

# Role of Beclin I expression in patients with hepatocellular carcinoma: a meta-analysis

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**Background and aim:** Beclin1 has been reported as a vital marker for a number of malignant tumors. However, the role of Beclin1 in hepatocellular carcinoma (HCC) remains inconclusive. Thus, we conducted a meta-analysis to assess the correlation between Beclin1 and its clinicopathological and prognostic values in HCC.

**Methods:** PubMed, Cochrane Library, Web of Science, EMBASE, Chinese CNKI, and Chinese WanFang databases were searched for published articles on Beclin1 expression in hepatocellular tissues. Standard-compliant articles were screened using the Newcastle–Ottawa Scale for strict quality control of the literature. The correlation of Beclin1 expression with the clinicopathological features and survival outcomes was analyzed. Pooled odds ratios and hazard ratios with 95% confidence intervals were calculated using STATA14.2.

**Results:** Eleven articles with 1,279 patients were included in this meta-analysis. Positive Beclin1 expression was found to be correlated with alpha fetoprotein, liver cirrhosis, and vascular invasion, but not with gender, age, HBsAg, size of tumor, number of tumors, differentiation, and TNM stage. Positive Beclin1 expression was also associated with favorable 5-year overall survival and disease-free survival rates.

**Conclusion:** Our meta-analysis indicated that positive Beclin1 expression was negatively related to alpha fetoprotein, liver cirrhosis, and vascular invasion in HCC. Beclin1 could be used as a prognostic biomarker for HCC.

**Keywords:** Beclin1, hepatocellular carcinoma, prognosis, meta-analysis

## Introduction

Primary liver cancer is one of the most common malignancies in the digestive system and it has a poor prognosis. Hepatocellular carcinoma (HCC) comprises about 90% of all types of primary liver cancer and is the third most common cause of cancer-induced mortality.<sup>1</sup> The Asia-Pacific region has a high incidence of liver cancer, with People's Republic of China accounting for more than 50% of new cases of liver cancer worldwide annually.<sup>2</sup> Currently, treatment for liver cancer is mainly based on surgery, transarterial chemoembolization, chemotherapy, sorafenib-targeted drug therapy, radiofrequency, and so on. These comprehensive treatment measures significantly improve the cure rate, effectively extending patients' life time.<sup>3</sup> However, primary liver cancer is prone to early metastasis, which when combined with low surgical resection and postoperative metastasis and recurrence, greatly affect the efficacy of treatment.<sup>4,5</sup> Numerous patients miss the opportunity of surgical treatment because of the lack of specific means for early detection and early treatment of liver cancer. Thus, a specific index of early predictions of liver cancer and the pathogenesis of HCC have recently drawn research interest.

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Changes in autophagic activation have been associated with the progression and development of tumors.<sup>6</sup> Beclin1, which is located on the long arm of human chromosome 17 and about 150 kb in length, is a key protein that regulates autophagy and is regarded as a hallmark of autophagy initiation. Beclin1 plays an important role in the development and progression of various human malignancies.<sup>7</sup> Beclin1 has been identified as a reliable biomarker in many cancers, such as gastric cancer,<sup>8</sup> colorectal cancer,<sup>9</sup> cervical cancer,<sup>10</sup> and breast cancer,<sup>11</sup> and it has been related to the clinical features and prognosis of tumors. A meta-analysis of Beclin1 and gastric cancer has shown that Beclin1 expression is negatively correlated with tumor differentiation and TNM staging.<sup>12</sup> By contrast, another meta-analysis has demonstrated that Beclin1 expression is positively associated with tumor metastasis, poor prognosis, and overall survival (OS) in colorectal cancer.<sup>13</sup> Beclin1 expression has also been found to be poorly expressed in HCC; however, its association with clinicopathological characteristics and prognostic value remains inconclusive. Qiu et al<sup>14</sup> have indicated that Beclin1 is poorly expressed in HCC, relative to the adjacent tissue; positive Beclin1 expression has indicated a better prognosis. Notably, Wu et al<sup>15</sup> have demonstrated that Beclin1 expression is not related to clinical features and prognosis. Osman et al<sup>16</sup> have found that Beclin1 expression is only associated with HBsAg; therefore, a meta-analysis needs to be conducted to explore the relationship between Beclin1 expression and its clinicopathological characteristics and prognostic value in HCC.

## Methods

### Search strategy

Computer retrieval of commonly used biomedical databases, including Pubmed, Cochrane Library, Web of Science, EMBASE, Chinese CNKI, and Chinese WanFang, was conducted, and the search ended on September 1, 2017. The key words included the following: “beclin1” or “beclin-1” or “Atg6” and “hepatocellular carcinoma” or “hepatic tumor” or “liver tumor” or “hepatic cancer” or “liver cancer” or “HCC.”

### Eligibility criteria

A study was included in the meta-analysis if all of the following inclusion criteria were met: 1) availability of the full text of the article; 2) the patients in the literature had a definitive diagnosis of HCC and clinicopathological or survival information was included in the article; and 3) determination of Beclin1 expression by immunohistochemistry (IHC).

Studies were excluded if the case or control sources were unclear, and the pathological diagnosis was unclear. Republished studies using the same data source included only those with higher methodological quality.

### Data extraction

All data were extracted, including the name of the first author, publication year, number of patients, region of origin, patient characteristics, and hazard ratios (HRs) with 95% confidence interval (CI) for OS, by 2 investigators (Chaojie Liang and Hua Ge), independently. Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the articles. Discrepancies were resolved by discussion, re-extraction, or third-party adjudication.

