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Review article

N-telopeptide as a potential diagnostic and prognostic marker for bone metastasis in human cancers: A meta-analysis

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ABSTRACT

Purpose: Whether *N*-telopeptide of type I collagen (NTx) can be applied for diagnosis and prognostic prediction of bone metastasis in human cancers is still conflicting. This study aimed to investigate the diagnostic and prognostic value of NTx for cancer patients with bone metastasis.
Methods: Embase, PubMed, Chinese National Knowledge Infrastructure and Wanfang databases were retrieved to collect related publications. In diagnostic meta-analysis, the sensitivity (SEN) and specificity (SPE) were calculated. Hazard ratio (HR) with 95% confidence interval (95% CI) was used in the prognostic meta-analysis. Sensitivity and publication analyses were conducted for potential heterogeneity sources.
Results: The pooled SEN and SPE were 77% (72–81%) and 80% (75–84%) for 45 diagnostic studies. A higher diagnostic efficacy was obtained from NTx combining with other markers (AUC: 0.94 (0.92–0.96)) for bone metastasis of human cancers, especially for lung cancer (AUC: 0.87 (0.84–0.90)), breast cancer (AUC: 0.83 (0.79–0.86)) and prostate cancer (AUC: 0.88 (0.85–0.90)) in Asian people (AUC: 0.86 (0.83–0.89)). For the value of NTx on prognosis of human cancers with bone metastasis, the pooled HR was 2.12 (1.74–2.58) for high versus low NTx level, indicating high NTx level would increase the risk of poor overall survival.
Conclusion: Our results indicated serum NTx combining with other markers can become a feasible biomarker for the diagnosis and prognosis prediction for bone metastasis of different cancers, including lung cancer, breast cancer and prostate cancer in Asian people.

1. Introduction

Bone metastasis is a common complication of malignant tumors, which is a very important indicator for staging, predicting prognosis, and determining treatment options for primary malignant tumors. Early diagnosis and treatment of bone metastases can reduce the occurrence of bone-related events and improve the life quality of patients [1]. Currently, the diagnosis and efficacy evaluation of bone metastases from malignant tumors mainly relies on imaging methods. However, the present diagnostic methods for bone metastases have different shortcomings such as expensive, low sensitivity and high false positive rate, that cannot meet clinical needs. Therefore, there is an urgent need for a feasible, inexpensive, specific, non-invasive detection method for clinical diagnosis [2].

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The changes in biochemical indicators of bone metabolism are significantly earlier than the morphological changes found in imaging when bone metastasis occurs. However, traditional biochemical indicators of bone metabolism are susceptible to multiple factors, resulting to a relative low specificity and limited application in clinical practice. Recently, several biochemical indicators of bone metabolism, such as *N*-telopeptide of type I collagen (NTx), type I collagen cross-linked carboxy terminal peptide (ICTP), carbon terminal peptide (CTx), and deoxypyridinol (DPD), have been recognized as sensitive indicators of bone resorption and have been used in clinical evaluation of metabolic bone diseases [2]. Some studies have shown that they are also useful markers in the diagnosis and treatment of metastatic bone tumors [3]. And NTx and ICTP are considered to be the most promising biochemical indicators of bone metabolism [2].

As prominent collagen of skeletal system, type I collagen accounts for 90% of organic constituents in bone [4,5]. NTx, as metabolite of collagen, could be released from bone to circulating system and then subsequently drained into urine by kidney [6]. Researches indicated that levels of NTx from serum and urine tended to increase during the bone metastasis of malignant tumors [6,7], which was related to both appearance and severity level of bone metastasis [8–10]. Numerous studies have suggested that serum and urine NTx might be used as an accessible tool for the early diagnosis and prognosis prediction of cancer patients with bone metastasis [8,11,12]. However, due to different specimen, ethnicity and profiling, there is a conflicting conclusion from different articles. Some studies found a significant association between high NTx level and poor prognosis of cancer patients [13,14]. However, other researchers suggested that there was no association between NTx and cancer prognosis [15,16]. Moreover, Li W et al. found that NTx could be used for diagnosis of bone metastasis, with high sensitivity of 98.3% [17], but research by Ulrich U et al. showed a relative low sensitivity of NTx (44.0%) for diagnosis of cancer bone metastasis [18]. Regrettably, no relevant meta-analysis existed to systematically assess the efficacy of NTx level on both early diagnosis and prognosis prediction for human cancer with bone metastasis.

Overall, evaluation of the detection and prognosis efficacy of NTx for bone metastasis of different cancers is urgently needed. Therefore, this study aimed to systematically evaluate the efficacy of NTx on exact diagnosis and precise prognostic prediction for cancer patients with bone metastasis.

2. Materials and methods

2.1. Search strategy

Our meta-analysis was based on the Preferred Reporting Items for meta-analyses (PRISMA). We searched PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI) and Wanfang databases for all relevant publications that assessed the value of NTx for early diagnosis and prognostic prediction in human cancers with bone metastasis. The searching items were as listed: ((*N*-telopeptide of type I collagen) or (*N*- telopeptide type I collagen) or (*N*-telopeptide) or (NTx telopeptide) or NTx) and (neoplasms or cancer or tumor or carcinoma) before December 31, 2022. Moreover, reference lists of the reviews were searched to obtain potential articles.

2.2. Literature enrollment

There were a series of criteria for records inclusion as well as exclusion in this study. For literature inclusion: 1) The enrolled participants were cancer patients with or without bone metastasis; 2) The diagnostic or prognostic efficacy of NTx on cancer bone metastasis was evaluated; 4) True negative (TN), true positive (TP), false negative (FN), false positive (FP) or hazard ratio (HR) with its 95% confidence interval (95% CI) could be retrieved; while exclusion criteria included: 1) Unrelated articles, duplicate publications, meta-analysis or reviews; 2) Records with incomplete data or the same individuals.

