

The efficacy and safety of apatinib for refractory malignancies: a review and meta-analysis

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Background and purpose: Apatinib is a novel, oral, small-molecule tyrosine kinase inhibitor that targets VEGFR-2. Recent clinical trials have revealed its broad-spectrum anticancer effect. However, most recent studies of apatinib have involved single-arm studies with insufficient cases, different doses of drugs, and different incidences of adverse events (AEs), which has resulted in a lack of accurate measurement of the efficacy and safety of apatinib. Thus, we performed this meta-analysis to evaluate the efficacy and safety of apatinib.

Methods: In total, 21 studies from five databases (PubMed, ScienceDirect, ClinicalTrials.gov, China National Knowledge Infrastructure [CNKI], and Cochrane Library) were included in this meta-analysis. All statistical analyses in this meta-analysis were performed using Stata 14.0 software. We used objective response rate (ORR) and disease control rate (DCR) to evaluate the efficacy of apatinib for five major types of solid tumors. Additionally, we used the total incidence of AEs and the incidence of the three most common grade 3–4 AEs to evaluate the safety of apatinib.

Results: The pooled results for the efficacy of apatinib in the treatment of different types of solid tumors revealed that patients treated with apatinib exhibited good disease control. In addition, it was likely that an increased dose of apatinib resulted in an increased ORR in lung and breast cancer and an increased DCR in liver and gastric cancer. Although AEs appeared in 84% of patients included in this meta-analysis, most of these AEs were of grades 1–2 and were well tolerated and controlled. The most common grade 3–4 AEs included hypertension, hand-foot syndrome, and proteinuria. Importantly, there were no significant differences in these grade 3–4 AEs with higher doses of apatinib.

Conclusion: Apatinib is a novel VEGFR-2 inhibitor with proven efficacy and safety for solid tumors. The meta-analysis reveals the broad-spectrum anticancer effect of apatinib.

Keywords: apatinib, solid tumors, objective response rate, disease control rate, adverse events

Background and purpose

The incidence of malignant tumors has increased rapidly in recent years, especially in China. According to a report on cancer incidence and mortality in different areas of China, 3.8 million new malignant tumor cases were diagnosed in 2014. The crude incidence of malignant tumors in 2014 was $278.1/10^5$, whereas the crude mortality was $167.89/10^5$.¹ Therefore, more effective cancer treatments are needed.

VEGF was first identified by Folkman et al in the 1970s.² Briefly, VEGF, which is mitogenic for endothelial cells and is responsible for the formation of new capillaries, plays an important role in tumor growth and metastasis.^{2,3} The physiological VEGF family consists of six growth factors, namely VEGF-A, VEGF-B, VEGF-C,

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VEGF-D, VEGF-E, and PLGF. The VEGFR family includes three protein tyrosine kinases: VEGFR-1 (Flt-1), VEGFR-2 (Flt-1/KDR), and VEGFR-3 (Flt-4). The combination of VEGF and VEGFR induces angiogenesis and vasculogenesis through p38MAPK, Raf/MEK/ERK, and PI3K/PKB signaling pathways.^{4,5} Given that VEGFR-2 plays a more important role in the signaling pathways, small-molecule tyrosine kinase inhibitors mostly target VEGFR-2.

Apatinib, also known as YN968D1, is a novel, oral, small-molecule tyrosine kinase inhibitor that targets VEGFR-2 as well as c-Kit and c-SRC tyrosine kinases.⁶ Apatinib was approved and launched in China in 2014 for subsequent-line treatment of gastric cancer.⁷ Recent clinical trials have revealed its broad-spectrum anticancer effect. However, most recent studies of apatinib have involved single-arm studies with insufficient cases, different doses of drugs, and different incidences of adverse events (AEs), resulting in a lack of accurate measurement of the efficacy and safety of apatinib. Thus, we performed this meta-analysis to evaluate the efficacy and safety of the novel VEGFR-2 inhibitor apatinib.

Methods

Search strategy for studies

From April 2018 to May 2018, two authors (Sun DT and Hou HL) searched five databases independently, namely PubMed, ScienceDirect, ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI), and Cochrane Library. All MeSH terms of the keywords (apatinib, YN968D1) were used in the search.

Any disagreement regarding study inclusion was resolved through discussion by all authors. In addition, we contacted the corresponding authors of some of the studies if the databases failed to provide sufficient information.

Literature selection criteria

All clinical trials that evaluated the efficacy and safety of apatinib in the treatment of solid tumors were considered eligible for the analysis. Two authors (Sun DT and Hou HL) completed the screening of the literature independently. The inclusion criteria were as follows: 1) study types – Phase II clinical trials or retrospective analysis; 2) participant types – patients with solid tumors; 3) intervention types – patients were treated with apatinib only with different doses; 4) outcome measure types – disease control rate (DCR), objective response rate (ORR), the incidence of \geq grade 3 AEs, or at least one of these outcomes should be provided in the included studies; and 5) full text was available.

The exclusion criteria were as follows: studies were case reports, reviews, or meta-analyses, duplicates, or involved animal or cell experiments, and full text was not available via other means.

Data extraction

Two authors (Sun DT and Hou HL) completed the related literature data extraction independently. The following data were extracted: study ID, cancer types, number of patients, dose and frequency of apatinib treatment, disease baseline before apatinib treatment, Eastern Cooperative Oncology Group status, and study phase. The details of the 21 studies included^{8–28} are presented in Table 1. In addition, we extracted the research indicators selected by this meta-analysis, including ORR (ORR = complete response [CR] + partial response [PR]), DCR (DCR = CR + PR + stable disease), and the incidence of \geq grade 3 AEs. The results of data extraction were discussed by all authors.

Quality assessment

Two authors (Zhang CT and Zhang XC) assessed the quality of the studies independently after reading the full text of each study. We used the Newcastle–Ottawa Scale (NOS) to assess the quality of non-randomized controlled trials in this meta-analysis.²⁹ The quality of a study was considered “poor” if the NOS score was <4 . If the score was 4–6, we considered the study to be of “moderate” quality. A study with a score of 7–9 was considered to be of “high quality”. The NOS scores of the 21 studies included are presented in Table 1, and the quality assessment details are presented in Table 2.

Statistical analysis

All statistical analyses in this meta-analysis were performed using Stata 14.0 software (Stata Corp., College Station, TX, USA). The results were expressed as incidences and 95% CIs. In this meta-analysis, we used a random-effect model to perform the statistical analyses, and chi-squared test and I^2 statistic were used to assess the inter-study heterogeneity. A P -value >0.1 and $I^2 < 50\%$ indicated that the heterogeneity was not statistically significant. If the P -value was <0.1 and I^2 was $>50\%$, significant heterogeneity was noted between the studies. Therefore, subgroup analyses were used to assess the heterogeneity. Begg’s and Egger’s tests were used to evaluate the publication bias in this meta-analysis.

Meta-analysis results

Figure 1 presents the flowchart of selection of the 21 included studies. A total of 879 references were identified after database

