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Introduction

Osteosarcoma is the most common primary bone tumor in children and young adults.¹ The incidence of osteosarcoma in the general population is two to three cases per million per year, but in adolescence, the annual incidence is higher and peaks at eight to eleven cases per million per year at 15–19 years of age.² It is characterized by the proliferation of malignant mesenchymal cells that form osteoid bone.³,⁴ The tumor occurs predominantly in the metaphysis (the sites of bone growth), presumably because proliferation makes the osteoblastic cells in this region acquire mutations that could lead to cell transformation.⁵,⁶ In all, 10%–15% of patients with newly diagnosed osteosarcoma have detectable metastases at diagnosis, of which >90% occur in the lungs.⁷,⁸ Treatment of the disease was mainly limb amputation, and the survival rate was 10%–20% before 1970s when chemotherapy was not included as part of therapeutic protocols.⁹,¹⁰ With the introduction of multidrug chemotherapy and advanced surgery, the 5-year survival rate has significantly improved to 60%–80%.¹⁰–¹³ However, the treatment of osteosarcoma is still unsatisfactory for the risk of local relapse and the development of metastasis.¹²,¹⁴ For these patients, they have <20% chance of long-term survival, despite aggressive therapies that have
largely unchanged during the past 30 years.\textsuperscript{13} To improve
the clinical outcomes for patients with poor prognosis, it is
Crucial to identify novel biomarkers for prognostic assess-
ment and therapeutic targets to osteosarcoma.

Hypoxia is a key element that plays a critical role in
the development and progression of tumors.\textsuperscript{16,17} Hypoxia-
inducible factor-1 (HIF-1), a major transcription factor that
mediates adaptive responses to low oxygen tension, is a het-
erodimeric protein consisting of the following two subunits:
HIF-1\textsubscript{α} and HIF-1\textsubscript{β}.\textsuperscript{18} HIF-1\textsubscript{β} is constitutively expressed,
while HIF-1\textsubscript{α} is regulated by oxygen levels that determine
HIF-1 activity.\textsuperscript{19,20} HIF-1\textsubscript{α} is a hallmark of tumor hypoxia,
which is widely expressed in solid tumors. The HIF-1\textsubscript{α} expres-
sion has been noted in many different types of malign-
nancies, including carcinoma of lung,\textsuperscript{21} pancreas,\textsuperscript{22} liver,\textsuperscript{23}
breast,\textsuperscript{24} esophagus,\textsuperscript{25} colon,\textsuperscript{26} and ovary,\textsuperscript{27} and has been
associated with adverse clinical outcomes. HIF-1\textsubscript{α} is also
reported to be related to poor prognosis in osteosarcoma, but
the results of the existing literature are inconsistent or even
conflicting.\textsuperscript{28–36} Therefore, we conducted a meta-analysis
of these studies to evaluate the relation of HIF-1\textsubscript{α} protein
expression with clinicopathological factors and prognosis of
osteosarcoma.

Methods

Search strategy and selection criteria

The electronic databases of PubMed, Embase, and Web of
Science were searched for studies that investigated the prog-
nostic significance of HIF-1\textsubscript{α} in osteosarcoma to be included
in the present meta-analysis. The search ended on August 1,
2015, and no lower date limit was applied. The search terms
used were as follows: “osteosarcoma” or “bone sarcoma”
or “osteogenic sarcoma” and “HIF-1\textsubscript{α}” or “HIF-1 alpha”
or “hypoxia-inducible factor-1α” or “hypoxia-inducible
factor-1α”. A comprehensive search of reference lists of
all review articles and selected papers was performed to
identify additional reports.

