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Prognosis of limb-salvage treatment of osteosarcoma in adolescent patients: a meta-analysis

LIRONG WANG[1], YONG FAN[2], YU ZHOU[2] and GANG ZHONG[3,4]

[1]Department of Nursing, The People's Hospital of YueChi County, Guang'an, Sichuan 638373; [2]Department of Orthopedic Surgery, The People's Hospital of RenShou County, Meishan, Sichuan 620500; [3]Department of Orthopedic Surgery; [4]Trauma Center, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, P.R. China

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Abstract. To evaluate the effectiveness of limb-salvage treatment for osteosarcoma in adolescent patients, a comprehensive search on PubMed, Embase and Cochrane Library was conducted. Studies with a clear diagnosis of osteosarcoma were included and duplicate publications, studies without full text or incomplete information, those with an inability to extract data, divergent definitions of exposure, animal experiments, reviews, and systematic reviews were excluded. The data were analyzed using STATA 15.1. The findings of the present study revealed that overall survival (OS) and progression-free survival (PFS) of patients with osteosarcoma in the limb-salvage treatment group were significantly longer than those in the amputation treatment group [hazard ratio (HR)=0.71; 95% confidence interval (CI): 0.63-0.80; P=0.000 vs. HR=0.60; 95% CI: 0.48-0.76; P=0.000]. Additionally, the five-year OS rate for patients in the limb-salvage treatment group was higher than that in the amputation group [odds ratio (OR)=4.48; 95% CI: 2.74-7.31; P=0.000]. However, the local recurrence rate was notably higher in the limb-salvage treatment group compared with the amputation treatment group (OR=2.68; 95% CI: 1.50-4.77; P=0.001). Furthermore, the results indicated no significant difference in distant metastasis rates between the limb-salvage treatment group and the amputation treatment group (OR=0.32; 95% CI: 0.10-1.06; P=0.062). In conclusion, the present meta-analysis underscores the potential of limb-salvage therapy for adolescent patients with osteosarcoma. The OS and PFS of patients undergoing limb-salvage surgery are longer than those of amputation, with a higher five-year OS rate and a similar rate of distant metastasis. However, the local recurrence rate of limb-salvage surgery is significantly higher than that of amputation.

Correspondence to: Dr Gang Zhong, Department of Orthopedic Surgery, West China Hospital, Sichuan University, 37 Guoxue Alley, Chengdu, Sichuan 610041, P.R. China
E-mail: zg730927@163.com

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Introduction

Osteosarcoma, a primary malignant bone tumor originating from bone mesenchymal cells, is one of the most prevalent malignancies affecting children, adolescents and young adults (1-3). Despite its rarity, ~1,000 new cases are diagnosed in the United States each year (4). Osteosarcoma manifests in primary and secondary forms, together accounting for nearly 20% of all primary bone tumors (5). Characterized by its highly aggressive nature, osteosarcoma often metastasizes early, with the lung being the most frequent site for distant metastases. At the time of diagnosis, the majority of patients already present with lung micro-metastases, which serve as the primary cause of death (6).

Current treatment options for osteosarcoma include surgical procedures, chemotherapy, biological immunotherapy, molecular targeted therapy and other similar approaches. The five-year overall survival (OS) rate following comprehensive osteosarcoma treatment ranges from 66-82% (7). The standard treatment protocol typically involves neoadjuvant chemotherapy, followed by surgery and adjuvant chemotherapy (8). Increasing evidence suggests that limb-sparing surgery is gradually replacing amputation in the treatment of osteosarcoma (9,10). Nevertheless, some studies argue that early and aggressive tumor removal through amputation effectively prevents further fracture development, making it a preferable choice for osteosarcoma cases complicated with pathological fractures (11,12).

Han *et al* (13) conducted a meta-analysis of articles published before 2015, comparing amputation with limb-salvage surgery in patients with osteosarcoma, demonstrating higher five-year survival rates and improved functionality with limb-salvage surgery. Another meta-analysis published in 2022 compared the efficacy of limb-salvage surgery and amputation in patients with osteosarcoma treated with neoadjuvant chemotherapy (14).

