Aidi injection combined with chemotherapy in the treatment of cancer patients: a systematic review of systematic reviews and meta-analyses

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The objective of the study was to evaluate and summarize the evidence from systematic reviews and meta-analyses regarding the efficacy and safety of Aidi injection combined with chemotherapy in the treatment of cancer patients. PubMed, EMBASE, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Chong qing VIP databases, and Wanfang databases were searched for systematic reviews/meta-analyses on the topic of Aidi treating cancer patients published from inception to 20 December 2020. Google Scholar and OpenGrey were searched for grey literature and International Prospective Register of Systematic Reviews for ongoing reviews. Two investigators independently selected eligible studies, extracted data, and assessed the methodological quality of included systematic reviews/meta-analyses using the measurement tool to assess systematic reviews 2 (AMSTAR-2) tool, and the strength of evidence was assessed with the grade of recommendation,assessment, development, and evaluation (GRADE) system. Twenty-seven systematic reviews/meta-analyses were identified in the study. The methodological quality of all 27 systematic reviews/meta-analyses were critically low when evaluated by AMSTAR-2, and the evidence quality of all outcomes rated as either low or very low based on the GRADE system. The available evidence is currently insufficient to support or refute the use of Aidi in the treatment of cancer patients, thus high-quality trials with large sample sizes are needed to explore its efficacy and safety in cancer patients. *Anti-Cancer Drugs* **32: 991–1002 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Cancer is a serious public health problem and has emerged as a leading cause of death globally [1]. Patients with advanced stage usually lose the opportunity for surgical therapy, and chemotherapy is then a major treatment option for disease control [2]. Chemotherapy drugs not only kill tumor cells, but also kill normal tissue cells, thereby they can lead to series of toxic side effects, such as hepatoxicities and gastrointestinal toxicities [3]. Chemotherapy-induced toxicities can decrease the medication adherence, result in poor quality of life (QOL), and increase the risk of chemotherapeutic failure [4]. Therefore, how to improve the efficacy and safety of chemotherapy has become an important issue for clinicians.

In China, there has been a long history of using traditional Chinese medicine (TCM) as one kind of adjuvant medicine, combined with chemotherapy in practice for the treatment of cancer patients [5]. Aidi injection, a TCM, is an extraction obtained from astragalus, ginseng, cantharis, and acanthopanax, with many pharmacological activities, including anti-tumor activity, enhancement of immunity, and relief of chemotherapy-related toxicities [6]. In recent years, the application of Aidi combined with chemotherapy has been widely used in the treatment of lung cancer, primary liver cancer, gastric carcinoma, and colorectal cancer, and there have been a number of systematic reviews and meta-analyses on the effect of Aidi combined with chemotherapy for cancer patients [7–33]. However, the treatment benefits of Aidi combined with chemotherapy for cancer patients are still unclear due to the differences of methods, and quality of systematic reviews/meta-analyses. Thus, we conduct an overview to evaluate the methodological quality of the systematic reviews/meta-analyses and describe the quality of evidence on their outcomes [7–33], in order to identify the effect of Aidi in cancer treatment and to provide advices for future research.

Methods

Inclusion criteria

Type of studies. Studies were systematic reviews or meta-analyses written in English or Chinese.

Population. Cancer patients.

Intervention. Patients in the intervention group were given Aidi combined with chemotherapy.

Comparison. Patients in the control group were given chemotherapy alone.

Outcomes. The outcomes investigated included tumor response, survival, QOL, and adverse events. Tumor response were evaluated according to response evaluation criteria in solid tumors or WHO. Indicators used were complete response (CR), partial response (PR), stable disease, and progressive disease. The objective response rate (ORR) was equal to CR plus PR, and the disease control rate (DCR) was equal to CR plus PR and stable disease. The survival was assessed using 1-year overall survival rate (one-year overall survival rate). According to Karnofsky Performance Status (KPS) scale, QOL was considered to be improved if KPS score increased 10 points or higher after treatment. Adverse events were including leukopenia, thrombocytopenia, anemia, gastrointestinal reaction, hepatotoxicity, and nephrotoxicity according to the WHO or common terminology criteria for adverse events version.

Exclusion criteria

We excluded literature reviews (non-systematic reviews/meta-analyses), case reports, animal studies, data, or the full text are unavailable.

Literature search strategy

We searched PubMed, EMBASE, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Chong qing VIP databases, and Wanfang databases for all systematic reviews/meta-analyses on the topic of Aidi combined with chemotherapy in treating cancer patients from inception to 20 December 2020. The following search terms included Aidi injection, Aidi, cancer, malignancies, transcatheter arterial chemoembolization, and chemotherapy. We also investigated google scholar, OpenGrey, International Prospective Register of Systematic Reviews, and the reference lists of primary included systematic reviews/meta-analyses to find the other eligible studies. The search was limited to articles published in English and Chinese. Two investigators performed the literature search independently, and any discrepancies were resolved with the third investigator.

Study selection

Two investigators independently selected the eligible studies based on the inclusion and exclusion criteria. Any disagreements were resolved through discussion and consultation with a third investigator.

Data extraction

Two investigators, respectively, extracted data from the eligible studies. The items extracted from each study included first author, publication year, tumor types, numbers of included trials and participants, number and design of included primary studies, quality assessment methods, intervention and comparator summary, and outcomes of each included reviews.

Quality assessment

Two investigators separately evaluated the methodological quality of included systematic reviews/meta-analyses by using the measurement tool to assess systematic reviews 2 (AMSTAR-2) assessment [34], which contains 16 items. From 16 items, 7 of them were critical items (items: 2, 4, 7, 9, 11, 13, and 15). The situation of each item should be fully considered and categorized into four levels, namely, high, moderate, low, and critically low. Any disagreements were resolved by discussion and adjudication by a third investigator.

Quality evaluation of evidence

Two investigators independently use the grade of recommendation,assessment, development, and evaluation (GRADE) system (pro 3.2 Software) to assess the evidence quality of related outcomes and classifies evidence quality into four levels: high, moderate, low, and very low [35]. Randomized Controlled Trial (RCT) was set as the high quality, but five factors could reduce the quality of evidence, including risk of bias (RoB), inconsistency, indirectness, imprecision, and other considerations. Any disagreements were resolved by discussion and consultation with a third investigator.