2.3. Data extraction and quality assessment

The following variables were collected by two author, respectively: authors, publication date, median or mean age, ethnicity, the number of participants, specimen of NTx and testing method; types of cancer; follow-up time and outcome, TP, FP, FN, TN, HR and its 95% CI. HR was reformatted as high NTx level versus low NTx level. Quality of these articles was evaluated by the Quality Assessment of Diagnostic Accuracy Studies 2 guidelines (QUADAS-2) and the Newcastle-Ottawa Scale (NOS)for diagnosis meta-analysis and prognostic meta-analysis, respectively [19,20].

2.4. Statistical analysis

RevMan 5.3 (version 1.4) and STATA 11.0 (College Station, TX) were used for statistical analysis. Bivariate effect-regression models were established to calculate the overall sensitivity (SEN), specificity (SPE), negative likelihood ratio (NLR) [(1-SPE)/SPE)], positive likelihood ratio (PLR) [(SEN/(1-SEN)], diagnostic odds ratio (DOR) [PLR/NLR] and HR with 95% CI. The area under the curve (AUC) of summary receiver operating characteristic (SROC) curve was also calculated. Moreover, studies' heterogeneity was assessed by the Q test and I^2 value [21]. A random synthesis analysis would be performed if $I^2 \geq 50\%$ or *P* value of Q tests less than 0.05. Otherwise, a fixed pooled meta-analysis would be performed.

We conducted the meta-regression and subgroup analyses to explore heterogeneity sources through classifying the prominent variables into different subgroups according to the cutoff from the enrolled original publications. Different subgroups for diagnostic analysis were listed as follows: grouped by ethnicity: Asian or Caucasian; specimen: serum, plasma, and urine; sample size:$\geq$100 and $<$ 100; profiling: NTx alone or combining with other biomarkers; cancer-type: breast cancer, lung cancer, prostate cancer, thyroid cancer

and multiple cancers; reference: creatinine or not applicable; cutoff: pre-specified or not pre-specified. Deek's funnel plot asymmetry test was performed for publication bias if *P* value less than 0.01 [22]. For prognostic meta-analysis, the Begg's and Egger's tests were conducted for the assessment of publication bias. Furthermore, subgroup analysis was conducted grouped by ethnicity (Asian, Caucasian or mixed ethnicities), specimen (serum or urine), outcome (overall survival (OS) or progression-free survival (PFS), sample size ($\geq$100 and $<$100), cutoff (pre-specified or not pre-specified), type of cancer (breast cancer, lung cancer and prostate cancer), reference (creatinine or not applicable), source of NTx (baseline or on-study), age ($<$60 or$\geq$60), type of analysis (univariate or multivariate). Moreover, the sensitivity analysis was conducted for both diagnosis meta-analysis and prognosis meta-analysis. All analyses were based on previous published studies, thus no ethical approval and patient consent were required.

3. Results

3.1. Literature search

As shown in Fig. 1, 2352 eligible articles were enrolled, of which 542 duplicated articles were excluded. Another 1134 unrelated publications and 597 reviews were then removed. Moreover, another 17 articles with incomplete data or the same participants were excluded. Ultimately, 62 publications from 1997 to 2022 were enrolled [2,13,23–38]. 44 articles assessed the diagnostic value of NTx for bone metastasis of human cancers [2,3,13,23–34,38–41], 20 records evaluated the efficacy of prognostic prediction of NTx in human cancers [13,15,38,42–50].

3.2. Diagnostic meta-analysis

3.2.1. Study characteristics and quality assessment

45 articles with 4849 participants were included and Table 1 displayed the main characteristics of these studies. Participants were

