Systematic Review and Meta-Analysis

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# Efficacy and safety assessment of S-1-based regimens comparing to intravenous fluorouracil-based ones in Asian patients with metastatic colorectal carcinoma

## A system review and meta-analysis

Jianxin Chen, MD[a], Junhui Wang, MD[b,*]

**Abstract**

**Background:** We performed the present systematic review and meta-analysis to evaluate the efficacy and safety for S-1-based regimens comparing to intravenous fluorouracil-based ones in Asian patients with metastatic colorectal carcinoma (mCRC).

**Methods:** Eligible prospective and controlled randomized clinical trials (RCT) were included, of which data were extracted by inclusion criteria and exclusion ones. Odds ratio (OR) and Hazard ratio (HR) of outcomes including objective response rate (ORR), disease control rate (DCR), progressive-free survival (PFS), overall survival (OS), and adverse events (AEs) were explored for the final analysis between the 2 groups.

**Results:** A total of 23 eligible prospective, controlled RCTs including 2269 patients were enrolled for the pooled analysis. With the meta-analysis of available data, the results of the present research showed that there was no statistical difference on short-term efficacy including ORR (HR = 0.85, 95% CI: 0.71–1.01; $P = .07$) or DCR (HR = 0.88, 95% CI: 0.69–1.11; $P = .27$), as well as long-term efficacy including PFS (HR = 1.00, 95% CI: 0.90–1.11; $P = .98$) or OS (HR = 0.95, 95% CI: 0.82–1.10; $P = .50$). In addition, the incidences of AEs including leucopenia, neutropenia, and vomiting were statistically lower in S-1-based regimens comparing to intravenous fluorouracil-based ones, regardless of all grade or high grade (all $P < .05$). However, there were no significant differences detected among other AEs including anemia, thrombocytopenia, increased alanine aminotransferase concentration, stomatitis, anorexia, diarrhea, hand–foot syndrome (HFS), or sensory neuropathy among the 2 groups (all $P > .05$).

**Conclusions:** The present meta-analysis revealed that S-1-based regimens might be associated with comparable efficacy, as well as lower risk of leucopenia, neutropenia, and vomiting at all/high grade comparing to intravenous fluorouracil-based ones in Asian patients with mCRC.

**Abbreviations:** AE = adverse event, aGC = advanced gastric cancer, CI = confidence interval, DCR = disease control rate, ECOG PS = eastern cooperative oncology group performance status, HFS = hand foot syndrome, HR = hazard ratio, KPS = Karnofsky scores, mCRC = metastatic colorectal carcinoma, OR = odds ratio, ORR = objective response rate, OS = overall survival, PFS = progressive-free survival, RCT = randomized clinical trial.

**Keywords:** Asian, colorectal carcinoma, intravenous fluorouracil, meta-analysis, S-1

## 1. Introduction

With its high incidence and mortality rate, colorectal carcinoma (CRC) has been presented as one of the most severe public issues all over the world.[1] According to the relative data in Asian, there were an estimated 607,000 new cases and 332,000 deaths in 2012.[2] While in China, CRC has emerged as the fifth most common cancer in 2015, which has resulted in 191,000 deaths annually.[3] Regimens containing intravenous fluorouracil and leucovorin combined with either oxaliplatin (also known as FOLFOX) or irinotecan (FOLFIRI) have still been the cornerstone as the treatment in patients with metastatic colorectal carcinoma (mCRC) or advanced disease, though the supplements of targeted agents in selective circumstances, such as bevacizumab and cetuximab may contribute to the regression of tumor as well as the extension of survival time.[4] However, the essential device of an indwelling central venous catheter might brought be with some potential problems, such as thrombosis, infection, as well as lower compliance for patients. Therefore, a more convenient formulation with comparable efficacy instead of intravenous fluorouracil might be a better choice for selective patients.

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*The ethical approval was waived as the present study is a systematic review. This article does not contain any studies with animals performed by any of the authors.*

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S-1, an oral fluoropyrimidine, of which combinative formulation of 3 pharmacological compounds, including tegafur, gimeracil, and oteracil potassium, at a molar ratio of 1:0.4:1, has become an alternative agent and widely used among Asian patients with advanced or metastatic advanced gastric cancer (aGC), breast cancer, and pancreatic carcinoma.[5–7] In recent years, S-1 has also been attempted for the alternative choice during the treatment of mCRC among Asian patients. The clinical research SOFT (Trial Registration Number: JapicCTI-090699), an open-label, non-inferiority, randomized phase 3 trial has been performed in pan-Japan, the results of which revealed that SOX (oxaliplatin, S-1) plus bevacizumab is non-inferior to mFOLFOX6 (oxaliplatin, intravenous fluorouracil, leucovorin) plus bevacizumab in terms of progressive-free survival (PFS) or median survival time (mOS) in patients with mCRC.[8] Furthermore, another non-inferiority, randomized phase 2/3 study, also known as FIRIS (ClinicalTrials.gov Number: 00284258), had been conducted in the same period almost, results of which showed that the mOS was 17.4 months in the FOLFIRI (irinotecan, intravenous fluorouracil, leucovorin) group and 17.8 months in the IRIS (irinotecan, S-1) group (hazard ratio [HR] 0.900; 95% confidence interval (CI) 0.728–1.112). On the basis of that, the investigators recommended that IRIS was non-inferior to FOLFIRI for OS as second-line chemotherapy for mCRC, and IRIS could be an option for second-line chemotherapy of mCRC. In addition, a majority of small scaled prospective trials, which compared the efficacy and safety between S-1-based regimens and intravenous fluorouracil-based ones in Asian patients with mCRC, has reported their results. However, owning to their naturity of small sample size, clinical application value might be limited. Therefore, the meta-analysis and systematic review was conducted to compare the efficacy and safety between agents of S-1 and intravenous fluorouracil in a larger population of Asian patients with mCRC to confirm its value further.

