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Prognostic Significance of Survivin Expression in Osteosarcoma Patients: A Meta-Analysis

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Background: Osteosarcoma is the most common primary bone malignancy and has poor prognosis. Survivin has been identified as an independent prognostic factor for a majority of cancers. In the present study, we evaluated the effect of survivin expression on the clinical outcome of osteosarcoma patients.




Material/Methods: Online electronic databases were searched for related articles published between 2000 and 2015. Odds ratio (OR) and risk ratio (RR) with their 95% confidence intervals (CI) were employed to calculate the significance.

Results: Overall, a total of 20 relevant studies were selected, including 1030 patients. No significant heterogeneity was observed among included studies ($P > 0.01$, $I^2 < 50\%$). Survivin was expressed in 68.6% of all cases. Our results show that survivin expression increased the 5-year overall survival (RR=0.48, 95% CI=0.32–0.71, $P=0.0002$) and rate of postoperative recurrence (RR=1.80, 95% CI=1.09–2.97, $P=0.02$). It was associated with the grade of osteosarcoma (Enneking clinical stage, IIb–III vs. I–IIa: OR=5.26, 95% CI=3.76–7.34, $P < 0.00001$; Price's grade, III vs. I+II: OR=2.04, 95% CI=1.16–3.61, $P=0.01$), metastasis, and soft tissue invasion of osteosarcoma (OR=6.25, 95% CI=3.74–10.45, $P < 0.00001$; OR=6.15, 95% CI=3.74–10.11, $P < 0.00001$). No relationship was found between survivin expression and sex, age, or tumor size in patients with osteosarcoma.

Conclusions: Our results suggest that survivin can function as a new diagnostic biomarker for osteosarcoma and be used as a reference index to determine pathology classification of osteosarcoma, providing new targets for gene therapy of osteosarcoma.

MeSH Keywords: **Gene Expression • Osteosarcoma • Prognosis**

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Background

Osteosarcoma originates from primitive bone-forming mesenchymal cells and is the most common primary bone malignancy in children and adults. It can occur in any bone and accounts for approximately 20% of all primary malignant bone tumors [1,2]. Its occurrence is influenced by ethnicity, age, sex, tumor size, genetic susceptibility, and environmental insults [3]. The incidence rates of osteosarcoma for all races and sexes are 4.0 and 5.0 for the age range 0–14 years and 0–19 years per year per million persons, respectively [4]. Although adjuvant and neo-adjuvant chemotherapy has somewhat improved the survival rate, it remains essentially unchanged during the past 30 years, probably due to chemoresistance to anti-osteosarcoma therapy [5], with a 68% 5-year overall survival rate [6]. Moreover, 75–85% of cases are high-grade osteosarcomas with poor prognosis and a high mortality rate. Therefore, there is an urgent need to explore biomarkers to predict the grade and outcome of this disease, and to develop new treatment strategies.

The survivin gene, located on human chromosome 17q25, consists of 4 exons and 3 introns [7]. It is expressed in a 16.5-kD protein belonging to the inhibitor of apoptosis (IAP) family [8]. The expression of survivin can regulate the cell cycle, inhibit apoptosis, promote cell proliferation, and enhance angiogenesis [9]. It is expressed in almost all malignancies, but is rarely detected in healthy differentiated adult tissues [10]. Survivin is a multifunctional protein, and studies have identified that up-expression of survivin is uniformly associated with inhibition of apoptosis in various cellular systems, while its down-expression leads to enhanced spontaneous cell death [11,12]. Survivin was proven to be a primary chemotherapeutic target and biomarker for prognosis in various malignancies [13,14]. Studies on clinical specimens have shown that survivin expression functions as a therapeutic target in breast cancer [15], Merkel cell carcinoma [16], endometrial cancer [17], renal cell carcinoma [18], and other cancers [19].

In osteosarcoma, survivin is overexpressed and is considered to be important in protecting cells from apoptosis [20]. Although numerous studies during recent decades have found a correlation between survivin expression levels and osteosarcoma risk, the results remain unclear. Therefore, we performed this meta-analysis based on all published articles on this issue to systematically evaluate the effect of survivin expression on osteosarcoma.