Table I Main characteristics of the included studies

Study	Cancer type	Number of patients	Dose and frequency	Disease baseline	ECOG status	Study phase	Quality assessment (NOS)
Hu et al (2014) ⁸	Breast cancer	38	500 mg, po, qd	Treatment failure and metastasis	0–1	II	6
Liu and Wu (2017) ⁹	Breast cancer	20	850 mg, po, qd	Treatment failure and metastasis	0–1	II	6
Yuan et al (2017) ¹⁰	Breast cancer	27	425 mg, po, qd	Treatment failure and metastasis	1–2	NA	6
Shi et al (2017) ¹¹	Lung cancer	72	250 mg, po, qd	TNM staging: IIIb–IV Treatment failure	0–2	II	5
Jiao and Li (2017) ¹²	Lung cancer	42	500 mg, po, qd	Treatment failure and metastasis	NA	NA	5
Yang (2017) ¹³	Lung cancer	30	500 mg, po, qd	TNM staging: IIIb–IV; Treatment failure and metastasis	1–2	II	5
Li et al (2016) ¹⁴	Lung cancer	22	425 mg, po, qd	TNM staging: IIIb–IV; Treatment failure and metastasis	1–2	II	5
Nie et al (2017) ¹⁵	Lung cancer	28	500 mg, po, qd	TNM staging: IV; Treatment failure and metastasis	0–2	II	5
Fang et al (2018) ¹⁶	Lung cancer	36	500 mg, po, qd	Treatment failure and metastasis	0–2	II	5
Ruan et al (2017) ¹⁷	Gastric cancer	42	850 mg, po, qd	Treatment failure and metastasis	1–2	II	6
Zhang et al (2018) ¹⁸	Gastric cancer	23	500 mg, po, qd	Treatment failure and metastasis	0–1	NA	6
Zhang et al (2016) ¹⁹	Gastric cancer	20	500 mg, po, qd	TNM staging: IV; Treatment failure and metastasis	NA	NA	5
Yao et al (2017) ²⁰	Gastric cancer	30	500 mg, po, qd	Treatment failure and metastasis	1–3	NA	5
Lang et al (2017) ²¹	Gastric cancer	14	850 mg, po, qd	TNM staging: IV; Treatment failure and metastasis	NA	NA	5
Yu et al (2018) ²²	Liver cancer	31	250 mg, po, qd	Treatment failure and metastasis	NA	II	6
Song et al (2017) ²³	Liver cancer	a: 15 b: 25 c: 13	a: 250 mg, po, qd b: 500 mg, po, qd c: 850 mg, po, qd	Treatment failure	2–4	NA	6
Qin et al (2017) ²⁴	Liver cancer	a: 53 b: 51	a: 850 mg, po, qd b: 750 mg, po, qd	Treatment failure and metastasis	0–1	II	6
Liang et al (2018) ²⁵	Colorectal cancer	36	425–750 mg, po, qd	Treatment failure and metastasis	0–1	NA	6
Gou et al (2018) ²⁶	Colorectal cancer	36	250 mg, po, qd	Treatment failure and metastasis	0–1: 69.4% ≥2: 30.6%	NA	5
Sun et al (2017) ²⁷	Colorectal cancer	14	425 mg, po, qd	TNM staging: IV; Treatment failure and metastasis	1–2	II	5
Wang et al (2017) ²⁸	Colorectal cancer	17	500 mg, po, qd	TNM staging: IV; Treatment failure and metastasis	0–3	NA	5

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not applicable; NOS, Newcastle–Ottawa Scale; po, orally; qd, once a day.

searches (PubMed 166, CNKI 329, Cochrane Library 47, ScienceDirect 150, ClinicalTrials.gov 187). Then, 537 references remained after duplicates were removed. Twenty-nine references remained after the first screening. Eight studies were excluded based on the following reasons: four were case reports or case series, one was a duplicate, and three involved cell experiments. Finally, 21 studies with a total of 735 patients were included for the assessment of efficacy and safety of apatinib.

The efficacy of apatinib

Apatinib in lung cancer

Six studies with a total of 230 patients evaluated the efficacy of apatinib in lung cancer. The pooled DCR of apatinib

for lung cancer patients was 82% (95% CI: 77%–87%; Figure 2A). The pooled ORR of apatinib for lung cancer patients was 20% (95% CI: 14%–25%). Subgroup analysis revealed that patients who were administered a 500 mg dose of apatinib exhibited an increased ORR compared with patients who received a <500 mg dose (23%, 95% CI: 16%–29% vs 16%, 95% CI: 8%–23%; Figure 2B).

Apatinib in liver cancer

Three studies with a total of 188 patients evaluated the efficacy of apatinib in liver cancer. The pooled DCR of apatinib for liver cancer patients was 51% (95% CI: 37%–64%). Subgroup analysis revealed that patients who received ≥750 mg apatinib

Table 2 Quality assessment of the included studies

Study	Representatives of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was present at the start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts
Hu et al (2014) ⁸		0			0			
Liu and Wu (2017) ⁹		0			0			
Yuan et al (2017) ¹⁰		0			0			
Shi et al (2017) ¹¹		0			0		0	
Jiao and Li (2017) ¹²		0			0		0	
Yang (2017) ¹³		0			0		0	
Li et al (2016) ¹⁴		0			0		0	
Nie et al (2017) ¹⁵		0			0		0	
Fang et al (2018) ¹⁶		0			0		0	
Ruan et al (2017) ¹⁷		0			0			
Zhang et al (2018) ¹⁸		0			0			
Zhang et al (2016) ¹⁹		0			0		0	
Yao et al (2017) ²⁰		0			0		0	
Lang et al (2017) ²¹		0			0		0	
Yu et al (2018) ²²		0			0			
Song et al (2017) ²³		0			0			
Qin et al (2017) ²⁴		0			0			
Liang et al (2018) ²⁵		0			0			
Gou et al (2018) ²⁶		0			0		0	
Sun et al (2017) ²⁷		0			0		0	
Wang et al (2017) ²⁸		0			0		0	

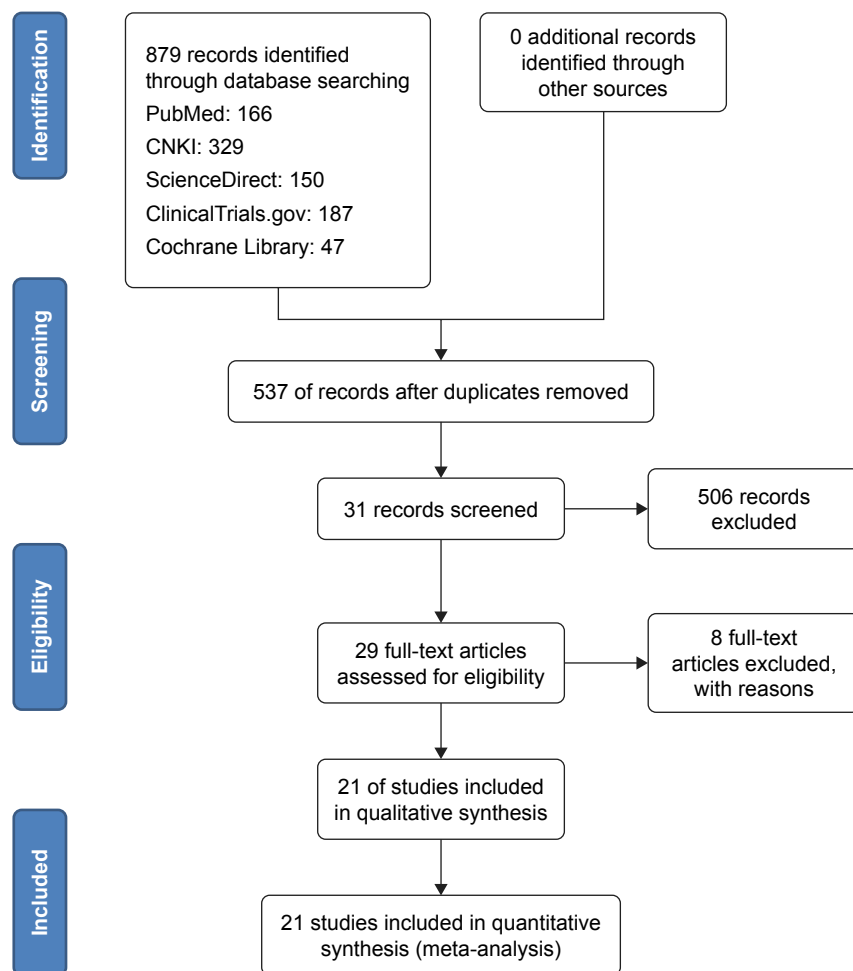


Figure 1 Flowchart of the article selection process.

exhibited an increased DCR compared with patients who received <750 mg (62%, 95% CI: 53%–71% vs 33%, 95% CI: 19%–48%; Figure 3A). The pooled ORR of apatinib for liver cancer patients was 18% (95% CI: 13%–24%; Figure 3B).

Apatinib in gastric cancer

Five studies with a total of 129 patients evaluated the efficacy of apatinib in gastric cancer. The pooled DCR of apatinib for gastric cancer patients was 66% (95% CI: 52%–79%). Subgroup analysis demonstrated that patients who received 850 mg apatinib exhibited an increased DCR compared with those patients who were administered 500 mg apatinib (79%, 95% CI: 68%–89% vs 56%, 95% CI: 40%–72%; Figure 4A). The pooled ORR of apatinib for gastric cancer patients was 10% (95% CI: 5%–15%; Figure 4B).

