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Prognostic role of CD82/KAI1 in multiple human malignant neoplasms: a meta-analysis of 31 studies

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Abstract: Tetraspanin CD82, also known as KAI1, was revealed as an attractive prognostic tumor biomarker in recent studies. However, some results of these studies remained debatable and inconclusive. Therefore, we conducted a meta-analysis to clarify the precise predictive value of CD82 in various neoplasms. Qualified studies were identified up to April 27, 2017, by searching PubMed, EMBASE, and the Web of Science. In total, 29 eligible studies were ultimately enrolled in this meta-analysis. Pooled hazard ratios (HRs) with 95% CIs of overall survival and disease/recurrence/progression-free survival were calculated to evaluate the correct prognostic role of CD82. Statistical analysis demonstrated that high expression of CD82 was significantly associated with enhanced overall survival (HR =0.56, 95% CI: 0.47–0.67) and disease/recurrence/progression-free survival (HR =0.42, 95% CI: 0.30–0.59) in cancer patients. Furthermore, we also conducted the subgroup analysis and the results revealed that CD82 was associated with favorable outcomes in cancer patients. Taken together, CD82 could be a promising biomarker for predicting the prognosis of patients with malignant neoplasms, and the biological functions of CD82 are of great research value of the subject.

Keywords: CD82, KAI1, prognosis, meta-analysis

Introduction

Tetraspanins are a family of 34 proteins, which are involved in diverse functions such as B- and T-cell activation, platelet aggregation, migration, proliferation, morphogenesis, and tumor cell progression.[1] The key feature of tetraspanins is their potential to associate with each other and with a multitude of molecules from other protein families.[2,3] CD82, also known as KAI1, belongs to tetraspanin family associated not only with extensive physiological processes, but also in pathological situations such as cancer invasion and metastasis,[4,5] and its differential expressions are found in various normal and malignant tissues,[6–8] which indicate that CD82 may play a pivotal role in cancer growth, progression, motility, invasion, and metastasis.[9]

A number of studies have demonstrated that decreased CD82 expression in tumor tissues was associated with unfavorable survival in cancer patients.[10–15] Whereas in some individual studies focused on gastric carcinoma,[16] osteosarcoma,[17] colorectal carcinoma,[18] and clear cell renal cell carcinoma,[19] increased expression of CD82 might predict diverse, even opposing outcome. The discrepancies between these studies highlight the importance of evaluating the prognostic significance of CD82 in human malignant neoplasms. Therefore, we conducted this systematic review using meta-analysis to shed light on the relationship between CD82 expression and the prognosis of patients with carcinoma.

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Methods

Search strategy

We searched online databases, including PubMed, EMBASE, and Web of Science, to identify relevant literature published until April 27, 2017. For the literature retrieval, combinations of the keywords were used as follows: ("cancer" or "carcinoma" or "neoplasm" or "tumor" or "tumour") and ("KAI1" or "CD82") and ("prognostic" or "prognosis" or "survival" or "outcome" or "recurrence" or "relapse"). The following criteria should be considered to select the published studies: 1) human, English publications; 2) a relationship of CD82 expression with cancer prognosis. In addition, we searched for studies published in Chinese to comprehensively understand the role of miRNA-205 in cancer. In order to supplement our literature search, the bibliographies in these studies were also carefully scanned.

Quality assessment

To evaluate the retrieved studies, they should include clear definitions of the following: 1) the study population and country; 2) the study design; 3) assay method to determine CD82 expression: immunohistochemistry (IHC), quantitative reverse transcription-polymerase chain reaction (qRT-PCR), or Western-blot; 4) the prognosis or survival assessment; 5) the detected tumor and pathology information; 6) the cutoff point of CD82; and 7) the follow-up duration (Table 1). Sensitivity analyses and published bias were performed to promote the quality of this meta-analysis. A flow diagram of the study selection process is presented in Figure 1.

Data extraction

All data from eligible studies were extracted independently; ambiguous data were reviewed in detail. Parameters of these literatures were extracted from each single paper, including the first author's surname, publication year, patients' median or mean age, nationality, dominant ethnicity, number of patients, investigating method, cutoff value, follow-up time, and hazard ratios (HRs) for prognostic outcomes (overall survival [OS] and disease/recurrence/progression-free survival [DFS/RFS/PFS]) along with their 95% CI and *p*-values. If only Kaplan–Meier curves were available, data were extracted from graphical survival curves to extrapolate HRs with 95% CIs using previously described methods.[20–22] All of the aforementioned data are comprehensively detailed in Tables 1 and 2.

Statistical analysis

We quantified the effect of heterogeneity via $I^2=100\%\times(Q - df)/Q$. A random-effects model (DerSimonian–Laird method) was applied if $p<0.10$ or $I^2>50\%$; otherwise, a fixed-effects model (Mantel–Haenszel method) was used instead.[23] In addition, we classified the enrolled studies into subgroups to reduce the influence of heterogeneity. The publication bias was evaluated by the Begg's funnel plot and Egger linear regression test with a funnel plot.[24] Sensitivity analysis was also tested. All *p*-values were calculated using a two-sided test, and $p<0.05$ was considered statistically significant. Statistical analyses were performed via the Stata 12.0 (StataCorp, College Station, TX, USA) and Microsoft Excel (V.2007, Microsoft Corporation, Redmond, WA, USA).

Results

Summary of enrolled studies

A total of 157 studies were retrieved from PubMed, EMBASE, and Web of Science. After initial scanning of titles and abstracts, 93 studies were excluded because they were review articles/letters or non-English publications, were not associated with CD82 or prognosis/survival. The remaining 64 records were downloaded as full text and accessed very carefully. Among them, 35 potentially suitable studies were excluded because they lacked sufficient survival data (HRs and 95% CIs), did not report comprehensive data, or extracted their survival data from an existing database. Ultimately, 29 studies were considered eligible for our meta-analysis. The inclusion and exclusion reasons for candidate studies are presented in detail in Figure 1.

