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Review

S-1 combined with paclitaxel may benefit advanced gastric cancer: Evidence from a systematic review and meta-analysis

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ABSTRACT

Background: Gastric cancer, as one of the increasingly common malignancies, has experienced high morbidity throughout many countries at present. Currently, chemotherapy regimen with more efficacy and safety for advanced gastric cancer (AGC) is needed. We aimed to assess the clinical efficacy and safety of S-1 combined with paclitaxel (PTX) for AGC by performing a systematic review and meta-analysis of the published studies.

Method: All published randomized controlled trials (RCTs) of S-1 combined with PTX for AGC were searched. Studies that included patients with locally advanced or metastases' gastric cancers were included. We searched the databases included Cochrane Library of Clinical Comparative Trials, MEDLINE, Embase, American Society of Clinical Oncology meeting abstracts and China National Knowledge Internet (CNKI) from 2000 to 2018. We searched the database up to January 2018. The first endpoint was overall survival (OS). Other endpoints were progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR). Safety analyses were also performed.

Results: A total of 7 trials (including 1407 patients, 711 patients in intervention group and 696 patients in control group) were included in the present analysis. S-1 combined with PTX significantly improved the OS [HR = 0.78, 95% CI: 0.60–0.97, P = 0.000],PFS [HR = 0.70, 95% CI: 0.55–0.85, P = 0.000], ORR [RR = 1.30, 95%CI: 1.05–1.60, P = 0.017] and DCR [RR = 1.15, 95%CI: 1.04–1.27, P = 0.008] of patients with AGC. The grade 3 or 4 haematological and non-hematologic toxicities were anemia [RR = 1.71, 95% CI: 1.04–2.79, P = 0.03], neutropenia [RR = 1.65, 95% CI: 1.32–2.06, P < 0.0001] and anorexia [RR = 1.66, 95% CI: 1.05–2.64, P = 0.03] respectively.

Conclusion: S-1 combined with PTX may be a good choice for patients with AGC. S-1 plus PTX experienced more efficacy and safety when compared with S-1 alone or S-1 plus other drugs.

1. Introduction

Gastric cancer (GC), as one of the increasingly common malignancies, has experienced high morbidity throughout many countries at present. It was estimated that gastric cancer has been the fifth most frequently diagnosed cancer worldwide [1,2]. GC is the second most common cause of death from cancer worldwide, and its 5-year survival rate less than 50% [3]. Although the incidence of GC has reduced, it remains one of the most common causes of cancer-related mortality in Asian [4]. In Japan and China, the incidence of GC remains high [5]. Since the early gastric cancer (EGC) patients has no obvious symptoms, the disease would commonly developed to the advanced stage and 5-year survival rate less than 15% for AGC (defined as the cancer tissue has invaded the gastric wall muscle layer, serous layer, regardless of the size of the lesion, or metastasis) with adjacent organ invasion [6]. Surgery is the main treatment choice for GC [6]. However, due to the lack of symptoms and without proper screening, many patients have developed as advanced disease when diagnosed, even with metastasis of peritoneal, distant metastasis or adjacent organ invasion which led to lack of chance for surgical resection [7]. Most patients with AGC have low radical resection rate and high recurrence rate [5]. The prognosis of AGC is still very poor, especially no resects and recurrent AGC, the median overall survival for best supportive treatment only 3–5 months [6]. Chemotherapy is another main treatment option for patients with AGC [8]. The median overall survival of 8–12 months has been reported in patients undergoing chemotherapy compared with best supportive

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treatment [9]. With the diversified development of chemotherapy regimens, the chemotherapy for GC becomes more and more important [10]. Postoperative chemotherapy with a novel oral fluoropyrimidine S-1 (combination of tegafur [prodrug of fluorouracil; 5-chloro-2,4-dihydropyridine] and oxonic acid) following complete resection has not been associated with a significant survival benefit in patients with advanced gastric cancer [11]. Currently, chemotherapy regimen with more efficacy and safety for AGC is needed [12].

S-1 is a new generation of oral anti-neoplastic agents in fluorouracil, it includes tegafur and two types of regulator: gimeracil and oteracil potassium [13]. The functions of three compositions are as follows: the tegafur is the precursor of 5-FU, which has good oral bioavailability and can be converted into 5-FU in vivo [14]. Gimeracil can inhibit the catabolism of 5-FU and maintain a high blood concentration in tumor tissues [15]. Oteracil potassium can block the phosphorylation of 5-FU, which affects the distribution of 5-FU in the gastrointestinal tract, thus reduce the toxic effects of 5-FU [16]. In Japan, S-1 was approved for treatment of AGC in 1999. According to statistics, there are more than 80% of the cases used S-1 for the chemotherapy of AGC in Japan; and the treatment effectiveness (CR + PR) can reach to 44.6% [17]. PTX is another anti-cancer drugs approved in the 1990s, which induced stability of tubulin polymerization and inhibited microtubule depolymerization, inhibiting the division and proliferation of cancer cells [11,18]. But various studies suggest that the mono-drug response rate for PTX was only 17%–33%, and the combination chemthearpy response rate can reach to 50%–60% [19]. Clinical studies have confirmed that S-1 combined with PTX was associated with almost equivalent safety and a lower progressive disease rate compared with PTX plus 5-FU for AGC [5]. A series of researches in Japan reflect the advantages in terms of efficacy and safety for S-1 combined with PTX in AGC [20–23]. So the regimen of S-1 combined with PTX is expected to become one of ideal strategy in AGC chemotherapy [5].

This study applied the method of meta-analysis to pooled analysis the relevant RCTs, and systematically reviewed the efficacy and safety of S-1 plus PTX for AGC. Our study would provide a reliable reference in clinical for selecting a reasonable chemotherapy regimen of AGC.

2. Materials and methods

2.1. Inclusion criteria

All published phaseII/III clinical trials of RCTs comparing S-1 combined with PTX vs. Other regimens for AGC were included in our analysis. Blindness of the trial was not necessary. The inclusion criteria were: (1) Patients were pathologically diagnosed with TNM stage of II, III and IV GC; (2) The age more than 18 years older, and gender were not limited; (3) Patients have been accepted or not accepted a locally treatment such as surgery, radiotherapy or chemotherapy, and progression or recurrence; (4) The expectancy life more than 3 months; (5) The chemotherapy drugs as PTX or S-1were not used in the prior; (6) The main viscera function were normally; (7) The patient's ECOG scores were less than 2 [20].