## 2. Patients and materials

### 2.1. Search strategy

A literature review has been developed with the key words, such as "S-1", "colorectal cancer", "fluorouracil", and their synonyms for published, prospective, controlled randomized clinical trials (RCTs), among databases including Medline, Embase, Google Scholar, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Data up to the date of June 28, 2018. The references listed in the included literatures were also reviewed for the possible enrollment. Meeting abstracts were excluded because of the potential insufficiency of the interested data. All procedures during the literature search and screening were conducted by the 2 investigators (by Chen and Wang). The 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 (PRISMA) statement.

### 2.2. Inclusion and exclusion criteria

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

(1) Patients included in the research should be histologically or cytologically diagnosed as metastatic colorectal carcinoma (stage IV), the stage of which can be found when referring to 7th edition of the American Joint Committee on Cancer staging system.[9]
(2) Prospective, controlled RCTs that comparing the efficacy and safety between S-1-based regimens and intravenous fluorouracil-based ones in patients with mCRC conducted in Asian population.
(3) One of the following outcomes should be reported at least: objective response rate (ORR), disease control rate (DCR), progressive-free survival (PFS), overall survival (OS), and adverse events (AEs).

Accordingly, the following exclusion criteria were adopted.

(1) Non-controlled or single-arm researches.
(2) RCTs performed among non-Asian population.
(3) Ongoing clinical trials or researches reported in meeting abstracts without integrated article published.
(4) Any reviews, letter, meta-analysis, case reports or comments.
(5) For repeated published articles or the same study reported during different period, the most complete and updating data was selected with the others excluded.
(6) The language was not in English or Chinese.

### 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 between the 2 reviewers. The essential information extracted from the enrolled studies including first author's names, publication year, regions, number of patients, gender, Eastern Cooperative Oncology Group performance status (ECOG PS) or Karnofsky scores (KPS), treatment schedules, drug exposure, and the outcomes. Outcomes in the present analysis were set as ORR (patients evaluated as partial response or complete response according to the criteria of 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, gastrointestinal reaction, skin, and nervous toxicities.

### 2.4. Quality assessment of included studies

The quality of the included studies was evaluated with the criteria of 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, which were presented with "risk of bias graph" and "risk of bias summary".

### 2.5. Statistical analysis

All the data in the present study were analyzed with software RevMan version 5.3. ORR, DCR, and AEs were calculated with odds ratio (OR). HRs were extracted for the assessment of PFS and OS. Software Engauge and relative methods from literatures were adopted for the extraction of PFS or OS in case of the presentation of K–M curves, rather than HRs reported in selective included researches.[10,11] 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

heterogeneity existed. Random effect model or fixed effect one were applied for the analysis of data of heterogeneous or not. Meta-regression with software STATA version 12.0 was conducted to evaluate the influence of the duration of drug exposure on the ORR. Each AE at all grades and at high grade was pooled analyzed and presented in a same forest plot. Random effect model was used for the conflicting results of heterogeneity detection between AE at all grades and high grade as the consideration for a cautious and conservative result. Potential publication bias was detected with funnel plot in software RevMan 5.3.

### 2.6. Ethical approval

The ethical approval was waived as the present study is a systematic review. This article does not contain any studies with animals performed by any of the authors.

## 3. Results

### 3.1. Literature search

Our database search retrieved 828 publications, from which 447 articles were selected after duplicates deleted. With the screening of the abstracts, 42 prospective, controlled clinical trials were absorbed for the potential enrollment. After full text carefully reviewed, a total of 23 available researches including 2269 patients were considered eligible for the final analysis. A flow diagram which detailed the selection of included studies was presented in Figure 1.

All the included clinical trials were performed during the period from 2011 to 2017. There were 4 studies conducted in Japan and the remaining 19 in China. The performance status of the included patients was 0 to 2 according to ECOG PS or KPS ≥70. All patients included had received S-1-based regimens or intravenous fluorouracil-based ones for the treatment. There