Results

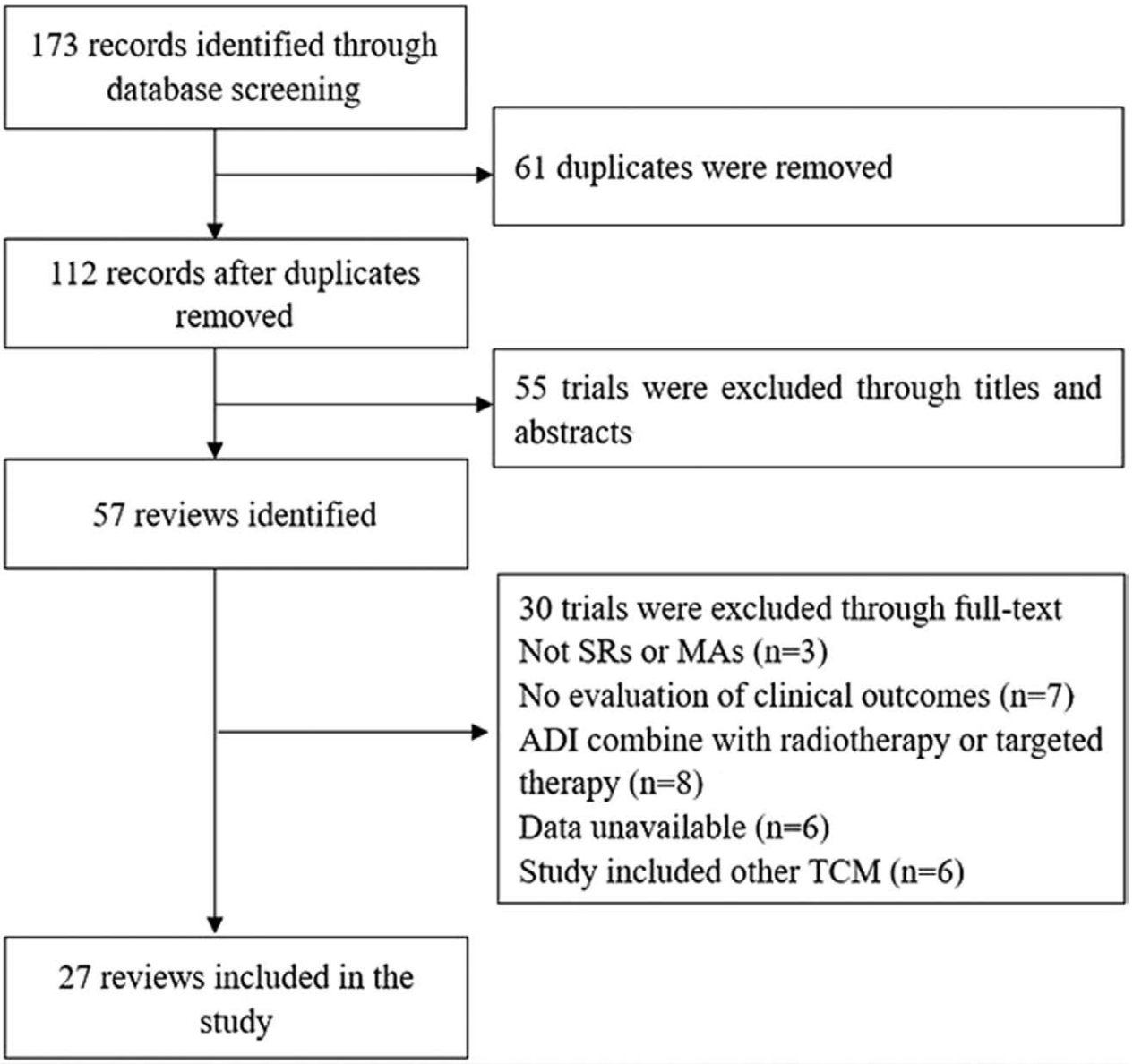
Study selection

A total of 173 studies were identified through database searching, and 61 duplicated studies were identified and removed. After screening the titles and abstracts of the remaining 112 records, 55 records were excluded because of irrelevant topic. Thus, 57 potentially studies were selected for full-text screening. Of these, 30 articles were excluded for the following reasons: studies were not systematic reviews/meta-analyses ($n=3$) [36–38]; studies did not evaluate clinical outcomes ($n=7$) [39–45]; Aidi combine with radiotherapy or targeted therapy ($n=8$) [46–53]; data unavailable ($n=6$) [54–59]; and studies included other TCM ($n=6$) [60–65]. Finally, a total of 27 systematic reviews/meta-analyses were included in this overview [7–33]. The study selection process is presented in Fig. 1.

Characteristics of included studies

The 27 systematic reviews/meta-analyses included in our study were published between 2009 and 2020. Of these, 12 of them were published in English language [7–18], and the remaining 15 were published in Chinese language [19–33]. The tumor types including lung cancer,

Fig. 1



PRISMA flowchart of study selection for inclusion in systematic review. PRISMA, preferred reporting items for systematic reviews and meta-analyses; TCM, traditional Chinese medicine.

colorectal cancer, malignant lymphoma, hepatic carcinoma, gastric carcinoma, and ovarian cancer. The number of RCTs included in each review ranged from 7 to 80, and the total participants ranged from 453 to 6279. The outcomes investigated included tumor response, survival, QOL, and adverse effects. Regarding the quality assessment tool, a total of 21 systematic reviews/meta-analyses used Cochrane RoB tool [7,8,10–13,15–20,22–26,28–30,33], 3 systematic reviews/meta-analyses used the Jadad score [21,27,32], 1 study used both Cochrane RoB tool and Jadad score [31], and 1 meta-analysis used both Cochrane RoB and methodological section of CONSORT statement to evaluate the quality of the included RCTs [14]. But one meta-analysis have not presented the details of quality assessment [9]. The main characteristics of included reviews are listed in Table 1.

Quality of included studies

According to AMSTAR-2 classification, the overall quality of the systematic reviews/meta-analyses was critically low with all studies identified as having more than one critical flaw with or without noncritical weakness. All systematic

Table 1 Characteristics of included reviews

Systematic reviews/ meta-analyses (Refs.)	Tumor types	No. patients	No. included studies	Quality evaluation tool	intervention group	Control group	Outcomes	Meta-analysis conducted?
Xiao *et al.* (2020a) [7]	Lung cancer	6279	80 RCTs	Cochrane RoB	Aidi + Chemotherapy	Chemotherapy alone	①②⑨⑩	Yes
Xiao *et al.* (2020) [8]	NSCLC	4053	54 RCTs	Cochrane RoB	Aidi + NP	NP alone	①②③④⑤⑥⑦⑧⑨⑩	Yes
Wang *et al.* (2016) [9]	Malignant lymphoma	513	8 RCTs	NA	Aidi + CHOP	CHOP alone	①③⑤⑥	Yes
Zhao *et al.* (2016) [10]	NSCLC	1012	12 RCTs	Cochrane RoB	Aidi + NP	NP alone	①③⑤⑥⑦⑧	Yes
Chen *et al.* (2018) [11]	Hepatic carcinoma	1611	22 RCTs	Cochrane RoB	Aidi + TACE	TACE alone	①③④⑤⑧⑨	Yes
Xiao *et al.* (2018a) [12]	NSCLC	2837	36 RCTs	Cochrane RoB	Aidi + Docetaxel-based chemotherapy	Docetaxel-based chemotherapy	①②③⑤⑥⑦⑧⑨⑩	Yes
Dai *et al.* (2018) [13]	Hepatocellular carcinoma	774	20 RCTs	Cochrane RoB	Aidi + TACE	TACE alone	①③④⑤⑧⑨	Yes
Wang *et al.* (2015) [14]	Gastric carcinoma	1927	32RCTs	Cochrane RoB + CONSORT statement	Aidi + Chemotherapy	Chemotherapy alone	①②③④⑤⑥⑦⑧⑨⑩	Yes
Xiao *et al.* (2016) [15]	NSCLC	1390	17 RCTs	Cochrane RoB	Aidi + Platinum-based chemotherapy	Platinum-based Chemotherapy alone	①②	Yes
Xiao *et al.* (2017) [16]	NSCLC	2582	36 RCTs	Cochrane RoB	Aidi + GP	GP alone	①②③⑤⑥⑧⑨⑩	Yes
Wang *et al.* (2018) [17]	NSCLC	4081	42 RCTs	Cochrane RoB	Aidi + Platinum-based chemotherapy	Platinum-based chemotherapy alone	①②③④⑤⑥⑦⑧⑨⑩	Yes
Xiao *et al.* (2018) [18]	NSCLC	2058	31 RCTs	Cochrane RoB	Aidi + Paclitaxel-based chemotherapy	paclitaxel-based chemotherapy alone	①②③⑤⑥⑦⑧⑨⑩	Yes
Wang *et al.* (2010) [19]	NSCLC	800	11 RCTs	Cochrane RoB	Aidi + TP	TP alone	①③⑤⑥⑦⑧⑨⑩	Yes
Yang and Ding (2012) [20]	NSCLC	1104	15 RCTs	Cochrane RoB	Aidi + GP	GP alone	①③⑧	Yes
Liu (2019) [21]	Gastric cancer	851	11 RCTs	Jadad system	Aidi + S-1	S-1 alone	⑤⑥⑧	Yes
Han *et al.* (2016) [22]	NSCLC	1153	15 RCTs	Cochrane RoB	Aidi + GP	GP alone	①③⑤⑥⑦⑧⑨⑩	Yes
Zheng *et al.* (2017) [23]	Hepatic carcinoma	2306	33 RCTs	Cochrane RoB	Aidi + TACE	TACE alone	①③④⑤⑧⑨	Yes
Zhang*et al.* (2014) [24]	Malignant lymphoma	453	7 RCTs	Cochrane RoB	Aidi + CHOP	CHOP alone	①③⑤⑥⑧	Yes
Li *et al.* (2019) [25]	Colorectal cancer	653	8 RCTs	Cochrane RoB	Aidi + FOLFIRI	FOLFIRI alone	①②⑤⑧	Yes
Qiu *et al.* (2019) [26]	Ovarian cancer	1323	21 RCTs	Cochrane RoB	Aidi + Chemotherapy	Chemotherapy alone	①③⑤⑥⑧	Yes
Nian *et al.* (2015) [27]	Breast cancer	759	11 RCTs	Jadad system	Aidi + Chemotherapy	Chemotherapy alone	①③⑧	Yes
Li and Ning (2011) [28]	Gastric carcinoma	952	15 RCTs	Cochrane RoB	Aidi + Chemotherapy	Chemotherapy alone	①③④⑤⑥⑦⑧⑨⑩	Yes
Yuan *et al.* (2010) [29]	Hepatocellular carcinoma	1065	16 RCTs	Cochrane RoB	Aidi + Chemotherapy	Chemotherapy alone	①③④⑤	Yes
Li and Lin (2016) [30]	Colorectal cancer	1062	14 RCTs	Cochrane RoB	Aidi + Chemotherapy	Chemotherapy alone	①③⑤⑥⑦⑧	Yes
Gong *et al.* (2013) [31]	Hepatic carcinoma	1598	21 RCTs	Cochrane RoB +Jadad system	Aidi + TACE	TACE alone	①⑤⑥⑦⑧⑨	Yes
Wu *et al.* (2017) [32]	NSCLC	1207	9 RCTs	Jadad system	Aidi + Chemotherapy	Chemotherapy alone	①③⑤⑦⑧	Yes
Zhao *et al.* (2016) [33]	NSCLC	1025	16 RCTs	Cochrane RoB	Aidi + TP	TP alone	①③⑤⑥⑧	Yes