2.2. Exclusion criteria

The exclusion criteria were: (1) The cancer transferred to central nervous system; (2) Patients with serious adverse effects of chemotherapy, medical disease or acute infection; (3) Patients can not take medicine oral; (4) Patient has serious allergy history of chemotherapy drug; (5) Patients are ongoing a treatment which interaction with PTX or S-1; (6) Pregnancy or lactation women; (7) Patients with acute tumor which can affect survival.

2.3. Selection of studies

We searched the databases included Cochrane Library of Clinical Comparative Trials, MEDLINE, Embase, American Society of Clinical Oncology meeting abstracts and China National Knowledge Internet (CNKI) from 2000 to 2018. The censor date was up to January 2018. The search terms included “paclitaxel”, “S-1”, “advanced gastric cancer” and “randomized trial” combined with AND/OR. The search also included all of the mesh terms. No search restrictions were imposed. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. Review articles were also obtained to identify other possible studies.

2.4. Data extraction and management

Two reviewers independently assessed the eligibility of each trial. According to the include and exclude criteria, the two researchers check the results of the study and determine whether it included in the analysis by reading the title, abstract and full text.

Authors, year of publication, country of patients, sample size, chemotherapy regimen, and cycles of chemotherapy, follow-up period, curative effect and adverse events of each eligible trial were recorded. The first endpoint was OS. Other endpoints were PFS, ORR and DCR. Safety analyses were also performed. Two reviewers independently made extracts from each study.

2.5. Assessment of risk of bias in included studies

The quality evaluation was according to the standard of RCT recommended for Cocharane 5.1.0 handbook. Evaluation indicators include: (1) The randomization method; (2) Allocation concealment; (3) Blinding of participants, personnel and outcome assessors; (4) Incomplete/missing outcome data; (5) Selective reporting; (6) other potential threats to validity. Quality assessment conducted by two researchers independently.

In addition, the work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

2.6. Statistical analysis

We used Stata 12.0 software to performed calculations and statistical tests. Time-to-event (survival) data (OS and PFS) were using hazard ratio (HR) for the pooled effect. Dichotomous data (ORR, DCR and adverse effect) were using relative risk (RR) for the pooled effect. The pooled effect adopts interval estimation and hypothesis testing. The interval estimation were using 95% confidence interval (95% CI), and the hypothesis testing were using the Q statistics. When $I^2 \geq 50\%$ indicated substantial heterogeneity exists. The fixed-effects model was used if there was no significantly heterogeneity between the trials. Otherwise, the random-effects model was used. If there was an obvious heterogeneity existed between the trials, the descriptive analysis was carried out only. There was a statistically significant existed, if the $P < 0.05$. Using forest plots to represent a single study and its pooled HR and RR. The funnel plot was used to describe the publication bias.

2.7. Summary of findings

We evaluated the quality of evidence of the two primary outcomes (Overall survival and Progression-free survival), and one secondary, outcome (Toxicity) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented it in “Summary of Findings” tables. The GRADE system classifies the quality of evidence in one of four grades:

a. High: Further research is very unlikely to change our confidence in the estimate of effect;
b. Moderate: Further research is likely to have an impact on our

confidence in the estimate of effect and may change the estimate;
c. Low: Further research is very likely to have an important impact on our confidence on the estimate effect and is likely to change the estimate;
d. Very low: Any estimate of effect is very uncertain. The quality of evidence were to be downgraded by one (serious concern) or two levels (very serious concern) for the following reasons: risk of bias, inconsistency (unexplained heterogeneity, inconsistency of results), indirectness (indirect population, intervention, control, outcomes) and imprecision (wide confidence intervald, single trial). The quality could also be upgraded by one level due to large summary effect.

3. Results

3.1. Results of the search

According to the retrieval strategy and data collection methods, 755 relevant articles were retrieved. We removed 725 articles by reading the title and abstract and 30 articles were included preliminarily. The 17 repetitive reported or non-RCTs articles were eliminated and 13 articles may conforming to criteria. After reading the full text according to the criteria and filtered data integrity, seven RCTs and a total of 1407 patients were included eventually. The details are listed in Fig. 1.

3.2. Included studies

3.2.1. General characteristics and types of participants

A total of 1407 cases were included in 7 trials [14,20–25], the maximum numbers of cases in single trial were 710 and minimum cases were 44. There were 1457 male patients and 629 of female patients. The Chinese patients were 355 and the Japanese patients were 1052. Patients have definite pathological diagnosis as AGC. There have no statistically difference between the experimental group and control group. The details are listed in Table 1 and Table 2.

3.2.2. Types of interventions

In all of the trials, one trial adopted the PTX plus S-1 vs. PTX plus UFT regimen; one trial adopted the PTX plus S-1 vs. S-1 plus Irinotecan regimen; three trials adopted the PTX plus S-1 vs. S-1 plus 5-Fu regimen; one trial adopted the PTX plus S-1 vs. S-1 regimen; one trial adopted the PTX plus S-1 vs. S-1 plus cisplatin regimen.

3.2.3. Types of outcome measures

All trials included in the study were described detailed definition of the various indicators. The endpoints were OS、PFS、ORR、DCR, and safety were for haematological toxicity and non-haematological toxicity. No treatment-related deaths reported.

3.3. Risk of bias in included studies

The risk of bias in included trials was assessed according to the standard of RCT recommended for Cocharane 5.1.0 handbook. All of the 7 trials mentioned random sequence generation. Two trials described the specific methods of random, and two trials clearly described the process of chemotherapy. One trial has mentioned that the nurse opened the envelope, and then doctor selected specific regimen according to the scheme. And here we think that good implemented to the patient's blind method. Three trials without use blind method. The details are listed in Fig. 2 and Fig. 3.