The main features of the 29 enrolled studies are systematically summarized in Tables 1 and 2. Twenty-two studies reported patient OS, one focused on RFS, and six investigated OS as well as DFS or PFS. Eight of the studies focused on Caucasian populations, which mainly came from European countries, and 21 focused on Asian populations, of which 10 were from China, 9 from Japan, 1 from India, and 1 from Korea. As for cancer type, malignant neoplasms assessed in these studies included colorectal carcinoma, gastric carcinoma, breast cancer, laryngeal squamous cell carcinoma (LSCC), esophageal squamous cell carcinoma (ESCC), and oral squamous cell carcinoma (OSCC). Among the 29 studies, the pathological types of adenocarcinoma (AdenoCa), squamous carcinoma (SqCa), transitional cell carcinoma (TCC), sarcoma, and melanoma were covered. All of these studies were retrospective in design and determined CD82 expression using tissue samples. IHC and qRT-PCR were used in the majority of all eligible studies to detect CD82 expression, and Western-blot analysis was conducted in one study. When we analyzed the HR and 95% CI in each study, we extracted two sets of data from the same article

Table 1 Main characteristics of studies included in the meta-analysis

First author, publication year	Case nationality	Dominant ethnicity	Median or mean age	Study design	Malignant disease	Main type of pathology	Detected sample	Assay method	Survival analysis	Source of HR	Maximum months of follow-up
Zhu, 2017[10]	China	Asian	59.4	R	Colorectal carcinoma	AdenoCa	Tissue	IHC	OS	Reported	96
Lu, 2016[12]	China	Asian	57.7	R	Gastric carcinoma	AdenoCa	Tissue	IHC	OS	Reported	95
Singh, 2016[11]	India	Asian	49	R	Breast cancer	AdenoCa	Tissue	qRT-PCR	OS	SC	36
Guo, 2015[16,a]	China	Asian	48	R	Gastric carcinoma	AdenoCa	Tissue	IHC	OS	SC	60
Guo, 2015[16,b]	China	Asian	48	R	Gastric carcinoma	AdenoCa	Tissue	qRT-PCR	OS	SC	60
Wu, 2015[32]	China	Asian	62.1	R	Colorectal carcinoma	AdenoCa	Tissue	IHC	OS	Reported	108
Han, 2015[36]	China	Asian	45.6	R	Breast cancer	AdenoCa	Tissue	IHC	OS	Reported	NM
Yu, 2014[13]	China	Asian	62.1	R	LSCC	SqCa	Tissue	IHC	OS/DFS	Reported	NM
Kwon, 2014[19]	Korea	Asian	55.8	R	CCRCC	AdenoCa	Tissue	IHC	OS	Reported	223
Tang, 2014[14,c]	Canada	Caucasian	60	R	Melanoma	Melanoma	Tissue	IHC	OS	Reported	120
Tang, 2014[14,d]	Canada	Caucasian	60	R	Melanoma	Melanoma	Tissue	IHC	OS	Reported	60
Zhang, 2013[37]	China	Asian	58.7	R	LSCC	SqCa	Tissue	IHC	OS	SC	NM
Zhang, 2013[38]	China	Asian	59.6	R	LSCC	SqCa	Tissue	WB	OS	SC	84
Wu, 2012[15]	China	Asian	58.6	R	NSCLC	AdenoCa	Tissue	IHC	OS	Reported	88
Knoener, 2012[33]	Germany	Caucasian	NM	R	Gastric carcinoma	AdenoCa	Tissue	IHC	OS	SC	163
Guo, 2009[39]	China	Asian	60	R	Hepatocellular carcinoma	AdenoCa	Tissue	IHC	OS	SC	24
Protzel, 2008[34]	Germany	Caucasian	66.5	R	Penile carcinoma	SqCa	Tissue	IHC	OS	SC	125
Miyazaki, 2005[40]	Japan	Asian	61	R	ESCC	SqCa	Tissue	IHC	OS	SC	60
Leavey, 2005[17]	America	Caucasian	11	R	Osteosarcoma	Sarcoma	Tissue	IHC	OS/PFS	SC	NM
Farhadieh, 2004[41]	Australia	Caucasian	65	R	OSCC	SqCa	Tissue	IHC	OS/DFS	Reported	258
Goncharuk, 2004[42]	America	Caucasian	65	R	NSCLC	AdenoCa	Tissue	IHC	OS	SC	NM
Su, 2004[50]	Japan	Asian	64	R	Bladder cancer	TCC	Tissue	IHC	RFS	Reported	78
Hashida, 2003[18]	Japan	Asian	62.8	R	Colorectal carcinoma	AdenoCa	Tissue	IHC	OS/DFS	Reported	85.9
Imai, 2002[43]	Japan	Asian	62.6	R	OSCC	SqCa	Tissue	qRT-PCR	OS	SC	60
Schindl, 2001[44]	Austria	Caucasian	56.8	R	Epithelial ovarian cancer	AdenoCa	Tissue	IHC	OS/DFS	Reported	130
Miyazaki, 2000[45]	Japan	Asian	61.8	R	ESCC	SqCa	Tissue	IHC	OS	SC	195.2
Yang, 2000[46]	America	Caucasian	NM	R	Breast cancer	AdenoCa	Tissue	IHC	OS	SC	NM
Sho, 1998[47]	Japan	Asian	66	R	Pancreatic cancer	AdenoCa	Tissue	IHC	OS	SC	62
Huang, 1998[48]	Japan	Asian	50	R	Breast cancer	AdenoCa	Tissue	IHC	OS/DFS	Reported	NM
Higashiyama, 1997[35]	Japan	Asian	63.7	R	NSCLC	AdenoCa	Tissue	IHC	OS	Reported	61.3
Adachi, 1996[49]	Japan	Asian	60	R	NSCLC	AdenoCa	Tissue	qRT-PCR	OS	Reported	58

Notes: [a,b]Data extracted from one study due to different assay methods (IHC and qRT-PCR). [c,d]Data extracted from one study due to different follow-up times (120 and 60 months). Study design is described as retrospective.
Abbreviations: AdenoCa, adenocarcinoma; CCRCC, clear cell renal cell carcinoma; DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; IHC, immunohistochemistry; LSCC, laryngeal squamous cell carcinoma; NM, not mentioned; NSCLC, non-small-cell lung cancer; OS, overall survival; OSCC, oral squamous cell carcinoma; PFS, progression-free survival; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; R, retrospective; RFS, recurrence-free survival; SC, survival curve; SqCa, squamous carcinoma; TCC, transitional cell carcinoma; WB, Western-blot.

