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Research paper

Prognostic factors in osteosarcoma: A study level meta-analysis and systematic review of current practice

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ABSTRACT

Background: A consensus has not yet been reached regarding the abilities of gender, age, tumor size, tumor location, histologic subtypes, and surgery in the prediction of survival in osteosarcoma. We aimed to disclose their prognostic significance by conducting a meta-analysis of all the published data from the last decade.

Materials and Methods: Electronic database searches were conducted in PubMed, Embase, and Web of Science for relevant articles published within the last ten years. The pooled hazard ratio (HR) and corresponding 95% confidence interval (CI) were obtained to evaluate the prognostic values of the target factors.

Results: A total of 18,126 patients from 40 studies were eventually included. Results indicated that gender (male vs. female: 1.21, 95% CI, 1.11–1.32; female vs. male: 0.85, 95% CI, 0.75–0.98), age (12–20 vs. ≤12: 1.37, 95% CI, 1.13–1.65; ≥20 vs. <20: 1.29, 95% CI, 1.08–1.55; ≥40 vs. <40: 1.63, 95% CI, 1.21–2.20; ≥50 vs. <25: 2.60, 95% CI, 1.92–3.53; ≥60 vs. <60: 1.11, 95% CI, 1.06–1.18), tumor location (non-extremities vs. extremities: 2.10, 95% CI, 1.76–2.51; proximal vs. distal femur: 3.68, 95% CI: 1.51–8.96; proximal vs. distal humerus: 3.15, 95% CI: 1.53–6.49), tumor size (≥5 vs. <5: 1.42, 95% CI, 1.09–1.86; >8 vs. ≤8: 1.55, 95% CI, 1.07–2.24; >9 vs. ≤9: 1.44, 95% CI, 1.05–1.96), chemotherapy response (poor vs. good: 2.45, 95% CI, 2.02–2.97; good vs. poor: 0.41, 95% CI, 0.34–0.48), and surgery (yes vs. no: 0.45, 95% CI, 0.36–0.57; amputation vs. salvage: 2.34, 95% CI, 1.47–3.74) were significantly associated with overall survival in osteosarcoma patients.

Conclusion: The meta-analysis demonstrated that male patients, older age, large tumor size, non-extremity osteosarcoma, proximal osteosarcoma, poor chemotherapy response, no surgical treatment, and amputation surgery were correlated with a poor prognosis in osteosarcoma patients.

1. Introduction

Osteosarcoma is a highly malignant bone tumor, characterized by its rapid growth rate, high local aggressiveness, and early metastasis to the lungs and distant bones [1]. It has a predilection for adolescents and young adults aged between 15 and 25, and is more frequently diagnosed in males [2]. Although osteosarcoma is a rare disease with an annual incidence of about 1–5 cases per million population, it is the most common primary malignant bone cancer with a low overall survival (OS) rate [3]. The introduction of resection and adjuvant and neoadjuvant chemotherapy lead to 5 year survival rates of more than 60% [4]. However, a large amount of patients still face a fatal outcome due to the development of drug resistance, tumor metastasis, and local relapse [2]. Therefore, finding valuable prognostic factors is crucial for predicting high-risk patients and preforming early treatments to improve the survival rate of osteosarcoma patients.

Among the possible prognostic factors, tumor size, metastatic disease at the time of diagnosis, histological grade, histologic response to neoadjuvant chemotherapy, and adequate surgical margins have consistently shown a strong correlation with survival in osteosarcoma patients [5,6]. However, some of the abovementioned markers involve the use of an invasive approach, making them uneasy to identify and suboptimal. To achieve maximum treatment efficacy and improve OS, more easily available and low-cost prognostic markers of osteosarcoma are needed. Generally, age at the time of diagnosis, tumor site, and tumor histological subtypes are desirable prognostic factors for the survival of osteosarcoma, with easy-to-use and cost-effective characteristics. However, the prognostic relevance of these factors is still controversial. Although the highest incidence of osteosarcoma is seen in the younger age groups with a peak incidence at the age of adolescence, several reports suggest that patients older than 40 are associated with a worse OS when compared with patients younger than 40 [7,8]. While

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some investigators have disproved any association between age and osteosarcoma prognosis [9], some have suggested there is a better prognosis for adolescents and adults [10], and others have reported that children fared better than adolescents and adults [11]. As for tumor location, several studies have reported the consistent conclusion that osteosarcomas of the extremities have a better survival than the axial osteosarcomas [12,13]. However, others have described a lack of association between tumor site and prognosis [14].

