



Serum cross-linked N-telopeptide of type I collagen for the diagnosis of bone metastases from solid tumours in the Chinese population: Meta-analysis

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Abstract

Objective: A meta-analysis to determine the diagnostic value of serum cross-linked N-telopeptide of type I collagen (NTx) for bone metastasis from solid tumours in the Chinese population.

Methods: Eligible case–control studies published up until 22 September 2014 were identified by searching the electronic literature databases PubMed[®], Web of Science, China National Knowledge Infrastructure and Wanfang using the keyword ‘NTx’ in combination with ‘cancer’. A meta-analysis of the diagnostic value of serum NTx for bone metastasis from solid tumours was undertaken.

Results: The meta-analysis included 14 studies (1279 patients: 668 with bone metastasis; 611 controls without bone metastasis). There was a significant relationship between serum NTx concentration and bone metastasis from solid tumours in the Chinese population (odds ratio 1.39, 95% confidence intervals 1.26, 1.51). Significant heterogeneity was found in this study, but no publication bias was observed.

Conclusion: Serum NTx concentration may play an important role in the diagnosis of bone metastasis from solid tumours in the Chinese population.

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Keywords

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Introduction

The skeletal system is one of the most common metastatic sites of solid tumours:¹ bone metastases have been found in ~70% of advanced breast and prostate cancer patients.² Bone metastases can cause substantial pain and increase the risk of fracture, decreasing health-related quality of life in affected patients.³

The presence of bone metastases is usually diagnosed by bone scintigraphy, bone radiography and magnetic resonance imaging (MRI). Research has also demonstrated the value of using bone biochemical markers for diagnosing solid tumours with bone metastases, including cross-linked N-telopeptide of type I collagen (NTx), deoxypyridinoline (DPD), and pyridinoline cross-linked C-telopeptide of type I collagen (ICTP).^{4,5}

Type I collagen is the principal collagen in the skeletal system, accounting for ~90% of the organic chemical constituents of bone.^{6,7} As one of the degradation products of collagen, NTx is released from bone into the blood when bone is resorbed and is subsequently drained by the kidney into the urine.³ Meanwhile, serum and urine levels of NTx are often increased when malignant tumours metastasize to bone.^{3,8} Therefore, the NTx that can be detected in urine and serum is associated with both the appearance and degree of severity of bone metastasis.^{9,10} Studies have shown that urinary NTx plays an important role in the diagnosis of patients with bone metastasis.^{10–12} Serum NTx concentrations are upregulated in patients with solid tumours and bone metastasis.^{7,13} The serum NTx concentration may

have a prognostic value in patients with prostate carcinoma at diagnosis.¹⁴ However, few studies have investigated the utility of serum NTx in the diagnosis of bone metastasis in patients with solid tumours, particularly in the Chinese population. The aim of this meta-analysis was to investigate the role of serum NTx concentrations in the diagnosis of bone metastasis in patients with solid tumours.

Materials and methods

Data sources and search strategy

This search was undertaken following the Meta-analysis Of Observational Studies in Epidemiology¹⁵ and the Cochrane Handbook for Systematic Reviews guidelines.¹⁶ Eligible case-control studies published up until 22 September 2014 were identified by searching the electronic literature databases PubMed®, Web of Science, China National Knowledge Infrastructure and Wanfang using the keyword 'NTx' in combination with 'cancer'. References were manually searched without any language limitations. Search results were initially screened by two authors (Y.D.Z. and J.C.) independently using titles and abstracts. Then, two other authors (M.H.Y. and Y.Y.Z.) independently reviewed the full texts of the articles identified during the initial screening. Any disagreements between the two authors were referred to the fifth author (Y.J.Z.).

Selection criteria

To be included in the meta-analysis, studies that detected serum NTx had to fulfil all of

the following criteria: (i) performed in a Chinese population presenting with solid tumours and bone metastasis; (ii) Chinese patients with solid tumours but without bone metastasis were used as controls; (iii) all patients were diagnosed with the primary tumour and/or the bone metastases by clinical, pathological, or imaging examinations.

Data extraction

Data were extracted from the included studies by two investigators (Y.D.Z and M.H.Y.) independently and in duplicate. If necessary, consensus was achieved by discussion and re-examination. The following data were extracted from eligible studies: surname of first author; year of publication; language of publication; primary cancer type included in the article; sample size; age (mean \pm SD); detection method for serum NTx level; serum NTx levels.

Quality assessment

Quality of the included studies was assessed by two investigators (Y.D.Z. and C.H.) independently and in duplicate, using pre-defined criteria based on Newcastle–Ottawa Scale (NOS) criteria.¹⁷ Discrepancies regarding NOS scores were resolved by discussion and consultation with an additional reviewer (Y.J.Z.).