### Quality assessment

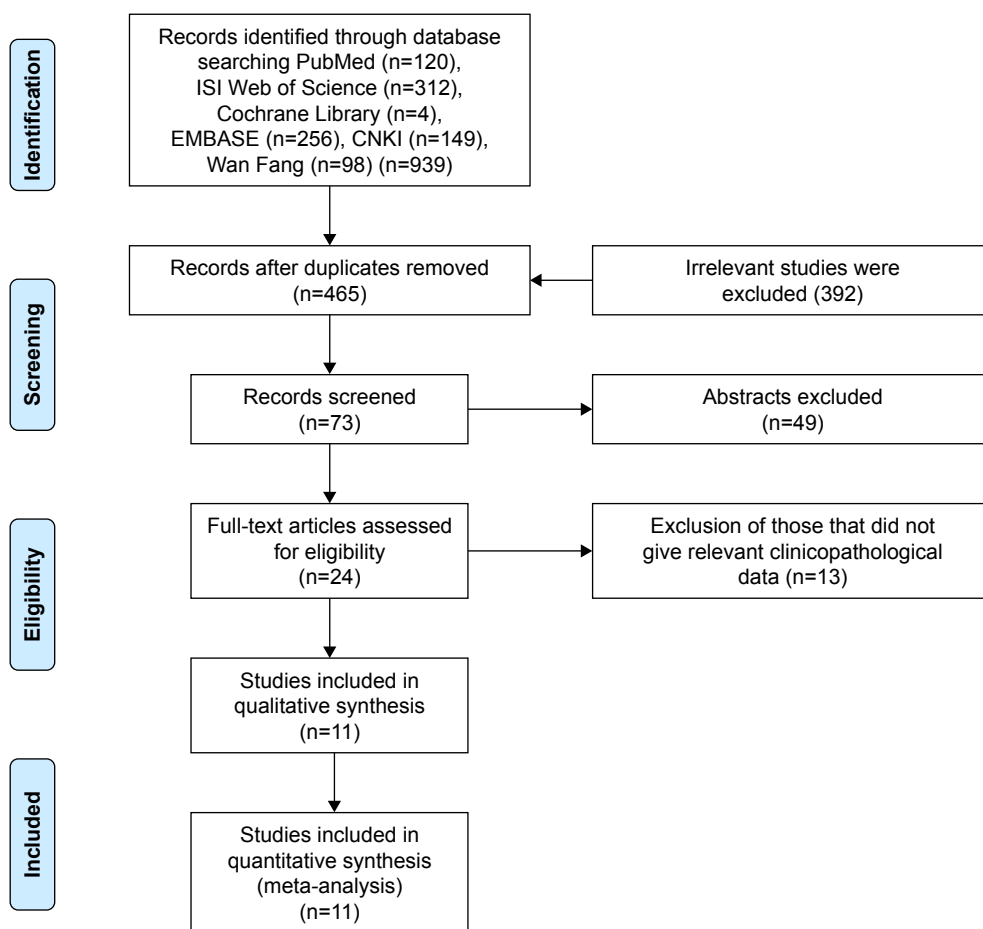
We used NOS to assess the quality of the included articles, and articles were considered of good quality when the NOS score  $\geq 6$  and of poor quality when the NOS score  $\leq 5$ . All articles included in this meta-analysis were of high quality.

### Statistical analysis

Pooled odds ratios (ORs) with 95% CIs were used to assess the association between positive Beclin1 expression and clinicopathological features calculated using STATA 14.2 (StataCorp LLC, College Station, TX, USA). The  $\chi^2$ -based *Q*-test and *I*<sup>2</sup> test were used to evaluate the heterogeneity between the studies. The heterogeneity was considered significant when *I*<sup>2</sup> values  $> 50\%$  and PHet  $\geq 0.1$ . Random- or fixed-effects model was used in accordance with the results of heterogeneity analysis, and subgroup analysis by sample size or the NOS score was calculated to analyze the source of heterogeneity. We used Engauge Digitizer 10.0 (GitHub, Inc., San Francisco, CA, USA) to extract the survival data from a Kaplan–Meier curve in the articles. A favorable prognosis in the positive Beclin1 expression group was considered when HR  $< 1$  and if the 95% CI did not cross 1. Potential publication bias was analyzed using Begg’s funnel plot test.

## Results

A total of 939 potential studies were collected from the database, as shown in Figure 1; 915 studies were removed because these articles were non-Beclin1-related, did not involve tests in tumor tissues, or were duplicated, as determined after their titles and abstracts were reviewed. A total of 24 studies were assessed by reading the full text; 13 studies were excluded because of the lack of cut-off values for Beclin1 expression



**Figure 1** Flow diagram of study selection.

or insufficient information. Eleven<sup>14-24</sup> eligible articles were ultimately included in this meta-analysis. Table 1 summarizes the characteristics of the articles. Published from 2007 to 2015, these studies included a total of 1,279 patients with HCC. The sample sizes of these studies ranged from 43 to 300; 6 studies included  $\leq 100$  patients, and 5 studies included  $> 100$  patients. The 11 studies were from the following regions: 9 from People's Republic of China, 1 from Korea, and 1 from Egypt. Six of these studies were published in English, and the others were in Chinese. Each of these studies obtained a score  $\geq 6$  in methodological assessment, which indicates high quality.

## Meta-analysis of clinicopathological characteristics

The correlation between Beclin1 expression and the clinicopathological features of HCC was assessed. As shown in Table 2 and Figure 2, positive Beclin1 expression was negatively associated with alpha fetoprotein (AFP) (OR =0.58, 95% CI = [0.42, 0.81],  $p=0.001$ , fixed effect), liver cirrhosis

(OR =0.69, 95% CI = [0.48, 0.99],  $p=0.045$ , fixed effect), and vascular invasion (OR =0.39, 95% CI = [0.18, 0.85],  $p=0.017$ , random effect). However, Beclin1 expression was not significantly associated with gender (OR =0.80, 95% CI = [0.43, 1.48],  $p=0.477$ , random effect), age (OR =1.12, 95% CI = [0.84, 1.49],  $p=0.444$ , fixed effect), HBsAg (OR =1.13, 95% CI = [0.81, 1.58],  $p=0.479$ , fixed effect), tumor size (OR =1.04, 95% CI = [0.91, 1.19],  $p=0.528$ , fixed effect), tumor number (OR =1.08, 95% CI = [0.73, 1.60],  $p=0.691$ , fixed effect), differentiation (OR =0.64, 95% CI = [0.38, 1.10],  $p=0.104$ , random effect), and TNM stage (OR =1.11, 95% CI = [0.81, 1.54],  $p=0.438$ , fixed effect).

