Efficacy and safety of surufatinib in the treatment of advanced solid tumors: A systematic evaluation and meta-analysis

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Abstract. Previous retrospective studies have suggested that surufatinib is effective for treating advanced solid tumors; however, the efficacy and safety of this drug needs to be investigated further via high-quality evidence or randomized controlled trials. In the present study, a meta-analysis was carried out to evaluate the safety and effectiveness of surufatinib for patients with advanced solid tumors. Systematic, electronic literature searches were conducted using PubMed, EMBASE, Cochrane Library and ClinicalTrials.gov. The disease control rate (DCR) of surufatinib in solid tumors was 86% [effect size (ES), 0.86; 95% confidence interval (CI), 0.82-0.90; I^2=34%; P=0.208] and the objective response rate was 16% (ES, 0.16; 95% CI, 0.12-0.21; I^2=48%; P=0.103), while the progressive disease rate was only 9% (ES, 0.09; 95% CI, 0.05-0.15; I^2=68%, P=0.014). Surufatinib showed different degrees of adverse reactions during the treatment of solid tumors. Among these adverse events, the incidence of increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 24% (ES, 0.24; 95% CI, 0.18-0.30; I^2=45.1%; P=0.141) and 33% (ES, 0.33; 95%CI, 0.28-0.38; I^2=63.9%; P=0.040), respectively. In the placebo-controlled trial, the relative risks (RRs) of elevated AST and ALT were 1.04 (95% CI, 0.54-2.02; I^2=73.3%; P=0.053) and 0.84 (95% CI, 0.57-1.23; I^2=0%; P=0.886), respectively. Overall, surufatinib was characterized by a high DCR and a low disease progression rate, thus indicating that it could exert a good therapeutic effect on solid tumors. Additionally, surufatinib showed a lower RR for adverse effects compared with other treatment modalities.

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Introduction

The treatment of advanced or recurrent metastatic solid tumors has been a major challenge in the medical community, with limited treatment options and a poor prognosis. Furthermore, the incidence of advanced solid tumors such as neuroendocrine tumors (NETs) is still increasing globally (1). As the most notable means for the treatment of unresectable tumors, molecularly targeted drugs such as everolimus, sunitinib and capecitabine have been developed and widely used in previous years (2-4). Vascular endothelial growth factor (VEGF) is a key mediator of tumor angiogenesis, and it is also considered an important therapeutic target, receiving increasing attention from researchers working on targeted molecular drugs (5). Surufatinib, also known as sulfatinib in the past, is a potent, small-molecule tyrosine kinase inhibitor (TKI), which selectively targets VEGF receptor (VEGFR)-1, -2 and -3, fibroblast growth factor receptor-1 (FGFR-1) and colony-stimulating factor-1 receptor (CSF-1R) (6).

Previous clinical studies revealed that surufatinib had a notable effect on pancreatic and extra-pancreatic NETs (7,8), and this drug also showed a high objective response rate (ORR) for other solid tumors, such as cholangiocarcinoma thyroid cancer and ovarian cancer (9,10). However, high-quality evidence and verification studies by randomized controlled trials are needed to clarify the efficacy and safety of surufatinib. In the current study, a meta-analysis was conducted to evaluate the safety and efficacy of surufatinib in treating different types of advanced solid tumors. Overall, the present study aimed to investigate whether surufatinib could exert a practical effect on various solid tumors, including NETs, and whether it could be considered a safe drug for treating patients with solid tumors.

Materials and methods

Literature search. Literature screening was performed using four major electronic databases, specifically PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.

embase.com/), Cochrane Library (https://www.cochranelibrary.com/) and ClinicalTrials.gov (https://clinicaltrials.gov/). The key words 'surufatinib' or 'sulfatinib' were used in the database search. All screening results were divided into the categories 'irrelevant', 'non-sofatinib' and 'possibly relevant' based on the obtained study abstracts. When multiple publications for the same clinical trial were obtained, only the latest or most complete study was selected. The databases were searched between the dates that they were established and February 2022. To select the eligible studies, the manuscripts in the 'possibly relevant' category were reviewed according to the following inclusion criteria: i) Studies describing surufatinib in advanced solid malignancies; and ii) studies reporting tumor ORRs and/or toxicity. In addition, the following exclusion criteria were applied: i) Case reports, editorials, reviews, meta-analyses and review articles, as well as animal and experimental studies; and ii) non-English articles.

Data extraction. The following data were extracted from every selected article: Author(s), publication year, study design, number of patients enrolled, age and sex of patients, Eastern Cooperative Oncology Group-performance status (ECOG-ps) (11), as well as basic information, including primary tumor location and tumor staging and grading (12). Subsequently, stable disease (SD), progressive disease (PD), partial response (PR), ORR, disease control rate (DCR), duration of response and time to response were extracted from these articles. In addition, the adverse effects, including proteinuria, hypertriglyceridemia, diarrhea, hypertension, abnormal high levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and blood bilirubin, were added to the evaluation system.

