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Is ADC a rising star in solid tumor? An umbrella review of systematic reviews and meta-analyses

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Abstract

Background Antibody-drug conjugates (ADCs) combine the specificity of monoclonal antibodies with the potency of highly cytotoxic drugs and are known as panaceas, completely changing the treatment paradigm for solid tumors. Compared with other anti-cancer drugs, do they have better efficacy and lower toxicity risks? It is necessary to summarize and analyze the published clinical research data in this area to provide additional evidence-based evidence for clinical practice.

Objective To comprehensively assess and overview the efficacy and safety of antibody-drug conjugates for the treatment of solid tumors.

Design An umbrella review of systematic reviews and meta-analyses.

Methods Systematic search of eight electronic databases and one registration platform including Embase, PubMed, Cochrane Database of Systematic Reviews (CDSR), Web of Science (WoS), China National Knowledge Infrastructure (CNKI), Chinese BioMedical Literature Database (CBM), Wan Fang Data, China Science and Technology Journal Database (VIP) and international prospective register of systematic reviews (PROSPERO) on Aug 1, 2024, to identify relevant systematic reviews or meta-analyses. Three authors completed research screening and data extraction independently. AMSTAR 2 was used to evaluate the methodological quality of the included studies and the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) was performed to evaluate the quality of the evidence. We examined progression-free survival (PFS), overall survival (OS), objective response rate (ORR) as efficacy endpoints, and the incidence of adverse events (AEs) as safety profiles.

Results A total of 16 eligible publications, including 32 clinical studies, were included in the umbrella review. The methodological quality of the included study was poor, with 2 articles of moderate-quality (12.5%), 5 articles of low quality (31.25%), and 9 articles of critically low quality (56.25%). Only one third of the evidence was of high quality. Within the included studies, breast cancer accounted for four-fifths, 2 studies were gastric cancer, and 1 study was a solid tumor. The overall results showed that ADCs significantly increased PFS and OS in patients with solid tumors, and the risk of toxicity was within an acceptable range. ado-Trastuzumab emtansine (T-DM1) and Trastuzumab

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deruxtecan (T-Dxd) treatment of human epidermal growth factor receptor 2(HER2) low/positive advanced metastatic breast cancer significantly prolonged PFS and OS, but the ORR showed a significant advantage. Compared with the chemotherapy group, T-Dxd significantly prolonged OS and PFS in gastric cancer patients, while T-DM1 did not. In other cancer types (ovarian cancer, renal cell carcinoma, and malignant pleural mesothelioma), ADCs tended to extend overall survival or progression-free survival compared with controls, but the difference was not statistically significant.

Conclusions Based on the available evidence, in breast cancer, ADCs were proved to with significant improvements in prolonging survival time and demonstrates a tolerable safety profile. Meanwhile, ADCs were proved to have enormous potential for the treatment of solid tumors. However, well-designed, multi-center RCTs need to further identify its potential in various solid tumors.

Systematic review registration PROSPERO CRD 42,024,564,517.

Keywords Antibody-drug conjugates, ADCs, Solid tumor, Efficacy, Safety, Umbrella Review

Introduction

Cancer has long been a global challenge with a high disease burden [1]. Cytotoxic chemotherapy constitutes the foundation of traditional anticancer treatment [2, 3]. However, there is a contradiction between the treatment of advanced and metastatic solid tumors and the current treatment, it is always a goal to further explore effective treatments for solid tumors. With the development of targeted and immunotherapy [4], a new type of drug for the targeted delivery of chemotherapy drugs to solid tumors has emerged. Antibody-drug conjugates (ADCs) are often referred to as a "*magic bullet*" for cancer treatment because they combine the tumor-targeting properties of the antibody component with the potency of cytotoxic drugs [5]. ADCs are complex therapeutic agents consisting of 3 key components (antibody, linker, and payload) [6, 7]. To be more specific, innovative linkers and payloads enhance drug delivery to tumor cells and improve activity against cancers that heterogeneously express targeted antigens. Theoretically, ADCs could improve the efficacy of the chemotherapy and reduce systemic exposure and toxicity. In 2013, T-DM1 was approved by the FDA for the treatment of metastatic breast cancer (MBC), becoming the first approval for this drug class [8]. Until Nov 1, 2024, FDA and China has approved 7 ADCs for solid tumor. ADCs have become the cornerstone of effective therapeutics in solid and hematological malignancies. In the large phase III EMILIA trial in patients with breast cancer, anti-HER2 ADC T-DM1 achieved higher response rates, longer PFS and OS, and a lower incidence of grade 3/4 adverse events than the combination of lapatinib and capecitabine [9]. It is noteworthy that positive results from the head-to-head DESTINY-Breast03 phase 3 trial comparing T-DXd versus T-DM1 for HER2-positive metastatic BC. Findings indicated that the risk of disease progression or death was lower among those who received T-DXd than among those who received T-DM1 [10]. With these compelling results, T-DXd may become a standard treatment for patients progressing, while challenging the status of T-DM1 for HER2-positive breast cancer. Enfortumab vedotin against nectin-4 for the treatment of locally advanced or metastatic urothelial malignancies and sacituzumab govitecan against TROP2 for the treatment of triple-negative breast cancer are landmark, because they provide treatment alternatives for diseases with limited therapeutic options [11, 12]. In the open-label, randomized, phase III trial, Trastuzumab Duocarmazine (T-Duo) significantly reduced the risk of progression in patients with advanced HER2 + breast cancer who have progressed during/after ≥ 2 HER2-targeted therapies or after T-DM1 [13], but it is still under approval for listing. In patients with platinum-resistant epithelial ovarian cancer, mirvetuximab soravtansine (MIRV) showed a more manageable safety profile than chemotherapy, but it did not result in a significant improvement in PFS compared with chemotherapy [14]. Whether it's the expansion of indications for marketed ADC drugs or the approval of new indications, ADCs are growing at a breakneck pace.