Apatinib in breast cancer

Three studies with a total of 85 patients evaluated the efficacy of apatinib in breast cancer. The pooled DCR of apatinib

for breast cancer patients was 66% (95% CI: 55%–76%; Figure 5A). The pooled ORR of apatinib for lung cancer patients was 16% (95% CI: 6%–26%). Subgroup analysis revealed that patients who were administered an 850 mg dose of apatinib exhibited an increased ORR compared with those patients who received <850 mg apatinib (40%, 95% CI: 4%–76% vs 14%, 95% CI: 4%–23%; Figure 5B).

Apatinib in colorectal cancer

Four studies with a total of 103 patients evaluated the efficacy of apatinib in colorectal cancer. The pooled DCR of apatinib for breast cancer patients was 79% (95% CI: 70%–87%; Figure 6A). The pooled ORR of apatinib for lung cancer patients was 13% (95% CI: 7%–20%; Figure 6B).

The safety of apatinib

AEs mostly occurred in every patient treated with apatinib (84% CI: 77%–92%; Figure 7A); however, most were of

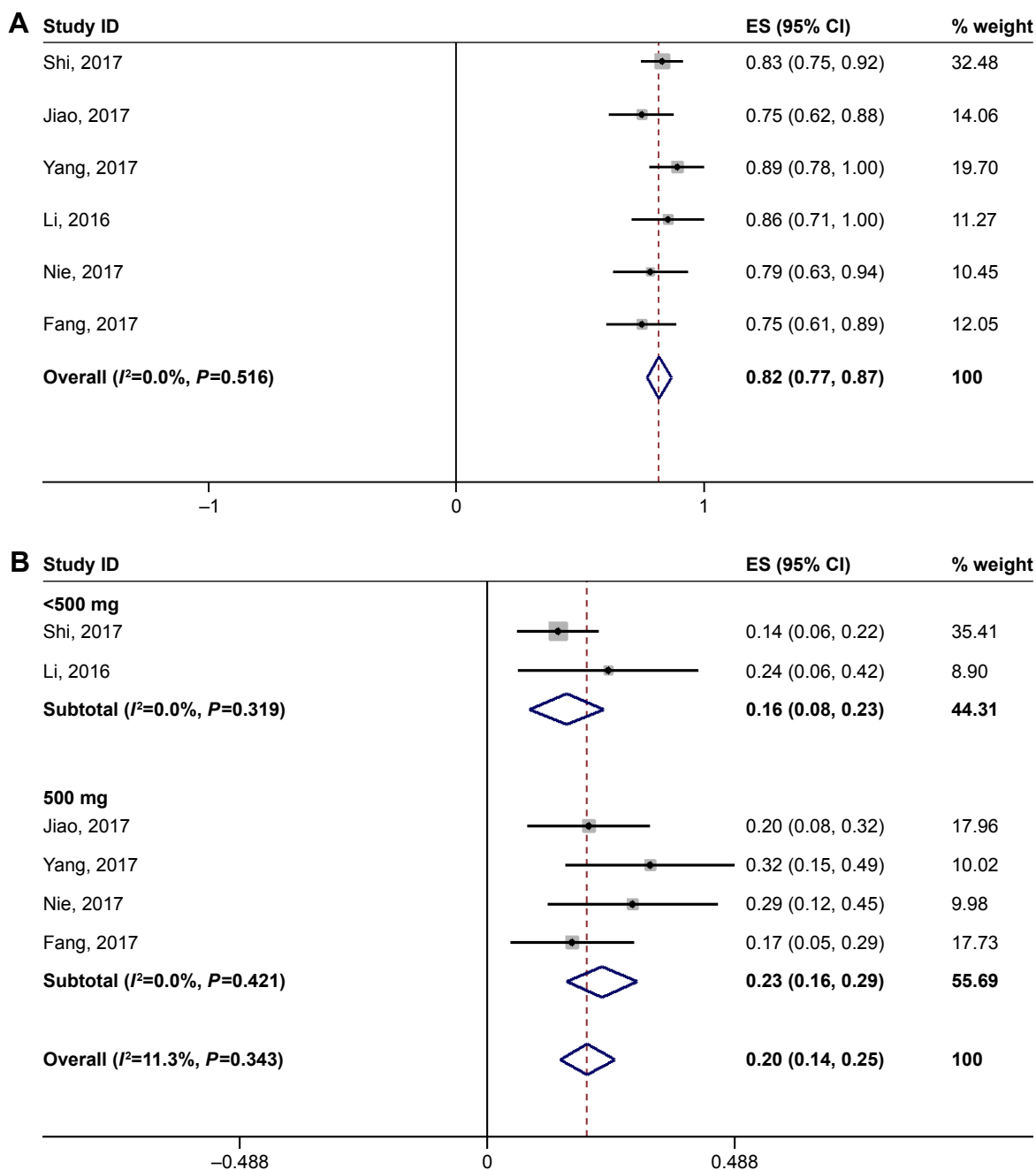


Figure 2 The DCR (A) and ORR (B) of apatinib in the treatment of lung cancer.

Note: Weights are from random effects analysis.

Abbreviations: DCR, disease control rate; ES, effect size; ORR, objective response rate.

grades 1–2 and were well tolerated and controlled, including secondary hypertension, hand-foot syndrome, proteinuria, fatigue, mucositis, anemia, leukopenia, thrombocytopenia, increased bilirubin, increased transaminase, diarrhea, vomiting, and rashes. The most common grade 3–4 AEs included secondary hypertension (7% CI: 5%–10%; Figure 7B), hand-foot syndrome (6% CI: 3%–8%; Figure 7C), and proteinuria (4% CI: 2%–7%; Figure 7D).

Publication bias

Egger's and Begg's tests were performed to evaluate the publication bias of all results in this meta-analysis. The test results were consistent with most of the results in this meta-analysis except the ORR of lung cancer (Egger's test: 0.012; Begg's test: 0.260). Given that Egger's test is more sensitive than Begg's test in evaluating publication bias,³⁰ we considered that publication bias exists for the ORR results of lung

