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# Comparison of efficacy and safety of S-1 and capecitabine in patients with metastatic colorectal carcinoma
## A systematic review and meta-analysis

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## Abstract
**Background:** This study aimed to compare the efficacy and safety of S-1 and capecitabine in patients with metastatic colorectal carcinoma (mCRC).

**Methods:** Eligible prospective clinical trials were searched and available data were extracted. Odds ratio and hazard ratio of available outcomes including objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs) were pooled for analysis.

**Results:** A total of 6 studies including 828 patients were included. The results of pooled analysis showed no statistical difference in short-term efficacy including ORR (95% confidence interval [CI]: 0.68–1.19; $P = .48$) or DCR (95% CI: 0.65–1.29; $P = .61$), or long-term efficacy including PFS (95% CI: 0.75–1.08; $P = .26$) or OS (95% CI: 0.78–1.13; $P = .50$). Symptoms of diarrhea at any grade were more prevalent (95% CI: 1.21–2.29; $P = .002$) in patients treated with S-1, while hand-foot syndrome (HFS) at any grade (95% CI: 0.24–0.48; $P < .0001$) or high grade (95% CI: 0.09–0.48; $P < .0001$) was more frequent in capecitabine group. AEs including leucopenia, neutropenia, anemia, thrombocytopenia, vomiting, oral mucositis, stomatitis, elevated alanine transaminase, or peripheral neuropathy showed no statistical difference between S-1 and capecitabine group (all $P > .05$).

**Conclusions:** This meta-analysis reveals that S-1 has comparable efficacy, lower risk of HFS and higher incidence of diarrhea compared to capecitabine for treatment in patients with mCRC.

**Abbreviations:** AEs = adverse events, ALT = alanine transaminase, DCR = disease control rate, ECOG PS = eastern cooperative oncology group performance status, GC = gastric cancer, HFS = hand-foot syndrome, HR = hazard ratio, mCRC = metastatic colorectal carcinoma, OR = odds ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, RCT = randomized clinical trial, RECIST = response evaluation criteria in solid tumors, XELOX = capecitabine plus oxaliplatin.

**Keywords:** adverse events, capecitabine, efficacy, meta-analysis, S-1

## 1. Introduction

Colorectal cancer is the third most frequently diagnosed cancer and the third leading cause of cancer death all over the world.[1]

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Surgery, radical radiation, and radio-chemotherapy are the main treatments for patients with early-stage disease. However, systematic therapy with chemicals and targeted agents have been applied in palliative treatment, which focuses on the extension of life and improvement of quality of life.[2]

With the development of targeted agents, such as anti-epidermal growth factor receptor and anti-angiogenesis drugs, chemotherapeutics of fluorouracil, oxaliplatin, and irinotecan, how to maximize the efficacy of these agents for the treatment colorectal carcinoma becomes a significant issue for clinicians.[3] Capecitabine, an oral fluoropyrimidine, is the precursor of fluorouracil that has been approved as a candidate of infusion fluorouracil in clinical practice, especially in patients with metastatic colorectal carcinoma (mCRC).[4] However, hand-foot syndrome (HFS) has been the most common adverse event (AE) during the treatment with capecitabine, which has seriously limited its clinical application.[5]

S-1 is an oral fluoropyrimidine composed of 3 pharmacological compounds, including tegafur, gimeracil, and oteracil potassium, at a molar ratio of 1:0.4:1, and it has been widely used among Asian patients with advanced gastric cancer (aGC), breast cancer, and pancreatic carcinoma.[6–8] However, insufficient positive evidence has been obtained to establish its therapeutic value in patients with colorectal cancer. A large-scaled, open-label, non-inferiority, randomized, phase 3, multicentre trial (JCOG0910) explore the non-inferiority of S-1 compared with capecitabine as

adjuvant treatment in patients with stage III colorectal cancer, and 3-year disease-free survival was 82.0% (95% confidence interval [CI]: 78.5–85.0) for the capecitabine group and 77.9% (95% CI: 74.1–81.1) for the S-1 group (hazard ratio [HR], 1.23, 99.05% CI: 0.89–1.70; 1-sided $P_{non-inferiority}$ =.46). Thus adjuvant S-1 was suggested as not non-inferior to adjuvant capecitabine in terms of disease-free survival for patients with stage III colorectal cancer after D3/D2 surgery.

Up to now, several prospective studies have been performed to compare the efficacy and safety of S-1 with capecitabine. However, due to small sample size, clinical application value might be limited. Therefore, we performed meta-analysis and systematic review to compare the efficacy and safety of S-1 and capecitabine in a larger population of patients with mCRC to confirm its clinical value.