3.4. Effects of interventions

3.4.1. OS

There are 4 trials stated the overall survival data. The patients accepted other chemotherapy regimens with the average survival period was 11 months, one year survival rate was 46.3%. And patients adopted S-1 combined with PTX regimens with the average survival period was

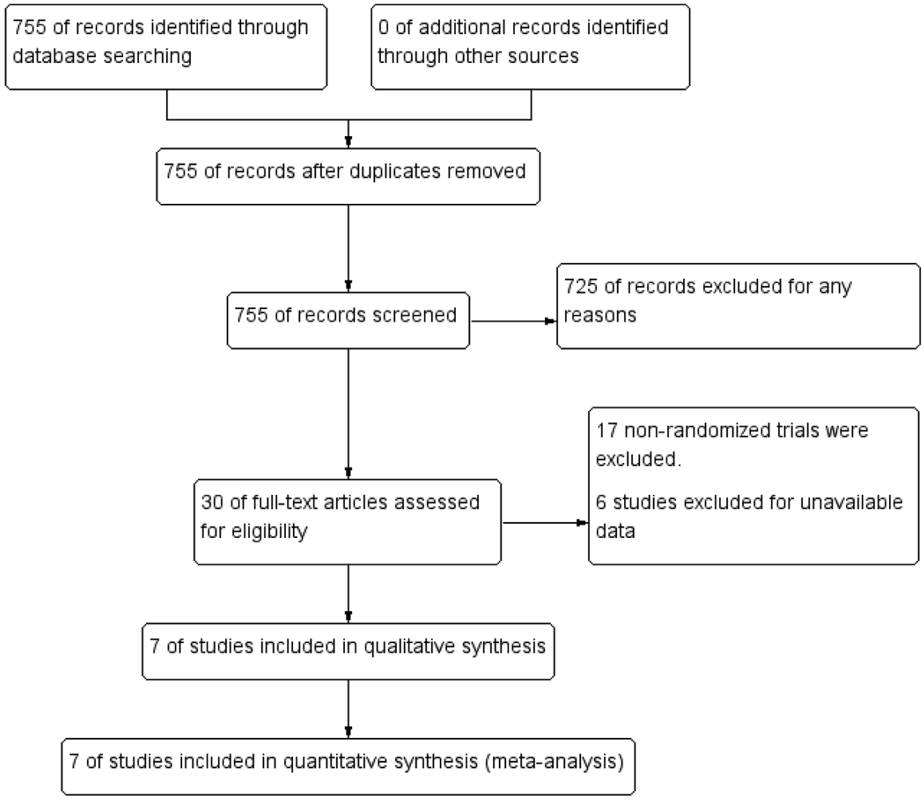

Fig. 1. Flow diagram of the search process and strategy for the efficacy and safety of S-1 combined with PTX for AGC.

Table 1
Characteristics of included studies for analysis of efficacy.

Studies	Year	Country	Total number	Number of patients		Treatments	
				S-1 + PTX	Non (S-1 + PTX)	Experimental arms	Control arms
Tsuburaya et al.	2014	Japan	710	355	355	(sequential) S-1: 80 mg/m^2, bid, day 1–14, 7d rest followed by three courses of intermittent weekly PTX: 80 mg/m^2, iv, 49 weeks.	(sequential) UFT: 267 mg/m^2, bid or tid, day 1–28, followed by three courses of intermittent weekly PTX: 80 mg/m^2, iv, 49 weeks.
Sugimoto et al.	2014	Japan	102	51	51	S-1: 40 mg/m2d, bid, day1–14; PTX: 50mg/m2, iv, day 1 and 8, q.3.w.	S-1: 40 mg/m2d, bid day, 1–21; Irinotecan: 80 mg/m^2, iv, day 1 and 15, q.5.w.
Huang et al.	2013	China	229	119	110	S-1: 80–120 mg/m2d, bid day 1–14; PTX: 60 mg/m^2, iv, day 1, 8 and 15, q.4.w.	5-FU: 500 mg/m2, iv, day 1–5; leucovorin 20 mg/m^2, iv, day 1–5; PTX: 60 mg/m^2, iv, day 1, 8and 15, q.4.w.
Wang et al.	2013	China	82	41	41	S-1: 40–60 mg/m^2, bid day 1–14; PTX: 60 mg/m^2, iv, day 1, 8and 15, q.4.w.	S-1: 40–60 mg/m^2, bid day 1–14.
Mochiki et al.	2012	Japan	83	42	41	S-1: 40 mg/m^2, bid day 1–14; PTX: 60 mg/m^2, iv, day 1, 8and 15, q.4.w.	S-1: 40 mg/m^2, bid day 1–21; Cisplatin: 60 mg/m^2, iv, day 8, q.5.w.
Nishikawa et al.	2012	Japan	157	80	77	(sequential), S-1: 80 mg/m^2, day 1–28, 2-wk rest followed by PTX; or (concurrent), S-1: 14 d and PTX: 50 mg/m^2, day 1, 8, q.3.w.	(sequential), intravenous 5-FU: 800 mg/m^2, iv,d1-5,followed by weekly PTX at 80 mg/m^2;or (concurrent), 5-FU:600 mg/m^2, iv,d1-5and weekly PTX at 80 mg/m^2, q.4.w.
Han et al.	2012	China	44	23	21	S-1: 80 mg/m^2, day 1–14, d 7 rest; PTX: 135 mg/m^2, iv, day 1, q.3.w.	PTX: 135 mg/m^2, iv, day 1; 5-FU: 500 mg/m^2, iv, day 1–5, q.3.w.

Table 2
Comparison of characteristics between S-1 + PTX and non-(S-1 + PTX) chemotherapy.

