Prognostic significance of cyclooxygenase-2 expression in patients with hepatocellular carcinoma: a meta-analysis

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Abstract

Introduction: Cyclooxygenase-2 (COX-2) is believed to be an important enzyme in the carcinogenesis of hepatocellular carcinoma (HCC). However, it is still controversial whether COX-2 expression can be regarded as a prognostic factor for HCC patients. We performed a systematic review and meta-analysis of studies assessing the clinical and prognostic significance of COX-2 expression in HCC.

Material and methods: Identification and review of publications assessing clinical or prognostic significance of COX-2 expression in HCC until November 1, 2014. A meta-analysis was performed to clarify the association between COX-2 expression and clinical outcomes.

Results: A total of 11 publications met the criteria and included 943 cases. Analysis of these data showed that COX-2 expression was not significantly correlated with capsular formation (OR = 0.84, 95% confidence interval (CI): 0.46–1.55, $p = 0.58$), tumor TNM stage (OR = 0.73, 95% CI: 0.23–2.33, $p = 0.59$), vascular invasion (OR = 1.04, 95% CI: 0.25–4.35, $p = 0.96$), tumor size (OR = 0.78, 95% CI: 0.21–2.86, $p = 0.71$), or tumor differentiation degree (OR = 1.08, 95% CI: 0.42–2.79, $p = 0.87$). However, in the identified studies, COX-2 expression was strongly associated with high alpha-fetoprotein level (OR = 1.83, 95% CI: 1.01–3.33, $p = 0.05$), HBsAg status (OR = 1.85, 95% CI: 1.13–3.03, $p = 0.01$), decreased overall survival (relative risk (RR): 1.54, 95% CI: 1.18–2.02, $p = 0.001$) and decreased disease-free survival (RR = 1.49, 95% CI: 1.22–1.81, $p < 0.001$).

Conclusions: This meta-analysis shows that COX-2 expression in HCC is associated with decreased overall and disease-free survival and thus marks a worse prognosis. Nevertheless, more large sample and well-designed studies are warranted to confirm this finding.

Key words: hepatocellular carcinoma, cyclooxygenase-2, prognosis, survival, meta-analysis.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the most common malignant primary tumor in the liver [1]. Despite improvements in treatment modalities during the past few decades, the prognosis of HCC is still very poor because of frequent intrahepatic metastasis and tumor recurrence [2].

Of the potential prognostic variables, cyclooxygenase (COX)-2 is of particular interest, as it may also offer the option of treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) [3]. Cyclooxygenases regulate the synthesis of prostaglandins and are thus the major target of NSAIDs [4]. Its two isoforms (COX-1 and COX-2) have different expression patterns, with COX-1 being expressed in a broad variety of tissues. COX-2 and its main product, prostaglandin E2 (PGE2), are inducible by growth factors and inflammatory stimuli. Additionally, COX-2 has been shown to participate in tumor development and progression [5]. Overexpression of COX-2 has been reported in many human malignancies, including head and neck carcinomas [6], esophagus [7], colon [8], breast [9], pancreas [10] and prostatic cancer [11]. These findings suggest that COX-2 may be involved in carcinogenesis and/or progression of certain types of human malignancies.

Over the past decade, several studies have evaluated the prognostic value of COX-2 protein expression in HCC, with conflicting results. Some concluded that COX-2 expression had no influence on survival, while others reported that COX-2 expression was predictive of a poor survival outcome for HCC [12–14]. In order to evaluate this question, we conducted a systematic review and meta-analysis to determine the association between COX-2 expression and common clinical and pathologic features of liver cancer.

Material and methods

Search strategy

The electronic databases of PubMed, Embase, and Wanfang were searched for studies that investigated the association of clinicopathological parameters and prognosis with COX-2 expression in HCC to be included in the present meta-analysis. Studies were examined, and an updated search was conducted on November 2014. The following search terms and combinations were used: "COX-2" or "PTGS2", as well as "hepatocellular carcinoma" or "HCC" or "liver cancer" or "liver tumor" or "liver neoplasms" or "hepatocellular carcinoma". The citation lists from all the retrieved studies were used to identify other relevant publications. Review articles were also scanned to identify additional eligible studies. The title and abstract of each identified study were scanned to exclude any irrelevant publications. The remaining articles were reviewed to determine whether they contained information on the topic of interest.