As shown in Table 3, subgroup analysis of gender, vascular invasion, and differentiation was conducted using the sample size and the NOS score to explore the potential sources of heterogeneity. Notably, while the subgroups were classified by sample size, Beclin1 expression was correlated with vascular invasion ( $n \leq 100$ : OR =0.13, 95% CI = [0.05, 0.34],  $p=0.000$ , fixed effect) in the subgroup with small

**Table 1** Characteristics of studies included in the meta-analysis

Author	Country	Tumor type	Number of patients	Laboratory method	Expression Cancer (+/-) Control (+/-)	Gender Male (+/-) Female (+/-)	Age >50(+/-) ≤50(+/-)	HbsAg Yes (+/-) No (+/-)
Chen <sup>17</sup>	People's Republic of China	HCC	76	IHC	64/12 22/52	51/9 13/3	13/2 51/10	44/8 21/4
Ding et al <sup>18</sup>	People's Republic of China	HCC	300	IHC	95/205 NA	79/173 32/16	53/103 42/102	79/174 16/31
Guo et al <sup>19</sup>	People's Republic of China	HCC	54	IHC	44/10 55/0	32/7 12/3	29/7 15/3	NA
Lee et al <sup>20</sup>	Korea	HCC	190	IHC	11/179 NA	8/150 3/29	2/91 9/88	7/130 4/49
Kang et al <sup>21</sup>	People's Republic of China	HCC	50	IHC	39/11 25/45	NA	27/7 12/4	35/7 4/4
Liang <sup>22</sup>	People's Republic of China	HCC	43	IHC	18/25 22/21	NA	5/8 13/17	18/20 0/5
Osman et al <sup>16</sup>	Egypt	HCC	65	IHC	33/32 NA	24/27 9/5	9/12 24/20	10/3 23/29
Qiu et al <sup>14</sup>	People's Republic of China	HCC	103	IHC	75/28 51/6	62/23 13/5	41/12 34/16	59/24 15/4
Wu et al <sup>15</sup>	People's Republic of China	HCC	156	IHC	73/83 NA	69/74 4/9	43/40 30/43	59/58 14/25
Yang et al <sup>23</sup>	People's Republic of China	HCC	50	IHC	39/11 49/1	31/8 8/3	25/7 14/4	25/7 14/4
He <sup>24</sup>	People's Republic of China	HCC	192	IHC	19/173 NA	18/160 1/13	NA	13/119 6/54

**Abbreviations:** AFP, alpha fetoprotein; DFS, disease-free survival; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; NA, not applicable; OS, overall survival; UICC, Union for International Cancer Control.

sample size but not in the subgroup with a large sample size. Heterogeneity in differentiation was mainly observed in both subgroups ( $n \leq 100$ ) ( $I^2=56.8\%$ ) ( $n > 100$ ) ( $I^2=51.7\%$ ); however, heterogeneity in gender ( $n > 100$ ) ( $I^2=70.1\%$ ) and in vascular invasion ( $n > 100$ ) ( $I^2=62.9\%$ ) were only observed in the groups with a large sample size. On the basis of the NOS score, Beclin1 expression was correlated with vascular invasion (NOS score  $\leq 7$ : OR =0.21, 95% CI =[0.07, 0.61],  $p=0.004$ , random effect). However, heterogeneity in both subgroups of differentiation and vascular invasion remained. These results indicated that heterogeneity in vascular invasion, tumor encapsulation, and TNM stage was most likely caused by the sample size and the NOS score.

### Meta-analysis of prognostic value

We evaluated the prognostic value of Beclin1 in HCC. As shown in Figure 3, positive Beclin1 expression was associated with favorable 5-year OS (HR =0.68, 95% CI =[0.41, 0.96],  $p < 0.00001$ , fixed effect) and disease-free survival (DFS) (HR =0.71, 95% CI =[0.51, 0.92],  $p < 0.00001$ , fixed effect).

### Publication bias

As shown in Figures 3 and 4, no publication bias was found for gender ( $p=0.406$ ), age ( $p=0.210$ ), HBsAg ( $p=0.210$ ),

AFP ( $p=0.403$ ), liver cirrhosis ( $p=0.536$ ), tumor size ( $p=0.1$ ), number of tumors ( $p=0.734$ ), differentiation ( $p=1$ ), TNM stage ( $p=0.386$ ), 5-year OS ( $p=1$ ), and DFS ( $p=1$ ), as determined by Begg's test. However, publication bias was observed for vascular invasion ( $p=0.035$ ), as shown in Figures 3 and 4. Sensitivity analysis indicated that no study substantially influenced the pooled OR, indicating the need to include more studies in future research.

