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Review Article

Correlation among the expression of CD133, CD90, and poor survival outcome in hepatocellular carcinoma: a meta-analysis

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Abstract: Background: A meta-analysis was conducted to investigate the association of overexpression of CD133 and CD90 with clinicopathological significance and prognostic importance in hepatocellular carcinoma (HCC) and to estimate whether CD133 and CD90 can be identified as biomarkers for evaluating risk of HCC occurrence. Methods: Relevant articles were retrieved from PubMed, EMBASE, the Cochrane Library, and Chinese CNKI. Additional authoritative papers cited in the retrieved articles, which were published before the deadline of December 2016, were also included. Pathologic characteristics of HCC were determined using Review Manager software version 5.2 and overall survival (OS) and disease-free survival (DFS) rates were determined with Stata statistical software, version 12.0. Results: Twenty qualified studies including 1,981 patients were analyzed. Our study suggests that the presence of cancer stem cells (CSCs) is meaningfully correlated with poor pathologic grading (pooled OR=2.31, 95% CI: 1.87-2.85, p<0.0001) and an advanced stage of carcinoma (pooled OR=3.05, 95% CI: 1.55-5.98, p=0.001). Meanwhile, both CD90 and CD133 overexpression failed to tightly associate with hepatitis, cirrhosis, a high AFP level, metastasis, or tumor number. Additionally, overexpression of CD133 was significantly correlated with worse survival outcomes including OS (pooled HR=1.96, 95% CI: 1.35-2.84, p<0.05) and DFS (pooled HR=1.89, 95% CI: 1.46-2.47, P<0.05). Overexpression of CD90 was also significantly associated with poor survival outcomes: OS (pooled HR=1.96, 95% CI: 1.35-2.84, p<0.05) and DFS (pooled HR=1.67, 95% CI: 1.21-2.30, p<0.05). Conclusion: Our meta-analysis suggests that overexpression of CD133 and CD90 is significantly associated with clinicopathological features and with worse survival outcomes. CD133 and CD90 could be utilized as potential biomarkers for HCC which might help to subgroup high-risk HCC patients characterized by earlier recurrence and poor overall survival after surgical or other treatments.

Keywords: Hepatocellular carcinoma, CD133, CD90, clinicopathological characteristics, survival outcome

Introduction

Hepatocellular carcinoma, a common malignancy and one of the most fatal cancers worldwide, remains difficult to treat. Currently, surgical resection and liver transplantation are the most popular and practical treatment strategies [1, 2]. However, prognosis of HCC is always poor due to frequent recurrence and transfer following surgery. In the past few years, CSCs in liver cancer tissues have been detected [3]. CSCs have an aggressive migration capacity and tumorigenicity which is closely connected with metastasis and recurrence in HCC. CSCs may also influence resistance to radiotherapy and chemotherapy, a factor responsible for the poor effectiveness of HCC treatments [4, 5].

Several studies have identified CD133 as a crucial role player in liver cancer. Suetsugu et al. [6] first indicated CD133 expression in Huh-7 cells, which are highly tumorigenic *in vitro* and *in vivo*. Some studies have reported an association among CD133, metastasis and invasion, as CD133-positive cells display more intensive capacities for colony formation and diffusion [7, 19]. CD90, a glycosylphosphatidylinositol glycoprotein, has been recognized as a CSC marker in HCC. Sukowati CH et al. [8] confirmed that CD90-positive cells have strong proliferation and self-renewal abilities and resistance to chemotherapeutics. Zhu L et al. [9] confirmed that $CD90^{+}CXCR4^{+}$ HCC cells significantly developed metastases in a mouse model. Recently, many investigators have tried to conclude

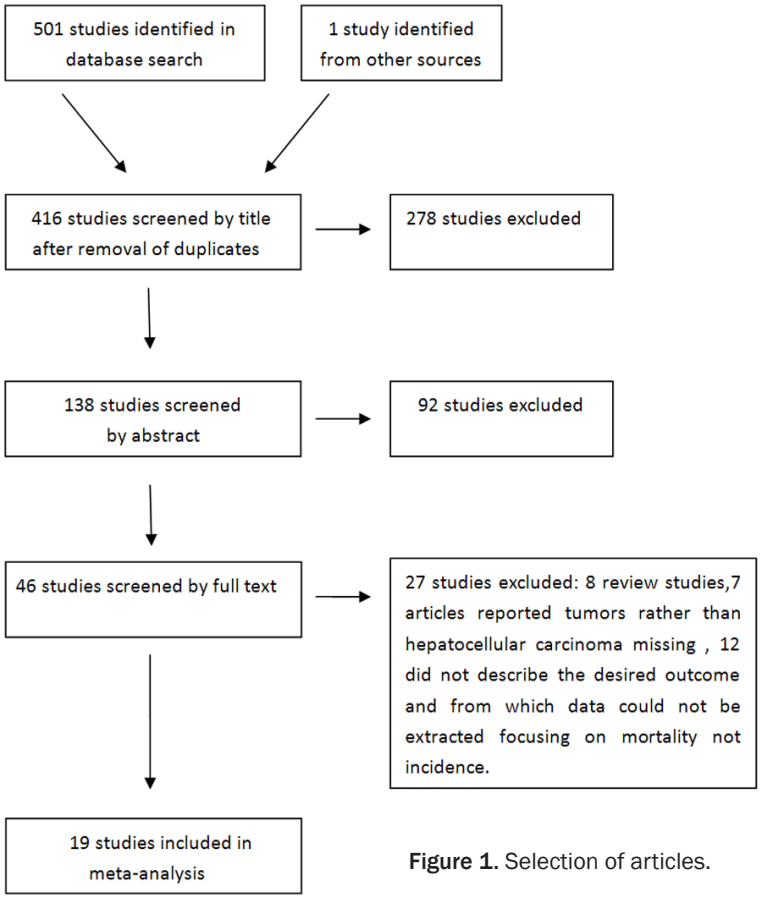


Figure 1. Selection of articles.

whether the existence of CSCs is correlated with clinicopathological factors and prognosis outcomes in HCC. Therefore, this meta-analysis was conducted to evaluate correlation among CD90 and CD133 overexpression and clinicopathological characteristics and prognosis in hepatocellular carcinoma.

Materials and methods

Search strategies

We retrieved articles indexed in EMBASE, PubMed, the Cochrane Library, and Chinese CNKI prior to December 2016. The following medical subject keywords were used:"Liver Neoplasms", "Hepatocellular Carcinoma", "Liver Cancer", "Hepatic Neoplasms", "Hepatic Cancer", "CD-90" OR "Thy-1", "CD133", "Prominin-1", and "Cancer Stem Cells". Every related free term was also searched.

Articles were included that conformed with the following criteria: (1) Hepatocellular carcinoma was diagnosed by histopathological examination; (2) Immunohistochemical staining was used to detect the expression of CD133 and CD90; (3) The literature described the association of CD-133 or CD90 overexpression with survival outcome or described the clinicopathological characteristics of liver neoplasms; (4) Studies contained adequate data to estimate an odds ratio (OR) with 95% confidence interval (CI) of clinicopathological parameters or a hazard ratio (HR) with 95% CI of OS or DFS. Meanwhile, studies including less than 20 patients were excluded. Patients with HCC, with BDTT, or those who had accepted TACE treatment were excluded. **Figure 1** displays the study screening process. To improve reliability, two independent reviewers evaluated the relevant articles and resolved any disagreements by discussion.

