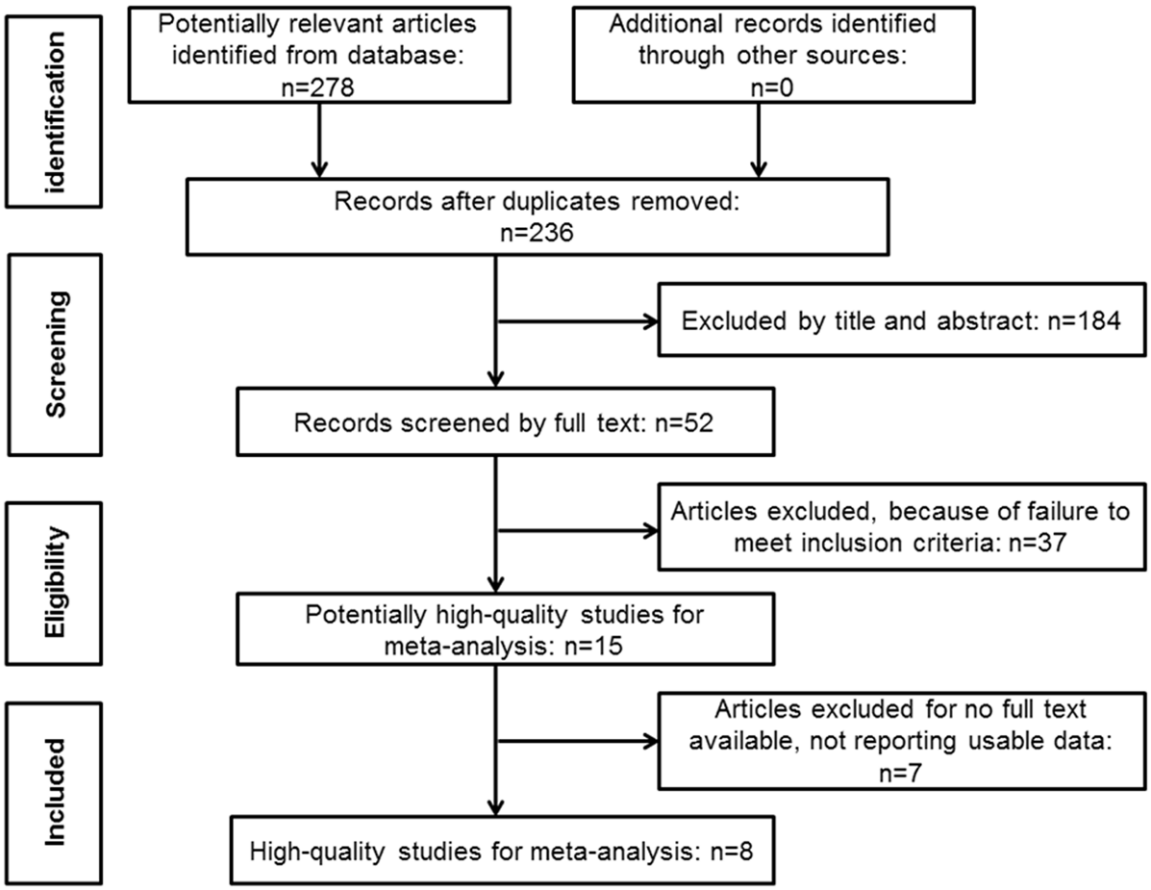


**Figure1.** The study selection and inclusion process.

In contrast, the detection of serum bone metabolic markers is cheap and easy to perform, and may assist in the early diagnosis and assessment of therapeutic results in bone metastasis [15-17]. BALP is the bone-specific isoform of alkaline phosphatase, which originates from many tissues, but primarily the liver and bone [18, 19]. BALP is a tetrameric glycoprotein found on the cell surfaces of osteoblasts [18, 19]. The exact function of BALP remains unknown. However, it has been suggested that it might play a role in mineralization of newly formed bone [15].

There have been studies reporting the use of serum BALP as a serum marker for bone metastases in patients with lung carcinoma, but the results are heterogeneous and even conflicting [20-22]. The practical value of these markers has yet to be fully evaluated. The objective of the present review was to synthesize and analyze the results from systematic selection of research papers that evaluated the diagnostic accuracy of serum BALP by directly diagnosis of bone metastasis in patients with lung carcinoma.