Inconsistent results among individual studies can be attributed to many factors, such as sample size, study design, and patients' baseline characteristics. Moreover, a single study cannot conclusively confirm the usefulness of particular prognostic marker for osteosarcoma. Thus, a systematic review and meta-analysis is needed. The objective of this study was to quantitatively and comprehensively assess the relationship between gender, age at the time of diagnosis, tumor size, tumor location, histologic subtypes, histological response to chemotherapy, and surgery with the prognosis of patients with osteosarcoma.

2. Materials and methods

2.1. Search strategy

A comprehensive search of PubMed, Embase, and Web of Science was conducted to identify relevant studies from January 1, 2009 to December 31, 2019. The search terms used were: (osteosarcoma OR osteogenic sarcoma) AND (survival OR overall survival OR prognosis), without any restrictions on language and status of publication. The search terms were kept broad so as to encompass all of the possibilities for applicable studies. Clearly immaterial reports from the initial search were excluded after a scan of the titles and abstracts. The potentially eligible studies were retrieved and reviewed as full-text. The reference lists of the eligible studies and reviews were also inspected for additional pertinent articles. Discrepancies between the reviewers were resolved by discussion.

2.2. Selection criteria

Studies meeting the following criteria were eligible and included: (1) Randomized clinical trials (RCTs) and prospective or retrospective cohort studies published between January 1, 2009 and December 31, 2019; (2) patients with pathologically or histologically confirmed osteosarcoma; (3) the correlation between gender, age at the time of diagnosis, tumor size, tumor location, histologic subtypes, chemotherapy response, or surgery and the prognosis of osteosarcoma patients was examined by overall survival and (4) studies provided sufficient information for extraction or estimation of hazard ratio (HR) and 95% confidence interval (CI) of OS. Articles were excluded if they: (1) Contained insufficient data for calculating an estimate of the HRs and 95% CI; (2) included patients with other types of sarcomas, such as Ewing sarcoma; (3) were review articles, case reports, abstracts, unpublished, and ongoing trials. When different publications reported the same or overlapping patients, only the latest publication or the one with the most complete data was included.

2.3. Data extraction and quality assessment

Two reviewers independently reviewed all of the eligible articles and extracted and recorded all of the required data using a standardized form. The following data were extracted: First author, year of publication, research location, sample size, patients' age, type of disease, multivariate analysis of prognostic indicators for OS, and HRs with their 95% CIs for OS. There were three methods of acquiring the HRs and 95% CIs for the studies: Directly obtained from articles without any adjustments; calculated from the number of comparator and reference group patients, total dead populations and log-rank test's P values; estimated data using Enguage Digitizer software to analyze Kaplan–Meier survival curves and then combined with maximal and minimal follow-up times to calculate the HR [15].

The methodological qualities of the included cohort studies were evaluated by two reviewers independently using the Newcastle–Ottawa Quality Assessment Scale (NOS). A study could score a maximum of 9 stars based on four domains, regarding patient selection, study comparability, follow-up, and outcome of interest. Studies with a score ≥ 7 were considered high quality.

2.4. Statistical analysis

All statistical analyses were performed with Stata software version 15.0 (Stata Corporation, College Station, TX, USA). The HRs and 95% CIs were used to assess the association between certain prognostic markers (gender, age at the time of diagnosis, tumor size, tumor location, histologic subtypes, chemotherapy response, and surgery) and OS. A HR > 1 indicated that the patients in the comparator group had a poor prognosis, while a HR < 1 meant that the patients in the comparator group had a better prognosis. Heterogeneity among the eligible studies was evaluated with chi-squared Q test and I^2 statistics. A random effects model was adopted for analysis when heterogeneity existed ($P < 0.05$ or $I^2 > 50\%$). Otherwise, a fixed effects model was used. Sensitivity analysis was performed by removing one study result at a time to test if a certain study altered the overall effect, and to verify the stability of the pooled results. The publication bias of the included studies was calculated with Deeks funnel plot and Egger's asymmetry testing. Publication bias was deemed to be present when $P < 0.05$. A P-value < 0.05 was considered statistically significant. This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

3. Results

3.1. Search results

After removal of duplicates, the initial electronic search identified 2645 publications for review. Only 169 articles remained after screening of the titles and abstracts. Others were excluded for irrelevant topics and non-human trials. Full-text reviews were performed on all 169 reports, and the following types of studies were removed: Inadequate data for meta-analysis (108); duplicate studies with an overlapping population or secondary studies (13); and other sarcoma studies (8). Eventually, 40 articles met the selection criteria and were enrolled in this meta-analysis [12,13,17–54]. Fig. 1 illustrates the process of the literature search.

