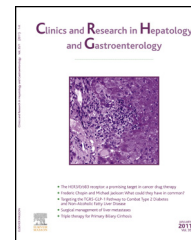




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ORIGINAL ARTICLE

# Protein expression of hypoxia-inducible factor-1 alpha and hepatocellular carcinoma: A systematic review with meta-analysis



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## Summary

**Purpose:** To investigate the relationship of protein expression of hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ) with clinicopathological factors and prognosis of hepatocellular carcinoma (HCC).

**Methods:** PubMed and Embase were searched from their inception through August 2013 for studies that reported the association between protein expression of HIF-1 $\alpha$  and HCC. Random effects meta-analyses were used to summarize the odds ratios (ORs) and 95% confidence intervals (CIs).

**Results:** Eight studies involving 851 patients with HCC were included. Protein expression level of HIF-1 $\alpha$  was not found to be related with capsule formation, cirrhosis, tumor size, and tumor differentiation of HCC, except vascular invasion. The positive association between HIF-1 $\alpha$  expression and vascular invasion of HCC was statistically significant (OR: 2.04, 95% CI: 1.31–3.18). As a prognostic factor, a high level of HIF-1 $\alpha$  expression would be associated with a poor disease-free survival (OR: 2.10, 95% CI: 1.48–2.97).

**Conclusion:** Higher level of HIF-1 $\alpha$  expression may indicate a bigger possibility of vascular invasion and a poorer prognosis of HCC.

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## Introduction

Hepatocellular carcinoma (HCC) is the main type of primary liver cancer, which is the fifth most common cancer worldwide and the third most common cause of cancer mortality. Its incidence have been rising in many countries [1,2]. The rapid progression of HCC, to a large degree, leads to the poor prognosis of this disease. A key to the malignant outcome of HCC is the hypoxic microenvironment. In the tissue of HCC, there are poorly vascularized regions, which are severely hypoxic and contribute to cancer progression by activating transcription factors. The transcription factors can promote cell survival, tumor angiogenesis and metastasis.

HCC hypoxia is also associated with resistance to radiation and chemotherapy [3,4]. Cellular responses to low oxygen tension are mainly mediated by the activation of hypoxia-inducible factors (HIFs), which consist of a constitutively expressed subunit (aryl hydrocarbon nuclear translocator) and an oxygen-regulated subunit. The oxygen-regulated subunits mainly include HIF-1 $\alpha$  and HIF-2 $\alpha$  [5]. HIF-1 $\alpha$  is overexpressed in a number of primary and metastatic human cancers, and its role is different in various cancers. The associations between HIF-1 $\alpha$  overexpression and poor patient survival have been found in cancers of brain, breast and ovary [6–8]. In addition, the relationship between HIF-1 $\alpha$  overexpression and improved patient survival is reported when referring to patients with non-small-cell lung carcinoma [9] and renal cell carcinoma [10]. HIF-1 $\alpha$  is also reported to be involved in HCC angiogenesis, invasion, metastasis, and prognosis in some studies [11–19], but the results of the existing literature are inconsistent or even conflicting.

We conducted a systematic review with meta-analysis of these reports to evaluate the relation of HIF-1 $\alpha$  protein expression with clinicopathological factors and prognosis of HCC, as well as the difference in the protein expression of HIF-1 $\alpha$  between HCC and paraneoplastic tissue.

## Methods

### Search strategy

The Meta-analysis of Observational Studies in Epidemiology Guideline [20] was followed to report the present review. We searched PubMed and Embase until August 2013 using the following terms: "HCC", "hepatocellular carcinoma", "liver cell carcinoma", "hepatic cell carcinoma", and "liver cancer", in combination with "hypoxia-inducible factor-1", "HIF-1", and "HIF-1 $\alpha$ ". The references cited in the articles or reviews were also screened.

### Study selection

Studies meeting the following criteria were selected:

- examined the relationship between HIF-1 $\alpha$  and clinicopathological parameters of HCC;
- utilized immunohistochemistry (IHC) to determine the protein expression of HIF-1 $\alpha$  in paraffin-embedded surgical specimens;

- reported sufficient data to estimate an odds ratio (OR) with 95% confidence interval (CI);
- used appropriate statistical methodology.

We excluded studies of non-observational design studies, case reports, letters, reviews, and editorial articles. Studies in which required data were not provided or could not be calculated were also excluded.

### Data extraction

Two investigators (S. Cao and S. Yang) independently extracted data from eligible studies, disagreements were resolved by discussion with a third author (C. Wu). For each study, the first author, publication year, number of eligible patients, laboratory method, and estimates of the association of interest were recorded. When referring to data about HIF-1 $\alpha$  expression, the detection is the results of the stabilization of the protein under hypoxic conditions.

### Statistical analysis

The meta-analysis was performed by the statistical software STATA version 11.0 (StataCorp LP, College Station Texas, USA). With regard to enumerative data, OR and 95% CI were applied. The heterogeneity of the data from eligible studies was evaluated by using the Q statistic (significance level at  $P < 0.10$ ).  $I^2$  statistic, which is a quantitative measure of inconsistency across studies [21], was also calculated. The  $I^2$  varies from 0% (no observed heterogeneity) to 100% (maximal heterogeneity).  $I^2$  value of  $\geq 50\%$  is considered to represent substantial heterogeneity. Random effect model [22] was used to pool data of included studies. Statistical significance was defined as a  $P$ -value less than 0.05.

## Results

### Study selection

We initially retrieved 483 unique citations from PubMed and Embase after excluding 438 duplicates until August 2013. 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-1 $\alpha$  in HCC. After examining the remaining nine articles, one was excluded due to not enough data to estimate odds ratio and its 95% CI [16]. Finally, eight studies were included in our meta-analysis. Fig. 1 shows the process of the study selection.

### Study characteristics

A total of eight studies involving 851 patients with HCC addressing HIF-1 $\alpha$  expression in HCC published from 2005 to 2011 met the criteria for this review. The detection method of immunohistochemistry was used for evaluating the protein expression of HIF-1 $\alpha$  in HCC specimens in all included studies. The definition of positive HIF-1 $\alpha$  staining varied among the studies, and the cut-off values in the studies ranged from 5% to 30%.

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