Statistical analysis

We used ORs with 95% CI to calculate associations between CD133 and CD90 expression and various clinicopathological features of HCC including tumor differentiation, tumor stage, AFP level, tumor capsule, hepatitis (including HBV or HCV infection), cirrhosis, metastasis, and vascular invasion. We also utilized HRs with 95% CI to evaluate correlation between the overexpression of CSCs and survival outcomes. HRs with 95% CI of overall survival and disease-free survival were not directly found in some literature, however, these studies provided Kaplan-Meier curves to describe survival outcomes. In these cases, the data were digitized and extracted using Engauge Digitizer 4.1 software to obtain the lnHR and variance by the methods provided by Tierney et al. [36] Heterogeneity was evaluated by Cochran w2 Q statistics and the I2 test which decided the use of either a fixed-effects or a random-effects model. We conclude from the study that heterogeneity exists if the *P*-value is less than 0.05 or if the I2 is greater than 50%. The funnel plot of Begg's or Egger's was applied to assess the

Table 1. Characteristics of the articles included in this study

References	Markers	Technology	Cutoff (IHC)	Number of patients	Age (mean/median)	Male (%)	Treatment	Cases (Marker+)	Control (Marker-)	NOS	Follow-up period (months)	HR
Chan et al.	CD133	IHC	NS	282	55.4	84	LR	38		5	240	2.08
Chen et al.	CD133	IHC	0%	387	NS	88	LR	216		6	96	1.21
Cheng et al.	CD90	IHC	NS	50	NS	NS	LR/LT	36	30	6	NR	
Guo et al.	CD133	IHC	5%	50	NS	NS	LR	42	10	6	NR	1.36
	CD90							32	13			3.28
Lingala et al.	CD133	IHC	5%	23	56.4	80	NS	10	3	6	NR	
Liu et al.	CD133	IHC	NS	245	48	84	LR	45	26	6	80	1.36
	CD90							91	82			2.09
Lu et al.	CD90	IHC	5%	59	55	83	LT	43	40	6	NR	1.8
Pan et al.	CD133	IHC	0%	70	55	57	LR	49	70	5	62	2.15
Sasaki et al.	CD133	IHC	0%	136	61	82	LR	30		6	90	1.46
Song et al.	CD133	IHC	1.32%	63	50.3	79	LR	26		6	60	2.87
Zhang et al.	CD90	IHC	NS	50	55	82	LR	46	20	6	NR	
Wu et al.	CD133	IHC	0%	190	58.7	93	LR	42		6	128	1.59
Yeh et al.	CD133	IHC	NS	154	56	74	LR	24		6	125	6.17
Yilmaz et al.	CD133	IHC	0%	35	64	86	LR	24	31	6	NR	
	CD90							9	63			
Yu et al.	CD133	IHC	NS	20	51	85	LR/LT	17		5	NR	
	CD90							18				
Wu XH et al.	CD133	IHC	NS	54	52	74	LR	39	14	6	NR	
	CD90							40				
Wong et al.	CD90	IHC	5%	164	57.5	84	LR	75	122	6	200	1.97
Xi Zhang et al.	CD90	IHC	5%	66	NS	90	LR	28		5	60	
Zhao et al.	CD90	IHC	NS	86	NS	67	LR	58	8	6	NR	2.09

Footnotes: IHC, immunohistochemistry; NS, not specified; LR, liver resection; LT, liver transplantation; NR, not reported; NOS Newcastle-Ottawa Scale. The value of HR that could not be obtained directly from published data was calculated using the method described in the 'Materials and methods' section.

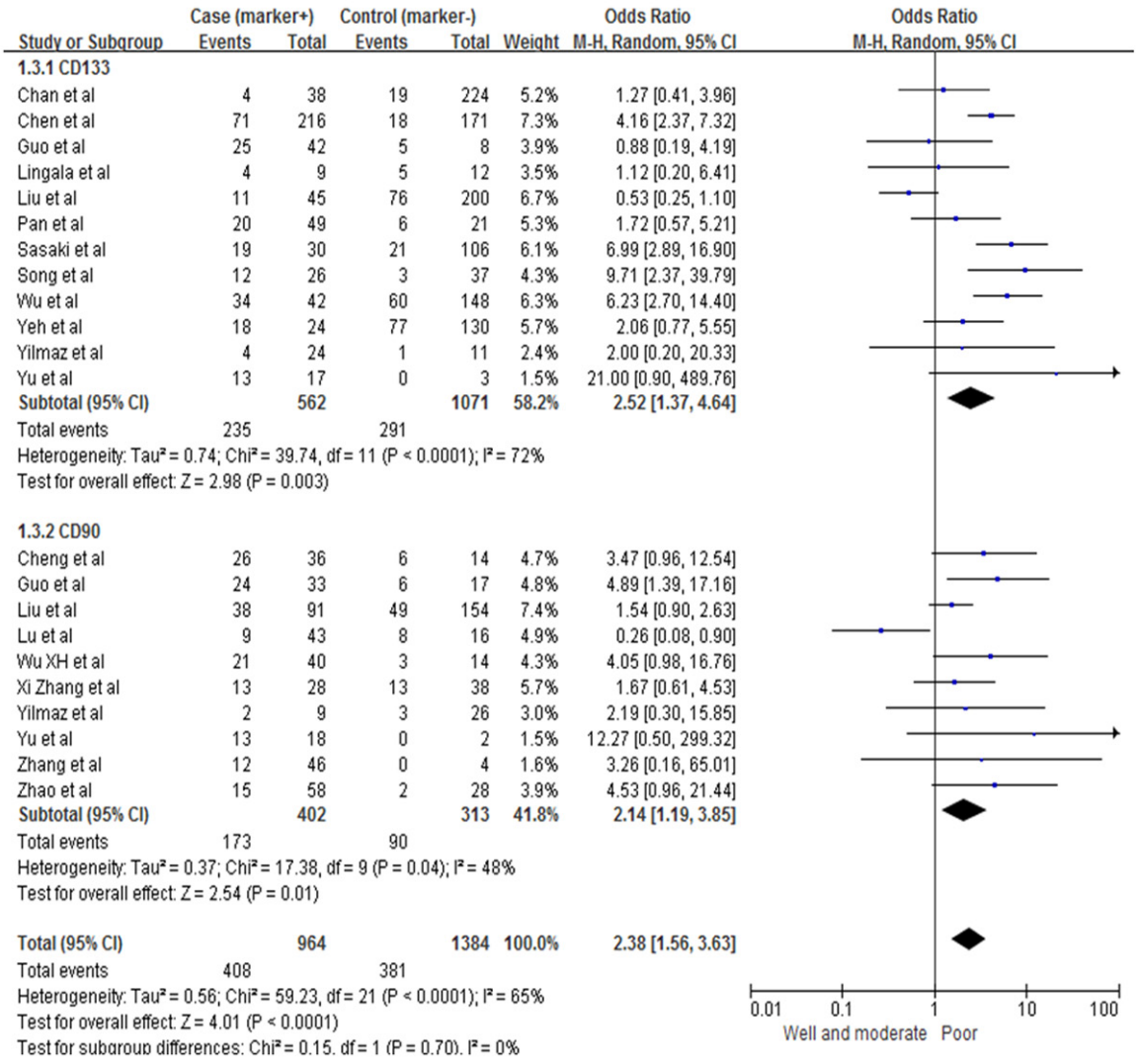


Figure 2. Association between stem cell markers and tumor differentiation.

publication bias. Cochrane Review Manager version 5.2 and Stata statistical software version 12.0 were used to calculate statistics from relevant studies. For sensitivity analysis, we further examined the included studies by deleting one study each time.