The present study primarily focused on the effectiveness of limb-salvage treatment for adolescent osteosarcoma patients. By conducting a meta-analysis of the published literature on osteosarcoma surgical treatment, the goal was to systematically evaluate the clinical efficacy of both limb-salvage treatment and amputation in order to determine the most appropriate treatment strategies for adolescent patients. The current meta-analysis aimed to provide guidance for the clinical treatment of osteosarcoma.

Materials and methods

Guideline, inclusion and exclusion criteria for literature selection. In the present study, the PRISMA guidelines (http://www.prisma-statement.org/) were followed. Inclusion criteria were as follows: a definitive diagnosis of osteosarcoma and articles written in English. Exclusion criteria included duplicate publications, reviews, editorials, single case reports and studies without full text, incomplete information, or studies from which data extraction was impossible.

Search strategy. PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/) and the Cochrane Library (https://www.cochranelibrary.com/) were searched for relevant literature. The search period extended from the inception of each database to September 2022. The search terms used included 'Osteosarcoma', 'Osteosarcoma Tumor', 'Osteogenic Sarcomas', 'Limb Salvage' and 'Amputation'. Specific search strings for each database were as follows: PubMed: 'osteosarcoma'[MeSH Terms] OR 'Osteosarcoma Tumor'[All Fields] OR 'Osteogenic Sarcomas'[All Fields] OR 'limb salvage surgery'[All Fields] OR 'amputation'[All Fields]; Embase: 'osteosarcoma'/limb salvage treatment'/amputation; Cochrane Library: (osteosarcoma): ti,ab,kw OR (limb salvage surgery): ti,ab,kw (word variations were also searched).

Literature screening and data extraction. The authors of the present study independently conducted literature search, screening and data extraction. Any uncertainties were resolved through discussion with the corresponding author. Extracted data included author, year, region, study type, number of cases, OS, progression-free survival (PFS), five-year OS rate, local recurrence rate and distant metastases rate.

Literature quality assessment. The authors of the present study independently used the Newcastle-Ottawa Scale (NOS) (15) to assess the quality of the included studies. Discrepancies were resolved through consultation or by seeking the opinion of a third party. The NOS comprises four items (four points) for 'Research Subject Selection', one item (two points) for 'Comparability between Groups' and three items (three points) for 'Outcome Measurement', with a maximum score of nine points. Studies scoring ≥7 were considered high quality, while those scoring <7 were deemed lower quality.

Statistical methods. Hazard ratios (HR) and 95% confidence intervals (CI) were used to evaluate OS and PFS, while odds ratios (OR) and 95% CI were used to assess the five-year OS rate, local recurrence rate and metastases rate. A fixed-effects model was employed for combined analysis if the heterogeneity test yielded $P \geq 0.1$ and $I^2 \leq 50\%$; otherwise, a random-effects model was applied if $P<0.1$ and $I^2>50\%$. Sensitivity analyses were conducted to explore sources of heterogeneity when necessary. The presence of publication bias was determined by assessing the symmetry of funnel plots. All data were analyzed using Stata (v.15.1; StataCorp LLC).

Results

Literature search outcomes. A comprehensive search of PubMed, Embase and Cochrane Library yielded 735 articles. After removing duplicates, a total of 467 unique articles remained. Upon reviewing the abstracts, a total of 305 articles were selected for further examination. Ultimately, after a thorough full-text evaluation, 11 articles were deemed suitable for inclusion in the meta-analysis (Fig. 1).

Baseline characteristics and quality assessment of included studies. The baseline characteristics and quality assessment of the included studies are presented in Table I. All studies had NOS scores of ≥7 points, indicating satisfactory quality.