Two independent reviewers (H-Y Ren and T Xie) assessed
the eligibility of studies by reviewing titles and abstracts
identified by the search. Differences were resolved by dis-
cussion with a third author (H-Y Li). The inclusion criteria
for primary studies were as follows: 1) HIF-1\textsubscript{α} expression
evaluated in the primary osteosarcoma tissues; 2) HIF-1\textsubscript{α} expression
detected by IHC (immunohistochemistry); 3) relationship demonstrated between HIF-1\textsubscript{α} expression and
osteosarcoma clinicopathological parameters or prognosis;
and 4) articles published as a full paper in English. The
exclusion criteria were as follows: 1) duplicate studies on
the same patients; 2) studies written in non-English; 3) case
reports, editorials, letters, reviews, abstracts, animal, or cell
studies; 4) not possible to extract the required data.

Data extraction and study assessment

Two investigators (H-Y Ren and T Xie) independently
extracted data from eligible studies, disagreements were
resolved by discussion with a third author (H-Y Li). The
following information was extracted: name of first author,
year of publication, country, sample size, age, sex, pathologic
grade, tumor stage, metastasis, tumor size, chemotherapy
response, tumor site, histological type, microvessel density
(MVD), and hazard ratio (HR) estimation. Methodologi-
ical quality of the included studies was assessed with the
Newcastle–Ottawa scale.\textsuperscript{37}

Statistical analysis

For each study with assessment of overall survival (OS) or
disease-free survival (DFS), the HRs and corresponding
95% confidence intervals (CIs) were extracted if the author
had provided the data. Otherwise, these data were calculated
according to the methods described by Parmar et al.\textsuperscript{38} Odds
ratios (ORs) were estimated for clinicopathological variables
(age, >20 vs \(\leq\)20 years old; sex, male vs female; tumor
stages, high vs low; metastasis, yes vs no; chemotherapy
response, poor vs good; tumor size, large vs small; tumor
site at tibia or femur vs elsewhere; and histopathology,
osteoblastic type vs other types). Continuous variables were
analyzed by the standard mean difference (SMD). Hetero-
geneity among studies was measured by \(Q\)-test and \(F\)-test
(\(P\)-value <0.10 was considered statistically significant for heterogeneity).\textsuperscript{39,40} The fixed effects model was used to com-
bine the individual HR or OR estimates when no significant
heterogeneity was identified among studies, otherwise, the
random effects model was used.\textsuperscript{41} Statistical significance was
defined as a \(P\)-value <0.05. Publication bias and sensitivity
analysis were not assessed for the primary outcome because
limited studies were included in each analysis. All statistical
analyses were conducted using software from the Cochrane
Collaboration (RevMan Version 5.0; Nordic Cochrane
Centre, Copenhagen, Denmark).

Results

Study selection

We initially retrieved 263 unique citations from PubMed,
Embase, and Web of Science after excluding duplicates
until August 1, 2015. Of these, the majority were excluded
after the first screening based on abstracts or titles because
they were reviews, case reports, letters, editorial articles, or not relevant to the protein expression of HIF-1α in osteosarcoma. After examining the remaining eleven articles, one was excluded due to insufficient data to be extracted, and one was excluded as it was the protein HIF-1 rather than HIF-1α analyzed in the study. Finally, nine studies were included in this meta-analysis. Figure 1 shows the process of the study selection. The main characteristics of the eligible studies are shown in Table 1. The list of records identified by database searching and the studies included in the meta-analysis are provided in the Supplementary materials.

Association of HIF-1α protein expression with survival outcomes

Four studies were included to analyse the association of HIF-1α expression with survival. Two studies reported the association on OS and three on DFS. When these studies were summarized quantificationally, we found that the pooled HR on OS was 3.0 (95% CI: 1.46–6.15) with no heterogeneity ($I^2=0\%$, $P=0.48$) (Figure 2A) and HR on DFS was 2.23 (95% CI: 1.26–3.92) with no heterogeneity ($I^2=0\%$, $P=0.45$) (Figure 2B). The results indicate that HIF-1α expression is associated with a poor prognosis in osteosarcoma.