Results

Description of studies

Based on the retrieval conditions, 501 total articles were searched and 1 study was obtained by analyzing the references of relevant articles. This analysis contained 1,981 patients. The smallest sample size of the included studies was 20 and the largest was 387. All positive cancer stem cell marker expression levels were detected by immunohistochemical staining methods. According to the marker expression levels, the patients were divided into positive and negative groups. CD133 was detected as the CSC marker in 13 articles [10-11, 13-15, 17-19, 21-25] while CD90 was considered as the CSC marker in 11 studies [12, 13, 15, 16, 20, 23-28]. Five studies utilized both CD90 and CD133 as CSC markers [13, 15, 23-25]. Fourteen articles reported Kaplan-Meier curves to assess the OS whereas only eight studies reported the DFS. **Table 1** shows the main features of all studies in this analysis.

Association among CSC markers and clinicopathological characteristics

In the subgroup analyses, we observed statistically significant associations of CD133-positive

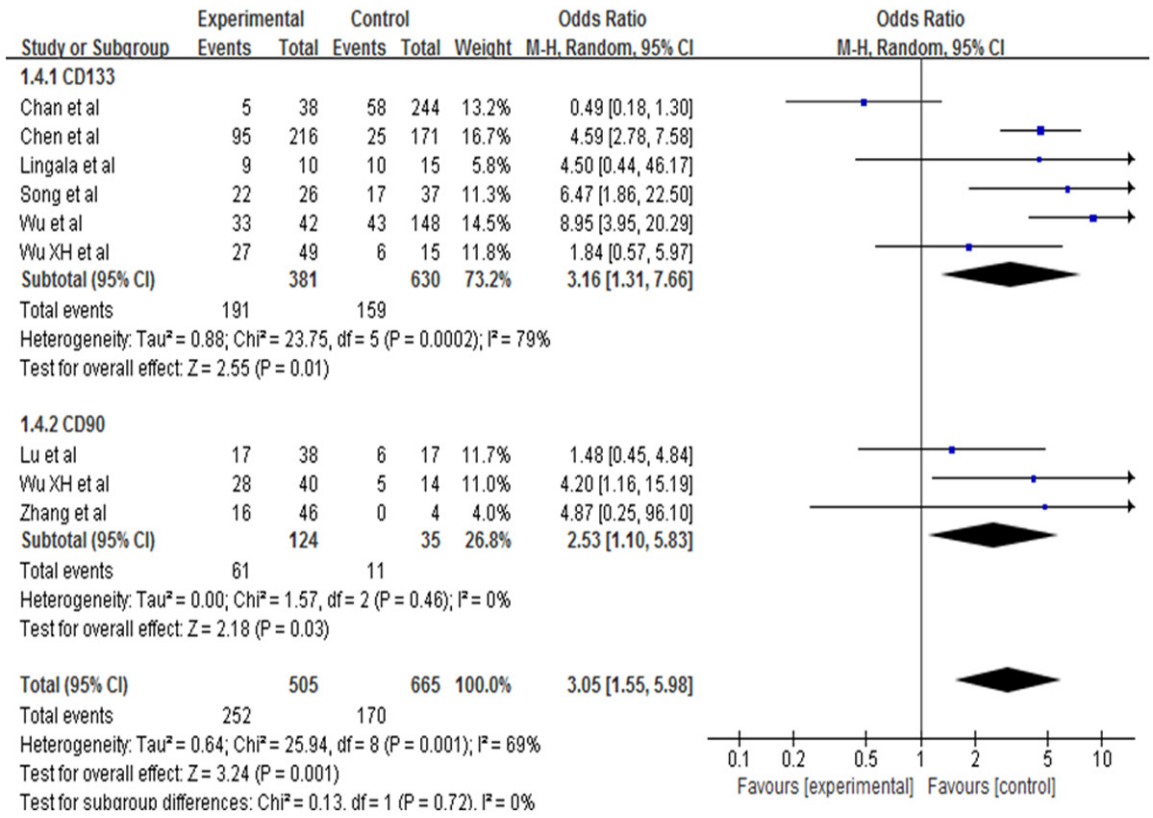


Figure 3. Association between stem cell markers and tumor grade.

Table 2. CD133 overexpression and clinicopathological characteristics in HCC

Clinicopathological characteristics	Studies (n)	Patients (n)	Analytical modle	Pooled OR (95% CI)	*P* value	Heterogeneity
HBV (negative vs. positive)	7	1148	REM	1.07 (0.54, 2.11)	0.85	Q Chi 0.54
HCV (negative vs. positive)	4	762	FEM	0.77 (0.43, 1.38)	0.38	Q Chi 0.43
Cirrhosis (absent vs. present)	5	787	REM	1.25 (0.66, 2.37)	0.48	Q Chi 0.66
AFP (absent vs. present)	8	1066	REM	1.05 (0.63, 1.76)	0.84	Q Chi P=0.05
Tumor differentiation (I+II vs. III+IV)	12	1633	REM	2.52 (1.37, 4.64)	0.003	Q Chi 1.37, 4.64
Tumor stage (I+II vs. III+IV)	6	1011	REM	3.16 (1.31, 7.66)	0.01	Q Chi 1.31
Tumor number (single vs. multiple)	6	857	FEM	1.33 (0.92, 1.91)	0.13	Q Chi 0.92
Tumor size (single 5 cm)	7	904	REM	0.84 (0.44, 1.58)	0.58	Q Chi 0.44
Vascular invasion (absent vs. present)	6	1163	REM	1.49 (0.85, 2.62)	0.16	Q Chi 0.85
Encapsulation (absent vs. present)	6	654	REM	0.47 (0.23, 0.96)	0.04	Q Chi 0.23
Metastasis (absent vs. present)	4	596	FEM	1.04 (0.51, 2.11)	0.92	Q Chi 0.51
Vascular thrombosis (absent vs. Present)	7	1283	FEM	1.81 (1.32, 2.48)	0.0002	Q Chi 2.32, 2.48

Footnotes: P<0.05 was considered to indicate statistically significant differences between CD133 expression and clinicopathological features; P>0.10 or I2>50% indicated the existence of heterogeneity; P<0.05 was representative of the significant publication bias; HBV hepatitis B virus, HCV hepatitis C virus, AFPα-fetoprotein, OR odds ratio, CI confidence interval, FEM fixed-eff ects model, REM random-effects model.

cells with certain clinicopathological parameters including carcinoma with low degree of differentiation (pooled OR=2.52, 95% CI: 1.37-4.64, P=0.003, random-effect), advanced stage of carcinoma (pooled OR=3.16, 95% CI: 1.31-7.66, P=0.01, random-effect), positive tumor capsule (pooled OR=0.47, 95% CI: 0.23-0.96, P=0.04, random-effect), and vascular thrombosis (pooled OR=1.81, 95% CI: 1.32-2.48, P=0.0002, fixed-effect). CD90-positive cells in HCC patients were also associated with biologically aggressive manifestations such as

Table 3. CD90 overexpression and clinicopathological characteristics in HCC

Clinicopathological characteristics	Studies (n)	Patients (n)	Analytical modle	Pooled OR (95% CI)	*P* value	Heterogeneity
HBV (negative vs. positive)	3	202	FEM	1.54 (0.63, 3.75)	0.34	Q Chi 0.63
Cirrhosis (absent vs. present)	2	145	REM	0.37 (0,.01, 9.30)	0.55	Q Chi 0.01
AFP (absent vs. pres)	7	381	FEM	0.81 (0.45, 1.47)	0.49	Q Chi 0.451
Tumor differentiation (I+II vs. III+IV)	10	715	REM	2.14 (1.19, 3.58)	0.01	Q Chi 1.19, 3.58
Tumor stage (I+II vs. III+IV)	3	159	FEM	2.53 (1.10, 5.83)	0.03	Q Chi 1.10
Tumor size (I+II vs. III+IV)	5	271	FEM	1.96 (1.07, 3.62)	0.03	Q Chi 1.07
Encapsulation (absent vs. present)	3	189	REM	0.43 (0.11, 1.70)	0.23	Q Chi 0.11
Vascular invasion (absent vs. present)	3	365	REM	3.21 (0.30, 34.70)	0.34	Q Chi 0.30
Vascular thrombosis (absent vs. present)	2	295	REM	1.68 (0.09, 33.26)	0.73	Q Chi 0.09, 33.26

Footnotes: P<0.05 was considered to indicate statistically significant differences between CD90 expression and clinicopathological features; P>0.10 or I2>50% indicated the existence of heterogeneity; P<0.05 was representative of the significant publication bias; HBV hepatitis B virus, HCV hepatitis C virus, AFPα-fetoprotein, OR odds ratio, CI confidence interval, FEM fixed-effects model, REM random-effects model.