Characteristics	S-1 + PTX	non-(S-1 + PTX)	RR (95% CI)	P value
No. of patients	711 (50.53%)	696 (49.47%)	1.02 [0.95, 1.10]	0.57
Gender, n (%)				
Male	512 (72.01%)	474 (68.10%)	1.06 [0.99, 1.13]	0.11
Female	199 (27.99%)	222 (31.90%)	0.88 [0.75, 1.03]	
Age, years				
Median	61	60	no	No
Range	20–84	20–89	no	No
ECOG performance status				
0	567 (79.74%)	564 (81.03%)	0.98 [0.93, 1.04]	0.54
1	129 (18.14%)	118 (16.95%)	1.07 [0.85, 1.34]	0.56
2	15 (2.12%)	14 (2.02%)	1.05 [0.51, 2.16]	0.9
Body surface area, m2				
< 1.25	71 (9.98%)	51 (7.33%)	1.36 [0.97, 1.92]	0.08
1.25–2.50	275 (38.68%)	268 (38.51%)	1.00 [0.88, 1.15]	0.95
> 2.5	365 (51.34%)	377 (53.02%)	1.30 [1.01, 1.67]	0.29
Previous adjuvant chemotherapy				
Yes	196 (27.57%)	203 (29.17%)	0.95 [0.80, 1.12]	0.51
No	515 (72.43%)	493 (70.83%)	1.02 [0.96, 1.09]	0.51
Histology				
Diffuse type	561 (78.90%)	537 (77.16%)	1.02 [0.97, 1.08]	0.43
Intestinal type	120 (16.88%)	130 (18.68%)	0.90 [0.72, 1.13]	0.38
Other not specify	30 (4.22%)	29 (4.16%)	1.01 [0.61, 1.67]	0.96
Primary tumor				
Yes	396 (55.70%)	387 (55.60%)	1.00 [0.91, 1.10]	0.97
No	315 (44.30%)	309 (44.40%)	1.00 [0.89, 1.12]	0.967
Disease status				
Unresectable	228 (32.07%)	234 (33.62%)	0.95 [0.82, 1.11]	0.54
Recurrent	483 (67.93%)	462 (66.38%)	1.02 [0.95, 1.10]	0.54
Metastatic sites				
Liver	172 (24.19%)	173 (24.86%)	0.97 [0.81, 1.17]	0.77
Peritoneum	182 (25.60%)	163 (23.42%)	1.09 [0.91, 1.31]	0.34
Abdominal	160 (22.50%)	179 (27.16%)	0.87 [0.73, 1.05]	0.16
Lymph node	177 (24.89%)	160 (22.99%)	1.08 [0.90, 1.30]	0.4
Bone	20 (2.81%)	17 (2.44%)	1.15 [0.61, 2.18]	0.66
Lung	19 (2.67%)	13(1.87%)	1.43 [0.71, 2.87]	0.31

14 months, one year survival rate was 61.0%. S-1 combined with PTX significantly improve the OS [HR = 0.78, 95% CI: 0.60–0.97, P = 0.000] for patients with AGC and have no obvious heterogeneity exist among different research [I^2 = 36.8%, P = 0.191]. The details are listed in Fig. 4.

3.4.2. PFS

There are 4 trials stated the progression-free survival data. The patients accepted other chemotherapy regimens with the average median progression-free survival was 4.9 months, and patients adopted S-1 combined with PTX regimens with the average median progression-free surial was 6.2 months. S-1 combined with PTX significantly improve the PFS [HR = 0.70, 95% CI: 0.55–0.85, P = 0.000] for patients with AGC and have no obvious heterogeneity exist among different research [I^2 = 36.0%, P = 0.196]. The details are listed in Fig. 5.

3.4.3. ORR

There are 6 trials stated the objective response rate data. The patients accepted other chemotherapy regimens with the average ORR was 31.4%, and patients adopted S-1 combined with PTX regimens with the average ORR was 40.8%. S-1 combined with PTX significantly improve the ORR [RR = 1.30, 95% CI: 1.05–1.60, P = 0.017] for patients with AGC and have no obvious heterogeneity exist among different research [I^2 = 33.4%, P = 0.185]. The details are listed in Fig. 6.

3.4.4. DCR

There are 6 trials stated the disease control rates data. The patients accepted other chemotherapy regimens with the average DCR was 66.5%, and patients adopted S-1 combined with PTX regimens with the average DCR was 75.2%. S-1 combined with PTX significantly improve

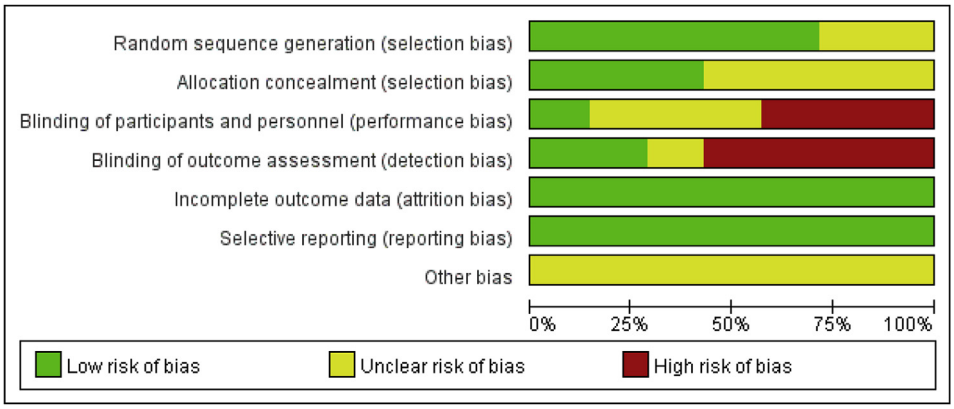

Fig. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

the DCR [RR = 1.15, 95% CI: 1.04–1.27, $P = 0.008$] for patients with AGC and have no obvious heterogeneity exist among different research [$I^2 = 0.0\%$, $P = 0.760$]. The details are listed in Fig. 7.

3.5. Safety

All of the trials were evaluated the adverse effects of chemotherapy, and 1404 patients were randomly assigned to receive S-1 combined with PTX treatment group (n = 711) and other regimen treatment group (n = 693). The details are listed in Table 3.

3.5.1. Hematologic toxicity

Meta-analysis of seven trials showed that the 3–4 grade incidence of anemia in S-1 combined with PTX treatment group was 1.71 times high than that in other regimen treatment group, and the difference has statistical significant [RR = 1.71, 95% CI: 1.04–2.79, P = 0.03] (see Table 4). The 3–4 grade incidence of neutropenia in S-1 combined with PTX treatment group was 1.65 times high than that in other regimen treatment group, and the difference has statistical significant [RR = 1.65, 95% CI: 1.32–2.06, P < 0.0001].

Meta-analysis of six trials showed that the 3–4 grade incidence of thrombocytopenia in S-1 combined with PTX treatment group was 2.95 times high than that in other regimen treatment group, but the difference has no statistical significant [RR = 2.95, 95% CI: 0.60–14.58, P = 0.18]. Meta-analysis of seven trials showed that the 3–4 grade incidence of leukopenia in S-1 combined with PTX treatment group was 1.24 times high than that in other regimen treatment group, but the difference has no statistical significant [RR = 1.24, 95% CI: 0.90–1.73, P = 0.19]. Meta-analysis of two trials showed that the 3–4 grade incidence of febrile neutropenia in S-1 combined with PTX treatment group was 0.32 times high than that in other regimen treatment group, but the difference has no statistical significant[RR = 0.32, 95% CI: 0.03–3.04, P = 0.32].