Results of meta-analysis. Firstly, the differences in OS following limb salvage and amputation surgeries for osteosarcoma were investigated. The analysis revealed that OS was significantly longer after limb-salvage surgery compared with amputation surgery (HR=0.71; 95% CI:0.63-0.80; P<0.001; I^2=36.9%; P=0.175; 5 articles included) (Fig. 2A). Moreover, the pooled results demonstrated that PFS after limb-salvage surgery was also significantly longer than after amputation surgery (HR=0.60; 95% CI: 0.48-0.76; P<0.001; I^2=0.0%; P=0.522; 2 articles included) (Fig. 2B). To further confirm the efficacy of limb-salvage surgery, the five-year OS rate was analyzed, which was 2.67 times higher after limb-salvage surgery compared with amputation surgery (OR=2.14; 95% CI: 1.86-2.45; P=0.037; I^2=57.9%; P<0.001; 6 articles included) (Fig. 2C).

Additionally, the local recurrence and distant metastasis rates between the two surgical approaches were compared. The local recurrence rate following limb-salvage surgery was significantly higher than after amputation (OR=2.58; 95% CI: 1.48-4.51; P=0.001; I^2=0.0%, P=0.748; 5 articles included) (Fig. 3A). However, there was no statistically significant difference in the distant metastasis rate between the two groups (OR=0.56; 95% CI: 0.25-1.28; P=0.169; I^2=0.0%; P=0.389; 3 articles included) (Fig. 3B).

Sensitivity analysis. Sensitivity analyses were conducted to assess the impact of individual studies on the overall meta-analysis results by sequentially excluding each study and recalculating the combined HR or OR values. The sensitivity analysis results are illustrated in Figs. S1-3. No study influenced excessively the meta-analysis outcomes, indicating that the findings of the present study are stable and reliable.

Publication bias. Due to the limited number of included articles (n<12) for each variable, publication bias was assessed by using funnel plots. As illustrated in Fig. 4, the funnel plots appeared asymmetric, suggesting potential publication bias in the present study.

Discussion

Prior to the 1970s, amputation was the standard treatment for osteosarcoma, yielding a five-year OS rate of <20%