## 2. Materials and patients

### 2.1. Literature search

A literature review among databases including Medline, Embase, Google Scholar, and the Cochrane Library was conducted up to June 6th, 2018 with the main keywords, such as "S-1," "colorectal cancer," "capecitabine" and their synonyms. The search was limited to prospective clinical trials published in English. However, meeting abstracts were excluded from the present searching due to the potentially insufficient data. The present meta-analysis was conducted in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and was reported according to the preferred reporting items for systematic reviews and meta-analyses statement.

### 2.2. Inclusion and exclusion criteria

The eligible studies were enrolled if they met all of the following criteria:

(1) Patients should be histologically or cytologically diagnosed as mCRC (stage IV) according to 7th edition of the American Joint Committee on Cancer staging system.[9]
(2) Prospective phase II/III randomized clinical trials (RCTs) that compared the efficacy and safety between S-1 based regimens and capecitabine based regimens in patients with mCRC.
(3) At least 1 of the following outcomes should be reported: objective response rate (ORR), disease control rate (DCR), median progression free survival, median overall survival, AEs.

The following exclusion criteria were adopted.

(1) Non-randomized or single-arm phase II trials.
(2) Ongoing clinical trials reported in meeting abstracts without integrated article published.
(3) Any review, letter, meta-analysis, case reports or comments.
(4) For repeatedly published articles or the same study reported during different period, the article with most complete data was selected with the others excluded.
(5) The published language was not in English.

### 2.3. Data extraction

The available data from the included studies were extracted independently by 2 investigators (Chen and Wang) with any controversy resolved by consensus. The essential information extracted from the enrolled studies included the first author's names, publication year, study type, regions, the previous lines, number of patients, gender, eastern cooperative oncology group (ECOG) performance status, treatment schedules, and the outcomes. Outcomes were ORR (patients evaluated as partial response or complete response according to the criteria of response evaluation criteria in solid tumors [RECIST] version 1.1), DCR (patients evaluated as partial response or complete response or stable disease according to RECIST version 1.1), PFS (randomization to death regardless of any causes), overall survival (OS; randomization to progression of any causes or death regardless of any causes), and AEs at any grade or at high grade (≥grade 3) including hematological toxicities and non-hematological toxicities.

### 2.4. Quality assessment of included studies

The quality of the included studies was evaluated with the criteria of the Cochrane Collaboration's tool for assessing risk of bias of RCTs by the 2 reviewers (Chen and Wang). The following items were adopted for the assessment: random sequence generation, allocation concealment, binding of participants and personnel, binding of outcome assessments, incomplete outcome data, selective reporting and other bias.

### 2.5. Statistical analysis

All data in the present study were analyzed with software RevMan version 5.3. ORR, DCR, and AEs were calculated with an odds ratio (OR). HRs were extracted for the assessment of PFS and OS. A $P$-value <.05 was considered statistically significant. Cochrane $Q$ test and inconsistency statistic ($I^2$) were applied for the heterogeneity evaluation among the included RCTs. A $P > .05$ and $I^2 < 50\%$ was supposed to show no significant heterogeneity. Random effect model or fixed effect model was applied for the analysis of data heterogeneity. Potential publication bias was detected with funnel plot in software RevMan version 5.3.

## 3. Results

### 3.1. Literature search

A total of 458 potential literatures were initially searched in databases including Medline, Google Scholar, and Cochrane Library. One hundred seventy-eight articles were removed because of duplications. Fifty-seven articles were further excluded from the property of prospective clinical trials, and 8 studies met the inclusion criteria. After full text review, 2 studies were eliminated because of the repeated report in different period (n=2). Accordingly, a total of 6 available clinical studies were considered eligible for final analysis. A flow diagram on the selection of included studies was presented in Figure 1.

A total of 828 patients were included in the final analysis and all of them received S-1 or capecitabine based regimens as the treatment. Most patients possessed a good performance (ECOG 0-1) to receive a double-drug treatment regimen. The characteristics of included trials were shown in Table 1.