① ORR; ② DCR; ③ QOL; ④ one-year overall survival rate; ⑤ Leukopenia; ⑥ Thrombocytopenia; ⑦ Anemia; ⑧ Gastrointestinal reaction; ⑨ Hepatotoxicity; ⑩ Nephrotoxicity.
CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; FOLFIRI, fluorouracil + folinic acid + irinotecan; GP, gemcitabine + cisplatin; NP, vinorelbine + cisplatin; RCT, Randomized Controlled Trial; RoB, risk of bias; S-1, tegafur/gimeracil/oteracil; TACE, transcatheter arterial chemoembolization; TP, paclitaxel + cisplatin.

Table 2 **Results of AMSTAR-2**

Study (Ref.)	1	2[a]	3	4[a]	5	6	7[a]	8	9[a]	10	11[a]	12	13[a]	14	15[a]	16	Overall quality
Xiao *et al.* (2020a) [7]	Yes	No	No	PY	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	CL
Xiao *et al.* (2020b) [8]	Yes	No	No	PY	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	CL
Wang *et al.* (2016) [9]	Yes	No	No	PY	No	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	CL
Zhao *et al.* (2016) [10]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	Yes	No	Yes	Yes	Yes	CL
Chen 2018 [11]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	No	Yes	Yes	Yes	Yes	CL
Xiao *et al.* (2018) [12]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	No	No	Yes	Yes	Yes	CL
Dai (2018) [13]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	No	No	No	Yes	Yes	CL
Wang *et al.* (2015) [14]	Yes	No	No	Yes	No	No	No	PY	Yes	No	No	No	No	No	Yes	No	CL
Xiao *et al.* (2016) [15]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	No	No	Yes	Yes	Yes	CL
Xiao *et al.* (2017) [16]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	No	No	Yes	Yes	Yes	CL
Wang *et al.* (2018) [17]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	No	No	No	Yes	Yes	Yes	CL
Xiao *et al.* (2018) [18]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	CL
Wang *et al.* (2010) [19]	Yes	No	No	Yes	Yes	Yes	No	PY	Yes	No	Yes	No	Yes	No	Yes	No	CL
Yang and Ding (2012) [20]	Yes	No	No	PY	No	No	No	PY	PY	No	No	No	No	Yes	Yes	No	CL
Liu (2019) [21]	Yes	No	No	PY	Yes	Yes	No	No	PY	No	No	Yes	No	Yes	Yes	No	CL
Han *et al.* (2016) [22]	Yes	No	No	PY	No	No	No	PY	PY	No	No	Yes	No	Yes	No	No	CL
Zheng *et al.* (2017) [23]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	No	No	Yes	Yes	No	CL
Zhang *et al.* (2014) [24]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	No	No	No	Yes	Yes	Yes	CL
Li *et al.* (2019) [25]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	Yes	No	No	Yes	Yes	No	CL
Qiu *et al.* (2019) [26]	Yes	No	No	PY	Yes	No	No	PY	Yes	No	No	No	No	Yes	No	No	CL
Nian *et al.* (2015) [27]	Yes	No	No	PY	Yes	Yes	No	PY	PY	No	Yes	No	No	Yes	Yes	No	CL
Li and Ning (2011) [28]	Yes	No	No	PY	No	No	No	PY	PY	No	Yes	No	No	No	Yes	No	CL
Yuan *et al.* (2010) [29]	Yes	No	No	PY	No	No	No	No	Yes	No	No	No	No	No	Yes	No	CL
Li and Lin (2016) [30]	Yes	No	No	PY	Yes	Yes	No	PY	Yes	No	No	No	No	No	No	No	CL
Gong *et al.* (2013) [31]	Yes	No	No	PY	Yes	Yes	No	PY	PY	No	No	No	No	No	Yes	No	CL
Wu *et al.* (2017) [32]	Yes	No	No	PY	No	No	No	PY	PY	No	No	No	Yes	No	Yes	No	CL
Zhao *et al.* (2016) [33]	Yes	No	No	PY	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	Yes	No	CL

1. Did the research questions and inclusion criteria for the review include the components of PICO? 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and, did the report justify any significant deviations from the protocol? 3. Did the review authors explain their selection of the study designs for inclusion in the review? 4. Did the review authors use a comprehensive literature search strategy? 5. Did the review authors perform study selection in duplicate? 6. Did the review authors perform data extraction in duplicate? 7. Did the review authors provide a list of excluded studies and justify the exclusions? 8. Did the review authors describe the included studies in adequate detail? 9. Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review? 10. Did the review authors report the sources of funding for the studies included in the review? 11. If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results? 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? 13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review? 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

AMSTAR-2, a measurement tool to assess systematic reviews 2; CL, critical low; RCT, randomized controlled trial; RoB, risk of bias.

[a]Critical items.

