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ORIGINAL RESEARCH

Association of caveolin-1 protein expression with hepatocellular carcinoma: a meta-analysis and literature review

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Background: Aberrant expression of caveolin-1 (CAV-1) is involved in the pathogenesis of hepatocellular carcinoma (HCC); however, the results have been inconsistent due to the small size of sample in the individual study.

Methods: We performed a meta-analysis and evaluated the association of CAV-1 protein overexpression and clinicopathological significance by using Review Manager 5.2. Pooled ORs and HR with corresponding CIs were calculated.

Results: Nine studies were included in the meta-analysis with 810 HCC and 172 cirrhosis patients. CAV-1 protein overexpression was correlated with the risk of cirrhosis; OR was 3.25, p=0.01. Furthermore, the rate of CAV-1 protein overexpression was significantly higher in HCC with cirrhosis than HCC without cirrhosis, suggesting that the CAV-1 protein overexpression likely initiated carcinogenesis in liver with cirrhosis and subsequently contributed to the progression of HCC. In addition, CAV-1 protein overexpression was strongly associated with poor differentiated HCC and invasion; ORs were 2.61 and 2.71, respectively. CAV-1 protein overexpression was strongly correlated with poor overall survival in patients with HCC; HR was 0.4, p=0.03.

Conclusions: In summary, CAV-1 protein overexpression is at risk for liver cirrhosis and HCC derived from cirrhosis, and CAV-1 is also a promising prognostic predictor in HCC.

Keywords: hepatocellular carcinoma, caveolin-1, prognosis, diagnosis, overexpression

Background

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the third leading cause cancer-related mortality globally.[1–3] Although many advances have been made in the diagnosis and management of HCC, the prognosis of patients with HCC remains poor due to late diagnosis, high recurrence, and metastasis.[4,5] Therefore, it is critical to identify biomarkers for diagnosis and predict the prognosis of patients with HCC.

Caveolins are a family of scaffolding proteins that coat 50 to 100 nm plasma membrane invaginations known as caveolae.[6] There are three isoforms in the caveolin family: caveolin-1,[7] caveolin-2,[8] and caveolin-3.[8–13] Caveolin-1 is expressed in most cell types such as adipocytes, epithelial cells, and fibroblasts, where the protein is typically found co-expressed with caveolin-2.[8,14] Caveolin-2 is incapable of forming caveolae alone. Caveolin-3 has similar structure and function as caveolin-1, but caveolin-3 is expressed in skeletal, cardiac, and smooth muscle cells.[15] Recent evidence indicates that CAV-1 plays important roles in carcinogenesis by regulating cell

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proliferation, and its roles differ among distinct histological tumor types.[16] The aberrant expression of CAV-1 is involved in the pathogenesis of a variety of cancers. CAV-1 can act as a tumor suppressor or initiator, depending on the tissue of origin.[17] Overexpression of CAV-1 in hepatocarcinogenesis has been shown to protect HCC cells from apoptosis and enhance HCC cells' migration and invasion abilities.[18–21] However, the results were controversial due to the study's small sample size. In the present study, we pooled nine studies and performed a meta-analysis to evaluate the relationship between the overexpression of CAV-1 and clinicopathological significance in HCC.

Methods

Search strategy and selection criteria

To identify relevant published literature, we searched PubMed (1966 ~ 2018), Web of Science (1945 ~ 2018), EMBASE (1980 ~ 2018), and Google scholar.

The following terms were used for searching: caveolin-1 or CAV-1 and HCC, liver cancer or HCC. We included studies that met the following criteria: 1) the association between CAV-1 overexpression and clinicopathological significance in HCC; 2) the association of CAV-1 overexpression and prognosis in HCC patients. Articles were excluded if: 1) the study utilized the same population or overlapping database, 2) the study is about the association between CAV-1 mRNA expression and clinicopathological significance, 3) the studies utilized cell lines, mice, or human grafts; 4) conference abstracts, case reports, reviews, letters, editorials, and expert opinion that contain insufficient data. The detailed information of nine relevant citations is summarized in Table 1.

Data extraction and study assessment

Two reviewers extracted data from selected studies independently. Any discontent was discussed, and a consensus was reached for all issues. The following items were collected from each study: first author's name, year of publication, number of patients, stage of HCC, grade of HCC, overall survival (Kaplan Meier survival curve), CAV-1 expression, the quality of selection, comparability, exposure, and outcomes for study participants.