3.2. Study characteristics

Two of the eligible studies were an RCT design and the rest were retrospective cohort studies published between 2009 and 2019. Sample sizes ranged from 18 to 2849, with a total of 20,126 patients from 40 studies. Male patients accounted for around 60.1% of the whole population. Most of the studies included patients with primary high-grade osteosarcomas. Sixteen reports were multi-institutional and the rest were single-institutional. The research locations varied from study to study. The longest median follow-up period was 17 years. The NOS scores ranged from 3 to 8 stars with a median score of 6.8 (maximum 9), indicating that the included studies had a low to moderate quality. Detailed information on each study is presented in Table 1.

3.3. Prognostic value of gender on OS

Fourteen studies provided accessible data to analyze the effects of gender on OS. Six reports set a female group as reference, and eight studies set male patients as the reference. The heterogeneity test

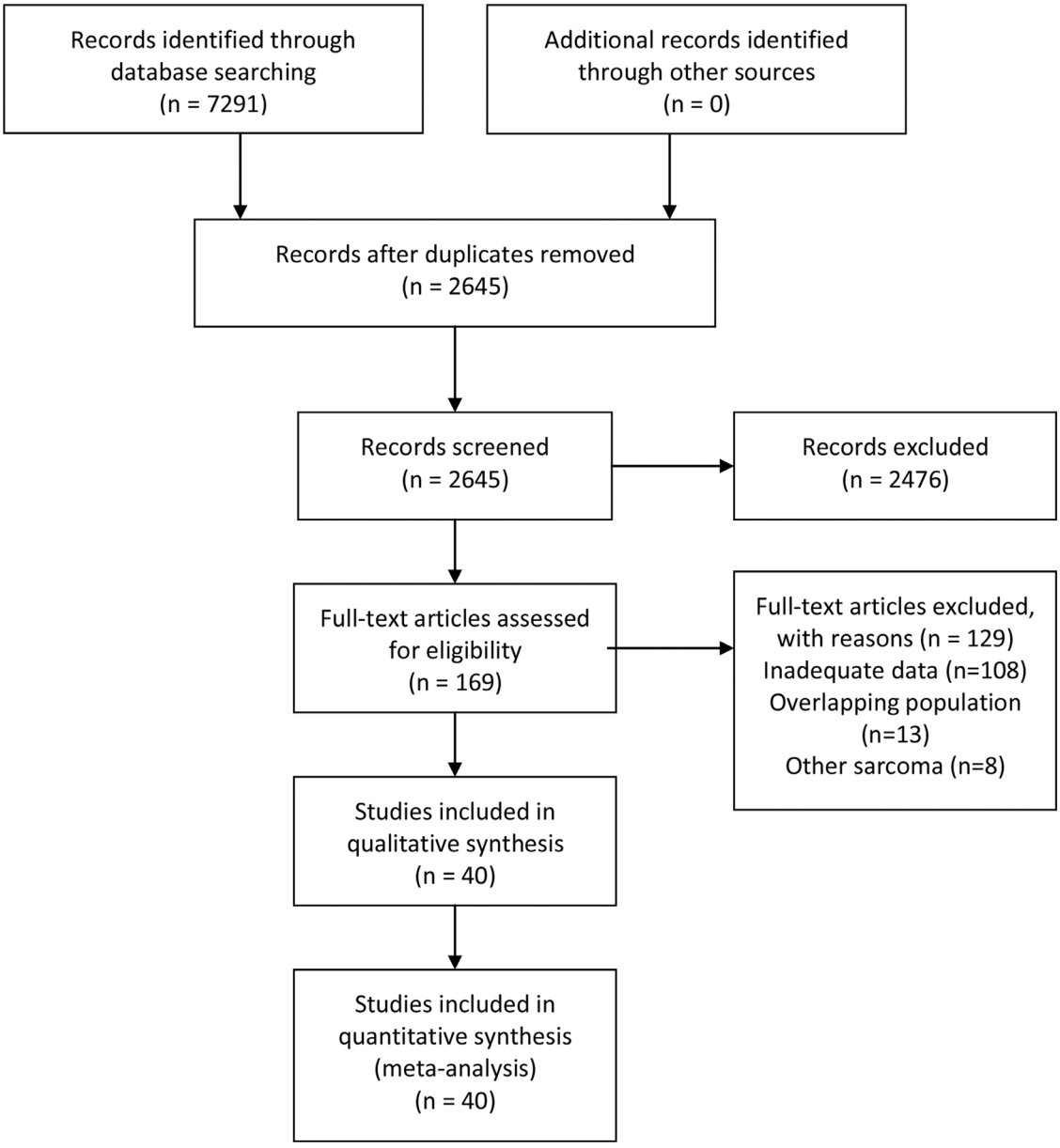

Fig. 1. Flow diagram of literature search and study selection.