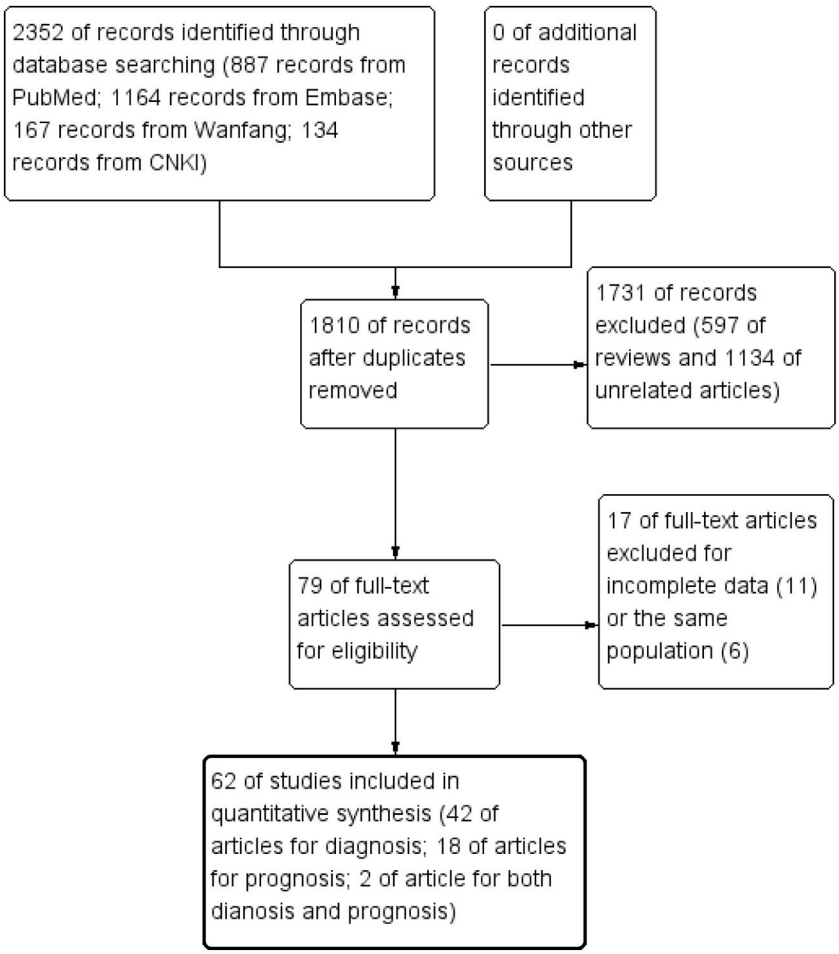

Fig. 1. Flow diagram of this meta-analysis for publication screening.

mainly Caucasian and Asian, with the mean age of 61.4. The major cancers were lung cancer, breast cancer, and prostate cancer. Serum and urine were the primary sources of samples. The NTx levels were mostly detected by the enzyme linked immunosorbent assay (ELISA), with creatinine as the most common endogenous normalization controls. Results of the methodological quality suggested general high quality of these included researches as shown in Fig. S1.

3.2.2. Pooled diagnostic efficacy

A random-effect model was conducted for the overall analysis due to the significant heterogeneity with I^2 for SEN and SPE of 77% (72–81%) and 80% (75–84%). The pooled SEN and SPE from total of 45 studies were 77% (72–81%) and 80% (75–84%) to distinguish cancer patients with bone metastasis from patients without bone metastasis (Fig. 2). The AUC, PLR, NLR, and DOR were 0.86 (0.82–0.88), 3.9 (3.1–4.8), 0.28 (0.23–0.35), and 14 (10–19), respectively (Fig. 3A).

3.2.3. Publication bias and sensitivity analysis

Deek's funnel plot was symmetry as shown in Fig. 3B with *P* value of 0.68, suggesting that there was no significant publication bias among the enrolled publications. Furthermore, sensitivity analysis also failed to find any possible sources of heterogeneity (Fig. S2).

3.2.4. Meta-regression and subgroup analyses

From the multivariate-meta-regression, we found that ethnicity ($P = 0.01$) was a major source of heterogeneity for SEN while pre-specified cutoff value ($P = 0.03$) could be used to explain the high heterogeneity for SPE (Fig. S3). The results of subgroup analyses

Table 1
The main features of 45 included studies in diagnostic meta-analysis.

Study ID	ethnicity	specimen	Sample size	age	male/female	Cancer-type	SEN (%)	SPE (%)
Miura H 1997	Asian	urine	127	59.0	57/70	multiple cancers	78.00	75.00
Izumi M 2001	Asian	urine	100	64.0	67/33	lung cancer	80.00	73.70
Ulrich U 2001	Caucasian	urine	106	58.5	0/106	breast cancer	44.00	79.00
Costa L 2002	Caucasian	urine	166	NA	NA	multiple cancers	50.00	85.40
Fukumitsu N 2002	Asian	urine	91	72.7	91/0	prostate cancer	51.10	79.50
Kiuchi K 2002	Asian	urine	32	NA	0/32	breast cancer	69.00	58.00
Jung K 2004	Caucasian	serum	117	65.9	117/0	prostate cancer	61.00	96.00
Chung J 2005	Asian	urine	151	62.0	105/46	lung cancer	73.00	84.00
Pectasides D 2005	Caucasian	serum	64	61.5	NA	breast cancer	87.10	45.50
Lv X 2007	Asian	urine	77	50.0	32/45	multiple cancers	82.50	83.80
Wang W 2007	Asian	serum	105	57.4	NA	multiple cancers	90.00	67.30
Wu X 2007	Asian	serum	63	59.1	27/36	thyroid cancer	58.10	80.00
Zhou D 2007	Asian	urine	108	59.4	40/68	multiple cancers	65.00	72.00
Li G 2010	Asian	urine	125	59.0	125/0	prostate cancer	83.30	84.70
Zhao R 2010	Asian	urine	54	NA	54/0	prostate cancer	71.40	76.50
Huang Q 2011	Asian	serum	120	NA	79/41	NSCLC	85.00	81.70
Lumachi F 2011	Caucasian	serum	35	63.0	24\11	NSCLC	56.20	89.50
Zhang H 2011	Asian	urine	89	59.8	60/29	multiple cancers	62.00	83.00
Zhang S 2011	Asian	serum	106	NA	57/49	lung cancer	90.16	84.44
Zhou Z 2011	Asian	serum	78	59.2	56/22	lung cancer	84.00	63.90
Bayrak S 2012	Caucasian	serum	65	64.1	65/0	lung cancer	90.24	43.40
Tamiya M 2012	Asian	serum	166	NA	128/38	lung cancer	61.60	89.20
Cai Y 2013	Asian	serum	108	53.2	66/42	multiple cancers	89.60	68.30
Deng L 2013	Asian	serum	73	69.2	73/0	prostate cancer	90.00	68.60
Li W 2013	Asian	serum	82	51.4	NA	lung cancer	98.30	95.50
Sun H 2013	Asian	serum	100	NA	66/34	lung cancer	75.80	76.50
Tamiya M 2013	Asian	serum	100	65.0	NA	lung cancer	40.00	87.00
Tamiya M 2013	Asian	urine	100	65.0	NA	lung cancer	48.00	86.00
Wang L 2013	Asian	serum	58	48.0	0/58	breast cancer	94.30	87.00
Washam C 2013	Caucasian	serum	111	68.6	0/111	breast cancer	81.00	100.00
Pan T 2014	Asian	urine	60	NA	39/21	multiple cancers	63.00	82.00
Chen H 2016	Asian	serum	79	69.0	79/0	prostate cancer	87.20	72.10
Lumachi F 2016	Caucasian	serum	50	NA	0/50	breast cancer	73.00	37.50
Wu Q 2018	Asian	plasma	126	64.0	101/25	lung cancer	65.10	84.30
Zhuang X 2018	Asian	serum	107	NA	NA	lung cancer	88.10	92.20
Cui Z 2020	Asian	serum	312	59.5	165/147	lung cancer	85.54	80.20
Gu L 2020	Asian	serum	100	62.5	70/30	lung cancer	86.00	60.50
Li S 2020	Asian	serum	136	74.9	136/0	prostate cancer	51.61	100.00
Zhao H 2020	Asian	serum	74	61.3	47/27	lung cancer	69.70	64.20
Ma H 2021	Asian	serum	208	53.7	105/103	lung cancer	73.15	64.00
Yang Y 2021	Asian	urine	124	62.6	73/51	lung cancer	68.33	81.30
Liu H 2022	Asian	serum	100	NA	100/0	Prostate cancer	90.52	88.62
Lu Q 2022	Asian	plasma	202	60.7	202/0	Prostate cancer	81.20	71.50
Song G 2022	Asian	serum	122	64.1	84/38	NSCLC	97.5	94.2
Zhang W 2022	Asian	serum	172	NA	0/172	breast cancer	82.28	41.94