3.5.2. Non-hematologic toxicity

Meta-analysis of seven trials showed that the 3–4 grade incidence of anorexia in S-1 combined with PTX treatment group was 1.66 times high than that in other regimen treatment group, and the difference has statistical significant [RR = 1.66, 95% CI: 1.05–2.64, P = 0.03]. Meta-analysis of other trials showed that the 3–4 grade incidence of fevers, fatigue, nausea, vomiting, diarrhea, stomatitis and sensory neuropathy in S-1 combined with PTX treatment group compared with other regimen treatment group the difference has no statistical significant. There were no treatment-related deaths in either group in the seven trials.

3.6. Publication bias

Funnel plots were conducted for assessing the publication bias of included literature and we could roughly assess the publication bias by seeing whether their shapes were of any obvious asymmetry. The funnel plot showed no clear evidence of publication bias existed (Egger's test: P = 0.174, Begg's test: P = 0.592; Fig. 8).

3.7 Grading of Recommendations Assessment

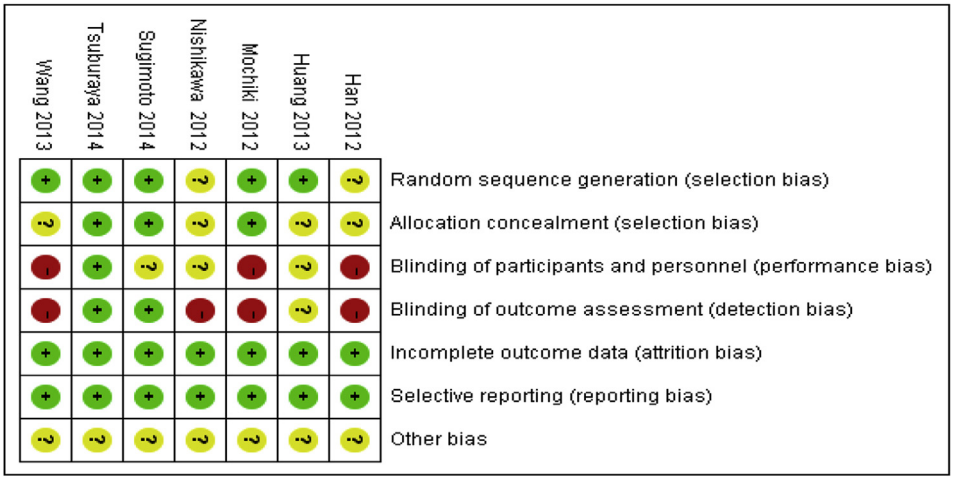

Fig. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

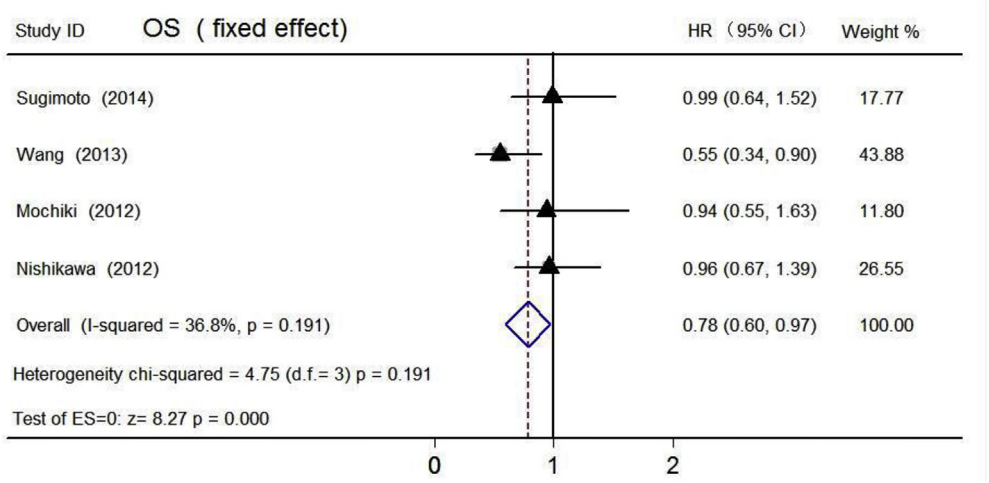

Fig. 4. The forest plot of OS for Chemotherapy of S-1 Combined with PTX of AGC.

4. Discussion

After years of exploration, the development on selecting a reasonable chemotherapy regimen of AGC was very rapidly. The clinical evidence from the systematic review or meta-analysis offered a scientific basis for the reasonable selection on chemotherapy regimens of AGC. From the initial meta-analysis about chemotherapy vs. best clinical support for AGC [9] to meta-analysis about S-1 based chemotherapy vs. non-S-1 based chemotherapy for AGC [1], and then to meta-analysis about S-1 based chemotherapy vs. S-1 mono-chemotherapy for AGC [26], finally to recently meta-analysis about S-1 combined with PTX vs. 5-FU combined with PTX for AGC [5]. All of the meta-analysis showed the superiority of the chemotherapy for AGC, and reflected the advantage of S-1 based chemotherapy regimens for the treatment of AGC also. The chemotherapy regimen of S-1 combined with PTX for AGC seems to be one of the most potential advantages. Therefore, our study applied the method of meta-analysis pooled relevant RCTs, and systematically reviewed whether there were advantages in efficacy and safety on chemotherapy regimen of S-1 combined with PTX for AGC.

In meta-analysis about S-1 based chemotherapy vs. non-S-1 based chemotherapy for AGC, 2176 patients were included in the 7 RCTs [1]. Compared with the non-S-1 based chemotherapy, S-1 based chemotherapy can improve the patients' ORR [RR = 1.300, 95% CI: 1.028–1.645], OS [HR = 0.89, 95% CI: 0.89–0.81, P = 0.025] and TTF [HR = 0.83, 95% CI: 0.83–0.75, P = 0.000] for AGC. And have lower risk for febrile neutropenia [RR = 0.225; P = 0.000)] and stomatitis [RR = 0.230; P = 0.230]. S-1 based chemotherapy can significantly extend the OS, PFS and TTF for patients with AGC in Asia.

