Original Article

Prognostic significance of CD47 in human malignancies: a systematic review and meta-analysis

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Background: High CD47 expression has been indicated to predict a poor prognosis in human malignancies. However, the prognostic significance remains inconsistent.

Methods: Eligible studies were identified in PubMed, Embase, Web of Science, and the Cochrane Library prior to July, 2017. Relevant articles were screened for overall survival (OS), disease-free survival (DFS), event-free survival (EFS), progression-free survival (PFS), and clinicopathological data. Hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were pooled using Stata v.14.0 and Revman v.5.3 software, respectively. We also investigated heterogeneity, sensitivity, and publication bias for OS.

Results: This meta-analysis investigated the prognostic value of CD47 expression in 38 cohorts reported in 17 articles with 7,229 cancer patients. We found that CD47 overexpression correlated with shorter OS in cancer patients (pooled HR =1.49; 95% CI: 1.36–1.62, P<0.001). Subgroup analyses revealed that CD47 upregulation was associated with poor OS across different cancer type, country, sample size, detection method, analysis type, HR obtained method, and Newcastle-Ottawa scores (NOS). Elevated CD47 expression also predicted poor DFS, EFS, and PFS.

Conclusions: Our findings suggested CD47 could be a useful prognostic indicator in cancer patients and may be a useful therapeutic target. However, additional studies are still needed to verify the clinical value of CD47 in human malignancies.

Keywords: Prognosis; CD47; malignancies; meta-analysis

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Introduction

CD47, also known as integrin-associated protein (IAP), is a transmembrane protein belonging to the immunoglobulin superfamily (1). CD47 is widely expressed on the surfaces of normal cells, especially hematopoietic cells. It interacts with signal regulatory protein alpha (SIRPα) to activate a signaling cascade in various phagocytic cells, including dendritic cells and macrophages (2). CD47 is overexpressed in a variety of hematopoietic malignancies and solid tumors, and appears to promote tumor proliferation, progression, and metastasis (3-5).

Numerous studies have associated high CD47 expression with poor survival, suggesting CD47 could be used as a prognostic factor in various cancers, including leukemia (6), prostate cancer (7), lung cancer (8) and hepatocellular carcinoma (9). However, conflicting results have also been reported (10,11), making the prognostic utility of CD47 in malignancies uncertain (12-14). We performed a meta-analysis to assess the value

of CD47 overexpression for predicting clinical outcomes, and to examine the association between CD47 and clinicopathological parameters in solid tumors.

Methods

Literature search

We systematically searched PubMed, Embase, Web of Science, and the Cochrane library for studies published before July 28, 2017 that evaluated the effects of CD47 expression in various cancers. The MeSH terms and text words included "CD47", "CD47 Antigens", "Integrin-Associated Protein p50", "Thrombospondin-1 Receptor CD47", "neoplasm", "malignancy", "cancer", "carcinoma", "tumor", "prognostic", "outcomes", and "survival". We also manually screened the references from included articles to identify additional potentially relevant studies.

Inclusion and exclusion criteria

Eligible studies satisfied the following inclusion criteria: (I) Iassessed CD47 expression in predicting prognosis in any type of human cancer; (II) used a cohort design; (III) CD47 was associated with OS, DFS, EFS, and PFS, and HRs with 95% CIs were directly reported or could be calculated from the data; and (IV) patients were divided into high and low CD47 expression groups.

Studies were excluded based on the following criteria: (I) conference abstracts, reviews, letters, editorials, or case reports; (II) experiments not performed on patient tissues; and (III) did not provide data for calculating HRs and 95% CIs. If multiple articles included data from the same patients, we included only the most informative and recent study.

Date extraction and quality assessment

Two investigators (HJ Zhao, F Pan) independently extracted data from included studies and assessed study qualities. Discrepancies were solved through a third investigator (YC Shi). The following data were recorded: first author's name, publication year, country, cancer type, sample size, follow-up time, tissues, detection method, cut-off value, analysis type, HR calculation method, outcome measures with HRs and corresponding 95% CIs, and clinicopathological parameters in solid tumors (such as patient sex, age, tumor differentiation, lymph node metastasis, distant metastasis, and TNM stage). For studies providing clinical outcome data, multivariate HRs were calculated prior to univariate HRs to assess the prognostic value of CD47 expression. For articles containing only Kaplan-Meier curves, survival data was extracted using Engauge Digitizer v.4.1, and HRs and 95% CIs were estimated using Tierney's method (15).

Article qualities were evaluated using the Newcastle-Ottawa scale (NOS). Scores ranged from 0–9, and we defined studies with NOS scores ≥7 as high quality. Studies included in this meta-analysis scored between 5 and 8.

Statistical analysis

HRs with corresponding 95% CIs were utilized to assess relationships between CD47 levels and patient clinical outcomes using Stata v.14.0 software (Stata Corporation, College Station, TX, USA). Odds ratios (ORs) were calculated to analyze associations between CD47 expression and clincopathological parameters using RevMan v.5.3 software. Statistical heterogeneity between studies was evaluated using Cochran's Q test and Higgins I-squared statistic (I^2). $P<0.05$ (Q test) and/or $I^2>50\%$ indicated heterogeneity. A random effects or fixed effects model was applied to pool HRs in the absence or presence of heterogeneity; a pooled HR >1 with $P<0.05$ indicated poor prognosis in patients with increased CD47 expression. Subgroup analyses were conducted to evaluate the effects of individual factors on the association between CD47 and patient prognosis. Sensitivity analysis was performed to evaluate the robustness of the meta-analysis results. Funnel plots and Begg's (rank correlation) and Egger's (regression asymmetry) tests were used to estimate publication bias (16). If publication bias did exist, the trim and fill method was performed to assess its influence on overall outcomes (17).

Results

Study characteristics

A total of 594 studies describing CD47 in various cancers were retrieved using our search strategy through different combinations of key terms (*Figure 1*). A total of 139 articles were excluded as duplicates, and 390 were excluded after screening titles and abstracts for unrelated studies. Of the remaining 65 studies, 17 articles containing 38 cohort studies (6,7,10,11,18-30) were included in this meta-analysis (*Table 1*). The 38 cohorts included 7,229 total patients, and study sample sizes ranged from 20–1,117 patients. The

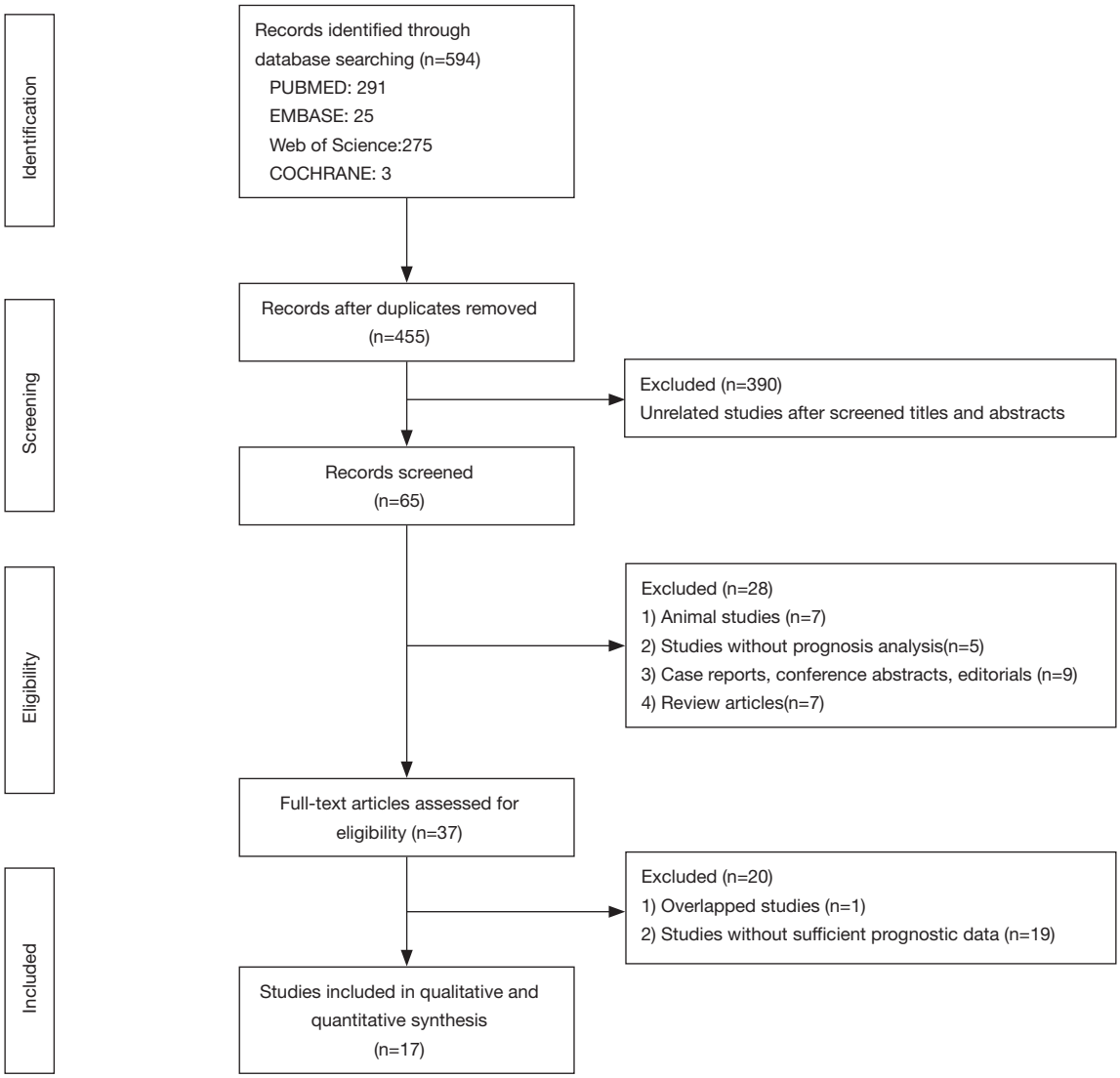

Figure 1 Study selection flowchart.

