Int J Clin Exp Med 2018;11(6):5469-5479
www.ijcem.com /ISSN:1940-5901/IJCEM0061423

Review Article

Correlation of ezrin expression level and clinical significance for patients with bone and soft tissue sarcomas: a meta-analysis

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Received May 29, 2017; Accepted March 13, 2018; Epub June 15, 2018; Published June 30, 2018

Abstract: Osteosarcoma, Ewing sarcoma, and chondrosarcoma are the most common malignancies of bone in the first 3 decades, which originates from primitive bone-forming mesenchymal cells. However, the prognostic value of Ezrin expression in osteosarcoma patients' survival or the clinical features remains controversial. In this regard, we conducted a meta-analysis to evaluate the correlation of Ezrin expression level and clinical significance for patients with bone and soft tissue sarcomas. Literature searches in PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBMdisc), WanFang Database were conducted from inception to January 2017 with no restriction to language. Methodological quality of the included studies was also assessed. Studies were pooled and summary hazard ratios (HRs) with corresponding confidence intervals (CIs) were calculated by using the STATA 12.0 software. A total of 19 clinical cohort studies with 1498 bone and soft tissue sarcomas patients were included for meta-analysis. The results of meta-analysis showed that high level of Ezrin expression was associated with poorer OS (HR=1.91, 95% CI: 1.72~2.12, P=0.001) and MFS (HR=1.63, 95% CI: 1.10~2.40, P=0.014). Subgroup analysis indicated that pooled HR estimate for overall survival was 1.75 (95% CI: 1.48-2.07, P=0.001) for patients with osteosarcoma, 1.92 (95% CI: 1.58-2.35, P=0.001) for patients with chondrosarcoma, 2.01 (95% CI: 1.64-2.45, P=0.001) for patients with synovial sarcoma, 2.21 (95% CI: 1.52-3.21, P=0.001) for patients with Ewing sarcoma, and 7.98 (95% CI: 1.79-35.39, P=0.006) for patients with malignant fibrous histiocytoma. However, there is no significant difference in EFS (HR=1.55, 95% CI: 0.59~4.07, P=0.374). Ezrin may be a novel biomarker in promoting tumor cell invasion and metastasis and with a great prognostic value for patients with bone and soft tissue sarcomas.

Keywords: Ezrin, bone tumor, osteosarcoma, Ewing sarcoma, overall survival, meta-analysis

Introduction

Osteosarcoma, Ewing sarcoma, and chondrosarcoma are the most common malignancies of bone in the first 3 decades, which originates from primitive bone-forming mesenchymal cells [1]. Osteosarcoma, comprising 2.4% of all malignant tumors, is the eighth most common type of childhood cancer, and mortality of which has been declining by 1.3% per year [2]. Furthermore, the incidence rates of osteosarcoma increase rapidly in adolescence (about 10~14 year old) and older adulthood (over 65 years old) [3]. In the past decades, the combination of multi-agent neoadjuvant chemotherapy has improved 5-year survival from 20% to 70% in patients without metastasis [4]. However, patients with metastatic disease or patients relapse with disseminated tumors usually have a poor prognosis and overall survival. To improve this situation, several attempts have been made to develop the novel methods for predicting and preventing metastasis, based on tumor metastasis-associated genes and proteins [5].

Ezrin, also identical to villin 2 or cytovillin, is a member of the Ezrin-Radixin-Moesin (ERM) family that acts as a membrane organizer and linker between the plasma membrane and cytoskeleton [6, 7]. It is involved in cell adhesion to the extra-cellular matrix and in cell-cell interaction, Rho mediated signal transduction pathway and the Akt mediated apoptotic pathway [8]. Present evidence suggested that Ezrin might play a vital role in human cancer. With a clinical research, a correlation between Ezrin expression and malignancy has been reported among

various human tumors, such as prostate cancer, colorectal cancer, melanoma and ovarian cancer [9-11]. However, the prognostic value of Ezrin expression in osteosarcoma patients' survival or the clinical features remains controversial. In this regard, we conducted a meta-analysis to evaluate the correlation of Ezrin expression level and clinical significance for patients with bone and soft tissue sarcomas.

Materials and methods

Literature search

Comprehensive electronic literature searches in PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBMdisc), WanFang Database were conducted from inception to January 2017 with no restriction to language. We used the following keywords and MeSH terms in conjunction with a highly sensitive search strategy: ("ezrin" or "villin 2" or "cytovillin") and ("osteosarcoma" or "chondrosarcoma" or "Ewing sarcoma" or "leiomyosarcoma" or "angiosarcoma" or "synovial sarcoma" or "malignant fibrous histiocytoma" or "liposarcoma" or "rhabdomyosarcoma"). A manual search based on references identified in the individual articles was also performed to find other potential studies.