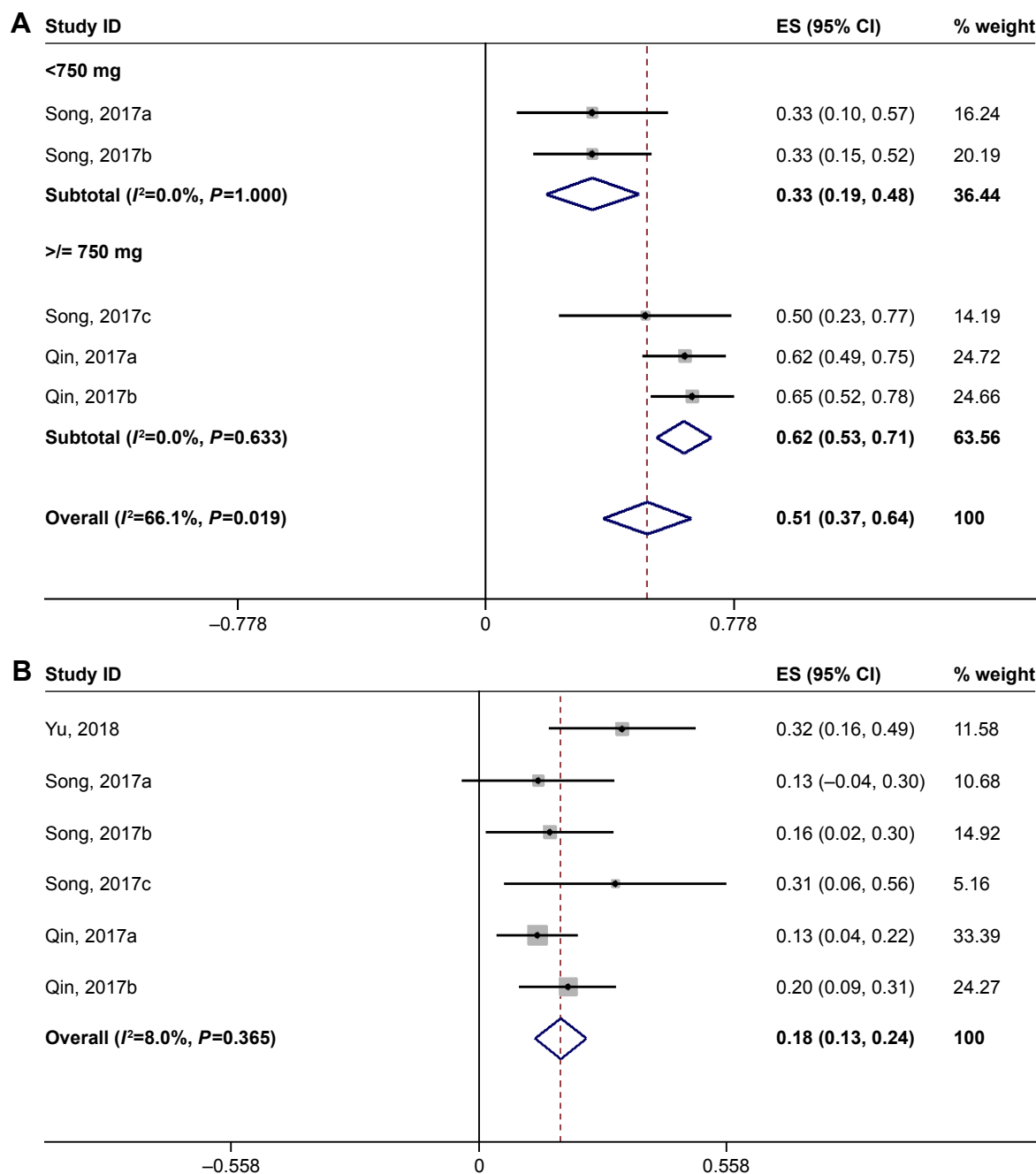


Figure 3 The DCR (A) and ORR (B) of apatinib in the treatment of liver cancer.

Note: Weights are from random effects analysis.

Abbreviations: DCR, disease control rate; ES, effect size; ORR, objective response rate.

cancer and the incidence of hypertension and hand-foot syndrome. The publication bias evaluation results are presented in Table S1.

Sensitivity analysis

The results of sensitivity analysis revealed no significant differences after omitting any one of the studies included, indicating that the results of this meta-analysis were

robust. The results of sensitivity analysis are presented in Figures S1–S13.

Discussion

Apatinib is a selective inhibitor of VEGFR-2 with broad-spectrum anticancer effect and is also stated to be involved in the regulation of autophagy.³¹ This meta-analysis involving 21 studies evaluated the efficacy and safety of apatinib in five

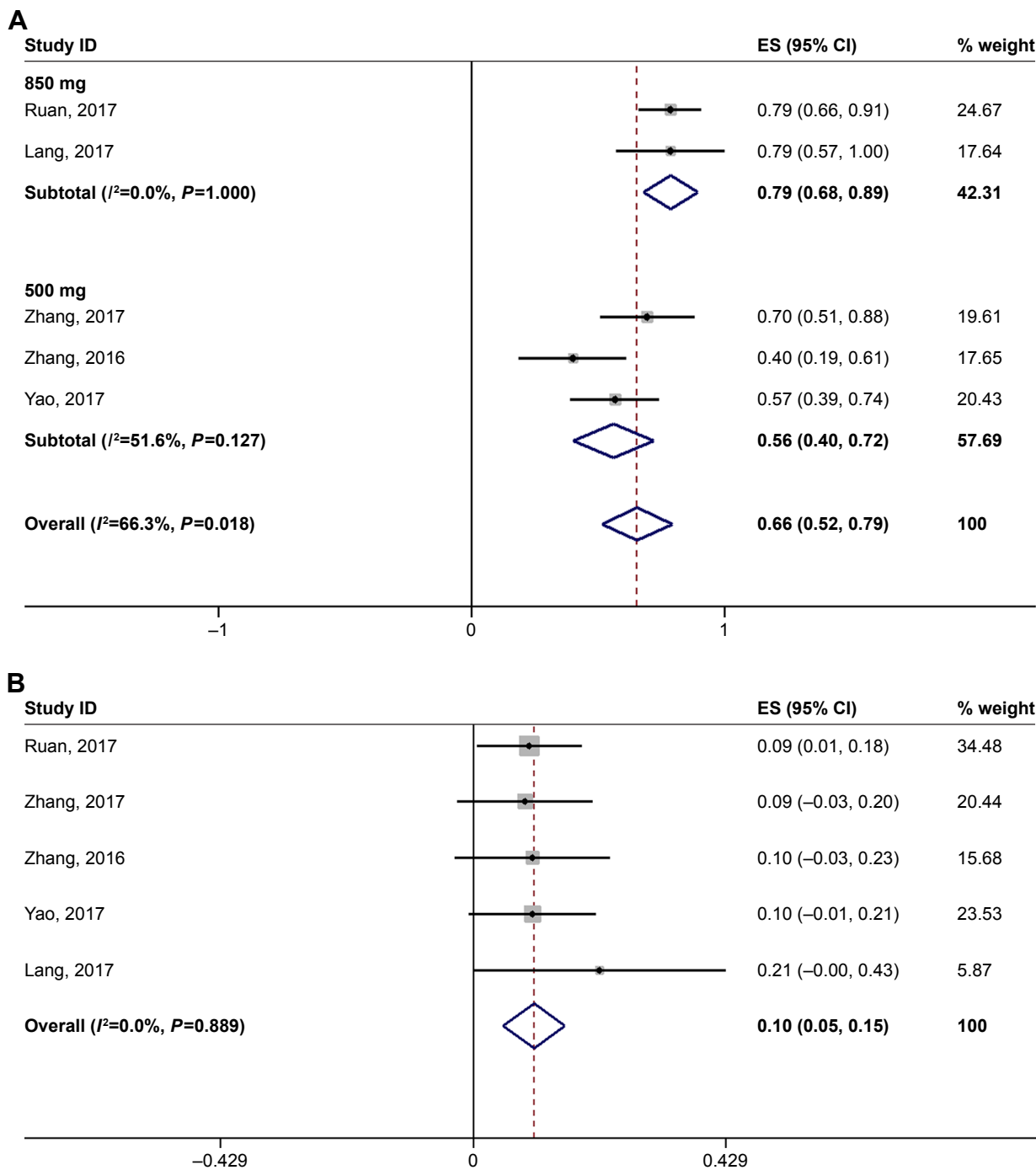


Figure 4 The DCR (A) and ORR (B) of apatinib in the treatment of gastric cancer.
Note: Weights are from random effects analysis.
Abbreviations: DCR, disease control rate; ES, effect size; ORR, objective response rate.

major types of solid tumors, namely lung cancer, liver cancer, gastric cancer, breast cancer, and colorectal cancer. The pooled results for the efficacy of apatinib in the treatment of different types of solid tumors revealed that apatinib exhibited good disease control (DCR: lung cancer 82%, liver cancer 51%, gastric

cancer 66%, breast cancer 66%, colorectal cancer 79%; ORR: lung cancer 20%, liver cancer 18%, gastric cancer 10%, breast cancer 16%, colorectal cancer 13%). In addition, it was likely that a higher dose of apatinib resulted in an increased ORR in lung cancer (500 mg, 23% vs <500 mg, 16%) and breast