Material and Methods

Search strategy

A comprehensive literature search was conducted in the online databases of Embase, Medline, PubMed, CNKI (China National

Knowledge Internet), and Wanfang to retrieve relevant articles published between January 2000 and 2015. The following MeSH terms: “osteosarcoma or osteogenic sarcoma”, “survivin or baculoviral inhibitor of apoptosis repeat-containing 5 or BIRC5”, “expression”, “survival”, and “prognosis”, as well as their combinations, were employed as the searching words. The references were manually searched as well. Our study only focused on human studies. When the same authors or laboratories reported 2 or more articles on the same issue or population, only the most recent full-text article was included.

Inclusion criteria

Eligible articles had to meet the following criteria: 1) evaluating the effect of survivin expression on prognosis of osteosarcoma patients; 2) patients with osteosarcoma were confirmed by at least 2 pathologists; 3) clinical stage and histological grading of osteosarcoma cases were graded according to the standard of Enneking criteria [21] and Price's grade [22], respectively; 4) osteosarcoma patients did not receive any chemotherapy or radio therapy before biopsy; and 5) the survivin expression was measured by immunohistochemistry (IHC) or reverse transcription-polymerase chain reaction (RT-PCR).

Exclusion criteria

The exclusion criteria were as follow: 1) studies were reviews or conference papers; 2) osteosarcoma patients received some therapy before biopsy; and 3) did not assess the prognostic role of survivin expression in osteosarcoma risk.

Data extraction

We assessed the quality of selected articles according to the description of Hayde et al. [23]. Two of our authors systematically evaluated articles independently to reach a consensus on each. Any disagreement was resolved by discussion with a third expert. The first author, published year, mean age, sex, disease stage, definition of positivity (cutoff value), sample size, and survivin-positivity were extracted from each study.

Statistical analysis

The pooled odds ratio (OR) and risk ratio (RR) with their corresponding 95% confidence intervals (CI) were used to evaluate the effect of survivin expression on prognosis of patients with osteosarcoma. The Z test was used to estimate the effect, with P-value less than 0.05 considered significant. Heterogeneity between studies was calculated by the Q test and I^2 test. When the effect was assumed to be homogeneous, the fixed-effects model was used and the random-effects model was used when it was heterogeneous. The RevMan 5.2 program was used to perform all the analysis, as described by Collaboration et al. [24].

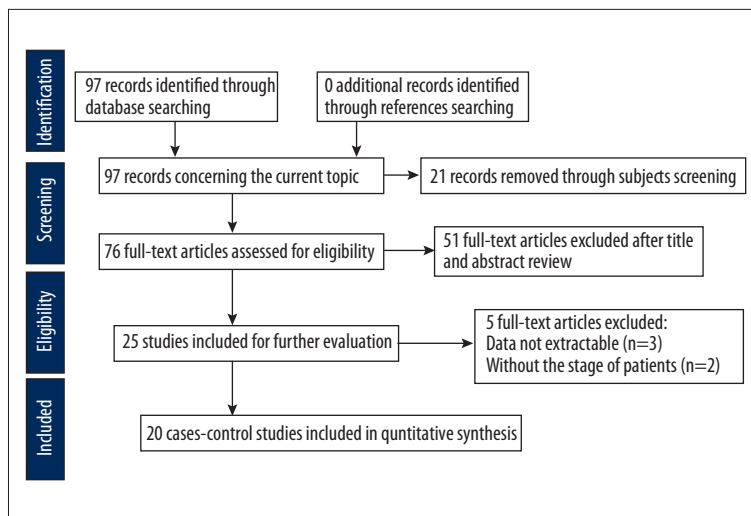


Figure 1. The search process.

Results

Characteristics of included studies

A total of 20 studies were finally included after applying the inclusion criteria. Figure 1 presents the selection process. The 20 articles (2 in English [25,26] and 18 in Chinese [27–44]) included 1030 osteosarcoma patients. All of them were conducted in Chinese populations. The sample size ranged from 27 to 95 subjects. Survivin expression was measured by HIC method, and was detected in 68.6% of all cases (707/1030). The main characteristics of included studies are shown in Table 1.