Quality evaluation. Based on the particular content of the seven studies selected, two quality assessment scales were used. Among the aforementioned studies, five were observational studies using Agency for Healthcare Research and Quality (AHRQ) scores (13), which included the following 11 items: i) A definition of the source of information (survey or record review); ii) a listing of the inclusion and exclusion criteria for exposed (case) and unexposed (controls) subjects or reference to previous publications; iii) an indication of the time period used to select patients; iv) an indication of whether all patients were included in the study over a period of time if not population-based; v) an indication of whether the evaluators of the subjective components of every study were masked into other aspects of the status of the patients; vi) a description of any assessments undertaken for quality assurance purposes, such as testing or re-testing of primary outcome measurements; vii) an explanation for patient exclusion; viii) a description of how confounding variables were assessed and/or controlled; ix) an explanation of how any missing data were handled in the analysis, if applicable; x) a summary of the patient response rates and completeness of data collection; and xi) a clarification of the expected follow-up, if any, and the percentage of patients for whom missing data or follow-up was obtained. There were three answer forms for the AHRQ scale: 'yes', 'no' or 'unclear'. The other two studies were randomized controlled trials (RCTs), and the Newcastle-Ottawa Scale (NOS) was used (14). The NOS scoring system included three aspects of evaluation: i) Selection; ii) comparability; and iii) outcome. Selection was assessed by four questions, comparability contained two options, while outcome was also evaluated by three questions. A total of 9 points were assigned.

Statistical analysis. The meta-analysis was performed using Microsoft Office Excel (Microsoft Corporation) and StataCorp Stata 15.1 (StataCorp LP) software. Data were first transformed into Freeman-Tukey double-arcsine, while the effect of treatment on the incidence of adverse event ratios and their 95% confidence intervals (95% CIs) were calculated using the DerSimonian and Laird method (15) for meta-analyses with random effects. To evaluate the heterogeneity among the included studies, Higgins's I^2 statistics and Q-tests were used. Q-test results are expressed as P-values. An I^2 value of <25% indicated that there was no heterogeneity among studies. Small, mild and strong heterogeneity were indicated by I^2 values of 25-50, 50-75 and >75%, respectively. Overall, strong heterogeneity was assessed using heterogeneity analysis. The results of the two RCTs were statistically analyzed in the meta-analysis as aforementioned. $P<0.05$ indicated a statistically significant difference. The current study was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) platform (https://inplasy.com/) under the registration number, INPLASY202260026.

Results

Search results. This systematic review was performed according to the guidelines for the meta-analysis of observational epidemiological studies (16). A total of 160 articles were identified across the aforementioned four major electronic databases. A total of 57 duplicate articles were identified and excluded. Following literature screening by title and abstract, a total of 76 irrelevant studies were also excluded. After full text reading, an additional 20 studies were excluded. Finally, seven clinical experimental studies that included 638 participants (8-10,17-20) were retained (Fig. 1). Among these seven studies, five studies were single-arm trials, with a medium or high score in the AHRQ scale (Table I), while the other two were multicenter RCTs, with a score of 7-9 defining high quality studies on NOS (Table II).

Treatment regimens. A total of 638 patients were included in the meta-analysis; 510 were assigned to treatment arms, of which 35 patients participated in a dose escalation study (19). These patients were equally divided into five groups and they were then treated with different concentrations of surufatinib (50, 100, 200, 300 and 400 mg) once daily and continuously for every 28-day cycle until disease progression, intolerable toxicity or withdrawal of consent. An additional 475 patients received 300 mg surufatinib once daily, in 28-day treatment cycles until disease progression, intolerable toxicity or withdrawal of consent (8-10,17-20). The 128 patients who participated in the RCT studies were randomly assigned in either the placebo or the control arms, and the results were not disclosed to the patients. Patients in the placebo group received 300 mg placebo every day, in