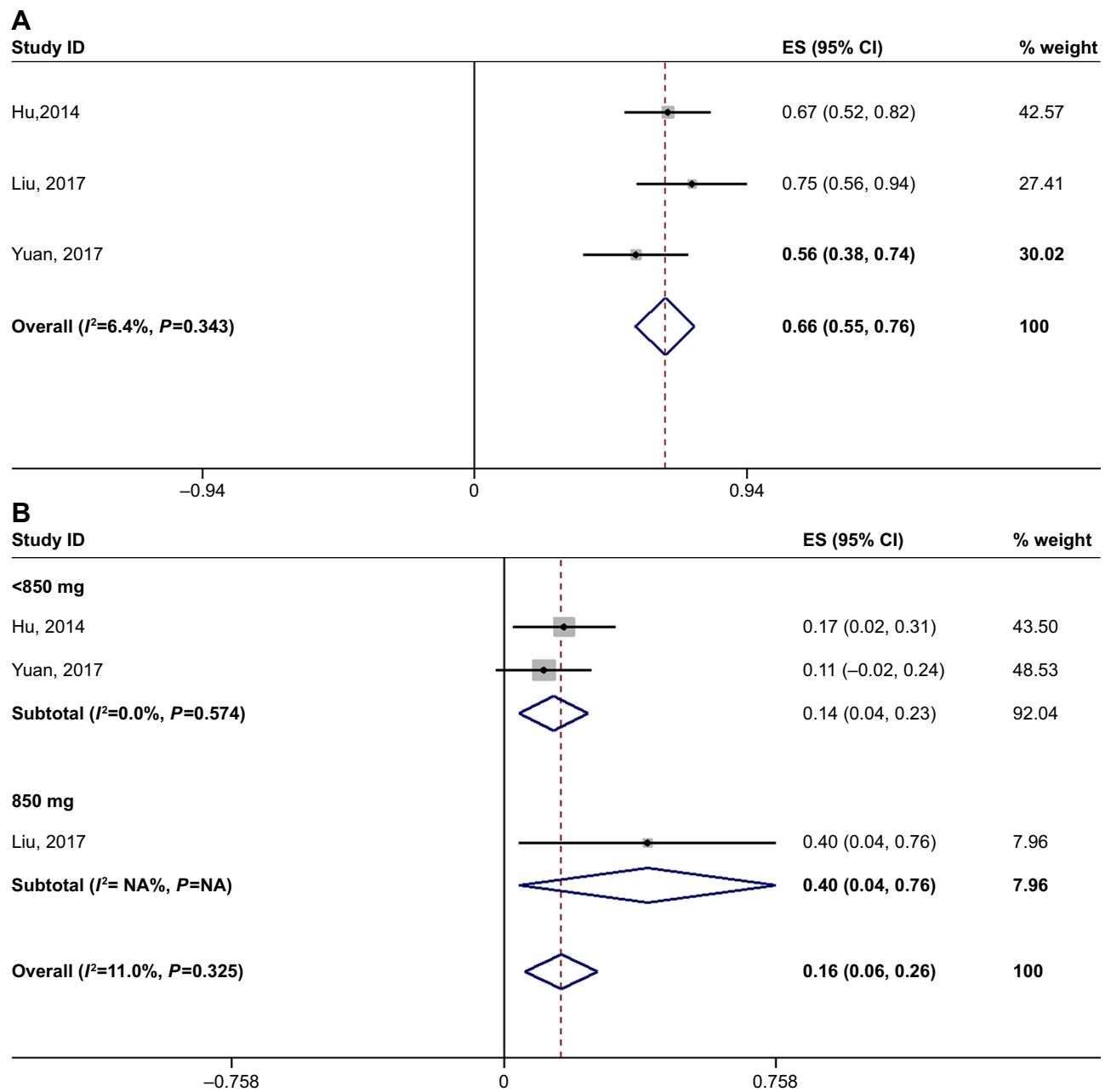


Figure 5 The DCR (A) and ORR (B) of apatinib in the treatment of breast cancer.

Note: Weights are from random effects analysis.

Abbreviations: DCR, disease control rate; ES, effect size; NA, not applicable; ORR, objective response rate.

cancer (850 mg, 40% vs <850 mg, 14%), and an increased DCR in liver cancer (≥ 750 mg, 62% vs <750 mg, 33%) and gastric cancer (850 mg, 79% vs 500 mg, 56%).

Although AEs appeared in 84% of patients in this meta-analysis, most were of grades 1–2 and were well tolerated and controlled. The most common grade 3–4 AEs were hypertension (7%), hand-foot syndrome (6%), and proteinuria (4%). Importantly, there were no significant differences in these grade 3–4 AEs with higher doses of apatinib (500, 750, and 850 mg).

In addition to the five major types of solid tumors reported in this meta-analysis, the efficacy of apatinib in other types of solid tumors was also demonstrated by clinical trials. The clinical trials of Li and Wang³² and Miao et al³³ revealed that apatinib is efficacious in esophageal cancer (DCR: 74.2%; ORR: 24.2%) and ovarian cancer (DCR: 68.9%; ORR: 41.4%), respectively. Apatinib was also found to be effective in prostate cancer³⁴ and thyroid cancer.³⁵

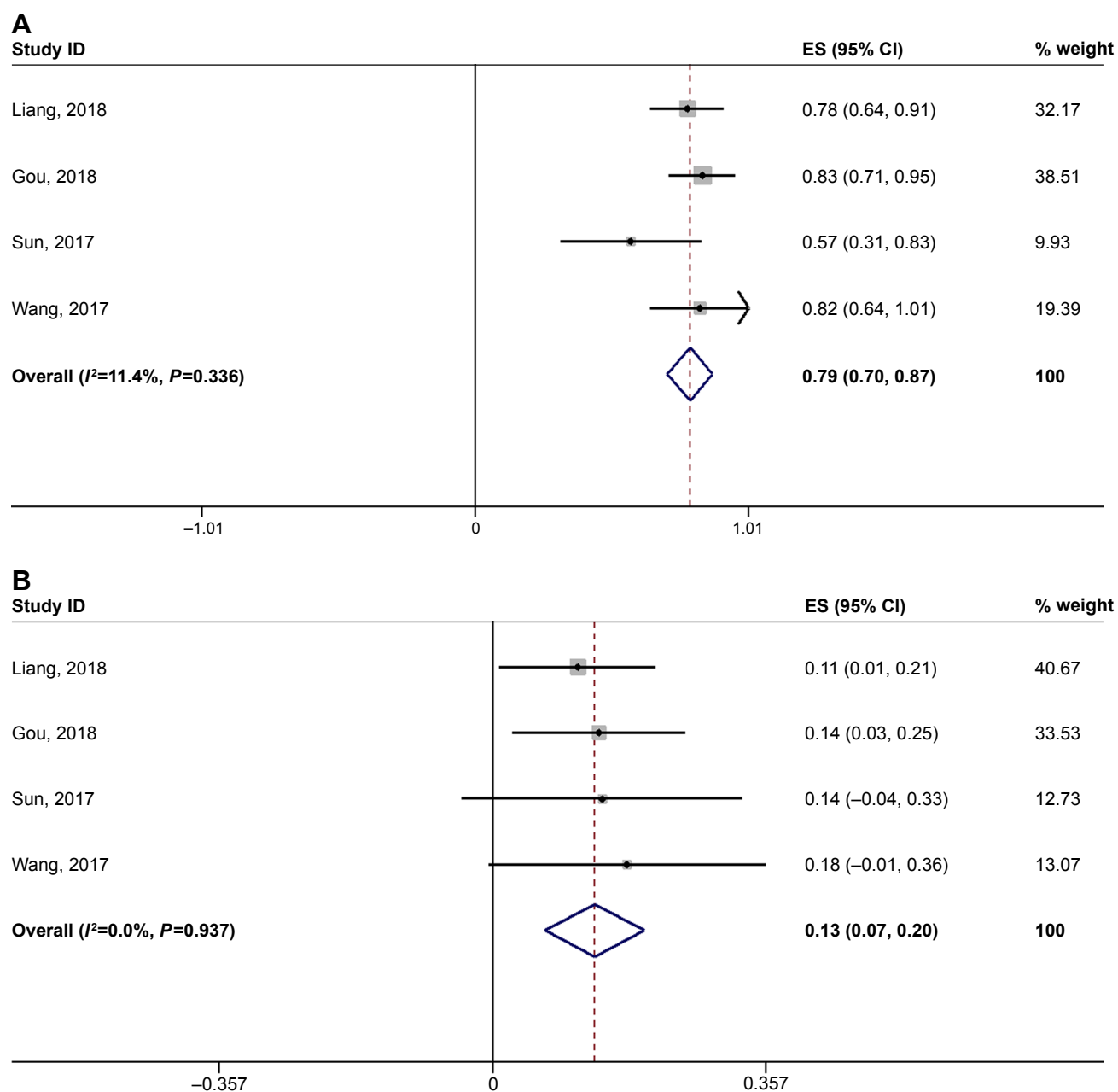


Figure 6 The DCR (A) and ORR (B) of apatinib in the treatment of colorectal cancer.

Note: Weights are from random effects analysis.