### 3.2. Quality assessment of the included studies

Four of 6 studies specifically reported the methods of randomization. Five studies were open-labeled and the other one did not report the status of blind during the trial, however, it
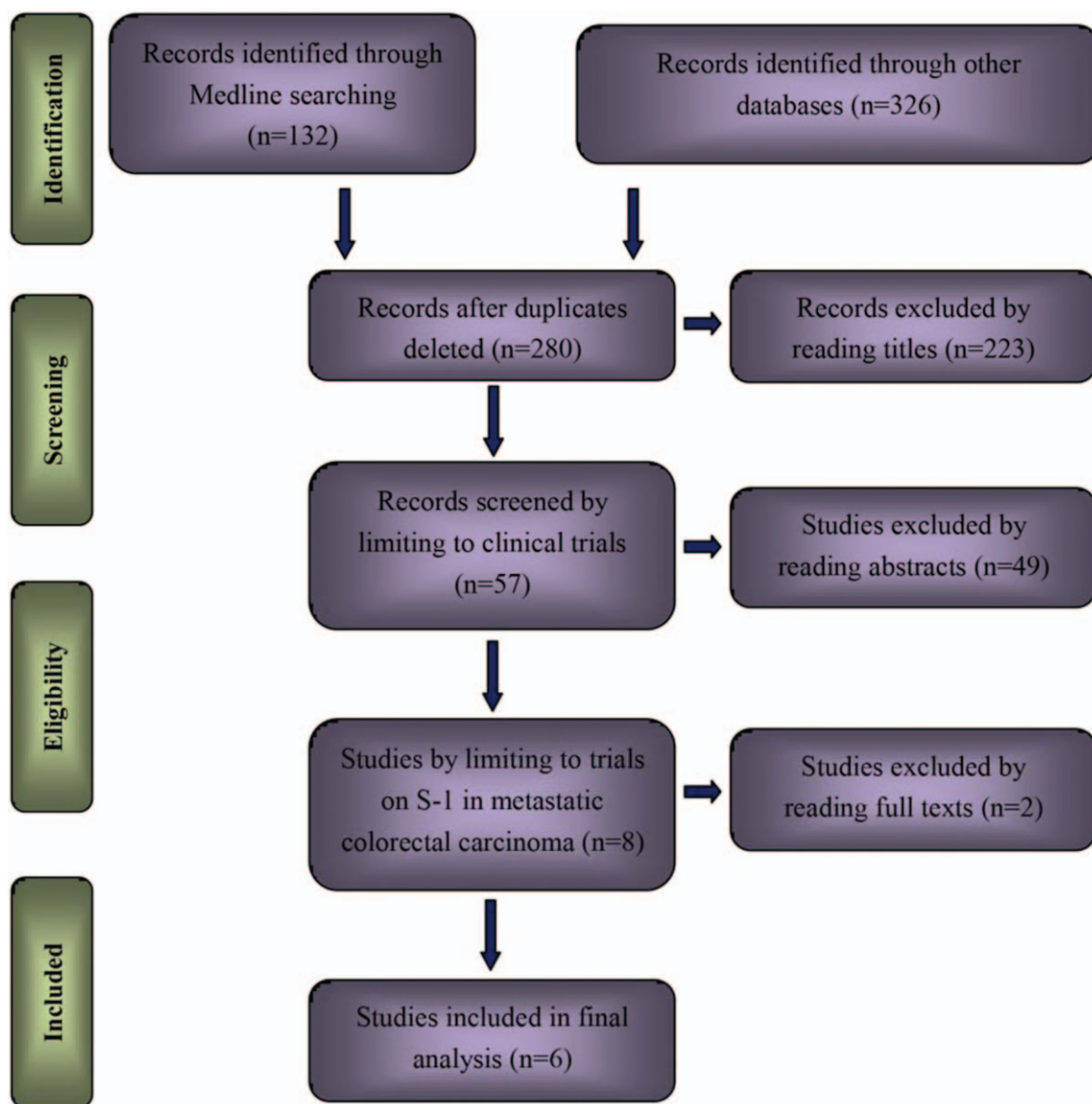
**Figure 1.** Study selection procedure with PRISMA flow diagram. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

was unlikely to affect the analysis according to the 2 investigators. Two of the included studies did not report the data of PFS and OS. The other of the studies satisfied the criteria of allocation concealment with low risk of bias. Results of the quality assessment were presented in Figures 2 and 3.

### 3.3. Short-term efficacy

The pooled OR for ORR was 0.90 (95% CI: 0.68–1.19; $P = .48$). Results of ORR with heterogeneity evaluation between subgroups with $I^2$ test showed no statistical heterogeneity ($I^2 = 46\%$, $P = .10$) (Fig. 4).

The pooled OR for DCR was 0.92 (95% CI: 0.65–1.29; $P = .61$). Results of ORR with heterogeneity evaluation between subgroups with $I^2$ test showed no statistical heterogeneity ($I^2 = 22\%$, $P = .15$) (Fig. 4).

### 3.4. Long-term efficacy

The pooled HR for PFS was 0.90 (95% CI: 0.75–1.08; $P = .26$). The pooled HR for OS was 0.94 (95% CI: 0.78–1.13; $P = .50$) (Fig. 5). Heterogeneity evaluation with $I^2$ test showed no statistical heterogeneity ($I^2 = 0\%$, $P = .46$ for PFS, $I^2 = 2\%$, $P = .36$ for OS, respectively).