Correction of survivin expression on Enneking clinical stage and Price's grade in patients with osteosarcoma

Sixteen articles assessed the effect of survivin expression on Enneking clinical stage, containing 845 patients. No significant heterogeneity was observed between studies. We divided patients into 2 groups by Enneking clinical stage: I–IIa and IIb–III groups included 489 and 356 patients, respectively. We found that the frequency of survivin expression was much higher in the IIb–III group than in the I–IIa group (82.4% vs. 51.7%). Our result demonstrated that there was a significant difference in survivin expression between these 2 groups (OR=5.26, 95% CI=3.76–7.34, $P<0.00001$) in a fixed-effects model, as shown in Figure 2A. Six articles concerned the Price's grade, including 302 patients. We also divided patients into 2 groups: the III group and the I+II group. Survivin expression was higher in the III group than that in the I+II group (80.8% vs. 66.2%). Our analysis showed that survivin expression was highest in the III group (OR=2.04, 95% CI=1.16–3.61, $P=0.01$), as shown in Figure 2B. These results indicate that survivin could be used as a reference index to determine pathology classification of osteosarcoma, providing new targets for gene therapy of osteosarcoma.

Association between survivin expression and sex, age, tumor size, metastasis, and tissue invasion of patients with osteosarcoma

A total of 14 articles concerned sex as a factor, including 407 males and 246 females. Although the survivin expression was higher in males than in females (69.5% vs. 63.8%), we did not find a significant difference between these 2 groups in survivin expression (OR=1.26, 95% CI=0.89–1.77, $P=0.19$), as shown in Figure 3. All the included studies focused on age as a factor. For the various age groups presented, we could not conduct statistical analysis, but the results from each study demonstrated that there was no relationship between survivin expression and age group ($P>0.05$). Six articles considered tumor size, and our results did not show a significant relationship between survivin expression and tumor size of osteosarcoma (≤ 5 cm versus. >5 cm: OR=1.00, 95% CI=0.45–2.24, $P=1.00$). Eight studies including 389 patients and 7 studies including 456 patients considered metastasis and soft tissue invasion. Our results show that survivin expression was corrected with metastasis and soft tissue invasion of osteosarcoma (OR=6.25, 95% CI=3.74–10.45, $P<0.00001$, Figure 4A; OR=6.15, 95% CI=3.74–10.11, $P<0.00001$, Figure 4B).

Association between survivin expression and 5-year overall survival in postoperative recurrence of osteosarcoma patients

Three articles exploring this relationship were selected, including 128 patients. Our result proved that survivin expression was significantly associated with increased 5-year overall survival (RR=0.48, 95% CI=0.32–0.71, $P=0.0002$) in a fixed-effects model, as shown in Figure 5A, suggesting that survivin might be an indicator of poor prognosis for osteosarcoma patients. Two articles considered postoperative recurrence. Our result showed that survivin increased the rate of postoperative recurrence (RR=1.80, 95% CI=1.09–2.97, $P=0.02$, Figure 5B).

Table 1. Main characteristic of included studies.