Table 3 GRADE system for grading the quality of evidence

Study (Ref.)	Outcomes (no. studies)	Quality assessment					No. patients		Effect		
		RoB	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Quality	Importance
Xiao *et al.* (2020a) [7]	Hepatotoxicity (78)	Serious	No serious	No serious	No serious	Strongly suspected	392/3112 (12.6%)	630/3049 (20.7%)	RR 0.61 (0.55–0.69)	Low	Important
	Nephrotoxicity (58)	Serious	No serious	No serious	No serious	Strongly suspected	235/2259 (10.4%)	378/2210 (17.1%)	RR 0.62 (0.53–0.72)	Low	Important
	ORR (76)	Serious	No serious	No serious	No serious	Strongly suspected	1545/2949 (52.4%)	1145/2889 (39.6%)	RR 1.32 (1.25–1.40)	Low	Critical
	DCR (75)	Serious	No serious	No serious	No serious	Strongly suspected	2503/2919 (85.7%)	2143/2859 (75%)	RR 1.15 (1.12–1.17)	Low	Critical
Xiao *et al.* (2020b) [8]	ORR (51)	Serious	No serious	No serious	No serious	Strongly suspected	933/1933 (48.3%)	693/1896 (36.6%)	OR 1.65 (1.45–1.88)	Low	Critical
	DCR (51)	Serious	No serious	No serious	No serious	Strongly suspected	1654/1958 (84.5%)	1421/1917 (74.1%)	OR 2.02 (1.71–2.38)	Low	Critical
	QOL (36)	Serious	No serious	No serious	No serious	Strongly suspected	730/1329 (54.9%)	394/1288 (30.6%)	OR 2.93 (2.48–3.46)	Low	Critical
	1-YR (6)	Serious	No serious	No serious	Serious	Strongly suspected	120/224 (53.6%)	106/227 (46.7%)	OR 1.35 (0.92–1.99)	Very low	Critical
	Leukopenia (35)	Serious	No serious	No serious	No serious	Strongly suspected	828/1338 (61.9%)	1025/1322 (77.5%)	OR 0.32 (0.26–0.40)	Low	Important
	Thrombocytopenia (21)	Serious	No serious	No serious	No serious	Strongly suspected	202/831 (24.3%)	317/816 (38.8%)	OR 0.42 (0.33–0.53)	Low	Important
	Anemia (17)	Serious	No serious	No serious	No serious	Strongly suspected	176/635 (27.7%)	249/622 (40%)	OR 0.47 (0.36–0.62)	Low	Important
	Gastrointestinal reaction (40)	Serious	No serious	No serious	No serious	Strongly suspected	803/1542 (52.1%)	1006/1514 (66.4%)	OR 0.42 (0.36–0.51)	Low	Important
	Hepatotoxicity (8)	Serious	No serious	No serious	No serious	Strongly suspected	18/248 (7.3%)	38/247 (15.4%)	OR 0.41 (0.23–0.75)	Low	Important
	Nephrotoxicity (5)	Serious	Serious	No serious	Serious	Strongly suspected	12/138 (8.7%)	27/137 (19.7%)	OR 0.35 (0.07–1.79)	Very low	Important
Wang *et al.* (2016) [9]	ORR (6)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	OR 1.68 (1.09–2.60)	Low	Critical
	QOL (5)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	OR 3.32 (1.97–5.58)	Low	Critical
	Leukopenia (7)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	OR 0.25 (0.17–0.39)	Low	Important
	Thrombocytopenia (6)	Serious	Serious	No serious	No serious	Strongly suspected	NA	NA	OR 0.34 (0.22–0.53)	Very low	Important
Zhao *et al.* (2016) [10]	ORR (12)	Serious	No serious	No serious	No serious	Strongly suspected	241/509 (47.3%)	200/503 (39.8%)	RR 1.20 (1.04–1.37)	Low	Critical
	QOL (9)	Serious	No serious	No serious	No serious	Strongly suspected	200/323 (61.9%)	112/310 (36.1%)	RR 1.72 (1.45–2.04)	Low	Critical
	Leukopenia (8)	Serious	No serious	No serious	No serious	Strongly suspected	110/330 (33.3%)	198/322 (61.5%)	RR 0.54 (0.45–0.64)	Low	Important
	Thrombocytopenia (4)	Serious	No serious	No serious	No serious	Strongly suspected	8/159 (5%)	36/151 (23.8%)	RR 0.21 (0.10–0.44)	Low	Important
	Anemia (4)	Serious	No serious	No serious	Serious	Strongly suspected	12/154 (7.8%)	22/154 (14.3%)	RR 0.55 (0.28–1.06)	Very low	Important
	Gastrointestinal reaction (5)	Serious	No serious	No serious	No serious	Strongly suspected	79/235 (33.6%)	100/224 (44.6%)	RR 0.74 (0.60–0.92)	Low	Important
Chen *et al.* (2018) [11]	ORR (22)	Serious	No serious	No serious	No serious	Strongly suspected	485/818 (59.3%)	369/793 (46.5%)	RR 1.28 (1.17–1.40)	Low	Critical
	QOL (22)	Serious	No serious	No serious	No serious	Strongly suspected	470/818 (57.5%)	255/793 (32.2%)	RR 1.78 (1.59–2.00)	Low	Critical
	1-YR (6)	Serious	No serious	No serious	No serious	Strongly suspected	142/279 (50.9%)	99/269 (36.8%)	RR 1.38 (1.15–1.65)	Low	Critical
	Leukopenia (10)	Serious	No serious	No serious	No serious	Strongly suspected	162/352 (46%)	239/337 (70.9%)	RR 0.65 (0.57–0.74)	Low	Important
	Gastrointestinal reaction (5)	Serious	Serious	No serious	No serious	Strongly suspected	66/184 (35.9%)	116/173 (67.1%)	RR 0.53 (0.43–0.66)	Very low	Important
	Hepatotoxicity (2)	Serious	Serious	No serious	No serious	Strongly suspected	33/92 (35.9%)	60/86 (69.8%)	RR 0.52 (0.38–0.71)	Very low	Important
Xiao *et al.* (2018) [12]	ORR (34)	Serious	No serious	No serious	No serious	Strongly suspected	679/1362 (49.9%)	518/1352 (38.3%)	RR 1.30 (1.19–1.42)	Low	Critical
	DCR (33)	Serious	No serious	No serious	No serious	Strongly suspected	1104/1337 (82.6%)	936/1327 (70.5%)	RR 1.17 (1.12–1.22)	Low	Critical
	QOL (22)	Serious	Serious	No serious	No serious	Strongly suspected	447/842 (53.1%)	256/834 (30.7%)	RR 1.73 (1.54–1.95)	Very low	Critical
	Leukopenia (26)	Serious	Serious	No serious	No serious	Strongly suspected	452/1007 (44.9%)	627/999 (62.8%)	RR 0.70 (0.61–0.79)	Very low	Important
	Thrombocytopenia (17)	Serious	No serious	No serious	No serious	Strongly suspected	153/715 (21.4%)	235/700 (33.6%)	RR 0.63 (0.53–0.75)	Low	Important
	Anemia (9)	Serious	No serious	No serious	No serious	Strongly suspected	85/353 (24.1%)	135/343 (39.4%)	RR 0.60 (0.48–0.75)	Low	Important
	Gastrointestinal reaction (26)	Serious	Serious	No serious	No serious	Strongly suspected	504/1060 (47.5%)	634/1053 (60.2%)	RR 0.76 (0.65–0.89)	Very low	Important
	Hepatotoxicity (7)	Serious	No serious	No serious	Serious	Strongly suspected	37/308 (12%)	52/293 (17.7%)	RR 0.69 (0.47–1.01)	Very low	Important
	Nephrotoxicity (5)	Serious	No serious	No serious	Serious	Strongly suspected	15/181 (8.3%)	26/173 (15%)	RR 0.56 (0.31–1.00)	Very low	Important
Dai *et al.* (2018) [13]	ORR (20)	Serious	No serious	No serious	No serious	Strongly suspected	447/785 (56.9%)	327/759 (43.1%)	RR 1.33 (1.21–1.47)	Low	Critical
	QOL (11)	Serious	No serious	No serious	No serious	Strongly suspected	217/406 (53.4%)	109/387 (28.2%)	RR 1.90 (1.59–2.27)	Low	Critical
	1-YR (7)	Serious	No serious	No serious	No serious	Strongly suspected	172/327 (52.6%)	121/321 (37.7%)	RR 1.40 (1.19–1.65)	Low	Critical
	Leukopenia (7)	Serious	Serious	No serious	No serious	Strongly suspected	143/333 (42.9%)	200/316 (63.3%)	RR 0.67 (0.58–0.78)	Very low	Important
	Gastrointestinal reaction (4)	Serious	Serious	No serious	No serious	Strongly suspected	44/147 (29.9%)	88/137 (64.2%)	RR 0.46 (0.35–0.61)	Very low	Important
	Hepatotoxicity (2)	Serious	Serious	No serious	No serious	Strongly suspected	33/92 (35.9%)	60/86 (69.8%)	RR 0.52 (0.38–0.71)	Very low	Important
Wang *et al.* (2015) [14]	ORR (28)	Serious	No serious	No serious	No serious	Strongly suspected	425/792 (53.7%)	343/787 (43.6%)	OR 1.52 (1.24–1.86)	Low	Critical
	DCR (24)	Serious	No serious	No serious	No serious	Strongly suspected	615/712 (86.4%)	557/708 (78.7%)	OR 1.77 (1.33–2.36)	Low	Critical
	QOL (20)	Serious	No serious	No serious	No serious	Strongly suspected	377/648 (58.2%)	208/643 (32.3%)	OR 3.02 (2.39–3.82)	Low	Critical
	1-YR (6)	Serious	No serious	No serious	Serious s	Strongly suspected	127/189 (67.2%)	115/198 (58.1%)	OR 1.51 (0.98–2.34)	Very low	Critical
	Leukopenia (16)	Serious	No serious	No serious	No serious	Strongly suspected	38/523 (7.3%)	97/529 (18.3%)	OR 0.34 (0.23–0.51)	Low	Important
	Thrombocytopenia (12)	Serious	No serious	No serious	No serious	Strongly suspected	10/392 (2.6%)	23/396 (5.8%)	OR 0.46 (0.22–0.96)	Low	Important
	Anemia (4)	Serious	No serious	No serious	No serious	Strongly suspected	9/113 (8%)	19/122 (15.6%)	OR 0.42 (0.18–1.00)	Low	Important
	Gastrointestinal reaction (13)	Serious	No serious	No serious	No serious	Strongly suspected	212/421 (50.4%)	298/427 (69.8%)	OR 0.34 (0.24–0.47)	Low	Important
	Hepatotoxicity (11)	Serious	No serious	No serious	No serious	Strongly suspected	43/344 (12.5%)	97/349 (27.8%)	OR 0.36 (0.24–0.54)	Low	Important
	Nephrotoxicity (7)	Serious	No serious	No serious	Serious	Strongly suspected	13/230 (5.7%)	17/226 (7.5%)	OR 0.74 (0.35–1.58)	Very low	Important