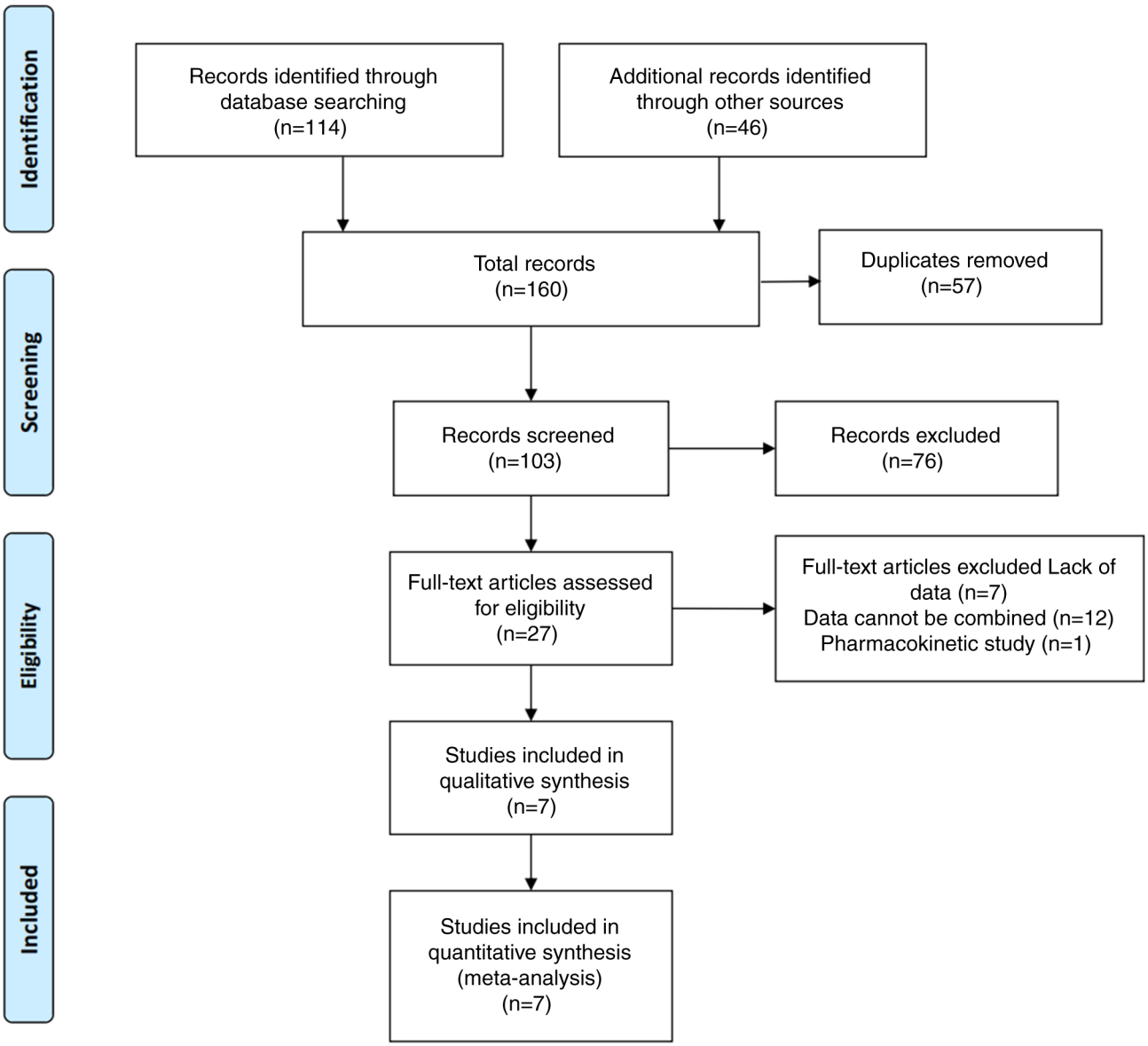

Figure 1. Selection of studies flow chart.

4-week treatment cycles, while patients in the control group received 300 mg of surufatinib once daily in 4-week treatment cycles until disease progression, intolerable toxicity, withdrawal of patient consent, poor compliance, use of other antitumour medication, pregnancy, loss to follow-up, or if the investigator deemed discontinuation to be in the patient's best interest (8,18) (Table III).

Tumor response. Tumor response was assessed in all studies using the Response Evaluation Criteria in Solid Tumors (21). The DCR range reported in four studies was 81-91%. The random effect analysis revealed that surufatinib exerted a favorable DCR in patients with advanced solid tumors (ES, 0.87; 95% CI, 0.84-0.91; I^2=34%; P=0.208; Fig. 2A). In addition, random effect analysis of the pooled results from five studies also indicated a beneficial ORR in patients with advanced solid tumors (ES, 0.14; 95% CI, 0.11-0.18; I^2=48%; P=0.103; Fig. 2B). PR in patients treated with surufatinib was reported in seven studies. The pooled results demonstrated that surufatinib significantly improved PR (ES, 0.13; 95% CI, 0.10-0.16; I^2=54.6%; P=0.051; Fig. 2C). Additionally, SD was reported in four studies. Overall, the analysis showed that SD was significantly improved in patients with solid tumors treated with surufatinib (ES, 0.71; 95% CI, 0.66-0.75; I^2=58.7%; P=0.064; Fig. 2D). Finally, the pooled results regarding PD were reported in five studies and suggested that surufatinib could also improve PD in the aforementioned group of patients (ES, 0.06; 95% CI, 0.04-0.09; I^2=68%; P=0.014; Fig. 2E).

Safety assessment. In terms of drug safety, the analysis of the pooled results from three studies suggested that treatment of patients with advanced solid tumors with surufatinib notably reduced the incidence of adverse events. The most common adverse effects in patients treated with surufatinib were proteinuria (ES, 0.70; 95% CI, 0.66-0.75; I^2=69.3%; P=0.011; Fig. 3A), followed by hypertension (ES, 0.64; 95% CI, 0.59-0.68; I^2=0%; P=0.588; Fig. 3B) and diarrhea

Table I. Healthcare research and quality scale score.

First author, year	Definition of source	Inclusion/exclusion criteria	Time period	Included over time	Masked evaluators	Quality assurance	Exclusion explanation	Confounding variable control	Missing data processing	Summary	Clarification of the follow-up	Total points	Quality	(Refs.)
Hamilton *et al*, 2019	Yes	No	Unclear	Unclear	Unclear	No	Yes	No	Yes	Yes	Yes	5	Medium	(19)
Chen *et al*, 2020	Yes	Yes	No	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	8	High	(10)
Xu *et al*, 2019	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	8	High	(17)
Dasari *et al*, 2020	Yes	No	Unclear	Unclear	Unclear	No	Yes	No	Yes	Yes	No	4	Medium	(20)
Xu *et al*, 2021	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9	High	(9)

Table II. Newcastle-Ottawa scale score.

	Selection				Comparability		Outcome				
First author, year	Case identification	Representation of cases	Choice of comparison	Determination of control	Analysis of the most important factors	The second important factor analysis	Determination of exposure factors	Same approach	No response rate	Score	(Refs.)
Xu *et al*, 20201st	1	1	-	1	1	1	1	1	-	7	(8)
Xu *et al*, 20202nd	1	1	-	1	1	1	1	1	-	7	(18)

Table III. Characteristics of the study.