Selection criteria

Diagnosis of HCC was proven by histopathological methods. Studies of COX-2 expression based on HCC tissue (after either surgical excision or biopsy sampling), rather than serum or any other kind of specimen, were included. All studies on the correlation of COX-2 expression with clinicopathological markers and the association of COX-2 expression with overall survival (OS) or disease-free survival (DFS) of HCC patients were included. For inclusion in the analysis, there was no limitation on the minimum number of patients of each study. When there were multiple articles by the same group based on similar patients and using the same detection methods, only the largest or the most recent article was included.

Data extraction

The following information was extracted from the retrieved papers: author, country of the patient, ethnicity, publication year, time of collection, histological type, tumor pathological stage, number of patients, research technique used, the ages of the patients, and the choice of cut-off scores for the definition of positive staining or staining intensity. Two major groups were established on the basis of the objective. One group clarified the association between the expression of COX-2 and clinicopathological parameters, including capsular formation, AFP level, HBsAg status, tumor TNM stage, vascular invasion, tumor size and differentiation degree. Meanwhile, the other group investigated the association between the expression of COX-2 and OS or DFS.

Statistical analysis

The meta-analysis was performed as previously described [15]. Odds ratio with 95% CI were used to evaluate the association between COX-2 and the clinicopathological features for HCC, including capsular formation, AFP level, HBsAg status, tumor TNM stage, vascular invasion, tumor size and differentiation degree. The relative risk (RR) was used for assessing the association of COX-2 and OS or DFS combined over studies. For those RRs that were not given directly in the published articles, the published data and figures from original papers were used to assess the RR according to the methods described by Parmar *et al.* [16]. Heterogeneity across studies was evaluated with the Q test and *p*-values. ORs and RRs were calculated by a random-effects model when the *p*-value was less than 0.05. Otherwise, a fixed-effects model was used. The Begg and Egger funnel plot was used to assess publication bias. Statistical analyses were estimated using Review manager software. *P*-values were two-sided, with significance at $p < 0.05$.

Results

Characteristics of the studies

A total of 224 articles were selected for the meta-analysis by browsing the PubMed, Embase,

and Wanfang databases. Out of this total, 206 were excluded after the title and abstract were reviewed, and seven articles were excluded after the full publications were reviewed (Figure 1). The reasons for exclusion were: (a) studies were not associated with the topic of interest; (b) authors of the article used neither histopathologic analysis nor close clinical and imaging follow-up for at least 6 months; (c) studies associated with other diseases (d); non-original articles; (e) data could not be extracted; and (f) repeated data from the same or similar population. Eventually, 11 publications met the criteria for the present analysis [12–14, 17–24]. The total number of patients was 943, and each study had 30 to 196 patients. The main characteristics of the eligible studies are summarized in Table I. A total of 11 articles dealt with clinicopathological factors. Moreover, the assessment of OS or DFS using the Kaplan-Meier method was reported in 8 of these articles.

Correlation of COX-2 expression with clinicopathological parameters

The association between COX-2 and several clinicopathological parameters is illustrated in