Statistical analyses

Odds ratios (ORs) of serum NTx concentrations and bone metastases from solid tumours were performed for each study. Forest plots and I^2 -test estimates were performed to explain heterogeneity for this meta-analysis. Sensitivity analysis re-estimated the meta-analysis by omitting each study in turn to confirm the stability of the analysis model. Funnel plot and Egger's linear regression test were used to investigate

the publication bias. All analyses were performed using STATA[®] version 12.0 (StataCorp, College Station, TX, USA).

Results

The study selection procedure is presented in Figure 1. The initial electronic database search identified 108 publications, of which 39 citations were excluded immediately due to duplication. A further 47 citations were excluded based on reading the titles and abstracts because they did not meet the inclusion criteria, as were an additional eight articles after the full-text review stage. Finally, 14 articles met the inclusion criteria and were included in this meta-analysis.^{18–31}

It should be noted that the analysis only included studies that were from China because the unit of measure used for NTx was the same across the Chinese studies. The main characteristics of the included studies are summarized in Table 1. These 14 studies included 1279 patients presenting with a solid tumour (including lung, breast, prostate and digestive system tumours) who had a serum NTx value at diagnosis. Of these patients, 668 had bone metastases and 611 did not have bone metastases. Serum NTx concentrations were measured using an enzyme-linked immunosorbent assay in each study.

Results of the meta-analysis showed significant heterogeneity existed ($I^2 = 84.3\%$, $P < 0.001$). There was significant association between serum NTx and solid tumours with bone metastases (OR 1.39, 95% confidence intervals 1.26, 1.51; $P < 0.001$) (Figure 2a). There was no significant publication bias (Begg's test: $z = -0.38$, $P = 0.702$; Figure 2b). Sensitivity analysis showed that no individual study significantly altered the pooled results for this meta-analysis (Figure 3). This study was unable to test the sensitivity and specificity of serum NTx concentrations because the majority of included studies did not measure this, and

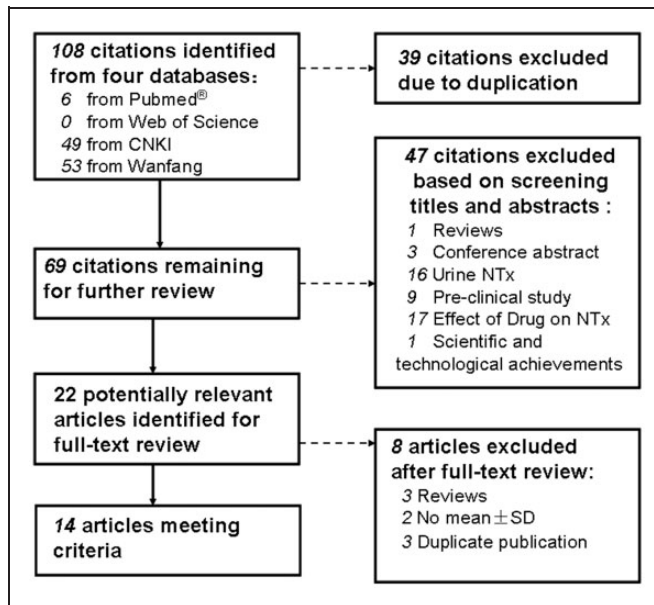


Figure 1. Flow diagram of identification and collection of eligible studies in a meta-analysis to evaluate the diagnostic value of serum concentrations of cross-linked N-telopeptide of type I collagen (NTx) in bone metastasis from solid tumours. CNKI, China National Knowledge Infrastructure.

Table 1. Main characteristics of the 14 eligible studies included in a meta-analysis to evaluate the diagnostic value of serum concentrations of cross-linked N-telopeptide of type I collagen (NTx) in bone metastases from solid tumours.^{18–31}