First author, year	Region	Type of study	Treatment regimen	Patients, n	Sex, no. of males/females	Mean age, years	ECOG	Types of tumor	Pathological stage, n	Funding	(Refs.)
Hamilton *et al*, 2019	USA	Open-label	Surufatinib, 50/100/200/300/400 mg qd; 28-day cycle	35	23/34	62	-	Any solid tumor	-	Hutchison MediPharma, Limited	(19)
			Surufatinib, 300 mg qd; 28-day cycle	22			-	Biliary tract cancers; Pancreatic NETs; Extra-pancreatic NETs	-		
Chen *et al*, 2020	China	Open-label	Surufatinib, 300 mg qd; 28-day cycle	32	31/28	59	12/47 (0/1)	Differentiated thyroid cancer	1/31 (TNM stage III/ TNM stage IV)	Hutchison MediPharma, Limited	(10)
				27				Medullary thyroid cancer	27 (TNM stage IV)		
Xu *et al*, 2019	China	Open-label	Surufatinib, 300 mg qd; 28-day cycle	42	25/17	46	32/10 (0/1)	Pancreatic NETs	7/35 (G1/G2)	Hutchison MediPharma, Limited	(17)
				39	19/20	54	22/17 (0/1)	Extrapancreatic NETs	9/30 (G1/G2)		
Dasari *et al*, 2020	USA	-	Surufatinib, 300 mg	32	-	-	-	Pancreatic NETs Extra-pancreatic NETs	-	-	(20)
Xu *et al*, 2020_{1st}	China	RCT	Surufatinib, 300 mg qd; 28-day cycle	129	73/56	52	72/57 (0/1)	Extra-pancreatic NETs	21/108 (G1/G2)	Hutchison MediPharma, Limited	(8)
			Placebo, 300 mg qd; 28-day cycle	69	35/34	54	46/23 (0/1)	Extra-pancreatic NETs	11/58 (G1/G2)		
Xu *et al*, 2020_{2nd}	China	RCT	Surufatinib, 300 mg qd; 28-day cycle	113	53/60	51	73/40 (0/1)	Pancreatic NETs	14/99 (G1/G2)	Hutchison MediPharma, Limited	(18)
			Placebo, 300 mg qd; 28-day cycle	59	31/28	48	43/16 (0/1)	Pancreatic NETs	9/50 (G1/G2)		

Table III. Continued.

First author, year	Region	Type of study	Treatment regimen	Patients, n	Sex, no. of males/females	Mean age, years	ECOG	Types of tumor	Pathological stage, n	Funding	(Refs.)
Xu *et al*, 2021	China	Open-label	Surufatinib of 300 mg qd; 28-day cycle	29	22/17	56.2	10/29 (0/1)	Intra-hepatic cholangio-carcinoma	1/28 (TNM stage III/ TNM Stage IV)	Hutchison MediPharma, Limited	(9)
				10				Extra-hepatic cholangio-carcinoma; Gallbladder cancer	10 (TNM stage IV)		

RCT, randomized controlled trial; qd, per day; TNM, Tumor-Node-Metastasis; NET, neuroendocrine tumors.

(ES, 0.50; 95% CI, 0.45-0.54; I^2=87.9%; P<0.001, Fig. 3C). Furthermore, increased AST (ES, 0.33; 95% CI, 0.28-0.38; I^2=63.9%; P=0.040; Fig. 3D) and ALT (ES, 0.23; 95% CI, 0.18-0.27; I^2=45.1%; P=0.141, Fig. 3E) levels were reported in four studies. Additionally, three studies showed that surufatinib enhanced the serum levels of thyrotropin (ES, 0.43; 95% CI, 0.38-0.48; I^2=44.6%; P=0.164; Fig. 3F), while hypertriglyceridemia was also reported in five studies (ES, 0.34; 95% CI, 0.30-0.39; I^2=35.6%; P=0.184; Fig. 3G). The I^2 value for diarrhea was 87.9%, indicating strong heterogeneity. Further sensitivity analysis resulted in a reduced I^2 value of 64.1% (ES, 0.43; 95% CI, 0.38-0.49; I^2=64.1%; P=0.039; Fig. 3H), supporting the robustness of the primary analysis. To stabilize the changes in the ES ratios, double-arcsine transformation was performed using the Freeman-Tukey transformation formula (Table IV).

Relative risk analysis. To further verify the results of the current meta-analysis, the results of two high-quality RCTs were analyzed. These two RCTs compared the effect of surufatinib between patients treated with surufatinib and those left untreated (placebo group). The RR ratios of adverse events were also recorded. The levels of AST were increased in the surufatinib group (RR, 1.08; 95% CI, 0.77-1.51), with mild heterogeneity (I^2, 73.4%; P=0.052; Fig. 4A). However, the difference between treatment and placebo groups was not statistically significant (P=0.658). Additionally, in both trials, increased ALT levels were observed in the surufatinib group (RR, 0.84; 95% CI, 0.57-1.23), without heterogeneity (I^2, 0%; P=0.886; Fig. 4B). Again, statistical significance was not reached (P=0.365). Among the other adverse events, the pooled results for proteinuria (RR, 1.39; 95% CI, 1.13-1.69) showed no heterogeneity (I^2, 0%; P=0.877; Fig. 4C) with a statistically significant difference (P=0.002). For diarrhea (RR, 2.25; 95% CI, 1.57-3.23), there was no heterogeneity (I^2, 0%; P=0.527; Fig. 4D), with a statistically significant difference (P<0.001). For hypertriglyceridemia (RR, 4.2; 95% CI, 2.26-7.81), the pooled results revealed no heterogeneity (I^2, 0%; P=0.886; Fig. 4E), with a statistically significant difference (P<0.001). For hypertension (RR, 2.82, 95% CI, 2.02-3.94), there was no heterogeneity (I^2, 2.8%; P=0.310; Fig. 4F), with a statistically significant difference (P<0.001). For increased blood bilirubin levels (RR, 2.08; 95% CI, 1.39-3.11), there was no heterogeneity (I^2, 0%; P=0.853; Fig. 4G), with a statistically significant difference (P<0.001). Finally, for increased thyroid hormone levels (RR, 4.63; 95% CI, 2.58-8.30), there was no heterogeneity (I^2, 0%; P=0.671; Fig. 4H), with a statistically significant difference (P<0.001).