Abbreviation: NSCLC, non-small cell lung cancer; SEN, sensitivity; SPE, specificity.

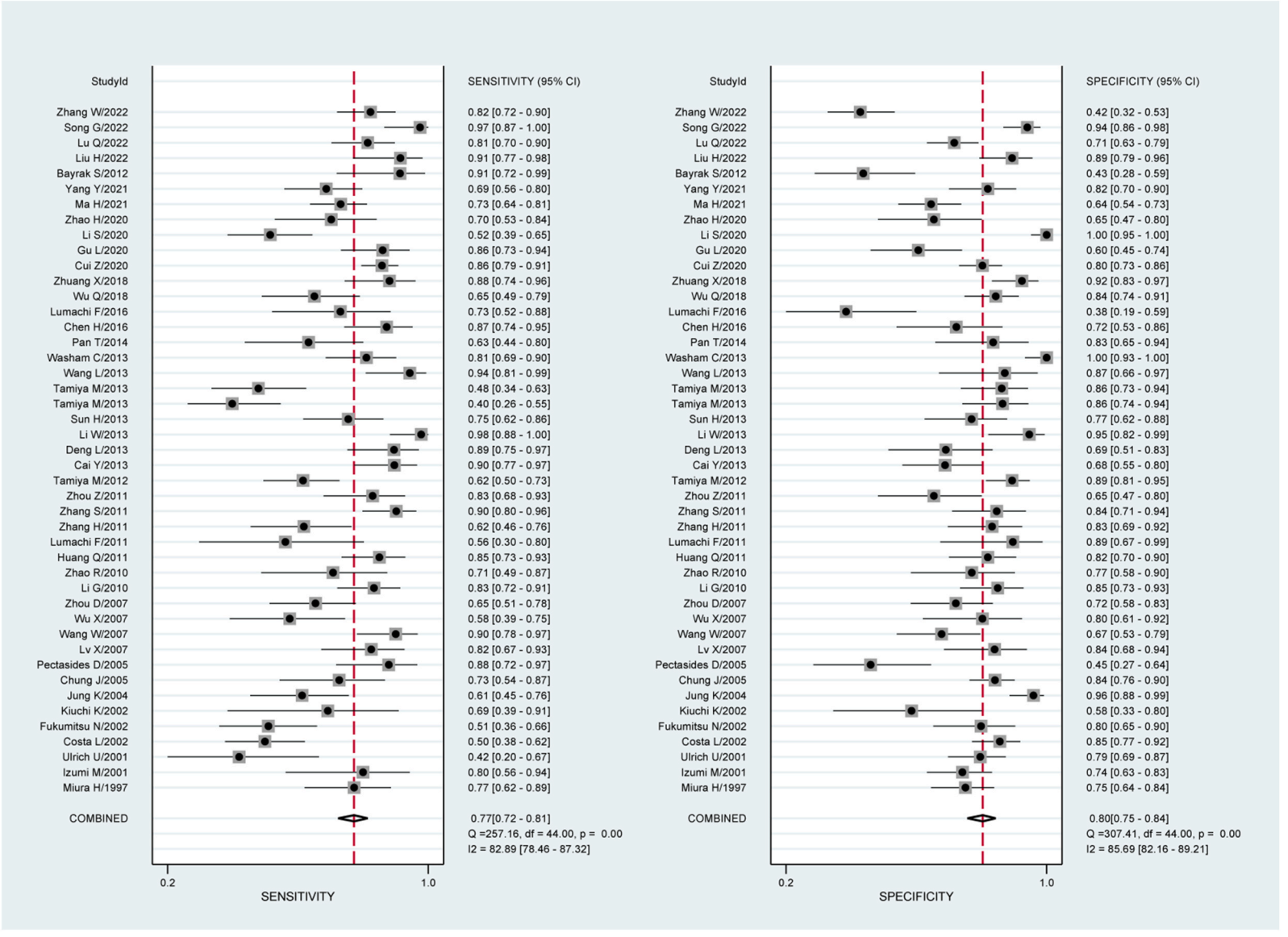

Fig. 2. Forest plots for sensitivity and specificity in the diagnosis analysis of NTx for bone metastasis of human cancers. Sensitivity and specificity were exhibited by square with 95% confidence interval presented by error bars for every study.

