The prevalence of bone metastasis in patients with gastric cancer : A systematic review and meta-analysis

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Research

Keywords: bone metastasis, gastric cancer, prevalence, meta-analysis

Posted Date: April 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-20326/v1

Abstract

Objective: To assess the prevalence of bone metastasis in patients with gastric cancer systematically.

Methods: Literatures that reported prevalence rates of bone metastasis in patients with gastric cancer were identified via PubMed, China National Knowledge Infrastructure (CNKI), Wanfang database and Weipu database from inception to October 2018. The methodological quality of the included studies was evaluated by Agency for Healthcare Research and Quality (ARHQ). Subgroup analyses were performed stratified by areas, years of publication, Tumor Node Metastasis (TNM) stages, pathological types and clinical characteristics. Publication bias was assessed with Egger's test and Begg's funnel plot.

Results: A total of 59 studies were eligible for inclusion and the methodological qualities of included studies were moderate to high. The pooled prevalence of bone metastasis in patients with gastric cancer was 8.1% (95%CI: 7.0%, 9.1%). Of all the included studies, thirty-three studies were conducted in China, and the pooled prevalence of China was 10.6%. From 1996 to 2000, the prevalence was 10.8% (95%CI: 5.6%, 16.1%), and it increased to 17.4% (95%CI: 8.5%, 26.3%) from 2001 to 2005. After that till now, the prevalence drastically decreased and maintained at a low level around 5.9%. The prevalence showed an increasing trend from 2.7% (95%CI: 0.0%, 5.4%) to 38.5% (95%CI: 20.6%, 56.3%) from TNM stage Ⅰ to stage Ⅳ. The prevalence was 4.5% (95%CI: 1.7%, 7.4%) in the well and moderately differentiated group, 19.0% (95%CI: 13.8%, 24.1%) in the poorly differentiated and undifferentiated group, 31.6% (95%CI: 2.9%, 60.3%) in the signet ring cell group, and 19.3% (95%CI: 11.8%, 26.9%) in the mucinous group, respectively.

Conclusion: The pooled prevalence of bone metastasis in patients with gastric cancer was 8.1%. The prevalence increased with the exacerbation of gastric cancer from TNM stage Ⅰ to stage Ⅳ and was inversely related to the degree of tissue differentiation. At the same time, it was also affacted by area and years.

Introduction

The prevalence of gastric cancer is still in the forefront of malignant tumors. People aged over 50 years old tend to suffer from it, with the main contributing factors being precancerous lesions, Helicobacter pylori infection, diet, environment and genetic factors, etc. [1, 2]. There are no obvious clinical symptoms in the early stages, while some symptoms of upper gastrointestinal tract, like upper abdominal discomfort, pain, emerge gradually. If not treated timely, it would be worse, which also would raise the risk of getting bone metastasis. Meanwhile, most patients feel painful brought by periostitis and periosteal thickening. Bone metastasis seems more common for patients diagonised with cancers related to breast, lung or prostate, compared with gastric cancer [1, 2]. The terminal stage of gastric cancer is the peak period of incidence and multiple bone metastasis seldom is found at early stage. Seldom, mucosal gastric cancer at early stage could give rise to multiple bone metastasis. Once dragonized the disease, patients with gastric cancer have a higher risk of death, with a reduced survival time, no more than 1 year [2].

The earlier gastric cancer is diagnosed and treated, the better prognosis is. As there is no obvious uncomfortable symptom in early cases, the patients with advanced gastric cancer occupy a considerable proportion in all newly diagnosed patients. The liver or lung metastasis in patients with gastric cancer often attracts much attention, while the bone metastasis is more likely to be ignored and not diagnosed at an early stage [3]. It is clear that biological behavior of advanced gastric cancer leads to the sinister prognosis. Bone metastasis caused by vascular tumor thrombus in patients with gastric cancer is not rare [4]. The advanced gastric cancer mostly has invaded the serosa, abdominal and peritoneum. And local recurrence, liver metastasis, bone metastasis and other related events would also occur. Bone metastasis in patients with gastric cancer develops at a rapid speed and patients often die because of disseminated or diffuse intravascular coagulation (DIC) in short time [4].

Different surveys have different results on the prevalence of bone metastasis in patients with gastric cancer. It is reported that the clinical prevalence is 0.46%~6.93% in China [5]and 1.2%~1.4% in foreign countries [6, 7]. After the autopsy, the prevalence is as high as 15.9%~17.6% [8]. To date, no meta-analysis on the prevalence of bone metastasis in patients with gastric cancer has been conducted. Accordingly, it seems that an international and pooled estimate based on the various populations is necessary.

The main objective of this systematic review and meta-analysis is to summarize all available data to give a description of a picture on the prevalence of bone metastasis in patients with gastric cancer. A better understanding of metastatic behaviors of patients with skeletal metastases from gastric cancer is helpful for developing diagnostic, therapeutic or follow-up strategies, so as to further improve the quality of life and prognosis.

Materials And Methods

Search Strategy

We conducted a systematic search of scientific databases, including PubMed, China National Knowledge Infrastructure (CNKI), Wanfang database and Weipu database to find relevant papers published from inception to October 2018. The search medical subject heading keywords and all fields were “gastric cancer” AND “bone metastasis”. In addition, a manual search was supplemented by verifying a secondary review of the reference lists of key publications to confirm additional relevant citations.

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

Inclusion and Exclusion Criteria

The criteria of included studies were as follows: (1) with sufficient information to estimate the pooled prevalence of bone metastasis in patients with gastric cancer; (2) published in either English or Chinese language.

The exclusion criteria of studies were: (1) irrelevant to our topic; (2) review; (3) duplicate data.

Study Selection and Data Extraction

Initially, two investigators independently screened all the titles and abstracts according to the keywords. Then full texts of the selected studies were further reviewed. Finally, the studies which met the inclusion criteria were included. The whole potentially relevant information from the included studies was independently reviewed by two investigators (Fang Zheng, Yuhui Zhang) by using a standardized form which was designed in advance. The following information was extracted from each suitable study: first author's name, year of publication, survey year, survey age, location, total sample size, number or prevalence rate of bone metastasis in patients with gastric cancer. When there was any disagreement during the whole procedure, a third investigator (Xingyu Chen) made the final decision.

Assessment of Methodological Quality

Two investigators independently evaluated the methodological quality of the included studies, using Agency for Healthcare Research and Quality (ARHQ) [9]. Of all the 11 items of ARHQ, item 11 "Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained" was not applicable for the prevalence study. So ARHQ items 1-10 were used for the assessment of methodological quality in our meta-analysis. (Table 1)

Table 1. Criteria used to assess the methodological quality of the studies.

Item	yes	no	unclear
1) Define the source of information (survey, record review).			
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications.			
3) Indicate time period used for identifying patients.			
4) Indicate whether or not subjects were consecutive if not population-based.			
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants.			
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements).			
7) Explain any patient exclusions from analysis.			
8) Describe how confounding was assessed and/or controlled.			
9) If applicable, explain how missing data were handled in the analysis.			
10) Summarize patient response rates and completeness of data collection.	-	-	-

Data Analyses

All statistical analyses were made using Stata software (version 11.0; Stata Corporation, College Station, Texas, USA) and the meta package was used to produce the pooled estimates, forest plot and publication bias assessment. The pooled prevalence estimate of bone metastasis in patients with gastric cancer and 95% confidence intervals (CIs) were calculated. A fixed-effect model was used when no heterogeneity was present (p>0.1, I^2<50%). Or else (p<0.1, I^2>50%), a random-effect model was selected. To determine possible causes of heterogeneity, subgroup analyses were conducted by areas, years of publication, tumor node metastasis (TNM) stage, pathological type and clinical features of bone metastases. Publication bias was assessed by visually inspecting a Begg's funnel plot and applying Egger's test to evaluate sources of variability. For all tests, p value < 0.05 was considered to be statistically significant.

Results

Literature Search

The authors had retrieved 1215 relevant studies by the title or abstract, among which 1088 were abandoned for the low relevance, and then reviewed the remaining ones further, among which 69 were excluded for the duplication and insufficiency. Finally, the essay analyzed 59 studies up to the standard [10-69]. The flow chart of study selection process was shown in Fig 1.