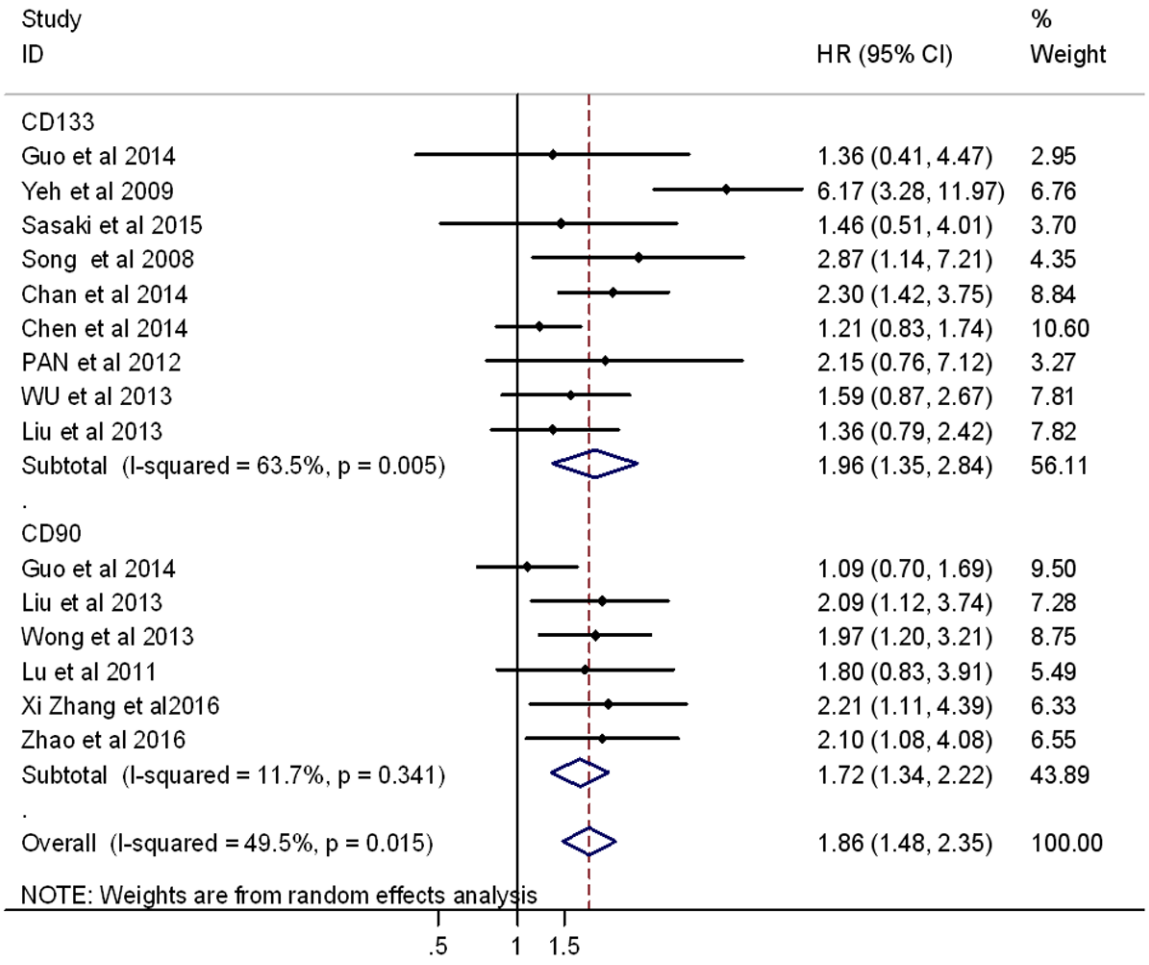


Figure 4. Meta-analysis of correlations among overexpression of CD133 and CD90 and OS in HCC patients.

poor tumor grading (pooled OR=2.14, 95% CI: 1.19-3.85, P=0.01, random-effect), advanced stage of carcinoma (pooled OR=2.53, 95% CI: 1.10-5.83, P=0.03, random-effect), and tumor size (pooled OR=1.96, 95% CI: 1.07-3.62, P=0.03).

Overall for the entire analysis, HCCs with the assumed CSC markers were correlated with poor carcinoma differentiation (pooled OR= 2.31, 95% CI: 1.87-2.85, P<0.00001) (**Figure 2**) and advanced stage of carcinoma (pooled OR=3.05, 95% CI: 1.55-5.98, P=0.03) (**Figure**

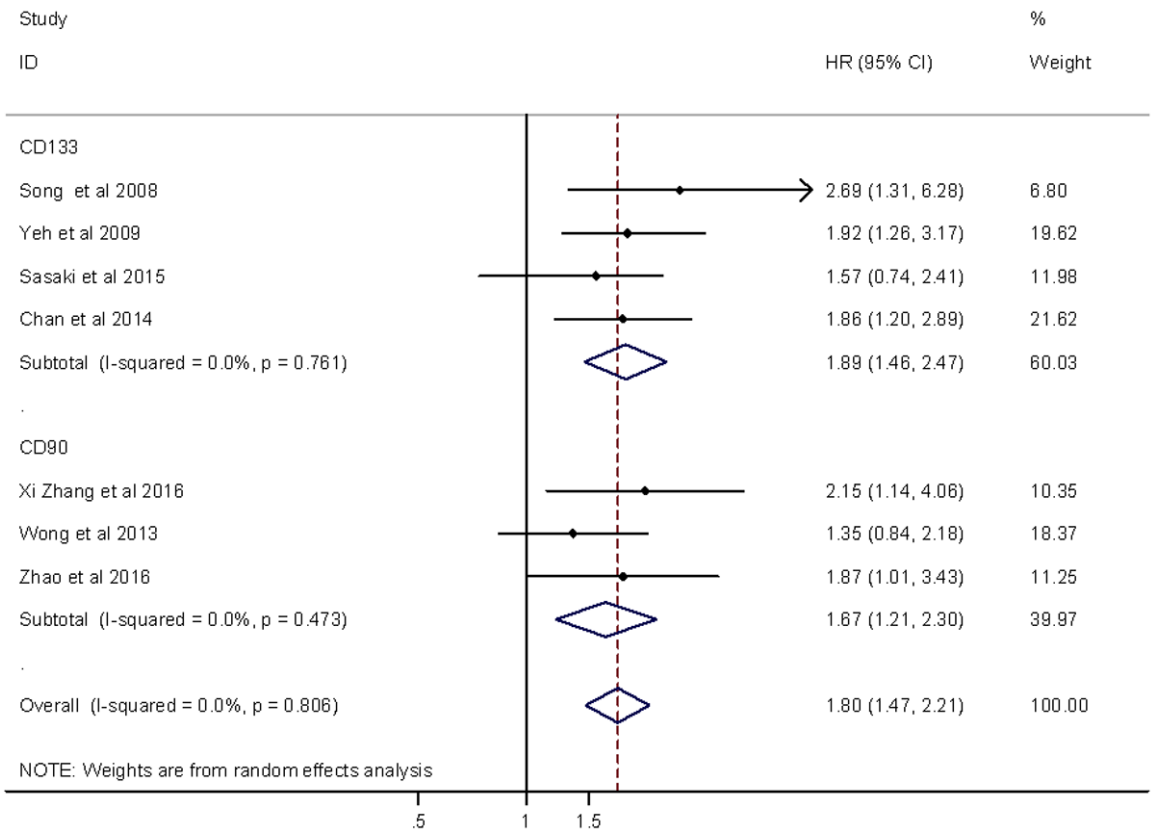


Figure 5. Meta-analysis of correlations among overexpression of CD133 and CD90 and DFS in HCC patients.