(*Continued*)

Table 3 (*Continued*)

Study (Ref.)	Outcomes (no. studies)	Quality assessment					No. patients		Effect		
		RoB	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Quality	Importance
Xiao *et al.* (2016) [15]	ORR (17)	Serious	No serious	No serious	No serious	Strongly suspected	334/701 (47.6%)	262/689 (38%)	RR 1.26 (1.12–1.42)	Low	Critical
	DCR (16)	Serious	No serious	No serious	No serious	Strongly suspected	545/681 (80%)	480/663 (72.4%)	RR 1.11 (1.04–1.17)	Low	Critical
Xiao *et al.* (2017) [16]	ORR (34)	Serious	No serious	No serious	No serious	Strongly suspected	655/1276 (51.3%)	490/1220 (40.2%)	RR 1.28 (1.17–1.39)	Low	Critical
	DCR (32)	Serious	No serious	No serious	No serious	Strongly suspected	1059/1228 (86.2%)	914/1178 (77.6%)	RR 1.11 (1.07–1.15)	Low	Critical
	QOL (22)	Serious	No serious	No serious	No serious	Strongly suspected	505/877 (57.6%)	262/825 (31.8%)	RR 1.81 (1.61–2.03)	Low	Critical
	Leukopenia (13)	Serious	No serious	No serious	No serious	Strongly suspected	279/544 (51.3%)	351/516 (68%)	RD -0.17 (-0.22 to -0.11)	Low	Important
	Thrombocytopenia (11)	Serious	No serious	No serious	No serious	Strongly suspected	165/476 (34.7%)	215/448 (48%)	RD -0.13 (-0.18 to -0.08)	Low	Important
	Gastrointestinal reaction (15)	Serious	No serious	No serious	No serious	Strongly suspected	237/587 (40.4%)	309/550 (56.2%)	RD -0.15 (-0.21 to -0.10)	Low	Important
	Hepatotoxicity (7)	Serious	No serious	No serious	Serious	Strongly suspected	38/296 (12.8%)	47/271 (17.3%)	RD -0.04 (-0.10–0.02)	Very low	Important
	Nephrotoxicity (5)	Serious	No serious	No serious	Serious	Strongly suspected	18/228 (7.9%)	25/208 (12%)	RD -0.04 (-0.10–0.02)	Very low	Important
Wang *et al.* (2018) [17]	ORR (41)	Serious	No serious	No serious	No serious	Strongly suspected	988/2073 (47.7%)	732/1935 (37.8%)	RR 1.26 (1.18–1.36)	Low	Critical
	DCR (41)	Serious	No serious	No serious	No serious	Strongly suspected	1733/2073 (83.6%)	1437/1935 (74.3%)	RR 1.13 (1.09–1.16)	Low	Critical
	QOL (21)	Serious	No serious	No serious	No serious	Strongly suspected	541/951 (56.9%)	281/892 (31.5%)	RR 1.80 (1.61–2.01)	Low	Critical
	1-YR (7)	Serious	No serious	No serious	No serious	Strongly suspected	317/617 (51.4%)	247/539 (45.8%)	RR 1.14 (1.02–1.28)	Low	Critical
	Leukopenia (18)	Serious	No serious	No serious	No serious	Strongly suspected	82/757 (10.8%)	158/726 (21.8%)	RR 0.49 (0.39–0.62)	Low	Important
	Thrombocytopenia (12)	Serious	No serious	No serious	No serious	Strongly suspected	5/500 (1%)	25/481 (5.2%)	RR 0.31 (0.15–0.64)	Low	Important
	Anemia (6)	Serious	No serious	No serious	No serious	Strongly suspected	10/239 (4.2%)	23/231 (10%)	RR 0.45 (0.23–0.87)	Low	Important
	Gastrointestinal reaction (16)	Serious	No serious	No serious	No serious	Strongly suspected	96/971 (9.9%)	165/858 (19.2%)	RR 0.51 (0.40–0.64)	Low	Important
	Hepatotoxicity (4)	Serious	No serious	No serious	No serious	Strongly suspected	5/176 (2.8%)	15/171 (8.8%)	RR 0.39 (0.17–0.92)	Low	Important
	Nephrotoxicity (2)	Serious	No serious	No serious	Very serious	Strongly suspected	0/95 (0%)	2/92 (2.2%)	RR 0.32 (0.03–3.05)	Very low	Important
Xiao *et al.* (2018) [18]	ORR (29)	Serious	No serious	No serious	No serious	Strongly suspected	525/961 (54.6%)	381/923 (41.3%)	RR 1.32 (1.20–1.46)	Low	Critical
	DCR (28)	Serious	No serious	No serious	No serious	Strongly suspected	787/929 (84.7%)	661/1893 (74%)	RR 1.14 (1.09–1.20)	Low	Critical
	QOL (19)	Serious	No serious	No serious	No serious	Strongly suspected	365/627 (58.2%)	190/622 (30.5%)	RR 1.89 (1.66–2.16)	Low	Critical
	Leukopenia (22)	Serious	Serious	No serious	No serious	Strongly suspected	302/759 (39.8%)	450/738 (61%)	RR 0.61 (0.51–0.74)	Very low	Important
	Thrombocytopenia (12)	Serious	Serious	No serious	No serious	Strongly suspected	96/419 (22.9%)	143/407 (35.1%)	RR 0.62 (0.45–0.87)	Very low	Important
	Anemia (4)	Serious	Serious	No serious	Serious	Strongly suspected	55/147 (37.4%)	67/139 (48.2%)	RR 0.64 (0.34–1.21)	Very low	Important
	Gastrointestinal reaction (23)	Serious	No serious	No serious	No serious	Strongly suspected	296/791 (37.4%)	468/766 (61.1%)	RR 0.59 (0.49–0.72)	Low	Important
	Hepatotoxicity (10)	Serious	No serious	No serious	No serious	Strongly suspected	37/376 (9.8%)	71/375 (18.9%)	RR 0.52 (0.36–0.75)	Low	Important
	Nephrotoxicity (9)	Serious	No serious	No serious	Serious	Strongly suspected	14/323 (4.3%)	26/322 (8.1%)	RR 0.56 (0.31–1.02)	Very low	Important
Wang *et al.* (2010) [19]	ORR (11)	Serious	No serious	No serious	No serious	Strongly suspected	214/403 (53.1%)	166/397 (41.8%)	RR 1.27 (1.10–1.47)	Low	Critical
	QOL (9)	Serious	No serious	No serious	No serious	Strongly suspected	191/321 (59.5%)	103/317 (32.5%)	RR 1.83 (1.53–2.20)	Low	Critical
	Leukopenia (11)	Serious	Serious	No serious	No serious	Strongly suspected	200/403 (49.6%)	275/397 (69.3%)	RR 0.71 (0.57–0.87)	Very low	Important
	Thrombocytopenia (6)	Serious	No serious	No serious	No serious	Strongly suspected	32/240 (13.3%)	52/238 (21.8%)	RR 0.59 (0.40–0.87)	Low	Important
	Anemia (3)	Serious	No serious	No serious	Serious	Strongly suspected	57/130 (43.8%)	57/126 (45.2%)	RR 0.94 (0.76–1.18)	Very low	Important
	Gastrointestinal reaction (8)	Serious	Serious	No serious	No serious	Strongly suspected	123/291 (42.3%)	164/289 (56.7%)	RR 0.75 (0.58–0.98)	Very low	Important
	Hepatotoxicity (4)	Serious	No serious	No serious	Serious	Strongly suspected	13/164 (7.9%)	20/158 (12.8%)	RR 0.63 (0.32–1.23)	Very low	Important
	Nephrotoxicity (4)	Serious	No serious	No serious	Serious	Strongly suspected	4/164 (2.4%)	10/158 (6.3%)	RR 0.42 (0.12–1.24)	Very low	Important
Yang and Ding (2012) [20]	ORR (15)	Serious	No serious	No serious	No serious	Strongly suspected	304/595 (51.1%)	218/519 (42%)	OR 1.51 (1.18–1.92)	Low	Critical
	QOL (15)	Serious	Serious	No serious	No serious	Strongly suspected	319/519 (61.5%)	149/455 (32.7%)	OR 3.37 (2.57–4.40)	Very low	Critical
	Gastrointestinal reaction (14)	Serious	No serious	No serious	No serious	Strongly suspected	216/545 (39.6%)	280/499 (56.1%)	OR 0.44 (0.33–0.57)	Low	Important
Liu (2019) [21]	Leukopenia (11)	Serious	No serious	No serious	No serious	Strongly suspected	127/431 (29.5%)	215/420 (51.2%)	OR 0.36 (0.27–0.49)	Low	Important
	Thrombocytopenia (8)	Serious	No serious	No serious	No serious	Strongly suspected	61/322 (18.9%)	128/311 (41.2%)	OR 0.32 (0.22–0.46)	Low	Important
	Gastrointestinal reaction (10)	Serious	No serious	No serious	No serious	Strongly suspected	129/392 (32.9%)	207/381 (54.3%)	OR 0.37 (0.27–0.50)	Low	Important
Han *et al.* (2016) [22]	ORR (14)	Serious	No serious	No serious	No serious	Strongly suspected	273/562 (48.6%)	200/543 (36.8%)	OR 1.57 (1.23–2.01)	Low	Critical
	QOL (11)	Serious	No serious	No serious	No serious	Strongly suspected	268/468 (57.3%)	131/436 (30%)	OR 3.20 (2.41–4.25)	Low	Critical
	Leukopenia (6)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	OR 0.52 (0.35–0.77)	Low	Important
	Thrombocytopenia (8)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	OR 0.43 (0.29–0.63)	Low	Important
	Anemia (3)	Serious	No serious	No serious	Serious	Strongly suspected	NA	NA	OR 0.82 (0.41–1.64)	Very low	Important
	Gastrointestinal reaction (13)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	OR 0.53 (0.40–0.69)	Low	Important
	Hepatotoxicity (6)	Serious	No serious	No serious	Serious	Strongly suspected	NA	NA	OR 0.74 (0.47–1.15)	Very low	Important
	Nephrotoxicity (5)	Serious	No serious	No serious	Serious	Strongly suspected	NA	NA	OR 0.70 (0.40–1.23)	Very low	Important