In general, ADCs bring new hope for solid tumor treatment. The safety and effectiveness of clinical use are worthy of discussion. We examined the amount and strength of the evidence, and the presence of biases. To objectively evaluate current research on the efficacy and safety of antibody-drug conjugates for the treatment of solid tumors, we conducted an umbrella review to provide an up-to-date and comprehensive resource for clinical care.

Methods

Data sources and searches

This study was conducted in accordance with Systematic Reviews and Meta-Analyses (PRISMA). The protocol for this review has been registered in PROSPERO, an international registry of prospective systematic reviews (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024564517).

Systematic search of eight electronic databases including Embase, PubMed, CDSR, WoS, CNKI, CBM, Wan

Fang Data and the VIP database was searched on Aug 1, 2024, to identify relevant systematic reviews or meta-analyses, and PROSPERO registration platform was also checked in Aug 1, 2024 to ensure that data from previously published systematic reviews or meta-analyses have been updated on the registry. We applied no restrictions regarding year or language. Both MeSH subject terms and free text terms (keywords) were used to search relevant articles. Search terms included: Various listed ADCs, antibody-drug conjugates, solid tumor, neoplasms, cancer, carcinoma, and systematic review, meta-analysis. There is no restriction of countries and authors. Otherwise, reference lists of pertinent retrieved articles were reviewed for additional studies. The detailed retrieval strategy was presented in Supplementary file 1.

Eligibility criteria and selection

The included studies met each of the following criteria: (1) systematic review or meta-analysis based on randomized controlled trials; (2) patients with solid tumors; (3) intervention: ADCs monotherapy or ADCs in combination with chemotherapy, targeted or immunotherapy; (4) control: non-ADCs therapy. The exclusion criteria were as follows: (1) retrospective studies and case reports; (2) studies that did not mention ADCs drug-associated safety or efficacy; (3) hematological neoplasms; (4) duplicate studies; (5) narrative review. Two researchers (Zhang and Lu) independently screened eligible title or abstract according to the inclusion and exclusion criteria. If the title or the abstract was inadequate to reach a final decision, we obtained the full paper. If there were disputes, it would be resolved by a third investigator (Qin).

Data extraction

Two reviewers independently extracted data (Wei, Zou). All data was collected using a pre-designed Excel extract sheet, including but not limited to the journal name, first author, publication year, country, type of ADC, study design, number of included studies, sample size, major findings (Study outcomes: HR with 95% CI for OS and PFS analysis), and adverse outcomes. For faster and more convenient quality evaluation, we also extracted the following data: study registration number, searching database, searching terms, language and time limitation, additional retrieval, double review model, quality assessment tool, statistical method, robustness of the results, sponsorship and conflicts of interest [15].

Methodological quality and certainty of evidence

The methodological quality of the included systematic reviews was independently assessed by two reviewers (Lu, Zhou) using the AMSTAR 2 tool [15]. The AMSTAR 2 tool has 16 items, seven (2, 4, 7, 9, 11, 13, and 15) of which are critical domains [15]. According to the evaluation guidelines, the methodological results of the included systematic reviews have been categorized as follows: high quality for no or one non-critical weakness; moderate quality for more than one non-critical weakness; low quality for one critical flaw with or without non-critical weaknesses and critically low quality for more than one critical flaw with or without non-critical weaknesses [14]. Two reviewers (Wei, Zou) independently assessed the quality of the evidence for the primary outcome using the GREAD tool [16].

Strategy for data synthesis

Meta-analysis was performed using STATA software. PFS and OS were analyzed by HR and 95% CI. As for ORR and incidence of adverse reactions, the binary data was analyzed by relative risk (RR) and 95% CI, and the continuous data was analyzed by mean difference (MD) and standard deviation (SD). If data synthesis was not possible, narrative synthesis could be used.

Results

Characteristics of included reviews

Overall, we searched for 253 studies and reviewed 69 full-text articles after exclusion by initial screening. 16 systematic reviews/ meta-analyses were finally included, with a 50/50 split between English and Chinese [17–32]. The detailed literature screening process is shown in Fig. 1.