### Discussion

Autophagy<sup>25,26</sup> is a normal physiological process to maintain a sufficient level of intracellular homeostasis. It is regarded as a natural, regulatory, and destructive mechanism in the cell that allows cells to systematically recover from unwanted or malfunctioning groups. The process plays a key role in cell development for the provision of nutrients and energy for cells and has been closely associated with cancer development in recent years. As a component of the hVps34/III PI3K complex, Beclin1 plays a vital role in autophagy.<sup>27</sup> The PI3K complex plays an important role in mediating the localization of other autophagocyanates in the precursor cell membrane, and cells die because of excessive self-loss during sustained stress and continuous progression of autophagy. The death of these cells is often characterized by autophagy; mainly the

Liver cirrhosis	AFP Positive (+/-) Negative (+/-) No (+/-)	Tumor size ≤5 cm (+/-) >5 cm (+/-)	Tumor number Single (+/-) Multiple (+/-)	Vascular invasion Yes (+/-) No (+/-)	Differentiation Low (+/-) High and Moderate (+/-)	UICC stage I, II (+/-) III, IV (+/-)	Survival	Quality score
57/11	35/7	28/5	NA	9/5	NA	27/7	N	7
7/1	29/5	36/7		55/7		35/5		
84/191	38/116	53/110	82/173	12/29	72/140	70/149	OS/DFS	8
11/14	57/89	42/95	13/32	83/176	23/65	25/56		
16/3	17/4	18/4	NA	11/9	21/2	20/5	N	7
28/7	27/6	26/6		33/1	23/8	28/1		
8/88	1/55	7/107	NA	NA	8/146	6/74	N	8
3/91	10/124	4/72			3/33	5/105		
NA	NA	11/8	NA	NA	18/8	NA	N	8
		28/3			21/3			
NA	9/8	7/12	NA	NA	4/6	NA	N	6
	9/17	11/13			14/19			
24/29	NA	25/19	22/21	NA	8/17	11/7	N	8
9/3		8/13	11/11		25/15	22/25		
58/25	44/20	NA	56/17	18/15	34/20	8/2	OS	9
17/3	31/8		19/11	57/13	41/8	67/26		
53/59	NA	44/41	45/56	19/16	62/75	37/35	OS/DFS	8
20/24		29/42	28/27	54/67	11/8	36/48		
36/10	14/4	25/7	NA	10/8	17/9	NA	N	6
3/1	25/7	14/4		29/3	22/2			
14/143	9/132	NA	NA	6/74	4/35	5/47	OS/DFS	7
5/39	10/41			13/99	15/138	14/126		

overexpression of Beclin1 and large amounts of autophagosomes produced by cells.<sup>28</sup> The downregulation of Beclin1 protein expression in various tumors indicates that tumor development is closely related to Beclin1-induced autophagic cell death.<sup>12,13</sup> Liang et al<sup>29</sup> indicated that Beclin1 protein expression was significantly reduced or even undetectable in the breast cancer cell line MCF-7, and stable transfection of Beclin1 could significantly improve autophagy and reduce tumorigenic ability. In addition, the downregulation of the autophagy gene Beclin1 can significantly reduce autophagy

to protect tumor cells from autophagic cell death, contributing to the continuous development of tumor cells.<sup>30</sup>

Genome instability is one of the hallmarks of tumor and is one of the important mechanisms of cell carcinogenesis. The instability of the cell genome is increased due to the environment of organism and metabolic stress. The monoallelic deletion of the autophagy gene Beclin1 can damage the cell autophagy ability and is not conducive to normal cells during metabolic stress survival, but promotes the occurrence of the tumor.<sup>31</sup> Kung et al<sup>32</sup> have demonstrated that

**Table 2** Beclin1 clinicopathological features for HCC

Heterogeneity							
Clinicopathological features	Number of studies	Number of patients	Pooled OR (95% CI)	PHet	I <sup>2</sup> (%)	p-value	Model used
Gender	9	1,186	0.80 (0.43–1.48)	0.028	53.4	0.477	Random
Age	10	1,087	1.12 (0.84–1.49)	0.558	0.0	0.444	Fixed
HbsAg	10	1,226	1.13 (0.81–1.58)	0.207	25.7	0.479	Fixed
AFP	9	1,008	0.58 (0.42–0.81)	0.269	20.3	0.001	Fixed
Liver cirrhosis	9	1,185	0.69 (0.48–0.99)	0.129	36.2	0.045	Fixed
Tumor size	9	984	1.04 (0.91–1.19)	0.343	11.0	0.528	Fixed
Vascular invasion	7	931	0.39 (0.18–0.85)	0.001	72.1	0.017	Random
Tumor number	4	624	1.08 (0.73–1.60)	0.476	0.0	0.691	Fixed
Differentiation	10	1,203	0.64 (0.38–1.10)	0.017	55.4	0.104	Random
TNM stage	8	1,143	1.11 (0.81–1.54)	0.487	0.00	0.438	Fixed

**Abbreviations:** AFP, alpha fetoprotein; CI, confidence interval; Fixed, fixed-effects model; HCC, hepatocellular carcinoma; OR, odds ratio; Random, random-effects model.

autophagic-deficient mouse models contain large amounts of damaged mitochondria, p62, and ubiquitin protein polymers. Massive accumulation of these substances can further induce reactive oxygen species production, leading

to increased chromosomal instability, significantly increasing the incidence of cancer. Beclin1 can effectively prevent gene mutations, improve genomic stability, and ultimately reduce the incidence rate of cancer. However, the relevant