## Methods

### *Search strategy*

A comprehensive systematic literature review of original researches studying the diagnostic accuracy test accuracy of BALP in lung carcinoma patients with bone metastases was performed searching the following electronic databases through February 15th 2015: PubMed, Embase, Cochrane library, Web of science, Ovid, BioMed central, Biosis previews and four Chinese databases (CBM, CNKI, VIP and Wan fang DATA). In addition we conducted supplementary searches in the references of the retrieved articles. Titles and abstracts were reviewed for relevance. Relevant prospective or retrospective cohort or case-control studies were included in the meta-analysis. Subject headings and keywords used in the search process included the following: “bone-specific al-

**Table 1.** Summary of the diagnostic results of the included studies

| Study | Year | Country | Assay method | NO. | TP | FP | FN | TN | SEN | SPE |
|---|---|---|---|---|---|---|---|---|---|---|
| Aruga A | 1997 | Japan | EIA | 91 | 28 | 3 | 35 | 41 | 44.4% | 93.2% |
| Alatas F | 2002 | Turkey | EIA | 52 | 24 | 14 | 3 | 11 | 89% | 44% |
| Ebert W | 2004 | Germany | CLIA | 138 | 11 | 0 | 38 | 89 | 22% | 100% |
| Kong QQ | 2007 | China | ECLI | 96 | 22 | 4 | 39 | 31 | 36.1% | 88.6% |
| Lumachi F | 2011 | Italy | ELISA | 35 | 6 | 3 | 10 | 16 | 37.5% | 84.2% |
| Bayrak SB | 2012 | Turkey | ELISA | 65 | 7 | 4 | 16 | 38 | 30.34% | 90.48% |
| Tang C | 2013 | China | ELISA | 265 | 82 | 31 | 48 | 104 | 63.1% | 77% |
| Xin Y | 2010 | China | ECLI | 90 | 20 | 2 | 30 | 38 | 40% | 95% |

EIA: Enzyme immunoassay; CLIA: Chemiluminescence immunoassay; ECLI: Electrochemiluminescence immunoassay; ELISA: Enzyme-linked immunosorbent assay; TP: True positive; FP: False positive; TN: True negative; FN: False negative; SEN: Sensitivity; SPE: Specificity.

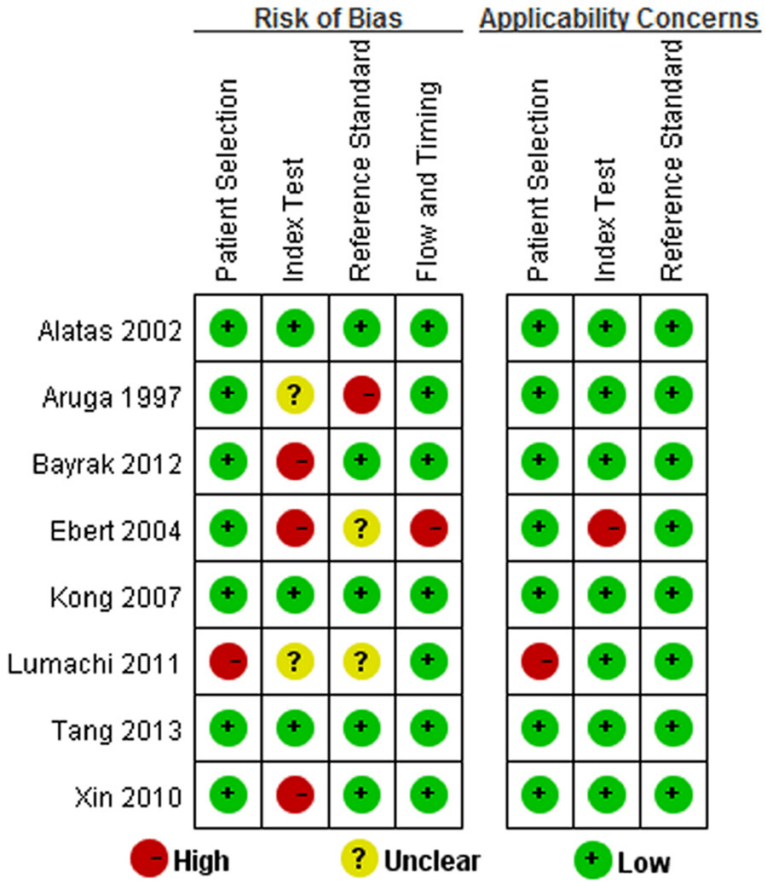


**Figure 2.** Presentation of QUADAS-2 results.

kaline phosphatase", "BAP", "BALP", "BSAP", "sBAP", "lung cancer", "lung carcinoma" and "lung neoplasms". The controlled vocabulary search terms for different databases are not identical. Therefore, search strategies need to be customized for each database.