Statistics analysis

ORs with 95% CIs were calculated by using a fixed- or random-effect model depending on heterogeneity (a fixed-effect model for I^2<50%, a random-effect model for I^2>50%). Further analysis was performed to compare CAV-1 overexpression among HCC versus normal tissue, cirrhosis versus normal liver, high grade of HCC versus low grade of HCC, and advanced stage HCC versus early stage HCC. Raw data were obtained from Kaplan–Meier survival curve, replotting on the log–log scale. This estimates the Cox regression coefficient. The output is the log HR and its standard error. HR with a 95% confidence interval was calculated for the association between CAV-1 expression and prognosis. All *p*-values were two-sided. Funnel plots were used to detect publication bias. All analysis was performed with Review Manager 5.2.

Results

Five hundred and twenty-five articles from database PubMed, Web of Science, Embase, and Google Scholar were screened, and nine articles were included in the meta-analysis (Figure 1). There were 810 HCC and 172 cirrhosis patients involved in the present study. Table 1 summarizes the clinicopathological characteristics of the patients from all of the included studies.

Newcastle Ottawa Quality Assessment Scale (NOQAS) was utilized to assess the quality of all included studies. The scales allocate a maximum of nine points for the quality of selection, comparability, exposure, and outcomes for study participants, and a score ≥7 indicates a good quality. Of the studies, three scored eight points, five scored seven points, and one scored six points. The studies were of a relatively high quality (Table S1) (Supplementary materials).

The rate of CAV-1 protein overexpression in HCC was not significantly higher than in normal liver tissue; OR was 5.36 with 95% CI 0.65–44.49, z=1.56, *p*=0.12 (Figure 2). However, CAV-1 protein overexpression was more frequently observed in cirrhosis than in normal liver tissues; OR was 3.25 with 95% CI 1.26–8.42, z=2.43, *p*=0.01 (Figure 3A). Furthermore, the frequency of CAV-1 protein overexpression in HCC with cirrhosis was significantly higher than in HCC without cirrhosis (Figure 3B); OR was 1.48 with 95% CI 1.01–2.17, z=2.00, *p*=0.05. The results indicate that the overexpression of CAV-1 protein can potentially contribute to the development of cirrhosis and subsequently lead to liver carcinogenesis. Whereas the frequency of CAV-1 protein overexpression in HCC was not significantly higher than in cirrhotic liver, OR was 1.53 with 95% CI 0.75–3.12, z=1.17, *p*=0.24 (Figure 3C).

Overexpression of CAV-1 protein was correlated with high grade of HCC; OR was 2.61 with 95% CI 1.09–6.26, z=2.16, *p*=0.03 (Figure 4). The rate of CAV-1 protein

Table 1 Main characteristics of included studies

Author	Year	Country	Sample Size			Grade		Tumor Size		Invasion		Stage		HR	HCC with cirrhosis	
			NCT	Cirrhosis	HCC	L	H	<5	≥5	+	–	I+II	III+IV		+	-
Liu[50]	2016	China	-	-	74/359	56/267	18/88	50/228	24/131	-	-	32/196	42/163	Log(HR): −0.4902 SE: 0.2794	63/294	11/65
Korhan[51]	2014	Turkey	0/5	5/42	12/60	-	-	-	-	-	-	-	-		-	-
Tse[20]	2012	China	4/16	39/101	43/117	20/58	22/57	15/42	28/76	29/66	13/52	-	-	Log(HR): −0.4972 SE: 0.4792	18/48	25/69
Tang[48]	2012	China	-	-	31/160	9/111	22/49	26/128	5/32	17/69	14/91	-	-	Log(HR): −2.1267 SE: 0.6382	28/119	3/41
Li[49]	2011	China	-	-	-	57/111	38/49	73/130	22/32	-	-	-	-	Log(HR) −1.7918 SE: 0.4779	74/119	21/41
Yang[41]	2010	China	-	-	-	-	-	-	-	14/23	25/50	30/53	9/20	Log(HR): 0.9979 SE: 0.5279	-	-
Zhang[19]	2009	China	-	-	-	-	-	4/21	22/54	17/26	9/49	9/30	17/45	Log(HR): −1.8158 SE:0.5883	-	-
Cokakli[18]	2009	Turkey	1/20	12/29	62/95	47/78	15/17	51/78	6/17	29/38	33/57	-	-		11/6	27/51
Yerian[26]	2004	USA	-	-	6/19	-	-	-	-	-	-	-	-		4/14	2/5

Abbreviations: NCT, normal control tissue; HCC, hepatocellular carcinoma; all the numbers mean CAV-1 high expression/total number (CAV-1 high expression and CAV-1 low expression); L, low grade; H, high grade.