studies were performed in five countries, including China, Japan, Germany, Switzerland, and the United States, and were published between 2009 and 2014. The studies included 12 different cancer types, with two acute lymphoblastic leukemia (ALL) (18), six acute myeloid leukemia (AML) (6), six non-Hodgkin lymphoma (NHL) (28), three lung cancer (LC) (19), one melanoma (20), seven ovarian cancer (21-24), three glioma (7), one glioblastoma (7), five breast cancer (25-27), one esophageal squamous cell carcinoma (ESCC) (29), two gastric cancer (GC) (10,11), and one osteosarcoma cohort (30). Seventeen (44.7%) cohorts were conducted in Asian populations, and 21 (55.3%) in non-Asians. The association between CD47 expression and survival was analyzed as overall survival (OS) in 32 cohorts (6,7,10,11,18-24,26-30), disease-free survival (DFS) in three cohorts (18,27,29), event-free survival (EFS) in five cohorts (6,28), and progression-free survival (PFS) in eight cohorts (7,19,20,28,30). CD47 detection methods differed between studies, and included immunohistochemical (IHC) staining, real time polymerase chain reaction (real time PCR), and Affymetrix arrays or other cDNA microarrays. CD47 cut-off values were inconsistent across different studies. Hazard ratios (HRs) for OS were directly reported for 22 cohorts and were calculated indirectly using the Kaplan-Meier curves provided for 10 cohorts.

Table 1 Main characteristics of the included cohorts

Author	Year	Country	Cancer type	Sample size	Follow-up (months)	Tissues	Detection method	Cut-off value	Analysis type	Outcome measures	HRs obtained method	Quality score
Chao *et al.* 1 (18)	2010	USA	ALL	207	60	BM	Affymetrix arrays	An optimal value	U	OS	R	7
Chao *et al.* 2 (18)	2010	USA	ALL	205	144	BM	Affymetrix arrays	An optimal value	U	DFS	R	7
Ravindra *et al.* 1 (6)	2009	USA	AML	285	96	BM	Affymetrix arrays	An optimal value	U	OS	R	7
Ravindra *et al.* 2 (6)	2009	USA	AML	242	96	BM	Affymetrix arrays	An optimal value	U	OS	R	7
Ravindra *et al.* 3 (6)	2009	USA	AML	137	96	BM	cDNA microarrays	An optimal value	U	OS, EFS	R	6
Ravindra *et al.* 4 (6)	2009	USA	AML	74	96	BM	Affymetrix arrays	An optimal value	M	OS, EFS	R	8
Ravindra *et al.* 5 (6)	2009	USA	AML	123	96	BM	Affymetrix arrays	An optimal value	K-M	OS, EFS	E	7
Ravindra *et al.* 6 (6)	2009	USA	AML	74	96	BM	Affymetrix arrays	An optimal value	K-M	OS, EFS	E	6
Liu *et al.* 1 (19)	2017	China	Lung cancer	100	>84	BM	Real time PCR	ROC curve	M	OS, PFS	R	8
Liu *et al.* 2 (19)	2017	China	Lung cancer	147	>84	BM	Real time PCR	ROC curve	M	OS, PFS	R	8
Liu *et al.* 3 (19)	2017	China	Lung cancer	70	>84	BM	Real time PCR	ROC curve	M	OS, PFS	R	8
Fu *et al.* (20)	2017	China	Melanoma	164	26.9 [2–59]	TT	IHC	ROC curve	U, M	OS, PFS	R	8
Liu *et al.* 1 (21)	2017	China	Ovarian cancer	29	50	TT	IHC	Mean fluorescent intensity	K-M	OS	E	5
Liu *et al.* 2 (21)	2017	China	Ovarian cancer	20	120	TT	IHC	Mean fluorescent intensity	K-M	OS	E	6
Li *et al.* (22)	2017	China	Ovarian cancer	153	>90	TT	IHC	Mean fluorescent intensity	K-M	OS	E	5
Wang *et al.* (23)	2015	China	Ovarian cancer	86	23–94	TT	IHC	Low (–/+); high (++/+++)	M	OS	R	8

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Country	Cancer type	Sample size	Follow-up (months)	Tissues	Detection method	Cut-off value	Analysis type	Outcome measures	HRs obtained method	Quality score
Tan *et al.* (24)	2015	China	Ovarian cancer	116	7–66	TT	IHC	Low (–/+); high (++/+++)	M	OS	R	8
Zhang *et al.* 1 (25)	2015	China	Breast cancer	837	NR	TT	Real time PCR	NR	K-M	OS	E	6
Zhang *et al.* 2 (25)	2015	China	Breast cancer	1117	NR	TT	Real time PCR	NR	K-M	OS	E	6
Baccelli *et al.* (26)	2014	Germany	Breast cancer	243	133.4	TT	IHC	Low [0–6]; high [7–12]	U	OS	R	7
Nagahara *et al.* 1 (27)	2010	Japan	Breast cancer	443	36 [2–72]	BM	Real time PCR	Compared with GADPH	U, M	DFS	R	7
Nagahara *et al.* 2 (27)	2010	Japan	Breast cancer	452	36 [2–72]	BM	Real time PCR	Compared with GADPH	U, M	OS	R	8
Chao *et al.* 1 (28)	2010	USA	NHL	233	>72	LN	Affymetrix arrays	An optimal value	U	OS	R	7
Chao *et al.* 2 (28)	2010	USA	NHL	181	NR	LN	Affymetrix arrays	An optimal value	U	OS	R	7
Chao *et al.* 3 (28)	2010	USA	NHL	127	>60	LN	IHC	An optimal value	U	OS	R	7
Chao *et al.* 4 (28)	2010	USA	NHL	126	>60	LN	IHC	An optimal value	U	PFS	R	7
Chao *et al.* 5 (28)	2010	USA	NHL	106	>60	PBMC B-CLL cells	cDNA microarrays	An optimal value	U, M	EFS	R	8
Chao *et al.* 6 (28)	2010	USA	NHL	90	>60	LN	cDNA microarrays	Median	U	OS	R	7
Suzuki *et al.* (29)	2012	Japan	ESCC	102	40 [1–126]	TT	Real time PCR	NR	K-M, M	OS, DFS	E/R	8
Yoshida *et al.* (10)	2015	Japan	Gastric cancer	115	>133	TT	IHC	Low (very weak or weak); high (moderate or strong)	U, M	OS	R	6
Sudo *et al.* (11)	2017	Japan	Gastric cancer	133	36–60	TT	IHC	NR	K-M	OS	E	6
Xu *et al.* (30)	2015	China	Osteosarcoma	30	>120	TT	Real time PCR	An optimal value	K-M	OS, PFS	E	5

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Country	Cancer type	Sample size	Follow-up (months)	Tissues	Detection method	Cut-off value	Analysis type	Outcome measures	HRs obtained method	Quality score
Willingham *et al.* 1 (7)	2011	Switzerland	Ovarian cancer	169	>60	TT	IHC	An optimal value	U	PSF	R	7
Willingham *et al.* 2 (7)	2011	Switzerland	Ovarian cancer	83	>144	TT	cDNA microarrays	An optimal value	U	PSF	R	7
Willingham *et al.* 3 (7)	2011	Switzerland	Glioma	248	>96	TT	Affymetrix arrays	An optimal value	U	OS	R	7
Willingham *et al.* 4 (7)	2011	Switzerland	Glioma	50	>48	TT	Affymetrix arrays	An optimal value	U	OS	R	7
Willingham *et al.* 5 (7)	2011	Switzerland	Glioma	85	>48	TT	Affymetrix arrays	An optimal value	U	OS	R	7
Willingham *et al.* 6 (7)	2011	Switzerland	Glioblastoma	191	>72	TT	Affymetrix arrays	An optimal value	U	OS	R	7

HR, hazard ratio; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; BM, bone marrow; TT, tumor tissue; LN, lymph node; K-M, Kaplan-Meier curve; U, univariate; M, multivariate; R, reported; E, extracted; IHC, immunohistochemistry; NR, not reported; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; PFS, progression-free-survival.

Association between CD47 expression and OS

To evaluate the relationship between CD47 expression and OS in cancer patients, we assessed 6261 patients in 32 cohorts. The fixed effect model was applied to calculate pooled HRs with corresponding 95% confidence intervals (CIs), because we found no significant heterogeneity among studies (I^2=0.00%, P=0.815). High CD47 expression was associated with unfavorable OS (HR =1.49; 95% CI: 1.36–1.62, P<0.001) (*Figure 2*).

Subgroup analyses according to cancer type indicated that high CD47 expression was associated with worse OS in hematologic malignancies (HR =1.52; 95% CI: 1.31–1.73, P<0.001), ovarian cancer (HR =1.43; 95% CI: 1.17–1.69, P<0.001), and glioma (HR =1.49; 95% CI: 1.19–1.80, P<0.001), and other cancers (HR =1.50; 95% CI: 1.14–1.86, P<0.001) (*Table 2*, *Figure S1*). Subgroup analyses were also performed based on country, sample size, detection method, analysis type, HR obtained method and NOS score (*Tables 2*,*S1*, *Figures S2-S7*). The pooled cDNA microarray results were less persuasive, possibly because only two cohorts were included in the analysis. The remaining combined HR values from the above subgroups were >1.00 (P<0.001). We found no significant heterogeneity. To further assess the stability of the pooled outcomes, we performed a sensitivity analysis for OS. Removal of any single study had no significant effect on the pooled HRs (*Figure 3*).