Study Characteristics and Quality Assessment of Included Studies

Of the 59 studies, the years of publication ranged from 1996 to 2018. The countries were China, Sweden, Japan, Turkey, Korea, Italy, America and the areas covered Asia, Europe, America. The sample size of included studies ranged from 30 to 19022. The prevalence of bone metastasis in patients with gastric cancer ranged from 0.00% to 55.56%. The characteristics of included studies were summarized in Table 2. The clinical features of bone metastasis in patients with gastric cancer were summarized in Table 3. The methodological qualities of included studies were moderate to high. Twenty-four studies were assessed with 5-7 items as "yes" and five studies were assessed with more than 7 items as "yes". The assessment results were shown in Table 4.

Table 2. Characteristics of included studies on the prevalence of bone metastasis in patients with gastric cancer.

First Author	Publication Year	Survey Year	The median Age of Survey (years)	Locations	Sample (N)	Patients (n)	Prevalence
Chen N [10]	1996	1989~1995	59.4	Zhe Jiang, China	678	45	6.64%
Feng WM [11]	1997	1989~1997	58.4	Zhe Jiang, China	462	36	7.79%
Xie CH [12]	1997	-	48.5	Guang Dong, China	131	54	41.22%
Yu HM [13]	1998	1989~1997	-	Shang Hai, China	876	20	2.28%
Dai XY [14]	1998	1990~1997	47.9	Jiang Su, China	206	14	6.80%
Yuan YJ [15]	2001	1989~1998	49.3	Zhe Jiang, China	635	53	8.35%
Chen YX [16]	2001	1993~1998	54.9	Jiang Su, China	1048	20	1.91%
Xiao BW [17]	2002	1996~1999	55.6	Zhe Jiang, China	254	36	14.17%
Chen DZ [18]	2003	1998~2003	55.5	Fu Jian, China	147	73	49.66%
Ding Y [19]	2004	-	-	Bei Jing, China	51	9	17.64%
Zhang B [20]	2006	2003~2006	52.1	Jiang Xi, China	63	35	55.56%
Hou PF [21]	2007	1979~2004	56.0	Fu Jian, China	161	2	1.24%
Lee KW [22]	2007	2002~2005	60.5	Korea	32	1	3.13%
Hiraiwa K [23]	2008	-	-	Japan	44	0	0.00%
Park Y [24]	2008	-	56.9	Korea	55	11	20.00%
Zheng SP [25]	2010	1995~2009	53.0	Guang Dong, China	252	2	0.79%
Zheng J [26]	2010	2006~2009	68.0	Tian Jin, China	58	5	8.62%
Lim DH [27]	2010	2008~2009	54.0	Korea	283	21	7.42%
Li CP [28]	2010	2007~2009	56.0	Tai Wan, China	45	2	4.44%
Bao JC [29]	2011	2003~2009	55.0	Guang Dong, China	112	12	10.71%
Peng SM [30]	2011	-	57.0	Guang Xi, China	156	25	16.03%
Ahn JB [31]	2011	1992~2010	55.4	Korea	2150	19	0.88%
Park HS [32]	2011	1998~2008	51.0	Korea	8633	203	2.35%
Hwang JE [33]	2011	2004~2009	-	Korea	402	28	6.97%
Ren Y [34]	2012	2006~2010	53.0	Shan Xi, China	193	89	46.11%
Jeong JH [35]	2012	2002~2009	52.5	Korea	104	9	8.65%
Hwang JE	2012	2006~2010	66.0	Korea	125	7	5.60%

[36]							
Park JM [37]	2013	1989~2008	56.4	Korea	1683	30	1.78%
Silvestris N [38]	2013	1998~2011	61.0	Italy	2080	208	10.00%
Ma DW [39]	2013	2003~2011	57.1	Korea	1485	138	9.29%
Le W [40]	2013	2010~2012	53.2	Jiang Xi, China	170	10	5.88%
Bao WJ [41]	2013	2011~2013	61.2	Jiang Su, China	73	19	26.03%
Kadokura M [42]	2013	2001~2011	64.0	Japan	208	18	8.65%
Lu BS [43]	2013	-	-	Shan Dong, China	97	34	35.05%
Hwang JE [44]	2013	2004~2010	56.0	Korea	146	10	6.85%
Nakamura K [45]	2014	2000~2010	62.0	Japan	1837	31	1.69%
Turkoz FP [46]	2014	2001~2013	57.8	Turkey	4617	176	3.81%
Koo DH [47]	2014	2000~2011	57.0	Korea	3888	266	6.84%
Xie XL [48]	2014	2011~2014	64.0	He Nan, China	168	23	13.69%
Yang P [49]	2014	2010~2011	51.0	He Nan, China	156	11	7.05%
Shen L [50]	2014	2009~2010	55.0	Bei Jing, China	202	7	3.47%
Hwang IG [51]	2014	1995~2010	55.0	Korea	68	29	42.65%
Zhong HQ [52]	2015	2008~2012	-	Jiang Xi, China	3612	97	2.69%
Zuo W [53]	2015	2012~2013	54.3	Guang Dong, China	51	3	5.88%
Riihimäki M [54]	2016	2002~2012	73.0	Sweden	7559	907	12.00%
Wang J [55]	2016	2007~2013	58.0	Liao Ning, China	310	11	3.55%
Sun FY [56]	2016	2013~2015	35.4	Shan Dong, China	100	7	7.00%
Shen W [57]	2016	2011~2015	63.5	Jiang Su, China	30	7	23.33%
Seo S [58]	2016	-	58.0	Korea	327	27	8.26%
Kawanaka Y [59]	2016	2010~2015	67.1	Japan	106	1	0.94%
Ding CM [60]	2017	2014~2016	61.8	Jiang Su, China	50	1	2.00%
Wang X [61]	2017	2009~2015	-	Liao Ning, China	133	2	1.50%
Kou FR [62]	2017	1996~2014	68.0	Bei Jing, China	2047	146	7.13%
Hultman B [63]	2017	2000~2009	70.5	Sweden	120	2	1.67%
Jota Mikami [64]	2017	2010~2015	66.0	Japan	622	34	5.47%
Wang QW	2018	1996~2014	56.4	Bei Jing,	176	10	5.68%

[65]				China			
Chen M [66]	2018	2010~2015	-	America	6532	784	12.00%
Hayashi K [67]	2018	2014~2015	62.1	Japan	37	5	13.51%
Qiu MZ [68]	2018	2010~2014	66.0	America	19022	966	5.08%
Narita Y [69]	2018	2005~2012	64.0	Japan	1107	30	2.71%

Table 3. Clinical features of bone metastasis in patients with gastric cancer.