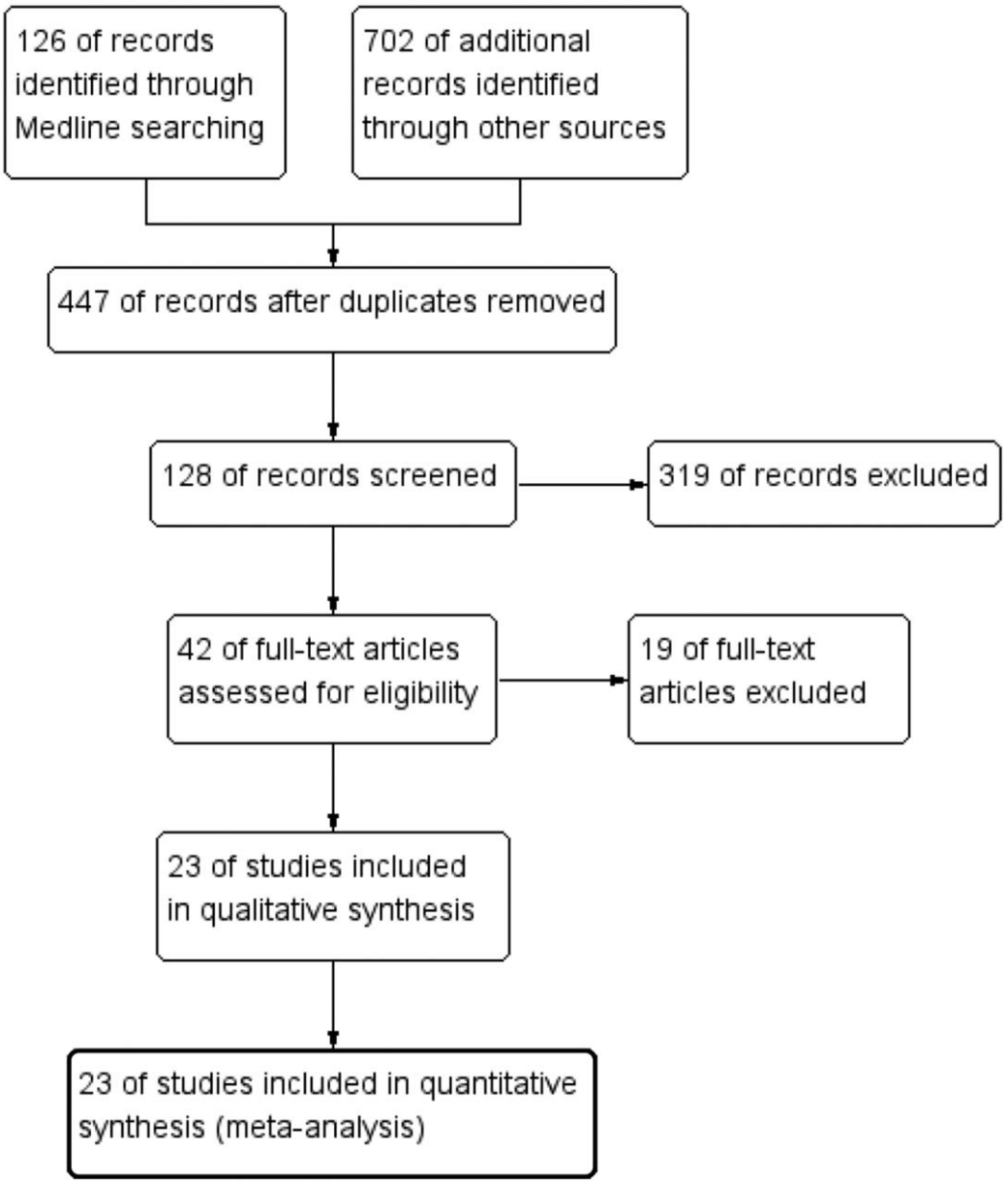


**Figure 1.** Study selection procedure with PRISMA flow diagram. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

**Table 1**

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

| Author yr | Region | Numbers (Arm I/Arm II) | Gender (male/female) (Arm I/Arm II) | ECOG PS/KPS | Regimens (Arm I/Arm II) | Outcomes | Drug exposure (weeks) |
|---|---|---|---|---|---|---|---|
| Baba 2017[8,12] | Japan | 256/255 | 170/86<br>159/96 | 0–1 | Bev+SOX<br>Bev+FOLFOX | ORR/DCR/PFS/OS/AE | 24/24 |
| Cai XD 2013[13] | China | 30/28 | 17/13<br>15/13 | 0–2 | SOX<br>FOLFOX | ORR/DCR | 12–18/18–36 (range) |
| Chen XM 2017[14] | China | 43/43 | 27/16<br>25/18 | 0–2 | SOX<br>FOLFOX | ORR/DCR/1-year SR/ AE | NR |
| Gao F 2016[15] | China | 57/57 | 39/18<br>37/20 | NR | SOX<br>FOLFOX | ORR/DCR/1,2-year SR | 6/8 |
| Gao YL 2013[16] | China | 31/33 | 19/12<br>19/14 | KPS>70 | IRIS<br>FOLFIRI | ORR/DCR/AE | NR |
| Han MY 2016[17] | China | 37/37 | 21/16<br>19/18 | NR | SOX<br>FOLFOX | ORR/DCR/AE | 6/4 |
| Hu YB 2015[18] | China | 20/23 | NR | KPS>80 | SOX<br>FOLFOX | ORR/DCR/AE | 24–30/24–30 (range) |
| Kato 2012[19] | Japan | 30/30 | 17/13<br>18/12 | 0–1 | Bev+IRIS<br>Bev+FOLFIRI | ORR/DCR/PFS/AE | 12/12 |
| Kong TD 2014[20] | China | 30/30 | 20/10<br>22/8 | 0–1 | SOX<br>FOLFOX | ORR/DCR/ | NR |
| Li AM 2017[21] | China | 45/45 | 25/20<br>26/19 | NR | SOX<br>FOLFOX | ORR/DCR/1-year SR/AE | NR |
| Liu Y 2014[22] | China | 23/23 | 30/16 for all | KPS>70 | SOX<br>FOLFOX | ORR/DCR/1,2-year SR/AE | 12–18/12–24 (range) |
| Li X 2015[23] | China | 22/21 | 24/19 for all | 0–2 | SOX<br>FOLFOX | ORR/DCR/AE | NR |
| Ning J 2017[24] | China | 29/29 | 20/9<br>15/14 | 0–2 | SOX<br>FOLFOX | ORR/DCR/PFS/AE | 15/16 |
| Tian SM 2011[25] | China | 25/24 | NR | 0–1 | IRIS<br>FOLFIRI | ORR/DCR/PFS/AE | 19.6/14.6 (mean) |
| Wang XL 2012[26] | China | 18/18 | 20/16 for all | KPS>70 | SOX<br>FOLFOX | ORR/DCR/AE | 16/16 |
| Wang Y 2013[27] | China | 22/21 | 12/10<br>12/9 | 0–2 | SOX<br>FOLFOX | ORR/DCR/AE | NR |
| Xie M 2013[28] | China | 23/22 | 16/7<br>14/8 | 0–2 | SOX<br>FOLFOX | ORR/DCR/AE | 12/12 |
| Xiong RH[29] 2012 | China | 35/30 | 21/14<br>19/11 | 0–2 | SOX<br>FOLFOX | ORR/DCR/AE | 12–18/16–24 (range) |
| Yamazaki 2015[30] | Japan | 56/49 | 33/23<br>23/26 | 0–1 | SOX<br>FOLFOX | ORR/DCR/PFS/OS/AE | 24/22 |
| Yang K 2013[31] | China | 30/28 | NR | NR | IRIS<br>FOLFIRI | ORR/DCR/AE | NR |
| Yasui 2015[32–34] | Japan | 213/213 | 120/93<br>123/90 | 0–1 | IRIS<br>FOLFIRI | ORR/PFS/OS/AE | 16/16 |
| Zhang JS 2015[35] | China | 45/44 | 30/15<br>28/16 | 0–2 | SOX<br>FOLFOX | ORR/DCR/AE | 15/20 |
| Zhong LX 2014[36] | China | 24/22 | 31/15 for all | KPS>70 | SOX<br>FOLFOX | ORR/DCR/AE | NR |