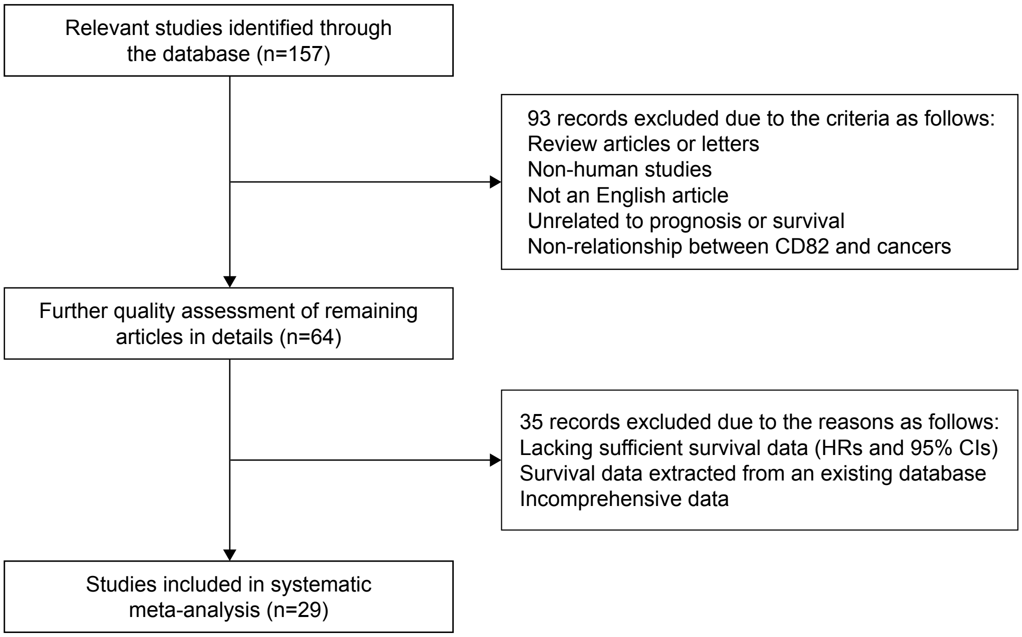

Figure 1 Flow diagram of the study selection process.
Abbreviation: HRs, hazard ratios.

due to different assay methods or different follow-up times in two studies (Guo et al[16] and Tang et al[14]). The source of HR and 95% CI was extracted from survival curves or article reports.

OS associated with CD82 expression

A total of 28 original studies were included to analyze the OS, with a random-effects model on account of the moderate heterogeneity (p=0.000, I^2=54.5%). The results indicated that CD82-positive expression was significantly associated with favorable OS in cancer patients (pooled HR =0.56, 95% CI: 0.47–0.67, $p<0.05$; Figure 2A). Subgroup study was then performed; increased CD82 expression was significantly associated with enhanced OS in the Asian patients (pooled HR =0.55, 95% CI: 0.43–0.70) as well in Caucasian (pooled HR =0.57, 95% CI: 0.47–0.70; Figure 3A). In tumor subgroup analysis, we found high expression of CD82 correlated with longer OS in colorectal carcinoma, gastric carcinoma, breast cancer, LSCC, and non-small-cell lung cancer (NSCLC) (Figure 3B). Due to insufficient studies, correlation between CD82 and OS in other tumor types have not been further analyzed. Stratification analyses for other subgroups are presented in detail in Figure 3C and D.

DFS/RFS/PFS associated with CD82 expression

Seven of the studies analyzed DFS/RFS/PFS. The heterogeneity between these studies was low (p=0.153, I^2=36.0%); thus, a fixed-effects model was applied to calculate a pooled HR of 0.42 (95% CI: 0.30–0.59). This result demonstrated that CD82 overexpression predicted low risk of cancer progression (Figure 2B). Ethnic and pathological subgroup analysis for DFS/RFS/PFS also demonstrated the protective effect of CD82 and that it may play a key role of progression in cancer patients (Figure 4).

Sensitivity analyses

In order to determine the robustness of the above results and evaluate the stability of results, a sensitivity analysis was performed by Stata12.0 software. Individual data that could affect the final conclusions have been deleted in advance (see footnote "f" in Table 2). The analyzed result from a fixed model suggested that our results are comparatively credible and stable (Figure 5A and B).

Publication bias

Begg's funnel and the Egger's test were used to evaluate the possible publication bias in this meta-analysis. The funnel plots of the publication bias are presented in Figure 5C and D. p-values calculated from Egger's test with higher detection effectiveness were 0.135 for OS, 0.610 for DFS/RFS/PFS, respectively, indicating no significant publication bias in the meta-analysis.

Discussion

In recent years, elaborate efforts have been invested to detect promising biomarkers for patients with multiple carcinomas.

Table 2 HRs and 95% CIs of patient survival or cancer progression relating to CD82 expression in eligible studies