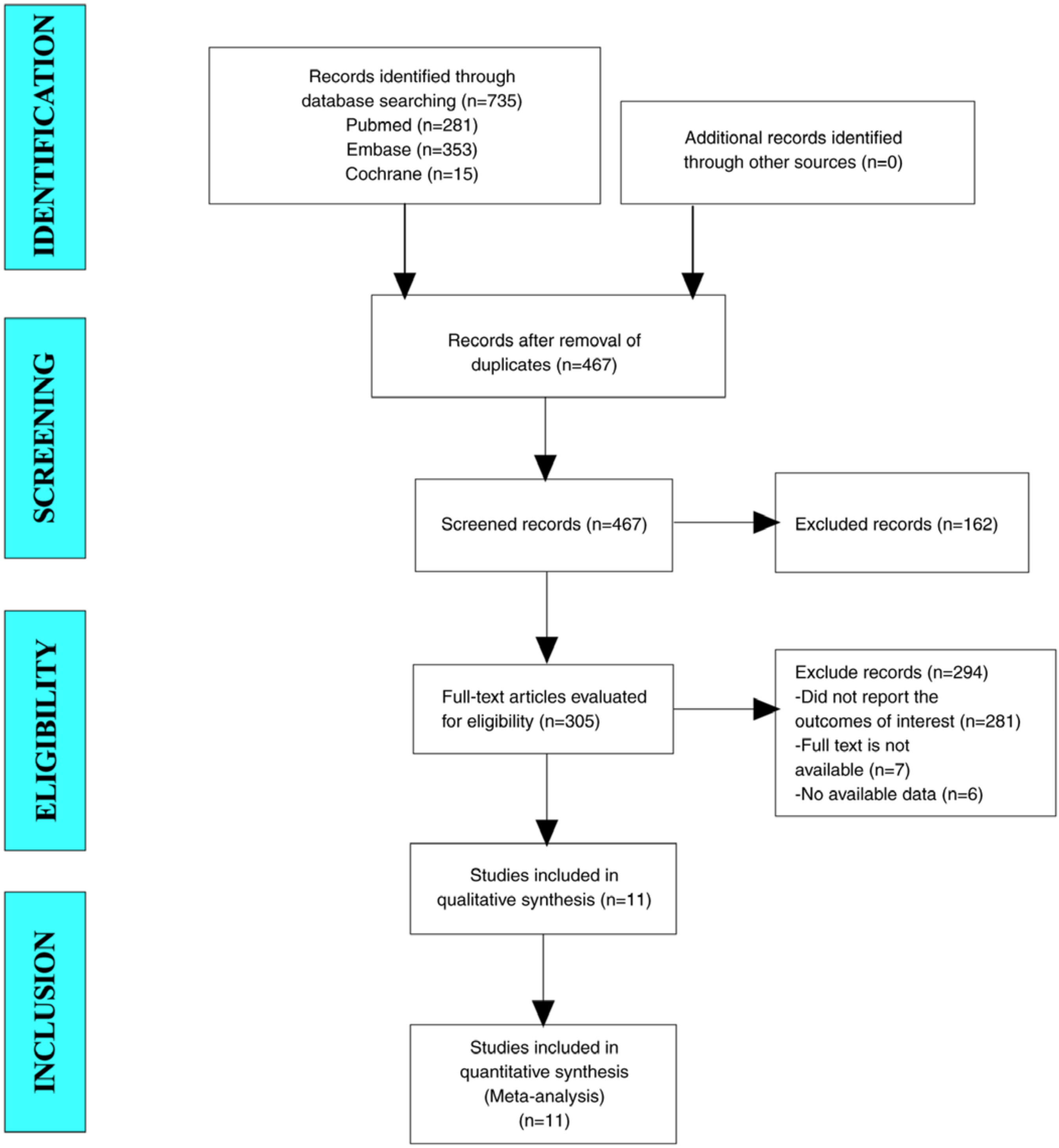

Figure 1. Flowchart illustrating the selection process for study inclusion.

post-surgery (16). However, previous advancements in neoadjuvant chemotherapy, imaging diagnostics, three-dimensional reconstruction technology and enhanced chemotherapy effects have contributed to a significant increase in patients with osteosarcoma opting for limb-salvage surgery over amputation (17-19). Nonetheless, existing literature presents contradictory findings regarding survival rates and local recurrence rates in patients undergoing limb salvage vs. amputation surgery (20). The present meta-analysis of 11 studies (encompassing 5,225 patients) aimed to provide clarity on these rates, including OS, PFS, five-year OS rate, local recurrence and distant metastasis for both limb salvage and amputation surgeries.

The findings of the present study revealed that patients in the limb-salvage treatment group exhibit longer OS and PFS than those in the amputation group (HR=0.71; 95% CI: 0.63-0.80; P<0.001 vs. HR=0.60; 95% CI: 0.48-0.76; P<0.001). Additionally, the five-year OS rate was higher in the limb-salvage group compared with the amputation group (OR=2.14; 95% CI: 1.86-2.45; P=0.037; I^2=57.9%;

Table I. Summary of baseline characteristics and quality assessment of included studies.

First author/s, year	Region	Research type	Number of cases		Sex		Age		Follow-up time (year)	NOS score	(Refs.)
			Limb salvage	Amputation	Limb salvage	Amputation	Limb salvage	Amputation			
Kaneuchi *et al*, 2022	UK	Cohort	65	17	32/50		8(3-9)		10	7	(23)
Qi *et al*, 2020	China	Cohort	2,447	916	1,330/1,117	578/388	/	/	5	7	(10)
Yasin *et al*, 2020	Malaysia	Cohort	81	25	/	/	/	/	10	7	(24)
Lin *et al*, 2018	China	Cohort	38	43	/	/	/	/	5	8	(25)
Puri *et al*, 2017	India	Cohort	552	186	521/217		19 (3-64)		3 (3-11)	7	(26)
Poudel *et al*, 2017	India	Cohort	77	18	64/31		/	/	2.8 (0.3-6.8)	8	(27)
Kamal *et al*, 2016	Indonesia	Cohort	37	42	/	/	17 (14-23)		/	8	(28)
Faisham *et al*, 2015	Malaysia	Cohort	80	41	/	/	19 (6-59)		3.9 (3-7)	8	(29)
Mavrogenis *et al*, 2012	Italy	Cohort	23	19	12/11	11/8	23 (10-51)	29 (7-78)	5.6 (0.7-23.9)	7	(20)
Bacci *et al*, 2002	Italy	Cohort	465	95	263/202	57/38	/	/	10.5 (5-17)	7	(30)
Abudu *et al*, 1996	UK	Cohort	27	13	26/14		18 (2-46)		4.6 (0.7-14.6)	7	(21)