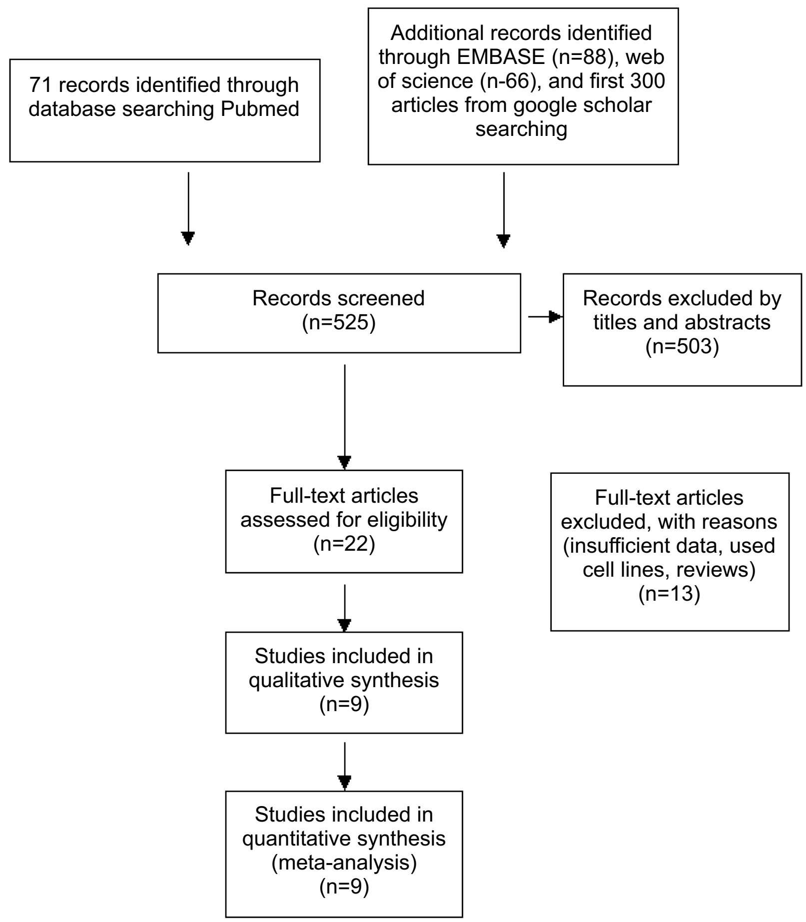

Figure 1 Flowchart of study selection.

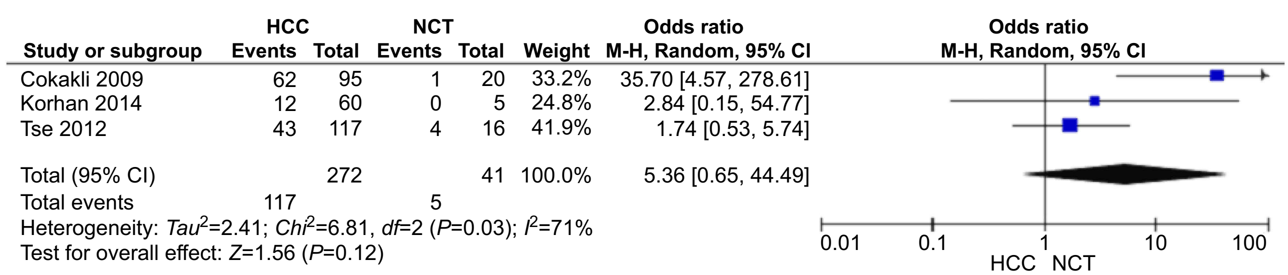

Figure 2 The pooled OR from three studies including 272 HCC patients and 41 normal liver specimen. The studies included investigating the CAV-1 overexpression between HCC and normal liver tissues. 272 HCC patients and 41 normal liver specimen with the combined OR being 5.36 (95% CI=0.65–44.49, p =0.12) are shown.
Abbreviations: HCC, Hepatocellular carcinoma; NCT, Normal control tissue;OR, Odds ratio.