AE = adverse event, Bev = bevacizumab, DCR = disease control rate, ECOG PS = eastern cooperative oncology group performance status, FOLFIRI = irinotecan + fluorouracil + calcium folinate, FOLFOX = oxaliplatin + fluorouracil + calcium folinate, IRIS = irinotecan + S-1, N/R = not reported, ORR = objective response rate, OS = overall survival, PFS = progressive-free survival, Ref = references, SOX = S-1 + oxaliplatin.

display the characteristics of including trials with respect to essential data in Table 1.

### 3.2. Quality assessment of the included studies

With the performance of quality evaluation within the criteria of Cochrane Collaboration's tool for assessing risk of bias of RCTs, 2 in 23 studies did not specifically report the methods of randomization in the article, and 1 study denied the disposition of randomization. Most of the included studies (22/23) were not developed with masking because of the comparison between oral based regimens and infusion ones. However, the bias of blinding of participants and outcomes were evaluated as low risk according to the reviewers' decision, as the blinding was not considered influence the outcomes significantly. As interesting data including ORR, DCR, PFS, OS, and AEs been selected and pooled analyzed in the present study, any deficiency of the data seemed as selective reporting. As a result, 14 in 23 studies were evaluated as reporting bias. Risk of bias summary and risk of bias graph were presented in Figure 2 and Figure 3.

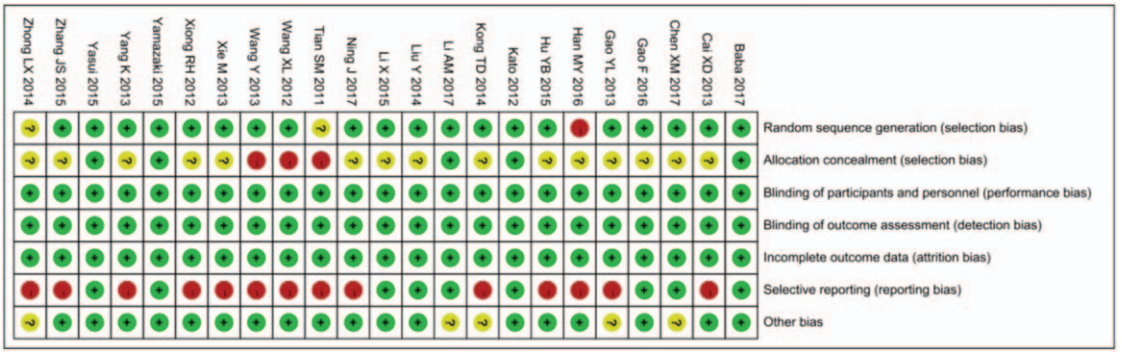


**Figure 2.** Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

### 3.3. Short-term efficacy

The pooled odds ratio (OR) for ORR was 0.85 (95% CI: 0.71–1.01; $P=.07$). Statistical difference was not detected between drug combinations (S-1 combined with oxaliplatin or irinotecan). Results of ORR with heterogeneity evaluation between subgroups with $I^2$ test showed no statistical heterogeneity ($I^2=0\%$, $P=.98$) (Fig. 4). In addition, the result of meta-regression conducted to evaluate the influence of the duration of drug exposure on ORR did not reveal significant difference ($P=.059$, 95% CI: 0.919–1.002).

The pooled OR for DCR was 0.88 (95% CI: 0.69–1.11; $P=.27$). Statistical difference was not detected between drug combinations (S-1 combined with oxaliplatin or irinotecan). Results of DCR with heterogeneity evaluation between subgroups with $I^2$ test showed no statistical heterogeneity ($I^2=0\%$, $P=.96$) (Fig. 5).

### 3.4. Long-term efficacy

The pooled HR for PFS was 1.00 (95% CI: 0.90–1.11; $P=.98$, Fig. 6). The pooled HR for OS was 0.95 (95% CI: 0.82–1.10; $P=.50$, Fig. 7). Results of heterogeneity evaluation with $I^2$ test showed no statistical heterogeneity. ($I^2=7\%$, $P=.37$ for PFS, $I^2=0\%$, $P=.72$ for OS, Respectively).

### 3.5. Adverse events

Comparative pooled analysis for AEs at any grade and high grade between S-1-based regimens and intravenous fluorouracil-based ones was developed among all the including studies. All the relative figures of forest plots were presented in the Appendix, http://links.lww.com/MD/D31.