Author	Year	Mean age (rang)	M/F	Enneking clinical stages				Price grade			Positivity
				I-IIa		IIb-III		I	II	III	
				P	T	P	T				
Lao KC	2003	36.5 (10–63)	32/10	8	18	19	24	18/31	–	9/11	5%
Nie T	2005	25.7 (10–66)	22/13	3	9	20	26				1%
Gao DX	2005	19 (16–61)	22/16					6/10	10/15	9/13	1%
Li YH	2006	19 (7–70)	52/33	20	38	44	47	9/20	25/34	30/31	–
Pan ZE	2006	19.8 (7–62)	28/18	6	17	23	29				5%
Yang TT	2006	21.6 (7–48)	50/24	20	33	38	41				5%
Duan GQ	2007	19.6 (9–40)	28/12	3	8	22	32				10%
Zhang CY	2007	–	31/15	8	17	24	29				5%
Liu XL	2008	22 (12–49)	26/13					7/10	11/14	13/15	10%
Liu ZC	2009	21 (13–61)	26/20					9/13	12/19	10/14	1%
Wang DH	2009	9.5 (4–14)	16/18	4	12	19	22				5%
Yang BJ	2009	21 (7–43)	23/15	4	15	13	23				5%
He WB	2010	23 (11–60)	34/18	15	21	23	31	12/16	13/16	13/20	1%
Ji XM	2010	29.1 (15–47)	54/35	19	36	45	53				5%
Sun CZ	2010	26.3 (6–38)	31/31								1%
Wu Q	2010	23.2 (12–32)	21/15	7	16	16	20				5%
Peng WM	2012	– (15–47)	58/37	21	40	47	55				25%
Xu YK	2012	69.45 (60–83)	40/30	19	35	31	35				10%
Li EH	2013	–	22/14	21	30	6	6				–
Tu R	2014	37.2	17/10	6	11	13	16				5%

‘–’ not applicable; P – positive number of survivin expression; T – sample size; Positivity – cut-point of survivin expression positive, n% represents that when the positive cells was more than this number, the survivin expression was recorded as positive, otherwise, it was recorded as negative.

Sensitivity analysis and publication bias

Individual studies were deleted on a time to verify the influence of each single study on the overall results in each comparison; our results showed that the pooled OR and RR were not significantly changed. The funnel plot was used to further evaluate publication bias among included studies. As shown in Figure 6, 1 dot represents 1 included study. The dot outside the funnel represents the study by He et al. When this study was omitted from our analysis, no obvious asymmetry presented, and the results remained unchanged. Moreover, the heterogeneity between studies was not significantly changed (Before: P=0.81, I²=0%; After: P=1.00, I²=0%). These results indicated that there was no publication bias.

Discussion

Osteosarcoma is the most common pediatric and adult bone tumor and can lead to a second incidence peak in the elderly. Current optimal treatments for osteosarcoma have improved the 5-year overall survival, but the prognosis and quality of life remain poor [45]. Recently, gene therapy for osteosarcoma has become an important topic in exploring new treatments in China and internationally. Researchers have identified that the survivin gene is highly expressed in osteosarcoma tissues and might be involved in osteosarcoma development. Therefore, we estimated the role of this gene in patients with osteosarcoma.

In our meta-analysis, we included a total of 20 articles. No significant heterogeneity was observed among studies. The