### 3.5. Adverse events

For the pooled analysis of AEs at any grade, the incidence of diarrhea was more frequent in S-1 based regimens, and OR was 1.66 (95% CI: 1.21–2.29; $P = .002$). The pooled OR of HFS was 0.34 (95% CI: 0.24–0.48; $P < .0001$), showing statistical difference between the 2 groups. However, AEs such as leucopenia, neutropenia, anemia, thrombocytopenia, vomiting, oral mucositis, stomatitis, elevated alanine transaminase

**Baseline characteristics of the researches included in present study.**

| Author, yr | Region | As lines | No. of patients | Gender (male/female) | ECOG (PS, 0–1/2) | Regimens | Outcomes | Ref |
|---|---|---|---|---|---|---|---|---|
| Zong 2018 | China | First | Arm I:57 Arm II:57 | Arm I:26/31 Arm II:27/30 | Arm I:51/6 Arm II:48/9 | Arm I: SOX Arm II:XELOX | ORR/DCR/PFS/OS/AE | [10] |
| Liu 2017 | China | First | Arm I: 27 Arm II:30 | Arm I:18/9 Arm II:17/13 | N/A | Arm I: SOX Arm II:XELOX | ORR/DCR/AE | [11] |
| Kwakman 2017 | Netherlands | First | Arm I: 80 Arm II:81 | Arm I:45/35 Arm II:56/25 | ArmI:72/8 ArmII:73/8 | Arm I: S-1±Bev ArmII:CAP±Bev | ORR/DCR/PFS/AE | [12] |
| Liu HQ 2015 | China | Second or further | Arm I: 35 Arm II:35 | Arm I:19/16 Arm II:20/15 | N/A | Arm I: SOX Arm II:XELOX | ORR/DCR/AE | [13] |
| Kim 2015 | Korea | First | Arm I: 42 Arm II:44 | Arm I:28/14 Arm II:27/17 | ArmI:40/2 Arm II:43/1 | Arm I:SOX Arm II:XELOX | ORR/DCR/PFS/OS/AE | [14] |
| Hong 2012 | Korea | First | Arm I: 168 Arm II:172 | Arm I:109/59 Arm II:102/70 | ArmI:164/4 Arm II:168/4 | Arm I: SOX Arm II:XELOX | ORR/DCR/PFS/OS/AE | [15] |

AE = adverse event, CAP = capecitabine, DCR = disease control rate, N/A = not applicable, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, SOX = S-1 plus oxaliplatin, XELOX = capecitabine plus oxaliplatin.
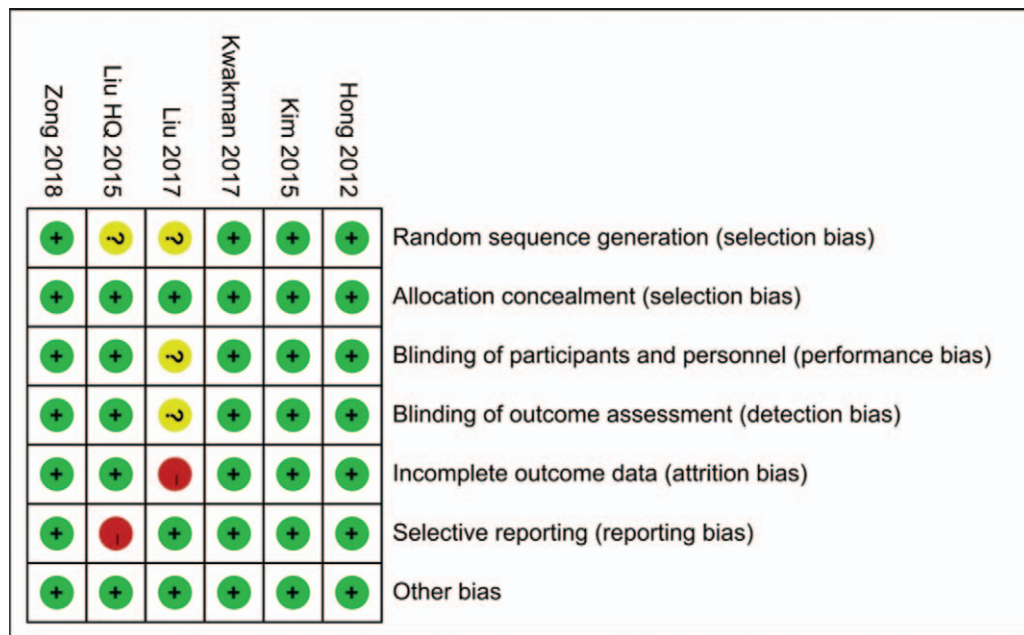


**Figure 2.** Risk of bias summary: each risk of bias item for each included study.

(ALT), and peripheral neuropathy did not show statistical difference between the 2 groups, and ORs and CIs were listed in Table 2.

For AEs at high grade, the incidence of HFS was more common in capecitabine based regimens, and OR was 0.20 (95% CI: 0.09–0.48; $P < .0001$). However, AEs such as leucopenia, neutropenia, anemia, thrombocytopenia, vomiting, oral mucositis, stomatitis, elevated ALT, and peripheral neuropathy did not show statistical difference between the 2 groups, and ORs and CIs were listed in Table 3.