Sixteen systematic reviews/ meta-analyses included contained 102 articles involving 32 clinical trials. 14 systematic reviews/meta-analyses targeting diseases were breast cancer, and 2 studies were solid tumors. Treatment drugs included 11 ADCs involving 5 tumor types, including Ovarian Cancer, Breast Cancer, Renal Cell Carcinoma, Gastric Cancer and Malignant Pleural Mesothelioma, as shown in Table 1.

Methodological quality assessment

The methodological quality of the included systematic reviews was evaluated according to the AMSTAR2 scale. The results showed that there were no high-quality articles, 2(12.5%) moderate-quality articles [22, 25], 5(31.25%) low-quality articles [17–19, 23, 31], and 9 (56.25%) critically low-quality articles [20, 21, 26–30, 32]. 14 studies had no pre-published protocols or plans, 8 studies did not perform double-person screening of literature, 4 studies did not perform double-person data extraction, and 2 studies did not perform risk bias assessment. 9 studies did not discuss and explain the risk of bias in results. 11 studies did not conduct publication bias judgments and possible impacts on the outcome indicators. The detailed information is shown in Fig. 2.

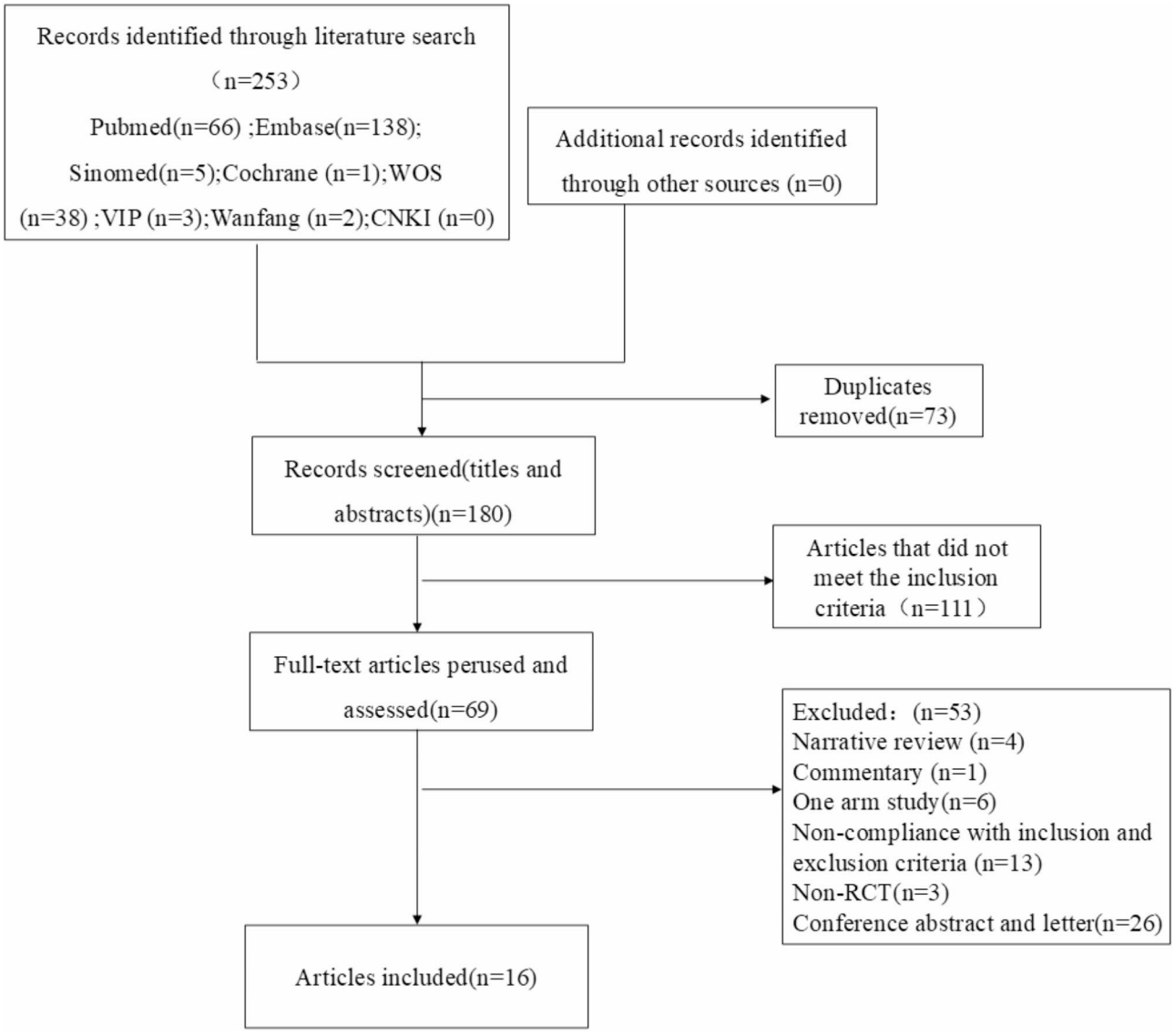

Fig. 1 PRISMA Flow diagram of the study selection process

Assessment of the quality of evidence

Of the 53 outcome indicators, 14 (26.4%) were rated as high quality, 20(37.7%) were rated as moderate quality and 19(35.8%) were rated of low-quality evidence. Most outcomes should be downgraded due to risk of bias and publication bias. Four outcomes should be upgraded due to large effect sizes. The detailed information is shown in Table 2.