In meta-analysis about S-1 based chemotherapy vs. S-1 mono-chemotherapy for AGC, 790 patients were included in 4 RCTs [26]. Compared with the S-1 mono-chemotherapy, S-1 based chemotherapy can significantly improve the patients' OS [HR = 0.77, 95%CI: 0.66–0.91, P = 0.002], PFS [HR = 0.58, 95%CI: 0.46–0.72, P = 0.000] and ORR [OR = 2.23, 95%CI: 1.54–3.21, P = 0.000] for AGC. Sensitivity analysis confirmed this association further. And have lower risk for 3–4 grade incidence of leucopenia [OR = 4.06, 95%CI: 2.11–7.81], neutropenia [OR = 3.94, 95% CI: 2.1–7.81] and diarrhea [OR = 2.41, 95%CI: 1.31–4.44]. S-1 based chemotherapy can significantly extend the OS, PFS and ORR for patients with AGC than S-1 mono-chemotherapy.

In meta-analysis about S-1 combined with PTX vs. 5-FU combined with PTX for AGC, 352 patients were included in 3 RCTs [5]. Results suggested that compared with 5-FU combined with PTX, S-1 combined with PTX increased patients' DCR [RR = 1.14, 95% CI: 1.00 1.30, P = 0.04] for AGC, and reduced the rate of progressive diseases rate [RR = 0.62, 95% CI: 0.39 0.98, P = 0.04]. S-1 combined with PTX significantly reduced the incidence of nausea [RR = 0.60, 95% CI: combined with PTX, S-1 combined with PTX with a good safety and efficacy for AGC. S-1 combined with PTX was a good choice for patients

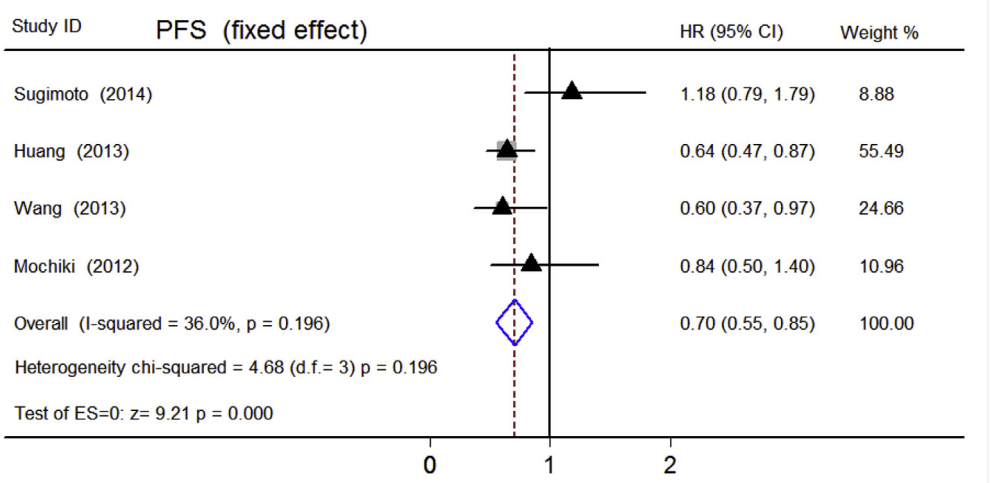

Fig. 5. The forest plot of PFS for Chemotherapy of S-1 Combined with PTX of AGC.

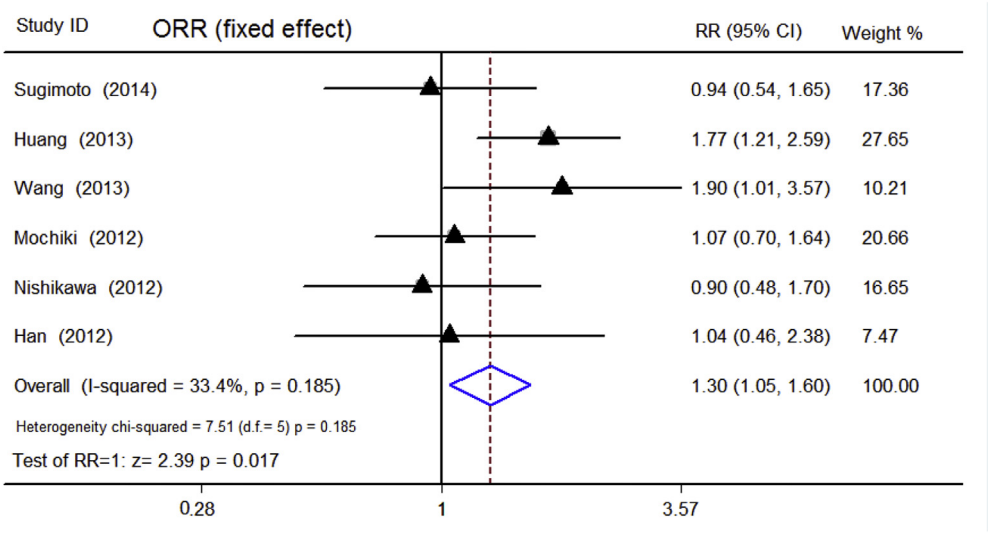

Fig. 6. The forest plot of ORR for Chemotherapy of S-1 Combined with PTX of AGC.

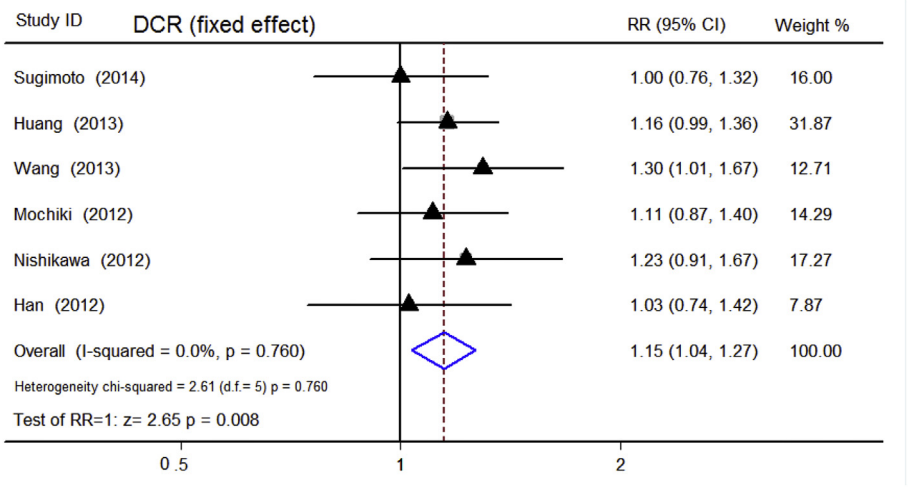

Fig. 7. The forest plot of DCR for Chemotherapy of S-1 Combined with PTX of AGC.

who will not tolerate continuous intravenous infusion.