### 3.6. Publication bias

Funnel plot of ORR did not reveal any significant publication bias (Fig. 6).

## 4. Discussion

To the best of our knowledge, this is the first meta-analysis to compare the efficacy and safety of S-1 and capecitabine in patients with mCRC. A total of 6 eligible prospective studies including 828 patients were enrolled for final analysis. We found no statistical difference in short-term efficacy including ORR (95% CI: 0.68–1.19; $P = .48$) or DCR (95% CI: 0.65–1.29; $P = .61$), or long-term efficacy including PFS (95% CI: 0.75–1.08; $P = .26$) or OS (95% CI: 0.78–1.13; $P = .50$). Symptom of diarrhea at any grade was more prevalent (95% CI: 1.21–2.29; $P = .002$) in patients treated with S-1, however, HFS at any grade (95% CI: 0.24–0.48; $P < .0001$) or high grade (95% CI: 0.09–0.48; $P < .0001$) was more frequent in capecitabine group. Moreover, AEs including leucopenia, neutropenia, anemia,
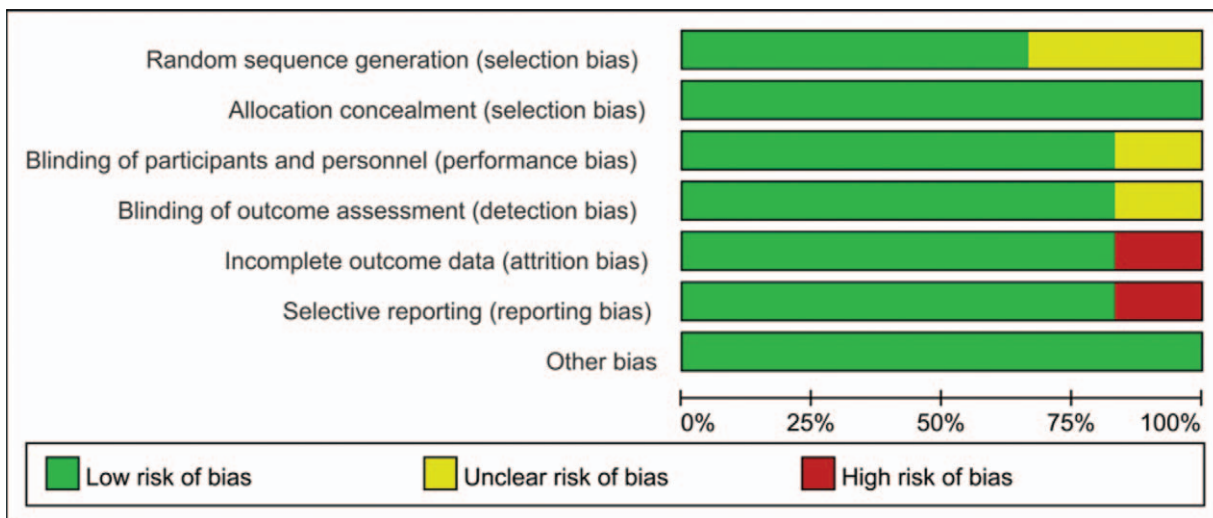
**Figure 3.** Risk of bias graph: each risk of bias item presented as the percentages among all included studies.

thrombocytopenia, vomiting, oral mucositis, stomatitis, elevated ALT, or peripheral neuropathy showed no statistical difference between S-1 and capecitabine group (all $P > .05$).

Due to the convenience of oral formulation, capecitabine has been used as an alternative agent in the treatment of mCRC.[10] Therefore, capecitabine based regimen (also known as capecitabine plus oxaliplatin [XELOX] or CapeOX) has been used as a more convenient regimen in patients with mCRC. However, high