As for pooled analysis of hematological toxicities, the incidences of leucopenia at all grade, as well as high grade were more frequent in intravenous fluorouracil-based regimens comparing to S-1-based ones, ORs of which were 0.57 (95% CI: 0.47–0.70; $P<.00001$) for all grade and 0.68 (95% CI: 0.50–0.92; $P=.01$) for high grade. The incidences of neutropenia at all grade and high grade were more severe in intravenous fluorouracil-based regimens comparing to S-1-based ones, ORs of which were 0.52 (95% CI: 0.41–0.66; $P<.00001$) for all grade and 0.38 (95% CI: 0.29–0.49; $P<.00001$) for high grade. In addition, there is no statistical difference for incidences of AEs including anemia, thrombocytopenia, or increased alanine aminotransferase concentration at all/high grade between S-1-based regimens and intravenous fluorouracil-based regimens (all $P>.05$, forest plots were presented in the Appendix, http://links.lww.com/MD/D31).

In terms to gastrointestinal reaction, the incidences of vomiting at all grade, as well as high grade were lower in S-1-based regimens comparing to intravenous fluorouracil-based ones, ORs of which were 0.33 (95% CI: 0.20–0.54; $P<.00001$) for all grade and 0.29 (95% CI: 0.17–0.51; $P<.0001$) for high grade. Besides, no significant difference was found between the 2 groups for the incidences of AEs including stomatitis, anorexia, or diarrhea (all $P>.05$, forest plots were presented in the Appendix, http://links.lww.com/MD/D31).