*Inclusion criteria*

Studies were considered eligible for inclusion if they met the following criteria: I) Study design. Observational studies (cohort or case-control studies). II) Population. Lung carcinoma patients with bone metastases, or without bone metastases. III) Diagnostic test. Serum BALP in lung carcinoma patients. IV) Reference test. The following reference tests were considered eligible: radiologic examination (X-ray, CT, MRI), histological examination, etc.

*Exclusion criteria*

Studies were excluded from the meta-analysis for the following reasons: I) Duplicate publication; II) No human studies; III) Necessary data could not be obtained.

*Study selection*

All the studies were reviewed by two reviewers independently based on titles and abstracts, and then the full texts of potentially eligible studies were retrieved for further assessment. We resolved disagreements by reaching a consensus through discussion.

*Data abstraction*

The following data was extracted from the included studies by two reviewers independently: authors, year of publication, journal, study design, number of eligible patients, and reference test for the analysis of SEN and SPE (the number of true positive (TP), false negative (FN), true negative (TN) and false positive (FP) results) for comparison of lung carcinoma patients diagnosed with bone metastases vs. control. Any disagreements were re-

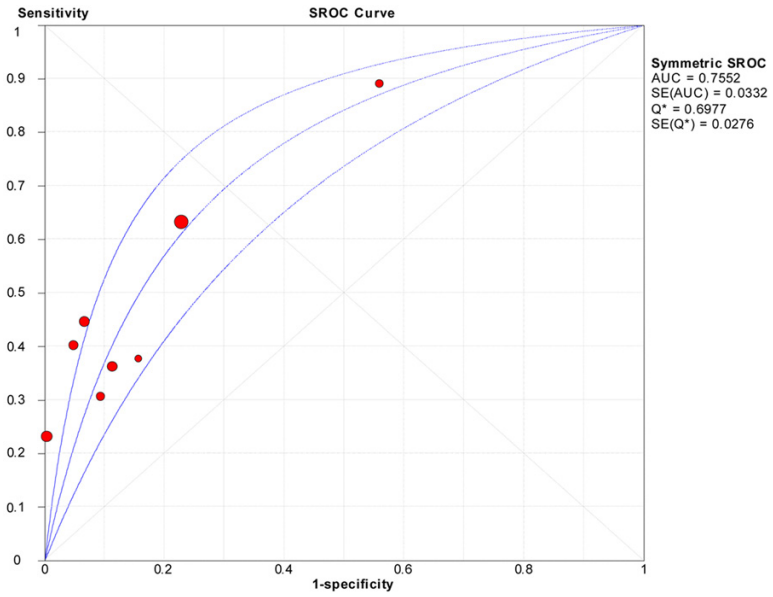


**Figure 3.** Summary receiver operating characteristic (SROC) curve for BALP in the diagnosis of Lung carcinoma patients with bone metastases in the 8 included studies.

solved through consultation with the third reviewer.

*Assessment of methodological quality*

The methodological quality of the included studies was independently assessed by two authors, using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool [23], which consists of four domains: patient selection, index test, reference standard, and flow and timing. QUADAS-2 is an updated version of this evidence-based quality tool. All domains are assessed for risk of bias and the first three domains are assessed for applicability by indicating a "low", "unclear", or "high" rating. This tool helps to evaluate the principal methodological risk of bias in systematic reviews of diagnostic test accuracy [24]. Specific coding instructions adapted for this review will be included for the reviewers. In case of doubt, a third and fourth reviewer were consulted.