We evaluated publication bias for all included studies using a vertical funnel plot and Begg's and Egger's tests. The funnel plot appeared asymmetrical (*Figure 4A*), implying potential publication bias, and Begg's test (P<0.001) and Egger's tests (P<0.001) (*Figure S8*) revealed publication bias. The trim and fill method was then used to assess the influence of this bias on the overall outcome. A symmetrical funnel plot was generated using the estimated hypothetical negative studies (*Figure 4B*). The adjusted pooled HRs, including 11 hypothetical studies, showed an association between elevated CD47 and poor OS (HR =1.53; 95% CI: 1.33–1.75, P<0.001). Trim and fill indicated that pooled HRs for OS were robust.

Association between CD47 expression and DFS, EFS, and PFS

In this meta-analysis, three cohorts (18,28,29) including 750 patients reported an association between high CD47 expression and DFS. No heterogeneity was observed

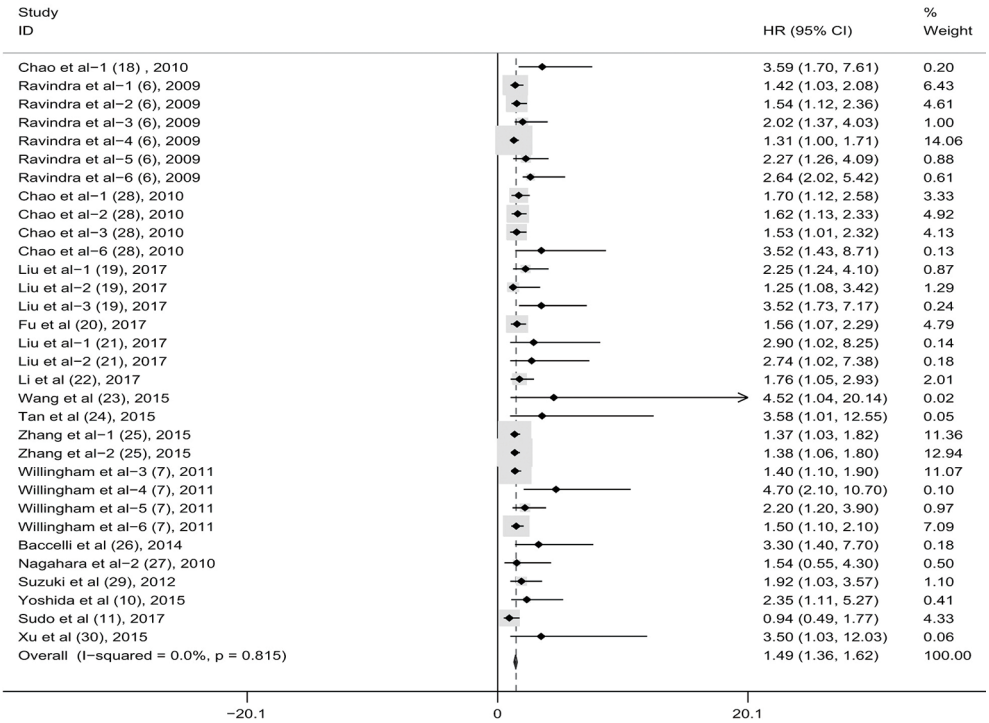

Figure 2 Forest plot of HR for the association between high CD47 expression and OS (6,7,10,11,18-30). HR, hazard ratio; OS, overall survival.

between studies (I^2=0.00%, P=0.540). Thus, we applied a fixed model to estimate the pooled HRs with corresponding 95% CIs. Pooled HRs revealed a potential positive association between high CD47 expression and poor DFS (HR =1.50; 95% CI: 1.11–1.89, P<0.001) (*Figure 5A*).

Two articles (6,28) involving five cohorts and 514 patients suggested an association between CD47 expression and EFS. The combined HRs showed that increased CD47 expression might be associated with worse EFS (HR =1.45; 95% CI: 1.13–1.76, P<0.001) (*Figure 5B*).

Five articles (7,19,20,28,30) involving eight cohorts and 889 patients reported an association between CD47 expression and PFS. The pooled HRs showed that elevated CD47 expression was associated with worse PFS (HR =1.57, 95% CI: 1.26–1.88, P<0.001) (*Figure 5C*).

Associations between CD47 expression and clinicopathological parameters

The pooled ORs and 95% CIs for clinicopathological parameters in solid tumors are shown in *Table 3*. There was no significant correlation between CD47 and gender, tumor differentiation, lymph node metastasis, distant metastasis, or TNM stage (P>0.05) (*Figures S9-S13*). The influence of CD47 expression on other clinicopathological parameters in solid tumors could not be determined, as insufficient data was provided.

Discussion

CD47 is a transmembrane protein belonging to the immunoglobulin superfamily and was first identified as a biomarker for human ovarian cancer in the 1980s (31,32). It is also widely expressed on the surfaces of normal cells, and is overexpressed in many types of cancer (1,33). SIRPα belongs to a multi-gene family of immune receptors, and is expressed on myeloid and neuronal cells in the central nervous system (34,35). CD47 could allow cancer cells to escape immune surveillance by activating a signaling cascade through SIRPα in phagocytic cells (33). The CD47-SIRPα axis is a critical regulator of myeloid cell activation and functions as a myeloid-specific immune checkpoint (6). High CD47 expression is associated with advanced prognosis in many cancer types (6,7,10,18-30), and blocking the CD47-SIRPα interaction promotes cancer cell eradication by phagocytes (36).

Table 2 Subgroup analyses for OS

Subgroup analysis	No. of studies	No. of patients	Pooled HR (95% CI)	P value	Heterogeneity	
					I^2 (%)	P value
Overall survival	32	6,261	1.49 (1.36–1.62)	<0.001	0.00	0.82
Cancer type						
Hematologic malignancies	11	1,773	1.52 (1.31–1.73)	<0.001	0.00	0.61
Ovarian cancer	7	2,358	1.43 (1.17–1.69)	<0.001	0.00	0.83
Glioma	4	574	1.49 (1.19–1.80)	<0.001	11.7	0.33
Others	10	1,556	1.50 (1.14–1.86)	<0.001	1.7	0.42
Country						
Asian	16	3,671	1.44 (1.23–1.65)	<0.001	0.00	0.77
Not-Asian	16	2,590	1.52 (1.35–1.69)	<0.001	0.00	0.62
Sample size						
≥100	22	5,653	1.48 (1.34–1.63)	<0.001	0.00	0.92
<100	10	608	1.52 (1.19–1.85)	<0.001	0.00	0.25
Detection method						
Affymetrix arrays	12	1,993	1.50 (1.32–1.68)	<0.001	0.00	0.55
cDNA microarrays	2	227	2.20 (0.95–3.45)	0.001	0.00	0.45
IHC	10	1,186	1.49 (1.16–1.82)	<0.001	0.00	0.62
Real time PCR	8	2,855	1.44 (1.19–1.69)	<0.001	0.00	0.67
Analysis type						
Non-multivariate	23	4,937	1.50 (1.35–1.65)	<0.001	0.00	0.71
Multivariate	9	1,324	1.45 (1.17–1.74)	<0.001	0.00	0.66
HR obtain method						
Reported	22	3,633	1.52 (1.36–1.69)	<0.001	0.00	0.83
Extracted	10	2,618	1.42 (1.19–1.65)	<0.001	0.00	0.48
NOS score						
≥7	22	3,616	1.53 (1.36–1.69)	<0.001	0.00	0.82
<7	10	2,645	1.41 (1.18–1.65)	<0.001	0.00	0.52

OS, overall survival; HR, hazard ratio; CI, confidence interval; IHC, immunohistochemical; PCR, polymerase chain reaction; NOS, Newcastle-Ottawa score.

We performed the present meta-analysis to assess the relationship between CD47 expression and tumor patient prognosis. Our analysis included 17 articles with 38 cohorts and 7,229 cases. We found that increased CD47 expression was associated with poor OS. Subgroup analyses revealed that CD47 overexpression was associated with poor OS stratified by cancer type, country, sample size, detection method, analysis type, HR obtained method and NOS score, without obvious heterogeneity. However, pooled results for cDNA microarrays were less persuasive, because only two cohorts used this method. Our findings indicated that cancer patients with elevated CD47 have worse OS, DFS, EFS, and PFS, and that CD47 could be a prognostic biomarker for patients with different cancers. CD47 might thus be an efficacious anti-cancer therapeutic target.