Inclusion criteria and exclusion criteria

Eligible studies for this meta-analysis met the following criteria: (1) all patients met the diagnostic criteria for osteosarcoma, chondrosarcoma, Ewing sarcoma, leiomyosarcoma, angiosarcoma, synovial sarcoma, malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma; (2) ezrin expression evaluated in the primary bone and soft tissue sarcomas tissues; (3) the study focused on the relationship of ezrin expression with clinical outcome for patients with bone and soft tissue sarcomas; (3) the studies reporting at least one endpoints: overall survival (OS), event-free survival (EFS), metastasis-free survival (MFS). The following studies were excluded from the meta-analysis: (1) duplicate articles on the same patients; (2) the original articles which did not report the correlation of ezrin expression level and clinical significance for patients with bone and soft tissue sarcomas; (3) review articles, case reports, abstracts, editorials, letters and meta-analysis; (4) articles without sufficient data to analyze after contacting the authors of the study; (5) duplicate publications.

Data extraction

Two reviewers independently extracted relevant data from the selected studies by using a predesigned data form. Any disagreements were resolved by discussion. Data retrieved from each publication included: (1) basic characteristics of each study: the first author, year of publication, ethnicity, sample size, average of age, positive ratio of ezrin, type of tumor, median follow-up time, detection method for ezrin, cut-off value; (2) clinical outcomes: overall survival (OS), event-free survival (EFS), metastasis-free survival (MFS).

Quality assessment

Quality assessment for each eligible study was carried out by the same two reviewers who independently read and scored each publication, according to Newcastle-Ottawa Scale (NOS) [12]. When discrepancy occurred, a third author was referred. Studies with NOS≥6 were considered to be in high quality.

Statistical analysis

Statistical analyses were performed using the software STATA 12.0. Heterogeneity was evaluated with a χ^2-based Q-test: if the *p*-value was higher than 0.1 or I^2 was lower than 50%, it demonstrated that all included studies were lacking of heterogeneity, and the Mantel-Haenszel method (fixed effect model) was used to merge the studies. Otherwise the random effect model was adopted. Calculation for dichotomous variables was carried out using the odds ratio (OR) and their 95% confidence interval (95% CI) as the summary statistic. Two-sided $P<0.05$ was considered statistically significant. Sensitivity analysis was performed to evaluate the stability of the results. Publication bias was evaluated by using the Begg's test and Egger's test.

Results

Study selection and characteristics of included studies

Initially, with the highly sensitive search strategy, a total of 399 articles were identified. We reviewed the titles and abstracts of all articles