*Data analysis*

Standard methods recommended for meta-analysis of diagnostic accuracy were used. The number of TP, TN, FP and FN were retrieved from each article by two investigators independently and entered into an excel datasheet [24, 25]. Discordant findings were assessed in a joint approach and authors asked for verification when in doubt. The MetaDiSc 1.4 (XI Cochrane Colloquium, Barcelona, Spain) was used to perform all data analysis. The following indexes of test accuracy were computed for each study: SEN, SPE, PLR, NLR, DOR and generate the bivariate SROC curve [25]. The DOR value ranges from 0 to infinity, with higher values indicating higher accuracy levels [26]. Data were presented as forest plots and receiver operating characteristic curves. Forest plots display the SEN and SPE of individual studies with the corresponding 95% confidence intervals. The receiver operating characteristic curves show individual study data points with size proportional to study weight [24, 27]. The area under the AUC represents an analytical summary of the test performance and illustrates the trade-off between SEN and SPE [24, 27]. The chi-square-based Q test and the inconsistency index $I^2$ were used to detect statistically significant heterogeneity across studies. When a significant Q test ($P<0.05$ or $I^2>50\%$) indicated heterogeneity among studies, the random-effect model (DerSimonian-Laird method) was conducted for the meta-analysis to calculate the pooled SEN, SPE, and other related indexes of the studies; Otherwise, the fixed-effect model (Mantel-Haenszel method) was chosen. Chi-square test was used to detect statistically significant heterogeneity across studies. Additionally, we also calculated the Spearman correlation coefficients. A strongly positive rank-correlation coefficient and a value of, 0.05 are indicative of a significant threshold effect.

## Results

*Search results*

A total of 278 titles and abstracts were preliminarily reviewed, of which 8 studies were available for the meta-analysis, including 848 lung carcinoma patients who received serum BALP tests [21, 22, 28-33]. **Figure 1** shows a flow diagram of the selection process. The characteristics of each study are shown in **Table 1**.

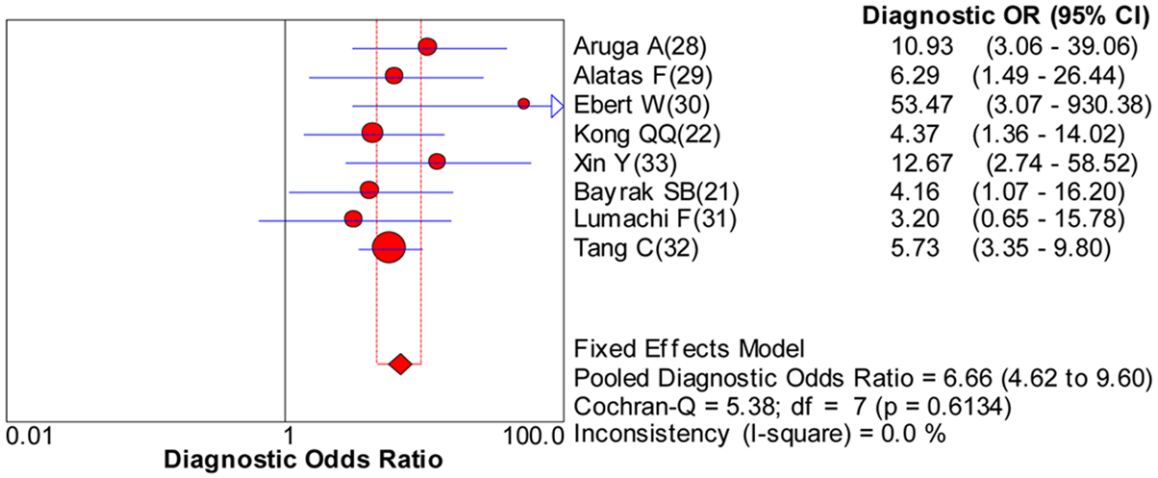


**Figure 4.** Forest plot for the diagnostic odds ratio (DOR) of BALP to diagnose Lung carcinoma patients with bone metastases. DOR (diagnostic odds ratio)=6.66 (95% CI, 4.62-9.60).

