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

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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 (AHRQ). 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 affected 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 diagnosed 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)

| 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 Size (N) |
|--------------|------------------|-------------|---------------------------------|-------------------------|-----------------|
| Chen N [10]  | 1996             | 1989~1995   | 59.4                            | Zhe Jiang, China       | 678             |
| Feng WM [11] | 1997             | 1989~1997   | 58.4                            | Zhe Jiang, China       | 462             |
| Xie CH [12]  | 1997             | -           | 48.5                            | Guang Dong, China      | 131             |
| Yu HM [13]   | 1998             | 1989~1997   | -                               | Shang Hai, China       | 876             |
| Dai XY [14]  | 1998             | 1990~1997   | 47.9                            | Jiang Su, China        | 206             |
| Yuan YJ [15] | 2001             | 1989~1998   | 49.3                            | Zhe Jiang, China       | 635             |
| Chen YX [16] | 2001             | 1993~1998   | 54.9                            | Jiang Su, China        | 104             |
| Xiao BW [17] | 2002             | 1996~1999   | 55.6                            | Zhe Jiang, China       | 254             |
| Name            | Year | Period          | Age  | Location          |
|-----------------|------|-----------------|------|-------------------|
| Chen DZ [18]    | 2003 | 1998~2003       | 55.5 | Fu Jian, China    |
| Ding Y [19]     | 2004 | -               | -    | Bei Jing, China   |
| Zhang B [20]    | 2006 | 2003~2006       | 52.1 | Jiang Xi, China   |
| Hou PF [21]     | 2007 | 1979~2004       | 56.0 | Fu Jian, China    |
| Lee KW [22]     | 2007 | 2002~2005       | 60.5 | Korea             |
| Hiraiwa K [23]  | 2008 | -               | -    | Japan             |
| Park Y [24]     | 2008 | -               | 56.9 | Korea             |
| Zheng SP [25]   | 2010 | 1995~2009       | 53.0 | Guang Dong, China |
| Zheng J [26]    | 2010 | 2006~2009       | 68.0 | Tian Jin, China   |
| Lim DH [27]     | 2010 | 2008~2009       | 54.0 | Korea             |
| Li CP [28]      | 2010 | 2007~2009       | 56.0 | Tai Wan, China    |
| Bao JC [29]     | 2011 | 2003~2009       | 55.0 | Guang Dong, China |
| Peng SM [30]    | 2011 | -               | 57.0 | Guang Xi, China   |
| Ahn JB [31]     | 2011 | 1992~2010       | 55.4 | Korea             |
| Park HS [32]    | 2011 | 1998~2008       | 51.0 | Korea             |
| Hwang JE [33]   | 2011 | 2004~2009       | -    | Korea             |
| Ren Y [34]      | 2012 | 2006~2010       | 53.0 | Shan Xi, China    |
| Jeong JH [35]   | 2012 | 2002~2009       | 52.5 | Korea             |
| Hwang JE [36]   | 2012 | 2006~2010       | 66.0 | Korea             |
| Park JM [37]    | 2013 | 1989~2008       | 56.4 | Korea             |
| Silvestris N [38]| 2013| 1998~2011       | 61.0 | Italy             |
| Ma DW [39]      | 2013 | 2003~2011       | 57.1 | Korea             |
| Le W [40]       | 2013 | 2010~2012       | 53.2 | Jiang Xi, China   |
| Bao WJ [41]     | 2013 | 2011~2013       | 61.2 | Jiang Su, China   |
| Kadokura M [42] | 2013 | 2001~2011       | 64.0 | Japan             |
| Lu BS [43]      | 2013 | -               | -    | Shan Dong, China  |
| Hwang JE [44]   | 2013 | 2004~2010       | 56.0 | Korea             |
| Nakamura K [45] | 2014 | 2000~2010       | 62.0 | Japan             |
| Turkoz FP [46]  | 2014 | 2001~2013       | 57.8 | Turkey            |
| Koo DH [47]     | 2014 | 2000~2011       | 57.0 | Korea             |
| Xie XL [48]     | 2014 | 2011~2014       | 64.0 | He Nan, China     |
| Yang P [49]     | 2014 | 2010~2011       | 51.0 | He Nan, China     |
| Shen L [50]     | 2014 | 2009~2010       | 55.0 | Bei Jing, China   |
| Hwang IG [51]   | 2014 | 1995~2010       | 55.0 | Korea             |
| Author       | Year | Time Period     | Score | Location          |
|--------------|------|-----------------|-------|-------------------|
| Zhong HQ     | 2015 | 2008~2012       | -     | Jiang Xi, China   |
| Zuo W        | 2015 | 2012~2013       | 54.3  | Guang Dong, China |
| Riihimäki M  | 2016 | 2002~2012       | 73.0  | Sweden            |
| Wang J       | 2016 | 2007~2013       | 58.0  | Liao Ning, China  |
| Sun FY       | 2016 | 2013~2015       | 35.4  | Shan Dong, China  |
| Shen W       | 2016 | 2011~2015       | 63.5  | Jiang Su, China   |
| Seo S        | 2016 | -               | 58.0  | Korea             |
| Kawanaka Y   | 2016 | 2010~2015       | 67.1  | Japan             |
| Ding CM      | 2017 | 2014~2016       | 61.8  | Jiang Su, China   |
| Wang X       | 2017 | 2009~2015       | -     | Liao Ning, China  |
| Kou FR       | 2017 | 1996~2014       | 68.0  | Bei Jing, China   |
| Hultman B    | 2017 | 2000~2009       | 70.5  | Sweden            |
| Jota Mikami  | 2017 | 2010~2015       | 66.0  | Japan             |
| Wang QW      | 2018 | 1996~2014       | 56.4  | Bei Jing, China   |
| Chen M       | 2018 | 2010~2015       | -     | America           |
| Hayashi K    | 2018 | 2014~2015       | 62.1  | Japan             |
| Qiu MZ       | 2018 | 2010~2014       | 66.0  | America           |
| Narita Y     | 2018 | 2005~2012       | 64.0  | Japan             |