First Author	Number of bone metastasis		Site of bone metastasis				Pattern of bone metastasis		Bone metastasis with visceral metastasis	
	Single	Multiple	Vertebrae	Pelvic bones	Ribs	Others	Synchronous	Metachronous	No	Yes
Chen N [10]	44 (97.8%)	1 (2.2%)	18 (40.0%)	9 (20.0%)	14 (31.1%)	<6 (13.3%)	5 (11.1%)	40 (88.9%)	-	-
Feng WM [11]	-	-	28 (77.8%)	18 (50.0%)	7 (19.4%)	<4 (11.1%)	-	-	-	-
Yu HM [13]	15 (75.0%)	5 (25.0%)	15 (75.0%)	2 (10.0%)	8 (40.0%)	<4 (20.0%)	-	-	-	-
Dai XY [14]	9 (64.3%)	5 (35.7%)	9 (64.3%)	4 (28.6%)	2 (14.3%)	<3 (21.4%)	-	-	-	-
Yuan YJ [15]	39 (73.6%)	14 (26.4%)	35 (66.0%)	16 (30.2%)	3 (5.7%)	<12 (22.6%)	23 (43.4%)	30 (56.6%)	22 (41.5%)	31 (58.5%)
Chen YX [16]	6 (30.0%)	14 (70.0%)	>10 (50.0%)	8 (40.0%)	5 (25.0%)	<5 (25.0%)	-	-	-	-
Chen DZ [18]	4 (5.5%)	69 (94.5%)	-	-	-	-	-	-	-	-
Nakanishi H [70]	4 (8.3%)	44 (91.7%)	-	-	-	-	12 (25.0%)	36 (75.0%)	28 (58.3%)	20 (41.7%)
Peng SM [30]	1 (4.0%)	24 (96.0%)	22 (88.0%)	12 (48.0%)	13 (52.0%)	<10 (16.7%)	-	-	-	-
Ahn JB [31]	5 (26.3%)	14 (73.7%)	17 (89.5%)	-	-	-	-	-	9 (47.4%)	10 (52.6%)
Park HS [32]	23 (11.3%)	180 (88.7%)	175 (86.2%)	108 (53.2%)	102 (50.2%)	<67 (33.0%)	126 (62.1%)	77 (37.9%)	31 (15.3%)	172 (84.7%)
Ren Y [34]	10 (11.2%)	79 (88.8%)	-	-	-	-	-	-	-	-
Park JM [37]	5 (16.7%)	25 (83.3%)	28 (93.3%)	12 (40.0%)	10 (33.3%)	<5 (16.7%)	-	-	8 (26.7%)	22 (73.3%)
Silvestris N [38]	65 (31.4%)	142 (68.6%)	42 (20.3%)	79 (38.3%)	-	Long Bones 109 (52.7%)	-	-	-	-
Bao WJ [41]	11 (57.9%)	8 (42.1%)	-	-	-	-	-	-	-	-
Zhang H [71]	8 (12.1%)	58 (87.9%)	56 (84.8%)	45 (68.2%)	<31 (47.0%)	<36 (54.5%)	28 (42.4%)	38 (57.6%)	30 (45.5%)	36 (54.5%)
Nakamura K [45]	6 (19.4%)	25 (80.6%)	29 (93.5%)	15 (48.4%)	14 (45.2%)	-	8 (25.8%)	23 (74.2%)	6 (19.4%)	25 (80.6%)
Turkoz FP [46]	31 (17.6%)	117 (66.5%)	>96 (54.5%)	51 (29.0%)	41 (23.3%)	<37 (21.0%)	66 (37.5%)	110 (62.5%)	50 (28.4%)	114 (64.8%)
Zhong HQ [52]	20 (20.6%)	77 (79.4%)	75 (77.3%)	40 (41.2%)	34 (35.1%)	-	30 (30.9%)	67 (69.1%)	16 (16.5%)	81 (83.5%)
Li ZM [72]	12 (12.0%)	88 (88.0%)	56 (56.0%)	28 (28.0%)	12 (12.0%)	4 (4.0%)	-	-	-	-
Kou FR [62]	27 (18.5%)	119 (81.5%)	112 (76.7%)	88 (60.3%)	-	-	51 (34.9%)	95 (65.1%)	35 (24.0%)	111 (76.0%)
Jota Mikami [64]	12 (35.3%)	22 (64.7%)	>19 (55.9%)	14 (41.2%)	10 (29.4%)	<5 (14.7%)	10 (29.4%)	24 (70.6%)	8 (23.5%)	26 (76.5%)
Zheng JP [73]	3 (7.0%)	40 (93.0%)	27 (62.8%)	<16 (37.2%)	<16 (37.2%)	<16 (37.2%)	26 (60.5%)	17 (39.5%)	5 (11.6%)	38 (88.4%)
Qiu MZ	-	-	-	-	-	-	-	-	487	479

[67]									(50.4%)	(49.6%)
Fan ZS [74]	-	-	126 (90.6%)	51 (36.7%)	35 (25.2%)	-	15 (10.8%)	124 (89.2%)	6 (4.3%)	133 (95.7%)

Table 4. AHRQ methodological quality assessments for the included studies.

First author	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10
Chen N [10]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Feng WM [11]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Xie CH [12]	yes	yes	no	yes	unclear	yes	unclear	yes	unclear	yes
Yu HM [13]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Dai XY [14]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Yuan YJ [15]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Chen YX [16]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Xiao BW [17]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Chen DZ [18]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Ding Y [19]	yes	yes	no	yes	unclear	yes	unclear	no	unclear	yes
Zhang B [20]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Hou PF [21]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Lee KW [22]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Hiraiwa K [23]	yes	yes	no	yes	unclear	yes	unclear	yes	unclear	yes
Park Y [24]	yes	yes	no	yes	unclear	yes	unclear	yes	unclear	yes
Zheng SP [25]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Zheng J [26]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Lim DH [27]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Li CP [28]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Bao JC [29]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Peng SM [30]	yes	yes	no	yes	unclear	yes	unclear	no	unclear	yes
Ahn JB [31]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Park HS [32]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Hwang JE [33]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Ren Y [34]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Jeong JH [35]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Hwang JE [36]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Park JM [37]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Silvestris N [38]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Ma DW [39]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Le W [40]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Bao WJ [41]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Kadokura M [42]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Lu BS [43]	yes	yes	no	yes	unclear	yes	unclear	yes	unclear	yes
Hwang JE [44]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Nakamura K [45]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Turkoz FP [46]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Koo DH [47]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Xie XL [48]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Yang P [49]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Shen L [50]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Hwang IG [51]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Zhong HQ [52]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Zuo W [53]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Riihimäki M [54]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes

Wang J [55]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Sun FY [56]	yes	yes	yes	yes	unclear	no	unclear	no	unclear	yes
Shen W [57]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Seo S [58]	yes	yes	no	yes	unclear	yes	unclear	yes	unclear	yes
Kawanaka Y [59]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Ding CM [60]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Wang X [61]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Kou FR [62]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Hultman B [63]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Jota Mikami [64]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Wang QW [65]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Chen M [66]	yes	yes	yes	yes	unclear	yes	unclear	no	unclear	yes
Hayashi K [67]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Qiu MZ [68]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes
Narita Y [69]	yes	yes	yes	yes	unclear	yes	unclear	yes	unclear	yes

The Result of Meta-analysis

Since there was heterogeneity among the studies (p=0.000, I^2=97.5%), the random-effect model was used to conduct the analysis. The pooled prevalence of bone metastasis in patients with gastric cancer was 8.1% (95%CI: 7.0%, 9.1%) and the

forest plot was shown in Fig.2. The subgroup analyses were conducted by different factors and were presented in Table 5.

Table 5. Prevalence of bone metastasis in patients with gastric cancer stratified by different factors.

	Stratified factors	No. of Studies	Prevalence rate	Lower limit	Upper limit	Heterogeneity I^2 (%)	p from test of heterogeneity	Model
Area								
	Asia	53	7.7%	6.7%	8.7%	95.5	0.000	Random
	China	33	10.6%	8.8%	12.4%	95.5	0.000	Random
	North China	12	11.7%	7.8%	15.6%	94.7	0.000	Random
	South China	21	10.0%	8.0%	12.1%	95.5	0.000	Random
	Korea and Japan	20	5.4%	4.2%	6.6%	95.3	0.000	Random
	Europe	4	6.9%	1.9%	12.0%	99.1	0.000	Random
	America	2	8.5%	1.7%	15.3%	99.6	0.000	Random
Years								
	1996~2000	5	10.8%	5.6%	16.1%	96.2	0.000	Random
	2001~2005	5	17.4%	8.5%	26.3%	97.9	0.000	Random
	2006~2010	8	9.3%	4.7%	13.8%	93.4	0.000	Random
	2011~2015	25	7.8%	6.5%	9.1%	96.9	0.000	Random
	2016~2018	16	5.9%	3.8%	8.0%	97.7	0.000	Random
TNM stage								
	□	3	2.7%	0.0%	5.4%	0.0	0.879	Fixed
	□	6	4.9%	2.9%	6.8%	0.0	0.878	Fixed
	□	9	14.3%	9.3%	19.2%	84.7	0.000	Random
	□	9	38.5%	20.6%	56.3%	97.2	0.000	Random
Pathological type								
	Well and Moderately Differentiated	8	4.5%	1.7%	7.4%	81.8	0.000	Random
	Poorly Differentiated and Undifferentiated	9	19.0%	13.8%	24.1%	95.4	0.000	Random
	Signet Ring Cell	4	31.6%	2.9%	60.3%	91.8	0.000	Random
	Mucinous	9	19.3%	11.8%	26.9%	78.7	0.000	Random

Note: TNM (Tumor Node Metastasis)

The areas covered Asia (China, Korea, Japan), Europe (Sweden, Italy, Turkey) and America. The prevalence of Asia was 7.7% (95%CI: 6.7%, 8.7%), of Europe was 6.9% (95%CI: 1.9%, 12.0%) and of America was 8.5% (95%CI: 1.7%, 15.3%), respectively. In China, there were 2 geographical zones, including North China and South China. Of all the included studies, thirty-three studies were conducted in China, twelve studies covering North China, twenty-one studies covering South China. The pooled prevalence of China was 10.6%, and the stratified prevalence of North China was 11.7%, of South China was 10.0%. Twenty studies were conducted in Korea and Japan, and the pooled prevalence of Korea and Japan was 5.4%. When stratified by publication years, studies were grouped into 5 periods from 1996 to 2018 with an interval of 5 years. The prevalence of bone metastasis in patients with gastric cancer was 10.8% (95%CI: 5.6%, 16.1%) from 1996 to 2000. It increased to 17.4% (95%CI: 8.5%, 26.3%) from 2001 to 2005. After that, the prevalence drastically decreased and maintained at a low level around 5.9% from 2006 to 2018.