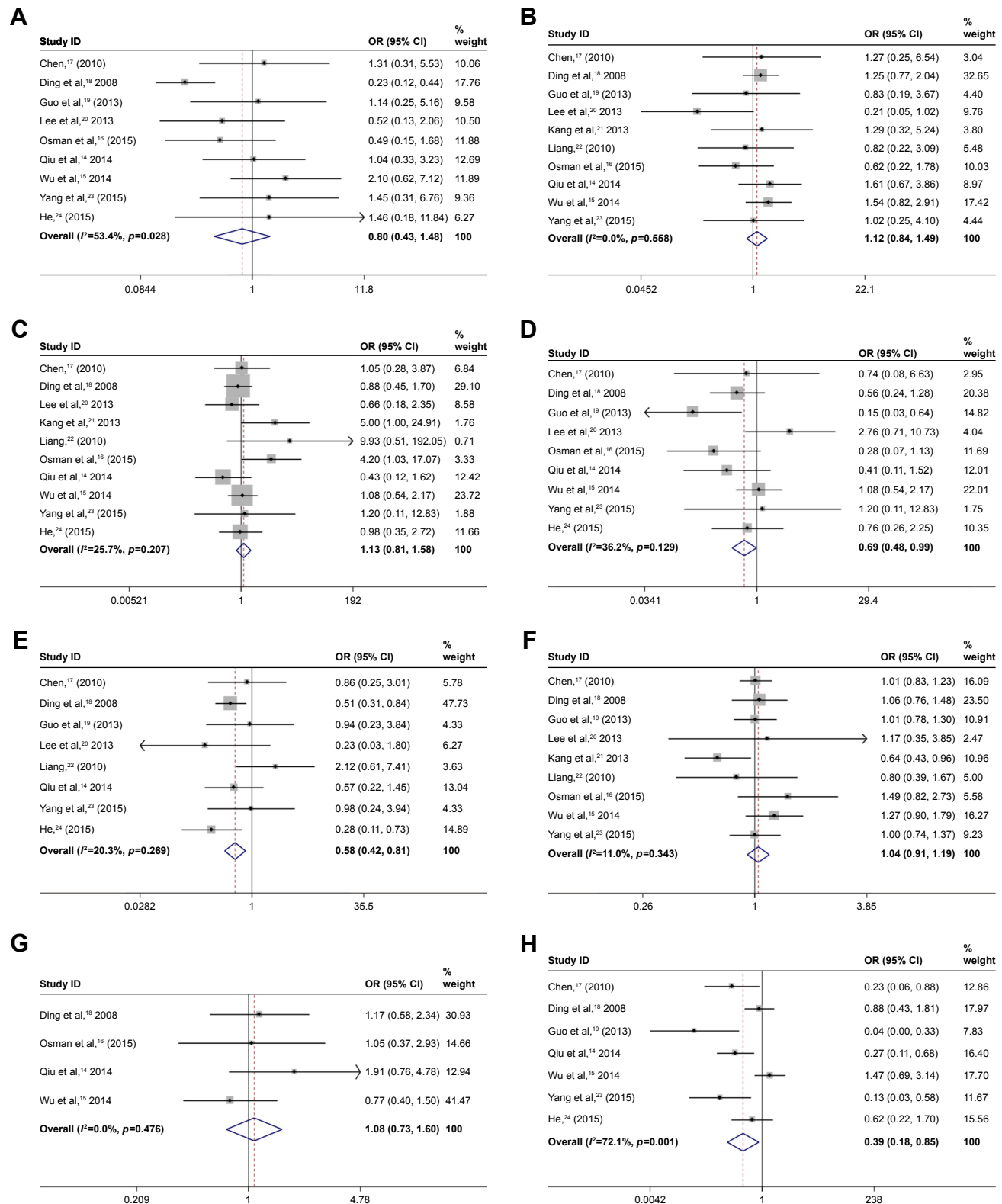
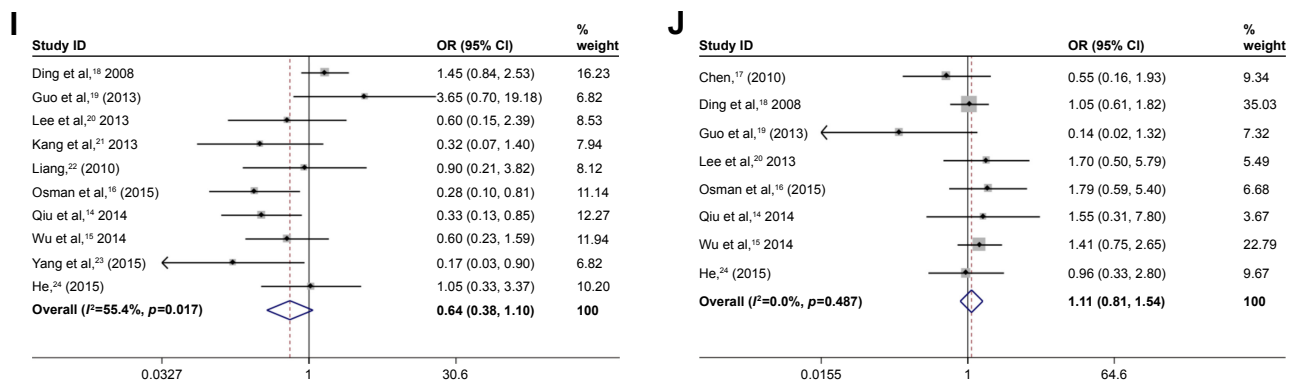


Figure 2 (Continued)



**Figure 2** Forest plot of studies evaluating the relationship between Beclin I expression and gender (A), age (B), HBsAg (C), liver cirrhosis (D), AFP (E), tumor size (F), number of tumors (G), vascular invasion (H), differentiation (I), and TNM stage (J). **Note:** Weights are from random effects analysis. **Abbreviations:** AFP, alpha fetoprotein; CI, confidence interval; OR, odds ratio.