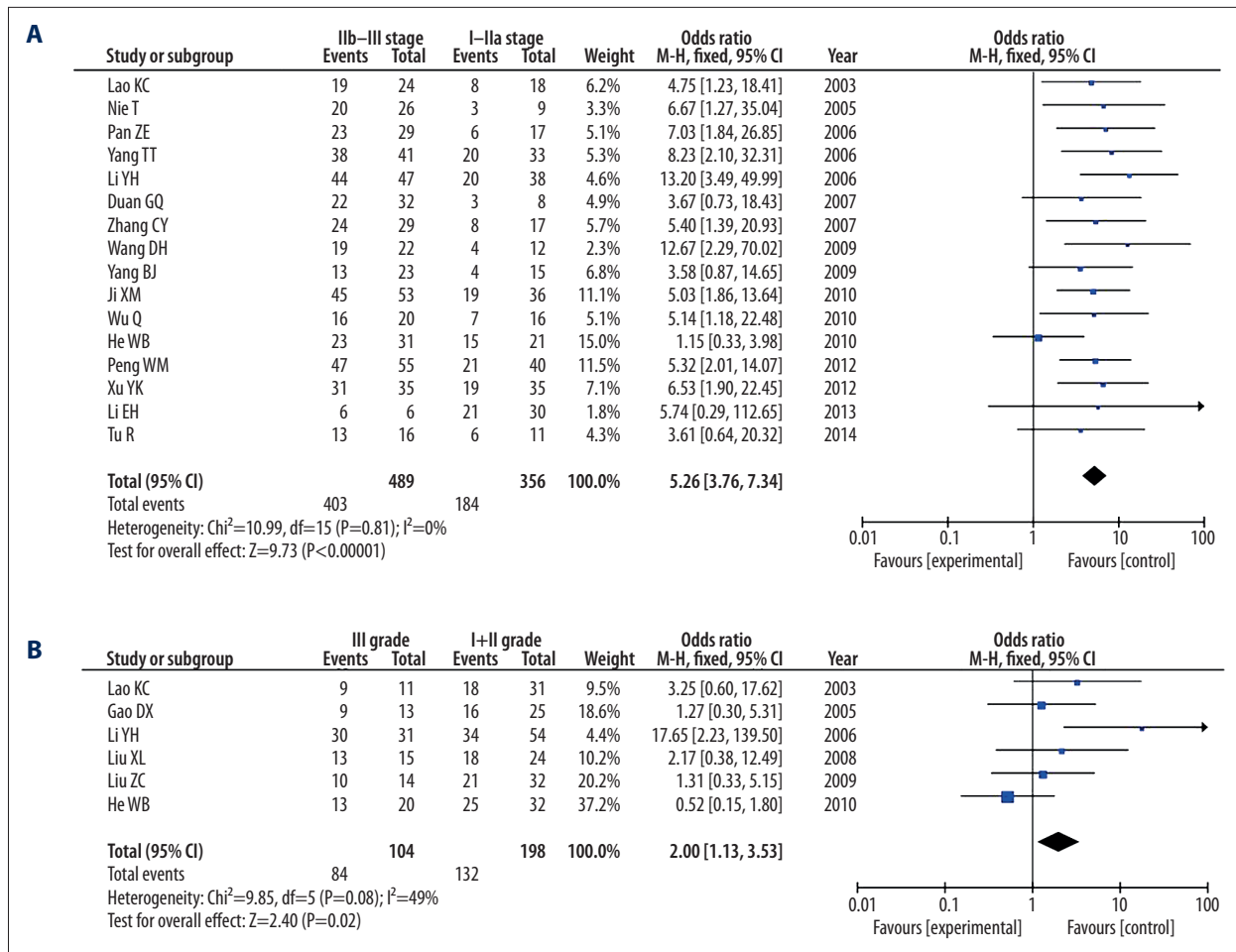


Figure 2. Forest plot of survivin expression on osteosarcoma grade ((A), Enneking clinical stage; (B) Price's grade).