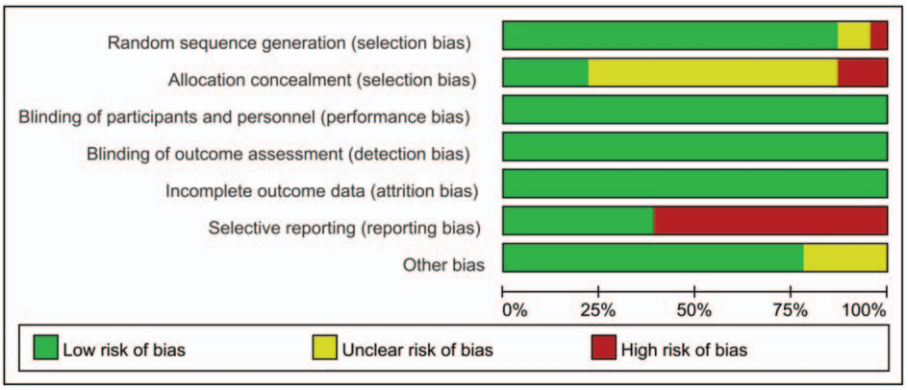


**Figure 3.** Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages among all included studies.

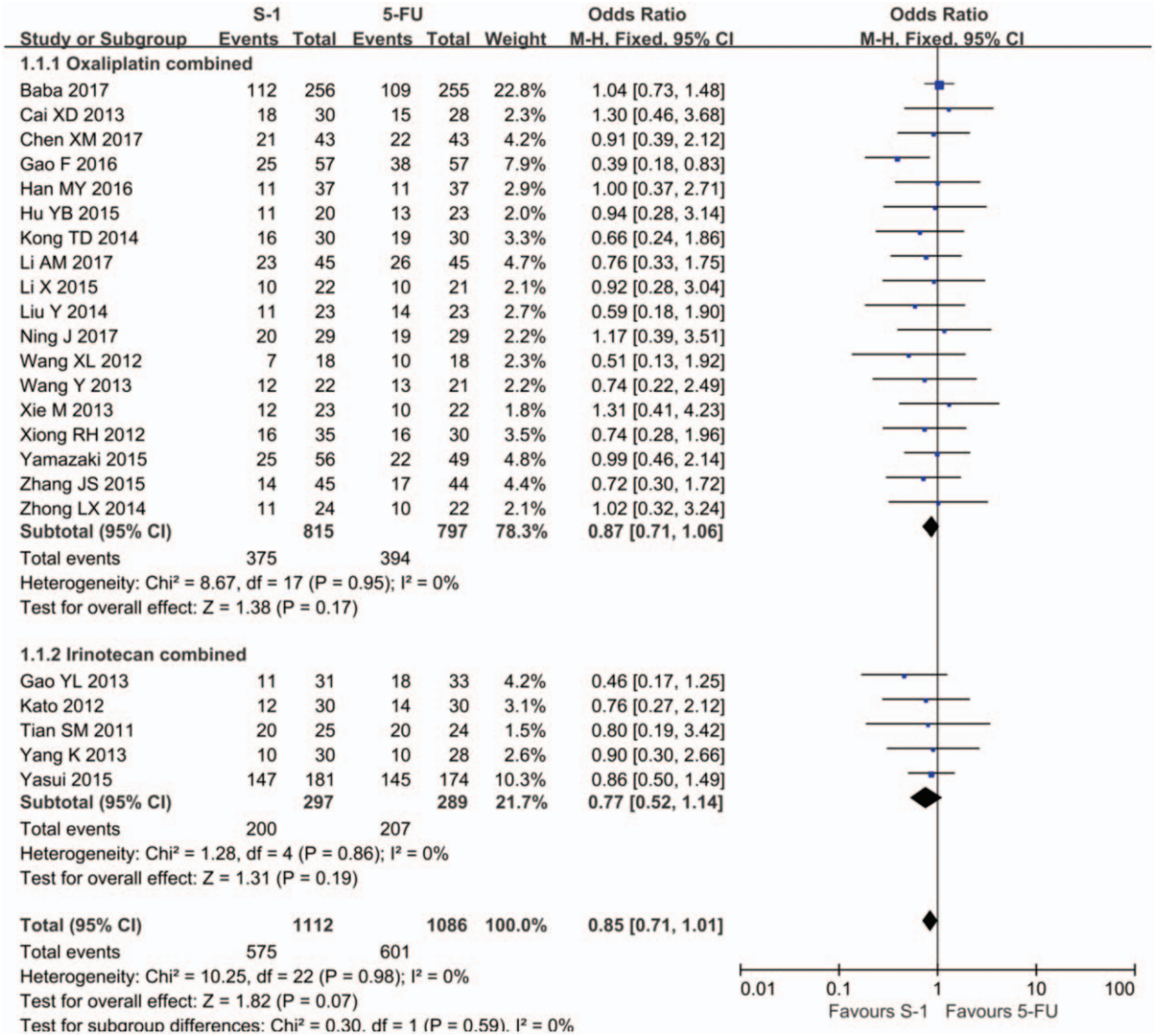


**Figure 4.** Forest plot of the odds ratio of ORR with their confidence intervals by subgroups combined with oxaliplatin or irinotecan. ORR = objective response rate.

Furthermore, the incidences of skin and nervous toxicities at all/high grade between the 2 groups were also assessed and pooled counted. However, the corresponding results revealed that there is no statistical difference between the 2 regimens whether of hand foot syndrome (HFS) or sensory neuropathy ($P > .05$), forest plots of which were shown in the Appendix, http://links.lww.com/MD/D31.

### 3.6. Publication bias

Funnel plot with ORR did not reveal a significant publication bias according to Figure 8.

## 4. Discussion

To the best of our knowledge, the present systematic review and meta-analysis are the most updating and largest scaled study conducted to compare the efficacy and safety of S-1-based regimens and intravenous fluorouracil-based ones in Asian patients with mCRC. A total of 23 eligible prospective, controlled clinical studies including 2269 patients were enrolled for the pooled analysis. With the meta-analysis of available data, the present research showed that there was no statistical difference on short-term efficacy including ORR (HR = 0.85, 95% CI: 0.71–1.01; $P = .07$)) or DCR (HR = 0.88, 95% CI: 0.69–1.11; $P = .27$), as well as long-term efficacy including PFS (HR = 1.00, 95% CI: 0.90–1.11; $P = 0.98$) or OS (HR = 0.95, 95% CI: 0.82–1.10; $P = .50$). In addition, the incidence of AEs including leucopenia, neutropenia, and vomiting were more statistically lower in S-1-based regimens comparing to intravenous fluorouracil-based ones, regardless of all grade or high grade. However, there is no significant difference detected among other AEs including anemia, thrombocytopenia, increased alanine aminotransferase concentration, stomatitis, anorexia, diarrhea, HFS, or sensory neuropathy among the 2 groups. With the reported results in the present pooled analysis, S-1-based regimens might be also recommended in the treatment of mCRC, especially in elder patients or that with poor performance status, in which insufficient marrow reserve might be more incidental.