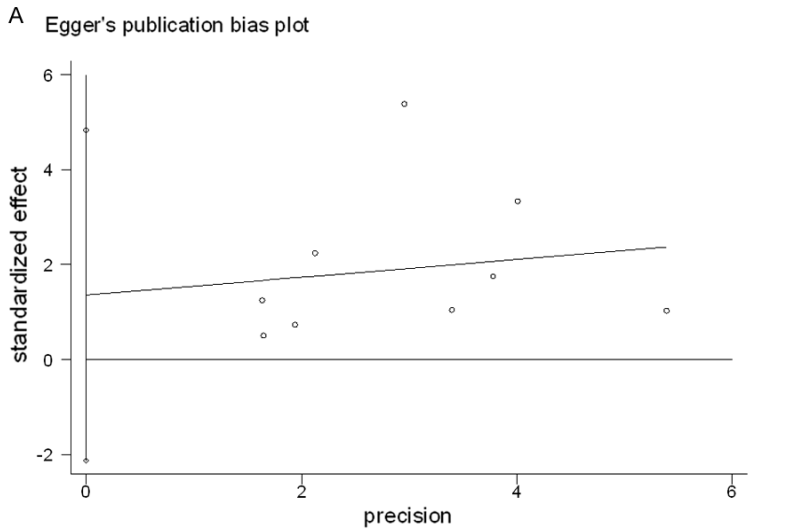
3). Nevertheless, we did not find statistically significant associations between expression of CSC markers and HBV (pooled OR=1.15, 95% CI: 0.69-1.93, P=0.60, random-effect), HCV (pooled OR=0.79, 95% CI: 0.44-1.43, P=0.60, fixed-effect), cirrhosis status (pooled OR=0.97, 95% CI: 0.47-2.01, P=0.94, random-effect), tumor size (pooled OR=1.17, 95% CI: 0.72-1.90, P=0.53, random-effect), and high level of AFP (pooled OR=0.95, 95% CI: 0.65-1.39, P=0.80, random-effect) (**Tables 2** and **3**).

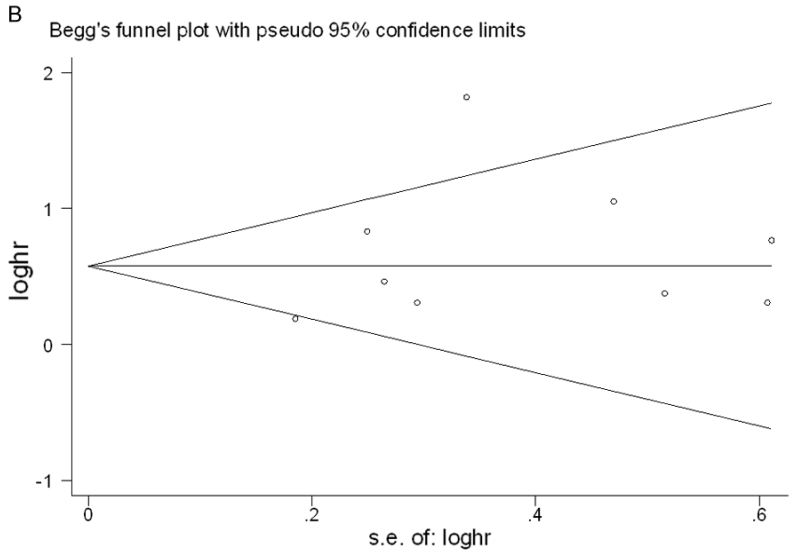
Correlation among CSC markers and survival outcomes in HCC patients

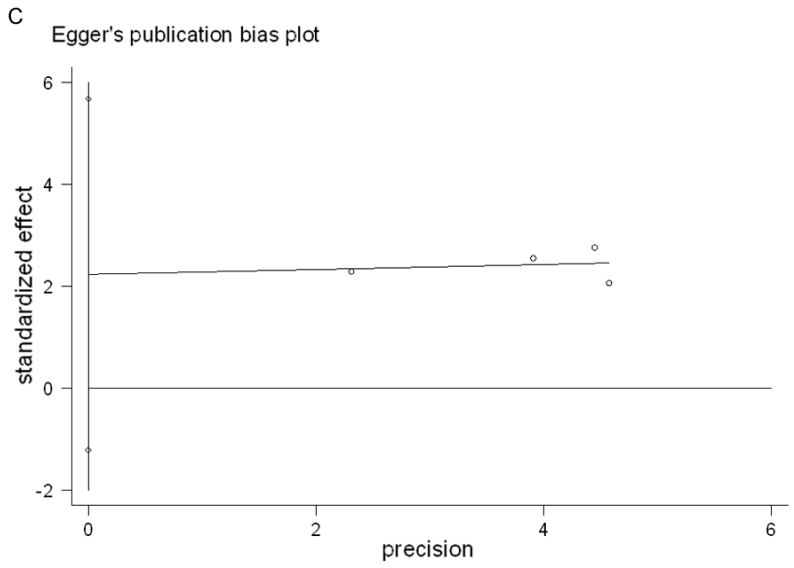
OS and DFS were used to assess the correlation between CSC markers and clinical characteristics of hepatocellular carcinomas. HRs with 95% CI, which were unmodulated, could be obtained from the Kaplan-Meier curves presented in the articles. Regarding the HR of overall survival, we found diversity between CD133 and CD90 markers (**Figures 4** and **5**). In this subgroup, nine studies showed the relationship between CD133-positive cells and overall survival (pooled HR=1.96, 95% CI: 1.35-2.84, p<0.05) and there was little heterogeneity (P=0.005 for the Q-test, I2=63.5% for the I2 test). On the other hand, six articles reported correlations between CD90 overexpression and overall survival (pooled HR=1.72, 95% CI: 1.34-2.22, p<0.05) with no heterogeneity (P=0.341 for the Q-test, I2=11.7% for the I2 test). The HR of DFS included four studies describing correlations in CD133 overexpression and disease-free survival (pooled HR= 1.89, 95% CI: 1.46-2.47, P<0.05) with no heterogeneity (P=0.761 for the Q-test, I2=0.0% for the I2 test). Three articles reported Kaplan-Meier curves for DFS in association with CD90. We calculated the correlation between high CD90 expression and disease-free survival (pooled HR=1.67, 95% CI: 1.21-2.30, p<0.05) with no heterogeneity (P=0.806 Q-test, I2= 0.0% I2 test).