overexpression was higher in stage III–IV HCC than in stage I–II, but there was no significant difference; pooled OR was 1.43 with 95% CI 0.95–2.17, z=6.79, *p*=0.09 (Figure 5). Overexpression of CAV-1 protein was strongly associated with HCC invasion, and the rate of CAV-1 protein overexpression in HCC with metastasis was 2.71 times higher than in HCC without metastasis; 95% CI was 1.26–8.42, z=2.12, *p*=0.03 (Figure 6). No statistically significant correlation was found between the rate of CAV-1 protein overexpression and the size of tumor; OR was 0.97 with 95% CI 0.58–1.62, z=0.12, *p*=0.90 (Figure 7).

CAV-1 protein overexpression was also closely related to poor overall survival in patients with HCC; pooled HR was 0.40 with 95% CI 0.17–0.93, z=6.79, *p*=0.01 (Figure 8).

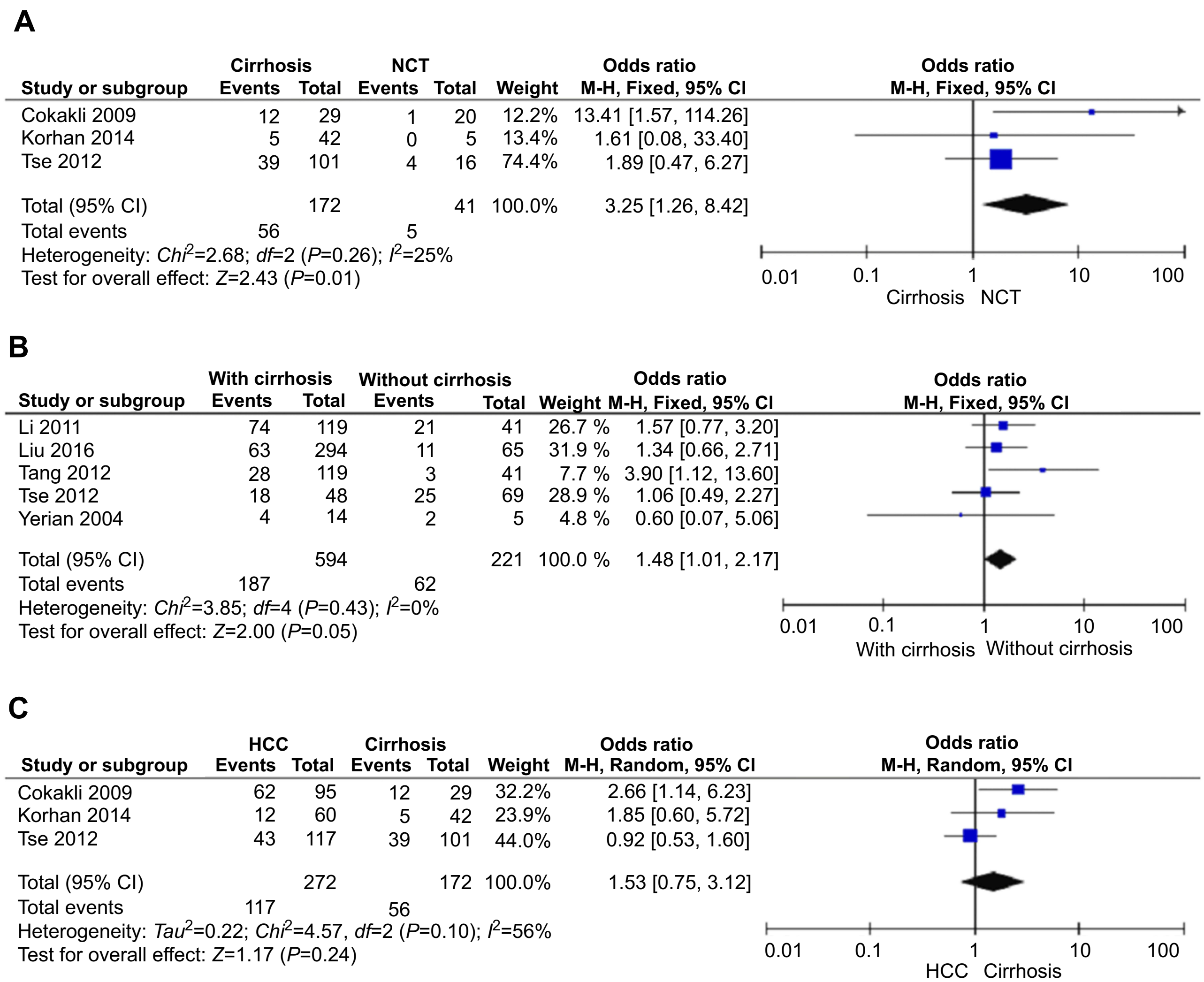

Figure 3 The pooled OR from studies in normal liver, cirrhosis, and HCC. (**A**) The studies included investigating the CAV-1 overexpression between 172 patients with cirrhosis and 41 normal liver specimens. The combined OR was 3.25, 95% CI=1.26–8.42, p=0.01. (**B**) The pooled OR from 5 studies included 594 HCC with cirrhosis patients and 221 HCC without cirrhosis patients, OR=1.48 (95% CI=1.01–2.17, p=0.03). (**C**) The studies included investigating CAV-1 overexpression between 272 patients with HCC and 172 patients with cirrhosis. The combined OR was 1.53, 95% CI=0.75–3.12, p=0.24.