Efficacy

Thirteen studies had evaluated the efficacy of ADCs in breast cancer [18, 20, 21, 23, 24, 26–31], and the results showed that in HER2-positive breast cancer, TDM-1 and T-Dxd had a good track record in prolonging PFS and OS. Results of meta-analysis indicated that compared with the control group, the OS and PFS of the T-DM1 group were significantly prolonged, with statistically significant differences. However, there was no significant difference in ORR between two groups. Meanwhile, the efficacy analysis showed that, compared with the non-T-DM1 treatment, the treatment regime with T-DM1 as neoadjuvant for early-stage HER-2 positive breast cancer showed notable improvement in the pathological completely response rate (OR = 1.90, 95% CI: [1.02, 3.51], $P = 0.04$). However, there was no statistically significant difference in the 3-year disease-free survival rate (OR = 1.16, 95% CI: [0.64,2.12], $P = 0.62$) and the breast-conserving rate (OR = 0.98, 95% CI: [0.67,1.43], $P = 0.91$). The results of the meta-analysis showed that compared with the control group, the T-Dxd treatment group had significantly higher overall survival, progression-free survival, overall response rate, clinical benefit rate, and

Table 1 Characteristics of the included studies

Systematic review/ meta-analysis	Condition	ADC class	Prospective registration	No of trials (No of participants) with data for meta-analysis	Outcomes	Systematic review/ meta-analysis quality (High/Moderate/ low/Critically low)
Xu Yinxue, 2023 [17]	Breast cancer	T-DM1、T-Dxd、SG	No	8(5577)	PFS, OS, ORR, CBR, AEs	LOW
Zhang Leyin, 2022 [22]	**Solid tumor**	T-DM1、T-Dxd、SG、AGS-16C3F、 Lifastuzumab Vedotin、Anetumab Raytansine、Glembatumumab Vedotin	Yes (PROSPERO)	11(4354)	PFS, OS, ORR, AEs	Moderate
Liu Ting, 2021 [18]	HER2-positive breast cancer	T-DM1	No	7(5118)	PFS, OS, AEs	LOW
Amani M. Cobert, 2020 [20]	HER2-positive breast cancer	T-DM1	No	7(5045)	AEs (hepatotoxicity)	Critically low
Yan Bingxue1,2021 [21]	HER2-positive breast cancer	T-DM1	No	8(1338)	pCR, DFS, breast conservation rate, AEs	Critically low
Yan Hongjing, 2017 [24]	HER2-positive MBC	T-DM1	No	11(3720)	PFS, OS, ORR, AEs	Critically low
Yan Bingxue2, 2021 [26]	HER2-positive MBC	T-DM1	No	5(3027)	PFS, OS, ORR, AEs	Critically low
Xue Hong, 2018 [27]	HER2-positive breast cancer	T-DM1	No	4(3179)	CR, PR, AEs	Critically low
Nusrat Jahan, 2021 [28]	HER2-positive breast cancer	T-DM1	No	3(1857)	AEs (Peripheral Neuropathy)	Critically low
Yang Danni, 2023 [23]	HER2-positive advanced breast cancer	T-DM1	No	9(6767)	PFS, OS, AEs	LOW
Guo Yimeng, 2020 [29]	HER2-positive breast cancer	T-DM1	No	7(4310)	PFS, OS, AEs	Critically low
Kuan Liu, 2022 [30]	HER2-positive breast cancer	T-DM1	No	7(5045)	AEs	Critically low
Yingchih Yeh, 2022 [31]	HER2positive locally advanced or metastatic breast cancer	T-DM1	No	4(2462)	PFS, OS, AEs	LOW
Zhang Xiaoqing, 2024 [32]	breast cancer	T-Dxd	No	3(1689)	PFS, OS, ORR, AEs	Critically low
Rui Ma, 2024 [25]	HER2-low/positive advanced breast cancer	T-DXd	No	3(1689)	PFS, OS, ORR, CBR, DOR, AEs	Moderate
Cai ZeLin,2023 [19]	solid tumors	T-Dxd	Yes (PROSPERO)	3(1268)	PFS, OS, ORR, DCR, AEs	LOW

Abbreviations: progressive-free survival (PFS); overall survival (OS); duration of response (DOR); overall response rate (ORR); and clinical benefit rate (CBR); disease-free survival (DFS); disease control rate (DCR); pathologic complete response (PCR); adverse events (AEs); human epidermal growth factor receptor 2 (HER2); sacituzumab govitecan (SG); ado-Trastuzumab emtansine(T-DM1); Trastuzumab deruxtecan (T-Dxd); international prospective register of systematic reviews (PROSPERO)

disease control rate [19, 25, 32]. The results of meta-analysis showed that Sacituzumab govitecan significantly prolonged the OS, PFS and ORR of triple-negative breast cancer compared with the control group, and the difference was statistically significant. However, the efficacy analysis showed that there was no significant difference in OS and PFS in the treatment of triple-negative breast cancer between the capecitabine and regime with Glembatumumab vedotin [22], as shown in Fig. 3.