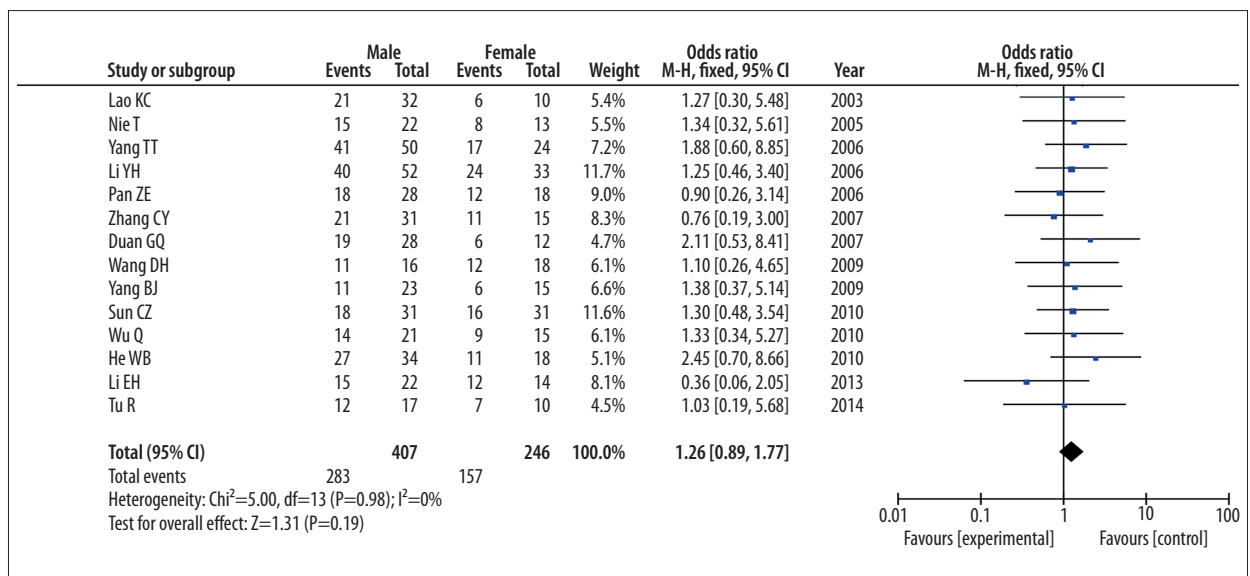


Figure 3. Forest plot of survivin expression on sex of patients with osteosarcoma.

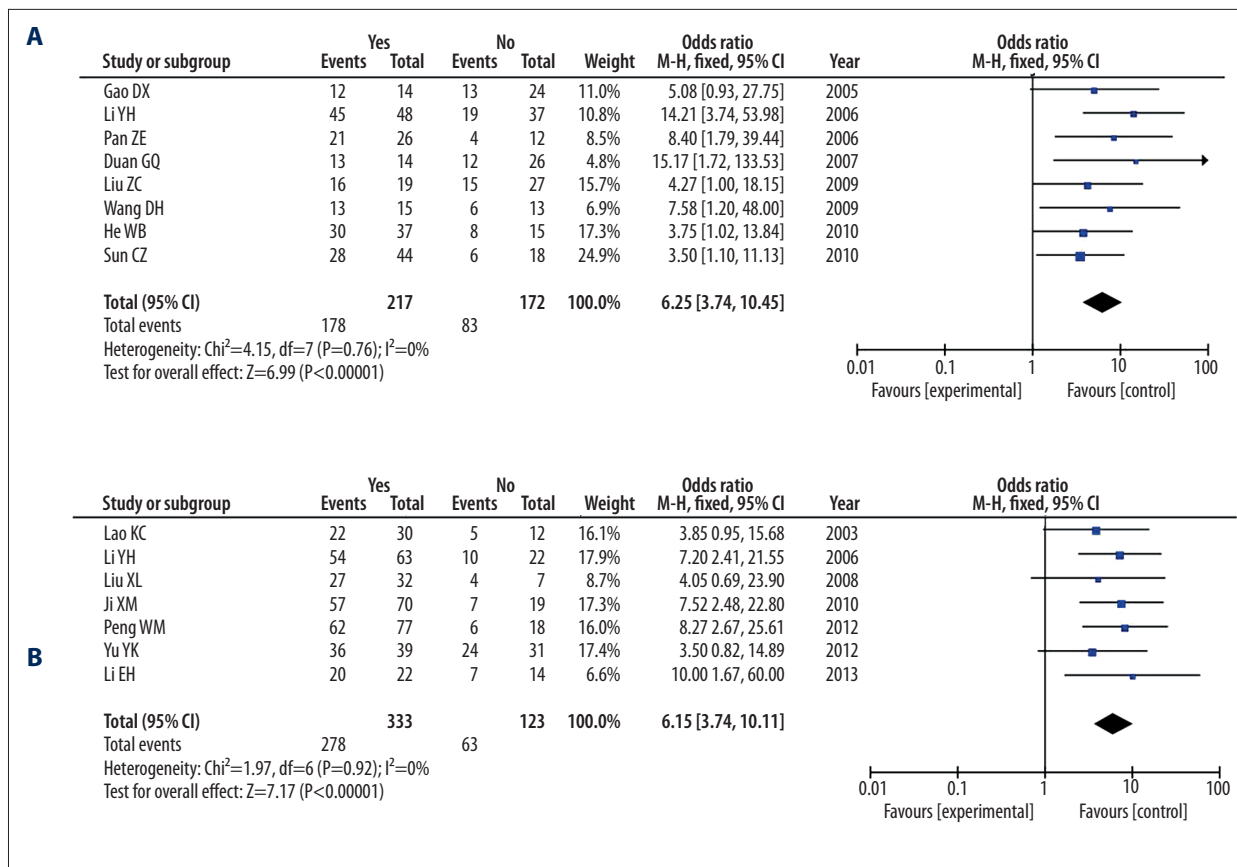


Figure 4. Correction of survivin expression on metastasis (A) and soft tissue invasion (B) of osteosarcoma patients.