Publication bias. Since a small number of studies were included in the meta-analysis, publication bias was not assessed. Therefore, bias might have occurred in the analysis and the evaluation of the research data.

Discussion

Different types of solid tumors, such as pancreatic NETs, extra-pancreatic NETs and biliary tract cancer, are characterized by different degrees of aggressiveness and require

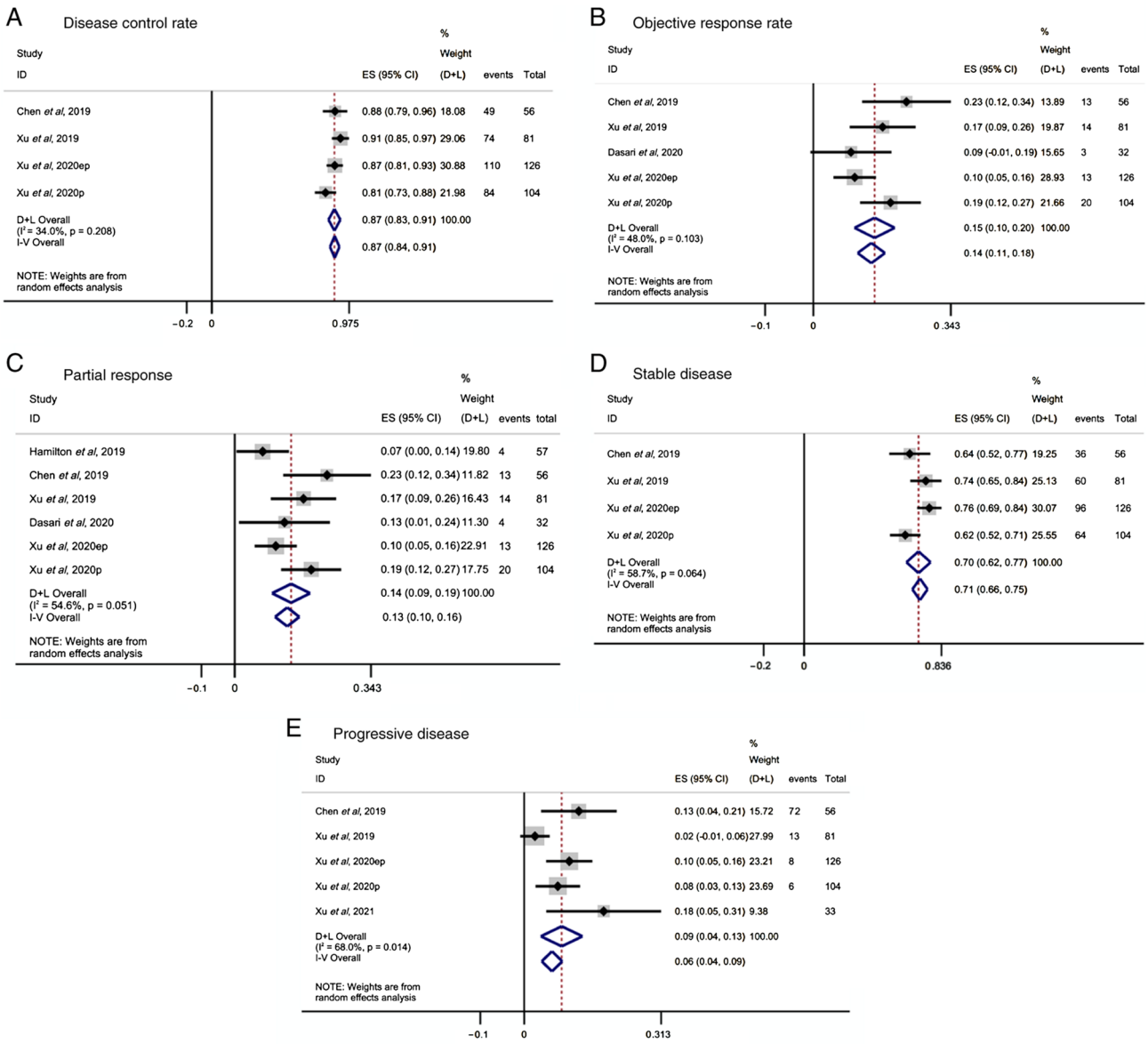

Figure 2. Analysis of drug efficacy in the treatment of different solid tumors. (A) Disease control rate, (B) objective response rate, (C) partial response, (D) stable disease and (E) progressive disease. CI, confidence interval; ES, effect size; D+L, Dersimonian-Laird; I-V, inverse variance.

different treatment approaches. Peptide receptor radionuclide therapy with lutetium-177 dotatate (177 Lu-DOTATATE) has been approved for advanced gastroenteropancreatic-NETs and the antiangiogenic agent sunitinib is mainly used for pancreatic NETs (22). In recent years, more and more researchers have paid increasing attention to the most common characteristics, such as abnormal angiogenesis and gene mutations, of different types of solid tumors, such as tumors of the uterus, pancreatic cancer and thyroid cancer (23,24), while investigating more effective treatment approaches for several of them (25-27).