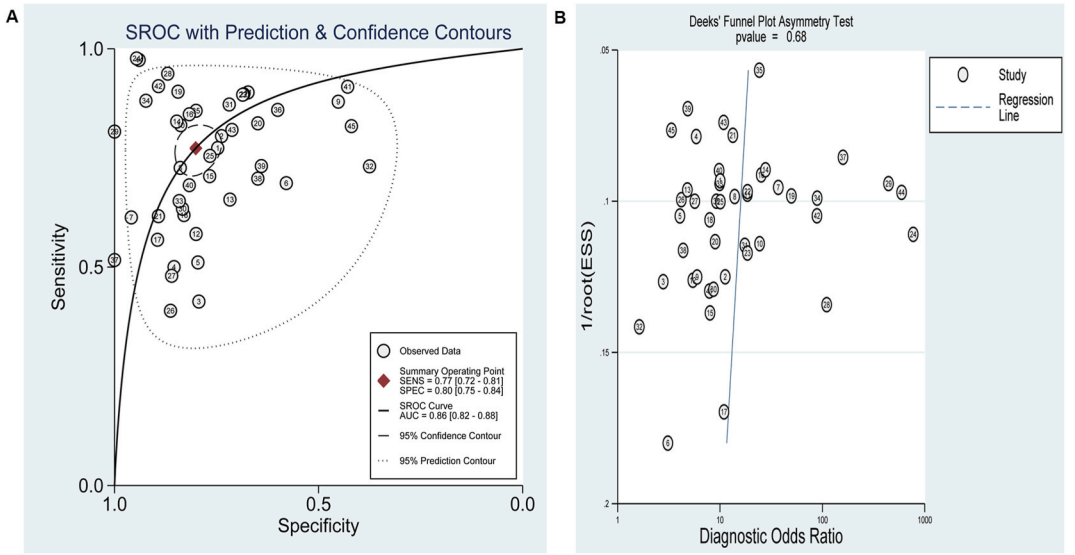

Fig. 3. SROC curve of NTx as diagnostic biomarker for bone metastasis of human cancers (A) and Deek's test for publication bias of these included studies (B).

were also summarized in Table 2,. Studies with serum obtained a higher diagnostic accuracy with SEN of 82% (76–87%), SPE of 81% (73–87%) and AUC of 0.88 (0.85–0.91) when compared with NTx from urine with SEN of 67% (60–73%), SPE of 80% (77–83%) and AUC of 0.82 (0.78–0.85). For the ethnicity, NTx showed a high diagnostic value in Asian population with SEN of 78% (73–83%), SPE of 80% (76–84%) and AUC of 0.86 (0.83–0.89) when compared with Caucasian participants with SEN of 71% (57–82%), SPE of 81% (57–93%) and AUC of 0.80 (0.76–0.83). In the subgroup of NTx profiling, NTx combining with other markers had a higher diagnostic accuracy with SEN of 90% (83–94%), SPE of 88% (83–91%) and AUC of 0.94 (0.92–0.96) when compared with the NTx alone with the SEN of 75% (71–79%), SPE of 78% (73–82%) and AUC of 0.83 (0.80–0.86). Moreover, NTx obtained pretty high diagnostic efficacy for lung cancer, breast cancer as well as prostate cancer, with AUCs of 0.87 (0.84–0.90), 0.83 (0.79–0.86) and 0.88 (0.85–0.90), respectively. Compared with not pre-specified cutoff value, studies with pre-specified cutoff value might obtain a higher diagnostic value with SEN of 82% (68–90%), SPE of 82% (73–89%) and AUC of 0.89 (0.86–0.91). However, no significant difference was observed in the diagnostic accuracy of NTx between different sample sizes.

Table 2
Subgroup analysis for the selected diagnostic studies.