Abbreviations: HCC, Hepatocellular carcinoma; NCT, Normal control tissue;OR: Odds ratio.

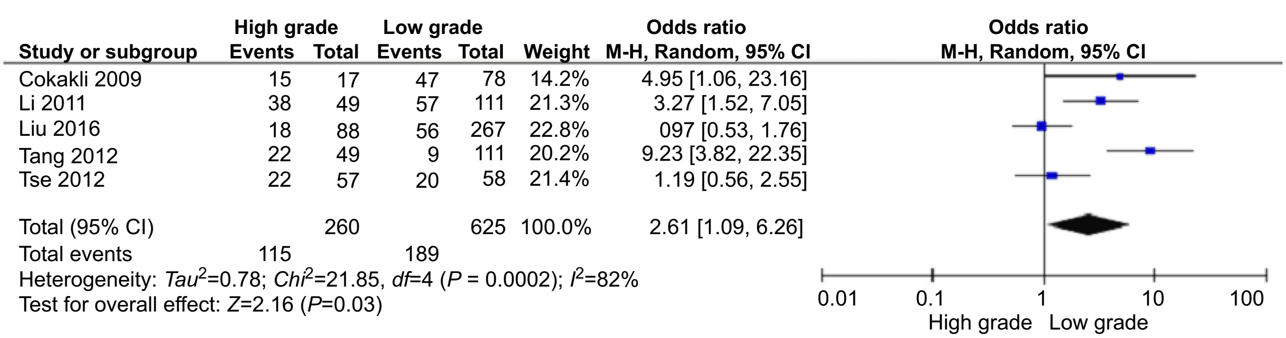

Figure 4 The pooled OR from studies in high and low grade of HCC. Pooled results of CAV-1 overexpression in different grades of HCC. The OR was 2.61, 95% CI=1.09–6.26, p=0.03.

Abbreviations: HCC, Hepatocellular carcinoma; ORs, Odds ratio; CI, Confidence interval.

Study or subgroup	Stage III-IV Events	Stage III-IV Total	Stage I-II Events	Stage I-II Total	Weight	Odds ratio M-H, Fixed, 95% CI
Liu 2016	42	163	32	196	57.8%	1.78 [1.06, 2.98]
Yang 2010	9	20	30	53	24.2%	0.63 [0.22, 1.77]
Zhang 2009	17	45	9	30	18.0%	1.42 [0.53, 3.80]
Total (95% CI)		228		279	100.0%	1.43 [0.95, 2.17]
Total events	68		71			

Heterogeneity: Chi^2=3.12, *df*=2 (*P*=0.21); I^2=36%
Test for overall effect: *Z*=1.71 (*P*=0.09)

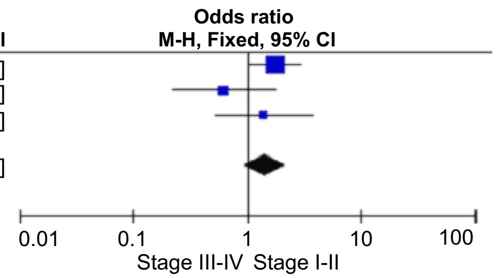

Figure 5 The pooled ORs from studies in different stages of HCC. Pooled results of CAV-1 overexpression in different stages of HCC. The pooled OR was 1.43, 95% CI=0.95–2.17, p=0.09.
Abbreviations: HCC, Hepatocellular carcinoma; ORs, Odds ratio; CI, Confidence interval.