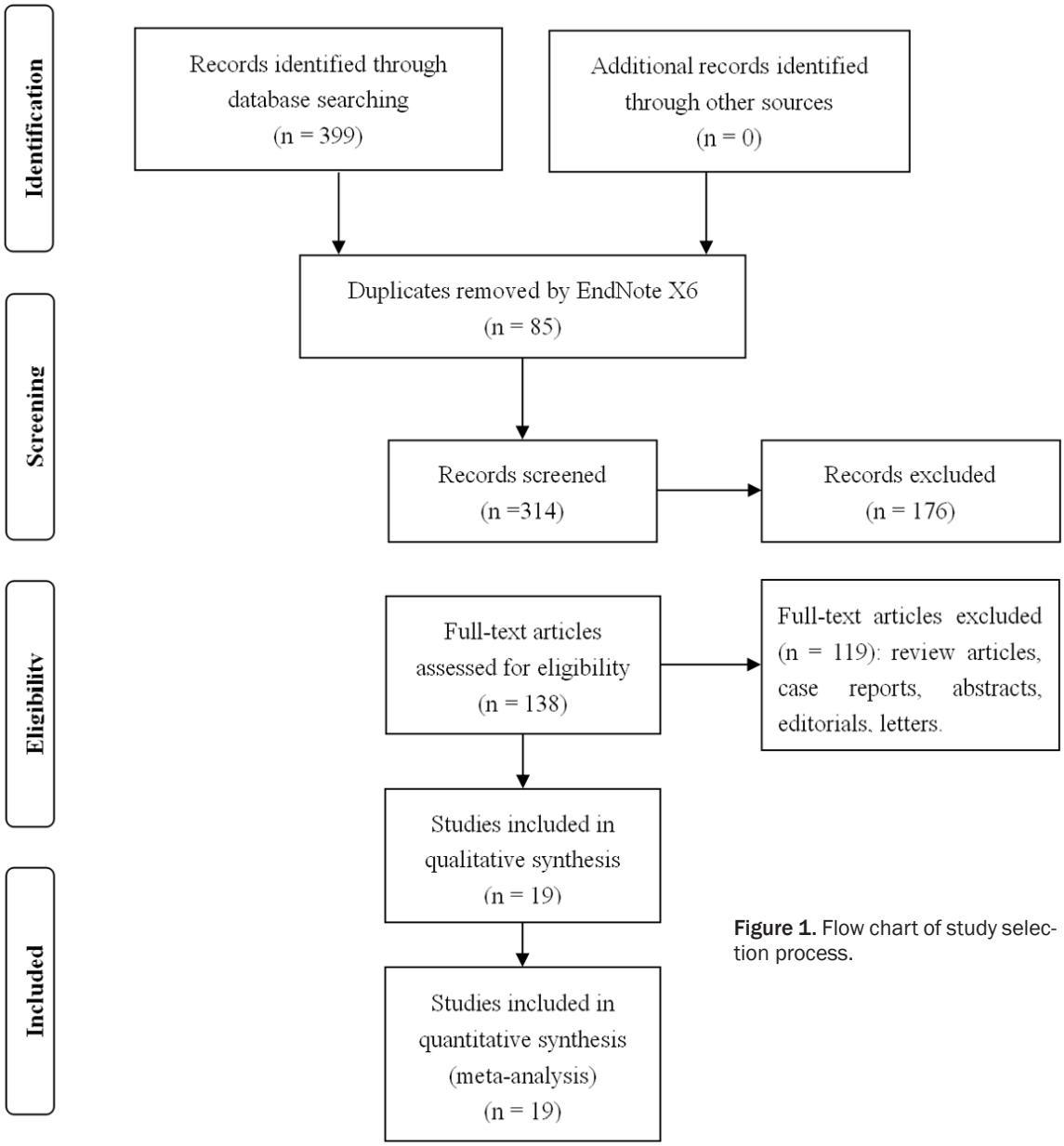

Figure 1. Flow chart of study selection process.

and excluded 176 articles; then 138 records were screened for eligibility and 119 full-text articles were excluded. Finally, 19 clinical cohort studies with 1498 bone and soft tissue sarcomas patients met our inclusion criteria for qualitative data analysis [13-31]. Detailed information about the flow chart of study selection process is reported in **Figure 1**.

Publication years of the eligible studies ranged from 2005 to 2017. Overall, there are 13 studies involving 1100 patients with osteosarcoma, 2 studies involving 132 patients with chondrosarcoma, 2 studies involving 125 patients with malignant fibrous histiocytoma, one study involving 53 patients with Ewing's sarcoma and one study involving 88 patients with synovial sarcoma. NOS scores were more than 6 in all studies (**Figure 2**). The detailed information of the included studies was summarized in **Table 1**.

Correlation between ezrin expression and overall survival for patients with bone and soft tissue sarcomas

Seventeen studies assessed the correlation of Ezrin expression with overall survival for pa-