First author, publication year	Assay method	Cutoff point	Case number		OS		DFS/RFS/PFS	
			High expression	Low expression	HR (95% CI) (U/M)	*p*-value	HR (95% CI) (U/M)	*p*-value
Zhu, 2017[10]	IHC	IRS scores ≥3 (range of 0–12)	65	139	0.302 (0.184–0.497)M	<0.001	NM	NM
Lu, 2016[12]	IHC	IRS scores ≥3 (range of 0–12)	134	191	0.648 (0.492–0.854)M	0.002	NM	NM
Singh, 2016[11]	qRT-PCR	NM	46	29	0.66 (0.26–1.68)U[e]	0.047	NM	NM
Guo, 2015[16,a]	IHC	>10% of tumor cells stained	28	100	1.07 (0.22–5.24)U[e]	<0.05	NM	NM
Guo, 2015[16,b]	qRT-PCR	NM	40	88	0.62 (0.19–1.98)U[e]	<0.05	NM	NM
Wu, 2015[32]	IHC	IRS scores ≥3 (range of 0–12)	56	118	0.430 (0.269–0.687)M	<0.001	NM	NM
Han, 2015[36]	IHC	IRS scores ≥3 (range of 0–12)	137	188	0.617 (0.462–0.823)M	0.001	NM	NM
Yu, 2014[13]	IHC	IRS scores ≥3 (range of 0–12)	34	49	0.226 (0.094–0.545)M	0.001	0.278 (0.119–0.647)M	0.003
Kwon, 2014[19]	IHC	>0% of tumor cells stained	98	546	1.513 (1.057–2.165)M	0.024	[f]	[f]
Tang, 2014[14,c]	IHC	IRS scores ≥8 (range of 0–12)	114	303	0.42 (0.29–0.63)M	0.0000147	NM	NM
Tang, 2014[14,d]	IHC	IRS scores ≥8 (range of 0–12)	114	303	0.59 (0.36–0.96)M	0.029	NM	NM
Zhang, 2013[37]	IHC	Accumulated points ≥80	52	48	0.54 (0.27–1.05)U[e]	NM	NM	NM
Zhang, 2013[38]	WB	NM	43	43	0.36 (0.17–0.77)U[e]	NM	NM	NM
Wu, 2012[15]	IHC	IRS scores >1 (range of 0–12)	19	31	0.039 (0.007–0.236)M	0.00	NM	NM
Knoener, 2012[33]	IHC	IRS scores ≥3 (range of 0–12)	168	103	0.77 (0.55–1.07)U[e]	0.2305	NM	NM
Guo, 2009[39]	IHC	>10% of tumor cells stained	21	59	0.81 (0.28–2.32)U[e]	0.022	NM	NM
Protzel, 2008[34]	IHC	>50% of tumor cells stained	17	13	0.34 (0.02–4.90)U[e]	0.0042	NM	NM
Miyazaki, 2005[40]	IHC	Ki index ≥39	48	43	0.48 (0.22–1.03)U[e]	0.0023	NM	NM
Leavey, 2005[17]	IHC	NM	16	31	1.14 (0.27–4.81)U[e]	0.28	0.99 (0.35–2.85)U[e]	0.24
Farhadieh, 2004[41]	IHC	>10% of tumor cells stained	15	42	0.52 (0.27–1.01)M	0.053	0.4 (0.2–0.8)M	0.009
Goncharuk, 2004[42]	IHC	Median	77	27	0.47 (0.23–0.97)U[e]	0.034	NM	NM
Su, 2004[50]	IHC	>50% of tumor cells stained	54	33	NM	NM	0.255 (0.111–0.588)M	0.0013
Hashida, 2003[18]	IHC	Scores ≥120 (range of 0–300)	63	83	0.903 (0.297–2.747)M	0.858	1.054 (0.431–2.577)M	0.909
Imai, 2002[43]	qRT-PCR	NM	25	18	0.51 (0.06–4.38)U[e]	NM	NM	NM
Schindl, 2001[44]	IHC	Scores ≥4 (range of 3–7)	48	59	0.45 (0.22–0.92)M	0.0282	0.3 (0.09–0.93)M	0.0372
Miyazaki, 2000[45]	IHC	>10% of tumor cells stained	36	19	0.41 (0.17–1.00)U[e]	0.024	NM	NM
Yang, 2000[46]	IHC	>5% of tumor cells stained	36	36	0.72 (0.20–2.61)U[e]	NM	NM	NM
Sho, 1998[47]	IHC	>50% of tumor cells stained	15	25	1.16 (0.29–4.64)U[e]	0.018	NM	NM
Huang, 1998[48]	IHC	HSCORE >50	44	65	0.442 (0.109–1.789)M	0.2528	0.360 (0.149–0.870)M	0.0234
Higashiyama, 1997[35]	IHC	>50% of tumor cells stained	65	135	0.700 (0.502–0.976)M	0.037	[f]	[f]
Adachi, 1996[49]	qRT-PCR	Gene conservation rate value >1.2	35	116	0.416 (0.175–0.986)M	0.046	NM	NM

Notes: The source of HR and 95% CI was extracted from survival curves or article reports. [a,b]Data extracted from one study due to different assay method (IHC and qRT-PCR). [c,d]Data extracted from one study due to different follow-up time (120 and 60 months). [e]HR calculated from survival curves. [f]Excluded due to its heterogeneity and publication bias.

Abbreviations: IHC, immunohistochemistry; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; WB, western-blot; NM, not mentioned; IRS, immunoreactivity score; HSCORE, the intensity and respective percentage cells that stain at each intensity were multiplied to reach a HSCORE that ranged from 0 to 300; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; PFS, progression-free survival; SC, survival curve; HR, hazard ratio; CI, confidence interval; U, univariate analysis; M, multivariate analysis.