Abbreviations: DCR, disease control rate; ES, effect size; ORR, objective response rate.

Admittedly, our meta-analysis has some limitations. Given that apatinib is a novel VEGFR-2 inhibitor produced in China, the participants of studies included in this meta-analysis were all Asians. However, some clinical trials have been undergoing in the USA, such as NCT03407976, NCT03396211, and NCT03042611. More data on the efficacy of apatinib in different populations will soon be obtained in the next few years. The efficacy of apatinib for other races must be confirmed by more clinical trials. In

addition, publication bias existed in several results of this meta-analysis, including the ORR of lung cancer and the incidence of grade 3–4 hypertension and hand-foot syndrome. Therefore, more clinical trials are needed to confirm our results.

In conclusion, this meta-analysis suggests that patients treated with apatinib exhibited good disease control. A higher dose of apatinib (500, 750, and 850 mg) significantly increased the ORR and DCR. AEs of apatinib were

noted in 84% of participants. However, most AEs were of grades 1–2 and were well tolerated and controlled. The incidences of the three most common grade 3–4 AEs were low (hypertension: 7%; hand-foot syndrome: 6%; proteinuria: 4%), and there were no significant differences between

the higher-dose and lower-dose groups. Additional clinical trials are needed to update our study and compare the efficacy of apatinib with other VEGFR-2 inhibitors and other small-molecule tyrosine kinase inhibitors to provide more information to patients.

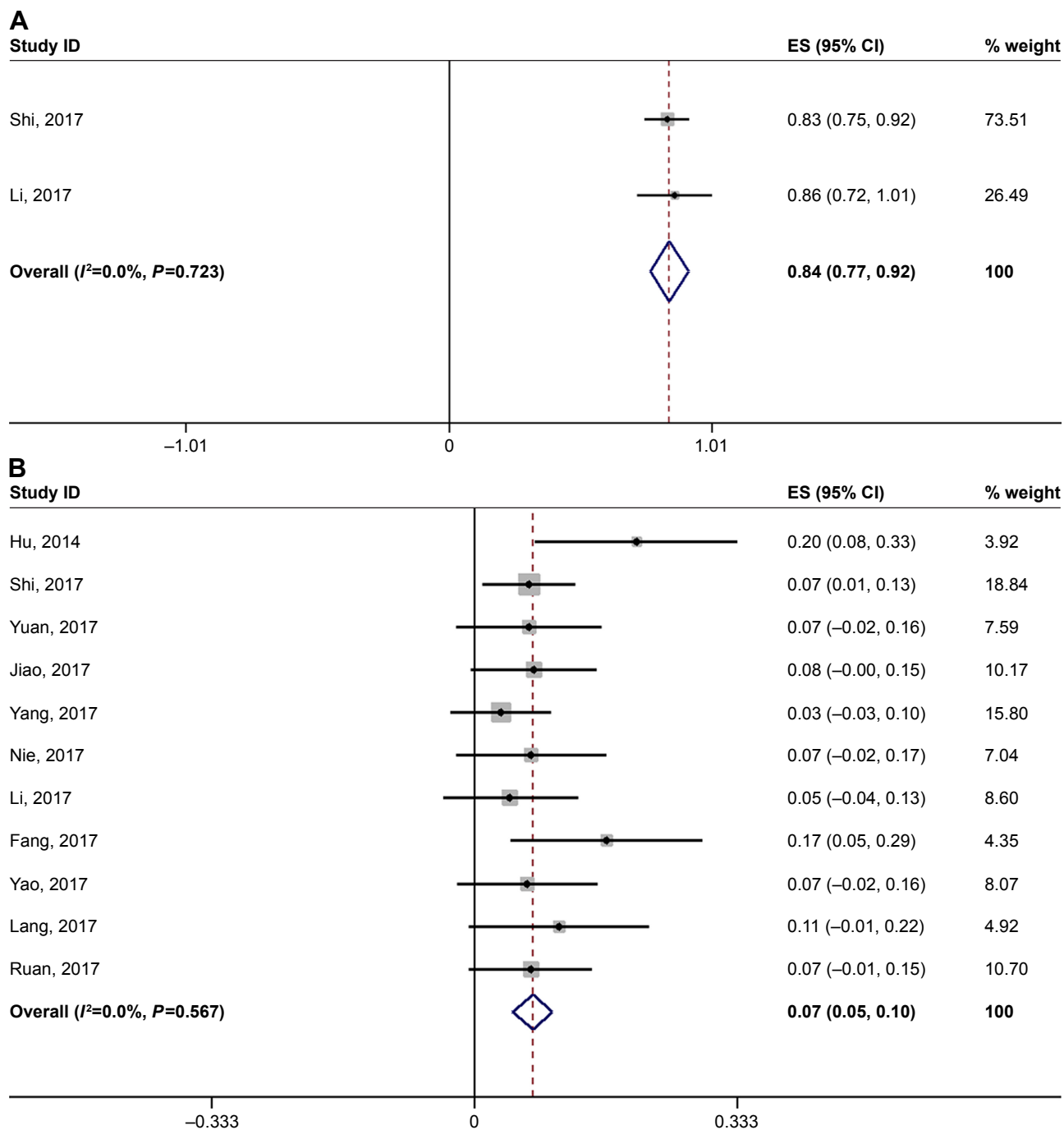


Figure 7 (Continued)

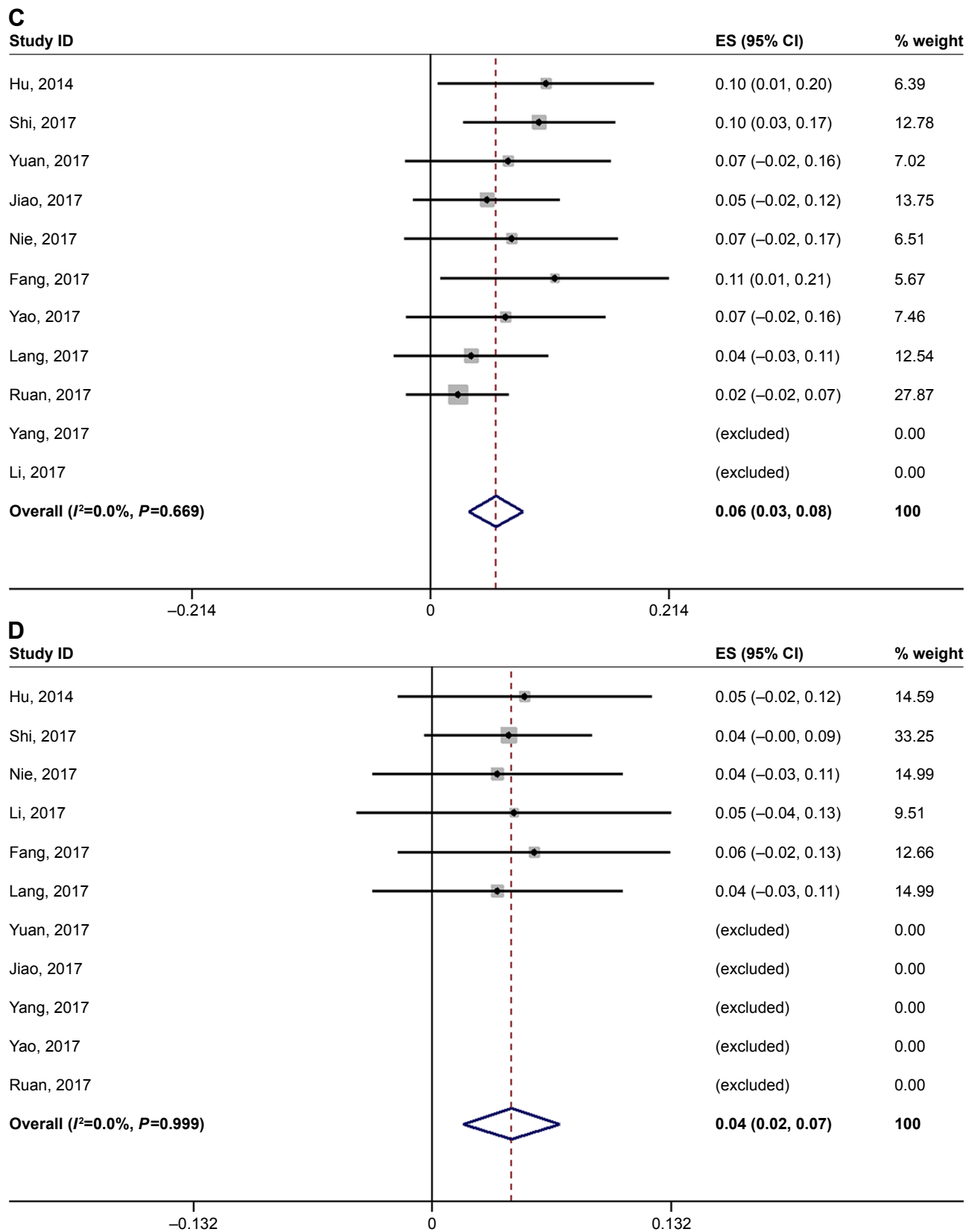


Figure 7 The total incidence of AEs and incidence of grade 3–4 AEs associated with apatinib treatment.