risk of HFS with the lack of specific therapeutic strategies has greatly limited its clinical application.[5] HFS presents as symptoms like insensitivity, blister, pain, and even ulceration of pressure parts including palm and pelma, which severely decrease the quality of life and lead to a discontinuation of treatment in selective patients.[11] Although several drugs including cyclooxygenase-2 inhibitor, lactic acid, and pyridoxine have been used, their efficacy to attenuate HFS symptoms
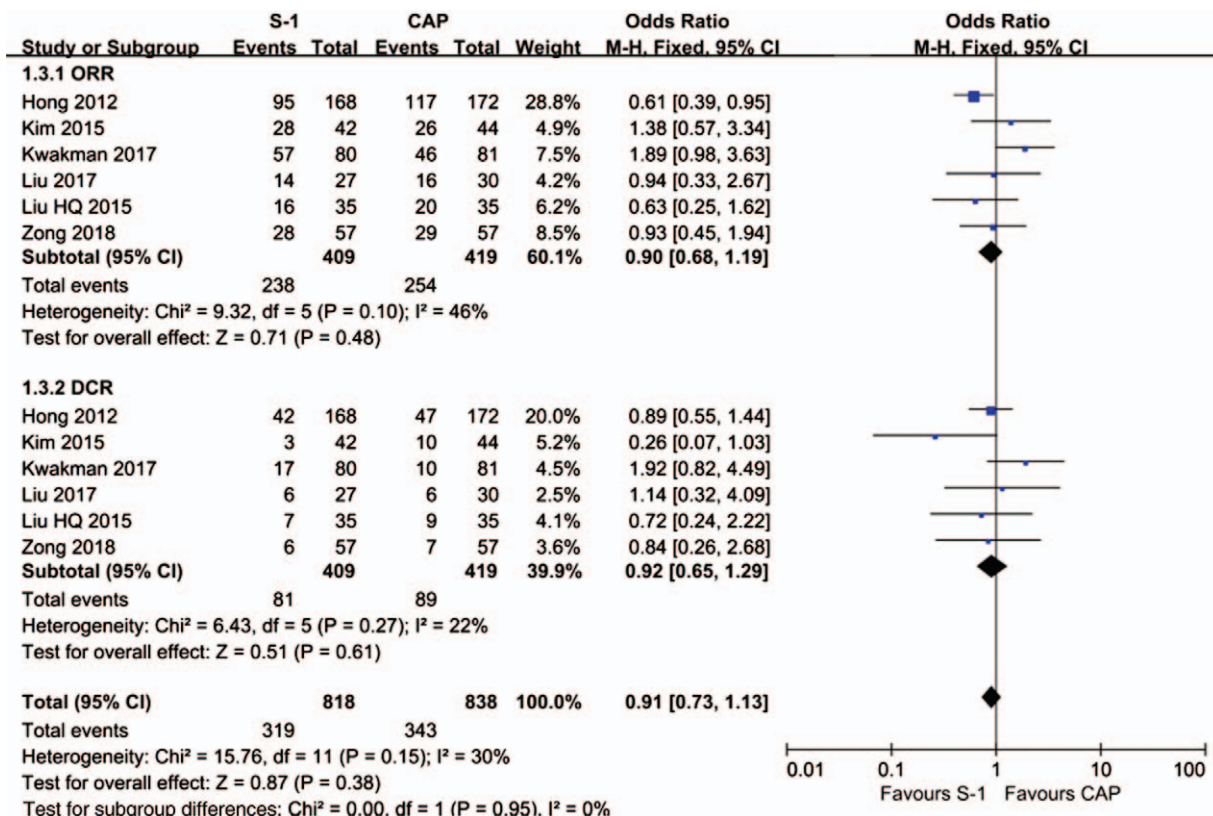


**Figure 4.** Forest plot of the ORs of the ORR and DCR with confidence intervals. DCR = disease control rate, ORR = objective response rate, ORs = odds ratio.
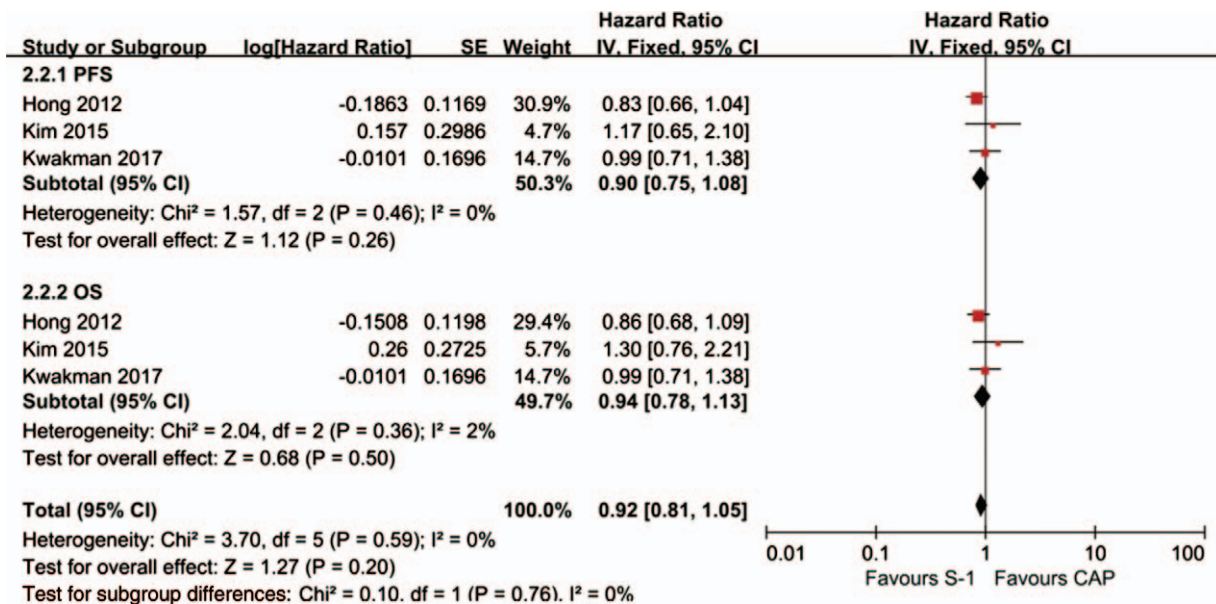
**Figure 5.** Forest plot of the HRs of the PFS and OS with confidence intervals. HRs = hazard ratio, OS = overall survival, PFS = progression-free survival.