Association of HIF-1α protein expression with clinicopathological factors

Based on the available data in the included studies, we analyzed the relationship of HIF-1α expression with nine clinicopathological factors of osteosarcoma (Table 2). Of these, four factors were found to be significantly related to HIF-1α expression: ORs were 21.33 (95% CI: 4.60–98.88) for pathologic grade (high vs low) (Figure 3A), 10.29 (95% CI: 3.55–29.82) for tumor stage (high vs low) (Figure 3B), 9.68 (95% CI: 1.87–50.18) for chemotherapy response (poor vs good) (Figure 3C), and 5.06 (95% CI: 2.87–8.92) for metastasis (yes vs no) (Figure 3D), respectively. However, no statistically significant relationship with HIF-1α expression was found.

Figure 1 Flow chart of study selection.
Table 1 Characteristics of studies included in this meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>HIF-1α expression</th>
<th>Sample size</th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Pathologic grade (high/low)</th>
<th>Tumor stage (high/low)</th>
<th>Metastasis (yes/no)</th>
<th>Tumor size (large/small)</th>
<th>Chemotherapy response (necrosis $&lt;90%$/$\geq90%$)</th>
<th>Tumor site (tibia or femur/elsewhere)</th>
<th>Histopathology (osteoblastic/others)</th>
<th>MVD (mean ± SD)</th>
<th>Survival</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al</td>
<td>PR China</td>
<td>Positive</td>
<td>17</td>
<td>11/6</td>
<td>11/6</td>
<td>14/3(^\text{a})</td>
<td>1/4</td>
<td>12/7(^\text{b})</td>
<td>17/2</td>
<td>10/7</td>
<td>–</td>
<td>28.29±3.17</td>
<td>OS/DFS 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>et al(^\text{28})</td>
<td></td>
<td>Negative</td>
<td>22</td>
<td>17/5</td>
<td>11/11</td>
<td>10/12(^\text{b})</td>
<td>1/1</td>
<td>11/9(^\text{b})</td>
<td>5/15</td>
<td>17/5</td>
<td>–</td>
<td>21.06±2.64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen et al</td>
<td>PR China</td>
<td>Positive</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>14/3(^\text{b})</td>
<td>14/3(^\text{b})</td>
<td>6/11</td>
<td>14/3(^\text{b})</td>
<td>–</td>
<td>–</td>
<td>45.96±5.52</td>
<td>– 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>et al(^\text{29})</td>
<td></td>
<td>Negative</td>
<td>8</td>
<td>–</td>
<td>2/6</td>
<td>2/6(^\text{b})</td>
<td>0/8</td>
<td>2/6(^\text{b})</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>– 7</td>
<td></td>
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<tr>
<td>Mizobuchi USA</td>
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<td>18</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11/7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>– 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>et al(^\text{30})</td>
<td></td>
<td>Negative</td>
<td>30</td>
<td>–</td>
<td>–</td>
<td>11/7</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>– 1</td>
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</tr>
<tr>
<td>Zeng et al</td>
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<td>25</td>
<td>18/7</td>
<td>14/11</td>
<td>–</td>
<td>–</td>
<td>14/11(^\text{b})</td>
<td>–</td>
<td>18/7</td>
<td>16/8</td>
<td>50.57±7.12</td>
<td>OS 6</td>
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<tr>
<td>Chen et al</td>
<td>PR China</td>
<td>Positive</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>17/0(^\text{b})</td>
<td>17/0(^\text{b})</td>
<td>10/7</td>
<td>–</td>
<td>17/0(^\text{b})</td>
<td>17/0(^\text{b})</td>
<td>28.91±4.10</td>
<td>– DFS 7</td>
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<tr>
<td>et al(^\text{32})</td>
<td></td>
<td>Negative</td>
<td>32</td>
<td>–</td>
<td>–</td>
<td>21/11(^\text{b})</td>
<td>9/23</td>
<td>–</td>
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<tr>
<td>El Naggar Canada</td>
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<td>12/1</td>
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<td>–</td>
<td>– – 6</td>
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</tr>
<tr>
<td>et al(^\text{33})</td>
<td></td>
<td>Negative</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>3/9</td>
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<td>–</td>
<td>–</td>
<td>– – 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo et al</td>
<td>PR China</td>
<td>Positive</td>
<td>78</td>
<td>65/13</td>
<td>46/32</td>
<td>19/59(^a)</td>
<td>40/38</td>
<td>38/41(^a)</td>
<td>–</td>
<td>65/13</td>
<td>55/23</td>
<td>–</td>
<td>– 8</td>
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<td></td>
</tr>
<tr>
<td>et al(^\text{34})</td>
<td></td>
<td>Negative</td>
<td>20</td>
<td>9/11</td>
<td>13/7</td>
<td>0/20(^b)</td>
<td>1/19</td>
<td>17/2(^b)</td>
<td>–</td>
<td>2/18</td>
<td>15/5</td>
<td>–</td>
<td>– 8</td>
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<tr>
<td>Guan et al</td>
<td>PR China</td>
<td>Positive</td>
<td>34</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>16/18</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>– 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>et al(^\text{35})</td>
<td></td>
<td>Negative</td>
<td>73</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>15/58</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>– 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu et al(^\text{36})</td>
<td>PR China</td>
<td>Positive</td>
<td>29</td>
<td>–</td>
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<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>– DFS 6</td>
<td></td>
<td></td>
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</table>