Two studies had evaluated the efficacy of ADCs in gastric cancer [19, 22]. And the results showed that compared with the control group, the OS, PFS and disease control rate (DCR) of the T-Dxd group were significantly prolonged, with statistically significant differences. However, subgroup analysis showed that patients with HER2 IHC3 + mutation had OS-related benefit (HR = 0.53, 95%CI: 0.28–0.78), while patients with HER2 IHC2+/ISH + mutation had no OS-related benefit (HR = 1.15,

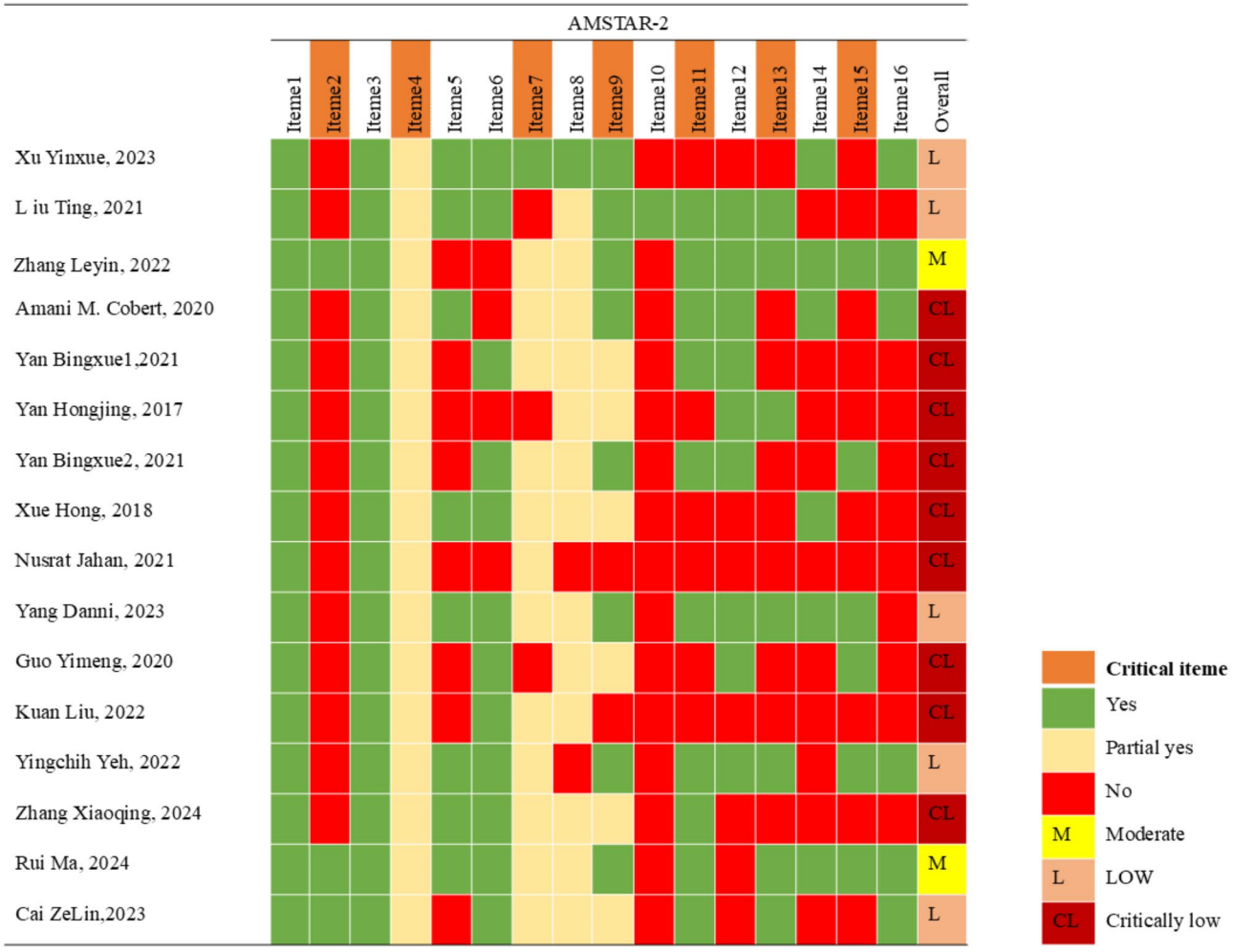

Fig. 2 Methodological quality of the included systematic reviews. Abbreviation: Assesing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2); Moderate (M); LOW (L); Critically low (CL)

95%CI: 0.16–2.14). Meanwhile, T-DM1 did not significantly prolong OS and PFS in gastric cancer patients compared with the chemotherapy group, as shown in Fig. 3.