In our study about a systematic review of the chemotherapy of S-1 combined with PTX for AGC, 1407 patients were included in seven II/III clinical RCTs. The chemotherapy regimens of S-1 combined with PTX significantly increased patients' OS [HR = 0.78, 95% CI: 0.60–0.97, P = 0.000], PFS [HR = 0.70, 95% CI: 0.55–0.85, P = 0.000], ORR [RR = 1.30, 95% CI: 1.05–1.60, P = 0.017] and DCR [RR = 1.15, 95% CI: 1.04–1.27, P = 0.008] for AGC. Grade 3–4 adverse events were anemia [RR = 1.71, 95% CI: 1.04–2.79, P = 0.03], neutropenia [RR = 1.65, 95% CI: 1.32–2.06, P < 0.0001] and anorexia [RR = 1.66, 95% CI: 1.05–2.64, P = 0.03]. The incidence of fever, fatigue, nausea, vomiting, diarrhea, stomatitis and nerve toxicity between the two groups had no statistical difference. Compared with other chemotherapy regimens, S-1 combined with PTX for AGC have longer OS and PFS, higher ORR and DCR. The grade 3–4 adverse events include neutropenia, anemia, and anorexia.

OS was the time for patients from randomized to the end of life due to various factors [15]. This index is often regarded as the best observation end point of oncology clinical trials [16]. In this systematic review 4 RCTs stated the OS data. Our study suggested that S-1 combined with PTX compared with other regimens significantly improve the OS in patients with AGC, and have no obvious heterogeneity among the trials. As for adverse events of chemotherapy as neutropenia, anemia, and anorexia most may be due to the side effects of the accumulation of chemotherapy drugs in the body. But all adverse events can be controlled, predicted and tolerance [16]. The mostly adverse events for S-1 combined with PTX are grade 3–4 hematologic toxicit y [16]. Currently, the application of recombinant-human granulocyte colony stimulating factor and erythropoietin in clinic improved the hematologic toxicity. For anorexia, that mostly because of the frequent therapy period of S-1 combined with PTX, which can be further improved by giving digestion medicine. For any meta-analysis, the current study results may have its limitations because of the research evidence was completely from the available researches. (1) The quality of researches would affect the results of meta-analysis. There are 7 trials included in our systematic review, but the blinded implementation is not enough in 3 trials may influence the evaluation of treatment response of S-1 combined with PTX for AGC. (2) There was no second-line treatment reported about S-1 combined with PTX for AGC, so this study did not consider they might impact on survival. (3) The results of systematic review need to be confirmed in the western countries, because all of seven RCTs in this study were from Asia.

Recently, a large number of studies introduced the application of albumin-bound PTX in many entities malignant tumor, including GC. Which used the natural characteristics of albumin, through the gp-60 (glycosylation capsule membrane protein) mediated the mechanism of

Table 3
Comparison of toxicity between S-1 + PTX chemotherapy and non-(S-1 + PTX)chemotherapy.

Toxicity Grade 3/4	Number of Trials	Incidence of Toxicity %		RR(95%CI)	P value
		S-1 + PTX	non-(S-1 + PTX)		
Haematological					
Anemia	7	42/711 (5.91%)	24/693 (3.46%)	1.71 [1.04, 2.79]	0.03
Neutropenia	7	171/711 (24.05%)	101/693 (14.57%)	1.65 [1.32, 2.06]	< 0.0001
Thrombocytopenia	6	6/592 (1.01%)	2/583 (0.34%)	2.95 [0.60, 14.58]	0.18
Leukopenia	7	74/711 (10.41%)	58/693 (8.37%)	1.24 [0.90, 1.73]	0.19
Febrile neutropenia	2	1/92 (1.09%)	3/89 (3.37%)	0.32 [0.03, 3.04]	0.32
Non-haematological					
Allergic reaction	1	3/355 (0.85%)	2/355 (0.56%)	1.50 [0.25, 8.92]	0.66
Fever	2	3/474 (0.63%)	3/465 (0.65%)	0.98 [0.20, 4.84]	0.98
Fatigue	7	25/711 (3.52%)	20/693 (2.89%)	1.218 [0.68, 2.17]	0.5
Anorexia	6	46/688 (6.69%)	27/672 (4.02%)	1.66 [1.05, 2.64]	0.03
Nausea	7	23/711 (3.23%)	15/693 (2.16%)	1.50 [0.79, 2.84]	0.22
Vomiting	6	6/669 (0.90%)	8/652 (1.23%)	0.73 [0.26, 2.10]	0.56
Diarrhea	7	25/711 (3.52%)	15/693 (2.16%)	1.62 [0.86, 3.06]	0.13
Stomatitis	6	5/592 (0.84%)	5/583 (0.86%)	0.99 [0.29, 3.38]	0.98
Abnormal total bilirubin	5	8/569 (1.41%)	5/562 (0.89%)	1.58 [0.52, 4.80]	0.42
Abnormal AST concentration	3	5/448 (1.12%)	9/444 (2.03%)	0.55 [0.19, 1.63]	0.28
Abnormal ALT concentration	3	6/448 (1.34%)	13/444 (2.93%)	0.46 [0.18, 1.19]	0.11
Serum creatinine concentration	3	0/447 (0.00%)	1/444 (0.23%)	0.33 [0.1, 8.11]	0.50
Sensory neuropathy	6	8/660 (1.21%)	5/645 (0.78%)	1.56 [0.51, 4.75]	0.43
Hepatic toxicity	2	7/199 (3.52%)	7/187 (3.74%)	0.94 [0.34, 2.63]	0.91
Hypotension	1	0/355 (0.00%)	1/355 (0.28%)	0.33 [0.01, 8.16]	0.50
Dyspnoea	1	2/355 (0.56%)	1/355 (0.28%)	2.00 [0.18, 21.96]	0.57
Motor neuropathy	1	2/355 (0.56%)	0/355 (0.00%)	5.00[0.24, 103.76]	0.30
Alopecia	1	4/119 (3.36%)	2/110 (1.82%)	1.85 [0.35, 9.89]	0.47
Rash	1	1/41 (2.44%)	2/41 (4.88%)	0.50 [0.05, 5.30]	0.57
Lacrimation	1	0/41 (0.00%)	1/41 (2.44%)	0.33 [0.01, 7.95]	0.50
Hyponatremia	2	1/83 (1.20%)	1/82 (1.22%)	0.99 [0.06, 15.53]	0.99
Weight loss	1	0/80 (0.00%)	2/77 (2.60%)	0.19 [0.01, 3.95]	0.29
Lassitude	1	9/80 (11.25%)	5/77 (6.49%)	1.73 [0.61, 4.94]	0.30
Muscle and joint pain	1	1/23 (4.35%)	2/21 (9.52%)	0.46 [0.05, 4.68]	0.51