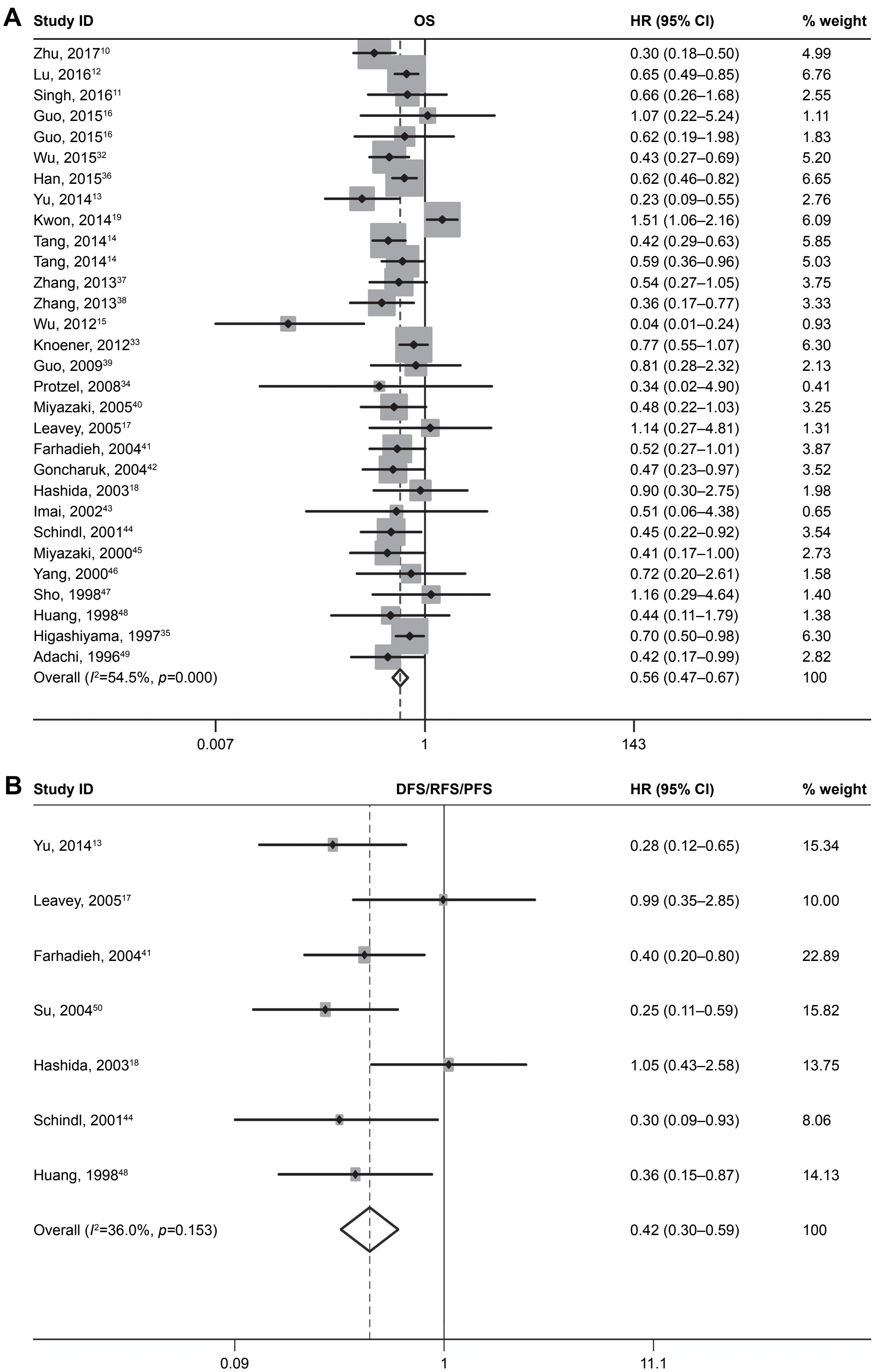

Figure 2 Forest plots of combined analyses associated with CD82 expression.

Notes: (**A**) OS and (**B**) DFS/RFS/PFS. Weights are from random effects analysis.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; ID, identifier; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival.

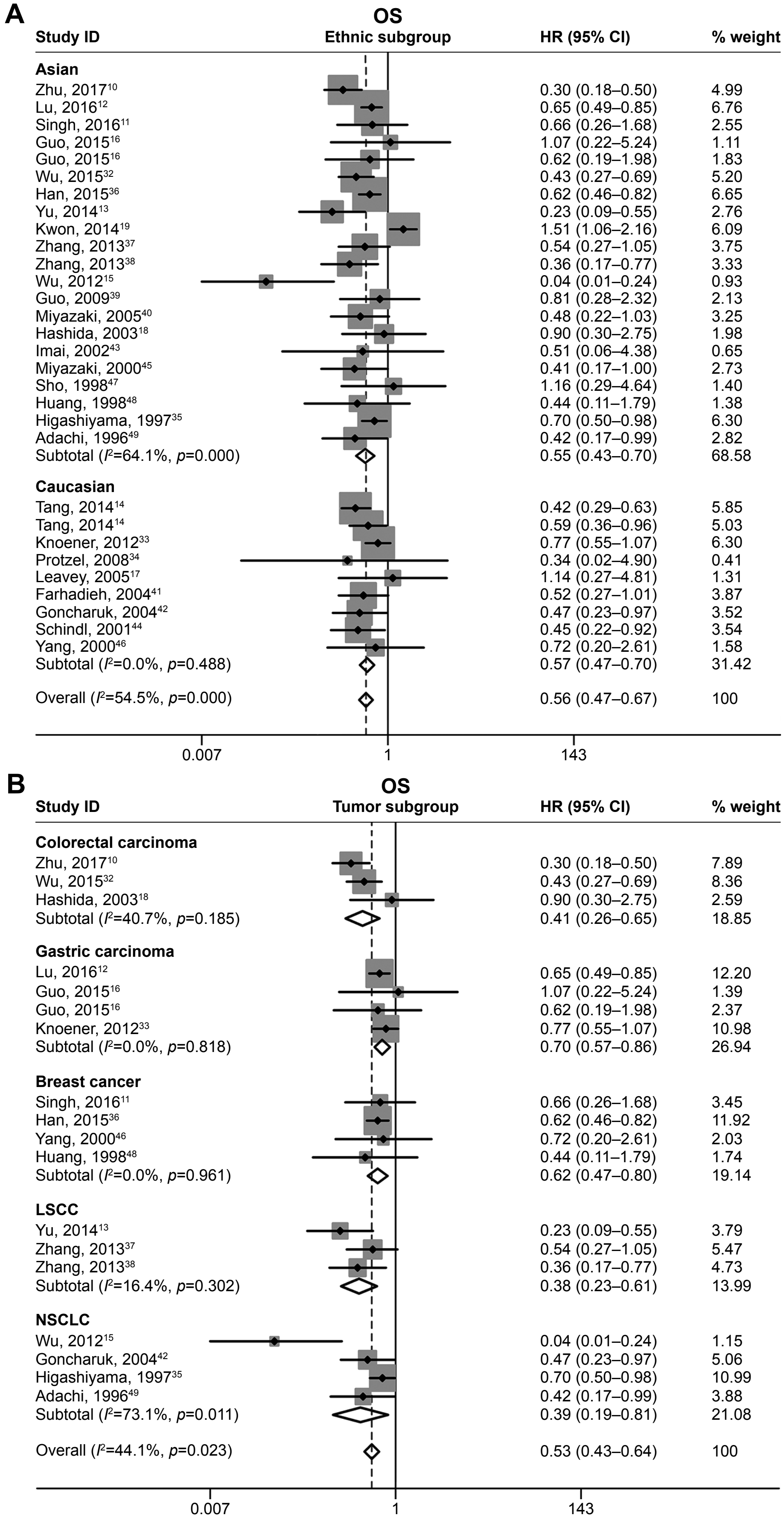

Figure 3 (*Continued*)