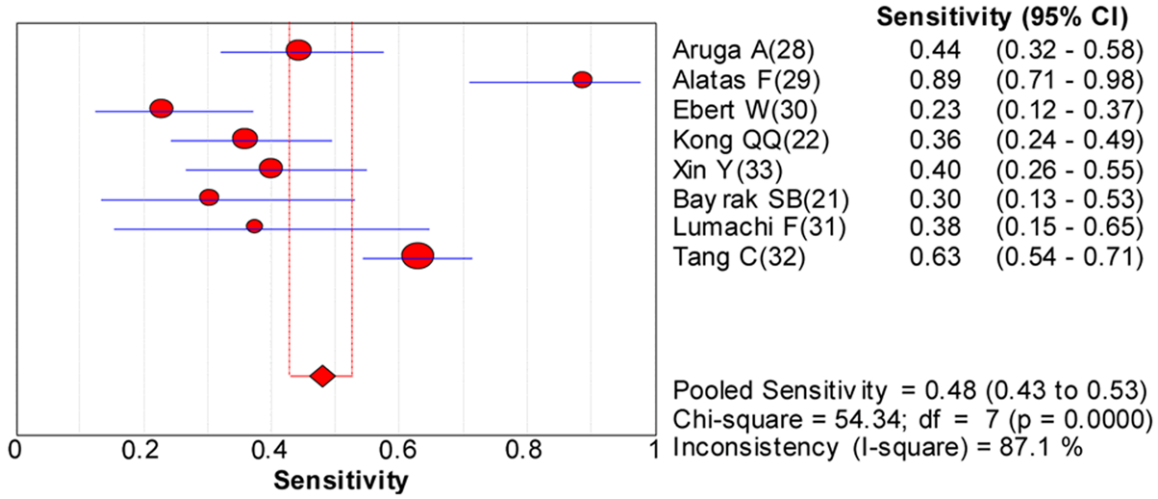


**Figure 5.** Forest plot for the sensitivity of BALP to diagnose Lung carcinoma patients with bone metastases. Sensitivity=0.48; (95% CI, 0.43-0.53).

*Assessment of methodological quality*

When using the QUADAS-2 tool to review the eight included articles, it was determined that three studies [22, 29, 32] had low risk of bias and low concern regarding applicability. Three studies [21, 28, 33] were found to be at risk for bias, but had low concerns regarding applicability. The final two studies [30, 31] were judged to be at risk of bias and as having concerns regarding applicability (**Figure 2**).

*The SROC*

The corresponding SROC (**Figure 3**) shows an AUC of 0.78 with standard error=0.02, and the pooled diagnostic accuracy ($Q^*$) was 0.72 with standard error=0.02, indicating high overall accuracy of BALP for the diagnosis of lung carcinoma patients with bone metastases.

The Spearman rank correlation coefficient was 0.64 ($P$=0.09), confirming that the variability across these studies could not be explained by differences in the diagnostic threshold.

*The pooled DOR*

Significant heterogeneity among the studies was not detected (Cochran Q statistic=5.38; $P$=0.61). A Forest plot for the DOR of BALP for the diagnosis of lung carcinoma patients with bone metastases was 6.66 with a corresponding 95% CI of 4.62-9.60, as shown in **Figure 4**.