Study or subgroup	Invasion (+) Events	Invasion (+) Total	Invasion (-) Events	Invasion (-) Total	Weight	Odds ratio M-H, Fixed, 95% CI
Cokakli 2009	29	38	33	57	27.5%	2.34 [0.94, 5.85]
Tang 2012	17	69	0	0		Not estimable
Tse 2012	29	66	13	52	35.9%	2.35 [1.06, 5.20]
Yang 2010	14	23	25	50	27.1%	1.56 [0.57, 4.25]
Zhang 2009	17	26	9	49	9.5%	8.40 [2.84, 24.83]
Total (95% CI)		222		208	100.0%	2.71 [1.71, 4.28]
Total events	106		80			

Heterogeneity: Chi^2=5.57, *df*=3 (*P*=0.13); I^2=46%
Test for overall effect: *Z*=4.26 (*P*<0.0001)

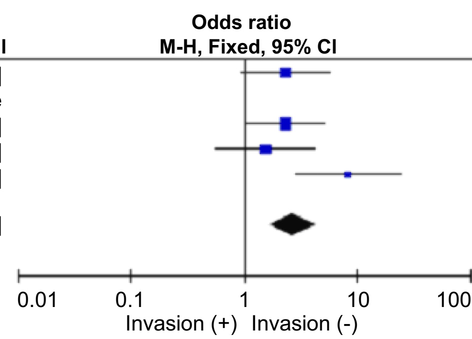

Figure 6 The pooled ORs from studies in different status of invasion. The pooled OR was 2.71, 95% CI=1.71–4.28, p<0.0001.
Abbreviations: ORs, Odds ratio; CI, Confidence interval.

Study or subgroup	>5cm Events	>5cm Total	≤ 5cm Events	≤ 5cm Total	Weight	Odds ratio M-H, Random, 95% CI
Cokakli 2009	6	17	51	78	13.2%	0.29 [0.10, 0.87]
Li 2011	22	32	73	130	18.0%	1.72 [0.75, 3.92]
Liu 2016	24	131	50	228	24.3%	0.80 [0.46, 1.37]
Tang 2012	5	32	26	128	14.0%	0.73 [0.26, 2.07]
Tse 2012	28	76	15	42	18.8%	1.05 [0.48, 2.30]
Zhang 2009	22	54	4	21	11.7%	2.92 [0.87, 9.87]
Total (95% CI)		342		627	100.0%	0.97 [0.58, 1.62]
Total events	107		219			

Heterogeneity: Tau^2=0.21; Chi^2=10.49, *df*=5 (*P*=0.06); I^2=52%
Test for overall effect: *Z*=0.12 (*P*=0.90)

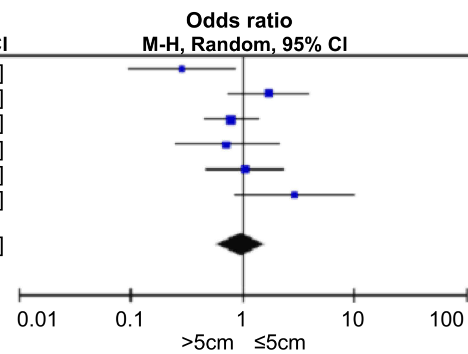

Figure 7 The pooled ORs from studies in different sizes of HCC. The pooled OR was 0.97, 95% CI=0.58–1.62, p=0.90.
Abbreviations: HCC, Hepatocellular carcinoma; ORs, Odds ratio, CI: Confidence interval.

A sensitivity analysis was performed by removing one study at a time, and the ORs were not significantly changed, indicating the stability of the present meta-analysis (S1, S2, S3, S4, S5, and S6). The funnel plots were largely symmetric (Figure 9), suggesting that publication biases do not exist in the meta-analysis of the relationship between CAV-1 overexpression and clinicopathological significance.