P<0.001). While Abudu *et al* (21) asserted that amputation surgery does not prolong OS despite improved eradication of local tumors, a different study argues that limb-salvage therapy does not impact patient survival rates (22). The present comprehensive and systematic analysis resolved these disputes, concluding that limb-salvage surgery is more effective than amputation surgery in treating osteosarcoma patients.

Concerning local recurrence rates, the present study observed that the limb-salvage group had a significantly higher rate compared with the amputation group (OR=2.58; 95% CI: 1.48-4.51; P=0.001). This contradicts the meta-analysis conducted by Han *et al* (13), which detected no differences in post-operative local recurrence rates between the two groups. This discrepancy highlights the need for clinicians to carefully consider the trade-off between therapeutic effects and local recurrence rates when selecting limb-salvage surgery for osteosarcoma treatment. Furthermore, the present study indicated no significant difference in distant metastasis rates between the limb salvage and amputation groups (OR=0.32; 95% CI: 0.10-1.06; P=0.062) (data not shown), aligning with the findings of Mavrogenis *et al* (20). However, due to the limited information on distant metastasis rates, this conclusion is based on only two studies and necessitates further investigation through high-quality randomized controlled trials.

Despite the aforementioned findings, the present study has certain limitations. The selection bias is the first limitation of the present analysis. All included articles are retrospective studies, with most of them possessing small sample sizes, which may introduce systematic and random errors. Secondly, factors such as tumor stage and metastasis could impact surgical outcomes, but the present study was unable to account for these variables due to the limited number of articles. This may contribute to the observed heterogeneity. Lastly, the inability to perform Egger's test for publication bias assessment may lead to potential bias. Consequently, while the present study offers more comprehensive evidence than previous research, the conclusions warrant further validation through large-sample randomized controlled trials of high quality.

In conclusion, the present meta-analysis underscored the efficacy of limb-salvage therapy as a viable treatment option for adolescent osteosarcoma patients. The OS and PFS rates of patients undergoing limb-salvage surgery surpass those of amputation. Furthermore, the five-year OS rate is notably higher in comparison with amputation, while the rate of distant metastasis remains analogous. However, it is important to note that the local recurrence rate of limb-salvage surgery is significantly higher than that of amputation.