Notes: \(^\text{a}\)Enneking III+ IIIB vs IIIA. \(^\text{b}\)Tumor volume $>50$ cm\(^3\) vs $\leq50$ cm\(^3\). \(^\text{c}\)Each "--" in the table means data not available. \(^\text{d}\)Enneking II+ III vs I. \(^\text{e}\)Tumor mass diameter $\geq5$ cm vs $<5$ cm. AJCC III+ IIIB vs IIIA. \(^\text{f}\)AJCC IVA vs II+ III.

Abbreviations: HIF-1α, hypoxia-inducible factor-1α; M, male; F, female; MVD, microvessel density; AJCC, American Joint Committee on Cancer; OS, overall survival; DFS, disease-free survival; SD, Standard Deviation.
among other five factors: ORs were 0.66 (95% CI: 0.15–2.87) for age (≤20 years vs >20 years) (Figure 4A), 0.88 (95% CI: 0.44–1.74) for sex (male vs female) (Figure 4B), 1.12 (95% CI: 0.22–5.76) for tumor size (large vs small) (Figure 4C), 2.02 (95% CI: 0.10–39.71) for tumor site (tibia or femur vs other sites) (Figure 4D), and 0.70 (95% CI: 0.28–1.73) for histopathology (osteoblastic vs other types) (Figure 4E).

### Association of HIF-1α protein expression with MVD

Three studies with 109 patients investigated the relationship between HIF-1α expression and MVD. The HIF-1α-positive expression group showed a significantly greater number of vessels than the HIF-1α-negative group (SMD =2.83, 95% CI: 2.28–3.39, P<0.00001). A fixed effects model was used because no heterogeneity was noted (P=0.2, F=38%) (Figure 5). It is demonstrated that overexpression of HIF-1α was significantly correlated with greater MVD.

### Discussion

In solid tumors, cells are commonly in a hypoxic state. The most important mediator identified to date of the cell’s response to hypoxia is the HIF-1 transcription factor. The activity of HIF-1 in tumors depends on the availability of the HIF-1α subunit, the levels of which increase under intratumoral hypoxic conditions and through the activation of oncogenes and/or inactivation of tumor suppressor genes. HIF-1α forms a heterodimer with HIF-1β. The dimer binds to highly conserved hypoxia-response elements in the promoter of target genes and activates their expressions to mediate acute and chronic adaptation to oxygen deficiency, including erythropoiesis, glycolysis, angiogenesis, inhibition of apoptosis, inhibition of cell differentiation, and promotion of cell invasion.