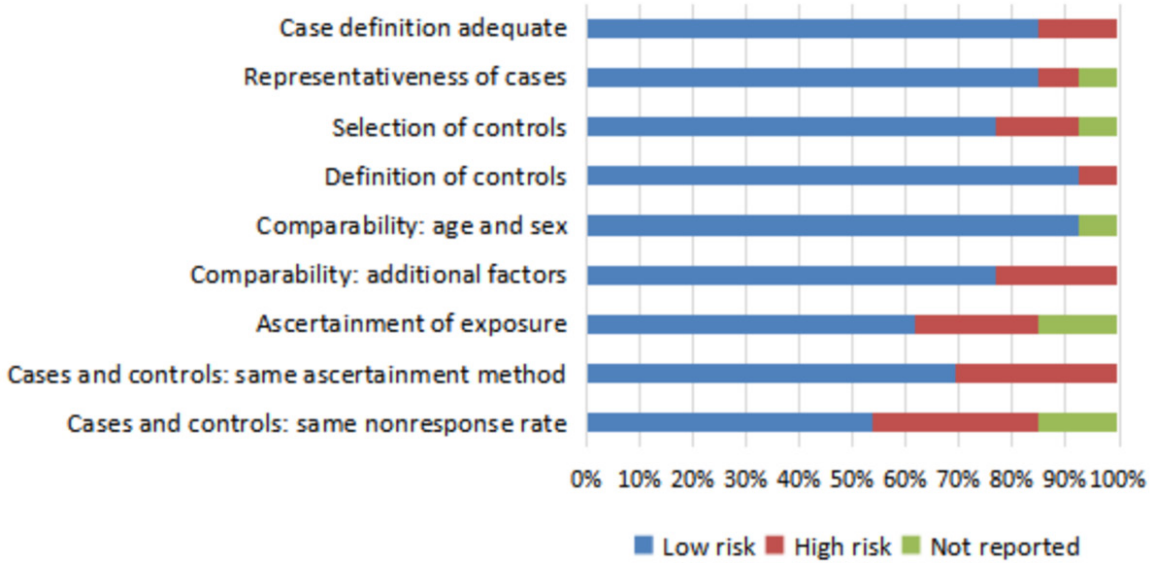

Figure 2. Quality assessment of included studies.

tients with bone and soft tissue sarcomas. The heterogeneity was not significant (I^2=42.5%, *P*=0.033). Under fixed-effect model, the result of meta-analysis showed that Ezrin expression was significantly associated with worse OS (HR=1.91, 95% CI: 1.72~2.12, *P*=0.001) (**Figure 3**).

We conducted subgroup analysis stratified by ethnicity, sample size, average of age, positive ratio of ezrin, tumor type, and NOS score. In the subgroup analysis stratified by the type of tumor, the pooled HR estimate for overall survival was 1.75 (95% CI: 1.48-2.07, P=0.001) for patients with osteosarcoma, 1.92 (95% CI: 1.58-2.35, P=0.001) for patients with chondrosarcoma, 2.01 (95% CI: 1.64-2.45, P=0.001) for patients with synovial sarcoma, 2.21 (95% CI: 1.52-3.21, P=0.001) for patients with Ewing sarcoma, and 7.98 (95% CI: 1.79-35.39, P=0.006) for patients with malignant fibrous histiocytoma (**Table 2**).

Correlation between ezrin expression and metastasis-free survival for patients with bone and soft tissue sarcomas

Six studies assessed the correlation of Ezrin expression with metastasis-free survival for patients with bone and soft tissue sarcomas. The heterogeneity was significant (I^2=62.5%, *P*=0.020). Under random-effect model, the result of meta-analysis showed that Ezrin expression was significantly associated with worse MFS (HR=1.63, 95% CI: 1.10~2.40, *P*=0.014) (**Figure 4**).

Correlation between ezrin expression and event-free survival for patients with bone and soft tissue sarcomas

Four studies assessed the correlation of Ezrin expression with event-free survival for patients with bone and soft tissue sarcomas. The heterogeneity was significant (I^2=89.2%, *P*=0.000). Under random-effect model, the result of meta-analysis showed that Ezrin expression was not significantly associated with EFS (HR=1.55, 95% CI: 0.59~4.07, *P*=0.374) (**Figure 5**).

Assessment of publication bias

Publication bias was assessed by Begg's funnel plot, in which log HRs were plotted against their corresponding standard errors (SEs). Visual evaluation of the Begg's funnel plots found no apparent asymmetry (**Figure 6**). Besides, Egger's test which provided statistic estimation did not find any publication bias (*P*=0.347), indicating that the publication bias was not significant among the included studies.

Discussion

Bone and soft tissue sarcomas are the third leading cause of tumor-related death in young adults and children [32]. For these patients,