indicated an absence of heterogeneity in both groups of comparisons (I^2 = 0%), thus a fixed effects model was applied for data pooling. The pooled HR was 1.21 (95% CI, 1.11–1.32; $P < 0.0001$) when females were the reference, and 0.85 (95% CI, 0.75–0.98; $P = 0.023$) when males were reference (Table 2). Both results suggest that male gender was significantly correlated with a poorer OS in osteosarcoma patients.

3.4. Prognostic value of age on OS

Seventeen studies investigated the relationship between age and OS. Since comparator and reference groups varied among the studies, we separated the analyses into five subgroups. The pooled HR was 1.37 (95% CI, 1.13–1.65; $P = 0.001$; I^2 = 0%) in the subgroup of 12–20s versus ≤12, 1.29 (95% CI, 1.08–1.55; $P = 0.006$; I^2 = 69.1%) when comparing patients ≥20 with <20s, 1.63 (95% CI, 1.21–2.20; $P = 0.001$; I^2 = 36.7%) in the subgroup of ≥40 versus <40s, 2.60 (95% CI, 1.92–3.53; $P < 0.0001$; I^2 = 0%) in a subgroup of ≥50 versus <25s, and 1.11 (95% CI, 1.06–1.18; $P < 0.0001$; I^2 = 97.0%) in a subgroup of ≥60 versus <60s, indicating that patients of an older age had a poorer OS than younger age patients (Table 3).

3.5. Prognostic value of tumor location on OS

The correlation between tumor location and OS was evaluated in 17 studies. Twelve reports selected extremity osteosarcomas as a reference and the pooled HR was 2.10 (95% CI, 1.76–2.51; $P < 0.0001$; I^2 = 26.3%). Two studies set non-extremity osteosarcomas as their reference and the pooled HR was 0.41 (95% CI, 0.17–0.99; $P = 0.048$; I^2 = 68.4%). Both results suggest that osteosarcomas of the extremities are associated with a better OS. Osteosarcomas in the upper or lower extremities did not have a significant correlation with OS, with a HR of 1.22 (95% CI, 0.87–1.71; $P = 0.244$; I^2 = 0%). The pooled results revealed that proximal osteosarcomas located in the femur, humerus, or fibula were indicative of a worse OS when compared to distal osteosarcomas (Table 4).

Table 1
Basic characteristics of the included studies.