Previous studies showed that blocking the CD47-

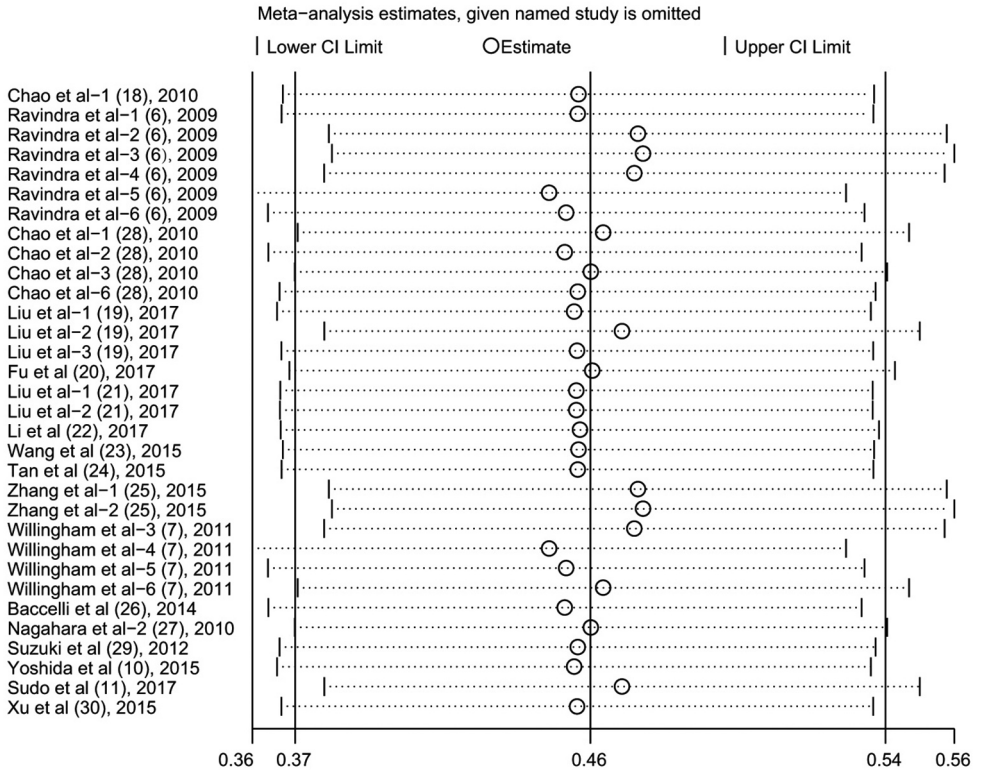

Figure 3 OS sensitivity analysis (6,7,10,11,18-30). OS, overall survival.

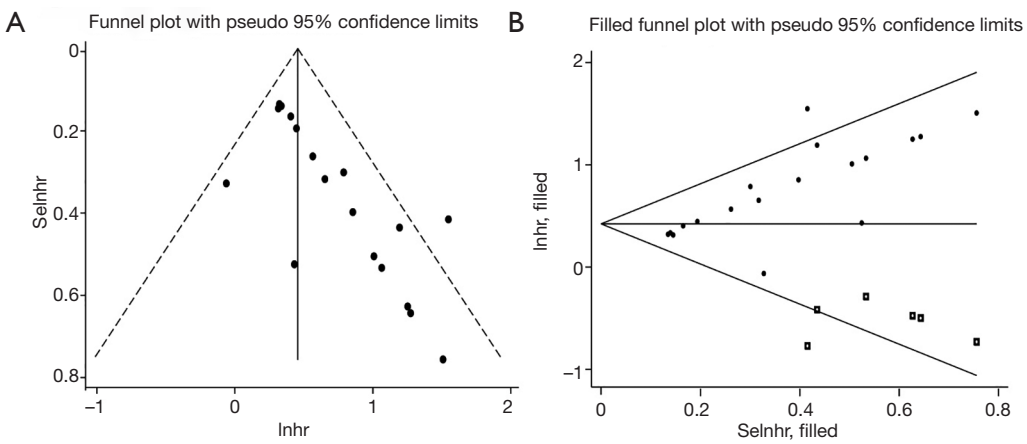

Figure 4 Funnel plots for CD47 expression and OS before (A) and after (B) trim and fill. OS, overall survival.

SIRPα interaction contributes to cancer cell eradication by stimulating macrophage phagocytosis and anti-tumor immune responses (6,12,28). Phagocytosis could induce secretion of cytokines and chemokines, recruiting additional immune cells to tumors, and amplifying the therapeutic effects of CD47 blockade (36). Myeloid immune cells (13), such as monocytes, granulocytes (37), and dendritic cells (38), and non-myeloid immune cells, such as T cells and natural killer (NK) cells, may also respond to CD47/SIRPα-blocking therapies (39). CD47 blockade appears to initiate or reinforce adaptive immune responses in murine models of lymphoma, lung cancer, and

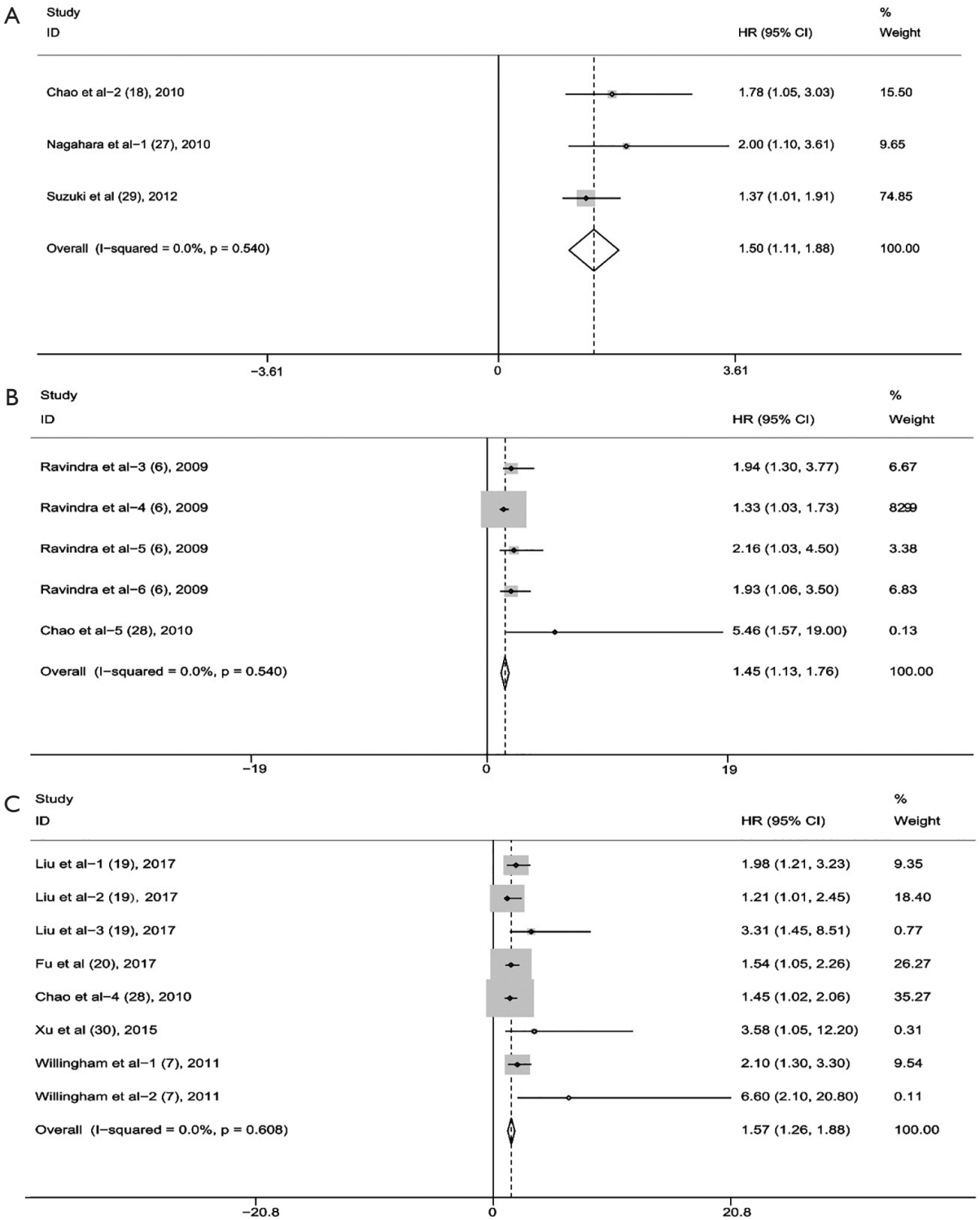

Figure 5 Forest plot of HR for the association between high CD47 expression and disease-free survival (DFS) (A), event-free survival (EFS) (B), progression-free survival (PFS) (C), separately (6,7,18-20,27-30). HR, hazard ratio.

Table 3 Associations between high CD47 expression and clinicopathological parameters

Clinicopathological parameter	No. of studies	No. of patients	Overall OR (95% CI)	P value	Heterogeneity		
					I^2 (%)	P value	Model
Gender (male *vs.* female)	3	399	1.01 (0.65–1.55)	0.98	0.00	0.90	Fixed effects
Tumor differentiation (poor-moderately *vs.* well)	5	1,004	1.14 (0.70–1.86)	0.60	64.00	0.02	Random effects
Lymph node metastasis (+ *vs.* –)	7	1,105	1.22 (0.94–1.57)	0.13	29.00	0.21	Fixed effects
Distant metastasis (+ *vs.* –)	4	851	1.56 (0.94–2.61)	0.09	39.00	0.18	Fixed effects
TNM stage (III–IV *vs.* I–II)	6	1,053	1.70 (0.83–3.44)	0.14	85.00	<0.001	Random effects

OR, odds ratio; CI, confidence interval.

ovalbumin (OVA)-expressing MC38 tumors (14,37). CD47 also induces caspase-independent cell death by regulating intercellular signaling, indicating that direct cytotoxicity to $CD47^+$ tumor cells might be a mechanism of action in CD47-targeting therapies (40,41).

To our knowledge, ours is the first meta-analysis associating high CD47 expression with poor prognosis in patients with various cancers. However, our analysis had several limitations. First, data were limited for some types of solid tumors, such as lung cancer, breast cancer, gastric cancer, glioblastoma, and melanoma, which reduced the statistical power of our findings. Second, detection method and cut-off value were inconsistent across the included studies, which may have resulted in statistical heterogeneity. Third, HRs extracted from Kaplan-Meier curves might not be as reliable as those reported directly in articles, and might introduce errors. Additionally, publication bias with respect to OS may have resulted from diverse data formats and the preference for positive results across publications. The funnel plot and Begg's and Egger's tests suggested the existence of publication bias, in part because few studies report negative results. However, trim and fill showed that the corrected pooled HRs did not reverse the pooled results, indicating that the positive correlation between high CD47 level and poor prognosis was not completely caused by a lack of negative results in the included studies. Still, more objective studies reporting both positive and negative results are needed to improve our analysis. Finally, our study size was relatively small and additional data are needed to strengthen our reporting power.