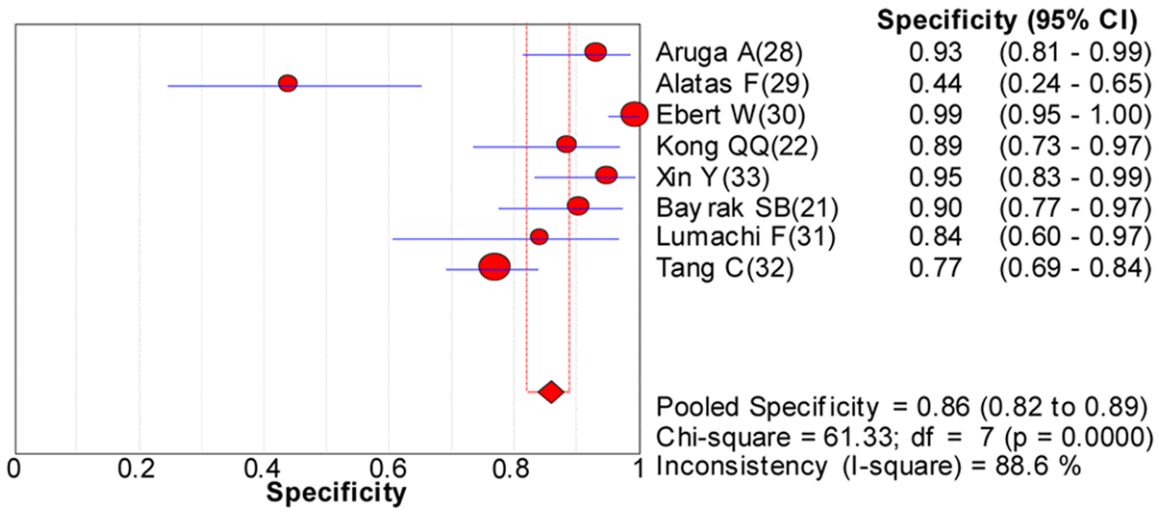


**Figure 6.** Forest plot for the specificity of BALP to diagnose Lung carcinoma patients with bone metastases. Specificity=0.86 (95% CI, 0.82-0.89).

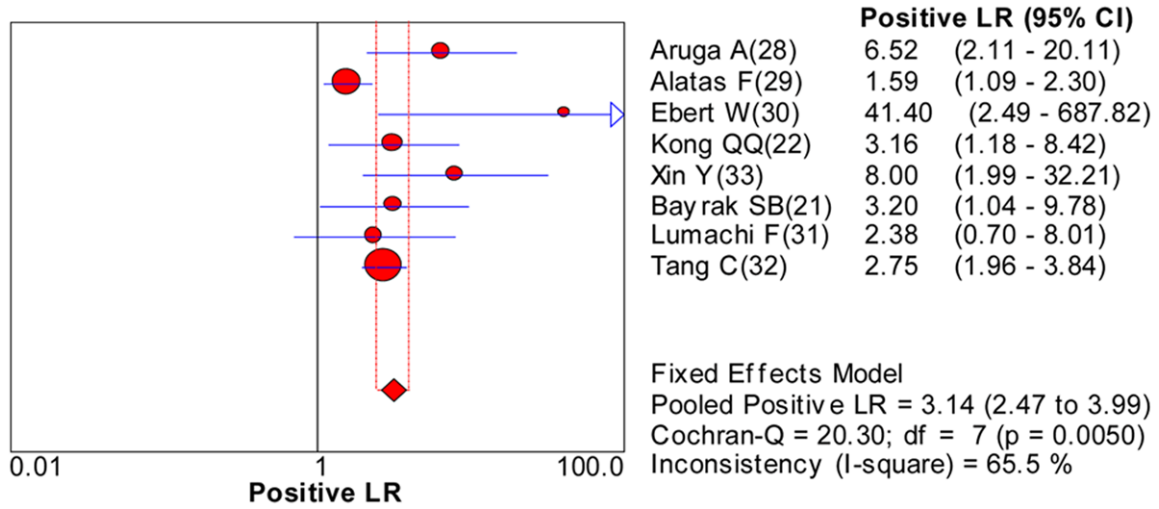


**Figure 7.** Forest plot for the positive likelihood ratio (PLR) of BALP to diagnose Lung carcinoma patients with bone metastases. PLR (positive likelihood ratio)=3.14 (95% CI, 2.47-3.99).

*The pooled sensitivity and specificity*

Significant heterogeneity among the studies was detected (SEN: chi-square=54.34, *P*=0.00), **Figure 5**). SPE: chi-square=20.31, *P*<0.0049, **Figure 6**). The SEN ranged from 22% to 89% (pooled, 48%; 95% CI, 43-53%), whereas SPE ranged from 44% to 100% (pooled, 86%; 95% CI, 82-89%).

*The pooled PLR and NLR*

Significant heterogeneity among the studies was also detected in the PLR (Cochran Q statistic=20.30, *P*=0.01, **Figure 7**). However, no significant heterogeneity was found in the NLR (Cochran Q statistic=19.40, *P*=0.01, **Figure 8**). The pooled PLR was 3.14 (95% CI, 2.47-3.99), and the pooled NLR was 0.62 (95% CI, 0.56-0.68).

Solid circles represent each study included in the meta-analysis. The size of each study is indicated by the size of the solid circle. The regression SROC curve summarizes the overall diagnostic accuracy. AUC (area under the curve)=0.78, $Q^*$=0.72.