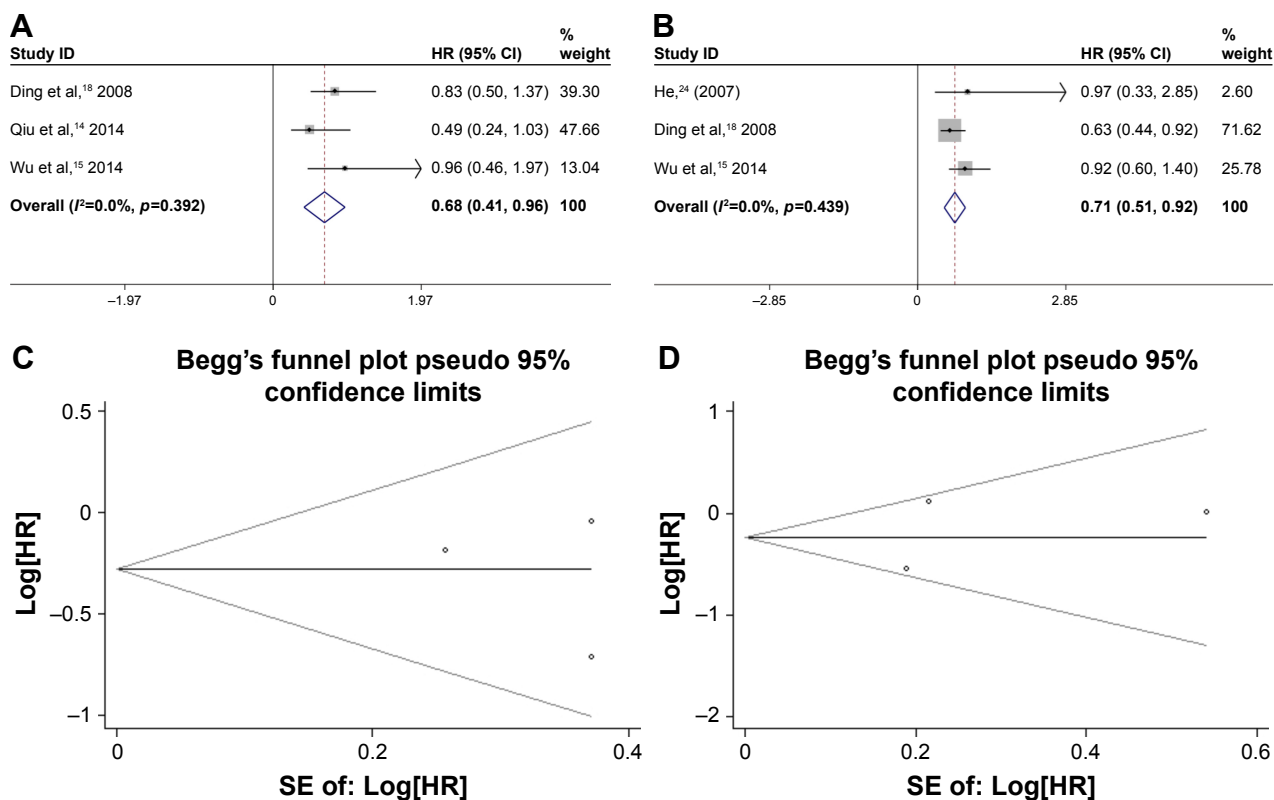
mechanism may function as a conservative housekeeping mechanism to maintain genomic stability by reducing harmful proteins, removing damaged organelles, and reducing DNA damage.<sup>33</sup> In the stage of tumor development, the role of autophagy may have either positive or negative consequences: it can promote tumor cell proliferation, but it can also inhibit tumor cell growth, which is closely related to the state of the tumor itself.<sup>34</sup> Beclin I has a proapoptotic function because of its BH3 domain.<sup>35</sup> Thus, Beclin I can inhibit tumor progression by promoting tumor cell apoptosis in tumor cells.

Recent studies have found abnormal Beclin I expression in HCC; however, results remain inconclusive. Lee et al<sup>20</sup> have demonstrated that Beclin I is not related to any clinicopathological features, such as the TNM stage and tumor size. Osman et al<sup>16</sup> have found similar results. Qiu et al<sup>14</sup> have indicated that Beclin I expression in HCC is significantly lower than that in normal and cirrhotic tissues. They have also shown that Beclin I expression is correlated with liver cirrhosis, Edmondson grade, and vascular invasion but not with gender, age, TNM stage, AFP level, number of tumors, and capsule integrity. In addition, low Beclin I expression

**Table 3** Subgroup analysis of tumor size and vascular invasion by sample size and NOS score

Subgroups	Number of studies	Number of patients	p-value	Pooled OR (95% CI)	PHet	I <sup>2</sup> (%)
<b>Gender</b>						
Sample						
n ≤ 100	4	344	0.863	0.94 (0.46–1.90)	0.650	0.0
n > 100	5	842	0.531	0.73 (0.28–1.94)	0.010	70.1
NOS score						
≤ 7	5	814	0.499	1.32 (0.59–2.92)	0.996	0.0
> 7	4	372	0.269	0.62 (0.26–1.45)	0.015	67.5
<b>Vascular invasion</b>						
Sample						
n ≤ 100	3	372	0.000	0.13 (0.05–0.34)	0.363	1.4
n > 100	4	559	0.333	0.71 (0.18–1.42)	0.044	62.9
NOS score						
≤ 7	4	368	0.004	0.21 (0.07–0.61)	0.080	55.6
> 7	3	563	0.500	0.73 (0.29–1.81)	0.019	74.6
<b>Differentiation</b>						
Sample						
n ≤ 100	5	262	0.195	0.64 (0.38–1.10)	0.055	56.8
n > 100	5	941	0.378	0.76 (0.41–1.40)	0.082	51.7
NOS score						
≤ 7	6	339	0.837	0.89 (0.30–2.65)	0.084	54.9
> 7	4	864	0.071	0.55 (0.28–1.05)	0.022	62.0

**Abbreviations:** CI, confidence interval; NOS, Newcastle–Ottawa Scale; OR, odds ratio.



**Figure 3** Pooled analysis for the association between Beclin1 expression and 5-year survival rate (**A**: forest plots, **C**: Begg's publication bias plot), DFS rate (**B**: forest plots, **D**: Begg's publication bias plot).