Discussion

Caveolins are a family of scaffolding proteins that coat 50 to 100 nm plasma membrane invaginations.[6,22] Lipid rafts play an important role in signaling crosstalk via bringing different proteins into proximity and promote interactions among receptors and intracellular signaling proteins.[23] Cirrhotic liver is related to macroregenerative and dysplastic nodules which are HCC precursor lesions. Our data

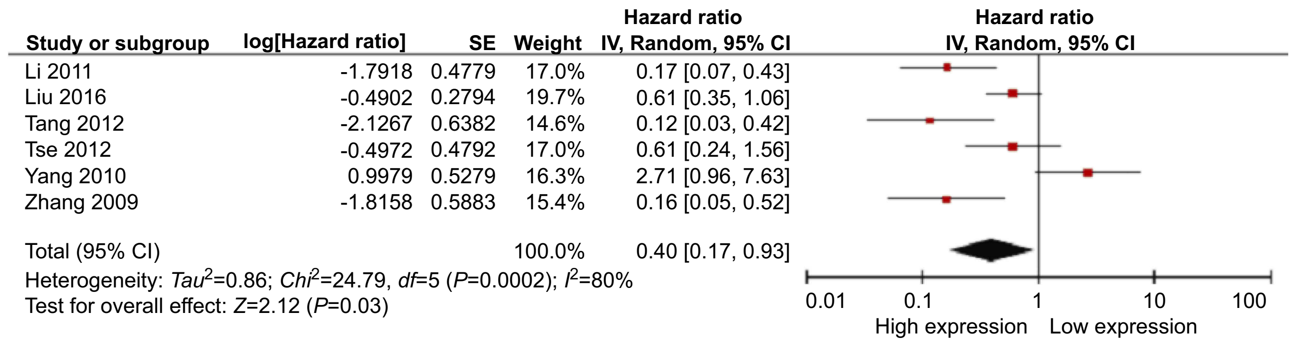

Figure 8 The pooled HR from studies for the association of CAV-1 expression with overall survival of HCC patients. Five studies are eligible for evaluation of OS and CAV-1 overexpression with 719 HCC patients. The pooled HR for OS showed that CAV-1 overexpression was associated with worse survival in HCC, HR=0.40, 95% CI=0.17–0.93, Z=2.12, p=0.03.

Abbreviations: HCC, Hepatocellular carcinoma, HR: Hazard ratio; CI, Confidence interval.

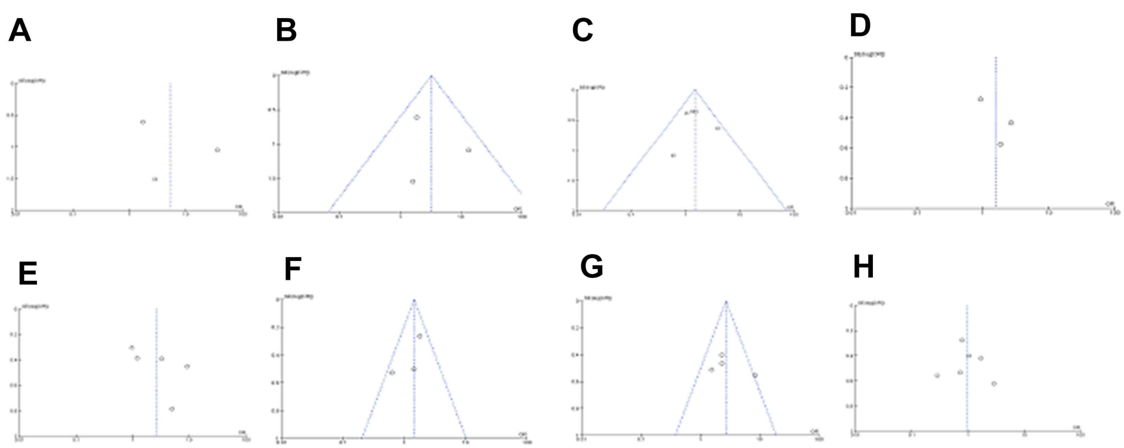

Figure 9 Funnel plots of publication bias in the meta-analysis of CAV-1 overexpression and clinicopathological features. (**A**) CAV-1 overexpression in HCC vs normal liver tissues, (**B**) Cirrhosis vs normal liver tissues, (**C**) HCC with cirrhosis vs HCC without cirrhosis, (**D**) HCC vs cirrhosis, (**E**) different grades of HCC, (**F**) different stages of HCC, (**G**) different status of invasion in HCC, (**H**) different sizes of HCC.