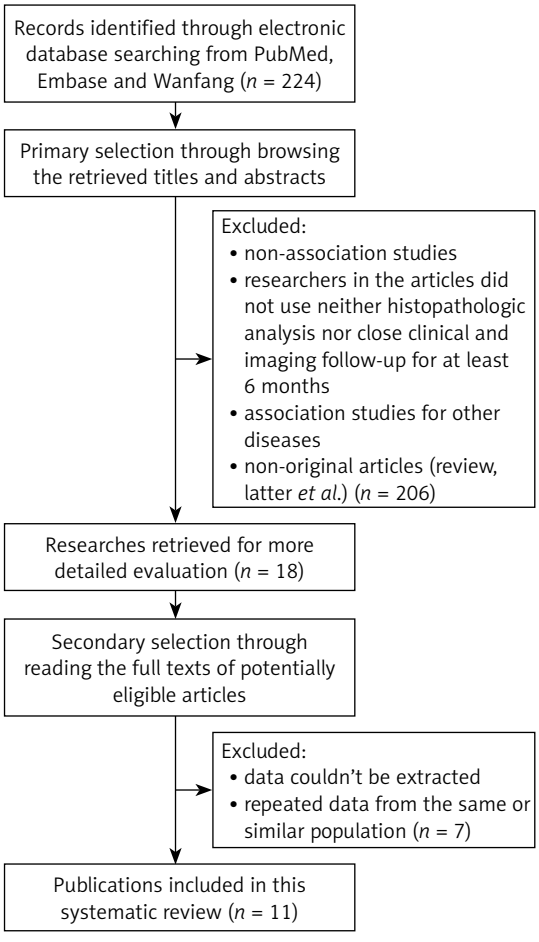


Figure 1. Flow diagram of article selection

Table I. Main characteristics and results of the eligible studies

Study	Patient's country	Ethnicity	Year	Time of collection	Pathological stage	Method	Number of patients	Age [years]	Follow-up [months]	Cut-off for COX-2 positive	Survival analysis
Kondo *et al.*	Japan	Asian	1999	ND	ND	IHC	61	ND	41	ND	DFS
Tang *et al.*	Hong Kong	Asian	2005	1998–2001	I–IV	IHC	100	ND	60	> 10% staining	OS
Iwamoto *et al.*	Japan	Asian	2006	1993–2001	I–IV	RT-PCR	59	28–80	61	ND	OS, DFS
El-Bassiouny *et al.*	Egypt	Caucasian	2007	ND	ND	IHC	30	40–55	ND	> 0% staining	ND
Yildirim *et al.*	Turkey	Caucasian	2008	1996–2006	I–IV	IHC	31	48–75	51	> 25% staining	OS
Schmitz *et al.*	Germany	Caucasian	2009	ND	I–IV	IHC	196	ND	20	> 0% staining	DFS
Liang *et al.*	China	Asian	2010	2007–2010	I–IV	IHC	59	24–68	ND	> 50% staining	ND
He *et al.*	China	Asian	2010	1998–2005	ND	IHC	124	19–78	48	> 50% staining	DFS
Li *et al.*	China	Asian	2011	2003–2005	I–III	IHC	52	28–76	ND	> 10% staining	ND
Yang *et al.*	China	Asian	2011	2000–2003	I–IV	RT-PCR	63	32–78	48	> 50% staining	OS
Soon *et al.*	Korea	Asian	2012	2003–2009	ND	IHC	168	30–54	80	> 25% staining	OS

Figure 2. COX-2 expression was significantly associated with high AFP level (pooled OR = 1.83, 95% CI: 1.01–3.33, p = 0.05 fixed-effect) and HBsAg status (pooled OR = 1.85, 95% CI: 1.13–3.03, p = 0.01 fixed-effect) (Figures 2 A and B).

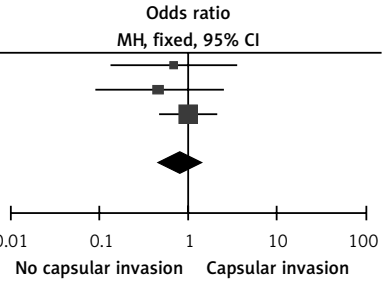
However, COX-2 expression was not associated with capsular formation (pooled OR = 0.84, 95% CI: 0.46–1.55, p = 0.58 random-effect) (Figure 2 C), tumor TNM stage (pooled OR = 0.73, 95% CI: 0.23–2.33, p = 0.59, random-effect) (Figure 2 D), vascular invasion (pooled OR = 1.04, 95% CI: 0.25–4.35, p = 0.96, random-effect) (Figure 2 E), tumor size (pooled OR = 0.78, 95% CI: 0.21–2.86, p = 0.71, random-effect) (Figure 2 F), or tumor differentiation degree (pooled OR = 1.08, 95% CI: 0.42–2.79, p = 0.87, random-effect) (Figure 2 G).

We also performed subgroup analysis by ethnicity, applied method, or cut-off value in HCC. A positive correlation between COX-2 expression and poor overall survival could be found in the

A

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, fixed, 95% CI
Kondo 1999	3	8	12	26	15.5	0.70 (0.14–3.56)
Liang 2010	33	43	14	16	20.8	0.47 (0.09–2.43)
He 2010	36	58	41	66	63.7	1.00 (0.48–2.06)
Total (95% CI)		109		108	100.0	0.84 (0.46–1.55)
Total events	72		67			

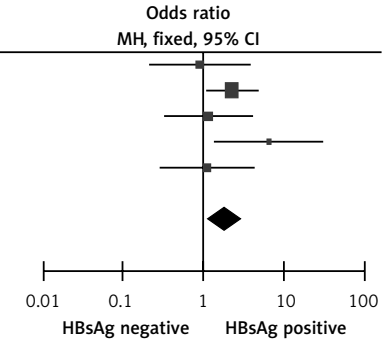
Heterogeneity: χ^2 = 0.74, df = 2 (p = 0.69); I^2 = 0%
Test for overall effect: Z = 0.55 (p = 0.58)