One study had evaluated the efficacy of ADCs in solid tumors [22]. The results showed that Lifastuzumab Vedotin had a tendency to prolong PFS and OS in patients with cervical cancer compared to control, but the difference was not statistically significant. Compared with chemotherapy, Anetumab Ravtansine did not show a significant advantage in PFS and OS in Malignant Pleural Mesothelioma as well as AGS-16C3F in Renal Cell Carcinoma patients, as shown in Fig. 3.

Safety

Six systematic reviews/meta-analyses of treatment-related adverse events (TRAEs), suggested that TRAEs in the T-Dxd group was higher than that in the control group (RR = 6.93, 95% CI (2.06, 23.25),$P = 0.002$) [19], and there was no significant difference in the results of other studies [18, 23, 27, 29, 32]. Six systematic reviews/meta-analyses TRAEs at grade 3 to 4 showed no significant difference between ADCs and control group [23, 26, 27, 29, 32]. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), nausea, constipation, left ventricular dysfunction (LVD), decreased appetite, pneumonitis and interstitial lung disease (ILD), hypertension and other adverse reactions increased significantly in ADCs group compared with control group. However, the incidence of TRAEs such as febrile neutropenia and alopecia in ADCs group were significantly lower than the control group. The combined results of thrombocytopenia, leukopenia, vomiting, asthenia, fatigue, abdominal pain, dyspnea, diarrhea and other adverse reactions were different, as shown in Supplementary file 1 for details.

Discussion

To our knowledge, this study is the first umbrella review that systematically assessed the relative effectiveness and safety of patients with solid tumors treated with ADCs.

Table 2 The quality of evidence of the included studies of outcomes

Study	Outcome	Degradation factor					Escalation factor			Quality of evidence
		Study limitations	Inconsistency of results	Indirectness of evidence	Imprecision	Reporting bias	Large effect size	a dose-response relation	all plausible biases	
Xu Yinxue [17]	PFS	-1				-1				LOW
	OS	-1				-1				LOW
	CBR	-1				-1				LOW
	ORR	-1				-1				LOW
	AEs	-1				-1				LOW
Zhang Leyin [22]	PFS	-1				-1				LOW
	OS	-1				-1				LOW
	ORR	-1				-1				LOW
	AEs	-1				-1				LOW
Liu Ting [18]	PFS	-1				-1				LOW
	OS	-1				-1				LOW
	AEs	-1				-1				LOW
Amani M. Cobert [20]	AEs	-1				-1				LOW
Yan Bingxue1 [21]	pCR	-1								Moderate
	DFS	-1								Moderate
Yan Hongjing [24]	PFS	-1								Moderate
	OS	-1								Moderate
	ORR	-1								Moderate
	AEs	-1								Moderate
Yan Bingxue2 [26]	PFS									High
	OS									High
	ORR									High
	AEs									High
Xue Hong [27]	PR	-1								LOW
	CR	-1								LOW
	AEs	-1								LOW
Nusrat Jahan [28]	AEs						1			High
Yang Danni [23]	PFS									High
	OS									High
	ORR									High
	AEs									High
Guo Yimeng	PFS									High

Table 2 (continued)

Study	Outcome	Degradation factor					Escalation factor			Quality of evidence
		Study limitations	Inconsistency of results	Indirectness of evidence	Imprecision	Reporting bias	Large effect size	a dose-response relation	all plausible biases	
[29]	OS									High
	AEs									High
Kuan Liu [30]	AEs	-1								Moderate
Yingchih Yeh [31]	PFS	-1								Moderate
	OS	-1								Moderate
	ORR	-1								Moderate
	AEs	-1								Moderate
Zhang xiaoqing [32]	PFS	-1								Moderate
	OS	-1								Moderate
	ORR	-1								Moderate
	AEs	-1								Moderate
Rui Ma [25]	PFS	-1								Moderate
	OS	-1								Moderate
	ORR	-1					1			High
	CBR	-1					1			High
	AEs	-1				-1				LOW
Cai ZeLin [19]	PFS	-1				-1				LOW
	OS	-1				-1				LOW
	ORR	-1				-1	1			Moderate
	DCR	-1				-1				LOW
	AEs	-1				-1				LOW

Abbreviations: progressive-free survival (PFS); overall survival (OS); duration of response (DOR); overall response rate (ORR); and clinical benefit rate (CBR); disease-free survival (DFS); disease control rate (DCR); complete response (CR); partial response (PR); adverse events (AEs)