Publication bias and sensitivity analysis

This meta-analysis of prognosis in HCC was limited by many inherent conditions. For instance,







the sample sizes of the included articles were generally small and lacked adequate survival data was an important obstacle to more accurate calculations. In the case of survival outcome and CD133, the shapes of the Begg's and Egger's funnel plots revealed no clearly unsymmetrical patterns in the outcomes of overall survival (P=0.602 in Begg's test; P=0.386 in Egger's test) and DFS (P=0.089 and P=0.108, in Begg's and Egger's tests, respectively). For CD90, our study revealed no distinct publication bias for overall survival (P=0.707 in Begg's test; P=0.156 in Egger's test) or disease-free survival (P= 0.296 in Begg's test; P= 0.08 in Egger's test) (**Figures 6**, **7** show the publication bias plots for OS and DFS of CD133 and CD90). To judge the effect of every article on overall influence, we conducted a sensitivity analysis for our study to determine that the meta-analysis was not decided by an individual study. After the removal of each article one by one, the results were not different.

Discussion

In the past few years, CD-133 and CD90 have been recognized as CSC markers in hepatocellular carcinoma. Therefore, we conducted this meta-analysis of 1,981 HCC patients to systematically assess any correlation among the CSC markers CD133 and CD90 and hepatocellular carcinoma. The results suggest

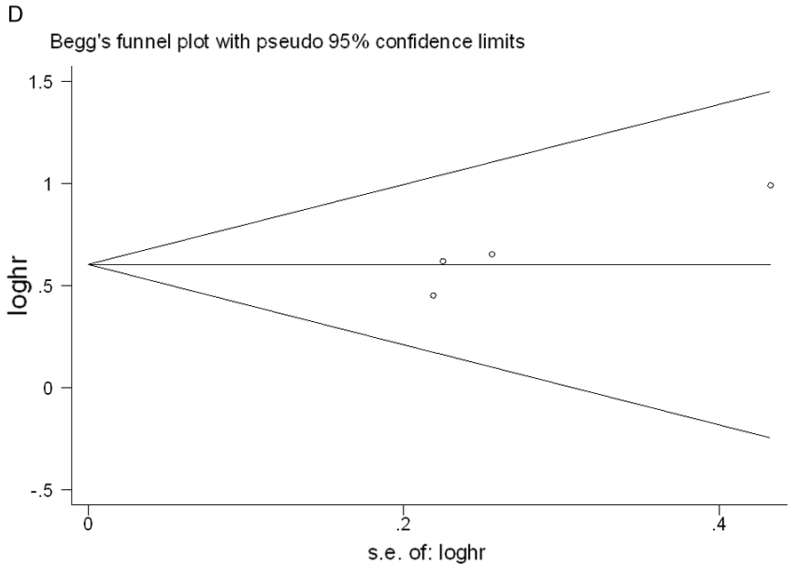


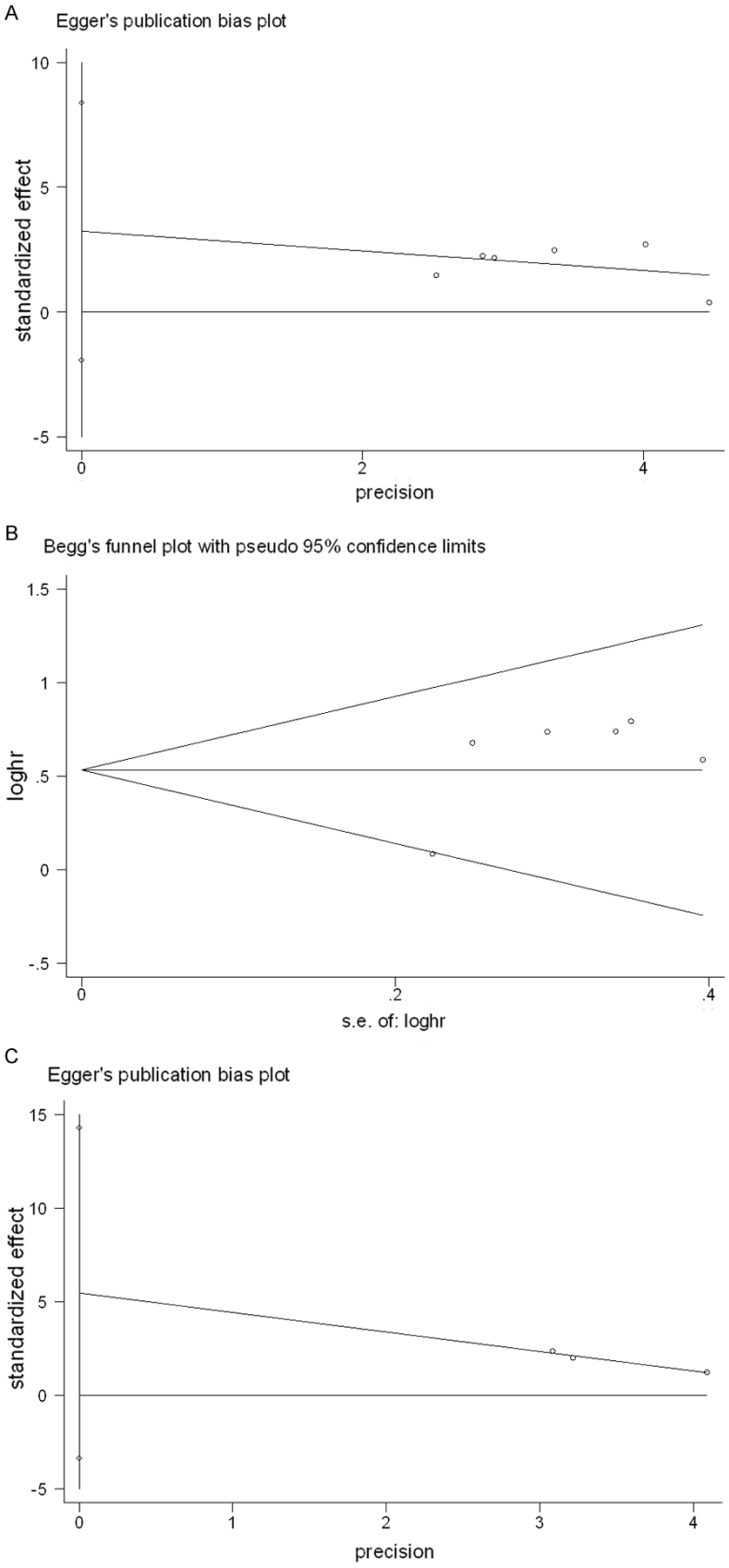
Figure 6. Egger's and Begg's publication bias plots for OS and DFS of CD133 (including A-D). (A) Egger's publication bias plot for the OS of CD133. (B) Begg's publication bias plot for the OS of CD133. (C) Egger's publication bias plot for the DFS of CD133. (D) Begg's publication bias plot for the DFS of CD133.

that CSC markers, particularly CD133 and CD90, are highly correlated with clinicopathological parameters and poor survival outcomes in HCC.

Chai S et al. [29] demonstrated CD133 as a target of miR-142-3p in its capacity to offer cancer-stem-cell-like features in liver cancer. Our findings support that CD133 overexpression is meaningfully correlated with low degree of differentiation carcinomas, advanced stage carcinomas, vascular thrombosis, and tumor encapsulation. Additionally, CD133 is considered a momentous factor for tumorigenesis and survival outcome in HCC. Tang KH et al. [30] reported that CD133 accelerates tumor vasculogenesis and stimulates self-renewal through the neurotensin/IL-8/CXCL1 signaling pathway, which influences the prognosis of hepatocellular carcinoma patients. In our current study, we conclude that CD133 is closely correlated with poor survival outcomes. On the other hand, our results show that CD133 is not tightly associated with hepatitis, cirrhosis, elevated levels of AFP, tumor size, tumor number, metastasis, and vessel invasion. These results are mostly in agreement with previous research, with the exception of the tumor capsule [31]. Many factors could explain this discrepancy. First, we included literature on the associations among CD133 overexpression and clinicopathological characteristics, overall survival, and disease-free survival of HCC. Second, we excluded the patients with HCC containing BDTT and patients who were treated after TACE or biological treatment. Third, we excluded sample sizes of less than 20 patients. In spite of this, we are looking forward to high quality research studies to illustrate this issue.