Author	Year	Region	Study design	Sample Size	Age	Male/Female	Patients	Follow-up (month)
Abdel-rehim [17]	2015	Egypt	Retrospective	61	24.59 ± 17.18	38/23	Primary osteosarcoma	Median 36
Aggerholm-pedersen [18]	2014	Denmark	Retrospective	169	20 (4–81)	103/66	High-grade osteosarcoma	–
Arshi [19]	2016	USA	Retrospective	648	48.1 ± 23.8	359/289	Primary osteosarcoma	–
Berner [20]	2015	Norway	Retrospective	424	–	246/178	High-grade osteosarcoma	Median 204
Berner [21]	2019	Norway	Retrospective	221	–	134/87	Extremity long bone osteosarcomas	–
Cates J [22]	2016	USA	retrospective	153	27 ± 15	67/83	Conventional high-grade osteosarcoma	108 (1 day-336)
Cates J [23]	2016	USA	Retrospective	131	21.7 ± 13.9	76/55	Conventional high-grade osteosarcoma	110 (11–339)
Cates J [24]	2017	USA	Retrospective	2493	22 ± 15	478/1015	Localized high-grade osteosarcoma	57 (3–140)
Chan [25]	2018	USA	Retrospective	18	20.8 ± 9.8	6/12	Osteosarcoma	Mean 128.4
Duchman [13]	2015	USA	Retrospective	2849	24 (1–60)	1604/1245	High-grade osteosarcoma	–
Faisham [26]	2015	Malaysia	Retrospective	163	19 (6–59)	107/56	Osteosarcoma	47 (36–84)
Fukushima [27]	2018	Japan	Retrospective	631	–	1930/1527	Osteosarcoma	–
González-Billalabeitia E [28]	2009	Spain	Retrospective	66	median 15	24/42	High-grade localised osteosarcomas	median 100
Hagleitner [29]	2011	Netherlands	Retrospective	102	17.8 (4.5–39.5)	56/46	Osteosarcoma	67.2 (28.8–360)
Hu K [30]	2017	China	Retrospective	106	19 (7–53)	62/44	Primary high-grade	
osteosarcoma	52 (7–80)							
Hung [31]	2016	China	Retrospective	202	8.1 ± 11.2	126/76	High-grade osteosarcoma	96 (32.4–236.4)
Iwata [32]	2013	Japan	Retrospective	86	61 (41–87)	39/47	High-grade osteosarcoma	57 (8–244)
Janeway [33]	2012	USA	Retrospective	1054	13.9 (1–30)	–	Osteosarcoma	–
Lee [34]	2015	USA	Retrospective	541	41.3 ± 21.2	267/274	Osteosarcoma	–
Li [35]	2017	China	Retrospective	216	median 17	122/94	Osteosarcoma	Median 42
Lin L [36]	2018	China	Retrospective	98	male: 18 (7–62);			
female: 15 (4–64)	60/38	High-grade osteosarcoma	29 (2 −122)					
Liu B [37]	2016	China	Retrospective	162	median 18	96/66	Osteosarcoma	28.2 (3.1–124.1)
Liu T [38]	2015	China	Retrospective	327	20 (10–44)	235/92	Osteosarcoma	Median 24
Loh AH [39]	2015	USA	Retrospective	173	13.6 (3.2–23.6)	94/87	High-grade osteosarcoma	median 69.6
Martin [40]	2018	USA	Retrospective	321	38 (21–57)	170/152	Osteosarcoma	–
McTiernan [41]	2012	UK	Retrospective	533	15 (12–19)	323/207 Missing 3	Localised osteosarcoma	118.8 (62.4–177.6)
Miwa S [42]	2013	Japan	Retrospective	51	21.2 (5–69)	28/23	High-grade osteosarcoma	44.6 (7–177)
Nataraj [43]	2015	India	Retrospective	237	17 (2–66)	–	Primary/secondary osteosarcoma	30 (2–123)
Nishida [44]	2009	Japan	Retrospective	95	68 (60–88)	44/51	Primary and secondary osteosarcomas	38 (2 −194)
Ogura [45]	2015	Japan	Retrospective	1070	20.2 ± 12.9	677/393	Osteosarcoma	94 (12–291)
Pruksakorn [12]	2015	Thailand	Retrospective	144	16 (4–73)	79/65	Osteosarcoma	–
Puri [46]	2017	India	Retrospective	853	19 (3–64)	603/250	High grade osteosarcomas	72 (36–132)
Qian [47]	2017	China	Retrospective	60	60 (14–93)	39/21	Primary osteosarcoma	108 (1 day-324)
Salah [48]	2014	Jordan	Retrospective	25	–	–	Osteosarcoma	25 (2–62)
Shi K [49]	2015	China	Retrospective	67	20 (11–75)	38/29	Osteosarcoma	–
Smeland S [50]	2019	USA/UK	RCT	2186	14 (11–17)	1285/1997	High-grade osteosarcoma	54 (38–73)
Whelan [51]	2012	European	RCT	1067	15 (12–18)	656/408	Localised extremity osteosarcoma	112.8 (60–174)
Vasquez [52]	2016	Peru	Retrospective	73	14 (5–17)	45/28	Primary high-grade osteosarcoma	30 (1.5–152)
Vasquez [53]	2017	Peru	Retrospective	55	13 (5–17)	36/19	Osteosarcoma	median 22
Zheng [54]	2018	China	Retrospective	2195	–	1214/981	Osteosarcoma	–

Table 2
Correlation between gender and overall survival in osteosarcoma.

Characteristics	No. of study	HR	95% CI	P	I^2
Female	6	1			
Male		1.21	1.11–1.32	<0.0001	0%
Male	8	1			
Female		0.85	0.75–0.98	0.023	0%

Table 3
Correlation between age and overall survival in osteosarcoma.

Characteristics	No. of study	HR	95% CI	P	I^2
≤12	4	1			
<12 and ≤20		1.37	1.13–1.65	0.001	0%
<20	10	1			
≥20		1.29	1.08–1.55	0.006	69.1%
<40	5	1			
≥40		1.63	1.21–2.20	0.001	36.7%
<25	2	1			
≥50		2.60	1.92–3.53	<0.0001	0%
<60	5	1			
≥60		1.11	1.06–1.18	<0.0001	97.0%

3.6. Prognostic value of tumor size on OS

Twelve studies investigated the influence of tumor size on OS. In the subgroups for tumor size, ≥5 cm vs. <5 cm, >8 vs. ≤ 8, and >9 cm vs. ≤9 cm, the pooled HRs were 1.42 (95% CI, 1.09–1.86; P = 0.01;

Table 4
Correlation between tumor location and overall survival in osteosarcoma.