Subgroups	No.of studies	SEN [95%CI]	SPE [95%CI]	PLR [95%CI]	NLR [95%CI]	DOR[95%CI]	AUC [95%CI]
NTx Profiling							
alone	44	0.75[0.71–0.79]	0.78[0.73–0.82]	3.4[2.8–4.1]	0.32[0.27–0.37]	11 [8–14]	0.83[0.80–0.86]
With other marker	14	0.90[0.83–0.94]	0.88[0.83–0.91]	7.2[5.0–10.4]	0.12[0.07–0.20]	61[28–130]	0.94[0.92–0.96]
Specimen							
urine	15	0.67[0.60–0.73]	0.80[0.77–0.83]	3.3[2.9–3.9]	0.42[0.34–0.51]	8 [6–11]	0.82[0.78–0.85]
serum	28	0.82[0.76–0.87]	0.81[0.73–0.87]	4.3[3.0–6.3]	0.22[0.17–0.29]	20 [12–33]	0.88[0.85–0.91]
Ethnicity							
Asian	37	0.78[0.73–0.83]	0.80[0.76–0.84]	3.9[3.2–4.8]	0.27[0.22–0.34]	15 [10–21]	0.86[0.83–0.89]
Caucasian	8	0.71[0.57–0.82]	0.81[0.57–0.93]	3.7[1.5–9.4]	0.36[0.24–0.55]	10 [3–33]	0.80[0.76–0.83]
Cancer-type							
Breast cancer	7	0.79[0.67–0.88]	0.72[0.43–0.90]	2.9[1.2–7.2]	0.29[0.15–0.54]	10 [2–41]	0.83[0.79–0.86]
Prostate cancer	9	0.76[0.65–0.85]	0.86[0.75–0.93]	5.5[3.1–9.7]	0.27[0.19–0.40]	20 [11–38]	0.88[0.85–0.90]
Lung cancer	18	0.79[0.71–0.86]	0.80[0.74–0.86]	4.1[2.9–5.6]	0.26[0.18–0.37]	16 [9–29]	0.87[0.84–0.90]
Multiple cancers	8	0.74[0.63–0.83]	0.77[0.71–0.82]	3.3[2.7–3.9]	0.33[0.23–0.48]	10 [6–15]	0.82[0.78–0.85]
Sample size							
≥100	28	0.76[0.70–0.82]	0.83[0.78–0.87]	4.5[3.4–6.0]	0.29[0.23–0.36]	16 [10–24]	0.87[0.83–0.89]
<100	17	0.79[0.71–0.85]	0.73[0.65–0.81]	3.0[2.2–4.0]	2.9[0.2–0.41]	10 [6–18]	0.83[0.79–0.86]
Cut off							
Pre-specified	7	0.82[0.68–0.90]	0.82[0.73–0.89]	4.6[3.0–6.9]	0.22[0.13–0.39]	21 [10–42]	0.89[0.86–0.91]
Not pre-specified	34	0.73[0.68–0.78]	0.80[0.74–0.85]	3.7[2.8–4.8]	0.33[0.28–0.40]	11 [8–16]	0.83[0.79–0.86]
Reference							
Creatinine	15	0.67[0.58–0.74]	0.80[0.77–0.83]	3.4[2.9–4.0]	0.41[0.32–0.52]	8 [6–12]	0.82[0.79–0.85]

Abbreviation: AUC, area under the curve; DOR, Diagnostic Odds Ratio; NLR, negative likelihood ratio; No: the number of the studies; PLR, positive likelihood ratio; SEN, sensitivity; SPE, specificity.

3.3. Prognostic meta-analyses

3.3.1. Studies' characteristics and methodological quality assessment

A total of 4898 cancer patients with average age of 64.2 were enrolled from 20 records on 24 studies, with the primary characteristics displayed in Table 3. The NTx levels from serum and urine were mainly measured by ELISA. And the OS and PFS were the major outcomes of these enrolled researches. Lung cancer, breast cancer and prostate cancer were the main cancer types. The assessment for studies' methodological quality was shown in Table 3.

Table 3
The main features of 24 included studies in prognostic meta-analysis.

id	ethnicity	age	sample size	male/ female	specimen	cancer	median follow-up time(month)	outcome	HR with 95% CI	NOS
Jung K 2004	Caucasian	NA	115	115/0	serum	prostate Cancer	36.1	OS	7.57 [2.65–21.6]	8
Brown J 2005	Caucasian	73	203	203/0	urine	prostate Cancer	NA	OS	2.40 [1.73–3.33]	8
Coleman R 2005	Caucasian	57.5	742	742	urine	breast cancer	27.2	OS	3.03 [2.04–4.51]	8
Coleman R 2005	Caucasian	72	435	435/0	urine	prostate Cancer	17.1	OS	4.10 [2.81–5.97]	8
Coleman R 2005	Caucasian	63	259	259	urine	NSCLC	6.3	OS	2.27 [1.49–3.47]	8
Coleman R 2005	Caucasian	62	343	343	urine	multiple myeloma	40.4	OS	2.40 [0.76–7.61]	8
Cook R 2006	Caucasian	71.7	643	643/0	urine	prostate Cancer	NA	OS	1.92 [1.56–2.36]	7
Lipton A 2007	Asian/ Caucasian/ African	58.2	328	2/326	urine	breast cancer	NA	OS	2.20 [1.42–3.41]	8
Hirsh V 2008	Asian/ Caucasian/ African	NA	144	94/50	urine	NSCLC	NA	OS	1.26 [0.89–1.80]	7
Lipton A 2008	Asian/ Caucasian/ African	NA	NA	NA	urine	prostate Cancer	NA	OS	2.44 [1.69–3.45]	8
Rajpar S 2010	Caucasian	66	94	94/0	urine	prostate Cancer	30	OS	3.01 [1.77–5.12]	8
Zhao X 2010	Asian	NA	60	0/60	serum	breast cancer	21.8	PFS	1.05 [1.02–1.08]	7
Jung K 2011	Caucasian	68	52	52/0	serum	prostate Cancer	52.5	OS	2.72 [1.36–5.46]	8
Som A 2012	Caucasian/ African	62	67	67/0	urine	prostate Cancer	NA	OS	1.47 [0.95–2.26]	6
Som A 2012	Caucasian/ African	60	125	125/0	urine	prostate Cancer	NA	OS	1.62 [1.15–2.29]	6
Barnadas A 2014	Caucasian	59.8	234	0/234	urine	breast cancer	NA	OS	2.19 [1.32–3.62]	7
Clemons M 2014	Caucasian	59	129	0/129	urine	breast cancer	NA	OS	2.42 [1.31–4.48]	9
Lara P 2014	Asian/ Caucasian/ African	69	778	778/0	serum	prostate Cancer	NA	OS	1.40 [1.27–1.54]	6
Pan T 2014	Asian	58	30	19,11	urine	lung cancer and gastrointestinal tumor	NA	OS	5.39 [1.3–22.37]	7
Fizazi K 2015	Caucasian	NA	NA	NA	urine	prostate Cancer	20	OS	2.28 [1.99–2.61]	8
Ferreira A 2016	Caucasian	63	71	71	urine	breast cancer	28.4	OS	1.59 [0.84–3.00]	8
Lipton A 2016	Asian/ Caucasian/ African	NA	NA	NA	urine	lung Cancer	NA	OS	1.83 [1.44–2.33]	8
Honda Y 2017	Asian	68	46	40/6	serum	hepatocellular carcinoma	11.5	OS	2.13 [1.02–4.44]	8
Shizuku M 2020	Asian	66	NA	NA	urine	breast cancer	20	OS	2.07 [0.85–5.31]	7

Abbreviation: 95% CI, 95% confidence interval; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; OS, overall survival; PFS, progression-free survival.