remained disputable.[4,12,13] An oral substitution with comparable efficacy and low risk of HFS might be the choice for patients suffering those symptoms.

The present analysis enrolled 6 prospective studies, most of which (5/6) were designed with S-1 based regimens as first-line therapy. Pooled results revealed that efficacy of S-1 based regimens was comparable with capecitabine based regimens. Analysis of the data of the prospective trial showed that the 1-year and 2-year survival rates were 73.6% and 39.1% in the S-1

plus oxaliplatin group, and 73.8% and 37.8% in the XELOX group, respectively, without statistical difference between the 2 groups (all $P > .05$).[14] However, due to the small size and single center design, it is necessary to confirm the therapeutic effect of S-1 based regimens in patients with mCRC before continuous infusion of fluorouracil.

A previous meta-analysis compared the efficacy and safety between S-1 and capecitabine in patients with aGC and mCRC.[15] The results showed that S-1 based regimens exhibited

**Table 2**

Comparison of the toxicities at all grade between S-1 based regimens and capecitabine based regimens in patients with mCRC.

| Toxicities | Trials | Events in S-1/CAP | P value | OR (95% CI) | Model | Heterogeneity P | $I^2\%$ |
|---|---|---|---|---|---|---|---|
| Leucopenia | 5 | 105/329 109/338 | .91 | 0.98 (0.62, 1.53) | F | .90 | 0 |
| Neutropenia | 2 | 100/210 94/216 | .85 | 0.89 (0.29, 2.75) | R | .02 | 82 |
| Anemia | 4 | 129/294 119/303 | .10 | 1.46 (0.93, 2.28) | F | .46 | 0 |
| Thrombocytopenia | 6 | 152/409 120/419 | .28 | 1.35 (0.79, 2.31) | R | .08 | 50 |
| Vomiting | 6 | 256/409 245/419 | .17 | 1.25 (0.91, 1.70) | F | .61 | 0 |
| Diarrhea | 4 | 154/325 118/332 | .002 | 1.66 (1.21, 2.29) | F | .40 | 0 |
| Oral mucositis | 3 | 25/119 26/122 | .99 | 0.99 (0.53, 1.86) | F | .91 | 0 |
| Stomatitis | 3 | 87/290 61/297 | .21 | 1.55 (0.79, 3.05) | R | .12 | 53 |
| Elevated ALT | 5 | 75/329 76/338 | .90 | 1.02 (0.70, 1.49) | F | .22 | 30 |
| Peripheral neuropathy | 5 | 216/329 178/338 | .26 | 1.66 (0.68,4.02) | R | .003 | 75 |
| HFS | 6 | 83/409 165/419 | .000 | 0.34 (0.24, 0.48) | F | .88 | 0 |

CAP = capecitabine, CI = confidence interval, F = fixed model, HFS = hand-foot syndrome, mCRC = metastatic colorectal carcinoma, OR = odds ratio, R = random model.

**Comparison of the toxicities at high grade between S-1 based regimens and capecitabine based regimens in patients with mCRC.**

| Toxicities | Trials | Events in S-1/CAP | P value | OR (95% CI) | Model | Heterogenity P | $I^2$% |
|---|---|---|---|---|---|---|---|
| Leucopenia | 5 | 12/329 15/338 | .58 | 0.80 (0.36, 1.77) | F | .91 | 0 |
| Neutropenia | 3 | 50/290 31/297 | .80 | 0.69 (0.04, 13.1) | R | .007 | 86 |
| Anemia | 4 | 22/294 18/303 | .45 | 1.29 (0.67, 2.49) | F | .83 | 0 |
| Thrombocytopenia | 6 | 50/409 26/419 | .34 | 1.64 (0.59, 4.59) | R | .06 | 53 |
| Vomiting | 6 | 19/409 26/419 | .31 | 0.73 (0.39, 1.35) | F | .89 | 0 |
| Diarrhea | 4 | 34/325 21/332 | .06 | 1.74 (0.98, 3.08) | F | .77 | 0 |
| Oral mucositis | 3 | 1/119 1/122 | 1.00 | 1.0 (0.06, 16.39) | F | N/A | N/A |
| Stomatitis | 3 | 4/290 2/297 | .46 | 1.72 (0.41, 7.30) | F | .76 | 0 |
| Elevated ALT | 5 | 6/329 15/338 | .07 | 0.44 (0.18, 1.08) | F | .25 | 26 |
| Peripheral neuropathy | 5 | 17/329 17/338 | .94 | 1.03 (0.52, 2.01) | F | .33 | 13 |
| HFS | 6 | 6/409 29/419 | .000 | 0.20 (0.09, 0.48) | F | .96 | 0 |