First author/year	Cancer Language type	Bone metastasis group		Without bone metastasis group		Method of measuring serum NTx
		Patients, n	Serum NTx, nmol/l	Patients, n	Serum NTx, nmol/l	
Wang, 2008 ¹⁹	Chinese Lung, breast	50	24.06 ± 10.67	55	13.16 ± 9.52	ELISA
Huang, 2009 ²⁰	Chinese Lung, breast, prostate, digestive system	51	25.70 ± 12.67	45	11.20 ± 4.74	ELISA
Chen, 2010 ²¹	Chinese Lung	32	25.97 ± 11.25	44	13.02 ± 8.76	ELISA
Lu, 2010 ²²	Chinese Breast	71	26.38 ± 13.51	45	13.32 ± 4.56	ELISA
Zhou, 2010 ²³	Chinese Lung	41	214.08 ± 262.45	37	80.38 ± 40.96	ELISA
Zhang, 2011 ²⁴	Chinese Lung	61	25.36 ± 11.07	45	12.16 ± 7.62	ELISA
Xie, 2011 ²⁵	Chinese Lung	32	25.01 ± 11.67	35	13.21 ± 7.59	ELISA
Huang, 2011 ²⁶	Chinese Lung	60	27.29 ± 5.71	60	18.00 ± 4.90	ELISA
Lu, 2012 ²⁸	Chinese Breast	51	27.75 ± 9.11	43	12.40 ± 4.24	ELISA
Cai, 2013 ²⁹	Chinese Lung, breast	48	25.64 ± 11.35	60	14.53 ± 9.78	ELISA
Deng, 2013 ³⁰	Chinese Prostate	38	25.38 ± 11.13	35	12.41 ± 7.04	ELISA
Li, 2013 ²⁷	Chinese Lung	45	27.76 ± 10.66	37	11.43 ± 3.44	ELISA
Sun, 2013 ¹⁸	Chinese Lung	53	46.18 ± 24.22	47	23.99 ± 9.05	ELISA
Wang, 2014 ³¹	Chinese Breast	35	16.98 ± 1.75	23	7.59 ± 1.47	ELISA

Serum NTx data presented as mean ± SD.

ELISA, enzyme-linked immunosorbent assay.

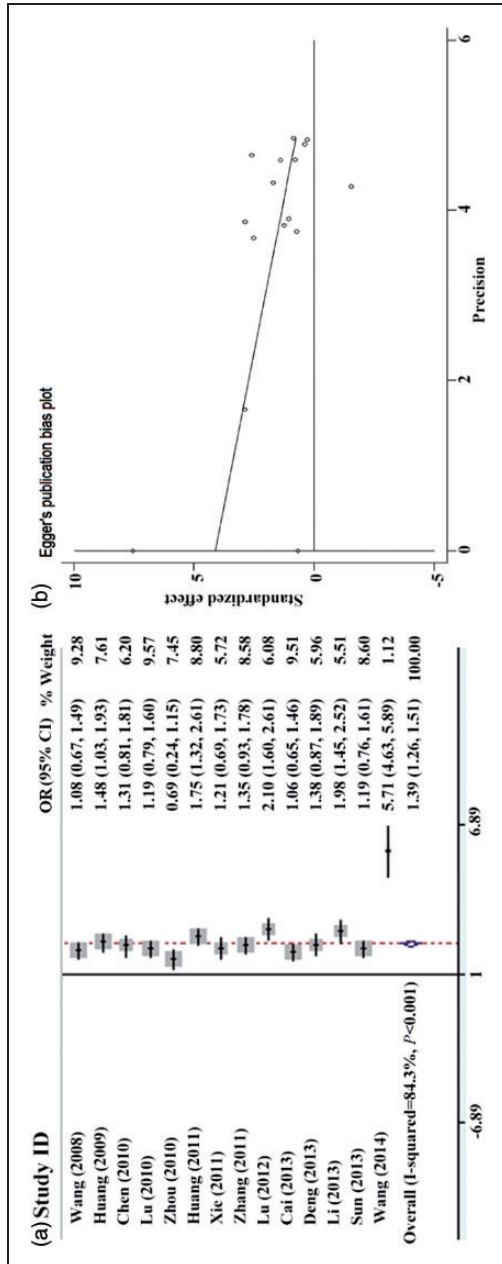


Figure 2. Forest plot for the diagnostic value of serum concentrations of cross-linked N-telopeptide of type I collagen in bone metastasis from solid tumours for 14 studies included in the meta-analysis (a) and Begg's funnel plot to evaluate the publication bias for this model (b). OR, odds ratio; CI, confidence interval.