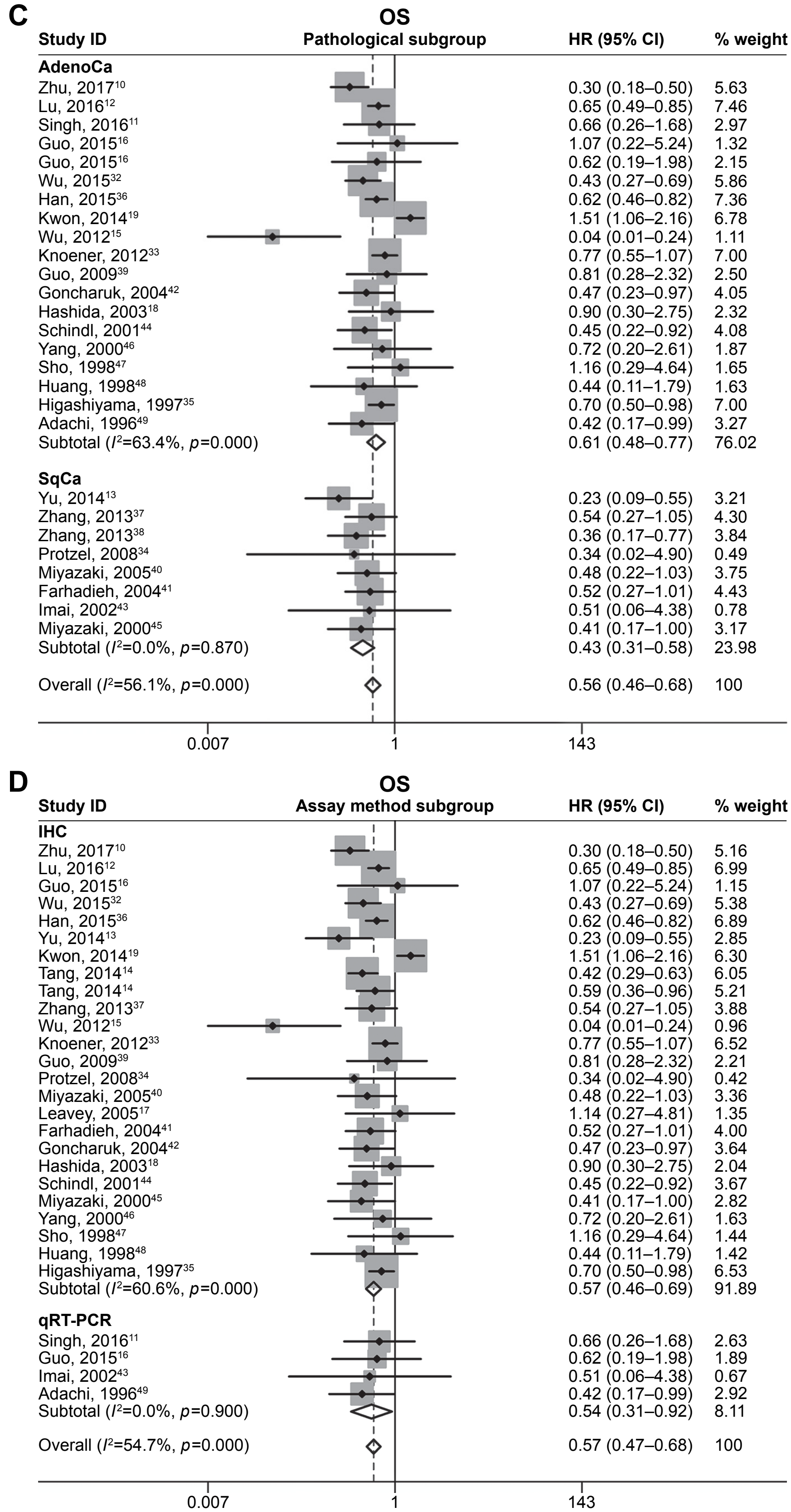

Figure 3 Forest plots of stratified analysis of the OS.

Notes: (**A**) Stratified by ethnic subgroup, (**B**) stratified by tumor subgroup, (**C**) stratified by pathological subgroup, and (**D**) stratified by assay method subgroup. Weights are from random effects analysis.

Abbreviations: AdenoCa, adenocarcinoma; HR, hazard ratio; ID, identifier; IHC, immunohistochemistry; LSCC, laryngeal squamous cell carcinoma; NSCLC, non-small-cell lung cancer; OS, overall survival; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; SqCa, squamous carcinoma.