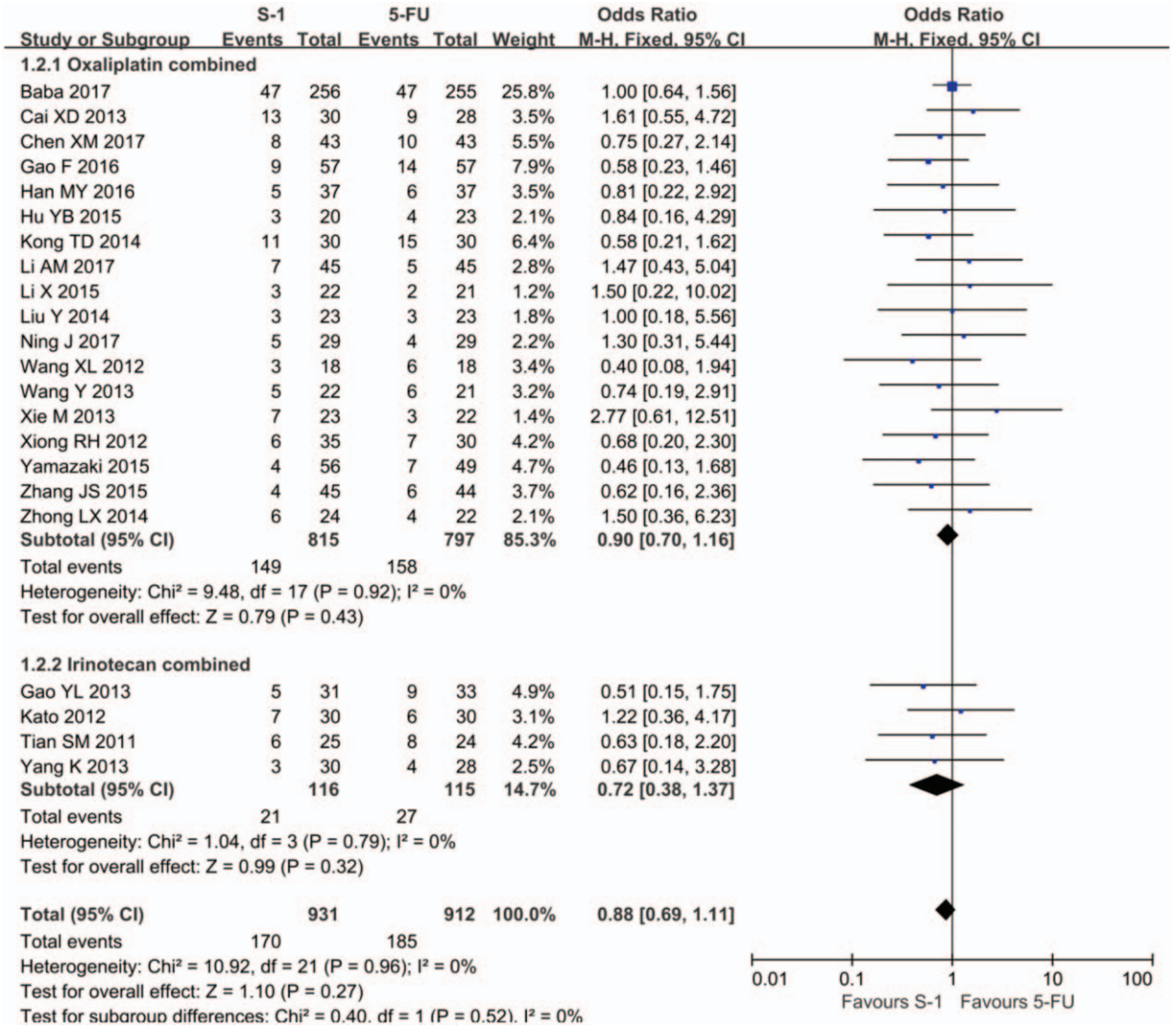


**Figure 5.** Forest plot of the odds ratio of DCR with their confidence intervals by subgroups combined with oxaliplatin or irinotecan. DCR = disease control rate.

Exactly, a pooled analysis focus on the similar issue had been reported in 2014 by YE, in which efficacy and safety of S-1-based regimens were also been compared with 5-fluorouracil-based ones.[37] However, the most updating outcomes of 2 landmark researches (SOFT and FIRIS) had not been reported then, especially the long-term efficacy such as PFS and OS, which might bring with meaningful missing data during the pooled analysis.[8,32] In addition, approximate twice trials were performed in the past 4 years, which have been supplemented in the present study. On the basis of which, the compiled analysis of all the available studies in the present meta-analysis might be more credible and dependable. In hence, we think it might be

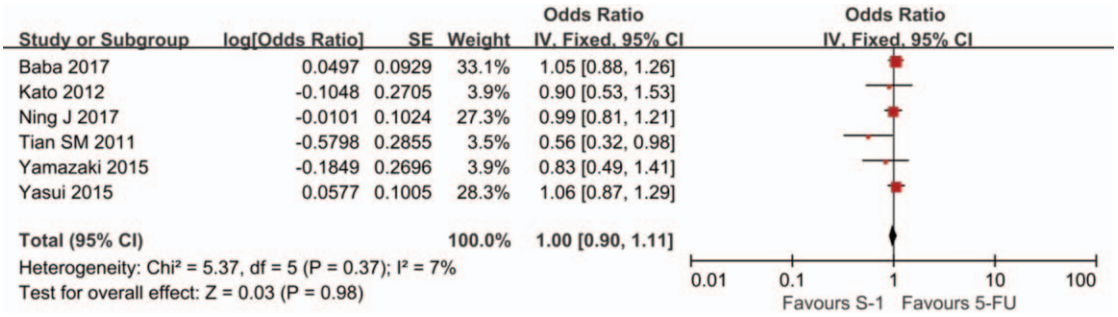


**Figure 6.** Forest plot of the HR of PFS with their confidence intervals. HR = hazard ratio, PFS = progressive-free survival.

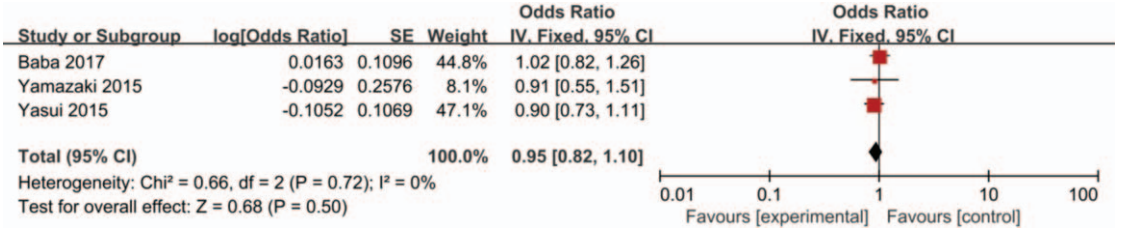


**Figure 7.** Forest plot of the HR of OS with their confidence intervals. HR = hazard ratio, OS = overall survival.

necessary to conduct the updating systematic review and meta-analysis.

According to the results, short term efficacy including ORR and DCR, which reflect the status of tumor regression, were reported among most of the included literatures. No statistical difference was detected between the 2 groups with a fixed model, which was considered as a more precise method comparing to random model in data with no heterogeneity. In terms to that, selective patients who received chemotherapy and/or targeted drugs as conversion therapy, that might have an opportunity to receive radical surgery further, may also be suitable to receive S-1-based regimens for the alternative choice. However, dose intensity of targeted agents including bevacizumab and cetuximab should be also modified to fit the 3-week regimen such as SOX. Long term efficacy covering PFS and OS was reported in 6 literatures merely in the present research; pooled results of the restricted data did not show any significant difference among the 2 groups. Nevertheless, the missing of the interested data might lead to attrition and reporting bias according to the evaluation of bias (Fig. 3), though no heterogeneity was found with a $Q$-test. In hence, further evaluation of long term efficacy between the 2 groups should be better to performing to reconfirm the conclusion in the future.