The subgroup analysis stratified by TNM stages showed that the prevalence of bone metastasis was 2.7% (95%CI: 0.0%, 5.4%), 4.9% (95%CI: 2.9%, 6.8%), 14.3% (95%CI: 9.3%, 19.2%), 38.5% (95%CI: 20.6%,

56.3%) when TNM stage of gastric cancer was □, □, □, □, respectively. The prevalence showed an increased trend with the exacerbation of gastric cancer.

When stratified by pathological types of gastric cancer, the prevalence was 4.5% (95%CI: 1.7%, 7.4%) in the well and moderately differentiated group, 19.0% (95%CI: 13.8%, 24.1%) in the poorly differentiated and undifferentiated group, 31.6% (95%CI: 2.9%, 60.3%) in the signet ring cell group, 19.3% (95%CI: 11.8%, 26.9%) in the mucinous group, respectively.

It was researched that approximate 70% patients had multiple or metachronous bone metastasis. The frequently affected sites were vertebrae (70.4%), pelvic bones (39.5%) and ribs (30.3%). Over 70% patients had both bone and visceral metastasis. It reminds that doctors should pay attention to monitor indicators of bone metastases regularly in gastric cancer patients.

Publication Bias

Based on the result of Egger's test, there was no significant publication bias in studies (t=-0.14, *p*=0.886). The Begg's funnel plot of publication bias was shown in Fig.3.

Discussion

The prevalence of bone metastasis of gastric cancer varies greatly from 0 to 55.56%, related to the following factors. Firstly, there is no unified diagnostic criteria for bone metastasis, for which the detection rate also varies and the positive rate of autopsy is higher than that of non-autopsy. Secondly, sample selection also affects the results. Whether being done surgery has a significant effect on the incidence of bone metastasis. Most of the patients have been advanced gastric cancer when they are found. Meanwhile, the recurrence rate and the incidence of distant metastasis are also affected by the operation methods and habits. Overall, the incidence of bone metastasis after operation is significantly lower than that without surgery. Finally, it is related to the difference of the follow-up time and the frequency of rechecking. At the same time, the quantity of the sample will also affect the overall data making it bias to the larger sample. These factors directly or indirectly affect the incidence of bone metastasis in gastric cancer.

To our knowledge, this is the first systematic review and meta-analysis examining the prevalence of bone metastasis in patients with gastric cancer. The results of this study showed that the pooled prevalence of 59 published studies was 8.1%.

Although bone metastasis in patients with gastric cancer occurs worldwide, the reported prevalence was various in different areas. In current meta-analysis, the pooled prevalence of Europe 6.9% was lower than that of Asia 7.7%. However, only 4 included studies were conducted in Europe. Unbalanced number of included studies in geographic regions might compromise accurate and sufficient information for heterogeneity. Studies were extremely more conducted in Asia, especially in China. As China has a vast territory covering 2 geographic zones, the distinction of the prevalence may be more obvious in different

zones. On the one hand, environmental conditions as well as genetic factors may solely or synergistically play a role in it, for different living things bred. Different environmental conditions breed different living things. Also, different ethnicities and cultures can bring diverse lifestyles and eating habits. Of the 2 geographic zones of China, most cities reported the prevalence of bone metastasis in patients with gastric cancer. The data of some cities were absent. In future, the data of these areas and Europe should be conducted and supplemented.

In general, the prevalence of bone metastasis in patients with gastric cancer showed a relatively decreased trend and remained at a low level of about 6% in recent decade. As bone metastasis in patients with gastric cancer mostly have belonged to the advanced gastric cancer, we assume that the decreasing prevalence may be beneficial from development of diagnostic tools, improvement of screening programs or therapeutic methods of gastric cancer. While, we also gradually start to pay more attention to healthy lifestyle brought by improved living standard. Of all the periods, the period from 2001 to 2005 witnessed a higher level at 17.4%. We assume that the rise of the prevalence was possibly related to the environmental pollution, influx of junk food into the market and the spread of the virus, etc. Just as severe acute respiratory syndromes (SARS) also occurred in this period. It involves a series of known and unknown environmental factors or biological behaviors of the tumor acting over time.

According to previous records, the risk factors of bone metastasis in patients with gastric cancer included young age, poorly differentiated and undifferentiated adenocarcinoma, especially mucinous adenocarcinoma, multiple lymph node metastasis, multiple metastatic carcinoma, tumor located in the gastric body, etc [16]. The present meta-analysis showed that the prevalence was as high as more than 30% in TNM stage Ⅳ. Moreover, the prevalence of patients in poorly differentiated and undifferentiated group and in the mucinous group were nearly 20%. The signet ring cell group had the highest prevalence of 31.6%. The pathological types have close relationship with vascular invasion. Low differentiated adenocarcinoma had its unique tumor habits, such as diffuse growth of tumor cells in a free loose state, tumor cells falling off easily leading to vascular embolization and into the circulatory system leading to bone metastasis [20]. Peritoneal implant and distant metastasis mostly occurred in parallel [26]. Low differentiated had a higher incidence of metastasis than high differentiation, and the biological behavior of it determines the poor prognosis, more susceptible to bone metastasis [29]. The rate of lymph node metastasis was 78.5% in postoperative gastric cancer patients with positive vascular invasion and 54.7% in patients with positive venous thrombosis [30]. Bone metastases in patients with invasion of lymph accounted for 76.9%, and patients with venous invasion accounted for 30% [39]. So vascular invasion should arouse sufficient attention. It was reported that there were 65.4% of the low differentiated gastric cancer occurring bone metastasis and the tissue types of bone metastasis were certainly low differentiated gastric cancer [40]. The inherent biological behavior of the tumor determines its clinical development and final outcome. Most scholars believe that the prevalence of bone metastasis in patients with gastric cancer is inversely related to the degree of tissue differentiation and is proportional to clinical TNM stage [54]. So the later pathological stage of gastric cancer is, the higher the prevalence of bone metastasis is. It is consistent with the results of current meta-analysis.

Despite we have conducted a comprehensive searching of the epidemiology of bone metastasis in patients with gastric cancer, several limitations should be considered in this meta-analysis. The available publications/studies were only from several countries. The data of unavailable countries are required to reflect the wide variation. Some characteristics of the patients, such as gender or age of onset, risk factors, etc., were not included in the subgroup analyses. These might exert an important influence on the prevalence. Some included studies had noted methodological flaws, especially related to selection and recruitment of samples. Control group with other diseases such as thyroid disease, breast disease, kidney disease was also selected in some studies. As a result, the estimates of prevalence may have been influenced in unpredictable ways and need continuous perfectibility for verifying our results.

In conclusion, the pooled prevalence of bone metastasis in patients with gastric cancer was 8.1%. The prevalence increased with the exacerbation of gastric cancer from TNM stage □ to stage □ and was inversely related to the degree of tissue differentiation. At the same time, it was also affacted by area and years. The current study provides basic information which is useful fordeveloping clinical strategies.

Abbreviations

1. China National Knowledge Infrastructure- CNKI;
2. a list of abbreviations a list of abbreviations a list of abbreviations a list of abbreviations a list of abbreviationsAgency for Healthcare Research and Quality- ARHQ;
3. Tumor Node Metastasis- TNM;
4. Diffuse Intravascular Coagulation- DIC.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Agree to publish the manuscript.