3.3.2. The overall and subgroup analyses

Random-effect model was performed due to the significant heterogeneity among these included publications ($I^2 = 93.8$, $P < 0.001$). The overall HR was 2.12 (1.74–2.58) for high versus low NTx level with $P < 0.001$ (Fig. 4), indicating NTx level significantly associated with prognosis of cancer patients with bone metastasis. Results from subgroup analysis, especially from the multivariate analysis, indicated NTx might not be used for the prognosis prediction for Asian population with HR and its 95% CI of 1.83 (0.95–3.50), $P = 0.069$. For all other subgroups, the higher the NTx level, the poorer the prognosis as shown in Table 4.

3.3.3. Publication bias and sensitivity analysis

Results of Egger's test and Begg's funnel plot for the publication bias were shown in Fig. S3 with P value of 0.415, indicating there was no obvious publication bias among these studies. Moreover, sensitivity analysis did not find any heterogeneity sources (Fig. S4).

4. Discussion

Bone metastasis is always related to the pathological fracture, spinal cord compression, hypercalcaemia, and high mortality for cancer patients with advanced stage [51]. Therefore, an accessible and effective marker for the early diagnosis and prognosis prediction of bone metastasis is urgent for cancer patients. Compared with the common bone scintigraphy scan, bone biomarkers in serum or urine would be relatively convenient and easy to measure without radioisotope, which could allow more frequent testing between bone scans. Research has indicated NTx is a useful bone marker to predict the skeletal-related events in patients with bone metastasis [52], which is often correlated with the extent or severity of bone metastasis [53]. Furthermore, NTx could be used to monitor the antiresorptive treatment with bisphosphonates for the metastatic bone from malignant cancers. Increased NTx levels might represent a poorer prognosis for cancer patients.

This present research tended to describe the diagnostic and prognostic value of NTx for cancer patients with bone metastases. Based on different studies and participants, we concluded NTx could be used as an ideal biomarker for early diagnosis and prognosis of bone metastasis for different cancers with high accuracy, especially the serum NTx (SEN of 82% (76–87%), SPE of 81% (73–87%)) through combining with other biomarkers (SEN of 90% (83–94%), SPE of 88% (83–91%)), for lung cancer, breast cancer and prostate cancer in Asian population with AUCs of 0.87 (0.84–0.90), 0.83 (0.79–0.86) and 0.88 (0.85–0.90). In addition, NTx could be used for the

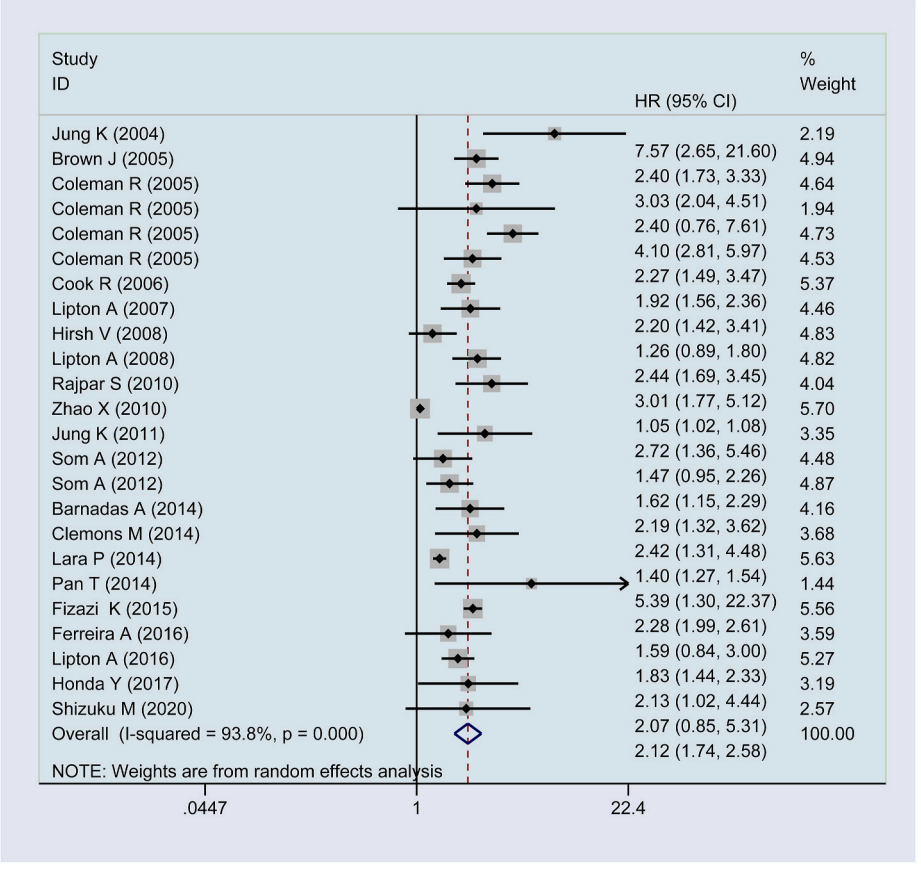

Fig. 4. Forest plots of NTx in prognosis prediction of human cancers with bone metastasis from overall analysis.