B

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, fixed, 95% CI
Yildirim 2008	9	15	10	16	16.8	0.90 (0.21–3.82)
He 2010	30	58	21	66	41.2	2.30 (1.11–4.77)
Liang 2010	31	43	11	16	19.4	1.17 (0.34–4.10)
Li 2011	33	43	3	9	5.0	6.60 (1.39–31.28)
Yang 2011	20	52	4	11	17.6	1.09 (0.28–4.22)
Total (95% CI)		211		118	100.0	1.85 (1.13–3.03)
Total events	123		49			

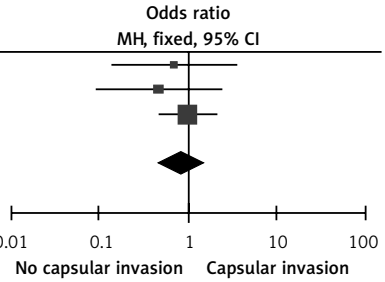
Heterogeneity: χ^2 = 4.95, df = 4 (p = 0.29); I^2 = 19%
Test for overall effect: Z = 2.43 (p = 0.01)



C

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, fixed, 95% CI
Kondo 1999	3	8	12	26	15.5	0.70 (0.14–3.56)
Liang 2010	33	43	14	16	20.8	0.47 (0.09–2.43)
He 2010	36	58	41	66	63.7	1.00 (0.48–2.06)
Total (95% CI)		109		108	100.0	0.84 (0.46–1.55)
Total events	72		67			

Heterogeneity: χ^2 = 0.74, df = 2 (p = 0.69); I^2 = 0%
Test for overall effect: Z = 0.55 (p = 0.58)



D

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, Random, 95% CI
Iwamoto 2006	23	35	14	24	24.4	1.37 (0.47–3.99)
Yildirim 2008	7	15	8	16	21.2	0.88 (0.21–3.59)
Liang 2010	11	43	13	16	21.0	0.08 (0.02–0.33)
Yang 2011	9	52	1	11	14.8	2.09 (0.24–18.47)
Li 2011	12	43	2	9	18.5	1.35 (0.25–7.47)
Total (95% CI)		188		76	100.0	0.73 (0.23–2.33)
Total events	62		38			

Heterogeneity: τ^2 = 1.15; χ^2 = 12.10, df = 4 (p = 0.02); I^2 = 67%
Test for overall effect: Z = 0.54 (p = 0.59)

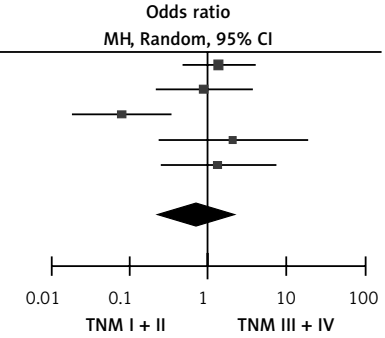


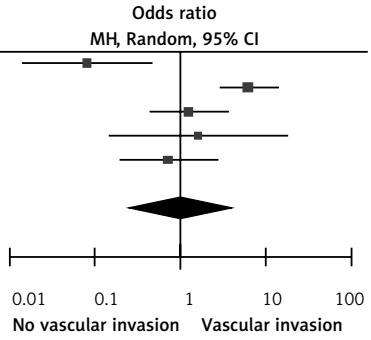
Figure 2. Forest plot of OR was assessed for association between stem cell markers and clinical pathologic features, such as AFP level (**A**), HBsAg status (**B**), capsular formation (**C**), tumor TNM stage (**D**)

E

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, Random, 95% CI
Liang 2010	2	43	6	16	18.4	0.08 (0.01–0.46)
He 2010	40	58	17	66	23.6	6.41 (2.93–14.02)
Iwamoto 2006	21	35	13	24	22.3	1.27 (0.44–3.63)
Kondo 1999	1	8	3	38	14.8	1.67 (0.15–18.45)
Schmitz 2009	58	177	4	10	20.9	0.73 (0.20–2.69)
Total (95% CI)		321		154	100.0	1.04 (0.25–4.35)
Total events	122		43			

Heterogeneity: $\tau^2 = 2.10$; $\chi^2 = 24.49$, $df = 4$ ($p < 0.0001$); $I^2 = 84\%$