Abbreviations: HCC, Hepatocellular carcinoma.

indicate that the CAV-1 protein overexpression in cirrhosis is significantly higher than in normal liver, suggesting that CAV-1 protein overexpression plays an important role in cirrhosis which then acts as an initiator of carcinogenesis. However, the rate of CAV-1 protein overexpression in HCC is not significantly increased compared to the rate of CAV-1 protein overexpression in normal liver. This is in line with the report that CAV-1 was overexpressed in cirrhotic liver[24,25] and was underexpressed in HCC.[26] Additionally, we found that the frequency of CAV-1 protein overexpression in HCC with cirrhosis is higher than in HCC without cirrhosis. Our data indicate that CAV-1 overexpression likely plays an essential role in liver cirrhosis, subsequently contributing to the development of the HCC that derived from cirrhosis.

There are three isoforms in caveolin family: caveolin-1, caveolin-2, and caveolin-3. Engeman et al reported that the genes encoding caveolin-1 were co-localized at D7S522 locus on human chromosome 7q31.1, which was commonly deleted in cancers of breast,[27,28] colon,[29,30] kidney,[31] prostate,[32,33] ovary,[34] lung,[35] and head and neck.[36] Therefore, they proposed that the caveolin-1 gene may be a tumor-suppressor gene candidate, its loss influences cancer cell survival and growth, and favor tumor progression,[37–42] indicating loss of CAV1 regulation is a critical step in the acquisition of transformed phenotype.[43] However, in later tumor stages, a re-expression of CAV1 seems to support invasion and metastasis.[44,45] CAV1 overexpression may act as an initiator during the early stage and promote invasion at late stages. Whether or not CAV1 functions as a suppressor during the development of HCC, further investigation is needed to be carried out.

Lipid rafts play a pivotal role in signaling crosstalk through bringing different proteins into proximity and facilitating interactions between receptors and intracellular signaling proteins.[23] CAV-1 function as scaffolding proteins that contribute to the assembly of a complex molecular platform, regulating endocytosis and transcytosis of molecules on the cell surface, and organizing signaling proteins that participate in cell proliferation, adhesion, and migration.[17,46] Our data indicate that the overexpression of CAV-1 in HCC is linked to an unfavorable clinicopathological status, including a low degree of differentiation and metastasis. Previous studies demonstrated that the disruption of CAV-1 expression in invasive HCC cells suppresses in vitro migration and invasion,[18,20,21] and also in vivo tumorigenicity and metastasis.[20,21,47] Our results are in agreement with the previous reports. Present data showed that the rate of CAV-1 protein overexpression was higher in stage III–IV HCC than in stage I-II, but there was no significant difference due to small number of sample.

Previous studies showed controversial results of the relationship between CAV-1 protein overexpression and overall survival due to a small samples size.[19,20,41,48–50] Yang et al reported that CAV-1 overexpression was correlated with better prognosis. However, our pooled HR from six studies indicate that the CAV-1 overexpression was significantly correlated with poor prognosis in patients with HCC. The high heterogeneity is due to the result from Yang et al's study. Taken together, CAV-1 protein overexpression can potentially be a prognostic predictor for patients with HCC.

There are a few limitations. First, the criteria for the definition of overexpression of CAV-1 protein varied across the included studies. Second, confounders may exist when looking at the association of CAV-1 overexpression with overall survival since some of the included studies did not adjust for important risk factors such as age, tumor size, and HCC stage.

Conclusions

Our results suggest that the overexpression of CAV-1 protein is associated with the risk of cirrhosis which is an early event of carcinogenesis in the liver and is associated with HCC that was derived from cirrhosis. CAV-1 is correlated with an unfavorable clinicopathological status, including a low degree of differentiation and metastasis. The overexpression of CAV-1 protein is associated with poor overall survival, suggesting that the overexpression of CAV-1 protein predicts a poor prognosis in patients with HCC.

Abbreviation list

CAV-1, caveolin-1; HCC, hepatocellular carcinoma; NOQAS, Newcastle Ottawa Quality Assessment Scale; NCT, normal control tissue.

Availability of data and material

All data generated and analyzed during this study are included in this published article.

Author contributions

All authors contributed to data analysis, drafting or revising the articles, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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