CD90, a GPI-anchored glycoprotein, exists primarily in hemamoebas and is involved in cell-cell and cell-matrix interactions [32]. Cellular expression of CD90 in cell lines of human HCC has been demonstrated to invoke a higher capacity of tumorigenicity [33]. CD90 is already considered to play an important role in HCC tumor initiation and progression by activating self-renewal, invasion, and migration through the Notch and Wnt/β-catenin signaling pathways and has demonstrated enhanced tumorigenicity, vascular invasion, and metastasis of liver cancer [34]. Our study demonstrates the statistical significance between CD90 overexpression and advanced tumor stage, poor tumor grading, and tumor size. Furthermore, high expression of CD90 was tightly correlated with poor DFS and OS. A previous study reported that CD90 overexpression has high specificity and sensitivity in predicting poor differentiation in HCC [35]. Therefore, CD90 overexpression may play a critical part in the assessment of clinical characteristics and survival outcomes which could serve as a new potential therapeutic target in hepatocellular carcinoma.

However, there remained some unavoidable limitations. First, the sample size of the studies included was small. Furthermore, the patients were mostly Asian, as articles written in languages other than English and Chinese were not included in this meta-analysis. Second, while we required positive detection of CSC markers via immunohistochemical staining, specific conditions such as different antibodies and scoring systems may have caused discrep-



ancies in this study since the cutoff value differed in those articles. Furthermore, we calculated the HRs of OS and DFS that were obtained from Kaplan-Meier curves as described by Tierney et al. [36] and this might have an influence on the accuracy of the results. In general, the heterogeneity in our article could be accepted.

A recent publication suggested that the PTEN/AKT/mTOR signaling pathway might play an important part in actuating recurrence and affecting prognosis in hepatocellular carcinoma [37]. It has also been suggested that positive expression of p-AKT and p-mTOR are correlated with overexpression of CD133 and CD90. Chen WC et al. [38] reported that $CD90^+$ cells from HepG2, Hep3B, and HuH7 cells may upregulate expression of CD133 via the CD90-integrin-AMPK-CD133 signaling axis in hepatocellular carcinoma and considered that molecules such as OSU-CG5 and others could restrain the signaling pathway. Our findings show that both CD133 and CD90 are significantly associated with clinicopathological characteristics and poor survival outcomes. Due to a lack of co-expression data in relevant HCC studies, we could not evaluate the relationship between HCC and co-expression of CSC markers. We look forward to more relevant searches to evaluate this hypothesis and provide a new biological molecule-targeted therapy.

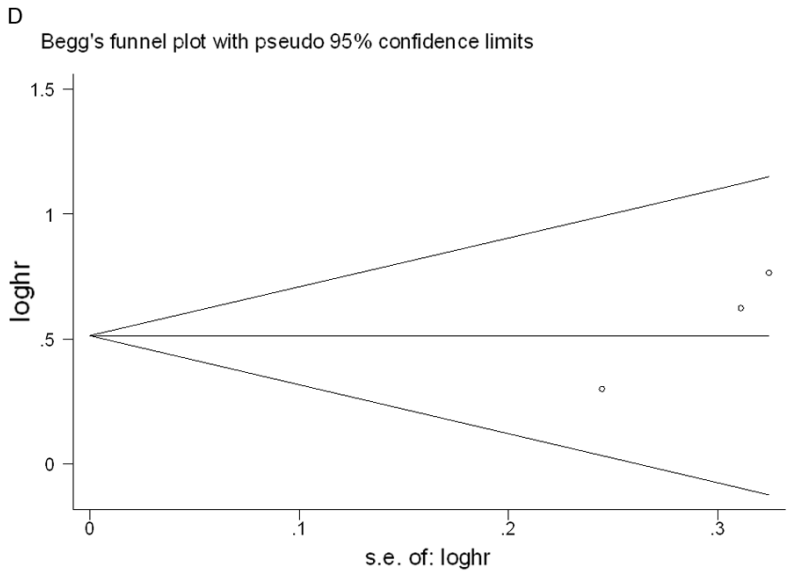


Figure 7. Egger's and Begg's publication bias plots for OS and DFS of CD90 (including A-D). (A) Egger's publication bias pot for the OS of CD90. (B) Begg's publication bias pot for the OS of CD90. (C) Egger's publication bias plot for the DFS of CD90. (D) Begg's publication bias plot for the DFS of CD90.

In summary, the results of our article indicate that positive expression of both CD133 and CD90 is significantly correlated with poor differentiation and advanced stage. Regarding survival outcomes, overexpression of both markers was tightly associated with poor OS and poor DFS. Our findings suggest that CD133 and CD90 could be utilized as potential biomarkers for HCC which might help to subgroup high-risk HCC patients characterized by earlier recurrence and poor overall survival after surgical or other treatments. We are looking forward to the potential of these new molecular-targeted therapies for hepatocellular carcinoma.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

HCC, Hepatocellular carcinoma; OS, Overall survival; DFS, Disease-free survival; CSCs, Cancer stem cells; OR, Odds ratio; CI, Confidence interval; BDTT, Bile duct tumor thrombi; TACE, Transcatheter arterial chemoembolization; HR, Hazard ratio; HBV, Hepatitis B virus; HCV, Hepatitis C virus; FEM, Fixed-effects model; REM, Random-effects model; IHC, Immunohistochemistry; NS, Not specified; LR, Liver resection; LT, Liver transplantation; NR, not reported; NOS, Newcastle-Ottawa Scale.

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References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA cancer J Clin 2011; 61: 69-90.

[2] Liu M, Jiang L, Guan XY. The genetic and epigenetic alterations in human hepatocellular carcinoma: a recent update. Protein Cell 2014; 5: 673-691.

[3] Chiba T, Zheng YW, Kita K, Yokosuka O, Saisho H, Onodera M, Miyoshi H, Nakano M, Zen Y, Nakanuma Y, Nakauchi H, Iwama A, Taniguchi H. Enhanced self-renewal capability in hepatic stem/progenitor cells drives cancer initiation. Gastroenterology 2007; 133: 937-950.

[4] Ji J, Wang XW. Clinical implications of cancer stem cell biology in hepatocellular carcinoma. Semin Oncol 2012; 39: 461-472.

[5] Rountree CB, Mishra L, Willenbring H. Stem cells in liver diseases and cancer: recent advances on the path to new therapies. Hepatology 2012; 55: 298-306.

[6] Suetsugu A, Nagaki M, Aoki H, Motohashi T, Kunisada T, Moriwaki H. Characterization of CD133+ hepatocellular carcinoma cells as cancer stem/progenitor cells. Biochem Biophy Res Commun 2006; 351: 820-824.

[7] Ma S, Chan KW, Hu L, Lee TK, Wo JY, Ng IO, Zheng BJ, Guan XY. Identification and characterization of tumorigenic liver cancer stem/progenitor cells. Gastroenterology 2007; 132: 2542-2566.