Table 4
Subgroup analysis for the selected prognostic studies.

Subgroups	No.of studies	HR [95%CI]	Z	*P*	I^2 (%)
Profiling					
Baseline NTX	16	1.91[1.53–2.39]	5.67	<0.001	93.9
On-study NTX	11	2.63[2.15–3.21]	9.36	<0.001	52.3
Age					
<60	5	2.55[2.02–3.21]	7.90	<0.001	0.0
≥ 60	13	2.08[1.68–2.58]	6.71	<0.001	76.5
Specimen					
urine	19	2.16[1.90–2.45]	11.82	<0.001	51.8
serum	5	1.60[1.19–2.16]	3.11	0.002	92.7
Ethnicity					
Asian	4	1.83[0.95–3.50]	1.82	0.069	72.0
Caucasian	13	2.36[2.15–2.58]	18.57	<0.001	43.3
Mixed	8	1.77[1.46–2.14]	5.82	<0.001	71.6
Outcome					
OS	23	2.16[1.86–2.52]	9.94	<0.001	76.1
PFS	8	1.52[1.17–1.97]	3.17	0.002	83.0
Cancer-type					
Breast cancer	7	1.96[1.24–3.08]	2.89	0.004	89.4
Prostate cancer	11	2.25[1.80–2.82]	7.03	<0.001	86.8
Lung cancer	3	1.72[1.27–2.33]	3.54	<0.001	59.3
Sample size					
≥100	13	2.20[1.76–2.75]	6.90	<0.001	82.0
<100	7	1.92[1.25–2.96]	2.96	0.003	82.6
Analysis type					
Univariate	21	2.14[1.83–2.50]	9.62	<0.001	77.7
Multivariate	3	1.83[0.81–4.13]	1.45	0.146	76.8
Cut off					
Pre-specified	12	2.31[1.95–0.74]	9.70	<0.001	53.6
Not pre-specified	12	1.86[1.49–2.34]	5.40	<0.001	91.7
Reference					
Creatinine	15	2.23[1.94–2.55]	11.52	<0.001	53.0
NA	9	1.72[1.35–2.19]	4.37	<0.001	89.1

Abbreviation: 95% CI, 95% confidence interval; HR, hazard ratio; NTX, *N*-telopeptide of type I collagen; OS, overall survival; PFS, progression-free survival.

prognosis prediction (HR: 2.12 (1.74–2.58)) in overall cancers with bone metastasis through serving as a risk factor. To further validate this prognostic indicator, our team has started building a population cohort for different human cancers since 2022. Up to now, a total of 192 cancer patients with complete clinical information have been enrolled, and are followed up every six months. Due to lack of enough survival data, this following-up study is still conducted, which might provide a favorable support for this present prognostic meta-analysis in the future.

Regardless of the conflicting results for the role of NTx in cancer diagnosis and prognostic prediction from different researches, we concluded that NTx would be an effective diagnostic and prognostic biomarker for human cancers. To our best knowledge, this current meta-analysis was the first one to collectively and systematically analyze the potential efficacy of NTx on clinical diagnosis and prognostic prediction in bone metastasis of different human cancers, though there have been several meta-analyses published that mainly focused on the correlation between NTx and its clinical application in single lung cancer or solid tumors in Chinese population [54,55]. Meta-analysis for lung cancer from 11 articles indicated a correlation between increased NTx and the incidence of lung cancer, with the overall sensitivity of serum NTx and urine NTx for discerning bone metastasis of 0.74 (95% CI = 0.67 to 0.79) and 0.77(95% CI = 0.67 to 0.86), respectively, which is consistent with this present result. As for the meta-analysis for solid tumors in Chinese population, it just analyzed the relationship between serum NTx concentration and bone metastasis from 14 original publications, without pooled analyzing the diagnostic effectiveness of NTx.

Despite the efforts, advantages, and strictly performed according to the PRISMA guidelines, several limitations still existed in our meta-analysis. Firstly, we should not neglect the high heterogeneity among these included publications. Although the meta-regression and subgroup analyses were conducted, the results made little achievements to find and reduce the heterogeneity. Furthermore, we might omit some articles that were not in Chinese or English or did not publish online. Moreover, 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. All these considerations could contribute to the potential bias during data synthesis, and large long-term researches were needed to give more definitive and robust evidence.

5. Conclusion

Generally, our meta-analysis suggested serum NTx could be an ideal and effective biomarker for clinical diagnosis for bone metastasis of different cancers, especially lung cancer, breast cancer and prostate cancer for Asian people; in addition, NTx might be an

accessible tool for prognostic prediction of both OS and PFS for cancer patients with bone metastasis.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Abbreviations

AUC	the area under the SROC curve
CNKI	Chinese national knowledge infrastructure
CTx	carbon terminal peptide
DOR	diagnostic odds ratio
DPD	deoxypyridinol
ELISA	enzyme linked immunosorbent assay
FN	false negative
FP	false positive
HR	hazard ratio
ICTP	type I collagen cross-linked carboxy terminal peptide
NLR	negative likelihood ratio
NOS	the Newcastle-Ottawa Scale
NTx	*N*-telopeptide of type I collagen
OS	overall survival
PFS	progression-free survival
PLR	positive likelihood ratio
PRISMA	preferred Reporting Items for meta-analysis
QUADAS-2	the Quality Assessment of Diagnostic Accuracy Studies-2
SEN	sensitivity
SPE	specificity
SROC	summary receiver operating characteristic
TN	true negative
TP	true positive.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15980.

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