Conclusions

Our results indicated that CD47 could serve as a useful biomarker to predict prognosis in cancer patients, and is a potential therapeutic target. Further data from large-scale, well-designed studies are needed to confirm our results.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.05.31). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 The NOS scores for every cohorts

Author	Year	Selection				Comparability	Outcome			Quality score
Chao *et al.* 1 (18)	2010	1	1	1	0	1	1	1	1	7
Chao *et al.* 2 (18)	2010	1	1	1	0	1	1	1	1	7
Ravindra *et al.* 1 (6)	2009	1	1	1	0	1	1	1	1	7
Ravindra *et al.* 2 (6)	2009	1	1	1	0	1	1	1	1	7
Ravindra *et al.* 3 (6)	2009	1	1	1	0	1	1	1	0	6
Ravindra *et al.* 4 (6)	2009	1	1	1	0	2	1	1	1	8
Ravindra *et al.* 5 (6)	2009	1	1	1	0	1	1	1	1	7
Ravindra *et al.* 6 (6)	2009	1	1	1	0	1	1	1	0	6
Liu *et al.* 1 (19)	2017	1	1	1	0	2	1	1	1	8
Liu *et al.* 2 (19)	2017	1	1	1	0	2	1	1	1	8
Liu *et al.* 3 (19)	2017	1	1	1	0	2	1	1	1	8
Fu *et al.* (20)	2017	1	1	1	0	2	1	1	1	8
Liu *et al.* 1 (21)	2017	1	1	1	0	0	1	1	0	5
Liu *et al.* 2 (21)	2017	1	1	1	0	0	1	1	1	6
Li *et al.* (22)	2017	1	1	1	0	0	1	1	0	5
Wang *et al.* (23)	2015	1	1	1	0	2	1	1	1	8
Tan *et al.* (24)	2015	1	1	1	0	2	1	1	1	8
Zhang *et al.* 1 (25)	2015	1	1	1	0	1	1	1	0	6
Zhang *et al.* 2 (25)	2015	1	1	1	0	1	1	1	0	6
Baccelli *et al.* (26)	2014	1	1	1	0	1	1	1	1	7
Nagahara *et al.* 1 (27)	2010	1	1	1	0	1	1	1	1	7
Nagahara *et al.* 2 (27)	2010	1	1	1	0	2	1	1	1	8
Chao *et al.* 1 (28)	2010	1	1	1	0	1	1	1	1	7
Chao *et al.* 2 (28)	2010	1	1	1	0	1	1	1	1	7
Chao *et al.* 3 (28)	2010	1	1	1	0	1	1	1	1	7
Chao *et al.* 4 (28)	2010	1	1	1	0	1	1	1	1	7
Chao *et al.* 5 (28)	2010	1	1	1	0	2	1	1	1	8
Chao *et al.* 6 (28)	2010	1	1	1	0	1	1	1	1	7
Suzuki *et al.* (29)	2012	1	1	1	0	2	1	1	1	8
Yoshida *et al.* (10)	2015	1	1	1	0	1	1	1	0	6
Sudo *et al.* (11)	2017	1	1	1	0	1	1	1	0	6
Xu *et al.* (30)	2015	1	1	1	0	0	1	1	0	5
Willingham *et al.* 1 (7)	2011	1	1	1	0	1	1	1	1	7
Willingham *et al.* 2 (7)	2011	1	1	1	0	1	1	1	1	7
Willingham *et al.* 3 (7)	2011	1	1	1	0	1	1	1	1	7
Willingham *et al.* 4 (7)	2011	1	1	1	0	1	1	1	1	7
Willingham *et al.* 5 (7)	2011	1	1	1	0	1	1	1	1	7
Willingham *et al.* 6 (7)	2011	1	1	1	0	1	1	1	1	7

NOS, Newcastle-Ottawa score.

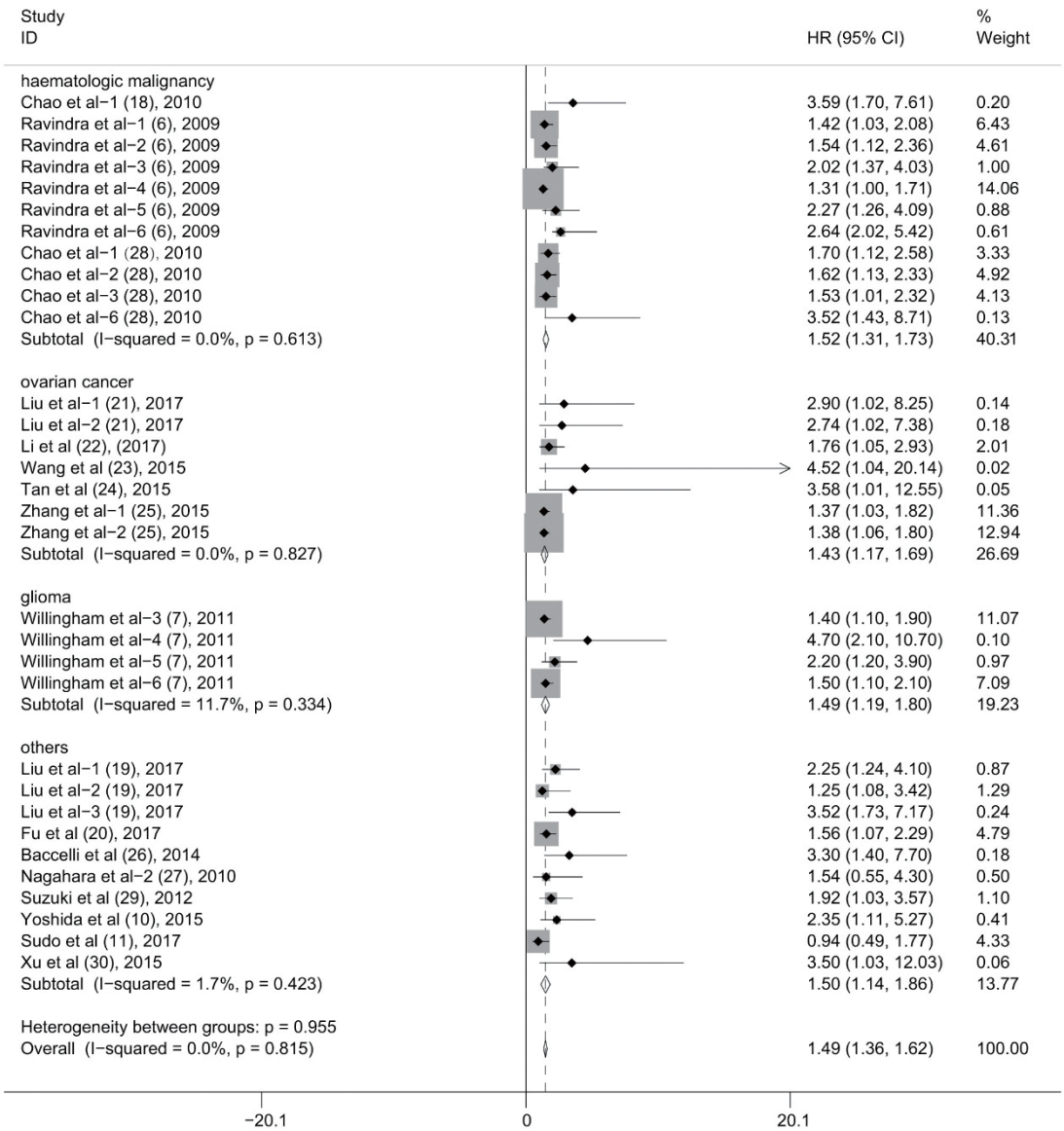

Figure S1 Forest plot of HR for OS stratified by cancer type (6,7,10,11,18-30). HR, hazard ratio; OS, overall survival.