Availability of data and material: All in the manuscript.

Competing interests: There is no competing interests.

Funding: Natural Science Foundation of Liaoning Province (201602837).

Authors' contributions:

Two investigators (Zheng Fang, Zhang Yuhui) independently evaluated the methodological quality of the included studies, using Agency for Healthcare Research and Quality (ARHQ). Zheng Fang did the statistical analysis using Stata software (version 11.0; Stata corporation, College station, Texas, USA). Zheng Fang and Zhang Yuhui coordinated the study and helped in drafting the manuscript. All authors read and approved the final manuscript.

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Disclosure statement: The authors have no commercial associations that might create a conflict of interest in connection with submitted manuscripts.

Acknowledgments: This work has been supported by Natural Science Foundation of Liaoning Province (201602837).

References

[1] Zhang GJ, Wang JF, Li WR, Zhang YP, Shen ZX. Clinical characteristics of bone metastasis from gastric cancer[J]. Chinese Journal of Clinical Oncology, 2015, 42(09) : 457- 459. http://dx.chinadoi.cn/10.3969/j.issn.1000-8179.20150049.

[2] He J, Zeng ZC, Yang P, Chen B, Jiang W, Du SS. Clinical features and prognostic factors for patients with bone metastases from prostate cancer[J]. Asian Journal of Andrology, 2012, 14(3):505-508. http://dx.chinadoi.cn/10.1038/aja.2012.24.

[3] Kobayashi M, Araki K, Matsuura K, Kawai S, Moriki T. Early gastric cancer giving rise to bone and brain metastases- A review of the Japanese literature. Hepatogastroenterology, 2002, 49: 1751-1754. https://doi.org/10.1136/gut.51.5.757.

[4] Zhang H, Zhang RP, Li FX, Quan JC, Liu H, Deng JY, et.al. Clinicopathological characteristics and prognostic analysis of bone metastasis in gastric cancer patients[J]. Chinese journal of gastrointestinal surgery, 2013, 16(4):354-357. http://dx.chinadoi.cn/10.3760/cma.j.issn.1671-0274.2013.04.014.

[5] Kimura A, Kawasaki H, Wajima N, Nakai M, Nakayama Y, Yonaiyama S, et.al. A case of rapidly fatal gastric cancer with disseminated carcinomatosis of the bone marrow[J] . Gan To Kagaku Ryoho, 2013, 40: 2322-4.

[6] Yoshikawa K, Kitaoka H. Bone metastasis of gastric cancer. Jpn J Surg 1983, 13: 173- 176. https://doi.org/10.1007/BF02469472.

[7] Yamamura Y, Kito T, Yamada E. Clinical evaluation of bone and bone marrow metastasis of gastric carcinoma. Jpn J Gastroenterol Surg 1985, 18: 2288-2293. https://doi.org/10.5833/jjgs.18.2288.

[8] Xu HM. Early diagnosis and treatment evaluation of bone metastasis in patients with gastric carcinoma[J]. China Journal of Practical Surgery, 1996, 16(11) : 644.

http://dx.chinadoi.cn/10.3321/j.issn:1005-2208.1996.11.003.

[9] Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et.al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. Journal of evidence-based medicine. 2015, 8(1) : 2-10. https://doi.org/10.1111/jebm.12141.

[10] Chen N, Zhang W, Feng WM, Chen ZX. Analysis of 45 bone metastasis in patients with gastric cancer[J]. Journal of Practical Medicine. 1996, 12(10) : 678- 679.

[11] Feng WM, Chen ZX, Chen N. Diagnosis and treatment of 36 bone metastasis in patients with gastric carcinoma. Chinese Journal of Clinical Cancer, 1997, 24(10) : 772- 773.

[12] Xie CH, Wang JQ. Study on related factors of bone metastasis in patients with gastric cancer[J]. Journal of Henan Medical University, 1997, 04: 1000- 1069. http://dx.chinadoi.cn/10.13705/j.issn.1671-6825.1997.04.019.

[13] Yu HM, Ding S, Sun JC. Analysis and treatment of 250 bone metastasis in patients with advanced cancer[J]. Tumor, 1998, 18(04) : 295- 298.

[14] Dai XY. Clinical analysis of 14 bone metastasis in patients with gastric cancer[J]. Journal of Oncology, 1998, 11(06) : 487.

[15] Yuan YJ. Clinical analysis of 53 bone metastasis in patients with gastric cancer[J]. Journal of Clinical Oncology, 2001, 06(03) : 252- 253. http://dx.chinadoi.cn/10.3969/j.issn.1009-0460.2001.03.021.

[16] Chen YX, Qin SK, Qian J, He ZM, Wang L, Shao ZJ, et al. Clinical analysis of 20 bone metastasis in patients with gastric cancer[J]. Chinese Journal of Oncology Clinical and Rehabilitation, 08(01) : 68- 69. http://dx.chinadoi.cn/10.3969/j.issn.1005-8664.2001.01.031.

[17] Xiao BW. Clinical Assessment of Bone Metastasis in 36 Postoperative Gastric Cancer Patients[J]. Chinese Journal of Clinical Oncology, 2002, 29(7) : 471- 473. http://dx.chinadoi.cn/10.1016/S0731-7085(02)00079-1.

[18] Chen DZ, Tang MD, Jin X. Clinical analysis of bone scintigraphy in 147 patients with gastric cancer[J]. Medical Journal, 2003, 25(04) : 56- 57. http://dx.chinadoi.cn/10.3969/j.issn.1002-2600.2003.04.034.

[19] Ding Y, Tian JH, Yao SL, Zhang SW, Shao MZ, Wei B, et al. Applications Value of ^{18}FDG- PET in Diagnosis of Gastric Cancer[J]. Journal of Isotopes, 2004, 17(01) : 27- 30. http://dx.chinadoi.cn/10.3969/j.issn.1000-7512.2004.01.007.

[20] Zhang B, Chen ZJ, Cheng LL. Analysis of Whole Body Bone Scanning by 63 Patients with Gastric Cancer[J]. The Practical Journal of Cancer, 2006, 21(06) : 626- 627.

http://dx.chinadoi.cn/10.3969/j.issn.1001-5930.2006.06.024.

[21] Hou PF, Zhang XF, Zheng ZW. Clinicopathological features of early gastric cancer and long-term outcome of surgical treatment[J]. Chinese Journal of Gastrointestinal surgery, 2007, 10 (2): 121- 121. http://dx.chinadoi.cn/10.3760/cma.j.issn.1671-0274.2007.01.013.

[22] Lee KW, Kim JH, Yun T, Song EK, Na II, Shin H, et.al. Phase II study of low-dose paclitaxel and cisplatin as a second-line therapy after 5-fluorouracil/platinum chemotherapy in gastric cancer[J]. Journal of Korean Medical Science, 2007, 22(6): S115–S121. https://doi.org/10.3346/jkms.2007.22.s.s115.

[23] Hiraiwa K, Takeuchi H, Hasegawa H, Saikawa Y, Suda K, Ando T, et.al. Clinical Significance of Circulating Tumor Cells in Blood from Patients with Gastrointestinal Cancers[J]. Annals of Surgical Oncology, 2008, 15(11):3092-3100. https://doi.org/10.1245/s10434-008-0122-9.

[24] Park Y, Kim JW, Kim DS, Kim EB, Park SJ, Choi WS, et.al. The Bone Morphogenesis Protein-2 (BMP-2) is Associated with Progression to Metastatic Disease in Gastric Cancer[J]. Cancer Research and Treatment, 2008, 40(3). https://doi.org/10.4143/crt.2008.40.3.127.

[25] Zheng SP, Wu LW. Surgical treatment of gastric cancer: clinical analysis of 252 cases. China Health Care, 2010, 19(14) : 35- 36.

[26] Zheng J, Gao S. Clinical value of ^{18}F-FDG PET/CT imaging in the diagnosis and stages of gastric carcinoma. Master Thesis of Medical University of Tianjin.