Notes: (A) AEs; (B) hypertension; (C) hand-foot syndrome; (D) proteinuria. Weights are from random effects analysis.

Abbreviations: AE, adverse event; ES, effect size.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Publication bias

Table S1 The Begg's and Egger's tests of the results in this meta-analysis

Results	Begg's tests	Egger's tests	Publication bias
Breast cancer ORR	0.296	0.182	(-)
Breast cancer DCR	1.000	0.962	(-)
Colorectal cancer ORR	0.734	0.206	(-)
Colorectal cancer DCR	0.308	0.190	(-)
Gastric cancer ORR	0.221	0.062	(-)
Gastric cancer DCR	0.806	0.293	(-)
Liver cancer ORR	0.452	0.200	(-)
Liver cancer DCR	0.806	0.150	(-)
Lung cancer ORR	0.260	0.012*	(+)
Lung cancer DCR	1.000	0.386	(-)
Total AEs	1.000	-	(-)
Proteinuria	0.348	0.600	(-)
Hypertension	0.005	0.007*	(+)
Hand-foot syndrome	0.029	0.013*	(+)

Note: *Publication bias exists.

Abbreviations: AE, adverse event; DCR, disease control rate; ORR, objective response rate.

Sensitivity analysis

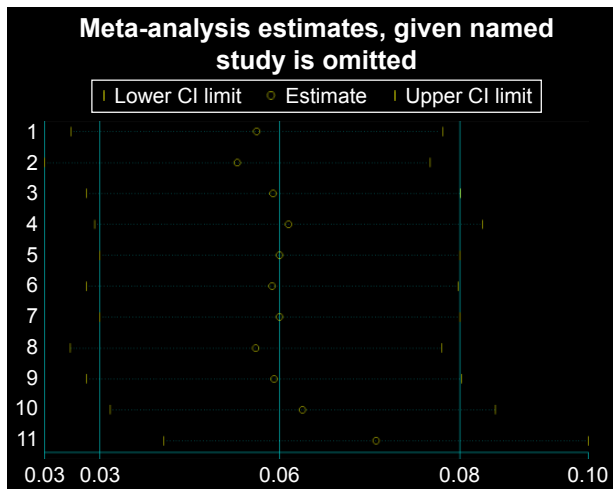


Figure S1 Hand-foot syndrome.

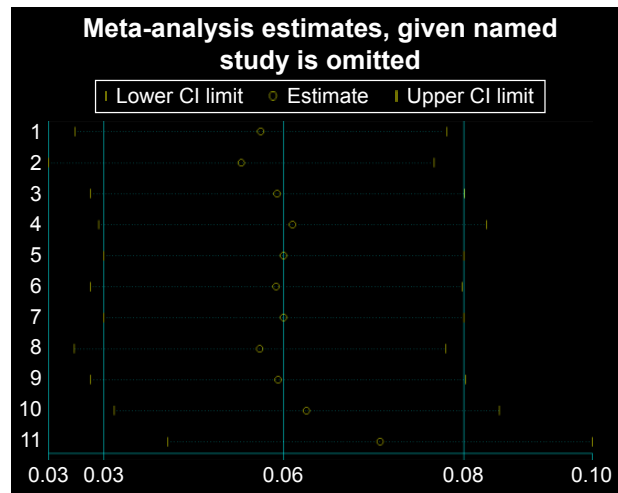


Figure S2 Hypertension.

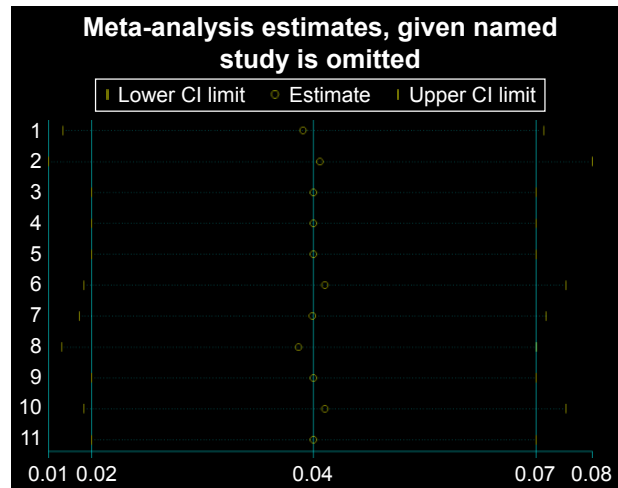


Figure S3 Proteinuria.

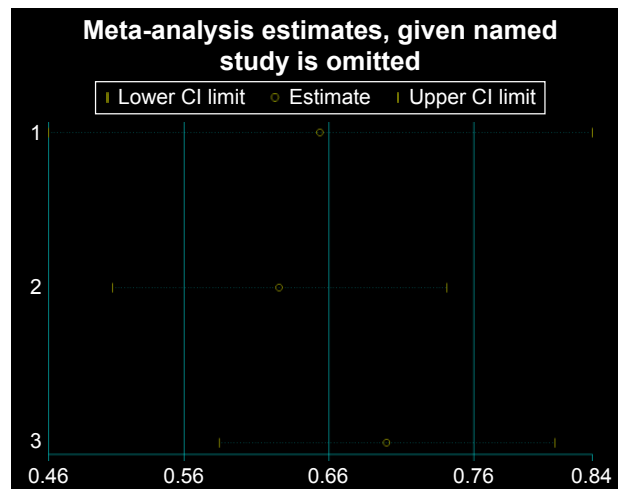


Figure S4 DCR of breast cancer.

Abbreviation: DCR, disease control rate.

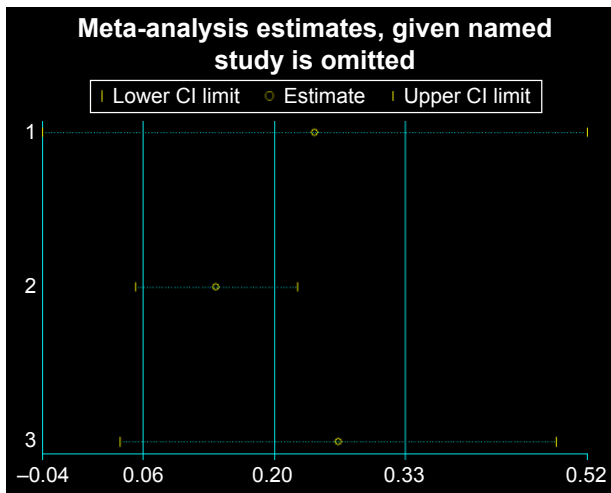


Figure S5 ORR of breast cancer.
Abbreviation: ORR, objective response rate.

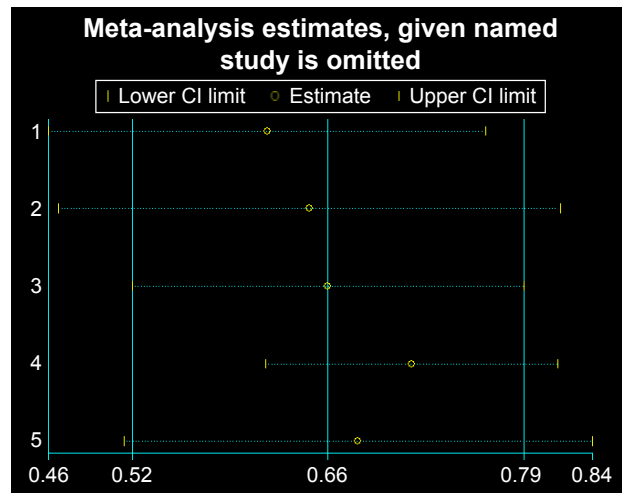


Figure S8 DCR of gastric cancer.
Abbreviation: DCR, disease control rate.