membrane translocation of endothelial cells and a combination with protein SPARC (a kind of acid secreted proteins that are rich with cysteine) with the interaction for tumor tissue uptake and accumulation of PTX [10,11,27–30]. On this basis, the albumin-bound PTX is applied to a variety of malignant tumor chemotherapy in the clinical researches, encouraging results have been achieved in recent years [11,27,31,32]. Predictably, the S - 1 type joint albumin in combination with paclitaxel on the treatment of advanced gastric cancer is an attractive option. In addition, the chemotherapy regimen of S-1 combined with PTX can be extended to preoperatively for gastrointestinal tumor and associated with radiation therapy [6,8,17,33].

This is the first time we use meta-analysis method merger analysis related RCTs and systematic evaluated the efficacy and safety of S-1 combined with PTX for AGC [5,7,9,34,35]. All in all, the results of meta-analysis showed that S-1 combined with PTX for AGC have long OS and PFS with high ORR and DCR also [36–40]. The grade 3–4 adverse events include neutropenia, anemia, and anorexia [3,10,41–43]. Considering the advantages of all the results, we should recommend the treatment of S-1 combined with PTX as a standard chemotherapy regimen for AGC, at least in Asia. In order to confirm these findings, extra

Table 4
Grading of Recommendations Assessment S-1 + PTX compared to non-(S-1 + PTX) for advanced gastric cancer (AGC) Grading of Recommendations Assessment.

Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Non-(S-1 + PTX)	Corresponding risk S-1 + PTX			
Overall survival Follow-up: 12 months	95 per 1000	75 per 1000 (58–93)	HR 0.78 (0.6–0.97)	424 (4 studies)	⊕⊕⊕⊖ moderate[1]
Progression-free survival Follow-up: 12 months	181 per 1000	130 per 1000 (104–156)	HR 0.70 (0.55–0.85)	496 (4 studies)	⊕⊕⊕⊖ moderate[1]
Objective response rate	297 per 1000	386 per 1000 (312–476)	RR 1.30 (1.05–1.6)	660 (6 studies)	⊕⊕⊕⊖ moderate[1]
Disease control rate	644 per 1000	741 per 1000 (670–818)	RR 1.15 (1.04–1.27)	660 (6 studies)	⊕⊕⊕⊖ moderate[1]
Grade3/4 anemia	35 per 1000	59 per 1000 (36–97)	RR 1.71 (1.04–2.79)	1404 (7 studies)	⊕⊕⊕⊖ moderate[1]
Grade3/4 neutropnia	146 per 1000	240 per 1000 (192–300)	RR 1.65 (1.32–2.06)	1404 (7 studies)	⊕⊕⊕⊖ moderate[1]
Grade3/4 anorexia	40 per 1000	67 per 1000 (42–106)	RR 1.66 (1.05–2.64)	1360 (6 studies)	⊕⊕⊕⊖ moderate[1]

NOTE: **Patient or population:** patients with advanced gastric cancer (AGC); **Settings:** first - and second - line treatments; **Intervention:** S-1 + PTX; **Comparison:** non - (S-1 + PTX).

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

[a] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in comparison group the relative effect of the intervention of the intervention of the intervention of the intervention of the intervention of the intervention of the intervention of the intervention of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio.

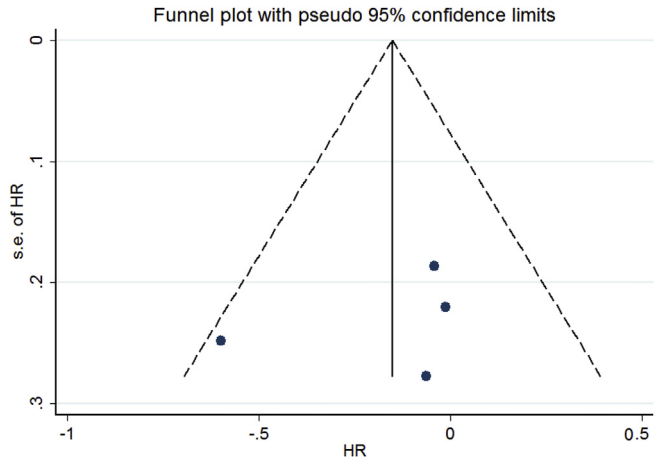

Fig. 8. Funnel plot of OS for Chemotherapy of S-1 Combined with Paclitaxel of AGC.

large RCTs and the western research is necessary [2,4,19,44].

There was moderate quality evidence from these studies suggesting longer progression-free survival from using S-1 combined with PTX regimen to AGC. However, findings need to be confirmed by larger, high-quality randomized clinical trials.

5. Conclusions

The present analysis showed that AGC patients receiving S-1 combined with PTX experienced better prognosis and may be a good choice for patients with AGC. Although the grade 3 or 4 haematological and non-hematologic toxicities (anemia, neutropenia and anorexia) were observed, no severe or deadly adverts were found. In conclusion, S-1 plus PTX displayed more efficacy and safety when compared with S-1 alone or S-1 plus other drugs.

Ethical Approval

Ethical Approval is not applicable.

Sources of funding

There is no funding for this work.

Author contribution

The authors on this paper all participated in study design. All authors read, critiqued and approved the manuscript revisions as well as the final version of the manuscript. Also, all authors participated in a session to discuss the results and consider strategies for analysis and interpretation of the data before the final data analysis was performed and the manuscript written. All authors have the appropriate permissions and rights to the reported data.

Conflicts of interest

The authors declare no relevant conflict of interest.

Trial registry number

reviewregistry570.

Guarantor

Ningning Bian.

Data statement

The material of this article is original research. All data in this manuscript is available and transparent for readers.

Provenance and peer review

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2018.11.010.

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