Characteristics	No. of study	HR	95% CI	P	I^2
Extremities	12	1			
Non-extremities		2.10	1.76–2.51	<0.0001	26.3%
Non-extremities	2	1			
Extremities		0.41	0.17–0.99	0.048	68.4%
Lower extremities	4	1			
Upper extremities		1.22	0.87–1.71	0.244	0%
Distal	4	1			
Proximal femur		3.68	1.51–8.96	0.004	74.7%
Distal	4	1			
Proximal humerus		3.15	1.53–6.49	0.002	71.9%
Distal	2	1			
Proximal tibis		2.80	0.31–25.23	0.358	78.1%
Distal	3	1			
Proximal fibula		2.41	1.02–5.67	0.045	38.6%

Table 5
Correlation between tumor size and overall survival in osteosarcoma.

Characteristics (mm)	No. of study	HR	95% CI	P	I^2
<5	3	1			
≥5		1.42	1.09–1.86	0.01	55.4%
≤8	6	1			
>8		1.55	1.07–2.24	0.02	86.2%
≤9	3	1			
>9		1.44	1.05–1.96	0.022	89.0%

I^2 = 55.4%), 1.55 (95% CI, 1.07–2.24; P = 0.02; I^2 = 86.2%), and 1.44 (95% CI, 1.05–1.96; P = 0.022; I^2 = 89.0%) respectively, suggesting that a larger tumor size is an indicator of worse OS in osteosarcoma patients (Table 5).

3.7. Prognostic value of histologic subtypes on OS

Six studies assessed the prognostic value of different histologic subtypes on OS. The results showed that chondroblastic osteosarcomas were correlated with a better OS when compared with conventional osteosarcomas (HR = 0.85; 95% CI, 0.74–0.98; P = 0.025; I^2 = 0%), while no significant differences were found on OS between fibroblastic, telangiectatic, and conventional osteosarcomas (Table 6).

3.8. Prognostic value of chemotherapy response on OS

Fourteen publications assessed the correlation between chemotherapy response and OS. A good responder was defined as a necrosis higher than 90% or less than 10% of viable tumor. Results indicated that good histological response to chemotherapy was a significant predictor of a better prognosis, with an HR of 2.45 (95% CI, 2.02–2.97; P < 0.0001; I^2 = 0%) when good responder was the reference, and an HR of 0.41 (95% CI, 0.34–0.48; P < 0.0001; I^2 = 43.3%) when poor responder was the reference (Table 7).

Table 6
Correlation between histologic subtypes and overall survival in osteosarcoma.

Characteristics	No. of study	HR	95% CI	P	I^2
Conventional	5	1			
Chondroblastic		0.85	0.74–0.98	0.025	0%
Conventional	5	1			
Fibroblastic		0.82	0.66–1.02	0.072	13.9%
Conventional	6	1			
Telangiectatic		1.19	0.75–1.89	0.452	74.0%

Table 7
Correlation between chemotherapy response and overall survival in osteosarcoma.

Characteristics	No. of study	HR	95% CI	P	I^2
≥90% necrosis	6	1			
<90% necrosis		2.45	2.02–2.97	<0.0001	0%
<90% necrosis	8	1			
≥90% necrosis		0.41	0.34–0.48	<0.0001	43.3%

Table 8
Correlation between surgery and overall survival in osteosarcoma.

Characteristics	No. of study	HR	95% CI	P	I^2
No	4	1			
Yes		0.45	0.36–0.57	<0.0001	19.0%
Salvage	4	1			
Amputation		2.34	1.47–3.74	<0.0001	79.2%
Amputation	3	1			
Salvage		0.78	0.62–0.98	0.035	0.00%

3.9. Prognostic value of surgery on OS

The effect of surgery on OS in osteosarcoma patients was demonstrated in 11 studies. Patients who underwent surgery had a better OS, with an HR of 0.45 (95% CI, 0.36–0.57; P < 0.0001; I^2 = 19.0%). As for the types of surgery, amputation was associated with a worse prognosis when compared to limb salvage, with an HR of 2.34 (95% CI, 1.47–3.74; P < 0.0001; I^2 = 79.2%) when limb salvage was the reference, and 0.78 (95% CI, 0.62–0.98; P = 0.035; I^2 = 0%) when amputation was the reference (Table 8).