[27] Lim DH, Park SH, Park KW, Kang JH, Oh SY, Hwang IG, et.al. Retrospective analyses of cisplatin-based doublet combination chemotherapy in patients with advanced gastric cancer[J]. BMC Cancer,10,1(2010-10-26), 2010, 10(1):583. https://doi.org/10.1186/1471-2407-10-583.

[28] Li CP, Chen JS, Chen LT, Yen CJ, Lee KD, Su WP, et.al. A phase II study of weekly docetaxel and cisplatin plus oral tegafur/uracil and leucovorin as first-line chemotherapy in patients with locally advanced or metastatic gastric cancer[J]. BRITISH JOURNAL OF CANCER, 2010, 103(9):1343-1348. https://doi.org/10.1038/sj.bjc.6605928.

[29] Bao JC, Zhou WL, Wang QS, Li CH, Huang YH. The Diagnostic Value of ^{18}F-FDG PET/CT Imaging in Recurrence and Metastasis of Gastric Cancer after Operation. Master Thesis of Southern Medical University. http://dx.chinadoi.cn/10.3969/j.issn.1008-1062.2010.10.005.

[30] Peng SM, Tan XD, Xie YS. Analysis on Characteristics of Whole Body Bone Scanning in 25

Patients with Gastric Cancer and Bone metastases. Chin J Med Imaging Technol, 2011, 27(01) : 204- 205. http://dx.chinadoi.cn/10.13929/j.1003-3289.2011.01.048.

[31] Ahn JB, Ha TK, Kwon SJ. Bone metastasis in gastric cancer patients[J]. J Gastric Cancer, 2011, 11: 38-45. https://doi.org/10.5230/jgc.2011.11.1.38.

[32] Park HS, Rha SY, Kim HS, Hyung WJ, Park JS, Chung HC, et.al. A Prognostic Model to Predict Clinical Outcome in Gastric Cancer Patients with Bone Metastasis. Oncology, 2011, 80: 142- 150. https://doi.org/10.1159/000328507.

[33] Hwang JE, Kim HN, Kim DE, Choi HJ, Jung SH, Shim HJ, et.al. Prognostic significance of a systemic inflammatory response in patients receiving first-line palliative chemotherapy for recurred or metastatic gastric cancer[J]. Bmc Cancer, 2011, 11(1):489. https://doi.org/10.1186/1471-2407-11-489.

[34] Ren Y, Zhang X, Zhuang K. An Analysis on Radioactive Bone Imaging in 297 Patients with Bone Metastasis from Gastrointestinal Cancer. China Cancer, 2013, 22(07) : 596- 598. http://dx.chinadoi.cn/10.11735/j.issn.1004-0242.2013.07.A017.

[35] Jeong JH, Lim SM, Yun JY, Rhee GW, Lim JY, Cho JY, et.al. Comparison of Two Inflammation-Based Prognostic Scores in Patients with Unresectable Advanced Gastric Cancer. Oncology, 2012, 83: 292- 299. https://doi.org/10.1159/000342376.

[36] Hwang JE, Kim HN, Kim DE, Shim HJ, Bae WK, Hwang EC, et.al. First-line single-agent chemotherapy for patients with recurrent or metastatic gastric cancer with poor performance status[J]. Experimental & Therapeutic Medicine, 2012, 4(4):562-568. https://doi.org/10.3892/etm.2012.644.

[37] Park JM, Song KY, O JH, Kim WC, Choi MG, Park CH. Bone Recurrence after Curative Resection of Gastric Cancer. J Gastric Cancer, 2013, 16(03) : 362- 369. https://doi.org/10.1007/s10120-012-0193-y.

[38] Silvestris N, Pantano F, Ibrahim T, Gamucci T, Vita FD. Natural History of Malignant Bone Disease in Gastric Cancer: Final Results of a Multicenter Bone Metastasis Survey. Gastric Carcinoma Bone Disease, 2013, 08(10) : e74402. https://doi.org/10.1371/journal.pone.0074402.

[39] Ma DW, Kim JH, Jeon TJ, Lee YC, Yun M, Youn YH, et.al. 18F-Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography for the Evaluation of Bone Metastasis in Patients with Gastric Cancer. Digestive and Liver Disease, 2013, 45: 769- 775. https://doi.org/10.1016/j.dld.2013.02.009.

[40] Le W, Xiong JP. The assess of the quality of life in cancer patients. Master Thesis of Medical University.

[41] Bao WJ, Mao XB, Ding CW, Li N. The Value of Radionuclide Whole Body Bone Imaging in the Diagnosis of Bone Metastasis in Patients with Gastric Cancer. Practical Medicine, 2013, 29(06) : 390-392.

[42] Kadokura M, Iwasa S, Honma Y, Kato K, Hamaguchi T, Yamada Y, et.al. Weekly paclitaxel as second-line chemotherapy in Japanese patients with advanced gastric cancer[J]. Anticancer Research, 2013, 33(10):4547. https://doi.org/10.1097/COC.0b013e31821dee4e.

[43] Lu BS, Zhao LM. Diagnostic value of Serum CA72-4, CA19-9 combined with whole body Bone Imaging in Bone Metastasis of gastric Cancer[J]. Chinese and Foreign Health Abstracts, 2013 (27): 109-110.

[44] Hwang JE, Hong JY, Kim K, Kim SH, Choi WY, Kim MJ, et.al. Class III β-tubulin is a predictive marker for taxane-based chemotherapy in recurrent and metastatic gastric cancer[J]. Bmc Cancer, 2013, 13(1):431-431. https://doi.org/10.1186/1471-2407-13-431.

[45] Nakamura K, Tomioku M, Nabeshima K, Yasuda S. Clinicopathologic Features and Clinical Outcomes of Gastric Cancer Patients with Bone Metastasis. Tokai J Exp Clin Med. , 2014, 39(04) : 193- 198.

[46] Turkoz FP, Solak M, Kilickap S, Ulas A, Esbah O, Oksuzoglu B, et.al. Bone Metastasis from Gastric Cancer: The Incidence, Clinicopathological Features, and Influence on Survival[J]. J Gastric Cancer, 2014, 14(03) : 164- 172. https://doi.org/10.5230/jgc.2014.14.3.164.

[47] Koo DH, Ryu MH, Ryoo BY, Seo J, Lee MY, Chang HM, et.al. Improving trends in survival of patients who receive chemotherapy for metastatic or recurrent gastric cancer: 12 years of experience at a single institution[J]. Gastric Cancer, 2015, 18(2):346-353. https://doi.org/10.1007/s10120-014-0385-8.

[48] Xie XL, Liu BP. Experimental and clinical study of multiple imaging agents PET/CT imaging in the evaluation of gastric cancer[D]. Zhengzhou University, 2014.

[49] Yang P, Gu XP, Zhang ZM. Expression of osteopontin in serum of patients with gastric cancer and its role in tumor metastasis[J]. Chinese Journal of Experimental surgery, 2014, 31 (7): 1570-1572. http://dx.chinadoi.cn/10.3760/cma.j.issn.1001-9030.2014.07.061.

[50] Shen L, Li J, Xu J, Pan H, Dai G, Qin S, et.al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study)[J]. Gastric Cancer, 2015, 18(1):168-176. https://doi.org/10.1007/s10120-014-0351-5.

[51] Hwang IG, Choi JH, Park SH, Oh SY, Kwon HC, Lee SI, et.al. Chemotherapy in advanced gastric cancer patients associated with disseminated intravascular coagulation[J]. Cancer Research & Treatment, 2014, 46(1):27-32. https://doi.org/10.4143/crt.2014.46.1.27.

[52] Zhong HQ, Zhang HQ, Lu S, He B, Mai WL, Wan YY. Clinical pathological analysis of 97 bone metastasis in patients with gastric cancer[J]. Chinese Journal of Cancer Prevented and Treated, 2015, 22(05) : 373- 377. http://dx.chinadoi.cn/10.16073/j.cnki.cjcpt.2015.05.011.

[53] Zuo W, Wu HB, Wang QS, Li HS, Zhou WL, Dong Y. The value of milk contrast medium filling method in the diagnosis of gastric cancer by 18F-FDG PET/CT [J]. Nuclear Technology, 2014, 37 (12): 29-34.

[54] Riihimäki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. Metastatic Spread in Patients with Gastric Cancer. Oncotarget, 2016, 07(32) : 52307- 52316. https://doi.org/10.18632/oncotarget.10740.