Table 1. Characteristics of included studies

Study ID	Ethnicity	Sample of size	Average of age (years)	Positive ratio of Ezrin	Type of Tumor	Median follow-up time (months)	Detection Method for Ezrin	Cut-off value	NOS score
Weng et al. 2005 [13]	Switzerland	50	60	50.00%	Chondrosarcoma	90 (50~134)	IHC	≥1	6
Sala et al. 2007 [14]	French	37	15	62.00%	Osteosarcoma	4.5 (10~150)	IHC	>1	7
Kim et al. 2007 [15]	North Korea	64	19.4	51.60%	Osteosarcoma	78.2 (12~137)	IHC	>1	6
Kim et al. 2007 [16]	North Korea	47	61	56.00%	Malignant Fibrous Histiocytoma	50 (9~218)	IHC	>1	6
Shen et al. 2008 [17]	China	56	18	67.90%	Osteosarcoma	22.4 (8~58)	IHC	>1	6
Ferrai et al. 2008 [18]	Italy	95	16	80.00%	Osteosarcoma	47 (10~115)	IHC	>1	6
Kim et al. 2009 [19]	North Korea	70	15.7	55.70%	Osteosarcoma	59.9	IHC	>1	6
Yang et al. 2010 [20]	China	51	21.4	56.80%	Osteosarcoma	NR	IHC	>1	7
Boldrini et al. 2010 [21]	Brazil	34	15.9	76.50%	Osteosarcoma	NR	IHC	>1	7
Cristofano et al. 2010 [22]	Italy	50	NR	86.00%	Osteosarcoma	117.6 (12~216)	IHC	>1	7
Huang et al. 2010 [23]	China	78	61	49.00%	Malignant Fibrous Histiocytoma	53.7 (2~201)	IHC	>1	8
Wang et al. 2010 [24]	China	256	16	64.00%	Osteosarcoma	22 (5.5~28.1)	RT-PCR	NR	7
Carneior et al. 2011 [25]	Switzerland	82	66	68.00%	Chondrosarcoma	48 (12~228)	IHC	>1	8
Min et al. 2012 [26]	China	256	19	59.80%	Osteosarcoma	42 (3~88)	IHC	>1	7
Guellec et al. 2013 [27]	French	36	18	97.20%	Osteosarcoma	77 (52~101.2)	IHC	>1	8
Abdou et al. 2015 [28]	Egypt	57	21.9	82.20%	Osteosarcoma	6~156	IHC	>1	7
Palmerini et al. 2015 [29]	Italy	88	37	91.00%	Synovial Sarcoma	72 (12~360)	IHC	>1	8
Lugowska et al. 2016 [30]	Poland	38	6~23	46.00%	Osteosarcoma	75 (13~135)	IHC	>1	6
Cash et al. 2017 [31]	USA	53	25~75	72.00%	Ewing Sarcoma	NR	IHC	>1	8

IHC: immunohistochemistry; RT-PCR: Real-time PCR; NR: not reported.