3.10. Sensitivity analysis and publication bias

Sensitivity analysis was performed to measure each study's effect on the pooled HR. In the comparison of distal versus proximal femur and humerus osteosarcomas, the HR was strengthened when removing Smeland et al., and the I^2 value dropped form 74.7% and 71.9% to 0%, respectively. In the analysis between chondroblastic and conventional osteosarcomas, the statistical significance disappeared when removing the studies of Cates et al., Zheng et al., or Whelan et al. In each of the other groups of analysis, no individual study dominantly affected the overall HR, indicating the robustness of the results.

Both Begg's funnel plot and Egger's testing were applied to estimate the publication bias in the meta-analysis. In the majority of the analysis, the Begg's funnel plot was quite symmetric and no publication bias was detected by Egger's test since all of the P-values were >0.05. On the other hand, publication bias might have existed in the analyses of age (P < 0.001) and tumor size (P = 0.001).

4. Discussion

The relationship of several prognostic markers, such as gender, age at the time of diagnosis, tumor size, tumor location, histological subtype, histological response to chemotherapy, and surgery, with the clinical outcomes of osteosarcoma have been recognized in quite a number of publications [2,55]. However, controversies still exist. In order to derive a more precise estimation of the correlation between the abovementioned factors and OS in patients with osteosarcoma, we carried out this meta-analysis. The results of the present study suggest that male gender, older age, larger tumor size, non-extremity osteosarcoma, proximal osteosarcoma, poor histological response to chemotherapy (<90% necrosis), no surgical treatment, and amputation surgery are potentially responsible for the poor OS of patients with osteosarcoma.

Our meta-analysis has shown that gender was a significant factor

associated with OS in patients with osteosarcoma, and male patients had worse OS when compared to females. The poorer prognosis of male patients might be attributed to several reasons. Previous epidemiologic studies confirmed that osteosarcoma is more common in male individuals, with an overall male:female incident rate ratio of 1.43:1 [56]. Also, males are affected more frequently than females at all ages and in all race groups [57]. Furthermore, the peak incidence of osteosarcoma in females is at ages 10–14 years, whereas for males this is 15–19 years, since females generally reach puberty earlier than males [2]. As suggested by our results, 12–20 year old patients had a worse OS than patients ≤12, and thus, male patients may have a poorer prognosis as well.

In the current study, we performed five groups of comparisons to reveal the prognostic value of age for osteosarcoma. All the results for the five groups showed a worse outcome with increasing age. Although the highest incidence was seen in the younger patient group with a peak incidence at the age of adolescence, different tumor biology in younger patients and a better tolerance of high-dose and intense chemotherapy may have led to a better clinical outcome when compared to older patients [29]. Many researchers have suggested that age is detrimental to clinical outcome, because osteosarcoma in older patients is more likely to be associated with delayed diagnosis, less tolerance of aggressive chemotherapy, difficulties with surgery, combination of unusual tumor locations, and the presence of comorbidities [7,58]. Also, osteosarcomas located in the axial skeleton and trunk, which have been shown to be a negative predictor of OS in both our study and previous investigations [59], appear more frequently in older patients.

Based on the outcomes from this study, tumor location also played a role in osteosarcoma prognosis. Results demonstrated a worse OS in non-extremity osteosarcomas when compared with the extremities. The non-extremity osteosarcomas in this meta-analysis included the axial skeleton, pelvis, trunk, and head and neck, which have all been suggested to be independent prognostic factors in patients with osteosarcoma [12,13,33]. Our study also suggested that proximally-located tumors were a significant negative prognostic marker for OS. However, some have argued that tumor location predicts survival only in patients without a pathological fracture [60]. This might explain why the prognostic value of proximal tumors was strengthened in the sensitivity analysis when the study of Semland S 2019 was removed, as this contained patients with pathological fractures. The size of the primary tumor was proven to be another important prognostic factor according to the study results, and a larger tumor size was associated with a poorer outcome. It has been suggested that the prognostic value of tumor location is closely tied to tumor size. Tumors located in the axial skeleton tend to be larger at diagnosis, and thus have a poorer OS when compared to tumors in the extremities.

Our study is the first to meta-analysis of the prognostic significance of histologic subtypes. Unlike a previous study which found a similar 5 year OS between osteoblastic and chondroblastic subtypes and a better OS towards fibroblastic and telangiectatic tumors [61], our analysis found that chondroblastic osteosarcomas predicted a better OS when compared with the osteoblastic subtype. While no significant prognostic value was identified in fibroblastic and telangiectatic subtypes. However, the results of chondroblastic versus osteoblastic osteosarcomas showed a lack of stability in the sensitivity analysis, and the prognostic value of the chondroblastic subtype cannot be confirmed without more thorough studies being conducted. Thus, the results of the current meta-analysis might suggest that histologic subtype is not a reliable factor for the prognosis of osteosarcoma.