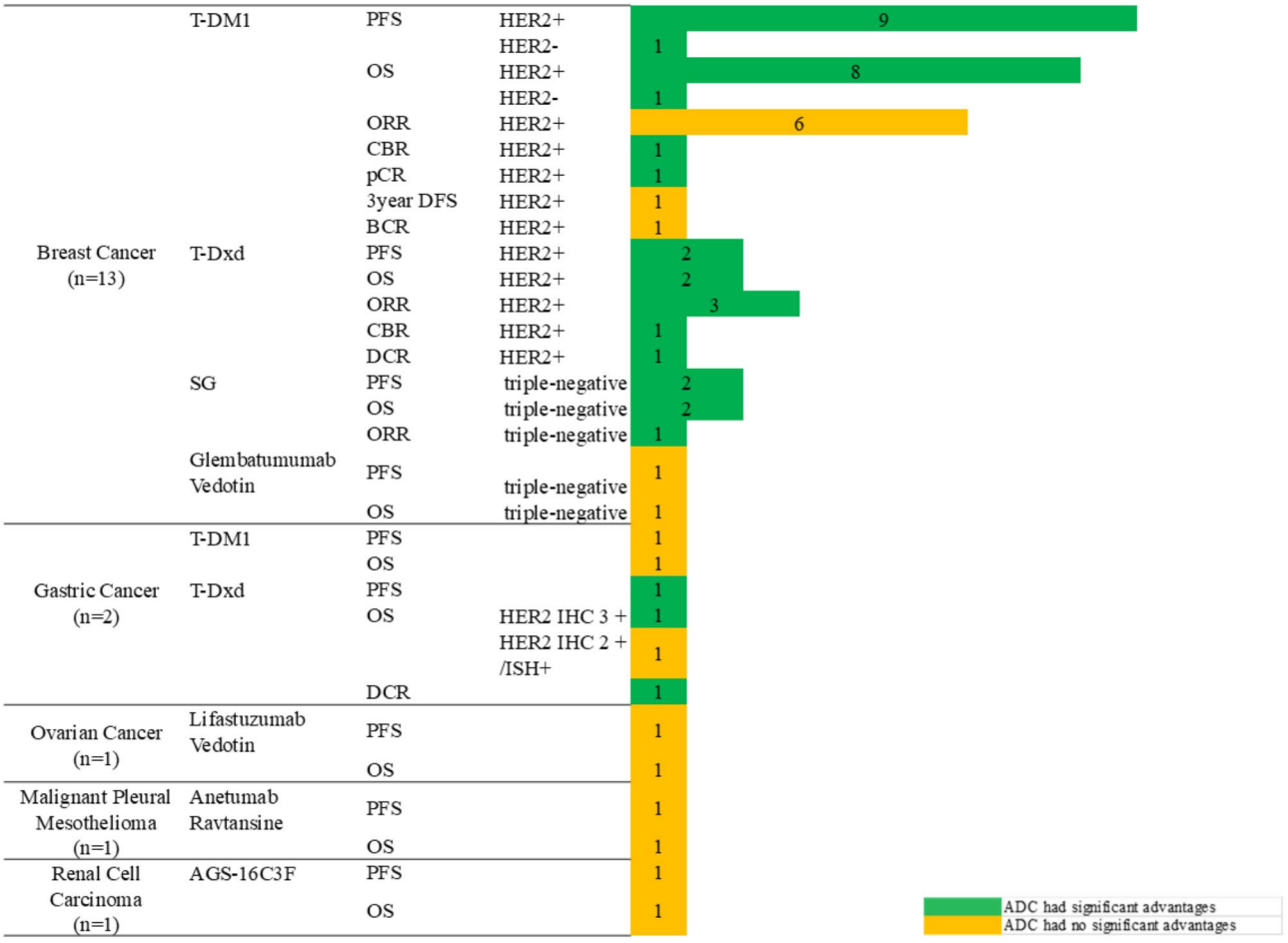

Fig. 3 Subgroup analyses and efficacy results in solid tumor. Abbreviations: progressive-free survival (PFS); overall survival (OS); duration of response (DOR); overall response rate (ORR); and clinical benefit rate (CBR); disease-free survival (DFS); disease control rate (DCR); pathologic complete response (PCR); adverse events (AEs); human epidermal growth factor receptor 2 (HER2); sacituzumab govitecan (SG); ado-Trastuzumab emtansine (T-DM1); Trastuzumab deruxtecan (T-Dxd); n, the number of included systematic reviews

We summarized data from published systematic reviews and meta-analyses to identify the most beneficial and effective treatments for patients. Our study showed that ADCs significantly prolonged PFS and OS in solid tumor. However, there was no significant advantage in ORR. T-DM1, T-Dxd treat HER2-low/positive advanced or metastatic breast cancer significantly prolonged the PFS and OS.