**Abbreviations:** CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OR, odds ratio; SE, standard error.

indicates a poor OS. However, Wu et al<sup>15</sup> have demonstrated that Beclin1 expression is not related to the clinical features and prognosis of HCC. In this meta-analysis, 1,279 patients from 11 articles were considered. Positive Beclin1 expression is associated with AFP, liver cirrhosis, and vascular invasion but not with gender, age, HBsAg, AFP, liver cirrhosis, tumor size, number of tumors, differentiation, and TNM stage. Eight studies with 1,008 patients are considered in this meta-analysis to explore the relationship between Beclin1 expression and AFP level. In 6 out of 8 studies, no relation was found between Beclin1 expression and the AFP level; however, the pooled results suggest a significant association between Beclin1 expression and the AFP level. Similarly, 8 of 9 studies and 3 of 7 studies have demonstrated that Beclin1 expression is not correlated with liver cirrhosis and vascular invasion; however, the pooled results indicate that Beclin1 expression is significantly related to liver cirrhosis and vascular invasion. In addition, we have indicated that positive Beclin1 expression can predict favorable 5-year survival and DFS rates. All pooled results have shown that Beclin1 is related to the development of HCC and that Beclin1 can be a potential prognostic biomarker for HCC.

In our meta-analysis, Beclin1 expression is only related to AFP, liver cirrhosis, and vascular invasion with respect to clinicopathological features; however, recent studies indicate that combined with other related genes, such as HIF-1 $\alpha$  and Bcl-xL, Beclin1 expression can considerably increase its clinical value. Ding et al<sup>18</sup> have demonstrated that Beclin1 expression is significantly correlated with tumor differentiation in Bcl-xL<sup>+</sup> patients but not in Bcl-xL<sup>-</sup> patients. Moreover, positive Beclin1 expression indicates higher OS and DFS in Bcl-xL-positive HCC. Similar results have been found between Beclin1 and apoptotic markers, such as Bcl-2 and Bax.<sup>36,37</sup> Osman et al<sup>16</sup> have found that Beclin-1 expression is closely related to tumor differentiation, TNM stage, tumor size, and number of tumors in the high HIF-1 $\alpha$  expression group among patients with HCC but not in the low HIF-1 $\alpha$  expression group. Thus, Beclin1 combined with other molecules can be used to diagnose HCC and predict its prognosis.

Significant heterogeneity was determined in our study. Although the study included subgroup analysis and sensitivity analysis, the source of heterogeneity was not clearly identified. However, the heterogeneity may result from different factors. One is the laboratory method. Our meta-analysis



included studies in which outcomes were assessed by IHC, a semiquantitative method, which can influence the quality of the antibody, incubation time, time of diaminobezidin staining, and so on. In addition, IHC has a subjective nature,

which may affect the evaluation. Another factor is the shortage of eligible articles for meta-analysis. High-quality, large-scale studies are needed to analyze the relationship between Beclin I and HCC.