Test for overall effect: $Z = 0.05$ ($p = 0.96$)

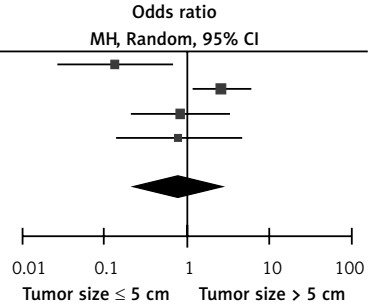


F

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, Random, 95% CI
Liang 2010	21	43	14	16	22.7	0.14 (0.03–0.67)
He 2010	46	58	39	66	30.7	2.65 (1.19–5.92)
Yang 2011	31	52	7	11	25.3	0.84 (0.22–3.25)
Li 2011	8	43	2	9	21.3	0.80 (0.14–4.60)
Total (95% CI)		196		102	100.0	0.78 (0.21–2.86)
Total events	106		62			

Heterogeneity: $\tau^2 = 1.25$; $\chi^2 = 11.49$, $df = 3$ ($p = 0.009$); $I^2 = 74\%$

Test for overall effect: $Z = 0.37$ ($p = 0.71$)



G

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, Random, 95% CI
Kondo 1999	1	8	17	38	10.3	0.18 (0.02–1.58)
Iwamoto 2006	4	35	6	24	15.3	0.39 (0.10–1.56)
El-Bassiouny 2007	5	20	4	10	13.7	0.50 (0.10–2.53)
Schmitz 2009	54	177	3	11	15.4	1.17 (0.30–4.58)
Liang 2010	15	43	7	16	16.9	0.69 (0.21–2.22)
Li 2011	32	43	2	9	13.0	10.18 (1.83–56.54)
Yang 2011	38	53	4	11	15.4	4.43 (1.13–17.38)
Total (95% CI)		379		119	100.0	1.08 (0.42–2.79)
Total events	149		43			

Heterogeneity: $\tau^2 = 1.03$; $\chi^2 = 16.85$, $df = 6$ ($p = 0.010$); $I^2 = 64\%$

Test for overall effect: $Z = 0.16$ ($p = 0.87$)

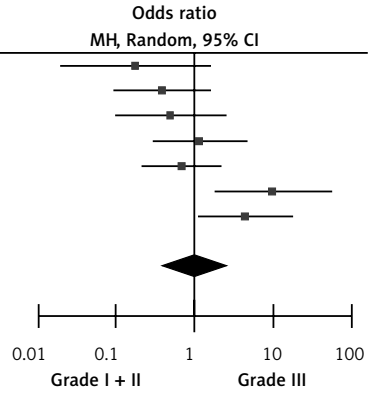


Figure 2 cont. Vascular invasion (**E**), tumor size (**F**), or tumor differentiation degree (**G**)

Table II. Subgroup analysis of the studies reporting the prognostic value of COX-2 expression on OS of hepatocellular carcinoma

Stratified analysis	Studies	Odds ratio		Model	Heterogeneity	
		OR (95 % CI)	P_{OR}		I^2 (%)	*P*-value
OS	5	1.84 (1.43–2.36)	< 0.0001	Fixed	19	0.29
Ethnicity:						
Caucasian	2	2.46 (1.51–4.02)	0.0003	Fixed	0	0.33
Asian	2	1.56 (1.18–2.06)	0.002	Fixed	0	0.44
Cut off:						
> 25%	1	1.28 (0.71–2.33)	0.41	Fixed	/	/
< 25%	3	1.98 (1.50–2.61)	< 0.0001	Fixed	22	0.28
Method:						
RT-PCR	2	1.56 (1.18–2.06)	0.002	Fixed	0	0.44
IHC	2	2.46 (1.51–4.02)	0.0003	Fixed	0	0.33

P_{OR} – p-value for odds ratio.

cut-off < 25%, Asian, Caucasian, RT-PCR and IHC subgroups (Table II).

COX-2 expression and prognosis of lung cancer

Using the methods described above, the OS and/or DFS of 802 patients in the 8 studies were analyzed. The main results of this meta-analysis are shown in Figure 3. A 5-year OS rate was extracted from 5 studies. The meta-analysis of the 5 studies for the prognostic value of COX-2 expression showed that COX-2 expression is associated with a poor OS. The combined RR was 1.54 (95% CI: 1.18–2.02, $p = 0.001$), without heterogeneity ($I^2 = 42\%$, $p = 0.14$) (Figure 3 A).