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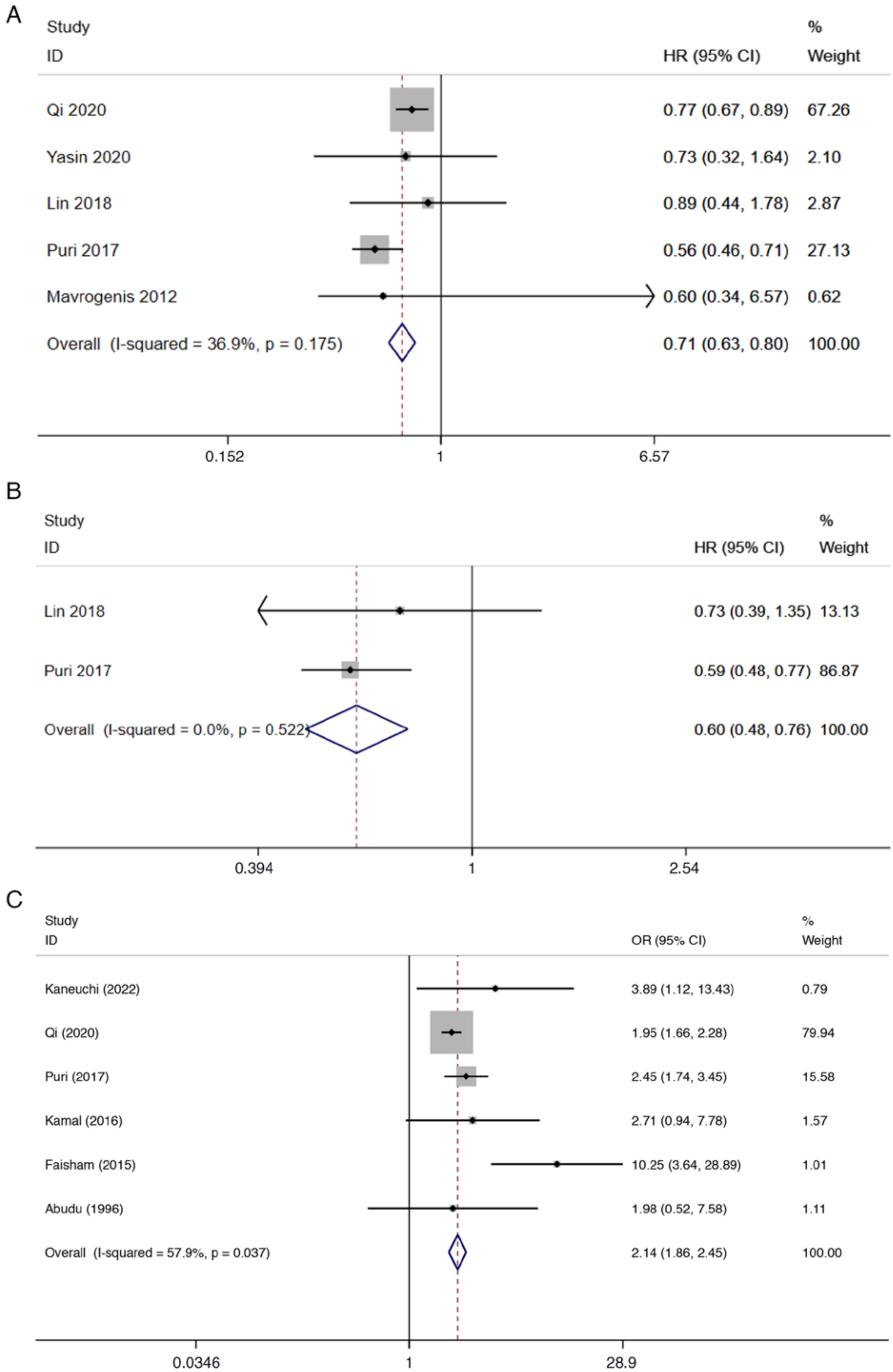

Figure 2. Comparisons of (A) OS, (B) progression-free survival and (C) 5-year OS rate between limb salvage and amputation in treating adolescent patients with osteosarcoma. OS, overall survival; HR, hazard ratio; CI, confidence interval; OR, odds ratio.