Table 3. Clinical features of bone metastasis in patients with gastric cancer.
| First Author | Number of bone metastasis | Site of bone metastasis |
|--------------|---------------------------|-------------------------|
|              | Single | Multiple | Vertebrae | Pelvic bones | Ribs |
| Chen N [10]  | 44 (97.8%) | 1 (2.2%) | 18 (40.0%) | 9 (20.0%) | 14 (31.1%) |
| Feng WM [11] | - | - | 28 (77.8%) | 18 (50.0%) | 7 (19.4%) |
| Yu HM [13]   | 15 (75.0%) | 5 (25.0%) | 15 (75.0%) | 2 (10.0%) | 8 (40.0%) |
| Dai XY [14]  | 9 (64.3%) | 5 (35.7%) | 9 (64.3%) | 4 (28.6%) | 2 (14.3%) |
| Yuan YJ [15] | 39 (73.6%) | 14 (26.4%) | 35 (66.0%) | 16 (30.2%) | 3 (5.7%) |
| Chen YX [16] | 6 (30.0%) | 14 (70.0%) | >10 (50.0%) | 8 (40.0%) | 5 (25.0%) |
| Chen DZ [18] | 4 (5.5%) | 69 (94.5%) | - | - | - |
| Nakanishi H [70] | 4 (8.3%) | 44 (91.7%) | - | - | - |
| Peng SM [30] | 1 (4.0%) | 24 (96.0%) | 22 (88.0%) | 12 (48.0%) | 13 (52.0%) |
| Ahn JB [31]  | 5 (26.3%) | 14 (73.7%) | 17 (89.5%) | - | - |
| Park HS [32] | 23 (11.3%) | 180 (88.7%) | 175 (86.2%) | 108 (53.2%) | 102 (50.2%) |
| 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%) |
| Silvestris N [38] | 65 (31.4%) | 142 (68.6%) | 42 (20.3%) | 79 (38.3%) | - |
| 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%) |
| Nakamura K [45] | 6 (19.4%) | 25 (80.6%) | 29 (93.5%) | 15 (48.4%) | 14 (45.2%) |
| Turkoz FP [46] | 31 (17.6%) | 117 (66.5%) | >96 (54.5%) | 51 (29.0%) | 41 (23.3%) |
| Zhong HQ [52] | 20 (20.6%) | 77 (79.4%) | 75 (77.3%) | 40 (41.2%) | 34 (35.1%) |
| Li ZM [72]   | 12 (12.0%) | 88 (88.0%) | 56 (56.0%) | 28 (28.0%) | 12 (12.0%) |
| Kou FR [62]  | 27 (18.5%) | 119 (81.5%) | 112 (76.7%) | 88 (60.3%) | - |
| Jota Mikami [64] | 12 (35.3%) | 22 (64.7%) | >19 (55.9%) | 14 (41.2%) | 10 (29.4%) |
| Zheng JP [73] | 3 (7.0%) | 40 (93.0%) | 27 (62.8%) | <16 (37.2%) | <16 (37.2%) |
| Qiu MZ [67]  | - | - | - | - | - |
| Fan ZS [74]  | - | - | 126 (90.6%) | 51 (36.7%) | 35 (25.2%) |