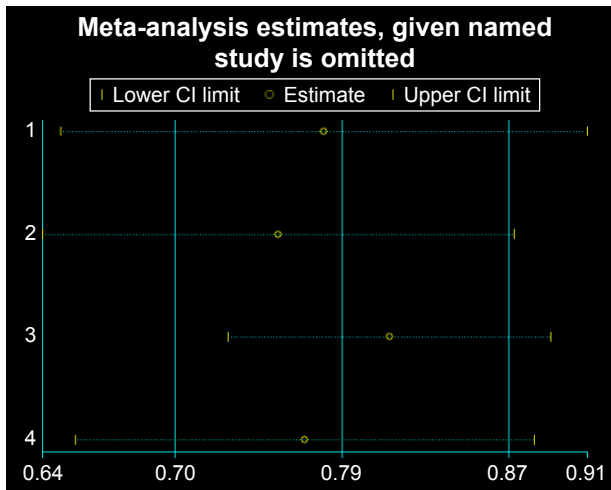


Figure S6 DCR of colorectal cancer.
Abbreviation: DCR, disease control rate.

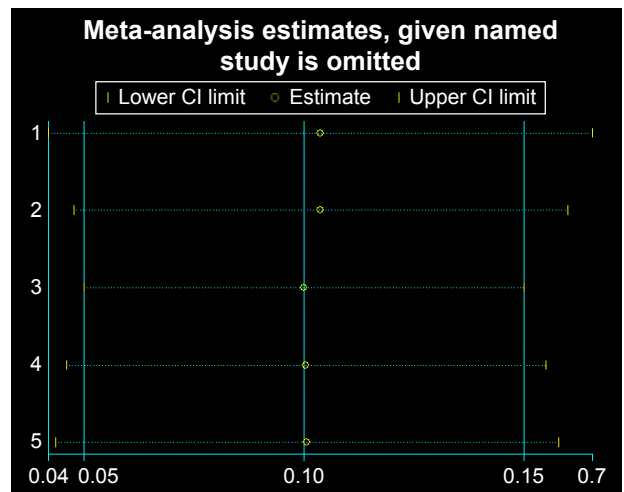


Figure S9 ORR of gastric cancer.
Abbreviation: ORR, objective response rate.

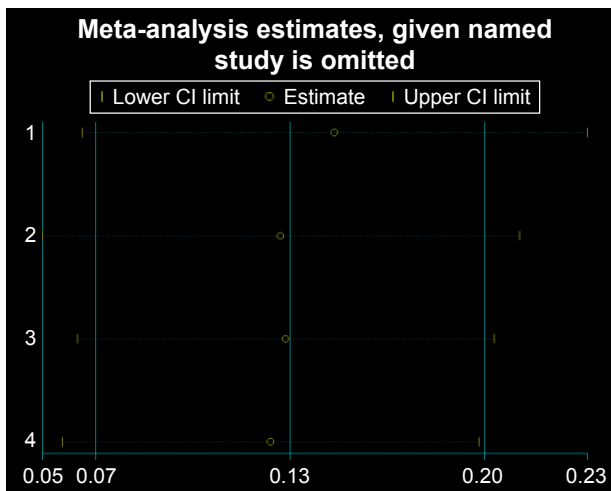


Figure S7 ORR of colorectal cancer.
Abbreviation: ORR, objective response rate.

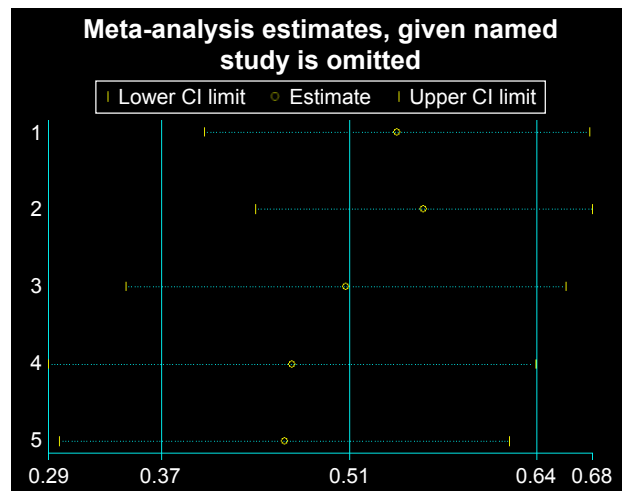


Figure S10 DCR of liver cancer.
Abbreviation: DCR, disease control rate.

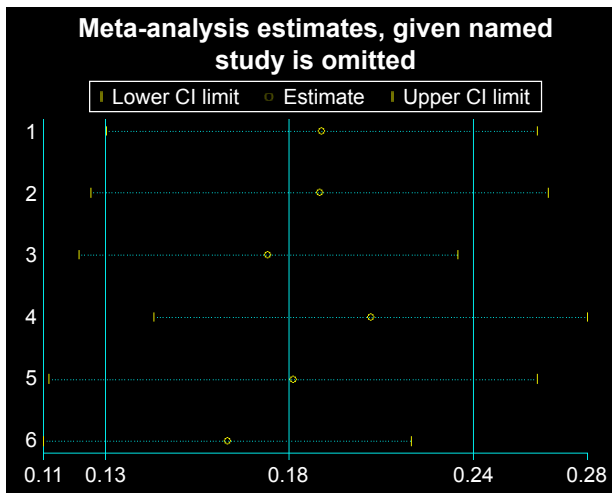


Figure S11 ORR of liver cancer.
Abbreviation: ORR, objective response rate.

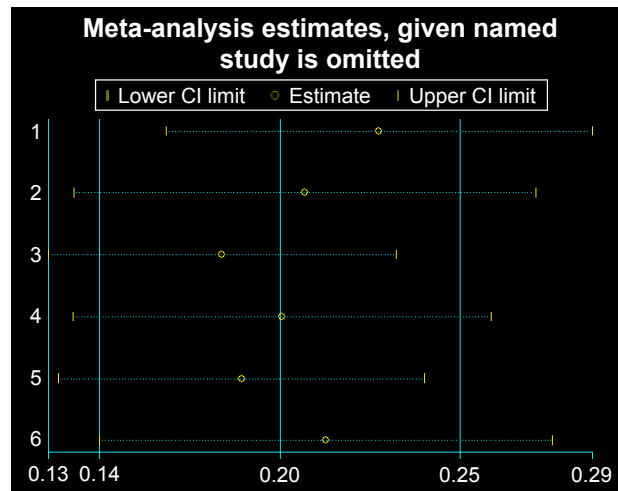


Figure S13 ORR of lung cancer.
Abbreviation: ORR, objective response rate.

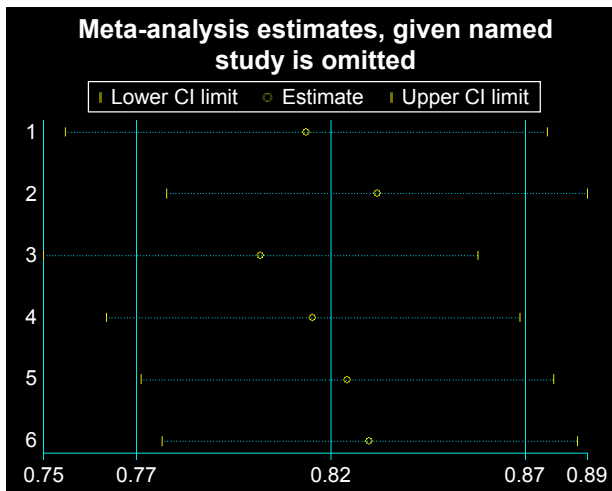


Figure S12 DCR of lung cancer.
Abbreviation: DCR, disease control rate.

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