CAP = capecitabine, CI = confidence interval, F = fixed model, HFS = hand-foot syndrome, mCRC = metastatic colorectal carcinoma, N/A = not applicable, OR = odds ratio, R = random model.

similar efficacy and safety profile compared to capecitabine based regimens, and S-1 was recommended as an alternative for capecitabine for the treatment in patients with aGC and mCRC. However, only 1 literature was included in the mCRC subgroup for the PFS and OS analysis.[16] Therefore, the pooled results of the present study with larger sample size might provide further confirmation of the suggestion.

Dose of the drugs is another factor which may affect the efficacy and safety in RCTs. The dose of S-1 adopted in the majority of studies (5/6) included in the present analysis was 40 mg/m$^2$ twice a day, which was in accordance with the dosage in aGC,[17,18] but was larger than that in the Caucasian population.[19] Several factors may be responsible for the negative efficacy of S-1 in the Caucasian population, such as polymorphic variants of cytochrome P450 (CYP) 2A6. The only included study on Caucasian population showed a beneficial outcome of S-1 compared to capecitabine in patients with mCRC.[20] It might be associated with high expression level of CYP 2A6 in colorectal carcinoma.[21] However, due to the limited data with small sample size of the expression level of CYP 2A6 in colorectal carcinoma, the association of the efficacy of S-1 with CYP 2A6 expression should be investigated further.

For AEs, the incidence of HFS at any grade or high grade was more beneficial for S-1 than capecitabine based regimens. In addition, the incidence of diarrhea was higher in S-1 based regimens compared to capecitabine based regimens, but the risk of diarrhea at high grade was similar between the 2 groups (95% CI: 0.98–3.08, P=.06). Thus S-1 induced diarrhea might be manageable in clinical practice. Furthermore, other AEs including leucopenia, neutropenia, anemia, thrombocytopenia, vomiting, oral mucositis, stomatitis, elevated ALT, or peripheral neuropathy showed no statistical difference between S-1 based regimens and capecitabine based regimens. These data suggest that S-1 might be an alternative candidate of capecitabine, in particular in mCRC patients with a high risk of HFS.

There are certain limitations in the present meta-analysis. First of all, the nature of small sample size of the eligible studies, as well as limited included studies, might cause potential publication bias. Moreover, most of the studies (5/6) included were from Asia. Our conclusions require further confirmation from studies conducted among population from Western countries. Furthermore, some data were not available from individual patients for each study. Finally, heterogeneous results were included.

In conclusion, this meta-analysis suggests that S-1 is associated with comparable efficacy and lower risk of HFS, but a higher incidence of diarrhea compared to capecitabine for the treatment of patients with mCRC. Further well-designed, prospective, randomized, large-scaled clinical trials are required to confirm the efficacy and safety of S-1 in patients with mCRC.
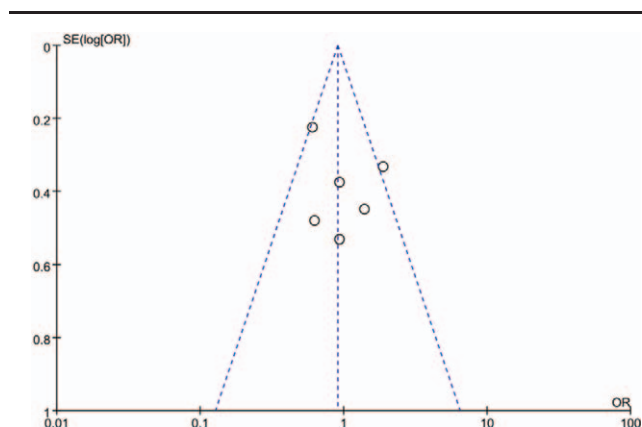


**Figure 6.** Funnel plot for publication bias with ORR. ORR = objective response rate.

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## Author contributions

Conceptualization: Jianxin Chen.
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Formal analysis: Jianxin Chen.
Investigation: Jianxin Chen, Tiancai Xu.
Methodology: Jianxin Chen.
Software: Junhui Wang.
Supervision: Junhui Wang.
Writing – review and editing: Tiancai Xu.

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