Table 4. AHRQ methodological quality assessments for the included studies.
| Author          | Response | Response | Response | Response | Diagnosis  | Diagnosis | Diagnosis | Diagnosis |
|-----------------|----------|----------|----------|----------|------------|-----------|-----------|-----------|
| Lee KW [22]     | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Hiraiwa K [23]  | yes      | yes      | no       | yes      | unclear    | yes       | unclear   | y         |
| Park Y [24]     | yes      | yes      | no       | yes      | unclear    | yes       | unclear   | y         |
| Zheng SP [25]   | yes      | yes      | yes      | yes      | unclear    | no        | unclear   | n         |
| Zheng J [26]    | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | n         |
| Lim DH [27]     | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Li CP [28]      | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Bao JC [29]     | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | n         |
| Peng SM [30]    | yes      | yes      | no       | yes      | unclear    | yes       | unclear   | n         |
| Ahn JB [31]     | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Park HS [32]    | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Hwang JE [33]   | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Ren Y [34]      | yes      | yes      | yes      | yes      | unclear    | no        | unclear   | n         |
| Jeong JH [35]   | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Hwang JE [36]   | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Park JM [37]    | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Silvestris N [38]| yes    | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Ma DW [39]      | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | n         |
| Le W [40]       | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Bao WJ [41]     | yes      | yes      | yes      | yes      | unclear    | no        | unclear   | n         |
| Kadokura M [42] | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Lu BS [43]      | yes      | yes      | no       | yes      | unclear    | yes       | unclear   | y         |
| Hwang JE [44]   | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Nakamura K [45] | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Turkoz FP [46]  | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Koo DH [47]     | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Xie XL [48]     | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | n         |
| Yang P [49]     | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Shen L [50]     | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Hwang IG [51]   | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Zhong HQ [52]   | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
| Zuo W [53]      | yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | n         |
| Riihimäki M [54]| yes      | yes      | yes      | yes      | unclear    | yes       | unclear   | y         |
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 |
|-------------------|----------------|----------------|-------------|-------------|---------------|
| **Area**          |                |                |             |             |               |
| Asia              | 53             | 7.7%           | 6.7%        | 8.7%        | 95.5          |
| China             | 33             | 10.6%          | 8.8%        | 12.4%       | 95.5          |
| North China       | 12             | 11.7%          | 7.8%        | 15.6%       | 94.7          |
| South China       | 21             | 10.0%          | 8.0%        | 12.1%       | 95.5          |
| Korea and Japan   | 20             | 5.4%           | 4.2%        | 6.6%        | 95.3          |
| Europe            | 4              | 6.9%           | 1.9%        | 12.0%       | 99.1          |
| America           | 2              | 8.5%           | 1.7%        | 15.3%       | 99.6          |
| **Years**         |                |                |             |             |               |
| 1996~2000         | 5              | 10.8%          | 5.6%        | 16.1%       | 96.2          |
| 2001~2005         | 5              | 17.4%          | 8.5%        | 26.3%       | 97.9          |
| 2006~2010         | 8              | 9.3%           | 4.7%        | 13.8%       | 93.4          |
| 2011~2015         | 25             | 7.8%           | 6.5%        | 9.1%        | 96.9          |
| 2016~2018         | 16             | 5.9%           | 3.8%        | 8.0%        | 97.7          |
| **TNM stage**     |                |                |             |             |               |
| I                 | 3              | 2.7%           | 0.0%        | 5.4%        | 0.0           |
| II                | 6              | 4.9%           | 2.9%        | 6.8%        | 0.0           |
| III               | 9              | 14.3%          | 9.3%        | 19.2%       | 84.7          |
| IV                | 9              | 38.5%          | 20.6%       | 56.3%       | 97.2          |
| **Pathological type** |          |                |             |             |               |
| Well and Moderately Differentiated | 8 | 4.5% | 1.7% | 7.4% | 81.8 |
| Poorly Differentiated and Undifferentiated | 9 | 19.0% | 13.8% | 24.1% | 95.4 |
| Signet Ring Cell  | 4              | 31.6%          | 2.9%        | 60.3%       | 91.8          |
| Mucinous          | 9              | 19.3%          | 11.8%       | 26.9%       | 78.7          |

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 Ⅰ, Ⅱ, Ⅲ, Ⅳ, 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 I to stage IV and was inversely related to the degree of tissue differentiation. At the same time, it was also affected by area and years. The current study provides basic information which is useful for developing 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 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.

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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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Figures
Records identified through database searching (English n=422; Chinese n=942) and Additional records identified through other sources (English n=10; Chinese n=30)

Records after duplicates removed (English n=424; Chinese n=791)

Records excluded with reasons: irrelevant to our topic (English n=292; Chinese n=525); review (English n=79; Chinese n=192).

Records screened (English n=53; Chinese n=74)

Full-text articles assessed for eligibility (English n=29; Chinese n=30)

Full-text articles excluded, with reasons: duplication (English n=4; Chinese n=13); not providing sufficient information (English n=20; Chinese n=31).

Studies included in qualitative synthesis (English n=29; Chinese n=30)

Studies included in quantitative synthesis (meta-analysis) (English n=29; Chinese n=30)
Figure 1

Flow diagram of the study selection process.
Records identified through database searching (English n=422; Chinese n=942)

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Studies included in quantitative synthesis (meta-analysis) (English n=29; Chinese n=30)
Figure 1

Flow diagram of the study selection process.

Figure 2

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

Records identified through database searching (English n=422; Chinese n=942)

Additional records identified through other sources (English n=10; Chinese n=30)
Figure 2

Flow diagram of the study selection process.
Figure 3

Funnel plot assessing publication bias in the prevalence of bone metastasis in patients with gastric cancer.
Figure 3

Forest plot of the pooled prevalence of bone metastasis in patients with gastric cancer.
Figure 4

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