(*Continued*)

Table 3 (*Continued*)

Study (Ref.)	Outcomes (no. studies)	Quality assessment					No. patients		Effect		
		RoB	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Quality	Importance
Zheng *et al.* (2017) [23]	ORR (30)	Serious	No serious	No serious	No serious	Strongly suspected	582/1086 (53.6%)	426/1040 (41%)	RR 1.31 (1.20–1.43)	Low	Critical
	QOL (23)	Serious	No serious	No serious	No serious	Strongly suspected	459/806 (56.9%)	233/765 (30.5%)	RR 1.86 (1.65–2.09)	Low	Critical
	1-YR (10)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	RR 1.44 (1.27–1.64)	Low	Critical
	Leukopenia (12)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	RR 0.73 (0.66–0.81)	Low	Important
	Gastrointestinal reaction (10)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	RR 0.59 (0.51–0.68)	Low	Important
	Hepatotoxicity (5)	Serious	No serious	No serious	No serious	Strongly suspected	NA	NA	RR 0.50 (0.38–0.65)	Low	Important
Zhang *et al.* (2014) [24]	ORR (5)	Serious	No serious	No serious	No serious	Strongly suspected	99/148 (66.9%)	78/142 (54.9%)	OR 1.67 (1.04–2.69)	Low	Critical
	QOL (5)	Serious	No serious	No serious	No serious	Strongly suspected	74/140 (52.9%)	38/137 (27.7%)	OR 2.94 (1.78–4.86)	Low	Critical
	Leukopenia (6)	Serious	No serious	No serious	No serious	Strongly suspected	88/205 (42.9%)	132/175 (75.4%)	OR 0.24 (0.15–0.38)	Low	Important
	Thrombocytopenia (5)	Serious	No serious	No serious	No serious	Strongly suspected	50/162 (30.9%)	78/132 (59.1%)	OR 0.32 (0.20–0.53)	Low	Important
	Gastrointestinal reaction (3)	Serious	No serious	No serious	No serious	Strongly suspected	48/138 (34.8%)	61/111 (55%)	OR 0.48 (0.28–0.83)	Low	Important
Li *et al.* (2019) [25]	ORR (7)	Serious	No serious	No serious	Serious	Strongly suspected	134/298 (45%)	114/295 (38.6%)	RR 1.16 (0.96–1.41)	Very low	Critical
	DCR (5)	Serious	No serious	No serious	No serious	Strongly suspected	177/226 (78.3%)	155/226 (68.6%)	RR 1.14 (1.02–1.28)	Low	Critical
	Leukopenia (5)	Serious	No serious	No serious	No serious	Strongly suspected	51/176 (29%)	81/173 (46.8%)	RR 0.62 (0.50–0.77)	Low	Important
	Gastrointestinal reaction (5)	Serious	No serious	No serious	No serious	Strongly suspected	63/202 (31.2%)	95/199 (47.7%)	RR 0.65 (0.52–0.83)	Low	Important
Qiu *et al.* (2019) [26]	ORR (21)	Serious	No serious	No serious	No serious	Strongly suspected	469/672 (69.8%)	331/651 (50.8%)	OR 2.38 (1.88–3.01)	Low	Critical
	QOL (15)	Serious	No serious	No serious	No serious	Strongly suspected	346/491 (70.5%)	195/480 (40.6%)	OR 3.85 (2.92–5.09)	Low	Critical
	Leukopenia (8)	Serious	No serious	No serious	No serious	Strongly suspected	21/244 (8.6%)	69/233 (29.6%)	RR 0.30 (0.19–0.47)	Low	Important
	Thrombocytopenia (8)	Serious	No serious	No serious	No serious	Strongly suspected	22/244 (9%)	63/241 (26.1%)	RR 0.36 (0.23–0.54)	Low	Important
	Gastrointestinal reaction (5)	Serious	No serious	No serious	No serious	Strongly suspected	12/153 (7.8%)	44/152 (28.9%)	RR 0.28 (0.16–0.50)	Low	Important
Nian *et al.* (2015) [27]	ORR (11)	Serious	No serious	No serious	No serious	Strongly suspected	315/403 (78.2%)	236/356 (66.3%)	RR 1.15 (1.05–1.26)	Low	Critical
	QOL (3)	Serious	No serious	No serious	Serious	Strongly suspected	34/105 (32.4%)	23/102 (22.5%)	RR 1.42 (0.91–2.19)	Very low	Critical
	Gastrointestinal reaction (3)	Serious	No serious	No serious	No serious	Strongly suspected	67/120 (55.8%)	67/112 (59.8%)	RR 0.90 (0.74–1.09)	Low	Important
Li and Ning (2011) [28]	ORR (14)	Serious	No serious	No serious	No serious	Strongly suspected	215/434 (49.5%)	165/410 (40.2%)	RR 1.24 (1.07–1.44)	Low	Critical
	QOL (11)	Serious	No serious	No serious	No serious	Strongly suspected	228/365 (62.4%)	112/357 (31.4%)	RR 1.98 (1.67–2.34)	Low	Critical
	1-SR (3)	Serious	No serious	No serious	Serious	Strongly suspected	68/111 (61.3%)	57/113 (50.4%)	RR 1.21 (0.96–1.53)	Very low	Critical
	Leukopenia (9)	Serious	No serious	No serious	No serious	Strongly suspected	18/325 (5.5%)	54/312 (17.3%)	RR 0.34 (0.22–0.55)	Low	Important
	Thrombocytopenia (5)	Serious	No serious	No serious	Serious	Strongly suspected	8/195 (4%)	15/195 (7.7%)	RR 0.58 (0.27–1.27)	Very low	Important
	Anemia (3)	Serious	No serious	No serious	Serious	Strongly suspected	3/111 (2.7%)	9/111 (8.1%)	RR 0.43 (0.15–1.29)	Very low	Important
	Gastrointestinal reaction (8)	Serious	No serious	No serious	No serious	Strongly suspected	151/301 (50.2%)	213/289 (73.7%)	RR 0.69 (0.61–0.78)	Low	Important
	Hepatotoxicity (5)	Serious	No serious	No serious	No serious	Strongly suspected	18/175 (10.3%)	36/171 (21.1%)	RR 0.50 (0.30–0.84)	Low	Important
	Nephrotoxicity (5)	Serious	No serious	No serious	Serious	Strongly suspected	8/175 (4.6%)	10/171 (5.8%)	RR 0.81 (0.34–1.90)	Very low	Important
Yuan *et al.* (2010) [29]	ORR (10)	Serious	No serious	No serious	No serious	Strongly suspected	322/595 (54.1%)	242/577 (41.9%)	RR 1.75 (1.37–2.23)	Low	Critical
	QOL (7)	Serious	No serious	No serious	No serious	Strongly suspected	258/444 (58.1%)	133/425 (31.3%)	RR 3.27 (2.45–4.37)	Low	Critical
	1-SR (6)	Serious	No serious	No serious	No serious	Strongly suspected	144/298 (48.3%)	100/296 (33.8%)	RR 2.21 (1.51–3.24)	Low	Important
	Leukopenia (7)	Serious	No serious	No serious	No serious	Strongly suspected	234/511 (45.8%)	334/496 (67.3%)	RR 0.31 (0.23–0.42)	Low	Important
Li and Lin (2016) [30]	ORR (12)	Serious	No serious	No serious	No serious	Strongly suspected	267/512 (52.1%)	220/487 (45.2%)	RR 1.40 (1.07–1.82)	Low	Critical
	QOL (11)	Serious	No serious	No serious	No serious	Strongly suspected	202/421 (48%)	94/394 (23.9%)	RR 3.06 (2.24–4.17)	Low	Critical