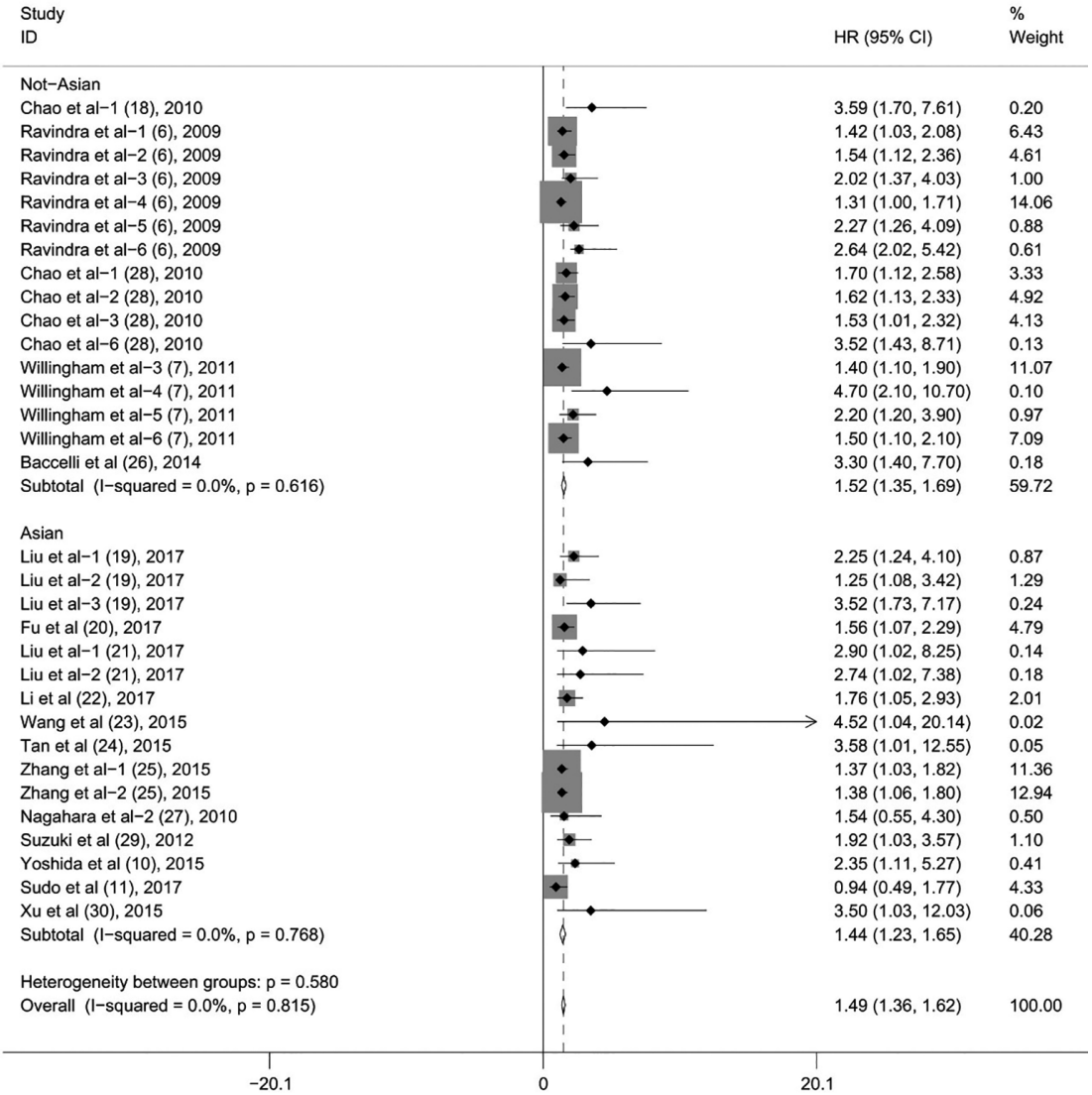

Figure S2 Forest plot of HR for OS stratified by country (6,7,10,11,18-30). HR, hazard ratio; OS, overall survival.

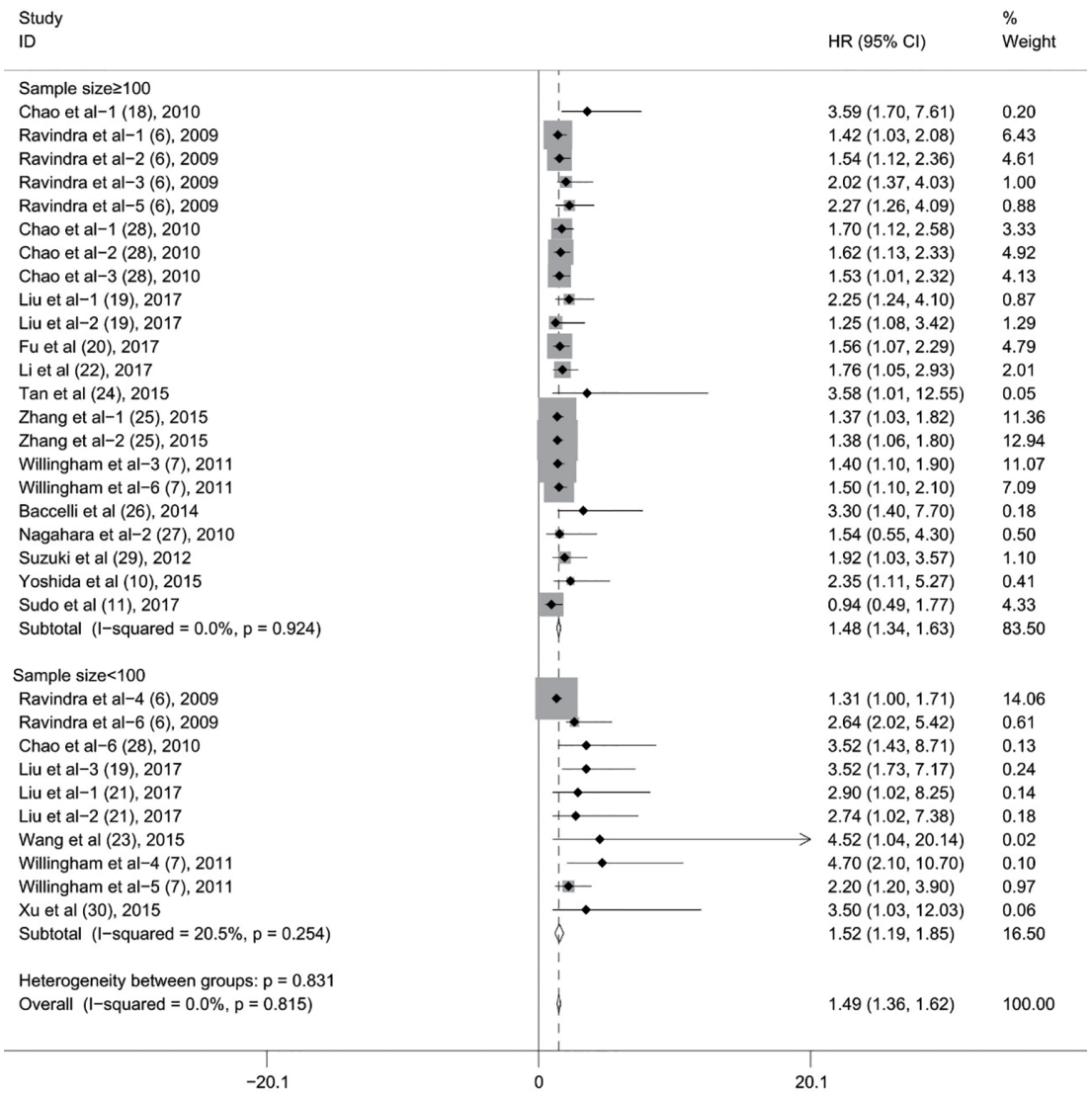

Figure S3 Forest plot of HR for OS stratified by sample size (6,7,10,11,18-30). HR, hazard ratio; OS, overall survival.

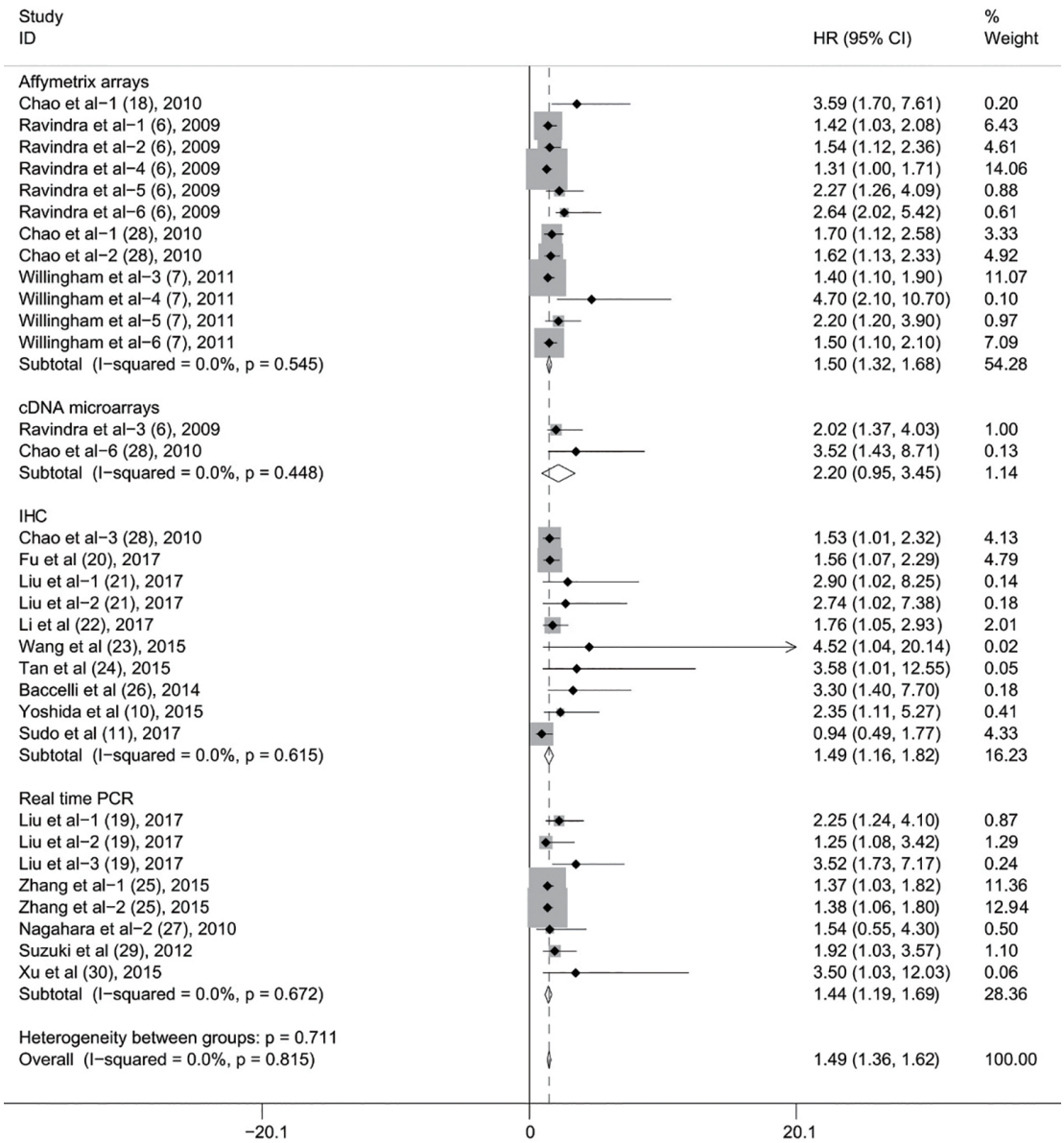

Figure S4 Forest plot of HR for OS stratified by detection method (6,7,10,11,18-30). HR, hazard ratio; OS, overall survival.