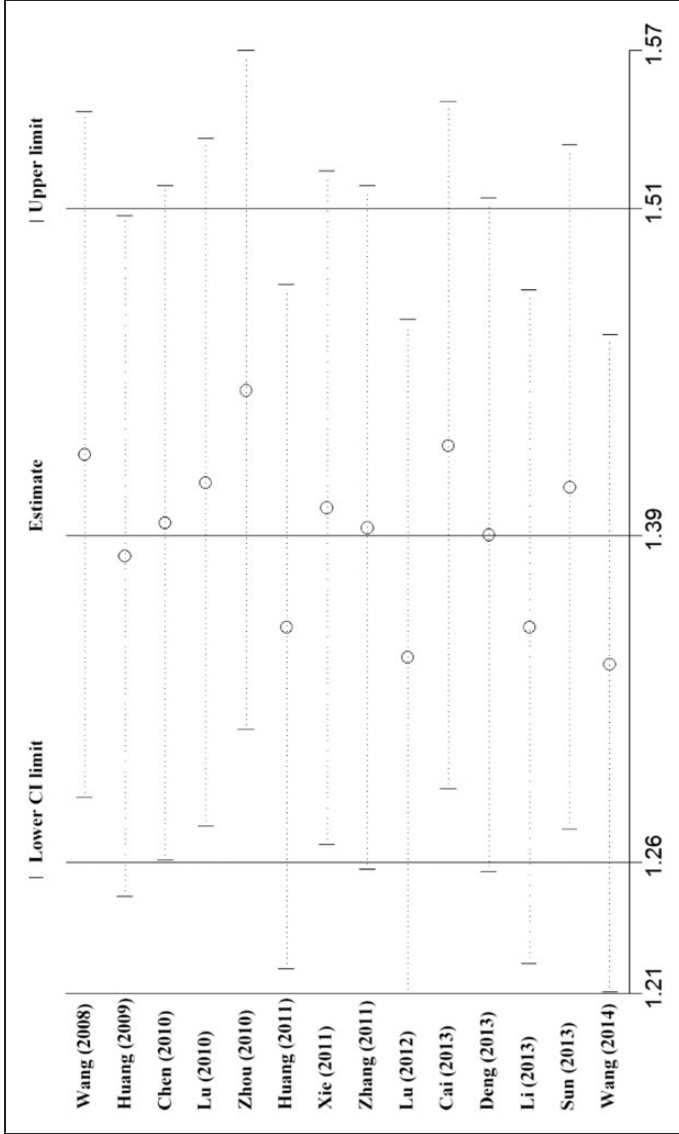


Figure 3. Sensitivity analysis of summary odds ratio coefficients for the diagnostic value of serum concentrations of cross-linked N-telopeptide of type I collagen in bone metastasis from solid tumours.

the diagnostic methods for bone metastases were different across the studies.

Discussion

This meta-analysis is the first systematic review describing the diagnostic value of serum NTx concentrations in identifying solid tumours with bone metastases in the Chinese population. These findings suggest that the serum NTx concentration might serve as a bone biomarker identifying the presence of bone metastases in patients with solid tumours in the Chinese population.

Significant heterogeneity occurred in this meta-analysis, while the sensitivity analysis showed that no individual study significantly altered the pooled result. Serum NTx concentrations in the study by Zhou and Zhang²³ were ~10-fold higher than those reported in the other studies.^{18–22,24–31}

Bone metastasis is a common cause of pathological fracture, hypercalcaemia, spinal cord compression, immobility and ultimate mortality in patients with advanced cancer.³² Therefore, early diagnosis of bone metastasis is very important for cancer patients. The common methods used to diagnose bone metastasis include bone radiography and MRI, but more usually a bone scintigraphy scan is undertaken. Although a bone scintigraphy scan measures aspects of bone metabolism and bone remodelling that are not achievable by the other methods, its frequency of use must be limited because it requires exposure of the patient to a radioisotope. In contrast, it is relatively easy and convenient to measure bone biomarkers in serum, which allows for more frequent testing in the intervals between bone scans.

Previous research has evaluated other bone metabolism biomarkers, including D-PYD, ICTP, and NTx, of which NTx is the most useful bone marker in predicting skeletal-related events in patients with

metastatic bone disease.³³ The serum NTx concentration is also associated with the extent of disease grade, a grade that is based on the extent or severity of bone metastasis.³⁴ NTx played an important role in monitoring antiresorptive treatment with bisphosphonates for bone metastasis from a solid tumour.⁶ This meta-analysis suggests the usefulness of serum NTx concentrations for diagnosing bone metastasis in Chinese patients with solid tumours. Increased serum NTx concentrations may suggest a poorer prognosis for patients with solid tumours. NTx could be developed as a new bone biomarker for the diagnosis of solid tumours with bone metastasis.

This current meta-analysis had several limitations. First, although no evidence of publication bias was found, the results were based on a relatively small number of studies with small sample sizes. Therefore, publication bias could not definitely be excluded. Secondly, significant heterogeneity existed in this meta-analysis. Some underlying heterogeneity may have been due to the age and sex of the patients, and variations in sample size, study design and methods used to determine serum NTx concentrations across the studies. Thirdly, the majority of included studies did not determine the sensitivity and specificity of serum NTx concentration and the diagnostic methods that had been used to confirm the presence of bone metastasis were different across the studies, so in turn, this meta-analysis was unable to measure sensitivity and specificity. Fourthly, this study did not conform to the PRISMA 2009 Guidelines. Large, well-designed studies are needed to provide more accurate data in both Chinese populations and in populations from around the world.

In conclusion, the serum NTx concentration may have a role to play in the diagnosis of bone metastasis in Chinese patients with solid tumours.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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