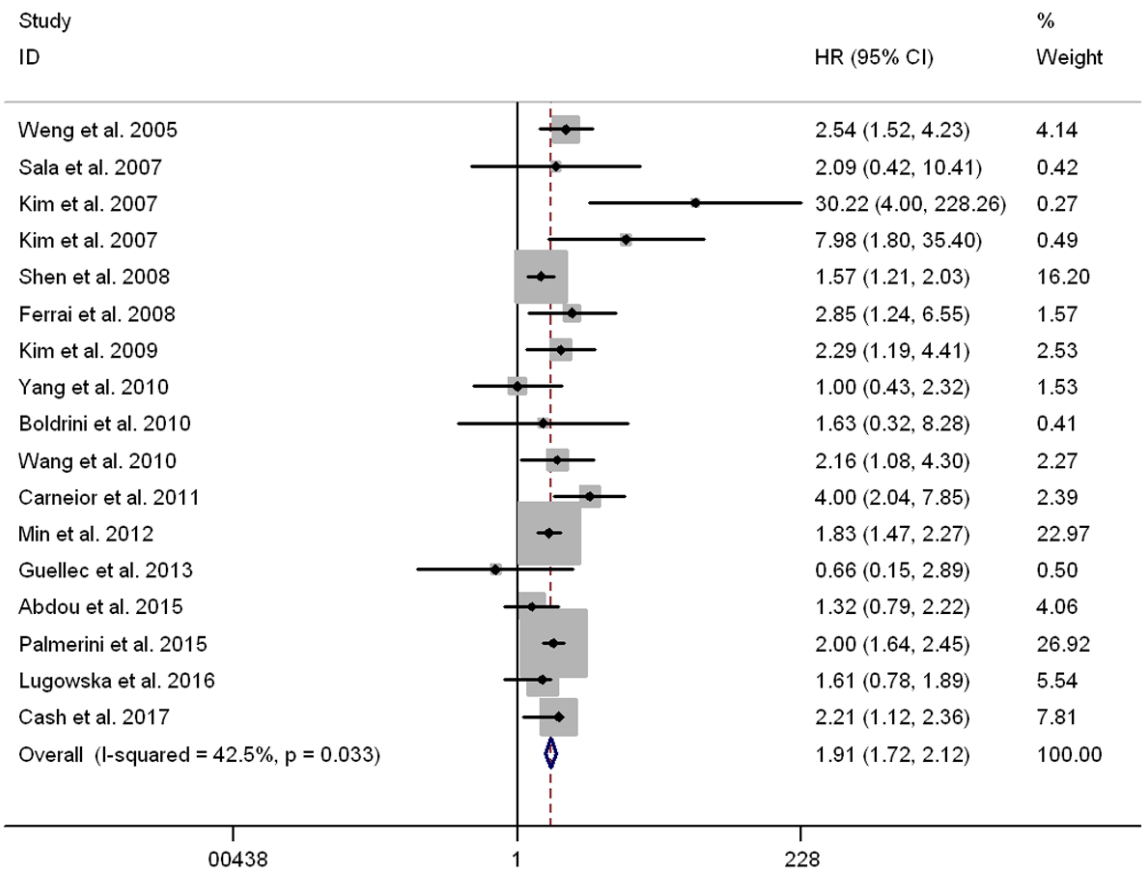

Figure 3. Forest plots of meta-analysis for the association between Ezrin expression and OS.

tumor metastasis is common and long-time survival is still poor [33]. Since metastatic sarcoma patients lose their surgical intervention opportunity, effective systematic therapies are important to improve life quality and prolong life [34]. Identification of prognostic biomarkers could help to discover new treatment targets and stratify patients for different treatments. Although have not applied to clinical treatment, several prognostic biomarkers of sarcoma have been discovered and may potentially contribute to the development of new therapy methods [35, 36].

Ezrin is encoded by Villin 2 gene, which identified as differently expressed between highly metastatic and non-highly metastatic osteosarcoma cell lines, using complementary DNA microarray [37]. As a member of the ERM family of proteins, Ezrin functions as a cross-linker between the actin cytoskeleton and the plasma membrane [38], which allows the cell to interact directly with its microenvironment and also plays a positive role in maintaining cell shape and polarity and facilitates membrane-trafficking pathways, cell signaling, cell migration, differentiation and growth regulation [39]. However, the occurrence, development, invasion and metastasis of malignant tumor are a process that was affected by multiple factors [40]. The variety biological function of Ezrin is related to biological characteristics of malignant tumor closely [41]. In the recent years, there has been mounting evidence that Ezrin expression enhancement than normal tissue in colorectal cancer [42], gastric cancer [43], bladder cancer [44], salivary gland adenoid cystic cancer [45] and others.

In the current meta-analysis, we aimed to investigate whether Ezrin expression affects the overall survival, event-free survival, metastasis-free survival for patients with bone and soft tissue sarcomas. The results of meta-analysis showed that high level of Ezrin expression was associated with poorer OS (HR=1.91, 95% CI: 1.72~2.12, P=0.001) and MFS (HR=1.63, 95% CI: 1.10~2.40, P=0.014). The subgroup analy-

Table 2. Subgroup-analysis of correlation between Ezrin expression and overall survival for patients with bone and soft tissue sarcomas

Subgroup		No. of studies	Meta-analysis		
			HR	95% CI	*p* value
Ethnicity	Caucasus	10	1.94	1.72-2.18	0.001
	Asian	7	1.83	1.48-2.26	0.001
Sample size	More than 50	12	1.95	1.74-2.18	0.001
	Less than 50	5	1.62	1.19-2.23	0.003
Average of age (years)	More than 50	5	2.03	1.72-2.41	0.001
	Less than 50	12	1.84	1.61-2.09	0.001
Positive ratio of Ezrin	More than 60%	10	1.89	1.69-2.12	0.001
	Less than 60%	7	1.99	1.52-2.60	0.001
Type of Tumor	Osteosarcoma	12	1.75	1.48-2.07	0.001
	Chondrosarcoma	2	1.92	1.58-2.35	0.001
	Synovial Sarcoma	1	2.01	1.64-2.45	0.001
	Ewing Sarcoma	1	2.21	1.52-3.21	0.001
	Malignant Fibrous Histiocytoma	1	7.98	1.79-35.39	0.006
NOS Score	More than 7	7	1.89	1.56-2.27	0.001
	Less than 7	10	1.91	1.72-2.12	0.001

NOS: Newcastle-Ottawa Scale.