It has been reported that VEGF and FGF can mediate the formation of tumor blood vessels in solid tumors to provide sufficient oxygen, thereby promoting tumor growth, cell migration and invasion (28-30). It has been also suggested that several VEGFR-targeted therapies are unsatisfactory, with numerous patients exhibiting no or a limited respond to treatment, possibly due to the induction of other pro-angiogenic pathways, including those of FGFR and CSF-1R that promote drug resistance (7,28-32).

Surufatinib is a novel, orally administered, small-molecule TKI of VEGFR-113, FGFR-1 and CSF-1R, which can reduce tumor angiogenesis and immune system evasion, and also enhance antitumor immunity (31) to treat pancreatic and extra-pancreatic NETs (32). Several systemic therapies have been approved for the treatment of NETs, including somatostatin analogue therapy, the TKI sunitinib, mammalian target of rapamycin inhibitors, peptide receptor radionuclide therapy (PRRT) and cytotoxic chemotherapy (23,31-33). The effect of aminokinase inhibitors can be counteracted by the induction of other proangiogenic pathways, including the FGFR-1 and CSF-1R signaling pathways (31). Therefore, the application of surufatinib could provide a solution to this issue to some extent. The first studies on surufatinib were performed in China, while the scope of its application has gradually expanded from NETs to several different types

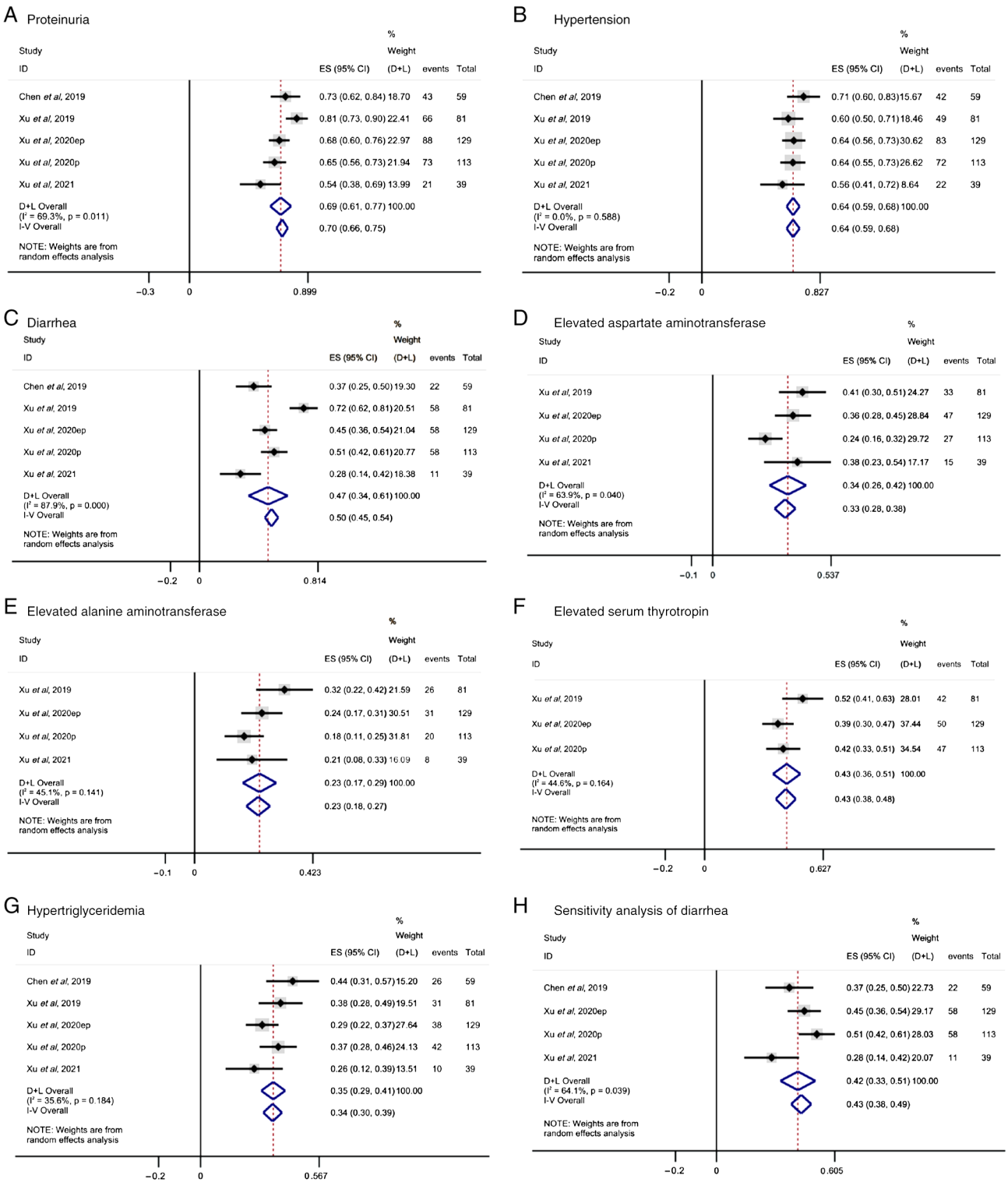

Figure 3. Adverse events occurring in the treatment of different solid tumors with surufatinib. (A) Proteinuria, (B) hypertension, (C) diarrhea, (D) elevated aspartate aminotransferase, (E) elevated alanine aminotransferase, (F) elevated serum thyrotropin, (G) hypertriglyceridemia and (H) sensitivity analysis of diarrhea. CI, confidence interval; ES, effect size; D+L, Dersimonian-Laird; I-V, inverse variance.