[55] Wang J, Qu JL, Li Z, Che XF, Zhang JD, Liu J, et al. A Prognostic Model in Metastatic or Recurrent Gastric Cancer Patients with Good Performance Status Who Received First-Line Chemotherapy. Translational Oncology, 09(03) : 256- 261. https://doi.org/10.1016/j.tranon.2016.04.004.

[56] Sun FY, Li JF, Han CW. Analysis of Prognostic Factors in Patients with Gastric Cancer after Radical Resection. Chin J Clinicians, 2016, 10: 139- 140.

[57] Shen W, Wu YW. The value of 18F-FDG PET/CT imaging in diagnosis and treatment of gastric cancer [D]. 2016.

[58] Seo S, Park SJ, Ryu MH, Park SR, Ryoo BY, Park YS, et.al. Prognostic impact of fibroblast growth factor receptor 2 gene amplification in patients receiving fluoropyrimidine and platinum chemotherapy for metastatic and locally advanced unresectable gastric cancers[J]. Oncotarget, 2017, 8(20):33844-33854. https://doi.org/10.18632/oncotarget.12953.

[59] Kawanaka Y, Kitajima K, Fukushima K, Mouri M, Doi H, Oshima T, et.al. Added value of pretreatment 18 F-FDG PET/CT for staging of advanced gastric cancer: Comparison with contrast-enhanced MDCT[J]. European Journal of Radiology, 2016, 85(5):989-995. https://doi.org/10.1016/j.ejrad.2016.03.003.

[60] Ding CM, Li N, Mao XB, Bao WJ, Li HL, Fan J. Diagnostic value of 18F-FDG SPECT/CT for recurrence and metastasis of gastric cancer after operation[J]. Jiangsu Medicine, 2017 (11). http://dx.chinadoi.cn/10.19460/j.cnki.0253-3685.2017.11.023.

[61] Wang X, Ban LY. Clinical characteristics of 133 patients with locally advanced gastric cancer after radical operation[D]. 2017.

[62] Kou FR, Lu M, Gong JF, Shen L. Single Center Analysis of the characteristics and Prognostic factors of 146 patients with Bone Metastasis of gastric Cancer[J]. Chinese Cancer Clinical, 2017, 44 (12): 594-599. http://dx.chinadoi.cn/10.3969/j.issn.1000-8179.2017.12.469.

[63] Hultman B, Gunnarsson U, Nygren P, Sundbom M, Glimelius B, Mahteme H. Prognostic factors in patients with loco-regionally advanced gastric cancer[J]. World Journal of Surgical Oncology, 2017, 15(1):172. https://doi.org/10.1186/s12957-017-1243-z.

[64] Mikami J, Kimura Y, Makari Y, Fujita J, Kishimoto T, Sawada G, et.al. Clinical outcomes and prognostic factors for gastric cancer patients with bone metastasis[J]. World Journal of Surgical Oncology, 2017, 15(1):8. https://doi.org/10.1186/s12957-016-1091-2.

[65] Wang QW, Zhang XT, Lu M. Impact of duration of adjuvant chemotherapy in radically resected patients with T4bN1-3M0/TxN3bM0 gastric cancer[J]. World Journal of Gastrointestinal Oncology, 2018, 10(1):31-39. https://doi.org/10.4251/wjgo.v10.i1.31.

[66] Chen M, Shu YQ. Influence of metastasis site on prognosis in patients with gastric adenocarcinoma. Chinese Clinical Oncology, 2018, 6:23-6. http://dx.chinadoi.cn/10.3969/j.issn.1009-0460.2018.06.013.

[67] Hayashi K, Yahata T, Muramoto R, Yamamoto N, Takeuchi A, Miwa S, et.al. Factors Associated With Discharge Destination in Advanced Cancer Patients With Bone Metastasis in a Japanese Hospital[J]. Annals of Rehabilitation Medicine, 2018, 42(3):477-482. https://doi.org/10.5535/arm.2018.42.3.477.

[68] Qiu MZ, Shi SM, Chen ZH, Yu HE, Sheng H, Jin Y, et.al. Frequency and clinicopathological features of metastasis to liver, lung, bone, and brain from gastric cancer: A SEER-based study[J]. Cancer Medicine, 2018, 7(Suppl 24). https://doi.org/10.1002/cam4.1661.

[69] Narita Y, Kadowaki S, Oze I, Kito Y, Kawakami T, Machida N, et.al. Establishment and validation of prognostic nomograms in first-line metastatic gastric cancer patients[J]. Journal of Gastrointestinal Oncology, 2018, 9(1):52-63. https://doi.org/10.21037/jgo.2017.11.08.

Figures

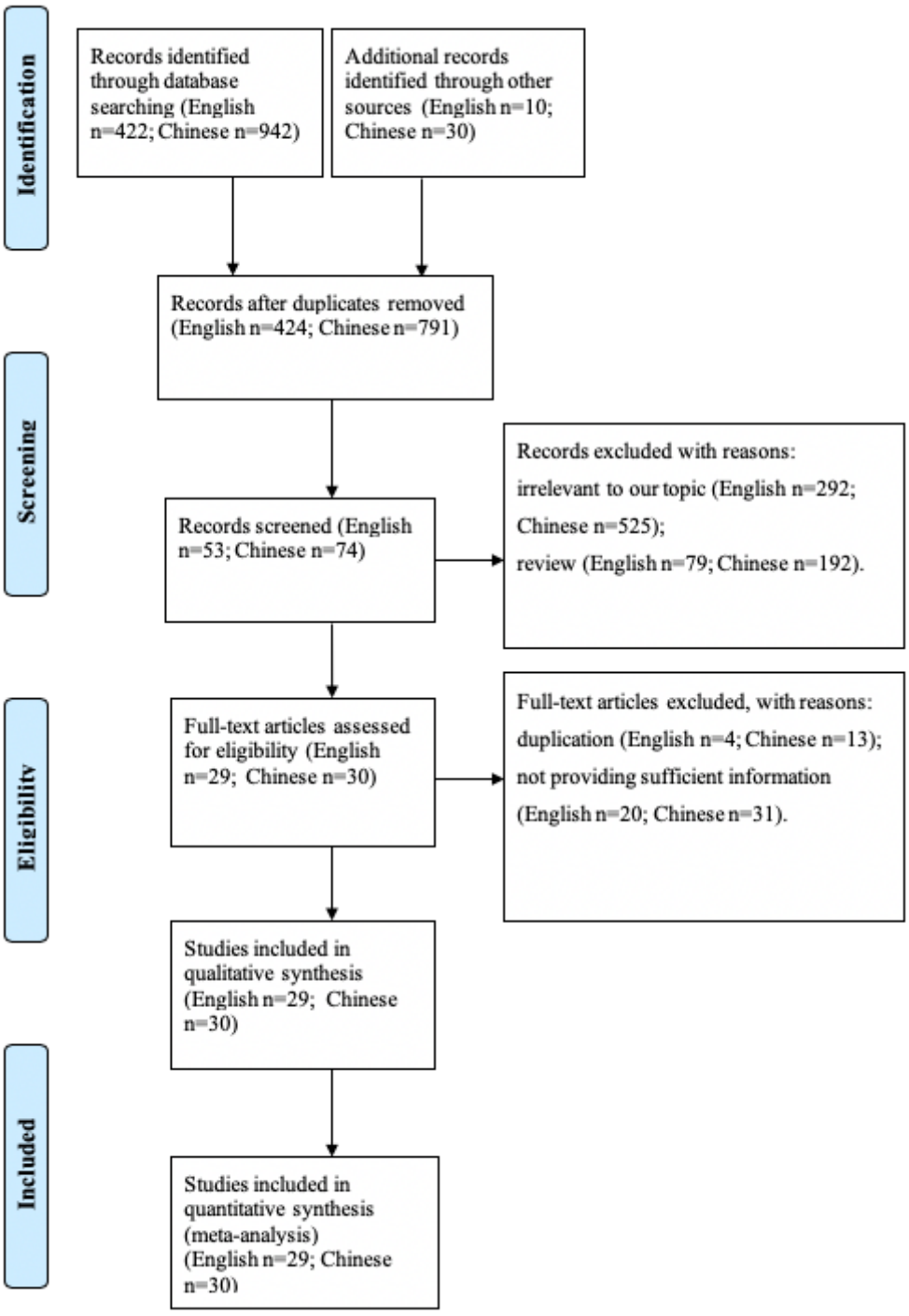

Figure 1

Flow diagram of the study selection process.