The development of chemotherapy and surgical treatment has significantly improved the survival of patients with osteosarcoma. In line with two previous systematic reviews, Davis et al. (included studies between 1973 and 1992) and Bramer et al. (included studies between 1992 and 2006), our study also demonstrated that a poor chemotherapy response (<90% necrosis) was a negative predictive factor for osteosarcoma survival [62,63]. From these consistent results, it is almost definite that chemotherapy response plays important role in the prognosis of osteosarcoma. However, some have argued that a good chemotherapy response does not necessarily link to better OS in all histologic subtypes. In previous reports, no differences in survival were found between patients with a chondroblastic type that responded well or poorly to chemotherapy [61,64]. Thus, the association between chemotherapy response and histologic subtype in osteosarcoma prognosis should be proven with future study of sufficient data. By understanding the relationship among the histologic subtypes, chemotherapy response, and survival in subtypes like chondroblastic osteosarcomas, additional and more suitable treatment could be introduction in time to improve the survival of these patients.

According to our study results, survival in favor of patients who underwent surgical treatment and patients who received limb salvage surgery, had a better OS when compared with amputation. In general, patients who are selected for limb salvage have no metastases at diagnosis; have absent or limited soft-tissue, joint and neurovascular involvement; achieve a good response to chemotherapy; show evidence of bony union after chemotherapy; and can obtain adequate surgical margins [65]. Patients who have a less favorable prognosis might decide to undergo amputation. As such, the worse OS in patients undergoing amputation might be attributed to this reason, and additional attention should be given to those patients to improve survival.

Compared with previous published materials, the current meta-analysis strengthened the prognostic significance of chemotherapy response and provided new insight into other predictive factors for osteosarcoma prognosis. In the study of Davis et al., the predictive value of sex, age, and tumor size in osteosarcoma survival was lost in multivariate analysis [62]. The insufficient data (only 4–6 studies were included in each group) might be the reason of these results. The study of Bramer et al. presumed that large tumors, age under 14 years, and male gender could independently predict a worse outcome [63]. However, the review did not perform any meta-analyses to confirm those assumptions. Our study, only using the multivariate analysis data, included more than 10 publications in the analysis of age, gender, and tumor size, and demonstrated a negative correlation between older age, male gender, and larger tumor size with poorer survival in patients with osteosarcoma. In addition, we separated studies according to different cut-off points, making our analysis much more rigorous. However, the results of the present analysis still need to interpreted with caution. The two reviews only included patients with extremity osteosarcomas, yet our study also included osteosarcomas located on the axial skeleton. As patients of an older age and with a larger tumor size had a greater axial tumor distribution [58,66], the prognostic significance of age and tumor size might be attributed to the inclusion of axial osteosarcomas. However, axial osteosarcomas only accounted for 2%–27% of the population in each included study, which was relatively low when compared with extremity osteosarcomas. Thus, axial tumors are not the only explanation for the prognostic value of age and size. Nevertheless, further study is still required to discover whether age and tumor size perform differently in the prognosis of osteosarcomas located in the extremities and axial skeleton.

Nonetheless, some limitations should be noticed. Although the Begg's and Egger's tests confirmed that publication bias only existed in two groups of analyses, they did not completely eliminate the possibility of other bias. Some of the analyses only included a small amount of studies, making the Begg's and Egger's tests not the ideal way to detect publication bias. The inclusion of only English publications, the tendency to publish positive findings over negative results, and the different methods of HR extraction might also bring about bias. In some subgroups, heterogeneity was significant among the included studies, however, limited data hampered the ability to perform subgroup analysis to further disclose the source of heterogeneity.

5. Conclusion

The results of this meta-analysis showed that there are significant correlations between gender, age at the time of diagnosis, tumor size, tumor location, chemotherapy response, and surgery and overall survival of patients with osteosarcoma. Male gender, older age, larger tumor size, non-extremity osteosarcoma, proximal osteosarcoma, poor response to chemotherapy, no surgical treatment, and amputation surgery were potentially responsible for poor prognosis in patients with osteosarcoma. Novel treatments should be given to patients who have been identified as high-risk to improve prognosis.

CRediT authorship contribution statement

Sun Xin: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Guo Wei:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing.

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.

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