Treatment with enfortumab vedotin and pembrolizumab resulted in significantly better outcomes than chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma [33]. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer, metastatic triple-negative breast cancer and advanced or metastatic non-small cell lung cancer showed good efficacy and safety [34–36]. Overall, ADCs significantly prolonged PFS and OS, but breast cancer accounted for a large proportion and had a great impact on the combined results. Nevertheless, For the other cancer types, Trastuzumab emtansine was not superior to taxane in patients with previously treated and HER2-positive advanced gastric cancer [37]. In patients with recurrent cervical cancer, second- or third-line treatment with tisotumab vedotin resulted in significantly greater efficacy than chemotherapy [38]. But PFS and/or OS were not significantly prolonged by AGS-16C3F in metastatic renal cell carcinoma [39], and Anetumab raytansine in malignant pleural mesothelioma [40, 41]. In a randomized, open-label phase II study, Lifastuzumab vedotin Q3W was well tolerated compared to doxorubicin, a peglycolated liposome, and improved objective response rates in patients with platinum-resistant ovarian cancer, but did not significantly prolong PFS [42]. Meanwhile, other studies have shown that Mirvetuximab soravtansine was effective in the treatment of advanced or recurrent ovarian cancer with FRa-positive expression [43] and Tisotumab vedotin had great potential for treating recurrence or metastatic cervical cancer [44]. Therefore, ADCs might bring new options for the treatment of

gynecologic oncology patients. Due to limitations of the original research, no synthetic results have been reported and further studies are still needed.

The primary goal of combining cytotoxic agents with monoclonal antibodies is to achieve targeted delivery of the payload, expanding the therapeutic window and ultimately reducing chemotherapy-related toxicity [45]. But targeted chemotherapy remains an unavoidable event of chemotherapy toxicity. TRAEs for HER2-targeted ADCs did not differ across cancer types and dosing regimens [46]. However, T-DXd appeared to have a higher average rate of adverse events compared to T-DM1 [46]. The study has shown that the T-DXd group had the highest rate of pneumonia, and non-small cell lung cancer had the highest rate of pneumonia of all tumor types [47]. Due to ADCs circulate in vivo as 3 distinct components including the conjugate, the naked antibody, and unconjugated molecules of the payload. And these 3 components determined the dose of unconjugated payload able to circulate freely and induce off-target toxicities [48]. Pharmacokinetic studies have shown this to be small for T-DM1, which may explain the low incidence of chemotherapy-related adverse events [49]. In clinical trials, ADCs showed good safety profile, but ALT, AST, nausea, constipation, LVD, decreased appetite, pneumonitis and ILD, and hypertension significantly increased significantly compared with the control group. However, due to the limitation of follow-up time, clinical trials may not be able to timely detect of the late AEs. Real-world study has shown that ADCs significantly increase the risk of sepsis in cancer patients [50]. ADCs may increase the risk of neurotoxicity in cancer patients, leading to serious mortality and being associated with the development of cardiovascular toxicity, and peripheral neuropathy [51, 52]. Therefore, in the process of practical clinical applications, attention should be paid to the risk of ADCs drug-related adverse reaction events. In addition, clinical drug monitoring should be strengthened to reduce the impact of adverse reactions on patients' prognosis and quality of life.

In terms of study methodology and quality of evidence, there was only one high-quality study, and less than one-third of the 53 outcome indicators had high-quality evidence. As we known, the absence of methodological critical entries will affect the quality of the study. The risk of bias and publication bias were the main factors leading to the evidence de-escalation.

ADCs have great therapeutic potential, but several key challenges need to be overcome to realize this potential, such as drug resistance, intra- and inter-tumor heterogeneity, and risk of TRAEs. Emerging ADCs paradigms, including bispecific and dual-loaded ADCs, show the potential to address drug resistance and tumor heterogeneity, while conditionally activated ADCs may increase tumor specificity and reduce the incidence of adverse events [53, 54]. Although the majority of our study was on breast cancer, there are limitations in terms of cancer types. However, the efficacy and safety of ADCs in other solid tumors have been progressively validated in clinical trials, and we will update our conclusions from time to time as future data become available.

Limitations

It is necessary to admit that our research has some limitations. First, ACDs such as Tisotumab Vedotin, mirvetuximab soravtansine, Disitamab vedotin, and others were not involved in our included studies due to the restriction of the type of inclusion of our studies to RCTs, which may have led to the exclusion of many systematic evaluations included in observational studies. Second, we did not analyze the original studies and all data originated from systematic reviews, so the quality of the evidence depends on the quality of the systematic reviews. Third, the heterogeneity was not solved in most of the results.

Conclusion

Our findings show that ADCs bring more options for breast cancer treatment and rewrites the breast cancer treatment landscape. Future research should focus on prospective, large-scale, multi-center clinical studies to verify the efficacy and safety of ADCs in other solid tumors except breast cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13726-8.

Supplementary Material 1

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Author contributions

Hua wei and Qian Jiang contributed to the study design; Yongjun Zhang and Xiaoli Qin conducted the literature search; Yongjun Zhang and Yun Lu conducted study selection and any disagreement was solved by Xiaoli Qin; Hua wei and Ya Zou extracted the data; Yun Lu and Lu Zhou assessed the methodological quality and Hua wei and Ya Zou assessed the quality of the evidence, any disagreement was solved by Qian Jiang; Hua wei and Yongjun Zhang wrote original draft preparation; all authors read, approved the final version and agreed on the submission of the manuscript.

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Data availability

The data were taken from publicly available publications and were therefore widely accessible. The dataset analyzed in this study is available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors. All the data involved in this study were extracted from published articles.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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