Osteosarcoma is a solid malignant tumor characterized by rapid growth and a high rate of metastasis. The hypoxic microenvironment that accompanies growth of the tumor mass would lead to increased expression of HIF-1α. A number of studies have investigated the role of HIF-1α expression in patients with osteosarcoma but have yielded inconsistent and inconclusive results. Therefore, we performed a meta-analysis of the published studies to derive an overall pooled estimation of the relationship between HIF-1α expression and prognosis. This study summarized nine articles, including 486 cases, and showed that overexpression of HIF-1α was associated with lower survival rate, higher MVD, metastasis, higher pathologic grade, tumor stage, and poor chemotherapy response in osteosarcoma.

Among the included studies, positive expression rate of HIF-1α had been reported in 31.78%–79.59% of osteosarcoma patients with mean rate of 52.0%. In agreement with other cancers, overexpression of HIF-1α in osteosarcoma correlates with vascular endothelial growth factor and apurinic/apyrimidinic endonuclease 1 expressions, which are responsible for angiogenesis. These results exhibited that significantly higher MVD appeared in the tumor tissue. Greater new blood vessels would increase tumor oxygenation, accelerate tumor growth as well as promote tumor invasion and migration to regional or distant sites, resulting in metastasis and higher...
Table 2 Quantitative analyses of HIF-1α expression and clinicopathological variables of osteosarcoma

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>Test of association</th>
<th>Test of heterogeneity</th>
<th>Meta-analysis model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (≤20 vs &gt;20)</td>
<td>3</td>
<td>182</td>
<td>OR (95% CI)</td>
<td>Z-test</td>
<td>P-value</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>3</td>
<td>182</td>
<td>0.66 (0.15–2.87)</td>
<td>0.56</td>
<td>0.58</td>
</tr>
<tr>
<td>Metastasis (yes vs no)</td>
<td>5</td>
<td>327</td>
<td>0.88 (0.44–1.74)</td>
<td>0.38</td>
<td>0.71</td>
</tr>
<tr>
<td>Pathologic grade (high vs low)</td>
<td>2</td>
<td>50</td>
<td>21.33 (4.60–98.88)</td>
<td>3.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumor stage (high vs low)</td>
<td>4</td>
<td>211</td>
<td>10.29 (3.55–29.82)</td>
<td>4.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Enneking III + IIIB vs IIA</td>
<td>1</td>
<td>39</td>
<td>5.60 (1.25–25.17)</td>
<td>2.25</td>
<td>0.02</td>
</tr>
<tr>
<td>Enneking II + III vs I</td>
<td>1</td>
<td>25</td>
<td>14.00 (1.84–106.46)</td>
<td>2.55</td>
<td>0.01</td>
</tr>
<tr>
<td>AJCC III + IIIB vs II A</td>
<td>1</td>
<td>49</td>
<td>18.72 (1.03–340.54)</td>
<td>1.98</td>
<td>0.05</td>
</tr>
<tr>
<td>AJCC IVA vs II + III</td>
<td>1</td>
<td>98</td>
<td>13.44 (0.78–232.68)</td>
<td>1.79</td>
<td>0.07</td>
</tr>
<tr>
<td>Chemotherapy response (necrosis &lt;90% vs ≥90%)</td>
<td>2</td>
<td>88</td>
<td>9.68 (1.87–50.18)</td>
<td>2.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Tumor size (large vs small)</td>
<td>4</td>
<td>207</td>
<td>1.12 (0.22–5.76)</td>
<td>0.14</td>
<td>0.89</td>
</tr>
<tr>
<td>&gt;50 cm³ vs ≤50 cm³</td>
<td>3</td>
<td>182</td>
<td>0.58 (0.13–2.54)</td>
<td>0.73</td>
<td>0.47</td>
</tr>
<tr>
<td>≤5 cm³ vs &lt;5 cm³</td>
<td>1</td>
<td>25</td>
<td>14.00 (1.84–106.46)</td>
<td>2.55</td>
<td>0.01</td>
</tr>
<tr>
<td>Tumor site (tibia or femur vs elsewhere)</td>
<td>3</td>
<td>182</td>
<td>2.02 (0.10–39.71)</td>
<td>0.64</td>
<td>0.46</td>
</tr>
<tr>
<td>Histopathology (osteoblastic vs other types)</td>
<td>2</td>
<td>136</td>
<td>0.70 (0.28–1.73)</td>
<td>0.78</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Note: The – indicates that data was not available.