of advanced solid tumors, thus attracting worldwide attention (8-10,17,18).

To the best of our knowledge, the present study was the first meta-analysis to particularly focus on the efficacy and safety of surufatinib in solid tumors. In the current meta-analysis, seven studies involving 638 patients suffering from different types of solid tumors, such as pancreatic NETs, extra-pancreatic NETs, biliary tract cancer and thyroid cancer, were included. The results of the meta-analysis revealed overall DCR, ORR, PR, SD and PD rates of 87, 14, 1, 71 and 6%, respectively. The results also showed that compared with 177Lu-DOTATATE PRRT, immunosuppressive agents, such as programmed cell death protein-1 (PD-1)/PD-ligand-1 (PD-L1) inhibitors and cytokine-induced killer cells, surufatinib resulted in higher

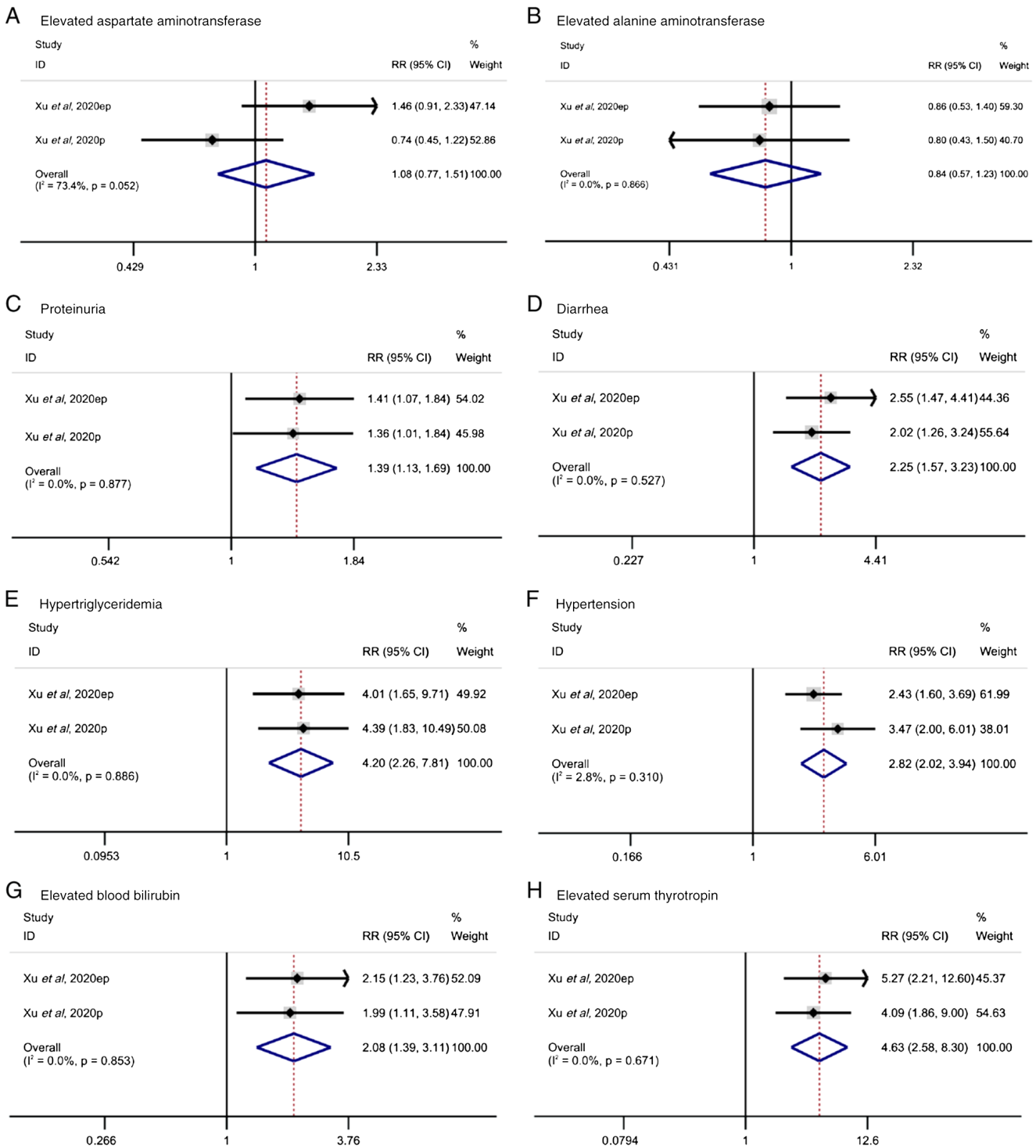

Figure 4. Adverse events occurring in the treatment of different solid tumors with surufatinib. (A) Elevated aspartate aminotransferase, (B) elevated alanine aminotransferase, (C) proteinuria, (D) diarrhea, (E) hypertriglyceridemia, (F) hypertension, (G) elevated blood bilirubin, (H) elevated serum thyrotropin. CI, confidence interval; RR, relative risk.