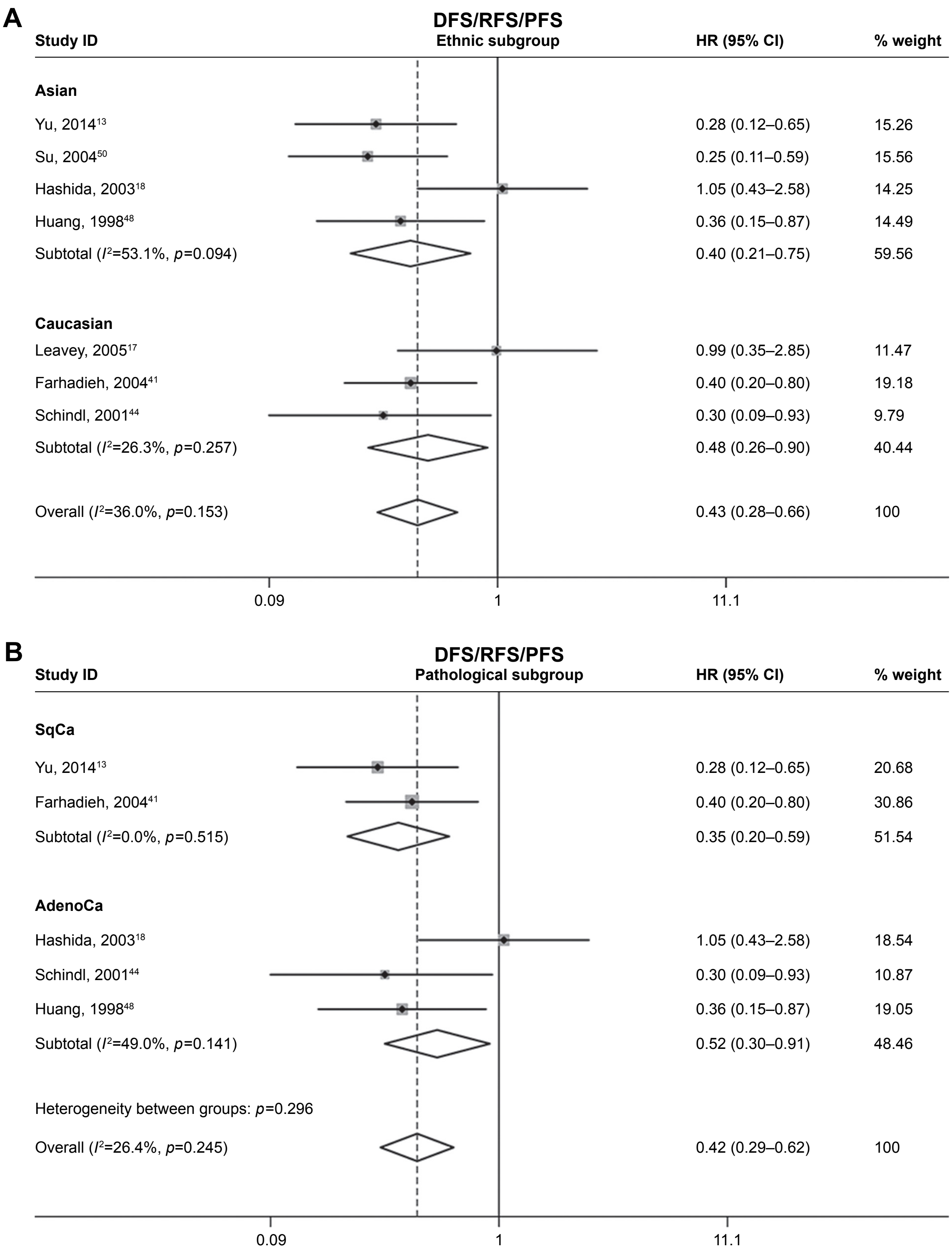

Figure 4 Forest plots of stratified analysis of the DFS/RFS/PFS.

Notes: (**A**) Stratified by ethnic subgroup and (**B**) stratified by pathological subgroup. Weights are from random effects analysis.

Abbreviations: AdenoCa, adenocarcinoma; DFS, disease-free survival; HR, hazard ratio; ID, identifier; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; SqCa, squamous carcinoma.

Tetraspanins are a family of integral membrane proteins with four transmembrane helices, a small extracellular loop, and a large extracellular loop. Recent studies have revealed the importance of tetraspanins in solid tumors and hematologic malignancies, and the expression of tetraspanins is associated with the tumor biologic characteristics.[4] Some members of this family are known as metastasis suppressor genes, while others are supposed to promote tumor progression.[1]