	Leukopenia (10)	Serious	No serious	No serious	No serious	Strongly suspected	166/391 (42.5%)	246/369 (66.7%)	RR 0.30 (0.21–0.42)	Low	Important
	Thrombocytopenia (6)	Serious	No serious	No serious	No serious	Strongly suspected	24/204 (11.8%)	43/186 (23.1%)	RR 0.43 (0.24–0.75)	Low	Important
	Anemia (2)	Serious	No serious	No serious	Serious	Strongly suspected	24/61 (39.3%)	31/60 (51.7%)	RR 0.49 (0.21–1.15)	Very low	Important
	Gastrointestinal reaction (6)	Serious	No serious	No serious	No serious	Strongly suspected	108/214 (50.5%)	129/194 (66.5%)	RR 0.50 (0.33–0.75)	Low	Important
Gong *et al.* (2013) [31]	ORR (21)	Serious	No serious	No serious	No serious	Strongly suspected	497/833 (59.7%)	350/765 (45.8%)	OR 1.77 (1.43–2.20)	Low	Critical
	Leukopenia (9)	Serious	No serious	No serious	No serious	Strongly suspected	114/322 (35.4%)	198/301 (65.8%)	OR 0.25 (0.17–0.36)	Low	Important
	Thrombocytopenia (3)	Serious	No serious	No serious	No serious	Strongly suspected	27/94 (28.7%)	47/83 (56.6%)	OR 0.25 (0.13–0.50)	Low	Important
	Anemia (1)	Serious	No serious	No serious	Very serious	Strongly suspected	5/28 (17.9%)	5/22 (22.7%)	OR 0.74 (0.18–2.96)	Very low	Important
	Gastrointestinal reaction (4)	Serious	Serious	No serious	Serious	Strongly suspected	52/134 (38.8%)	65/116 (56%)	OR 0.47 (0.21–1.07)	Very low	Important
	Hepatotoxicity (3)	Serious	No serious	No serious	No serious	Strongly suspected	20/139 (14.4%)	32/84 (38.1%)	OR 0.28 (0.11–0.72)	Low	Important
Wu *et al.* (2017) [32]	ORR (9)	Serious	No serious	No serious	No serious	Strongly suspected	275/640 (43%)	216/567 (38.1%)	OR 1.28 (1.01–1.62)	Low	Critical
	QOL (6)	Serious	No serious	No serious	No serious	Strongly suspected	135/248 (54.4%)	81/240 (33.8%)	OR 2.63 (1.78–3.88)	Low	Critical
	Leukopenia (6)	Serious	Serious	No serious	No serious	Strongly suspected	350/505 (69.3%)	330/443 (74.5%)	OR 0.51 (0.26–1.00)	Very low	Important
	Anemia (5)	Serious	No serious	No serious	Serious	Strongly suspected	39/160 (24.4%)	46/152 (30.3%)	OR 0.73 (0.43–1.24)	Very low	Important
	Gastrointestinal reaction (6)	Serious	No serious	No serious	No serious	Strongly suspected	126/253 (49.8%)	149/242 (61.6%)	OR 0.52 (0.35–0.78)	Low	Important

(*Continued*)

Table 3 ***(Continued)***

Study (Ref.)	Quality assessment							No. patients		Effect		
	Outcomes (no. studies)	RoB	Inconsistency	Indirectness	Imprecision	Other considerations		Intervention	Control	Relative (95% CI)	Quality	Importance
Zhao *et al.* (2016) [33]	ORR (16)	Serious	No serious	No serious	No serious	Strongly suspected		283/519 (54.5%)	207/506 (40.9%)	RR 1.34 (1.17–1.52)	Low	Critical
	QOL (13)	Serious	No serious	No serious	No serious	Strongly suspected		238/406 (58.6%)	138/401 (34.4%)	RR 1.69 (1.45–1.97)	Low	Critical
	Leukopenia (6)	Serious	Serious	No serious	No serious	Strongly suspected		52/210 (24.8%)	104/201 (51.7%)	RR 0.48 (0.38–0.62)	Low	Important
	Thrombocytopenia (4)	Serious	Serious	No serious	No serious	Strongly suspected		19/118 (16.1%)	41/109 (37.6%)	RR 0.45 (0.29–0.69)	Low	Important
	Gastrointestinal reaction (7)	Serious	Serious	No serious	No serious	Strongly suspected		57/226 (25.2%)	112/216 (51.9%)	RR 0.49 (0.38–0.63)	Low	Important

CI, confidence interval; DCR, disease control rate; GRADE, grade of recommendation, assessment, development, and evaluation; NA, not applicable/not available; ORR, objective response rate; OR, Odds ratio; QOL, quality of life; RoB, risk of bias; RR, relative risk.

reviews/meta-analyses reported the components of population, intervention, control group, and outcome (item 1), but no systematic reviews/meta-analyses mentioned the predefined protocol (item 2) and reasons for including only RCTs (item 3). Two studies used a comprehensive literature search strategy, while the remaining 25 systematic reviews/meta-analyses just achieved the partial searching on databases (item 4). Twenty systematic reviews/meta-analyses performed study selection in duplicate (item 5) and 20 systematic reviews/meta-analyses performed data extraction in duplicate (item 6). There were no systematic reviews/meta-analyses provided a list of excluded studies (item 7). Only 2 systematic reviews/meta-analyses described the included studies in adequate detail (item 8), while 4 systematic reviews/meta-analyses did not describe the details of included studies, and other 21 systematic reviews/meta-analyses just describe a part of information for the included studies. As for assessing the RoB, 19 systematic reviews/meta-analyses assessed the RoB and 7 systematic reviews/meta-analyses partially assessed the RoB (item 9). None of the systematic reviews/meta-analyses reported the source of funding (item 10). All systematic reviews/meta-analyses conducted meta-analyses, but only 14 systematic reviews/meta-analyses used appropriate statistical methods to combine the study findings (item 11), and 6 systematic reviews/meta-analyses assessed the potential impact of RoB of individual studies on the results of the data synthesis (item 12). Just six systematic reviews/meta-analyses took the RoB into consideration when discussing the results of the review (item 13). Nineteen systematic reviews/meta-analyses provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of review (item 14). All systematic reviews/meta-analyses performed quantitative synthesis, and 24 of them examined the publication bias and discuss its likely impact on the results of the reviews (item 15). Twelve systematic reviews/meta-analyses reported the conflict of interest (item 16). The details of AMSTAR-2 results are listed in Table 2.