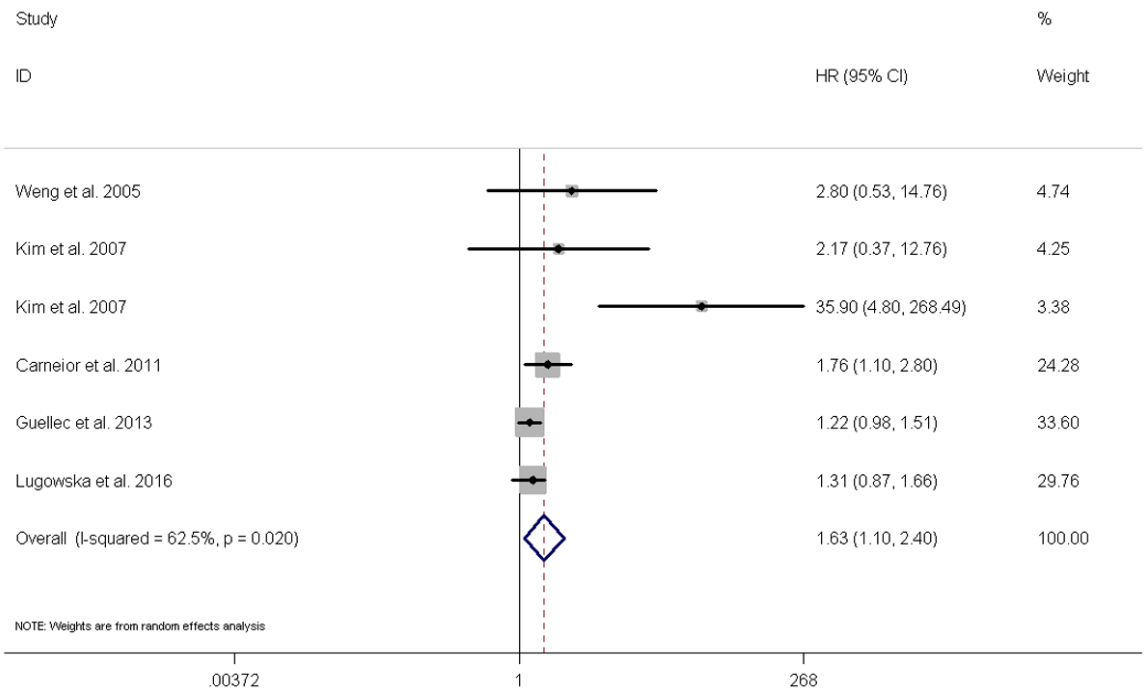

Figure 4. Forest plots of meta-analysis for the association between Ezrin expression and MFS.

sis indicated that pooled HR estimate for overall survival was 1.75 (95% CI: 1.48-2.07, *P*=0.001) for patients with osteosarcoma, 1.92 (95% CI: 1.58-2.35, *P*=0.001) for patients with chondrosarcoma, 2.01 (95% CI: 1.64-2.45, *P*=0.001) for patients with synovial sarcoma, 2.21 (95% CI: 1.52-3.21, *P*=0.001) for patients with Ewing sarcoma, and 7.98 (95% CI: 1.79-35.39, *P*=0.006) for patients with malignant fibrous histiocytoma. However, there is no sig-