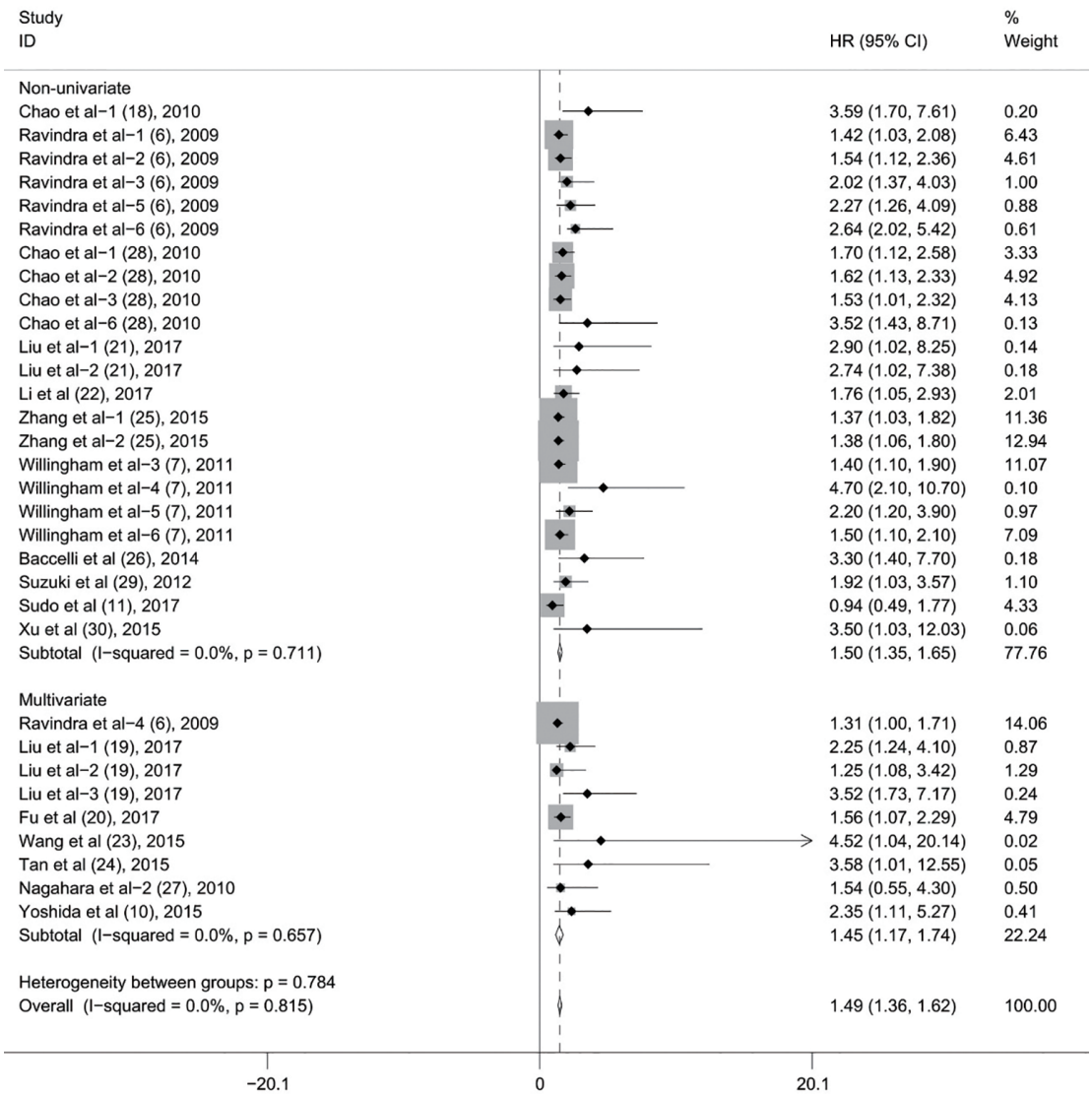

Figure S5 Forest plot of HR for OS stratified by analysis type (6,7,10,11,18-30). HR, hazard ratio; OS, overall survival.

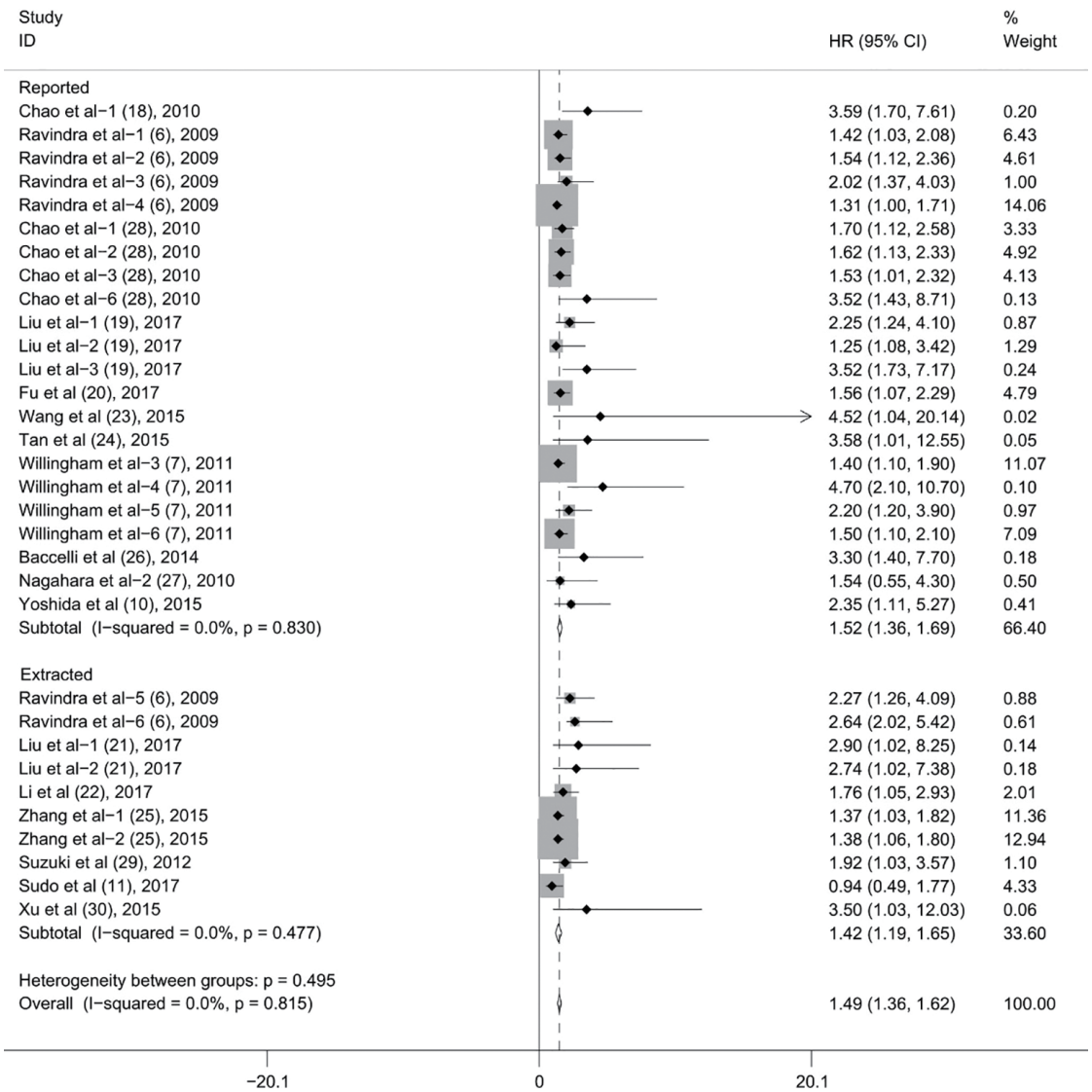

Figure S6 Forest plot of HR for OS stratified by HR obtained method (6,7,10,11,18-30). HR, hazard ratio; OS, overall survival.