[8] Sukowati CH, Anfuso B, Torre G, Francalnaci P, Croce LS, Tiribelli C. The expression of CD90/Thy-1 in hepatocellular carcinoma: an in vivo and in vitro sutdy. PLoS One 2013; 8: e76830.
[9] Zhu L, Zhang W, Wang J, Liu R. Evidence of CD90+CXCR4+ cells as circulating tumor stem cells in hepatocellular carcinoma. Tumor Biol 2015; 36: 5353-5360.
[10] Chan AW, Tong JH, Chan SL, Lai PB, To KF. Expression of stemness markers (CD133 and EpCAM) in prognostication of hepatocellular carcinoma. Histopathology 2014; 64: 935-950.
[11] Chen K, Li ZH, Jiang P, Zhang X, Zhang YJ, Jiang Y. CD44, CD133 and TF correlate with formation of portal vein tumor thrombus and poor prognosis in patients with hepatocellular carcinoma. J Third Mil Med Univ 2014; 36: 1068-1073.
[12] Cheng BQ, Jiang Y, Li DL, Fan JJ, Ma M. Upregulation of Thy-1 promotes invasion and metastasis of hepatocarcinomas. Asian Pac J Cancer Prev 2012; 13: 1349-1353.
[13] Guo Z, Li LQ, Jiang JH, Ou C, Zeng LX, Xiang BD. Cancer stem cell markers correlate with early recurrence and survival in hepatocellular carcinoma. World J Gastroenterol 2014; 20: 2098-2106.
[14] Lingala S, Cui YY, Chen X, Ruebner BH, Qian XF, Zern MA, Wu J. Immunohistochemical staining of cancer stem cell markers in hepatocellular carcinoma. Exp Mol Pathol 2010; 89: 27-35.
[15] Liu LL, Li W, Li YJ. Expression of CD133 and CD90 in hepatocellular carcinoma tissue and their clinical significance. Acta Academiae Medicinae Qindao Universitatis 2013; 49: 393-396.
[16] Lu JW, Chang JG, Yeh KT, Chen RM, Tsai JJ, Hu RM. Overexpression of Thy1/CD90 in human hepatocellular carcinoma is associated with HBV infection and poor prognosis. Acta Histochem 2011; 113: 833-838.
[17] QX Pan, ZJ Su, CR Wang, JL Zhuang. Expression of tumor stem cell markers EpCAM and CD133 in human primary hepatocellular carcinoma and their value in prognostic prediction. Tumor I 2012; 32: 628-633.
[18] Sasaki A, Kamiyama T, Yokoo H, Nakanishi K, Kubota K, Haga H, Matsushita M, Ozaki M, Matsuno Y, Todo S. Cytoplasmic expression of CD133 is an important risk factor for overall survival in hepatocellular carcinoma. Oncol Rep 2010; 24: 537-546.
[19] Song W, Li H, Tao K, Li R, Song Z, Zhao Q, Zhang F, Dou K. Expression and clinical significance of the stem cell marker CD133 in hepatocellular carcinoma. Int J Clin Pract 2008; 62: 1212-1218.
[20] Zhang X, Mi LL, Wang QX. Clinical significance and expression of CD90 in human hepatocellular carcinoma. Chin J Diffic and Compl Cas 2011; 12: 911-913.
[21] Wu LM, Chen XX, Cheng CT. Prognostic significance of expression of CD133, VEGF and CD-34 in hepatocellular carcinoma. Chin J Cancer Prev Treat 2013; 5: 37-41.
[22] Yeh CT, Kuo CJ, Lai MW, Chen TC, Lin CY, Yeh TS, Lee WC. CD133-positive hepatocellular carcinoma in an area endemic for hepatitis B virus infection. BMC Cancer 2009; 9: 324.
[23] Yilmaz G, Akyol G, Cakir A, Ilhan M. Investigation of diagnostic utility and expression profiles of stem cell markers (CD133 and CD90) in hepatocellular carcinoma, small cell dysplasia, and cirrhosis. Pathol Res Pract 2014; 210: 419-425.
[24] Yu XH, Xu LB, Liu C, Zhang R, Wang J. Clinicopathological characteristics of 20 cases of hepatocellular carcinoma with bile duct tumor thrombi. Digest Dis Sci 2011; 56: 252-259.
[25] Wu XH, Wang SX, Cui DP, Li JK, Yang BM. Expression and significance of CD133 and CD90 in hepatocellular carcinoma. Chin J Hepatol 2011; 19: 376-377.
[26] Wong E, Srivastava S, Yeoh KG, Teh M, Salto-Tellez M. Clinical and biological relevance of Thy-1/CD90 protein overexpression in human hepatocellular carcinoma. Journal of Oncopathology 2013; 1: 1-9.
[27] Zhang X, Jiang P, Shuai L, Chen K, Li Z, Zhang Y, Jiang Y, Li X. miR-589-5p inhibits MAP3K8 and suppresses CD90+ cancer stem cells in hepatocellular carcinoma. J Exp Clin Canc Res 2016; 35:176-188.
[28] Zhao RC, Zhou J, Chen KF, Gong J, Liu J, He JY, Guan P, Li B, Qin Y. The prognostic value of combination of CD90 and OCT4 for hepatocellular carcinoma after curative resection. Neoplasma 2016; 63: 288-298.
[29] Chai S, Tong M, Ng KY, Kwan PS, Chan YP, Fung TM, Lee TK, Wong N, Xie D, Yuan YF, Guan XY, Ma S. Regulatory role of miR-142-3p on the functional hepatic cancer stem cell marker CD133. Oncotarget 2014; 5: 5725-5735.
[30] Tang KH, Ma S, Lee TK, Chan YP, Kwan PS, Tong CM, Ng IO, Man K, To KF, Lai PB, Lo CM, Guan XY, Chan KW. CD133(+) liver tumor-initiating cells promote tumor angiogenesis, growth, and self-renewal through neurotensin/interleukin-8/CXCL1 signaling. Hepatology 2012; 55: 807-820.
[31] Zhong C, Wu JD, Fang MM, Pu LY. Clinicopathological significance and prognostic value of the expression of the cancer stem cell marker CD133 in hepatocellular carcinoma: a meta-analysis. Tumour Biol 2015; 36: 7623-7630.

[32] Rege TA, Hagood JS. Thy-1 as a regulator of cell-cell and cell-matrix interactions in axon regeneration, apoptosis, adhesion, migration, cancer, and fibrosis. Faseb J 2006; 20: 1045-1054.

[33] Yang ZF, Ho DW, Ng MN, Lau CK, Yu WC, Ngai P, Chu PW, Lam CT, Poon RT, Fan ST. Significance of CD90+ cancer stem cells in human liver cancer. Cancer Cell 2008; 13: 153-166.

[34] Luo J, Wang P, Wang R, Wang J, Liu M, Xiong S, Li Y, Cheng B. The notch pathway promotes the cancer stem cell characteristics of CD90+ cells in hepatocellular carcinoma. Oncotarget 2016; 7: 9525-9537.

[35] Liu R, Shen Y, Nan K, Mi B, Wu T, Guo J, Li M, Lv Y, Guo H. Association between expression of cancer stem cell markers and poor differentiation of hepatocellular carcinoma a meta-analysis. Medicine (Baltimore) 2015; 94: e1306.

[36] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.

[37] Su R, Nan H, Guo H, Ruan Z, Jiang L, Song Y, Nan K. Associations of components of PTEN/AKT/mTOR pathway with cancer stem cell markers and prognostic value of these biomarkers in hepatocellular carcinoma. Hepatology Research 2016; 46: 1380-1391.

[38] Chen WC, Chang YS, Hsu HP, Yen MC, Huang HL, Cho CY, Wang CY, Weng TY, Lai PT, Chen CS, Lin YJ, Lai MD. Therapeutics targeting CD90-integrin-AMPK-CD133 signal axis in liver cancer. Oncotarget 2015; 6: 42923-42937.