Dose of the S-1 used in the research is another factor which would affect the efficacy and safety profile in RCTs affirmatively. The dose of S-1 adopted in the most literatures included in present analysis was ranging from 40 to 60 mg/m$^2$ twice a day according to body surface area (BSA) ranging from 1.25 to 1.5 m$^2$, respectively, which was in accordance with the dosage used in patients with aGC.[38,39] It should be pointed out that the dose intensity used in Asian patients was larger than that in Caucasian population because of the diverse expression of polymorphic variants of cytochrome P450 (CYP) 2A6 between the races.[40] On account of that, the present systematic study focused on the Asian patients merely to reduce the population bias. Even so, because all the included studies were conducted in China and Japan, the conclusion of the present pooled results might be value-limited among the countries in South and West Asian.

As another oral analogous agent of fluorouracil, capecitabine has already been recommended as an alternative agent during the treatment of mCRC according to guidelines from National Comprehensive Cancer Network (NCCN).[41] However, high risk of HFS with its shortage of specific therapeutic strategies has greatly limited its clinical application.[42] HFS, a kind of skin toxicity, always 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.[43] Although several researches had attempted to release the symptom with kinds of drugs including cyclooxygenase-2 (COX-2) inhibitor,

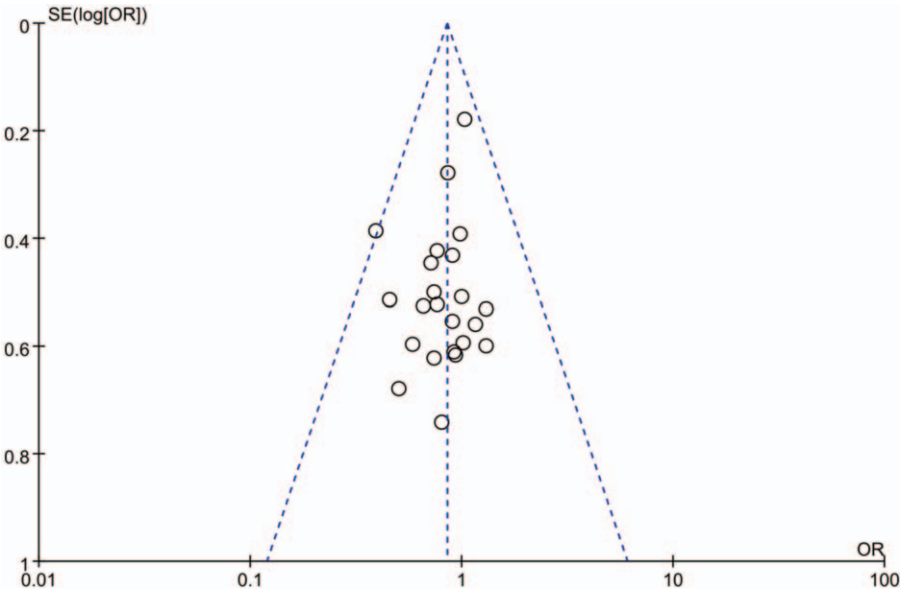


**Figure 8.** Funnel plot for publication bias with ORR. ORR = objective response rate.

lactic acid, and pyridoxine, the efficacy of which still remains disputable.[44–46] However, the incidence of HFS was similar between S-1 and intravenous fluorouracil according to pooled outcome presented in Appendix, http://links.lww.com/MD/D31 in the present study. Therefore, in terms to HFS, S-1 might have an advantage over capecitabine in the treatment of mCRC, which need well-designed, head-to-head, prospective trials to confirm further.

Of note, there are significant advantages for AEs of S-1-based regimens comparing to intravenous fluorouracil-based ones, especially in myelotoxicities, such as leucopenia and neutropenia according to the pooled analysis in the present study. In addition, the incidence of vomiting was milder in group treated with S-1, though with an oral delivery administration. Therefore, S-1-based regimens might be recommended to replace intravenous fluorouracil-based ones for elderly patients, poor performance status (PS = 2), and the ones who had suffered previous heavy treatment.

There were certain limitations in the present meta-analysis. First of all, the nature of small sample size in the majority of eligible researches, might bring with publication bias, which would limit the value of the conclusion in present analysis. Moreover, all of the included studies were performed in China and Japan, the conclusions of the present pooled results might be value-limited among the countries in the other areas of Asian, such as South and West Asian. Furthermore, interesting data was not obtained from individual patients for each research, which would have resulted in a comprehensive analysis. Finally, heterogeneous results were included. Pooled results of the present study might be influenced by events such as S-1-based regimens and the duration of the drug exposure. Although regimens included in the present study were specified by stratifying to identify the impact for the final pooled results, the discrepancy of the duration of drug exposure might also affect the pooled outcomes, which seemed intricate. Although the result of meta-regression, which conducted to evaluate the influence of duration of drug exposure on the efficacy assessment, did not reveal statistical affection of that ($P = .059$), however, only 15/23 included literatures reported the duration of the drug exposure, which might bring with another potential controversy. As it is known that, duration of the treatment might be determined by the drug toxicities, tolerance of the patients, and stage of the disease. In reverse, outcomes including efficacy of the treatment, survival time of the patients, and AEs may also be influenced by different duration of the treatment, which might lead to another potential bias of the results in the present study.

In summary, the present meta-analysis revealed that S-1-based regimens might be associated with comparable efficacy, as well as lower risk of leucopenia, neutropenia, and vomiting at all/high grade comparing to intravenous fluorouracil-based ones in Asian patients with mCRC. However, a well-designed, multi-center, population-crossed, prospective, randomized, and large-scaled clinical trial is required to reconfirm the efficacy and safety profile of S-1 further.

## Author contributions

JXC designed the study and wrote this manuscript. JHW retrieved database and reviewed the studies. JXC and JHW extracted data and performed the analysis. All of the authors have read and approved the final manuscript.

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