The meta-analysis of 4 applicable studies showed that COX-2 expression is associated with poor DFS. The combined RR was 1.49 (95% CI: 1.22–1.81, $p < 0.001$), without heterogeneity ($I^2 = 0\%$, $p = 0.59$) (Figure 3 B).

Sensitivity analysis

In order to test for a bias introduced by the low numbers of available eligible publications, we performed a sensitivity analysis. For this a single study involved in the meta-analysis was omitted for each round of analysis to investigate the influence of the individual data set of the particular study on the pooled ORs. We found that the corresponding pooled ORs were not essentially altered by subtraction of any study (data not shown), indicating that our results were statistically robust.

Publication bias

The funnel plots presented no evidence of publication bias in the studies of either outcome (Figure 4). No evidence for significant publication bias was found in OS (Egger's test, $p = 0.951$) and DFS (Egger's test, $p = 0.497$) studies.

Discussion

Hepatocellular carcinoma is one of the most vascular solid tumors and highly dependent on angiogenesis for tumor growth. However, relatively little is known of the role of various angiogenic factors in HCC compared with other common human cancers [25]. Several recent studies on COX-2 expression in other cancers show that COX-2 can induce angiogenesis via vascular endothelial growth factor (VEGF) and prostaglandin production and can also inhibit apoptosis [26]. Whether the COX-2 gene is a prognostic marker in patients with HCC has been studied extensively, but the conclusions are inconsistent. To the best of our knowledge, this is the first meta-analysis of published studies to evaluate the association between COX-2 expression and prognosis in HCC.

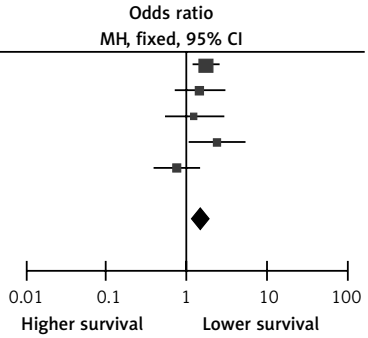
Heterogeneity analysis and sensitivity analysis were also critically performed to ensure the epidemiological credibility of this meta-analysis. The present results indicate that COX-2 expression is

A

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, fixed, 95% CI
Tang 2005	35	50	20	50	39.6	1.75 (1.19–2.57)
Iwamoto 2006	15	35	7	24	16.4	1.47 (0.71–3.05)
Yildirim 2008	7	15	6	16	11.5	1.24 (0.54–2.86)
Yang 2011	47	53	4	11	13.1	2.44 (1.11–5.36)
Soon 2012	5	9	19	26	19.3	0.76 (0.41–1.43)
Total (95% CI)		162		127	100.0	1.54 (1.18–2.02)
Total events	109		56			

Heterogeneity: $\chi^2 = 6.85$, $df = 4$ ($p = 0.14$); $I^2 = 42\%$

Test for overall effect: $Z = 3.18$ ($p = 0.001$)



B

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight (%)	Odds ratio MH, fixed, 95% CI
Kondo 1999	26	32	9	21	16.6	1.90 (1.13–3.19)
Iwamoto 2006	28	35	12	24	21.8	1.60 (1.04–2.47)
Schmitz 2009	24	61	2	5	5.7	0.98 (0.32–3.01)
He 2010	47	58	39	66	55.9	1.37 (1.08–1.74)
Total (95% CI)		186		116	100.0	1.49 (1.22–1.81)
Total events	125		62			

Heterogeneity: $\chi^2 = 1.92$, $df = 3$ ($p = 0.59$); $I^2 = 0\%$

Test for overall effect: $Z = 3.99$ ($p < 0.0001$)

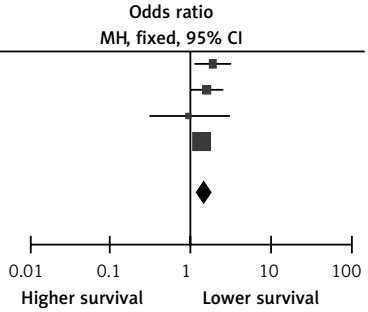


Figure 3. Analysis of COX-2 expression and survival of HCC patients. Forest plot of RR for overall survival (**A**) and disease-free survival (**B**) among included studies

