



## Review Article

## Study on the relationship between livin expression and osteosarcoma

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## ABSTRACT

**Objective:** The aim of this meta-analysis was to analysis the expression of livin in human osteosarcoma.**Methods:** We searched the Pubmed, Science Direct, Embase and Web of Science, CNKI, Wanfang and VIP for relevant original studies. Statistical analysis was performed by Stata 11.0 software.**Results:** Our study indicated that livin expressed in the osteosarcoma tissue was significantly higher than the control group (OR = 18.814, P c = 0.000, 95% CI: 10.973–32.257), and the positive expression of livin was correlated with the size of osteosarcoma tumor and Enncking staging (OR = 4.832, 95% CI: 2.198–10.621; OR = 4.851, 95% CI: 3.053–7.709, respectively).**Conclusion:** Livin was highly expressed in osteosarcoma, and osteosarcoma Enncking staging and tumor size were positively correlated, both may be involved in the occurrence and development of osteosarcoma, and be closely related to the prognosis of osteosarcoma patients.

## 1. Introduction

Osteosarcoma is an original malignant bone tumor and that is common in bone tumors, which accounts for 4–5 cases per million people per year [1]. The incidence of osteosarcoma is mainly for children, adolescents and young people [2,3]. In recent years, the incidence has been increasing year by year [4], which has a serious impact on social stability and the health of children, adolescents and young people [5].

The study found that the occurrence and development of osteosarcoma was closed with the abnormal apoptosis of cells [6], while the apoptosis of cells was mainly associated with the inhibitor of apoptosis protein (IAP). IAP is a class of important anti-apoptotic factors. A common feature of this family structure is that N-terminal contains one or more (currently found up to 3) tandem baculovirus IAP repeated sequence and C-terminal with or without a ring finger structure. Apoptosis is a common feature of tumor cells, so IAP family as a regulator of apoptosis is getting more and more attention. The human IAP family has now been found to have eight members, livin is a new member of the IAP family that contains a BIR domain and a RING finger domain. Livin blocks many pathways-induced apoptosis by inhibiting Caspase 3, 7 and 9. Livin is not expressed or lowly expressed in most normal adult tissues, but highly expressed in many human malignant tumor cell lines and most melanoma cell lines, suggesting that this factor may play an important role in tumorigenesis and development

[7]. Recent studies also found that livin was overexpressed in gastrointestinal tumors such as gastric cancer, intestinal cancer, pancreatic cancer and liver cancer. Yagihashi et al. showed that high expression of livin in patients with gastrointestinal cancer, and with the occurrence of human gastrointestinal cancer had a certain relationship [8]. Hofmann et al. displayed livin played an anti-apoptotic role in the pathogenesis of non-small cell lung cancer [9].

It had been reported that livin was overexpressed in various human malignancies, including osteosarcoma, and could inhibit apoptosis induced by many apoptotic stimulators [6]. Many studies had shown that livin protein level in osteosarcoma tissue was significantly higher than those in the control group [6,7,10–17]. Li et al. also showed that livin was involved in the tumorigenesis of human osteosarcoma [18].

The above results suggested that the high expression of livin may be closely related to the formation of certain types of human tumors. Further study of livin is of great significance for exploring the occurrence, progression, treatment and prevention of tumors. Osteosarcoma is a malignant tumor that seriously threatens the human and its treatment is also a big problem. At present, the study of livin expression in osteosarcoma has rarely been reported in China and abroad. Our research may provide a basis for further understanding of livin, revealing the possible biological mechanism of osteosarcoma and finding effective targets for clinical biomolecular drugs, which will bring new directions for the prevention and treatment of osteosarcoma.

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## 2. Materials and methods

### 2.1. Search strategy

We searched Pubmed, Science Direct, Embase and Web of Science together with three Chinese databases CNKI, Wanfang Data and VIP for relevant papers published before December 1, 2017. The search terms were used as follows: 'livin [MeSH]' and 'osteosarcoma [MeSH]'. References cited in all selected articles were manually searched for additional articles. Except for this, we sent e-mails to the authors to obtain data that did not show the results of the control group.

### 2.2. Selection criteria

All the included studies with the following characteristics: (1) Original research; (2) designed as case-control studies which evaluated the association between livin and osteosarcoma; (3) provided sufficient information to estimate odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs); (4) all cases should meet the diagnostic criteria of osteosarcoma (The patient was diagnosed by pathology); (5) the study was published in English or Chinese. In addition, exclusion criteria included: (1) drug intervention studies; (2) no control group study results data; (3) repeated studies; (4) studies about livin gene.