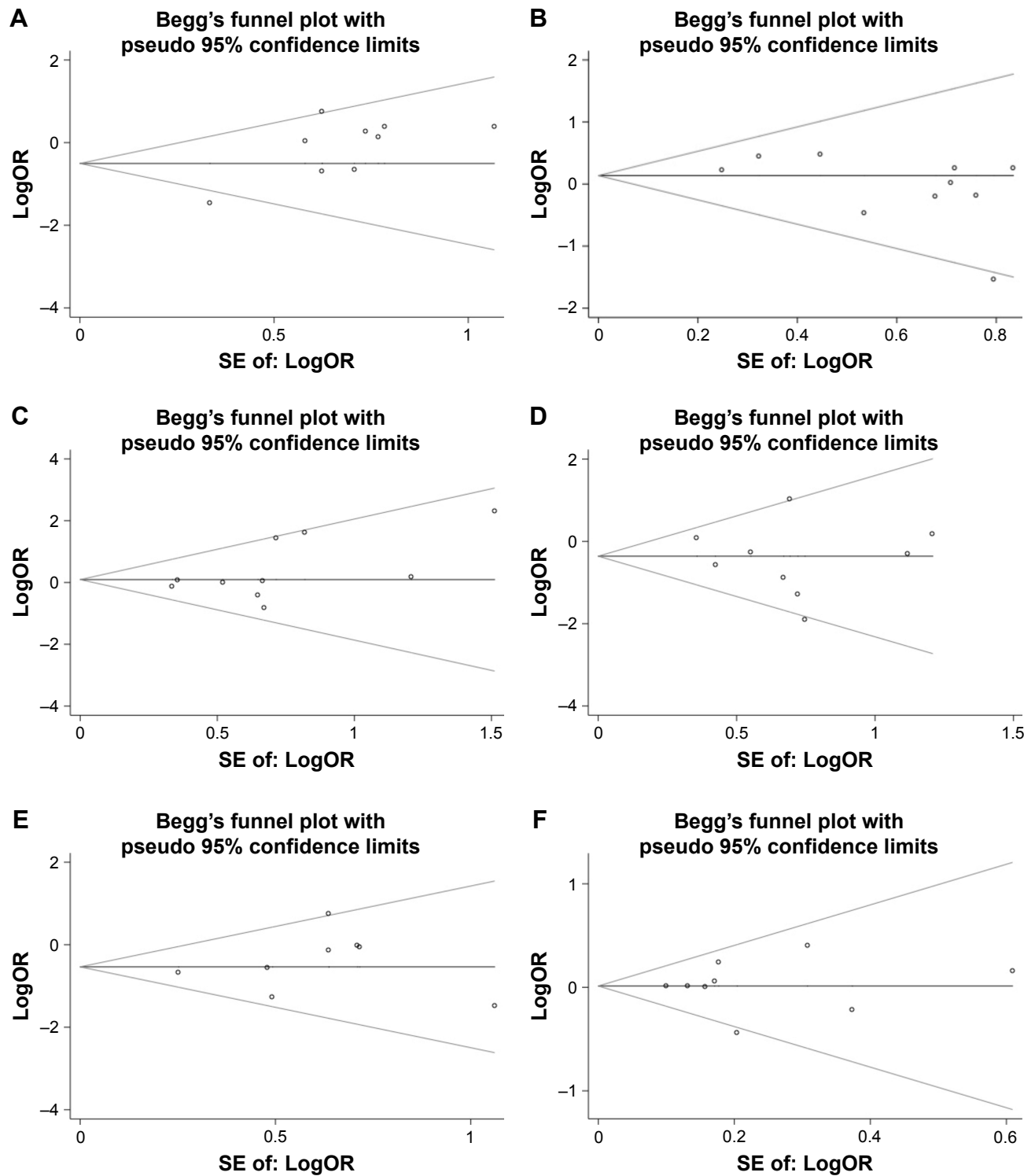
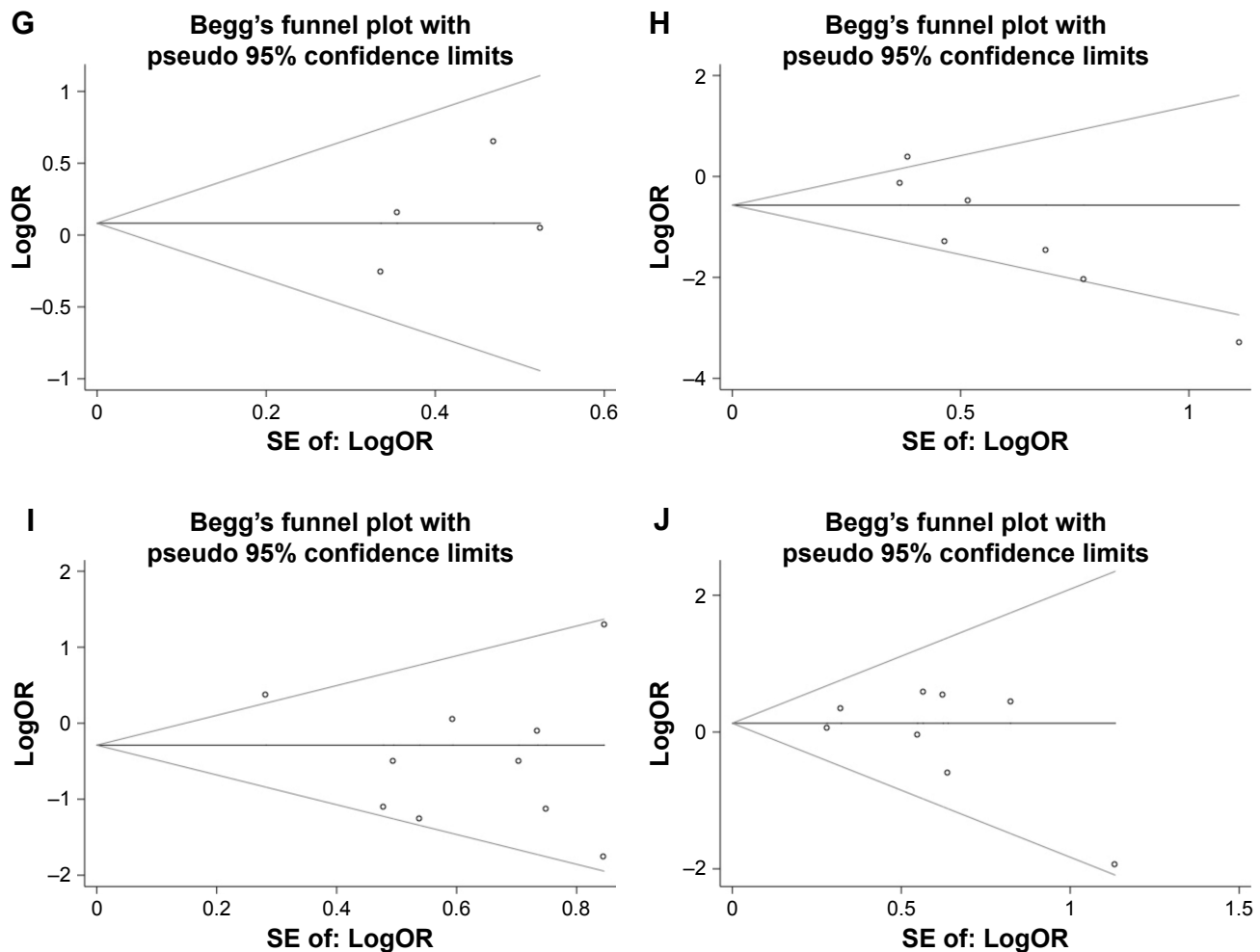


Figure 4 (Continued)



**Figure 4** Begg's publication bias plot for Beclin1-related studies: gender (A), age (B), HBsAg (C), liver cirrhosis (D), AFP (E), tumor size (F), number of tumors (G), vascular invasion (H), differentiation (I), and TNM stage (J).

## Limitations

Our meta-analysis has certain limitations: 1) more studies are needed to support the current conclusions; 2) this meta-analysis mostly included studies that were conducted in the People's Republic of China, so that the pooled results may be applicable for Chinese or Asian populations only; thus, more studies from other regions or countries should be included to support the results; 3) bias may be present because of the HRs derived from the survival curves in the studies.

## Conclusion

The results demonstrate that positive Beclin1 expression is negatively associated with AFP, liver cirrhosis, and vascular invasion in HCC. Moreover, Beclin1 may be used as a prognostic marker for HCC. However, these results should be verified by well-designed studies with a larger sample size.

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## Disclosure

The authors report no conflicts of interest in this work.

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