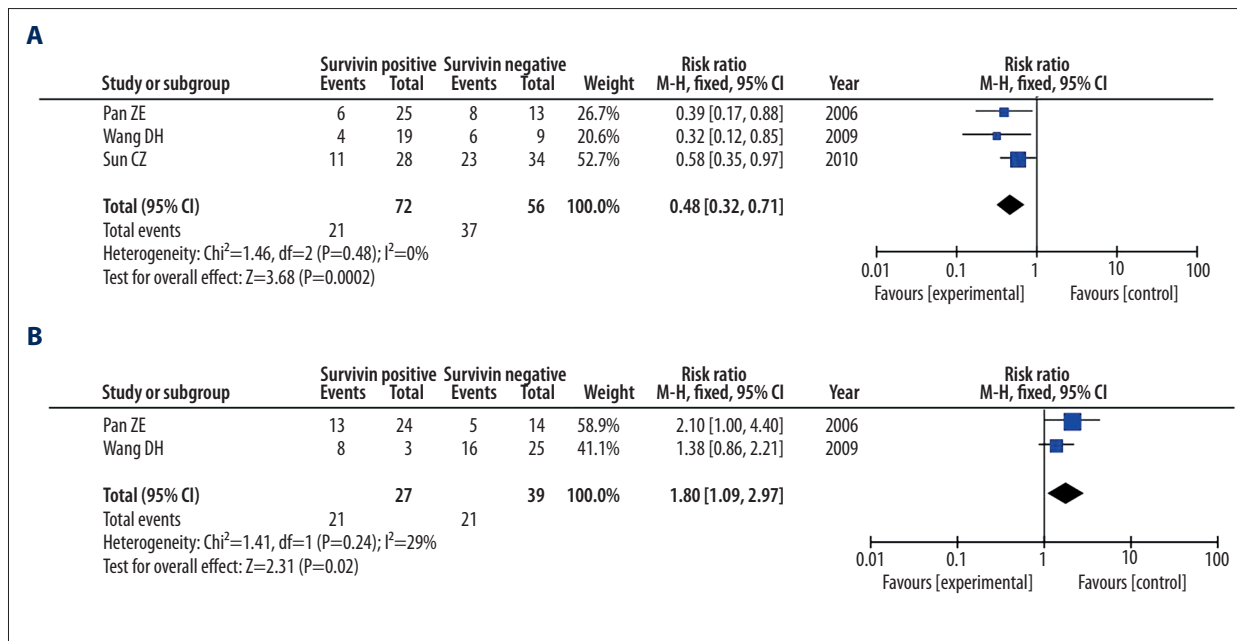


Figure 5. Correction of survivin expression on prognosis of osteosarcoma patients ((A), 5-year overall survival; (B), postoperative recurrence).

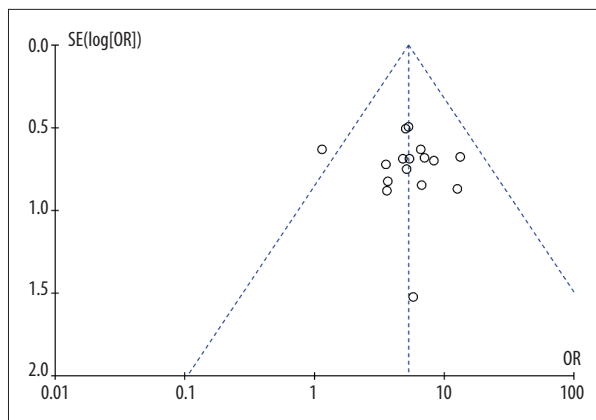


Figure 6. Funnel plot of survivin expression on Enneking clinical stage of osteosarcoma metastasis and soft tissue invasion, and postoperative recurrence in patients with osteosarcoma.