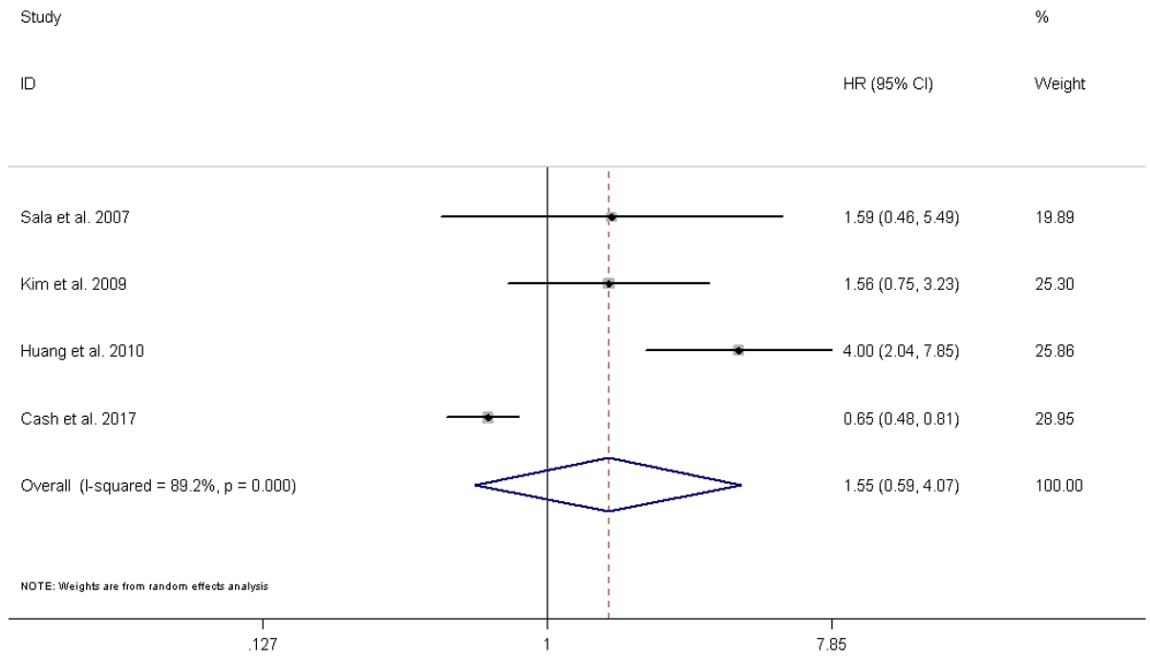

Figure 5. Forest plots of meta-analysis for the association between Ezrin expression and EFS.

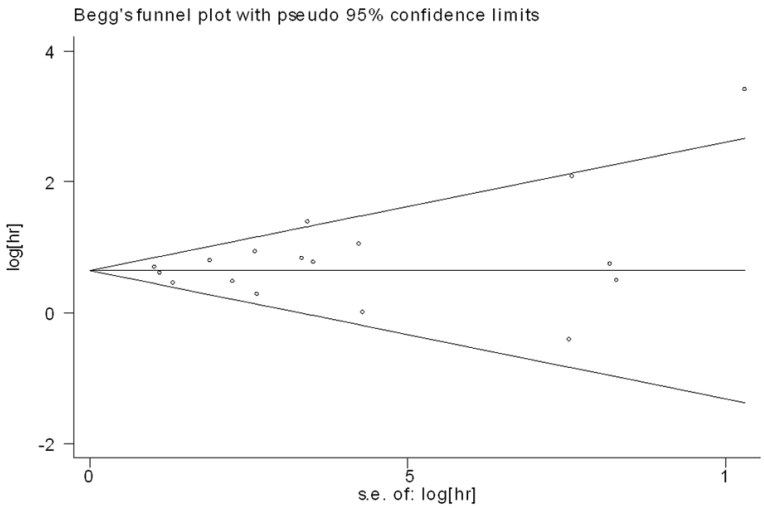

Figure 6. Begg's funnel plots for publication bias.

nificant difference in EFS (HR=1.55, 95% CI: 0.59~4.07, *P*=0.374). The results of our study may suggest that expression of Ezrin may be a novel biomarker in promoting tumor cell invasion and metastasis and with a great prognostic value for patients with bone and soft tissue sarcomas.

Nevertheless, the potential mechanisms by which the enhanced expression of Ezrin leads to an aggressive invasion and metastasis in the progression of bone and soft tissue sarcomas are still largely unknown [46]. It is established that Ezrin is both an important plasma membrane-cytoskeleton crosslinker and the binding partner of a plethora of molecules, and it is also responsible for the adhesion, invasion, and migration to cells or substrates during the multi-steps regulatory system [47]. Moreover, Ezrin also plays a critical role in signal transduction through the activation of small GTPase Ras [48]. In this regard, alternation in ezrin expression may in turn influence metastasis in osteosarcoma [49]. The results that our meta-analysis conducted may be explained by these points.

Meanwhile, it should be finally emphasized that there were some limitations in our meta-analysis: (1) the statistical heterogeneity of included studies existed in meta-analysis except overall survival analysis. The heterogeneity may be due to the different cut-off value, baseline characteristics of patients (such as age, race, tumor

stage, et al.), anti-bodies from different companies, and duration of follow-up. (2) part of HRs were obtained indirectly from the original papers, meaning that survival curves have been reconstructed to extract or calculate the HRs by authors; (3) the language of included studies was English, other types of languages were excluded; (4) several studies reported the original HR for EFS and MFS.

In conclusion, our study illustrated significant relationships of Ezrin expression with OS and MFS for patients with bone and soft tissue sarcomas. Thus, Ezrin expression could be a promising biomarker in predicting clinical outcome of patients with bone and soft tissue sarcomas. However, large-center studies with more comprehensive data are needed to strengthen our conclusions.

Disclosure of conflict of interest

None.

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