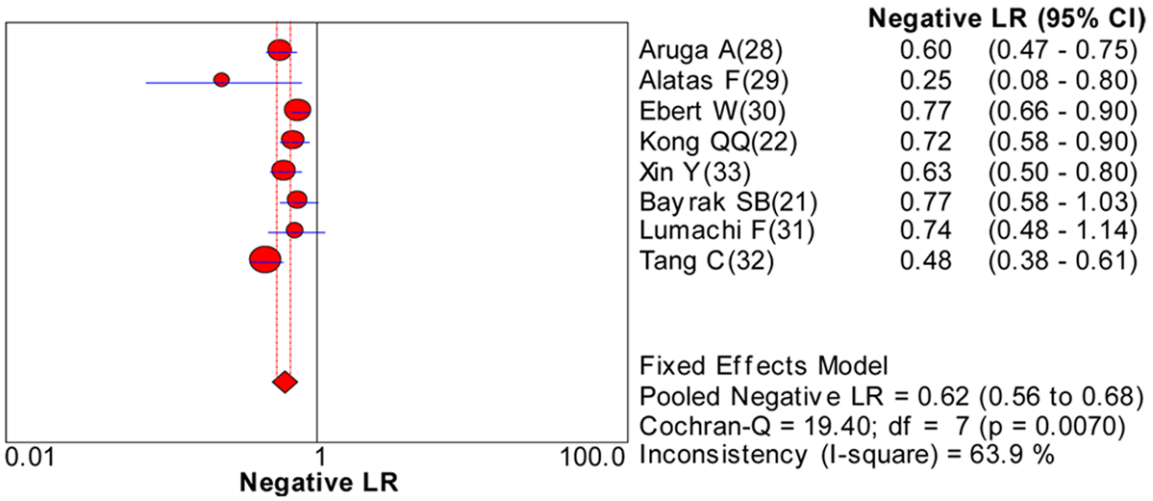


**Figure 8.** Forest plot for the negative likelihood ratio (NLR) of BALP to diagnose Lung carcinoma patients with bone metastases. NLR (negative likelihood ratio)=0.62 (95% CI, 0.56-0.68).

## Discussion

The early diagnosis of bone metastases may bring improvements of life quality and treatment to the lung carcinoma patients [1, 34, 35]. More and more attention has been paid to the improvement of early diagnosis of bone metastases [34]. The well-recognized screening method SPECT is not recommended for patients without evidence of bone pain, and it does not suit for continuous monitoring due to its high price and radioactivity [36, 37]. The increasing incidence of bone metastases worldwide has sparked a new interest in serum markers [20, 38, 39]. A number of new biochemical markers of bone turnover have been extensively studied in the clinical diagnosis [38, 39].

BALP is considered marker of matrix maturation (middle phase) and mineralization (late phase), respectively, in the phenotypic developmental sequence of osteoblasts [18, 40]. In particular, serum BALP has been increasingly used for the diagnosis of bone metastasis in patients with lung carcinoma [41]. In the same study, serum levels of BALP were significantly increased in lung carcinoma patients with bone metastases compared with those without bone metastases [21, 28-33]. In some other studies, BALP levels did not differ between the groups with and without metastasis but were found to be significantly higher than in the control group [22, 41]. Therefore, it was imperative to pool the results of individual studies to evaluate the diagnostic value of this method via meta-analysis. To evaluate the diagnostic and clinical valve of BALP a serological marker, we conducted this meta-analysis to provide a comprehensive and up-to-date analysis of the feasibility and accuracy of BALP for the diagnosis of bone metastases. As far as we know, this is the first meta-analysis about the diagnostic value of BALP for bone metastases.

In this meta-analysis, we show that the pooled SEN and SPE are 0.48 [95% CI (0.43 to 0.53)] and 0.86 [95% CI (0.82 to 0.89)] respectively. Thus, BALP enjoys it has higher SEN and SPE compared to conventional serum alkaline phosphatase (ALP) (SEN of 26.7%) and bone scan (SPE of 44.1%) [37]. It has higher sensitivity and SPE in effectively diagnosing of bone metastases. Glas et al. [26] found that the DOR combines the strengths of SEN and SPE as prevalence in dependent indicators and has the advantage of accuracy over a single indicator. The value of DOR ranges from 0 to infinity with higher values indicating better discriminatory test performance [22]. The DOR value of 6.66 indicates that the BALP could be a useful biomarker for bone metastases patients' diagnosis. AUC is calculated to evaluate accuracy of the selected indicator, and SROC is usually used to summarize overall test performance [42, 43]. To demonstrate excellent accuracy, the valve of AUC should be more than 0.97. An AUC of 0.93 to 0.96 is considered to be very good and 0.75 to 0.92 is good [38, 39]. In these studies, we show that BALP demonstrates good