results from statistical analysis demonstrated that survivin expression was positively associated with Enneking clinical stage, Price's grade, metastasis and soft tissue invasion, 5-year overall survival, and postoperative recurrence in patients with osteosarcoma ($P < 0.01$). However, this significant relationship was not found between survivin expression and sex, age, or tumor size of osteosarcoma patients ($P > 0.05$). Our results suggest that survivin expression might be involved in the occurrence, metastasis, prognosis, and recurrence of osteosarcoma, indicating that survivin may be an ideal target in diagnosis, treatment, and determining prognosis. This is the first meta-analysis systematically evaluating the effect of survivin expression on osteosarcoma.

Survivin is a prominent anti-apoptotic molecule. It is one of the rare proteins that can be differentially expressed in both tumor and normal tissue cells. This protein is widely overexpressed in many cancers, leading to uncontrolled cancer cell growth and resistance to both chemotherapy and radiation therapy [46]. High activity of the surviving gene was associated with poor prognosis and worse survival rates. Furthermore, survivin has been proposed as an attractive target for new anti-cancer interventions [47], and as an independent prognostic factor and inhibitor of apoptosis, proving to be a useful therapeutic target in cancer therapy [48].

In human osteosarcoma, Trieb et al. found that survivin expression was detected in the cytoplasm and nucleus of osteosarcoma, and nuclear localization of survivin expression was significantly related with prolonged survival [49]. Osaka et al. showed that high survivin mRNA levels were associated with metastasis in osteosarcoma patients, suggesting poor prognosis [50]. Wang et al. demonstrated that survivin expression could be used in grading the malignancy of osteosarcoma [51].

Dai et al. identified that the expression of survivin was clearly associated with response to chemotherapy in osteosarcoma patients, indicating survivin was a more valuable parameter [52]. Babaei et al. reported that the expression of survivin was limited to osteosarcoma cells and associated with high-grade malignancies [53]. Many studies have been also conducted on osteosarcoma in animals. In canines, survivin attenuation inhibited cell-cycle progression, increased apoptosis, mitotic arrest, and chemosensitivity, and works together with chemotherapy to significantly improve *in vivo* tumor control [54]. Survivin-directed therapies might be effective in treatment of canine osteosarcoma [55]. Survivin was also shown to be significantly associated with lung metastasis of osteosarcoma in an orthotopic mouse model [56].

Inhibition of survivin expression might provide new insights in exploring therapeutic methods. Studies have shown that antitumor activity was associated with significant inhibition of survivin expression in numerous tumors [57]. In human MG-63 osteosarcoma cells, antisense oligonucleotide targeting survivin could inhibit the proliferation and induce apoptosis of osteosarcoma, which might function as an effective strategy to improve therapeutic effect [58]. Survivin-specific siRNA, dramatically down-regulated by the transcription of the survivin gene, could effectively inhibit survivin expression and enhance drug sensitivity in patients with osteosarcoma [59]. Other genes may play a role in osteosarcoma through survivin. Survivin down-regulated by pSUPER-sh could markedly induce apoptosis, and may be a promising adjuvant in osteosarcoma chemotherapy [20].

Our meta-analysis has several limitations. Firstly, the populations of the included studies were all Chinese and our results may not be generalizable to other ethnic groups. Secondly, the cut-off points for survivin expression were not the same, which might influence the positivity rate. Thirdly, the number of included studies for some comparisons was small, which might affect our results. Lastly, other genes that may interact with survivin expression or be involved in the survivin-related pathways should be considered in the future.

Conclusions

Our results demonstrate that survivin expression is associated with Enneking clinical stage, Price's grade, metastasis and soft tissue invasion, 5-year overall survival, and postoperative recurrence in patients with osteosarcoma, indicating that survivin may be a useful therapeutic strategy for osteosarcoma. Further studies in different ethnic groups are needed.

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