Quality of evidence in concerned outcomes

The evidence level of all concerned outcomes assessed by the GRADE system was low or very low due to the RoB within the original studies, inconsistency, imprecision, and other considerations. The detail of GRADE system evaluation is shown in Table 3.

Objective response rate

Twenty-six systematic reviews/meta-analyses reported the ORR, 25 systematic reviews/meta-analyses showed that Aidi combined with chemotherapy significantly demonstrated an improvement in the ORR, but 1 meta-analysis showed no difference in improving ORR between the two groups. According to GRADE system, the quality of evidence for ORR was low reported in 25 systematic reviews/meta-analyses, and was very low reported in 1 meta-analysis.

Disease control rate

The DCR was reported in nine systematic reviews/meta-analyses, and all nine systematic reviews/meta-analyses indicated that Aidi plus chemotherapy could significantly improve the ORR. The quality of evidence for DCR was low.

Quality of life

Twenty-two systematic reviews/meta-analyses used KPS scores to assessed the QOL. Aidi plus chemotherapy was associated with a clinically significant increase in QOL in 21 systematic reviews/meta-analyses, but 1 meta-analysis showed that Aidi plus chemotherapy was not superior to the control group. The quality of evidence for QOL was low reported in 19 systematic reviews/meta-analyses, and was very low reported in 3 systematic reviews/meta-analyses.

One-year systematic review

Eight systematic reviews/meta-analyses assessed the one-year overall survival rate, five of them reported that combining the Aidi with chemotherapy significantly increased the one-year overall survival rate, but three systematic reviews/meta-analyses showed no significant difference between the two groups. The quality of evidence for one-year overall survival rate was low reported in five systematic reviews/meta-analyses, and was very low reported in three systematic reviews/meta-analyses.

Leukopenia

Twenty-three systematic reviews/meta-analyses investigated the leukopenia, these systematic reviews/meta-analyses indicated that Aidi with chemotherapy could significantly decrease the risk of developing leukopenia. The quality of evidence for leukopenia was low reported in 18 systematic reviews/meta-analyses, and was very low reported in 5 systematic reviews/meta-analyses.

Thrombocytopenia

Seventeen systematic reviews/meta-analyses reported the data of thrombocytopenia, 16 systematic reviews/meta-analyses showed that Aidi plus chemotherapy resulted in a lower risk of thrombocytopenia than that of chemotherapy alone, while 1 systematic reviews/meta-analyses showed no significant difference between the two groups. The quality of evidence for thrombocytopenia was low reported in 14 systematic reviews/meta-analyses, and was very low reported in 3 systematic reviews/meta-analyses.

Anemia

Twelve systematic reviews/meta-analyses estimated the anemia, six of them indicated that Aidi with chemotherapy could significantly decreased incidence of anemia, while other six systematic reviews/meta-analyses showed no significant difference between the two groups. The quality of evidence for anemia was low reported in four systematic reviews/meta-analyses, and was very low reported in eight systematic reviews/meta-analyses.

Gastrointestinal reaction

Twenty-three systematic reviews/meta-analyses reported the gastrointestinal reaction, the results of 21 systematic reviews/meta-analyses demonstrated that Aidi in combination with chemotherapy could reduce the incidence of gastrointestinal reaction, while the results of the other 2 systematic reviews/meta-analyses were not statistically significant. The quality of evidence for gastrointestinal reaction was low reported in 18 systematic reviews/meta-analyses, and was very low reported in 5 systematic reviews/meta-analyses.

Hepatotoxicity

Fourteen systematic reviews/meta-analyses evaluated the liver injury, 11 of them showed that, compared with control group, the number of patients with liver injury decreased significantly in Aidi plus chemotherapy group, but the remaining 3 systematic reviews/meta-analyses communicated no statistically significant differences regarding liver injury. The quality of evidence for liver injury was low reported in eight systematic reviews/meta-analyses, and was very low reported in six systematic reviews/meta-analyses.

Nephrotoxicity

Ten systematic reviews/meta-analyses measured the renal injury, three systematic reviews/meta-analyses showed that Aidi combined with chemotherapy had lower risk of renal injury, but reported data from other seven systematic reviews/meta-analyses showed no significant reduction in favor of the Aidi plus chemotherapy group. The quality of evidence for renal injury was low reported in one systematic reviews/meta-analyses, and was very low reported in nine systematic reviews/meta-analyses.

Discussion

The combination of Aidi and chemotherapy is a common strategy for cancer patients [66]. There is some evidence that it can improve the clinical efficacy and reduce adverse events in cancer patients, but still there is lack of widely agreed evidence for its effect [7–33]. This overview included 27 systematic reviews/meta-analyses to evaluate the role of Aidi in combination with chemotherapy. All the included systematic reviews/meta-analyses were regarded as critically low to low quality according to the AMSTAR-2 evaluation, mainly due to failure to provide a developed priori protocol, reasons for including only RCTs, a list of excluded studies, and the source of funding. These may lead to selection bias and reduce the reliability of the results to some extent.

Most systematic reviews/meta-analyses showed that Aidi plus chemotherapy were are associated with significantly improved clinical outcomes and reduced treatment-associated toxicity when compared to chemotherapy alone [7–33]. However, according to the GRADE system, the evidence quality of ORR, DCR, QOL, one-year overall

survival rate, leukopenia, thrombocytopenia, anemia, gastrointestinal reaction, hepatotoxicity, and nephrotoxicity were low or very low. The most frequent downgrading factors were: study limitations, inconsistency of results, imprecision, and reporting bias. Therefore, it is difficult to draw any definitive conclusions about the use of Aidi.

To the best of our knowledge, this is the first overview of systematic reviews/meta-analyses that specifically focus on the efficacy and safety of Aidi combined with chemotherapy for the treatment of cancer patients. Two independent reviewers systematically reviewed the literature, evaluated the methodological quality of systematic reviews/meta-analyses by using AMSTAR-2, and assessed the quality evidence of outcomes by using GRADE system. However, this review also has some limitations. First, using AMSTAR-2 tool and GRADE system to assess the methodological quality and evidence quality, respectively, is a subjective process. Although included systematic reviews/meta-analyses have been evaluated independently by two reviewers and examined by a third reviewer, there may still be some bias. Second, since all the included systematic reviews/meta-analyses were conducted in China among Chinese populations, it is uncertain whether the effects may change when Aidi is used in other ethnicity populations. Third, we did not retrieve data from initial trials and thereby were limited to the information and judgments of the reviewers who wrote the systematic reviews/meta-analyses. Fourth, search strategies, selection criteria, primary outcomes were varied between the included systematic reviews/meta-analyses, which lead a high heterogeneity among the 27 included systematic reviews/meta-analyses.

Conclusion

The current systematic reviews/meta-analyses revealed that Aidi plus chemotherapy might improve the clinical efficacy and reduce chemotherapy-induced toxicities, but according to AMSTAR-2 assessment and GRADE assessment, the methodological quality of included systematic reviews/meta-analyses was critical low, and the evidence quality of outcomes was low to very low. Therefore, more rigorously designed, randomized, multicenter, large sample trials are needed to further explore the efficacy, and safety of Aidi plus chemotherapy for the treatment of cancer patients.

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Conflicts of interest

There are no conflicts of interest.

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