Abbreviations: HIF-1α, hypoxia-inducible factor-1α; OR, odds ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.
Figure 3  Significant associations were revealed between HIF-1α expression and clinicopathological factors of histological grade (A), tumor stage (B), chemotherapy response (C), and metastasis (D).

Abbreviations: HIF-1α, hypoxia-inducible factor-1α; M–H, Mantel–Haenszel; CI, confidence interval.
cancer stage. In addition, the results showed that HIF-1α expression was significantly correlated with advanced grade of osteosarcoma. Treatment failure is commonly due to the development of chemoresistance. Results of this analysis revealed that overexpression of HIF-1α is significantly related to poor chemotherapy response, which was an important prognostic factor for osteosarcoma. Roncuzzi et al. reported that multidrug resistance phenotype of osteosarcoma was also mediated by HIF-1α. It was suggested that HIF-1α promoted the outward transport of intracellular doxorubicin by activating the P-glycoprotein expression and hindered apoptosis by regulating the expression of c-Myc and p21. Correlations of HIF-1α expression with prognostic factors for CXC chemokine receptor 4, cyclooxygenase 2,
heparanase, and differentiated embryonic chondrocyte gene 2 were also reported in osteosarcoma.\(^{31,32,34,36}\) Apparent pooled lower OS and DFS rates were found in patients with HIF-1\(\alpha\) overexpression, indicating poor prognostic value of HIF-1\(\alpha\) expression in osteosarcoma. It is reasonable to infer that hypoxia would be more evident when tumor size gets larger, and then higher level of HIF-1\(\alpha\) could be tested. However, with apparent heterogeneity, no significant correlation was found between HIF-1\(\alpha\) and tumor size in this study. More studies are needed to further explore this relation. No significant correlation of HIF-1\(\alpha\) expression with clinical variables of age, sex, tumor site, and histopathology of osteosarcoma appeared in this study.

Meanwhile, there were several limitations in this meta-analysis. First, most of the included studies were conducted in the People’s Republic of China. The reason may be that Chinese scientists attach more importance to improving the clinical outcomes for osteosarcoma patients. We included only studies that were published in English, studies unpublished or in other languages that meet the inclusion criteria may be missed. A tendency for journals to publish positive findings over negative results may also lead to an overestimation of the prognostic value. Second, the approach of extrapolating the HRs could introduce potential source of bias. When not reported in original articles, HRs were extrapolated from the survival curves or calculated from the provided data in the eligible studies according to the method of Parmar et al.\(^{38}\) The HR information obtained by statistical software unavoidably developed a decrease in accuracy. Third, significant heterogeneity was found across the selected studies when investigating the relationship of HIF-1\(\alpha\) expression with age, chemotherapy response, tumor size, and tumor site. More well-designed clinical studies with large cases of osteosarcoma should be performed to derive more accurate results. Tumor stages were evaluated by different systems and grouped with variant cutoffs among the included studies, which would make the results less reliable. Finally, assessment of the expression of HIF-1\(\alpha\) in the included studies was inconsistent. Differences in primary antibodies with varying dilutions, staining protocols, evaluation standards, and cutoff values for high HIF-1\(\alpha\) expression may contribute to heterogeneity.

Conclusion

In conclusion, the systematic review of the literatures shows that high expression of HIF-1\(\alpha\) in patients with osteosarcoma predicts low survival rate and poor clinicopathological characteristics. High HIF-1\(\alpha\) levels might be a valuable prognostic factor for osteosarcoma patients and predict high cancer stage, metastasis, and chemoresistance. To become a clinically useful prognostic marker for individual patients or a valid cancer drug target, these results need to be clearly confirmed by large, well-designed prospective study with appropriate multivariate analyses.

Acknowledgment

This work was supported by National Natural Science Foundation of China (grant numbers 81172547 and 30973444).

Disclosure

The authors report no conflicts of interest in this work.

References


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