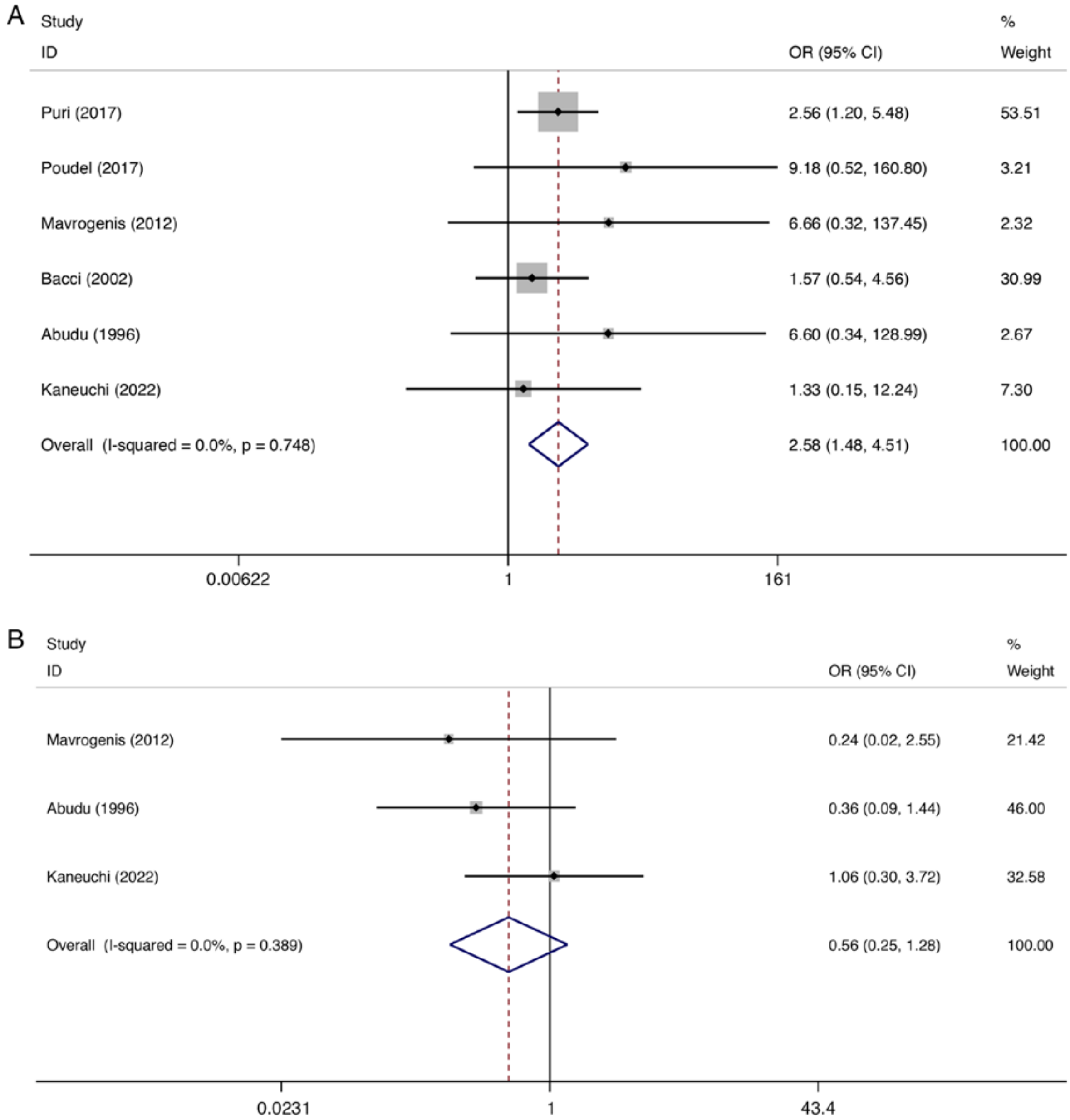

Figure 3. Comparisons of (A) local recurrence rate and (B) distant metastasis rate between limb salvage and amputation in treating adolescent patients with osteosarcoma. OR, odds ratio; CI, confidence interval.

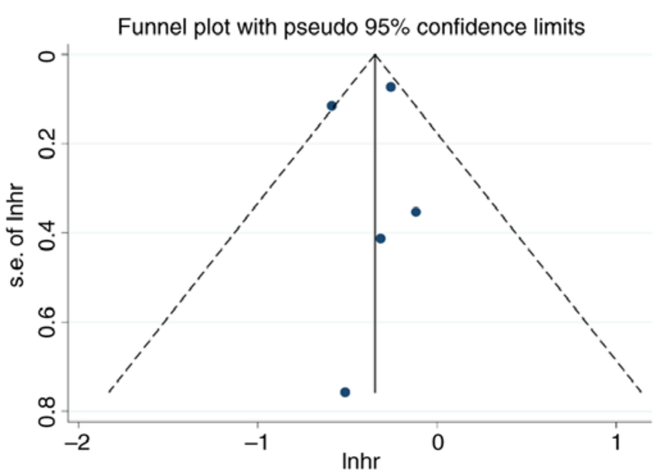

Figure 4. Funnel plot to evaluate potential publication bias. lnhr, natural logarithm of hazard ratio; SE, standard error.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LW performed the literature search, helped with data analysis, and drafted the manuscript. YF and YZ added new data to the present meta-analysis, and performed some statistical analysis. GZ conceptualized and designed the study. YF and YZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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