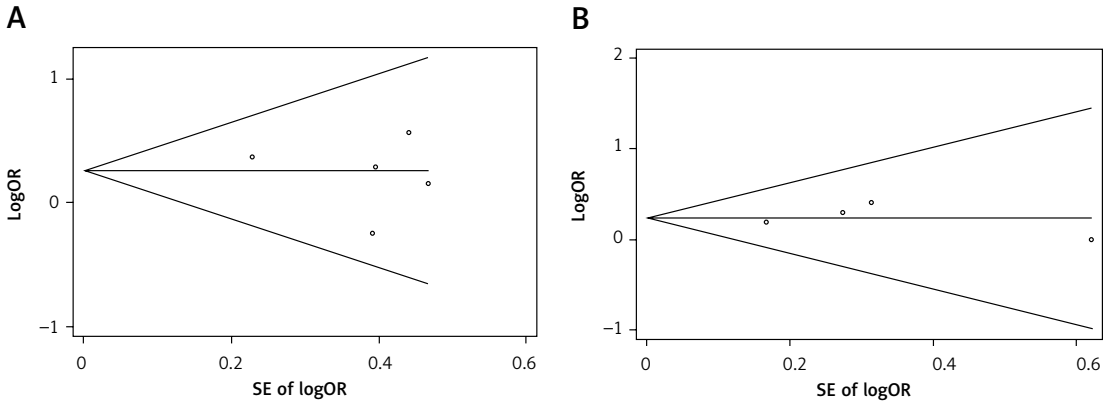


Figure 4. Begg's funnel plot estimated the publication bias of the included literature for OS (**A**) and DFS (**B**)

positively associated with high AFP level and HBsAg status, as well as poor prognoses for patients with HCC. However, we found no significant association between COX-2 positivity and capsular formation, tumor TNM stage, vascular invasion, tumor size or differentiation degree. This trend suggests that COX-2 can function as a prognostic factor for predicting the outcomes of HCC patients. Therefore, our data imply that elevated COX-2 expression can contribute to HCC development and progression, and the detection of the COX-2 aberrations may be useful for identifying poor prognoses in patients with HCC. Furthermore, COX-2 may be a therapeutic target for HCC because of the high expression rate of COX-2 in HCC lesions.

In recent years, mounting evidence from meta-analyses has also shown that COX-2 expression is associated with aggressive clinicopathological parameters and unfavorable prognoses in several human malignancies. Mascaux *et al.* found that high COX-2 expression was associated with a trend for shorter survival in stage I NSCLC patients [27]. Lee *et al.* reported that higher COX-2 expression may be an independent risk factor for low OS in patients with ovarian cancer [28]. Shao *et al.* demonstrated that COX-2 might play an important role in the progression of prostate cancer (PC), as high COX-2 expression correlated with stages T3-T4 of PC [29]. Huang *et al.* found that COX-2 expression was significantly associated with the age of patients, lymph node metastasis, tumor size, FIGO stage, histological type, and parametric involvement [30]. Moreover, COX-2 overexpression might be an unfavorable prognostic and a chemoradiation resistance predictive factor for cervical cancer. These findings further highlight that COX-2 may play an important role in cancer prognosis.

However, this meta-analysis has some limitations. First, the number of included studies, as well as the included HCC patients in each study, is relatively small. Thus, these factors might have reduced the power and accuracy of subcategory analysis [31]. Second, the OS and DFS outcomes were based on individual unadjusted RRs. Thus, a more precise assessment should be adjusted using other prognostic factors [32]. Third, no clear guidelines are available as regards the methods used for the evaluation of the levels of COX-2 in HCC patients. Such evaluation differs among all the studies. In the assessment of biomarkers, the use of a standard threshold has great importance. Although immunohistochemistry was the most commonly applied method, differences in the cut-off values for the positive COX-2 expression may have contributed to the observed heterogeneity. Subgroup analyses showed that the positive correlation between COX-2 expression and poor OS could not be found in the cut-off > 25% subgroups. Thus, standardized methods and cut-off points that classify COX-2 expression levels as "positive" or "negative" are urgently needed.

In conclusion, despite the limitations of this meta-analysis, our study suggests that COX-2 expression is significantly associated with worse prognosis in terms of shorter OS and DFS in patients with HCC. Hopefully this analysis will stimulate further research with rigid criteria and large study populations to resolve any remaining controversy over the role of COX-2 expression for the prognosis of HCC patients.

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Conflict of interest

The authors declare no conflict of interest.

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