DCR and SD rates, while PD also remained at a lower level. This supports the fact that surufatinib could exhibit a better efficacy in the treatment of solid tumors (21,34,35). The study by Xu *et al* (8) showed that at the time of data cut-off, 77 (60%) patients in the surufatinib group and 51 (74%) in the placebo group experienced progression-free survival (PFS) events. The median follow-up time for PFS was 13.8 months (95% CI, 11.1-16.7) and 16.6 months (95% CI, 9.2-not calculable) in the surufatinib and placebo groups, respectively. Additionally, the median investigator-assessed PFS time was 9.2 months (95% CI, 7.4-11.1) in the surufatinib group and 3.8 months (95% CI, 3.7-5.7) in the placebo group (HR, 0.33; 95% CI, 0.22-0.50; P<0.0001), which crossed the predefined P-value threshold (two-sided, P=0.015) for the interim analysis (8). The aforementioned findings also supported the beneficial effect of surufatinib on the prognosis of patients with solid tumors.

Table IV. Freeman-Tukey double arcsine transformation.

Parameter	Rate	95% CI	Post-conversion rate	Transformed 95% CI
DCR	0.87	0.84-0.91	0.86	0.82-0.90
ORR	0.14	0.11-0.18	0.16	0.12-0.21
PR	0.13	0.10-0.16	0.15	0.11-0.20
PD	0.06	0.04-0.09	0.09	0.05-0.15
Elevated ALT	0.23	0.18-0.27	0.24	0.18-0.30

DCR, disease control rate; ORR, overall response rate; PR, partial response; PD, progressive disease; ALT, alanine aminotransferase; CI, confidence interval.

In addition to analyzing the direct efficacy of surufatinib in the treatment of solid tumors, the present study also analyzed the adverse events that occurred during the treatment of patients with surufatinib. More specifically, three studies reported treatment-emergent adverse events with an overall incidence of 44%, and four articles mentioned increased AST and ALT levels with an incidence of 23 and 33%, respectively, while five studies reported proteinuria (70%), diarrhea (50%), hypertriglyceridemia (34%) and hypertension (64%). Increased thyrotropin serum levels were reported in three articles (43%).

When compared with a placebo, there was no statistically significant difference in increased AST and ALT levels in patients treated with surufatinib, thus indicating that surufatinib could not reduce the incidence of the aforementioned adverse reactions. However, there was a statistically significant difference in the incidence of proteinuria, diarrhea, hypertriglyceridemia, hypertension, increased blood bilirubin and thyrotropin serum levels between the placebo and surufatinib groups, suggesting that treatment of patients with advanced solid tumors with surufatinib could notably decrease the incidence of the aforementioned adverse events. Conclusively, overall analysis indicated that surufatinib could reduce the incidence of adverse events, indicating a satisfactory safety profile.

On the other hand, the RR of adverse events, such as diarrhea, hypertension and hyperbilirubinemia in patients treated with surufatinib was decreased compared with those treated with regorafenib (36). The incidence of gastrointestinal-related adverse events during the treatment of refractory thyroid cancer was lower in patients treated with surufatinib compared with that in patients treated with sorafenib (37). Additionally, surufatinib was associated with a lower incidence of diarrhea compared with sorafenib, sunitinib and pazopanib. Overall, the reduced RR of gastrointestinal-related adverse events suggested that surufatinib exhibited high safety in treating patients with solid tumors (38).

The current study analyzed the results of seven clinical studies with regard to the therapeutic effect of surufatinib on solid tumors, such as pancreatic NETs, extra-pancreatic NETs and cholangiocarcinoma. However, the present study had some limitations. Surufatinib was approved in China in December 2020 for the treatment of late-stage, well-differentiated, extrapancreatic NETs (39,40). Surufatinib has been filed for approval in China for the treatment of pancreatic NETs (41) and in the USA for the treatment of pancreatic and extrapancreatic NETs (42). Since surufatinib has been only recently used in clinical practice to treat advanced solid tumors (5), the currently available studies on surufatinib are limited. Further studies on different types of solid tumors are urgently needed. In addition, this was a single-ratio meta-analysis with high heterogeneity; even in the categorical analyses performed, the existence of partial heterogeneity could not be ruled out. However, the magnitude of the observed treatment effect, the consistency of the diarrhea incidence rates in the sensitivity analysis and the lower incidence of adverse events in patients treated with surufatinib compared with those treated with other agents, provided evidence of the clinically meaningful benefit of surufatinib.

In conclusion, the findings of the current meta-analysis suggested that surufatinib could be considered an effective and safe drug in the treatment of solid tumors. Additional clinical data and original studies of high quality are required to further validate the results of the present study and to provide more evidence to support the clinical applications of surufatinib.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TYC and YLC conceptualized the study and visualized the data. YLC collected and analyzed data. TYC wrote and prepared the original draft. WGF conceptualized and supervised the study. YCD and PT collected and analyzed data, and edited the manuscript. TXL and YFC analyzed data and edited the manuscript. LG performed the statistical analysis, supervised the study and edited the manuscript. All authors have read and approved the final version of the manuscript. TYC and YLC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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