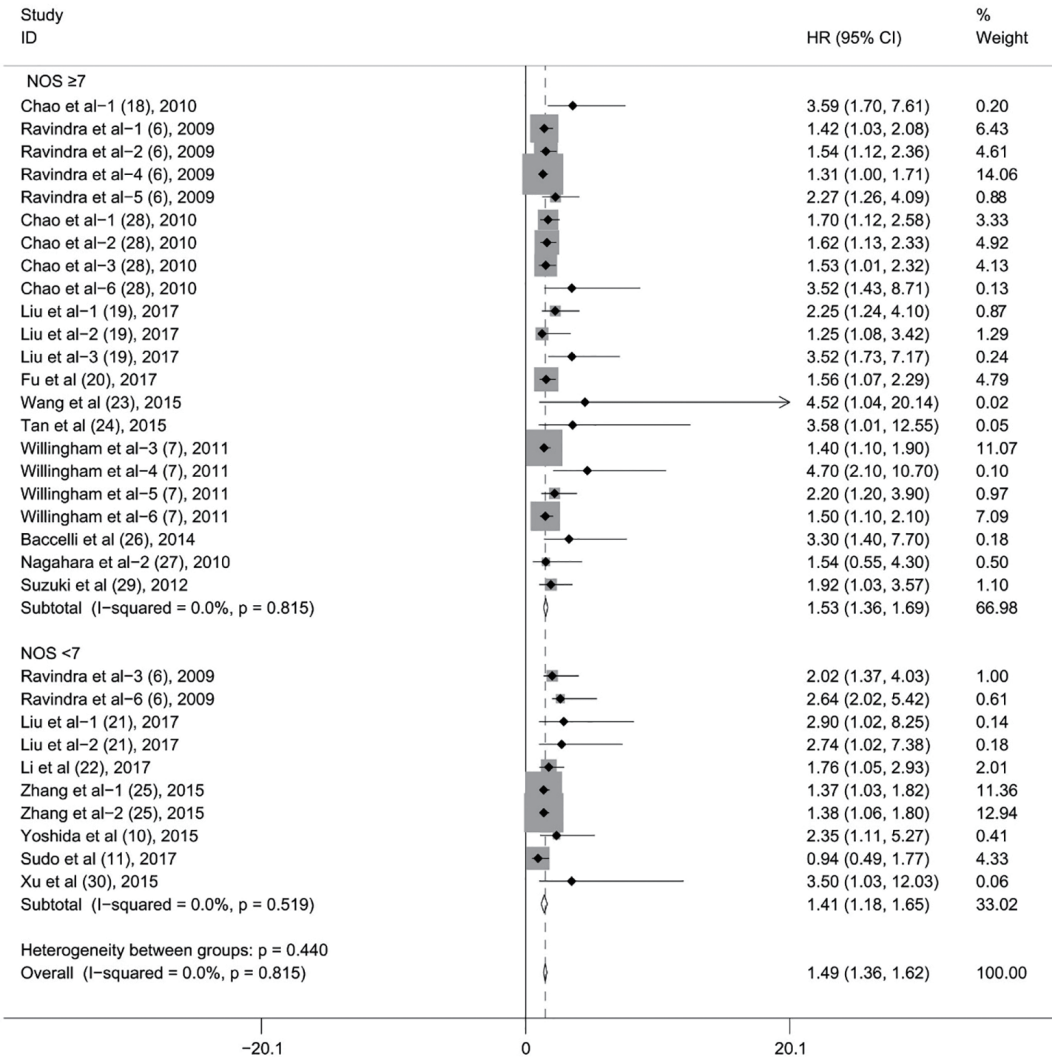

Figure S7 Forest plot of HR for OS stratified by NOS score (6,7,10,11,18-30). HR, hazard ratio; OS, overall survival; NOS, Newcastle-Ottawa score.

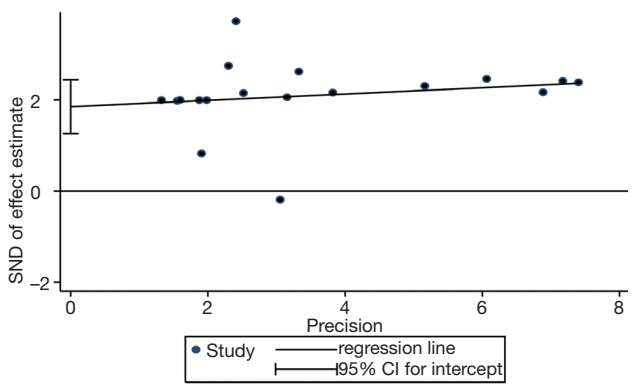

Figure S8 Egger's test for publication bias in OS analysis. OS, overall survival.

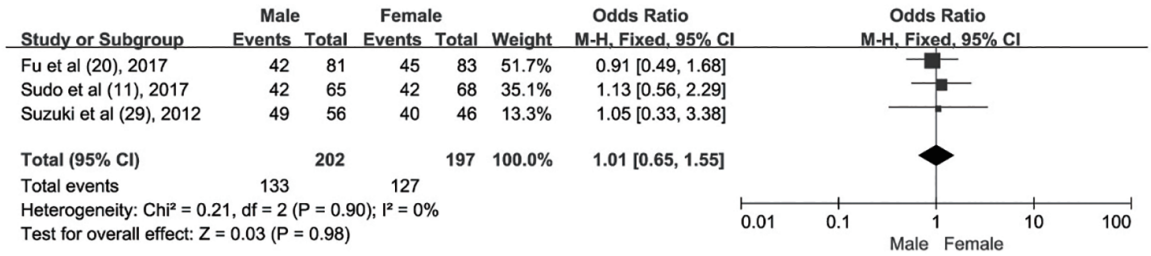

Figure S9 The correlation between high CD47 expression and gender (male *vs.* female) (11,20,29).

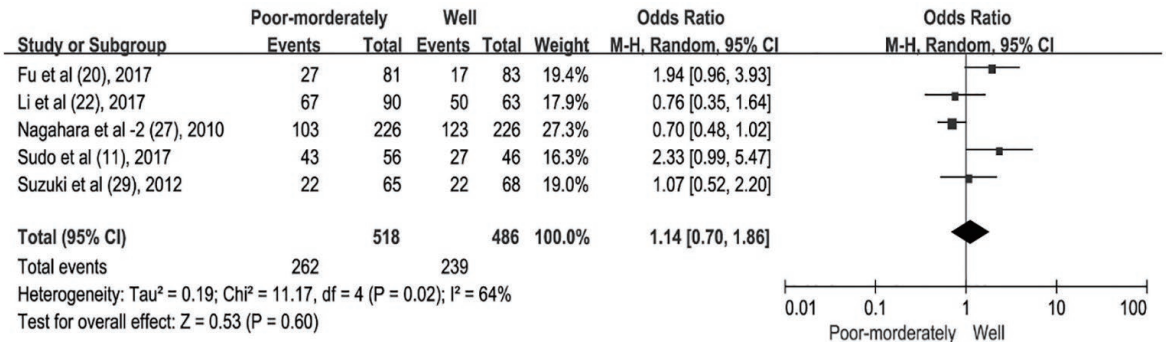

Figure S10 The correlation between high CD47 expression and tumor differentiation (poorly/moderately *vs.* well) (11,20,22,27,29).

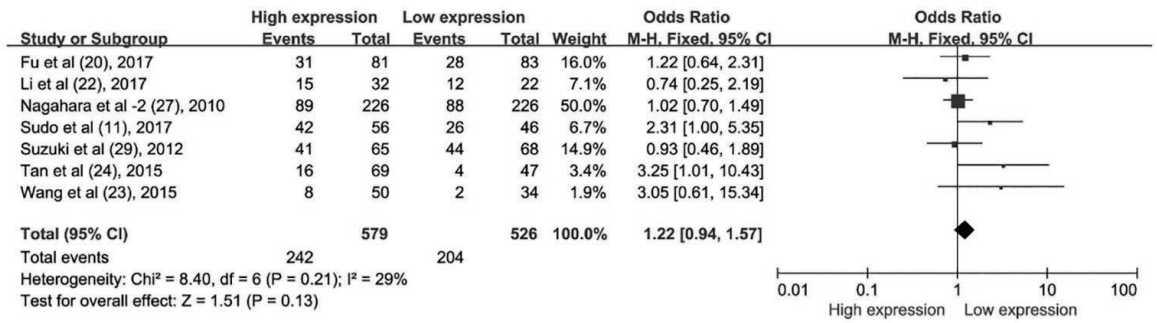

Figure S11 The correlation between high CD47 expression and lymph node metastasis (+ *vs.* –) (11,20,22-24,27,29).

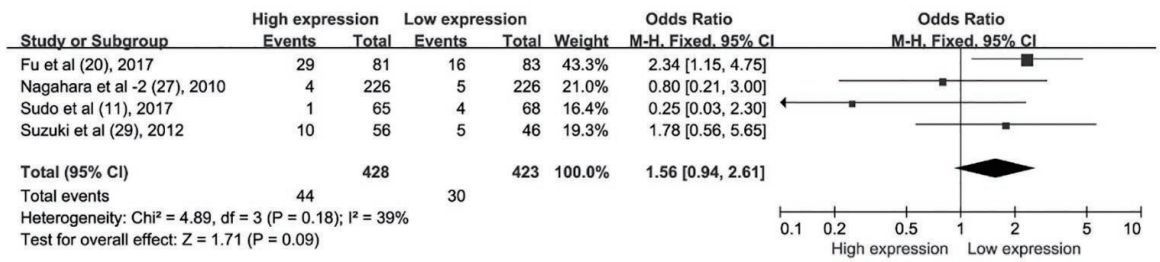

Figure S12 The correlation between high CD47 expression and distant metastasis (+ *vs.* –) (11,20,27,29).

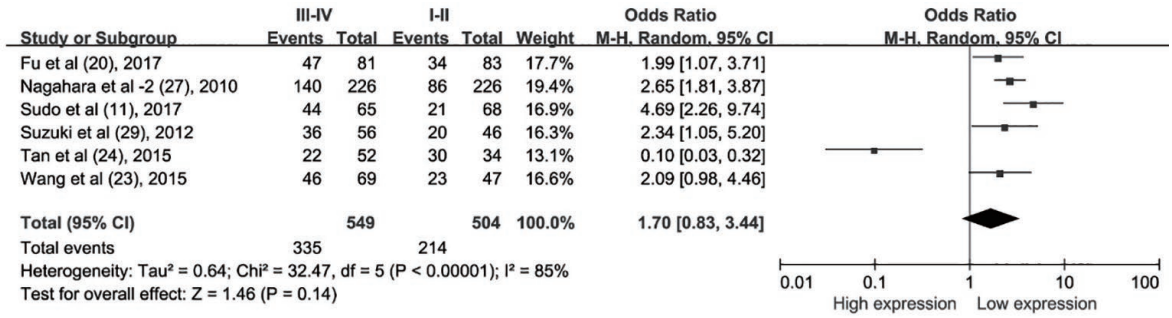

Figure S13 The correlation between high CD47 expression and TNM stage (III–IV *vs.* I–II) (11,20,23,24,27,29).