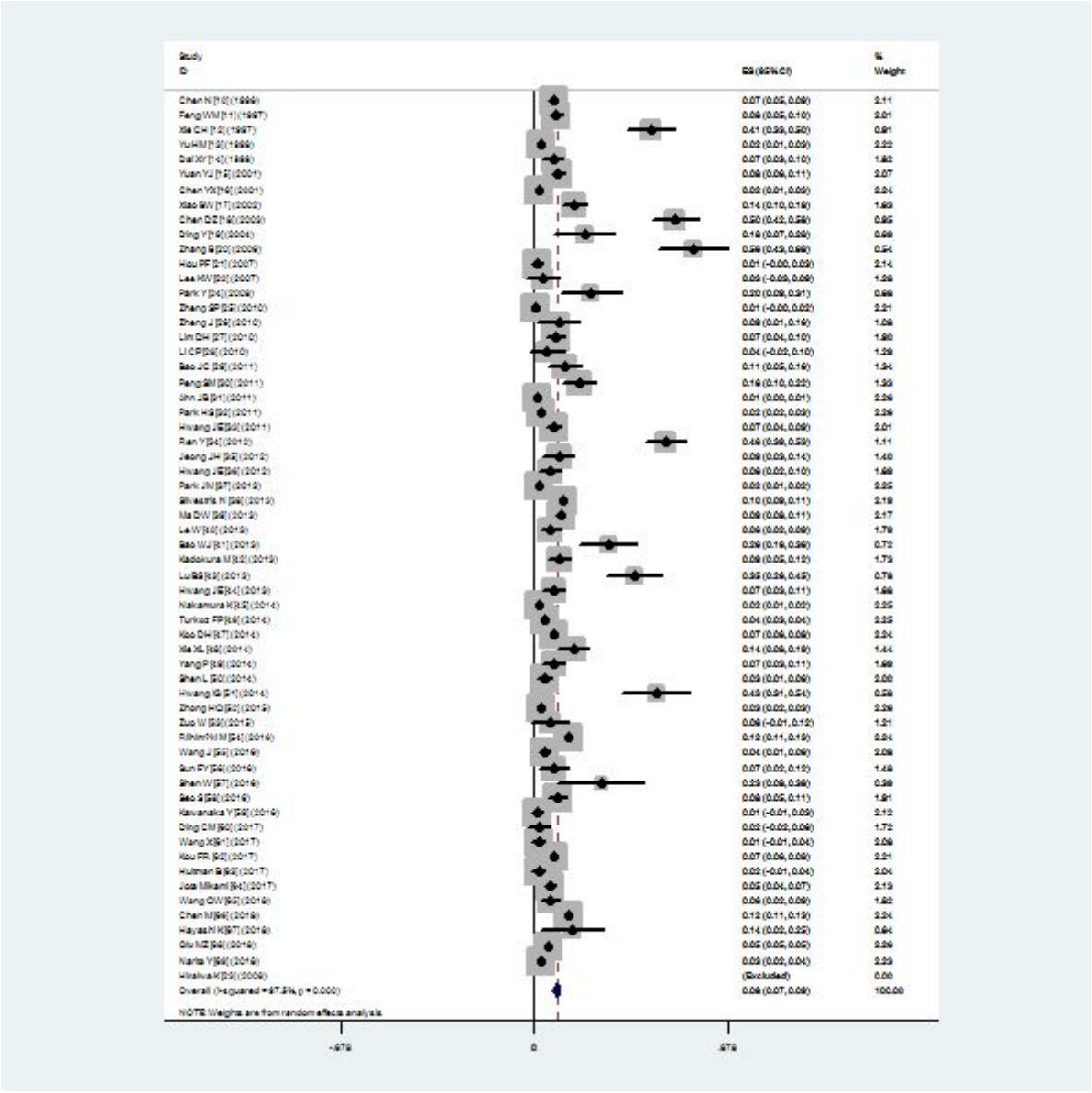

Figure 3

Forest plot of the pooed prevalence of bone metastasis in patients with gastric cancer.

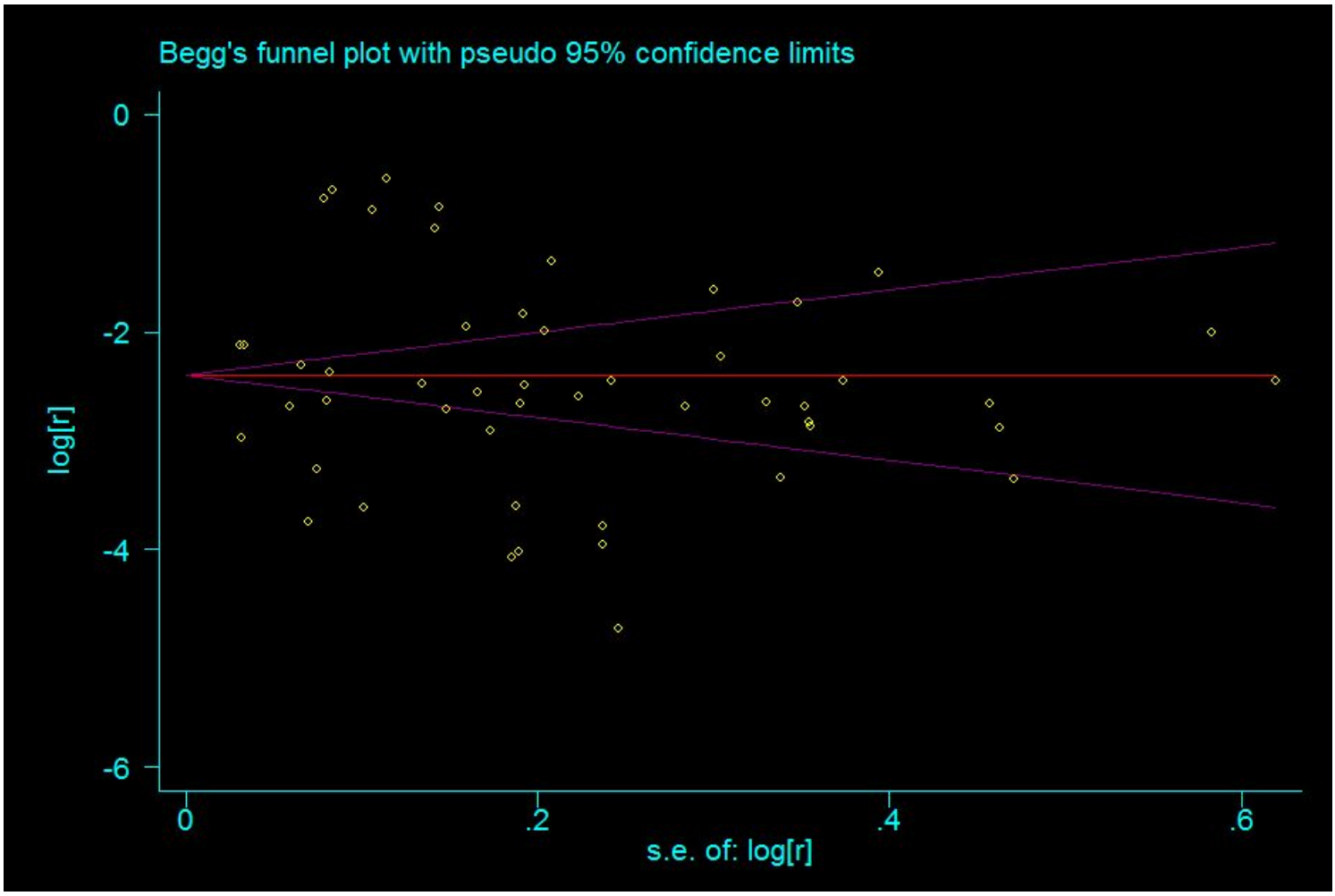

Figure 5

Funnel plot assessing publication bias in the prevalence of bone metastasis in patients with gastric cancer.