accuracy in the diagnosis of lung carcinoma, with an area under the ROC curve of 0.78. Overall, although the SEN is compromised, BALP has a good SPE in the diagnosis of bone metastases. The PLR and NLR are more meaningful indicators of diagnostic accuracy. A good diagnostic test may have high PLR (PLR>5) and low NLR (NLR<0.2) [24, 44]. However, the PLR and NLR value of this study did not meet these thresholds. In this meta-analysis, a PLR value of 3.14 demonstrated that lung carcinoma patients with bone metastases had approximately 3.14 times higher chance of testing positive than patients without bone metastases, and this was relatively high for clinical purposes. On the other hand, an NLR value of 0.62 revealed that a patient with bone metastases had a 62% chance of testing negative, and this method is therefore not sensitive enough to rule out bone metastases in the case of a negative test. These results suggest that a substantial proportion of patients might be incorrectly classified according to BALP. Based on the current pooled evidence, using BALP will help to diagnose bone metastases, but may not fully replace other routine diagnostic methods such as CT, MRI, bone scintigraphy screening and SPECT, which have been used for the diagnosis of bone metastases.

Heterogeneity is a potential problem when interpreting the results for all meta-analysis [24, 26]. One of the primary causes of heterogeneity in test accuracy studies is threshold effect, which arises when differences in sensitivities and specificities occur due to different thresholds used in different studies to define a positive or negative test result [24, 26]. As different thresholds were used among the 8 studies, we used the Spearman correlation coefficient to analyze the threshold effect. The Spearman correlation coefficient of sensitivity and 1-specificity is 0.64 ($P$=0.09), which indicates that the variability across these studies could not be explained by differences in the diagnostic threshold. We speculated that the heterogeneity was attributed to the ethnicity, etiology, assay methods and different geographical locations. We speculated that the limited number of eligible studies was the main factor that made subgroup analysis not possible. However, these hypotheses need to be investigated in the future study.

It is well recognized that the quality of special clinical tests can influence the outcome of a diagnostic accuracy study [45]. Both prospective and retrospective guidelines are designed to allow the clinician/researcher to differentiate the quality of study designs thus further refining which tests are proper for use in clinical practice [24, 45]. Nevertheless, combining the results of multiple studies increases the diagnostic accuracy of outcome estimates to the levels that are largely unachievable by standalone studies [24]. Furthermore, combining results from multiple studies can detect homogeneity among their results making estimated diagnostic accuracy generalizable to other clinics [24, 26]. Risk of publication bias assessment was considered inappropriate and not meaningful. Application among meta-analysis with small number of studies (n<10) yields low statistical power [26]. Therefore, publication bias assessment was not performed. Despite these limitations, homogeneous study results were observed for most parameters relating to the diagnostic accuracy of BALP. Therefore, we feel confident that the estimated parameters of diagnostic accuracy approach the levels achieved in a clinical setting.

This meta-analysis had some limitations. First, we only included eight studies that have a smaller number of cases. Therefore, the results of the trials in a pooled analysis were not robust. More studies are needed for future analyses. Second, we did not calculate the some covariates because sufficient raw data was not available from the selected articles. These probable covariates included tumor type, ethnicity, histology, assay methods and so on. Third, this meta-analysis was based on published studies; the exclusion of unpublished data is generally associated with an overestimation of the true effect, thus resulting in a publication bias.

## Conclusions

The present meta-analysis demonstrated that BALP has a role in the diagnosis of bone metastases. The results of this diagnostic method should be interpreted in parallel with clinical findings and other conventional tests. We believe that evaluation of the present diagnostic method will provide evidence to aid DOC in diagnosing bone metastases. However, it would not be recommended for using independently. Due to the limitations of the present meta-analysis, additional high-quality original studies are required to confirm the predictive value.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Wen-Yi Li, Department of Orthopedics, Hebei General Hospital, 348 West He-Ping Road, Shijiazhuang 050051, Hebei Province, P. R. China. Tel: +86 0311 85988160; Fax: +86 031185988574; E-mail: hbghgk@163.com

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