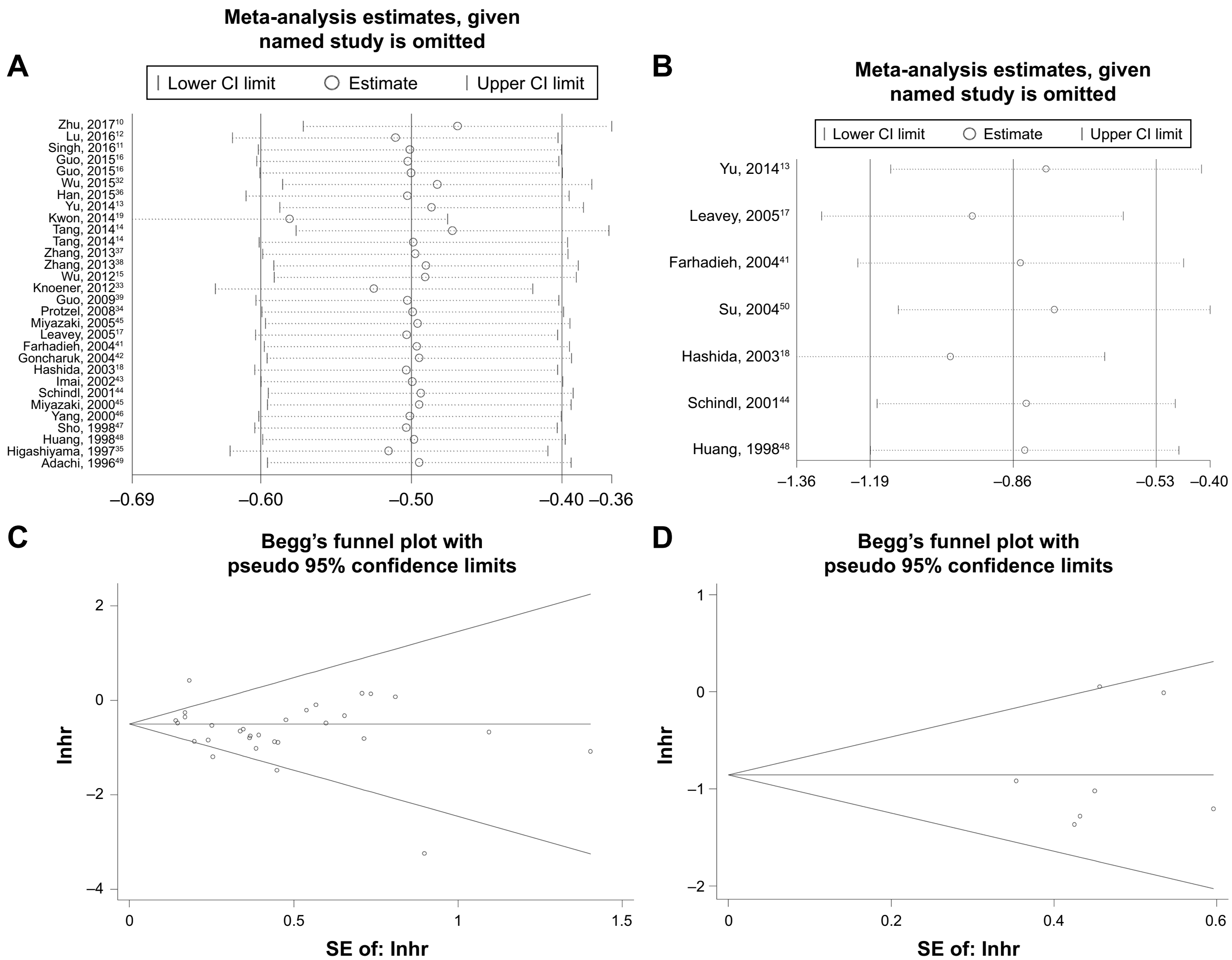

Figure 5 Sensitivity analysis under specific model and Begg's funnel plots of publication bias test.

Notes: (**A**) Effect of individual studies on the combined HR for OS, (**B**) effect of individual studies on the combined HR for DFS/RFS/PFS, (**C**) Begg's funnel plots of OS, and (**D**) Begg's funnel plots of DFS/RFS/PFS.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival.

CD82 is considered to be important in tetraspanin family given its differential expression between cancer and normal tissues. CD82 is downregulated in many types of cancers and loss of CD82, both protein and mRNA, is strongly correlated with poor prognosis in many malignancies.[9,25] Current understanding of CD82 function indicates that it is likely to be involved in detachment, motility/invasion, and cell survival, which are associated with various adhesion receptors (eg, integrins), receptor tyrosine kinases (eg, epithelial growth factor receptor [EGFR] and c-Met), and other signaling pathway molecules.[4,9,26] CD82 can interact with other tetraspanin proteins (eg, CD151 and CD81), integrins (eg, $\alpha_3\beta_1$, $\alpha_4\beta_1$, and $\alpha_5\beta_1$), and chemokines to regulate the migration, adhesion, and signaling of cells.[9,27,28] Integrins are not the only molecules that CD82 regulate, and studies have revealed that tetraspanins play a critical role in regulating receptor tyrosine kinase signaling in immune cells.[29,30] Odintsova et al reported that CD82 was a regulator of epithelial growth factor (EGF)-induced signaling and showed that the association of EGFR with the tetraspanin is critical in EGFR desensitization.[31] The diverse biological activities and molecular mechanisms of CD82 may partially contribute to the tumor prognosis in cancer patients.

In this meta-analysis, we first evaluated the correlation of CD82 with prognostic outcomes (OS, DFS/RFS/PFS) of patients with various cancers systemically. We also performed subgroup, sensitivity, and heterogeneity analyses to explore the effects of dominant characteristics from available studies. Many studies have reported that decreased expression of CD82 often predicts unfavorable outcome in cancers and the level of CD82 was negatively correlated with invasion of depth, vessel invasion, lymph node metastasis, distant metastasis, and TNM stages.[10,16,32–34] However, there are also some individual studies that came to a diverse, even opposing, conclusion in our included literature. Our prognosis analysis revealed the pooled HR of 0.56 (OS) and 0.42 (DFS/RFS/PFS), demonstrating that increased CD82 expression could be a favorable prognostic factor of various tumors. Similarly, in subgroup analysis based on the characteristics of the individual studies, we observed the statistically significant outcomes when data were stratified according to ethnicity, pathology, assay method, and tumor types. Although AdenoCa and squamous cell carcinoma have oncologically different characteristics, according to our study, high expression of CD82 correlated with longer OS or DFS/RFS/PFS in both types. Due to few relevant studies and small sample size, results of some tumors and pathologic types were not presented in the forest plot when we conducted the subgroup analysis. This means the conclusion should be considered with caution when we come across these neoplasms, including hepatocellular carcinoma, clear cell renal cell carcinoma, melanoma, osteosarcoma, and pancreatic cancer. Therefore, more existing investigations toward these tumors are needed for further evidence.

After extracting the data from studies, sensitivity analysis was conducted to check which individual data could affect the final conclusions. When we analyzed the stability of results, we found that if the data toward DFS/RFS/PFS from Higashiyama et al[35] and Kwon et al[19] were included in our review, they might have significant impact on the pooled significance. Therefore, we deleted these two sets of data in advance to ensure the stability of our analysis. The final results were assured that exclusion of any individual study alters little change of the pooled significance. We attributed this to the different ethnicity, tumor type, and pathological type, as well as the different source of HR. No obvious publication bias was detected in this meta-analysis, indicating our analysis was stable.

Despite the meta-analysis was performed with rigorous statistics, our conclusion still has several limitations for the following reasons. First, heterogeneity existed in the OS analyses and it was likely due to the different characteristics of the patients, such as age, ethnicity, tumor type, and pathological type, as well as the different source of HR. Second, most studies established their own varied expression cutoff, and a standard cutoff value was hard to define so that the pooled outcome may be different with the actual value. This may cause a bias in the results of the effectiveness of CD82 as a prognostic factor. Third, no independent investigation on Negroid was included in this meta-analysis, which might undermine the comprehensiveness to some extent. Fourth, the validity of results might be impaired due to the lack of prospective studies. Taking these limitations into consideration, our results should be interpreted rigorously, and more well-designed studies are needed to verify the function of CD82 in various carcinomas.

Conclusion

In summary, the significant relationship between high CD82 expression and favorable prognostic in various neoplasms was clearly revealed in this meta-analysis. The results indicated that CD82 could be a promising biomarker for predicting the prognosis of patients with malignant neoplasms, and the biological functions of CD82 are of great research value of the subject.

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Disclosure

The authors report no conflicts of interest in this work.

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