### 2.3. Data extraction

Two review authors (Du and Wang) extracted data from eligible studies independently. Discontents between reviewers were resolved by a third investigator (Zhao) to reach consensus. And the following items were recorded from each included studies: first author (year), sample size, detection method, source of controls, case collection time, average patient age, ethnicity.

### 2.4. Statistical analysis

All statistical data were performed with Stata11.0 software. The pooled OR with corresponding 95% confidence interval (CI) was designed to measure the strength of association between livin and osteosarcoma patients. We used the Higgins's ( $I^2$ ) test to calculate the heterogeneity. If the heterogeneity was statistically significant ( $I^2 > 50\%$  or the  $p$ -value of heterogeneity  $< 0.05$ ), the random effect-model was employed to combine the data. If not, the fixed-model was used. Publication bias was detected by the method of Egger's test. And sensitivity analysis was used to evaluate the stability of the result by excluding one study at a time.

## 3. Results

### 3.1. Search results

In Fig. 1, 107 articles were identified for initial review based on search criteria. 51 manuscripts were excluded because of irrelevant studies. In the remaining 56 articles, of which 22 were not clinical studies and eight were not case-control studies. After reading the full article, 16 studies were excluded. Finally, we adopted ten manuscripts published from 2008 to 2016 in our meta-analysis.

### 3.2. Study characteristics

In Table 1, there were ten researches containing 482 osteosarcoma patients and 211 controls. All of the eligible articles, the ethnicity involved was Asian only. Four immunohistochemistry detection methods were employed in the included studies such as Max Vision TM/AP, streptavidin peroxidase (SP), Western Blot and strept avidin-biotin complex (SABC). The control group included two categories: osteochondroma tissue and normal bone tissue. Among the articles, one

study lacked the case collection time and another manuscript was not provided the average patient age.

### 3.3. Association between livin and osteosarcoma

Our meta-analysis showed that livin expressed in the osteosarcoma tissue was significantly higher than the control group (OR = 18.814,  $P_c = 0.000$ , 95% CI: 10.973–32.257). Furthermore, the heterogeneity was very small ( $I^2 = 0.0\%$ ,  $p_h = 0.800$ ) (Fig. 2).

### 3.4. Correlation between livin expression and tumor clinicopathological features

In Table 2, eight studies and three studies were respectively assessed the correlation of livin expression with Enncking staging and tumor diameter in osteosarcoma patients. As for Enncking staging, the pooled OR of our study was 4.851 (95% CI: 3.053–7.709), indicating that livin expression was significantly associated with higher Enncking staging (IIB ~ III) (Fig. 4). For the tumor diameter, livin expression was significantly associated with larger tumor diameter (OR = 4.832, 95% CI: 2.198–10.621) (Fig. 5).

However, no statistically significant association was found in the analysis of gender, age, tumor site and pathological classification of the patients ( $P > 0.05$ ).

### 3.5. Sensitivity analysis

We performed a sensitivity analysis to examine the effect of each study on the pooled OR value and the result showed that none of the articles affected the result of our study.

### 3.6. Publication bias

Since the funnel plot was not symmetrical, it demonstrated that publication bias existed (Fig. 3).

## 4. Discussion

Our study demonstrated that livin significantly increased in osteosarcoma tissue, and osteosarcoma Enncking clinical stage and tumor size were positively correlated with the expression of livin. The heterogeneity was very low ( $I^2 = 0.0\%$ ,  $P_h = 0.800$ ), which displayed the differences between the studies we adopted were small. In the sensitivity analysis, the pooled OR and 95% CI direction of the study remained stable, indicating the results were consistent. What's more, when we analyzed the result by using the Z test ( $z = 10.67$ ,  $P = 0.000$ ), it remained showed statistical significance.

The diagnosis and treatment of osteosarcoma have always been the world problems [19]. Early diagnosis of osteosarcoma is difficult and its metastasis occurs early, which is easy to miss the best timing of surgery. At present, the main treatment of osteosarcoma is mainly surgical resection, supplemented by radiotherapy and chemotherapy comprehensive treatment. However, it is easy to recur after operation and the five-year survival rate is low. And the radiotherapy and chemotherapy are prone to tolerance and resistance, and the side effects are extremely great. Therefore, in order to study how to completely kill tumor cells and control the proliferation of tumor cells, biological treatments such as tumor molecules and genes are beginning to be emphasized. Immune targeting therapy of specific antigens in osteosarcoma tissue can identify both alien and non-cancerous cells and specifically kill tumor cells throughout the patient's body, thereby avoiding the side effects of radiotherapy and chemotherapy [12]. An important pathogenesis of osteosarcoma is the abnormality of the apoptosis system [10]. Therefore, finding the target of the apoptosis-related gene as the target of future osteosarcoma therapy is the key to defeat and cure osteosarcoma [10].

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